

Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study

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ABSTRACT

Background: Phase 3 trials found mRNA-1273 was highly effective in preventing COVID-19. We conducted a prospective cohort study at Kaiser Permanente Southern California (KPSC) to determine the real-world vaccine effectiveness (VE) of mRNA-1273 in preventing COVID-19 diagnosis and severe disease.

Methods: For this planned interim analysis, individuals aged ≥ 18 years receiving 2 doses of mRNA-1273 ≥ 24 days apart (12/18/2020-3/31/2021) were 1:1 matched with randomly selected unvaccinated individuals on age, sex, and race/ethnicity, with follow-up through 6/30/2021. Outcomes were COVID-19 diagnosis (SARS-CoV-2 positive molecular test or COVID-19 diagnosis code) or severe disease (COVID-19 hospitalization and COVID-19 hospital death). Adjusted hazard ratios (aHR) and confidence intervals (CI) were estimated by Cox proportional hazards models accounting for multiple comparisons. Adjusted VE was calculated as $(1 - \text{aHR}) \times 100$. Whole genome sequencing was performed on SARS-CoV-2 positive specimens.

Findings: This analysis included 352,878 recipients of 2 doses of mRNA-1273 matched to 352,878 unvaccinated individuals. VE (99.3% CI) against COVID-19 diagnosis was 87.4% (84.8-89.6%). VE against COVID-19 hospitalization and hospital death was 95.8% (90.7-98.1%) and 97.9% (66.9-99.9%), respectively. VE was higher against symptomatic (88.3% [98.3% CI: 86.1%-90.2%]) than asymptomatic COVID-19 (72.7% [53.4%-84.0%]), but was generally similar across age, sex, and racial/ethnic subgroups. VE among individuals with history of COVID-19 ranged from 8.2-33.6%. The most prevalent variants were Delta (47.1%), Alpha (21.4%), Gamma (11.4%), Epsilon (4.3%), and Iota (4.3%) among fully vaccinated individuals and Alpha (41.2%), Epsilon (18.2%), Delta (11.0%) and Gamma (8.6%) among unvaccinated individuals.

Interpretation: These interim results provide reassuring evidence of the VE of 2 doses of mRNA-1273 across age, sex, and racial/ethnic subgroups, and against asymptomatic and symptomatic COVID-19, and severe COVID-19 outcomes. Among individuals with history of COVID-19, mRNA-1273 vaccination may offer added protection beyond immunity acquired from prior infection. Longer follow-up is needed to fully evaluate VE of mRNA-1273 against emerging SARS-CoV-2 variants.

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Keywords: COVID-19; SARS-CoV-2; mRNA-1273; vaccine effectiveness; variants; matched cohort

RESEARCH IN CONTEXT

Evidence before this study

It is crucial to assess the real-world vaccine effectiveness (VE) of available COVID-19 vaccines, including mRNA-1273, to inform ongoing and future vaccination strategies. PubMed was searched for global observational studies published between December 1, 2020, and August 1, 2021, using the terms “COVID-19 AND (Moderna vaccine OR mRNA-1273) AND (effectiveness OR real-world) AND (observational OR cohort OR test-negative)”. Out of 32 articles retrieved, 7 were relevant to this topic. Overall, high VE of mRNA-1273 against SARS-CoV-2 infection (82·0–100%) and severe COVID-19 disease (86·0-95·7%) was reported. Additionally, high VE of mRNA-1273 against variants of concern B.1.1.7 (Alpha; 100%) and B.1.351 (Beta; 96·4%), was reported.

Added value of this study

This study is one of the first prospective cohort studies to assess several covariates of mRNA-1273 VE among a diverse real-world population. In this planned interim analysis, VE of mRNA-1273 was shown to be >80% against COVID-19 diagnosis, hospitalization, and death. VE was higher against symptomatic than asymptomatic COVID-19, similar across age, sex, and racial/ethnic subgroups, and lower among individuals with history of COVID-19.

Implications of all available evidence

This study, which fulfills commitments to multiple health authorities globally, provides reassuring evidence of the VE of 2 doses of mRNA-1273 against asymptomatic infection, COVID-19 diagnosis, and severe outcomes. Longer follow-up is needed to confirm lower VE among those with history of COVID-19 and to fully evaluate VE of mRNA-1273 against emerging SARS-CoV-2 variants.

INTRODUCTION

Following the sequencing of severe acquired respiratory syndrome coronavirus 2 (SARS-CoV-2), vaccines to prevent coronavirus disease 2019 (COVID-19) were rapidly developed. These included, among others, 2-dose mRNA-based COVID-19 vaccines, mRNA-1273 (Moderna Inc, Cambridge, USA) and BNT162b2 (Pfizer Inc, New York, USA; BioNTech Manufacturing GmbH, Mainz, Germany),^{1,2} and a 1-dose adenoviral vector COVID-19 vaccine, Ad26.COV2.S (Johnson & Johnson, NJ, USA).³ Subsequently, the United States (US) Food and Drug Administration granted emergency use authorization in December 2020 for mRNA-1273 in individuals aged ≥ 18 years and BNT162b2 in individuals aged ≥ 16 years,⁴⁻⁶ and in February 2021 for Ad26.COV2.S in individuals aged ≥ 18 years.⁷ As of August 31, 2021, 61.3% of the vaccine-eligible US population was fully vaccinated with a COVID-19 vaccine; among fully vaccinated individuals, the majority received mRNA-based vaccines (39% received mRNA-1273 and 53% received BNT162b2).⁸

In phase 3 randomized controlled trials, mRNA-1273 and BNT162b2 were 94.1% and 95.0% efficacious at preventing symptomatic, laboratory-confirmed COVID-19, respectively.^{1,2} As mass vaccination continues against COVID-19 in the US and globally, and as new SARS-CoV-2 variants of concern continue to emerge, there is an urgent need to continually evaluate the real-world effectiveness of COVID-19 vaccines. Real-world studies are critical as vaccine effectiveness (VE) could differ from vaccine efficacy assessed under trial conditions. Additionally, real-world studies are needed to evaluate VE in diverse populations at different time points and with longer follow-up;^{9,10} such data could inform vaccination strategies including selection of COVID-19 vaccine products and need for booster doses or different vaccine formulations offering broad protection against SARS-CoV-2 variants.

Several reports on real-world VE of mRNA-based vaccines have been published to date. In Qatar, VE of mRNA-1273 was 95.7% against severe, critical or fatal COVID-19 disease; high VE against infection with B.1.1.7 (Alpha) and B.1.351 (Beta) variants was also observed.¹¹ In Israel, several large studies in early 2021 reported VE of BNT162 of 92%-95% against COVID-19 infection and 92%-97% against severe disease.^{12,13} In the US, studies have focused on VE in specific populations such as health care personnel, the elderly, or military veterans, with VE estimates for early 2021 ranging from 82% to >98%.¹⁴⁻²¹ With

circulation of more transmissible SARS-CoV-2 variants such as Delta, however, breakthrough infections among mRNA-vaccinated individuals may be more common.²²⁻²⁴

Although several real-world studies have assessed VE for BNTb162b2 or mRNA-based vaccines combined, few studies have assessed VE for mRNA-1273, particularly among the general US population.²⁵⁻²⁷ Therefore, we evaluated the VE of mRNA-1273 in a planned interim analysis of a 5-year observational study within the Kaiser Permanente Southern California (KPSC) health care system in the US.

METHODS

Study setting

Here, we present interim results of an ongoing, matched, prospective cohort study at KPSC to evaluate the VE of mRNA-1273 in preventing COVID-19 diagnosis and severe disease. The study is a commitment to multiple health authorities globally, to continue evaluating the benefit-risk profile of mRNA-1273 post-authorization/licensure. The KPSC Institutional Review Board provided ethical approval for the study.

KPSC is an integrated health care system including more than 4.6 million members of diverse sociodemographic, racial, and ethnic backgrounds.²⁸ Comprehensive electronic health records (EHRs) capture details of patient care from inpatient, emergency department (ED), outpatient, and virtual care settings, with care received outside of the KPSC system captured through claims.

KPSC began mRNA-1273 administration to eligible individuals on December 18, 2020. In accordance with state public health guidelines,²⁹ individuals were prioritized for vaccination with mRNA-1273 or other available COVID-19 vaccines as follows: healthcare workers and long-term care residents (started December 2020); individuals aged ≥65 years, and workers in education and childcare, emergency services, and food and agriculture (started January 2021); individuals aged 18–64 years with underlying health conditions (started March 2021); and all individuals aged ≥18 years (started April 2021).

Molecular testing for SARS-CoV-2 at KPSC is widely available for individuals with or without symptoms who seek testing for any reason. KPSC also requires testing prior to procedures or hospital admission. The majority of samples are nasopharyngeal/oropharyngeal swabs or saliva samples, which are primarily

tested by RT-PCR using the TaqPath™ COVID-19 High-Throughput Combo Kit (Thermo Fisher Scientific, Pleasanton, USA); a smaller proportion of samples are tested using the Roche cobas® SARS-CoV-2 assay or the Roche cobas® SARS-CoV-2 & Influenza A/B assay (Roche Molecular Systems, Branchburg, USA). In March 2021, KPSC began sending all positive SARS-CoV-2 specimens to a commercial laboratory (Helix, San Diego, USA) for whole genome sequencing (WGS), as detailed in Supplementary Methods.

Study Objectives

The primary objectives of this planned interim analysis were to evaluate the VE of 2 doses of mRNA-1273 in preventing COVID-19 diagnosis and severe disease. Secondary objectives evaluated at this time point included the VE of 2 doses of mRNA-1273 in preventing asymptomatic vs. symptomatic COVID-19, and COVID-19 diagnosis stratified by age, sex, race/ethnicity, and history of COVID-19 diagnosis. Subsequent interim and final analyses throughout the 5-year study are planned to evaluate additional secondary objectives.

Study Population

Individuals aged ≥18 years who were members of KPSC for ≥12 months prior to index date (allowing a 31-day membership gap) through 14 days after the index date were eligible for inclusion in the study. The index date was defined as the date of receipt of the second dose of mRNA-1273 for vaccinated individuals and their matched unvaccinated counterparts. Individuals who received a COVID-19 vaccine other than mRNA-1273 prior to the index date, received 2 doses of mRNA-1273 <24 days apart, received any COVID-19 vaccine <14 days after the index date, had no health care utilization and no vaccination from the 2 years prior to the index date through the index date, or had a COVID-19 outcome <14 days after the index date were excluded.

For this interim analysis, eligible individuals who received 2 doses of mRNA-1273 at least 24 days apart (4-day grace period allowed prior to the recommended 28-day interval) from December 18, 2020 to March 31, 2021 were included in the vaccinated group. The unvaccinated comparison group comprised eligible individuals who had not received mRNA-1273 or any other COVID-19 vaccine as of the index date.

Unvaccinated individuals were randomly selected and 1:1 matched to vaccinated individuals by age (18–

44 years, 45–64 years, 65–74 years, and ≥75 years), sex, and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Non-Hispanic Asian, and Other/Unknown).

Exposure and Outcomes

The mRNA-1273 vaccine exposure was captured from KPSC EHR vaccination records. COVID-19 vaccine providers must document COVID-19 vaccine administration data daily to the California Immunization Registry (CAIR).³⁰ COVID-19 vaccinations received outside KPSC were regularly imported into the EHR from external sources, including CAIR, CalVax (Cal Poly Pomona mass vaccination site), Care Everywhere (system on the Epic EHR platform that allows different health care systems to exchange patient medical information), claims (e.g., retail pharmacies), and member self-report (with valid documentation).

The primary outcomes of the study were COVID-19 diagnosis, defined as a SARS-CoV-2 positive test or a COVID-19 diagnosis code ([Supplementary Table 1](#) and [2](#)); and severe COVID-19 disease, including COVID-19 hospitalization (hospitalization with a SARS-CoV-2 positive test or a COVID-19 diagnosis, or a hospitalization ≤7 days after a SARS-CoV-2 positive test, with chart review by a physician investigator [BKA] to confirm severe COVID-19 symptoms) and COVID-19 hospital death. A COVID-19 diagnosis was considered an incident diagnosis if there was no history of a COVID-19 diagnosis code or SARS-CoV-2 positive molecular test in the 90 days prior.³¹ We ascertained the first occurrence of incident COVID-19 diagnosis or severe COVID-19 disease ≥14 days after the index date.^{1,32}

For this interim analysis, asymptomatic COVID-19 cases were identified through positive SARS-CoV-2 tests ordered for individuals without COVID-19 symptoms (e.g., routine screening prior to procedures or hospital admission at KPSC, elective screening of KPSC employees, or testing requested for any other reason); these test orders were not used for individuals with symptoms. The remainder of the COVID-19 cases were considered symptomatic COVID-19 cases.

For individuals with history of a COVID-19 from March 1, 2020 to index date, a COVID-19 reinfection (>90 days after the most recent prior COVID-19 diagnosis code or SARS-CoV-2 positive test) during follow-up was assessed using two definitions. The first definition required a COVID-19 diagnosis code with chart-confirmed symptoms or a SARS-CoV-2 positive molecular test. The second, more specific definition

required a COVID-19 diagnosis code with chart-confirmed symptoms, a SARS-CoV-2 positive molecular test with chart-confirmed symptoms, or a SARS-CoV-2 positive molecular test with an intervening SARS-CoV-2 negative molecular test.

We followed-up individuals in the EHR for occurrence of COVID-19 outcomes until the end of the interim analysis period (June 30, 2021) or censoring events (termination of KPSC membership allowing for a 31-day gap, death, or receipt of a COVID-19 vaccine). Unvaccinated individuals no longer contributed unvaccinated person-time upon receipt of a first dose of mRNA-1273 during follow-up, and contributed vaccinated person-time upon receipt of an eligible second dose of mRNA-1273.

Other variables

Baseline characteristics were extracted from the EHR ([Supplementary Table 3](#)). Variables assessed at index date included age, sex, race/ethnicity, socioeconomic status (Medicaid, neighborhood median household income), medical center area, pregnancy status (by trimester), and KPSC physician/employee status. Variables assessed in the two years prior to index date included smoking and body mass index (BMI). Variables assessed in the year prior to index date included Charlson comorbidity score, autoimmune conditions (rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, multiple sclerosis, systemic lupus erythematosus), health care utilization (virtual, outpatient, ED, and inpatient encounters), preventive care (other vaccinations, screenings, and well-visits), chronic diseases (kidney disease, heart disease, lung disease, liver disease, diabetes), and frailty index.³³ Other variables included history of SARS-CoV-2 molecular test performed from March 1, 2020 to index date, irrespective of result, and immunocompromised status (HIV/AIDS, leukemia, lymphoma, congenital and other immunodeficiencies, asplenia/hyposplenia, and organ transplant any time prior to index date; and immunosuppressant medications at index date).

Statistical analyses

We described attributes of vaccinated and unvaccinated cohorts. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate, and continuous variables were compared using the two-sample t-test or Wilcoxon rank-sum test, as appropriate. Absolute standardized differences (ASD) were calculated to assess the balance of covariates; $ASD \leq 0.1$ was considered a negligible difference,³⁴

and potential confounders were determined by ASD >0·1. Matching variables (age, sex, and race/ethnicity) were considered important risk factors and kept in adjusted models.

We calculated overall incidence rates of COVID-19 diagnosis and of severe COVID-19 for vaccinated and unvaccinated cohorts (number of incident events divided by person-years). The cumulative incidences of COVID-19 diagnosis, hospitalization, and hospital death for the 2-dose vaccinated and unvaccinated individuals were estimated by the Kaplan-Meier method and compared by the log-rank test.

Unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) comparing COVID-19 diagnosis or severe COVID-19 disease in vaccinated and unvaccinated individuals were estimated by Cox proportional hazards regression models without and with confounder adjustment. Since multiple interim analyses are planned for this longitudinal study, the test significance level was adjusted using the Bonferroni correction to keep the overall Type I error below 0·05. As such, either 99·3% CIs (for VE against COVID-19 diagnosis, hospitalization, or hospital death) or 98·3% CIs (for VE against COVID-19 diagnosis by age, sex, race/ethnicity, history of COVID-19, and asymptomatic/symptomatic COVID-19 subgroups) were calculated based on the planned number of interim analyses over the course of the full study. Unadjusted VE (%) was calculated as $(1 - \text{unadjusted HR}) \times 100$. Adjusted VE (%) was calculated as $(1 - \text{adjusted HR}) \times 100$.

Statistical power calculations are presented in Supplementary Methods. All analyses were conducted using SAS software version 9.4, Cary, USA.

Distribution of SARS-CoV-2 variants by vaccination status

To better characterize variants circulating locally during the study period, we also described the distribution of variants among successfully sequenced specimens collected from March to June 2021 from recipients of 1 or 2 doses of mRNA-1273 and unvaccinated individuals. These data were derived from the broader KPSC population and were not directly linked to the eligible cohort for this interim analysis.

RESULTS

The study included 352,878 recipients of 2-doses of mRNA-1273 ('vaccinated', hereafter) and 352,878 unvaccinated individuals matched on age, sex, and race/ethnicity ([Supplementary Figure 1](#) and [Table 1](#)). Median age was 65 years (IQR 45–73 years), thus approximately half of individuals were aged <65 years. Overall, there were more females (59·4%) than males and more non-Hispanic White (38·7%) or Hispanic (32·4%) individuals than other racial/ethnic groups. Vaccinated and unvaccinated individuals had similar baseline distributions (ASD <0·1) of BMI, smoking, Charlson comorbidity scores, frailty, chronic diseases, immunocompromised status, autoimmune conditions, pregnancy, and ED visits and hospitalizations in the year prior to index date. Compared to unvaccinated individuals, fewer vaccinated individuals had a history of COVID-19 diagnosis, but more vaccinated individuals had received a molecular SARS-CoV-2 test. Vaccinated individuals also had more outpatient/virtual visits and preventive care visits in the year prior to index date, had a lower proportion with Medicaid, had higher median neighborhood income, and were more often KPSC physicians/employees. There were some differences in distributions of vaccinated and unvaccinated individuals across medical center areas. Approximately half of the index dates occurred in March 2021, with 44% occurring in February 2021 and 6% occurring in January 2021. Among the vaccinated group, only 88 (0·0%) individuals received mRNA-1273 concomitantly with another vaccine, as concomitant administration was not recommended during the study vaccination period. The median number of days between the first and second mRNA-1273 doses was 28 days (IQR 28–29).

During follow-up, COVID-19 diagnoses occurred among 289 vaccinated individuals and 1,144 unvaccinated individuals, with incidence rates per 1,000 person-years of 2·77 (95% CI: 2·47-3·11) and 20·20 (19·06-21·41), respectively ([Table 2](#)). Lower incidence rates per 1,000 person-years were observed for COVID-19 hospitalization (0·12 [0·07-0·21] for vaccinated and 3·21 [2·77-3·71] for unvaccinated individuals) and COVID-19 hospital death (0·01 [0·00-0·07] for vaccinated and 0·44 [0·30-0·65] for unvaccinated individuals). In Kaplan-Meier plots, cumulative incidence estimates of COVID-19 diagnosis, hospitalization, and hospital death were significantly higher for unvaccinated individuals compared to vaccinated individuals (log-rank test p-values <0·0001) ([Figure 1a-c](#)). Mean (standard deviation) follow-up time was 3·55 (0·61) months for vaccinated individuals and 1·93 (1·43) months for unvaccinated individuals.

For both vaccinated and unvaccinated individuals, incidence rates varied for asymptomatic vs. symptomatic COVID-19 diagnosis, by demographic variables, and by having a history of COVID-19 diagnosis ([Table 3](#)). Incidence rates were lower for asymptomatic vs. symptomatic COVID-19 diagnosis, higher among adults ages <65 years compared to those ages ≥65 years, and higher among non-Hispanic Black and Hispanic individuals compared to Non-Hispanic White or Non-Hispanic Asian individuals. When considering history of COVID-19, incidence rates were highest for unvaccinated individuals without a history of COVID-19.

The adjusted HR (95% CI) of COVID-19 diagnosis comparing vaccinated and unvaccinated individuals was 0.13 (0.11-0.14), yielding an adjusted VE of 87.4% (99.3% CI: 84.8%-89.6%) ([Table 2](#)). VE against COVID-19 hospitalization was 95.8% (90.7%-98.1%) and VE against COVID-19 hospital death was 97.9% (66.9%-99.9%). VE was higher against symptomatic COVID-19 (88.3% [98.3% CI: 86.1%-90.2%]) than asymptomatic COVID-19 (72.7% [53.4%-84.0%]), but was generally similar in subgroups by age, sex, and race/ethnicity, with point estimates ranging from 83.0% to 91.8%. VE among individuals with a history of COVID-19 ranged from 8.2% (0.0%-47.3%) to 33.6% (0.0%-65.8%), depending on reinfection definition ([Table 3](#)).

From March–June 2021, 5,081 SARS-CoV-2 positive specimens were successfully sequenced, of which 70 were from recipients of 2 doses of mRNA-1273 (“fully vaccinated”), 60 were from recipients of 1 dose of mRNA-1273 (“partially vaccinated”), and 4,951 were from unvaccinated individuals ([Figure 2](#)). Among fully vaccinated individuals, the most prevalent variants were 47.1% Delta (B.1.617.2, AY.2), 21.4% Alpha (B.1.1.7), 11.4% Gamma (P.1, P.1.1), 4.3% Epsilon (B.1.427, B.1.429), and 4.3% Iota (B.1.526, B.1.526.1, B.1.526.2). The most prevalent variants among partially vaccinated individuals were similar to unvaccinated individuals: 36.7% Alpha, 18.3% Epsilon, 15.0% Gamma, 5.0% Delta, and 3.3% Iota for partially vaccinated individuals and 41.2% Alpha, 18.2% Epsilon, 11.0% Delta, 8.7% Gamma, and 3.5% Iota for unvaccinated individuals.

DISCUSSION

These interim results from a prospective cohort study conducted confirm high effectiveness of mRNA-1273, with VE of 87.4% against COVID-19 diagnosis, 95.8% against COVID-19 hospitalization, and

97·9% against COVID-19 hospital death. The study included a large cohort of individuals eligible to receive mRNA-1273 for diverse reasons (health care workers, long term care residents, individuals aged ≥65 years, workers in education, childcare, emergency services, food and agriculture, and individuals aged 18-64 with underlying conditions) who were followed until June 2021, a period that overlapped with the emergence of Delta in the US.

Our results add to limited other reports of real-world VE estimates specific to mRNA-1273 among the general population, although other studies were primarily conducted when Alpha and Epsilon were dominant. A test-negative study conducted in California found VE of mRNA-1273 of 86·2% against SARS-CoV-2 infection (87·0% for BNT162b2), consistent with our results.²⁵ In addition, a retrospective cohort study in a large multi-state health care system found VE of 93·3% against a positive SARS-CoV-2 test (86·1% for BNT162b2) and 86·0% against hospitalization within 21 days of a positive SARS-CoV-2 test (88·8% for BNT162b2).²⁶

We found higher VE for mRNA-1273 against COVID-19 hospitalization and COVID-19 hospital death than against COVID-19 diagnosis. This is aligned with other studies suggesting that protection of mRNA-based vaccines is higher against more severe disease.^{1,15} Few previous studies have reported VE of mRNA-1273 against asymptomatic infections. In our study, we observed higher VE among symptomatic individuals than asymptomatic individuals.

The US Centers for Disease Control and Prevention (CDC) recommends COVID-19 vaccine for individuals with history of COVID-19.³⁵ Vaccination can further boost antibody levels in those with past infection and has the potential to improve durability and breadth of protection.³⁶ Several small studies showed that a single mRNA vaccine (BNT162b2) dose among individuals with evidence of prior SARS-CoV-2 infection boosted binding and neutralizing antibody and cell-mediated immune responses compared with individuals without a history of infection.³⁷⁻³⁹ Our study suggests that among individuals with history of COVID-19, mRNA-1273 vaccination may provide additional benefit (8·2-33·6%) beyond protection from natural infection, supporting current guidance that individuals with history of COVID-19 should be vaccinated. As immunologic data suggest that vaccination after COVID-19 infection produces more durable and broader protection compared to COVID-19 infection without vaccination,³⁶ further study

is needed to evaluate long-term protection of mRNA-1273 and protection against variants in those with history of COVID-19.

Results of WGS conducted for SARS-CoV-2 specimens positive by RT-PCR from the broader KPSC population from March to June 2021 suggest different distributions of variants among fully vaccinated individuals compared to partially vaccinated and unvaccinated individuals; however, specimens from fully vaccinated individuals may have been more likely to have lower viral loads that impeded successful sequencing. One study found only modest differences in VE of BNT162b2 against infection with B.1.617.2 (Delta) compared to B.1.1.7 (Alpha),⁴⁰ but further studies will be needed for mRNA-1273.

Our study has several other strengths and limitations. As one of the first population-based real-world studies reporting VE estimates specific to mRNA-1273, our study was conducted in a large integrated health care system with a diverse and stable population. EHRs enabled comprehensive capture of COVID-19 vaccine exposures, COVID-19 outcomes, and extensive demographic, care-seeking, and clinical covariates. The matched cohort design allows generalizability to the general population eligible for mRNA-1273, in contrast to test-negative designs in which generalizability is limited to those who are tested. Nevertheless, our study may be susceptible to residual confounding, for example, from factors that affect risk of COVID-19 exposure and are also associated with vaccination. Although misclassification of vaccine exposure is unlikely due to comprehensive capture of vaccinations within and outside of KPSC, misclassification of COVID-19 diagnosis may have occurred. This may have been due to false positive test results or erroneous entry of diagnosis codes from claims, or for those with history of COVID-19, if viral shedding persisted >90 days; such misclassification is likely to be non-differential, underestimating VE. In addition, we observed a lower incidence of asymptomatic as compared to symptomatic infections, which may reflect incomplete capture of asymptomatic infections, as most individuals are not regularly tested.

Additional interim and final analyses are planned over the course of the 5-year study to examine VE in additional subgroups (adolescents once authorized, individuals with chronic diseases, individuals who are immunocompromised, individuals with autoimmune conditions, frail individuals, pregnant women, and recipients of concomitant vaccinations); VE of 1 dose of mRNA-1273 against COVID-19 diagnosis and

severe COVID-19 disease; VE against SARS-CoV-2 variants; and durability of 2 doses of mRNA-1273 in preventing COVID-19 diagnosis and severe COVID-19 disease.

In conclusion, interim results of this matched cohort study with follow-up through June 2021 provide reassuring evidence of the effectiveness of 2 doses of mRNA-1273 against asymptomatic infection, COVID-19 diagnosis (including across age, sex, and race/ethnicity) and severe outcomes (COVID-19 hospitalization and death). Among those with history of COVID-19, mRNA-1273 vaccination may offer some additional protection beyond that afforded by natural infection. Longer follow-up is needed to fully evaluate effectiveness of mRNA-1273 against emerging SARS-CoV-2 variants.

Role of the funding source

Authors employed by Moderna, Inc contributed to study design, interpretation of the data, the writing of the manuscript, and the decision to submit the article for publication.

AUTHOR CONTRIBUTIONS

Contributions	Authors
Concept and design	KJB, LSS, LQ, CAT, HFT
Acquisition, analysis, or interpretation of data	KJB, LSS, LQ, BKA, AF, CAT, HFT
Drafting of the manuscript	KJB, LSS, AF
Critical revision of the manuscript for important intellectual content	LQ, BKA, YL, GSL, YT, HST, JET, CAT, HFT
Statistical analysis	LQ, YL, YT, JET
Obtained funding	CAT, HFT
Administrative, technical, or material support	CAT, GSL, HST, LSS
Supervision	CAT, HFT

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.

DECLARATION OF INTERESTS

KJB, LSS, LQ, BKA, YL, GSL, YT, AF, HST, JET, HFT are employees of Kaiser Permanente Southern California, which has been contracted by Moderna for the conduct of this present study. CAT is an employee of and a shareholder in Moderna Inc. KJB received funding from GlaxoSmithKline, Dynavax, Pfizer, Gilead, and Seqirus unrelated to this manuscript. LSS received funding from GlaxoSmithKline, Dynavax, and Seqirus unrelated to this manuscript. LQ received funding from GlaxoSmithKline and Dynavax unrelated to this manuscript. BKA received funding from GlaxoSmithKline, Dynavax, Seqirus and Pfizer unrelated to this manuscript. YL received funding from GlaxoSmithKline, Dynavax, Seqirus and Pfizer unrelated to this manuscript. GSL received funding from GlaxoSmithKline unrelated to this manuscript. YT received funding from GlaxoSmithKline unrelated to this manuscript. AF received funding from Pfizer, GlaxoSmithKline, CDC, and Gilead unrelated to this manuscript. HST received funding from GlaxoSmithKline, Pfizer, ALK, and Wellcome unrelated to this manuscript. JET received funding from Pfizer unrelated to this manuscript. HFT received funding from GlaxoSmithKline and Seqirus unrelated to this manuscript; HFT also served in advisory boards for Janssen and Pfizer.

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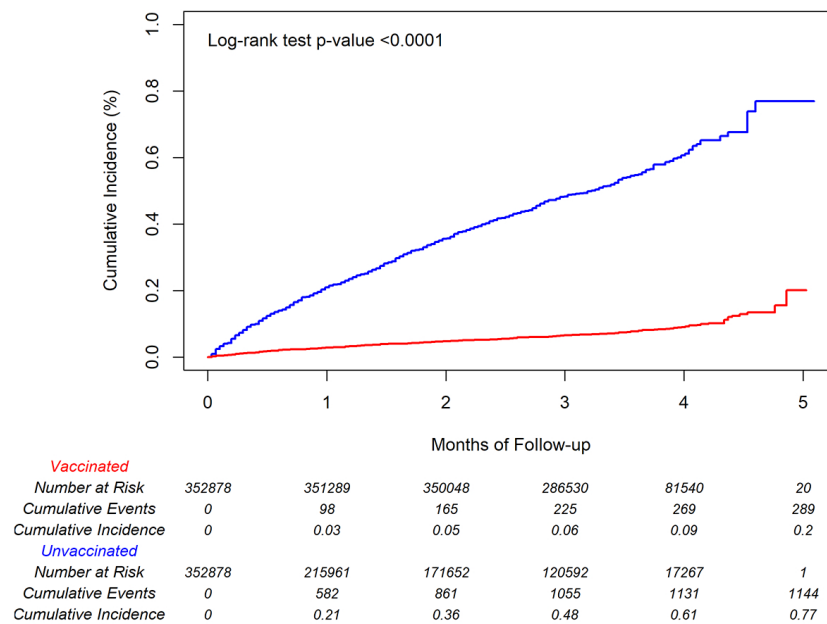
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Figure Legend

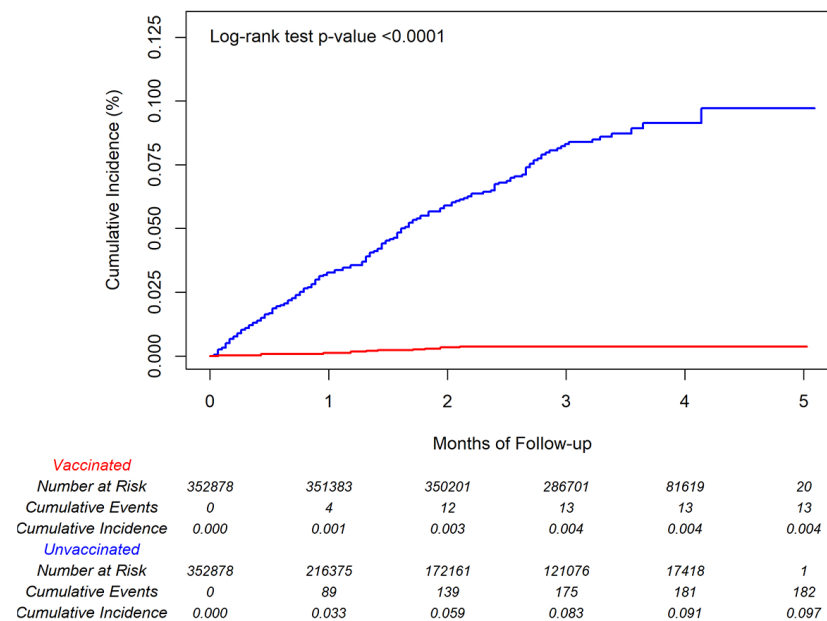
Figure 1. Cumulative incidence estimates of COVID-19 diagnosis, COVID-19 hospitalization, and COVID-19 death by vaccination status in 2-dose mRNA-1273 vaccine cohort

Figure 2. Distribution of SARS-CoV-2 variants from March to June 2021 at KPSC, by vaccination status

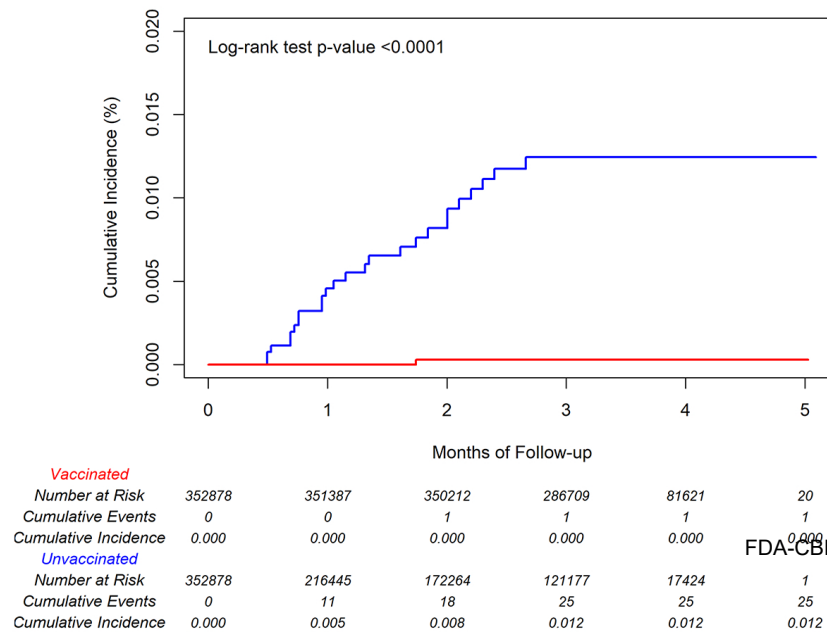
A. COVID-19 diagnosis

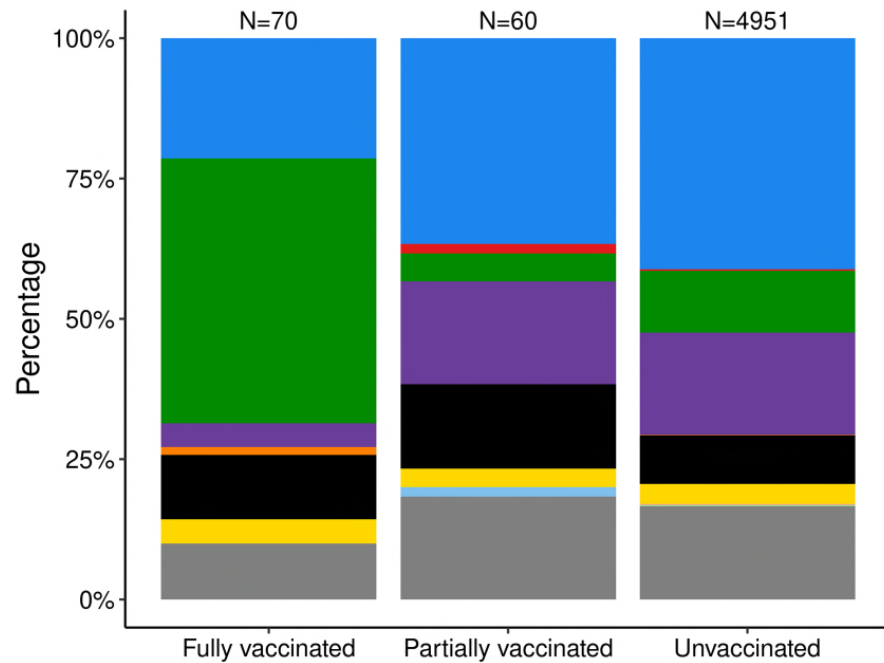


B. COVID-19 hospitalization



C. COVID-19 hospital death





			Fully vaccinated	Partially vaccinated	Unvaccinated
	WHO label	Lineage	N=70, n (%)	N=60, n (%)	N=4951, n (%)
	Alpha	B.1.1.7	15 (21.4)	22 (36.7)	2040 (41.2)
	Beta	B.1.351	0 (0.0)	1 (1.7)	12 (0.2)
		B.1.351.3	0 (0.0)	0 (0.0)	1 (0.0)
	Delta	AY.2	8 (11.4)	1 (1.7)	113 (2.3)
		B.1.617.2	25 (35.7)	2 (3.3)	431 (8.7)
	Epsilon	B.1.427	1 (1.4)	2 (3.3)	238 (4.8)
		B.1.429	2 (2.9)	9 (15.0)	664 (13.4)
	Eta	B.1.525	1 (1.4)	0 (0.0)	6 (0.1)
	Gamma	P.1	8 (11.4)	9 (15.0)	424 (8.6)
		P.1.1	0 (0.0)	0 (0.0)	3 (0.1)
	Iota	B.1.526	0 (0.0)	2 (3.3)	116 (2.3)
		B.1.526.1	2 (2.9)	0 (0.0)	40 (0.8)
		B.1.526.2	1 (1.4)	0 (0.0)	19 (0.4)
	Kappa	B.1.617.1	0 (0.0)	1 (1.7)	2 (0.0)
	Lambda	C.37	0 (0.0)	0 (0.0)	11 (0.2)
	Zeta	P.2	0 (0.0)	0 (0.0)	7 (0.1)
	Other	Other	7 (10.0)	11 (18.3)	824 (16.6)

Table 1· Baseline characteristics of 2-dose mRNA-1273 vaccinated and unvaccinated cohort

	Vaccinated N=352878	Unvaccinated N=352878	Absolute Standardized Difference
	n (%)	n (%)	
Age at index date, years			N/A
18-44	84052 (23·8)	84052 (23·8)	
45-64	85685 (24·3)	85685 (24·3)	
65-74	109268 (31·0)	109268 (31·0)	
≥75	73873 (20·9)	73873 (20·9)	
Sex			N/A
Female	209707 (59·4)	209707 (59·4)	
Male	143171 (40·6)	143171 (40·6)	
Race/Ethnicity			N/A
Non-Hispanic White	136479 (38·7)	136479 (38·7)	
Non-Hispanic Black	26235 (7·4)	26235 (7·4)	
Hispanic	114157 (32·4)	114157 (32·4)	
Non-Hispanic Asian	53843 (15·3)	53843 (15·3)	
Other/Unknown	22164 (6·3)	22164 (6·3)	
Body mass index ^a			0·0750
<18·5	3962 (1·1)	6361 (1·8)	
18·5 - <25	91604 (26·0)	92737 (26·3)	
25 - <30	115276 (32·7)	109259 (31·0)	
30 - <35	67435 (19·1)	65857 (18·7)	
35 - <40	29021 (8·2)	28700 (8·1)	
40 - <45	11403 (3·2)	11582 (3·3)	
≥45	6094 (1·7)	6769 (1·9)	
Unknown	28083 (8·0)	31613 (9·0)	
Smoking ^a			0·0470
No	261648 (74·1)	254378 (72·1)	
Yes	68339 (19·4)	73230 (20·8)	
Unknown	22891 (6·5)	25270 (7·2)	
Charlson comorbidity score ^b			0·0663
0	206661 (58·6)	217936 (61·8)	
1	57928 (16·4)	52271 (14·8)	
≥2	88289 (25·0)	82671 (23·4)	
Frailty index ^b			0·1472
Quartile 1	91442 (25·9)	78980 (22·4)	
Quartile 2	80354 (22·8)	102239 (29·0)	
Quartile 3	91145 (25·8)	85158 (24·1)	
Quartile 4	89937 (25·5)	86501 (24·5)	
Chronic diseases ^b			
Kidney disease	35044 (9·9)	32114 (9·1)	0·0283
Heart disease	17187 (4·9)	18642 (5·3)	0·0188
Lung disease	36690 (10·4)	33049 (9·4)	0·0346
Liver disease	11119 (3·2)	10757 (3·0)	0·0059
Diabetes	68075 (19·3)	63930 (18·1)	0·0301
Immunocompromised	12306 (3·5)	10070 (2·9)	0·0362
HIV/AIDS	1428 (0·4)	749 (0·2)	
Leukemia, lymphoma, congenital and other immunodeficiencies, asplenia/hyposplenism	4794 (1·4)	4226 (1·2)	
Organ transplant	1209 (0·3)	861 (0·2)	
Immunosuppressant medications	6923 (2·0)	5808 (1·6)	
Autoimmune conditions ^b	12562 (3·6)	11277 (3·2)	0·0202
Rheumatoid arthritis	5992 (1·7)	5476 (1·6)	
Inflammatory bowel disease	1981 (0·6)	1692 (0·5)	

Psoriasis and psoriatic arthritis	4372 (1·2)	3775 (1·1)	
Multiple sclerosis	553 (0·2)	584 (0·2)	
Systemic lupus erythematosus	846 (0·2)	746 (0·2)	
Pregnant at index date	1220 (0·3)	2820 (0·8)	0·0601
1st trimester	502 (0·1)	798 (0·2)	
2nd trimester	407 (0·1)	984 (0·3)	
3rd trimester	311 (0·1)	1038 (0·3)	
History of COVID-19 diagnosis ^c	23152 (6·6)	35876 (10·2)	0·1305
History of SARS-CoV-2 molecular test ^c	133865 (37·9)	116859 (33·1)	0·1008
Number of outpatient and virtual visits ^{a,d}			0·2560
0	24225 (6·9)	41711 (11·8)	
1-4	101161 (28·7)	123530 (35·0)	
5-10	105273 (29·8)	94542 (26·8)	
≥11	122219 (34·6)	93095 (26·4)	
Number of emergency department visits ^{a,d}			0·0633
0	302454 (85·7)	295516 (83·7)	
1	36349 (10·3)	39195 (11·1)	
≥2	14075 (4·0)	18167 (5·1)	
Number of hospitalizations ^{a,d}			0·0802
0	336442 (95·3)	330181 (93·6)	
1	13029 (3·7)	17142 (4·9)	
≥2	3407 (1·0)	5555 (1·6)	
Preventive care ^a	294962 (83·6)	234773 (66·5)	0·4021
Medicaid	16741 (4·7)	27283 (7·7)	0·1238
Neighborhood median household income			0·1224
< \$40,000	14128 (4·0)	17262 (4·9)	
\$40,000-\$59,999	62153 (17·6)	70737 (20·0)	
\$60,000-\$79,999	79584 (22·6)	87153 (24·7)	
\$80,000+	196775 (55·8)	176858 (50·1)	
Unknown	238 (0·1)	868 (0·2)	
KPSC physician/employee	26234 (7·4)	6356 (1·8)	0·2709
Concomitant vaccination ^e	88 (0·0)	N/A	
Time between first and second doses, days			N/A
mean (sd)	29·20 (3·25)	N/A	
Index date			N/A
January 2021	19141 (5·4)	19141 (5·4)	
February 2021	152986 (43·4)	152986 (43·4)	
March 2021	180751 (51·2)	180751 (51·2)	

^a Defined in the two years prior to index date

^b Defined in the one year prior to index date

^c Defined based on all available medical records from March 1, 2020 to index date

^d Indicator of overall health care utilization / care-seeking

^e Among subjects with concomitant vaccines: influenza vaccine (37·5%), Tdap (19·3%), shingles vaccine (14·8%), PCV13/PPSV23 (12·5%), and other vaccine (17·0%); 68·2% concomitant with 1st dose and 33·0% concomitant with 2nd dose.

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: Incidence rates, hazard ratios, and VE of 2 doses of mRNA-1273 vaccine in preventing COVID-19 diagnosis, hospitalization, and hospital death

Outcomes	Vaccinated (N=352878)		Unvaccinated (N=352878)		Hazard Ratio (95% CI)		VE (95% CI)		VE (99.3% 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	Adjusted ^a
COVID-19 diagnosis	289	2.77 (2.47-3.11)	1144	20.20 (19.06-21.41)	0.14 (0.13-0.16)	0.13 (0.11-0.14)	85.5% (83.5-87.3%)	87.4% (85.6-89.1%)	87.4% (84.8-89.6%)
COVID-19 hospitalization	13	0.12 (0.07-0.21)	182	3.21 (2.77-3.71)	0.04 (0.02-0.07)	0.04 (0.02-0.08)	95.8% (92.6-97.6%)	95.8% (92.5-97.6%)	95.8% (90.7-98.1%)
COVID-19 hospital death	1	0.01 (0.00-0.07)	25	0.44 (0.30-0.65)	0.02 (0.00-0.17)	0.02 (0.00-0.16)	97.7% (83.1-99.7%)	97.9% (84.5-99.7%)	97.9% (66.9-99.9%)

^a Adjusted for covariates age, sex, race/ethnicity, frailty index (in quartiles), history of COVID-19 diagnosis, history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, preventive care, Medicaid, neighborhood median household income, KPSC physician/employee status, medical center area.

Table 3: Incidence rate, hazard ratio, and VE of 2 doses of mRNA-1273 vaccine in preventing COVID-19 diagnosis by age, sex, race/ethnicity, history of COVID-19, and asymptomatic/symptomatic COVID-19 subgroups

	Vaccinated (N=352878)		Unvaccinated (N=352878)		Hazard Ratio (95% CI)		VE (95% CI)		VE (98.3% 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	Adjusted ^a
Overall									
Asymptomatic	35	0.34 (0.24-0.47)	66	1.17 (0.92-1.48)	0.33 (0.22-0.50)	0.27 (0.18-0.42)	67.2% (50.3-78.3%)	72.7% (57.6-82.4%)	72.7% (53.4-84.0%)
Symptomatic	254	2.44 (2.15-2.76)	1078	19.04 (17.93-20.21)	0.13 (0.12-0.15)	0.12 (0.10-0.13)	86.6% (84.6-88.3%)	88.3% (86.5-89.9%)	88.3% (86.1-90.2%)
Age at index date, years									
12-17				22.71 (20.45-25.22)	0.17 (0.13-0.21)	0.13 (0.10-0.16)	83.3% (78.9-86.7%)	87.2% (83.6-90.1%)	87.2% (82.7-90.6%)
18-44	93	3.58 (2.92-4.39)	350	26.43 (23.67-29.51)	0.13 (0.10-0.16)	0.11 (0.09-0.15)	87.3% (83.7-90.1%)	88.7% (85.3-91.4%)	88.7% (84.5-91.8%)
45-64	83	3.18 (2.56-3.94)	316	16.59 (14.73-18.68)	0.11 (0.08-0.15)	0.11 (0.08-0.14)	88.6% (84.7-91.5%)	89.4% (85.6-92.1%)	89.4% (84.6-92.7%)
65-74	54	1.77 (1.36-2.31)	272	16.02 (13.97-18.36)	0.17 (0.13-0.23)	0.17 (0.12-0.23)	82.5% (76.6-86.9%)	83.0% (76.8-87.6%)	83.0% (75.2-88.4%)
≥75	59	2.72 (2.11-3.51)	206						
Sex				20.84 (19.35-22.44)	0.14 (0.12-0.17)	0.12 (0.10-0.14)	85.9% (83.3-88.1%)	87.9% (85.6-89.9%)	87.9% (85.0-90.3%)
Female	175	2.81 (2.42-3.26)	702	19.27 (17.55-21.15)	0.15 (0.12-0.18)	0.13 (0.11-0.17)	85.0% (81.6-87.9%)	86.6% (83.3-89.2%)	86.6% (82.5-89.7%)
Male	114	2.71 (2.26-3.26)	442						
Race/Ethnicity				17.46 (15.83-19.26)	0.13 (0.10-0.16)	0.11 (0.09-0.14)	87.1% (83.7-89.8%)	88.7% (85.5-91.1%)	88.7% (84.7-91.6%)
Non-Hispanic White	86	2.15 (1.74-2.66)	399	25.60 (21.19-30.94)	0.11 (0.07-0.18)	0.11 (0.07-0.17)	88.6% (82.1-92.8%)	89.2% (82.6-93.4%)	89.2% (80.6-94.0%)
Non-Hispanic Black	23	3.04 (2.02-4.58)	107	25.11 (22.92-27.51)	0.18 (0.15-0.22)	0.16 (0.13-0.19)	81.7% (77.8-84.9%)	84.4% (80.9-87.2%)	84.4% (80.0-87.8%)
Hispanic	142	4.24 (3.60-5.00)	462	15.83 (13.20-18.99)	0.10 (0.06-0.15)	0.08 (0.05-0.13)	90.5% (84.8-94.0%)	91.8% (86.6-94.9%)	91.8% (85.1-95.5%)
Non-Hispanic Asian	22	1.32 (0.87-2.01)	116						
History of COVID-19 diagnosis				21.66 (20.42-22.98)	0.12 (0.11-0.14)	0.11 (0.09-0.12)	87.8% (85.9-89.4%)	89.3% (87.6-90.8%)	89.3% (87.2-91.1%)
No	245	2.51 (2.22-2.85)	1104		0.91 (0.59-1.40)	0.92 (0.58-1.45)	9.1% (0.0-41.0%)	8.2% (0.0-41.8%)	8.2% (0.0-47.3%)
Yes ^b	44	6.50 (4.84-8.73)	40	7.07 (5.19-9.64)	0.69 (0.41-1.16)	0.66 (0.38-1.15)			
Yes ^c	27	3.99 (2.73-5.81)	31	5.48 (3.85-7.79)			31.1% (0.0-59.0%)	33.6% (0.0-61.5%)	33.6% (0.0-65.8%)

^a Adjusted for covariates: age (not adjusted in the age subcohort analysis), sex (not adjusted in the sex subcohort analysis), race/ethnicity (not adjusted in the race/ethnicity subcohort analysis), frailty index (in quartiles), history of COVID-19 diagnosis (not adjusted in the history of COVID-19 diagnosis subcohort analysis), history of SARS-CoV-2 molecular test, number of outpatient and virtual visits, preventive care, Medicaid, neighborhood median household income, KPSC physician/employee status, medical center area.

^b Cases in this category were defined as having a COVID-19 diagnosis code with chart-confirmed symptoms or a SARS-CoV-2 positive molecular test, with no history of a COVID-19 diagnosis code or SARS-CoV-2 positive molecular test in the 90 days prior.

^c Cases in this category were defined as having a COVID-19 diagnosis code with chart-confirmed symptoms, a SARS-CoV-2 positive molecular test with chart-confirmed symptoms, or a SARS-CoV-2 positive molecular test with an intervening SARS-CoV-2 negative molecular test; cases also had no history of a COVID-19 diagnosis code or SARS-CoV-2 positive molecular test in the 90 days prior.

Supplementary Material

Real-world effectiveness of the mRNA-1273 vaccine against COVID-19: Interim results from a prospective observational cohort study

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Table of Contents

Supplementary Methods	3
Supplementary Table 1. COVID-19 diagnosis codes.....	4
Supplementary Table 2. Procedure codes for SARS-CoV-2 molecular tests	5
Supplementary Table 3. ICD-10 diagnosis codes for subgroup conditions, and for covariates to be considered as potential confounders.....	6
Supplementary Figure 1. Flow chart for 2-dose mRNA-1273 vaccine 1st interim analysis cohort.....	8

Supplementary Methods

Whole genome sequencing approach

KPSC began sending all positive SARS-CoV-2 specimens to a commercial laboratory (Helix, California, USA) for whole genome sequencing (WGS) beginning March 2021. In Helix workflow, SARS-CoV-2 genome capture was accomplished using hybridization capture with the xGen COVID-19 Capture Panel (Integrated DNA Technologies, Iowa, USA). Specimens were sequenced using the NovaSeq 6000 Sequencing System S1 Reagent Kit v1.5 (300 cycles) (Illumina, California, USA). Sequence reads were aligned to the SARS-CoV-2 reference genome (NCBI accession NC_045512.2) and the human transcriptome (GENCODE v37) using BWA-MEM, and variants were called using the Haplotyper algorithm (Sentieon Inc, California, USA). Consensus sequences (FASTA) required each allele to have at least 5 unique reads with at least 80% of the reads supporting the allele.

Statistical power calculations

Assuming that at least 80,000 KPSC members would receive 2 doses of mRNA-1273 between December 2020 and March 2021, an incidence of 30 COVID-19 diagnoses or 2 COVID-19 hospitalizations per 1000 unvaccinated adult KPSC members during an average 4-month follow-up period (accounting for possible censoring), and a 1:1 matching ratio, we estimated that we would have >99.9% power to detect a VE of 70% or greater using a 2-sided test with $\alpha=0.007$ (i.e., 0.05 adjusted for 6 interim analyses and 1 final analysis).

Supplementary Table 1. COVID-19 diagnosis codes

Code type	Diagnosis code	Diagnosis code description
KPSC internal code	12459073	CORONAVIRUS COVID-19 ACUTE RESPIRATORY DISTRESS SYNDROME
KPSC internal code	12459074	CORONAVIRUS COVID-19 PNEUMONIA
KPSC internal code	12459075	CORONAVIRUS COVID-19 ACUTE BRONCHITIS
KPSC internal code	12459076	CORONAVIRUS COVID-19 LOWER RESPIRATORY INFECTION
KPSC internal code	12459077	ASYMPTOMATIC CORONAVIRUS COVID-19 DISEASE
KPSC internal code	12459078	CORONAVIRUS COVID-19 DISEASE
KPSC internal code	12459108	COVID-19
KPSC internal code	12459208	CORONAVIRUS COVID-19 TEST POSITIVE BY OUTSIDE LABORATORY
KPSC internal code	12459285	CORONAVIRUS COVID-19 DISEASE IN PREGNANCY, FIRST TRIMESTER
KPSC internal code	12459286	CORONAVIRUS COVID-19 DISEASE IN PREGNANCY, SECOND TRIMESTER
KPSC internal code	12459287	CORONAVIRUS COVID-19 DISEASE IN PREGNANCY, THIRD TRIMESTER
KPSC internal code	12459288	CORONAVIRUS COVID-19 DISEASE IN PREGNANCY, UNSPECIFIED TRIMESTER
KPSC internal code	12459289	CORONAVIRUS COVID-19 DISEASE IN CHILDBIRTH
KPSC internal code	12459290	CORONAVIRUS COVID-19 DISEASE, POSTPARTUM
KPSC internal code	12459293	CORONAVIRUS COVID-19 DISEASE IN PREGNANCY
KPSC internal code	12459785	CORONAVIRUS COVID-19 MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN
KPSC internal code	12460641	CORONAVIRUS COVID-19 MULTISYSTEM INFLAMMATORY SYNDROME IN ADULT
KPSC internal code	12460683	PNEUMONIA DUE TO CORONAVIRUS DISEASE 2019
ICD-10 code	U07.1	COVID-19
ICD-10 code	J12.82	PNEUMONIA DUE TO CORONAVIRUS DISEASE 2019

Supplementary Table 2. Procedure codes for SARS-CoV-2 molecular tests

Procedure code	Procedure Description	Lab test type*
258971	SARS-COV-2 (COVID-19), INFLUENZA A, INFLUENZA B, MULTIPLEX NAA, HIGH THROUGHPUT	Symptomatic
87635AF	SARS-COV2, NAA (COVID-19), HEALTHCARE WORKER, HOME COLLECTION	Asymptomatic
87635J	SARS-COV-2, NAA (COVID-19), SEND-OUT LAB	Symptomatic
87635L	SARS-COV-2, NAA (COVID-19), REFERRAL LAB 3	Symptomatic
87635M	SARS-COV-2, NAA (COVID-19), KP LAB	Symptomatic
87635P	SARS-COV-2, (COVID-19), RNA, QUALITATIVE RT-NAA	Symptomatic
87635S	SARS-COV-2, QUALITATIVE, NAA (COVID-19), EXPEDITED, KP LAB	Asymptomatic
87635Y	SARS-COV2, NAA (COVID-19), HOME COLLECTION TEST	Asymptomatic
87636A	SARS-COV-2 (COVID-19), INFLUENZA A + B, MULTIPLEX NAA	Symptomatic
87635AA	SARS-COV-2, NAA (COVID-19), HEALTHCARE WORKER	Asymptomatic
87635V	SARS-COV-2, NAA (COVID-19), SURVEILLANCE	Asymptomatic

* The test type will only be used in the first interim analysis as a preliminary approach to identify asymptomatic COVID-19 cases.

Supplementary Table 3. ICD-10 diagnosis codes for subgroup conditions, and for covariates to be considered as potential confounders

Covariate	ICD-10 codes
Immunosuppressant conditions	
Leukemia	C90.1*, C91.*-C93.*, C94.0*-C94.4*, C94.8*, C95.*
Lymphoma	C81.*-C86.*, C88.4, C96.*, D45
Congenital and other immunodeficiencies	D61.09, D61.3, D61.82, D61.9, D70.0, D71, D80.0, D80.1, D80.5, D80.8, D81.*, D82.*, D83.*, D84.0, D84.1, D84.9, D89.81*, D89.82, D89.9, E31.0, E70.330, G11.3, Q82.4, Q89.0*
Asplenia/hyposplenia	D57.00, D57.01, D57.02, D57.1, D57.2, D57.20, D57.21, D57.211, D57.212, D57.219, D57.4, D57.40, D57.41, D57.411, D57.412, D57.419, D57.8, D57.80, D57.81, D57.811, D57.812, D57.819, D73.0, Q89.01, Q89.09, Z90.81
Autoimmune conditions	
Rheumatic disease	M05.*, M06.*, M31.5, M32.*-M34.*, M35.1, M35.3, M36.0
Inflammatory bowel disease	K50.*, K51.*
Psoriasis	L40.*
Psoriatic arthritis	L40.5*
Multiple sclerosis	G35
Systemic lupus erythematosus	M32.1, M32.8, M32.9
Charlson comorbidity	
Myocardial Infarction	I21.*, I22.*, I25.2
Congestive Heart Failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.*, I50.*, P29.0
Peripheral Vascular Disease	I70.*, I71.*, I73.1, I73.8*, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8*, Z95.9
Cerebrovascular Disease	G45.*, G46.*, H34.0*, I60.*-I69.*
Connective tissue disease	M05.*, M06.*, M31.5, M32.*-M34.*, M35.1, M35.3, M36.0
Dementia	F00.*-F03.*, F05.1, G30.*, G31.1
Chronic pulmonary disease	I27.8*, I27.9, J40.*-J47.*, J60.*-J67.*, J68.4, J70.1, J70.3
Peptic ulcer disease	K25.*-K28.*
Diabetes mellitus	E10.*-E14.*
Paraplegia and hemiplegia	G04.1, G11.4, G80.1, G80.2, G81.*, G82.*, G83.0, G83.1*-G83.3*, G83.4, G83.9
Renal disease	I12.0, I12.9, I13.1*, N03.2-N03.7, N05.2-N05.7, N18.*, N19.*, N25.0, Z49.0*-Z49.2*, Z94.0, Z99.2
Liver disease	B18.*, I85.0*, I86.4, I98.2, K70.0, K70.1*-K70.4*, K70.9, K71.1*, K71.3, K71.4, K71.5*, K71.7, K72.1*, K72.9*, K73.*, K74.*, K76.0, K76.2-K76.7, K76.8*, K76.9, Z94.4
Cancer: any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	C00.*-C26.*, C30.*-C34.*, C37.*-C41.*, C43.*, C45.*-C58.*, C60.*-C76.*, C81.*-C85.*, C88.*, C90.*-C97.*
Metastatic Solid Tumor	C77.*-C80.*
Chronic diseases	
Kidney disease	I12.0, I12.9, I13.1*, N03.2-N03.7, N05.2-N05.7, N18.*, N19.*, N25.0, Z49.0*-Z49.2*, Z94.0, Z99.2
Heart disease	I21.*, I22.*, I25.2, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.*, I50.*, P29.0

Lung disease	I27.8*, I27.9, J40.*-J47.*, J60.*-J67.*, J68.4, J70.1, J70.3
Liver disease	B18.*, I85.0*, I86.4, I98.2, K70.0, K70.1*-K70.4*, K70.9, K71.1*, K71.3, K71.4, K71.5*, K71.7, K72.1*, K72.9*, K73.*, K74.*, K76.0, K76.2-K76.7, K76.8*, K76.9, Z94.4
Diabetes mellitus	E10.*-E14.*

Supplementary Figure 1. Flow chart for 2-dose mRNA-1273 vaccine 1st interim analysis cohort

