TITLE PAGE

Title: Early evidence of COVID-19 vaccine effectiveness within the general population of California

Authors: Kristin Andrejko, BS[1,*], Jake Pry, PhD[2,*], Jennifer F. Myers, MPH[2], Nicholas P. Jewell, PhD[1,3], John Openshaw, MD[2,4], James Watt, MD, MPH,[2] Seema Jain, MD,[2,†] Joseph A. Lewnard, PhD[1,5,6,†,§] on behalf of the California COVID-19 Case-Control Study Team[‡]

1. Division of Epidemiology and Biostatistics, School of Public Health, University of California at Berkeley, Berkeley, CA
2. California Department of Public Health, Richmond, CA
3. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom
4. Stanford Woods Institute for the Environment, Stanford University, Palo Alto, California, United States
5. Division of Infectious Diseases & Vaccinology, School of Public Health, University of California, Berkeley, Berkeley, California, United States
6. Center for Computational Biology, College of Engineering, University of California, Berkeley, Berkeley, California, United States

* KA and JP contributed equally to the study.
† SJ and JAL jointly supervised the study.

§ Corresponding author:
Joseph A. Lewnard, PhD
Room 5410
2121 Berkeley Way
Berkeley, California 94720
United States
Tel.: +1 (510) 664-4050
E-mail: jlewnard@berkeley.edu

‡ Members of the California COVID-19 Case-Control Study Team are listed in the main text.

KEY POINTS

Question: How effective are mRNA-based vaccines in preventing SARS-CoV-2 infection in the context of general population use?

Findings: In this test-negative design case-control study, fully immunized individuals experienced 86% protection against SARS-CoV-2 infection. Partial protection was evident following receipt of a first dose, and in the first two weeks after receipt of a second dose. Concerns over vaccine safety or side effects are the most common reason for hesitancy among individuals who have not yet been vaccinated.

Meaning: The ongoing rollout of mRNA-based vaccines is preventing COVID-19 in the general population, despite widespread circulation of SARS-CoV-2 variants of concern.

ABSTRACT

Importance: Evidence is needed to determine COVID-19 vaccine effectiveness under real-world conditions of use.

Objective: To determine the effectiveness of authorized vaccines against COVID-19 in the context of substantial circulation of SARS-CoV-2 variants of concern, and identify vaccine uptake barriers.

Design: We recruited cases (testing positive) and controls (testing negative) based on SARS-CoV-2 molecular diagnostic test results from 24 February-7 April 2021. Controls were individually matched to cases by age, sex, and geographic region. We identified cases and controls via random sampling within predetermined demographic strata. We conducted enrollment and administered study questionnaires via telephone-based facilitated interviews.

Setting: Population-based surveillance of all SARS-CoV-2 molecular diagnostic testing reported to the California Department of Public Health. During the study period, 69% of sequenced SARS-CoV-2 isolates in California belonged to variants of concern B.1.1.7, B.1.427, or B.1.429.

Participants: We enrolled 645 adults aged ≥18y, including 325 cases and 320 controls

Exposures: We assessed participants' self-reported history of COVID-19 vaccine receipt (BNT162b2 and mRNA-1273). Individuals were considered fully vaccinated two weeks after second dose receipt.

Main Outcomes and Measures: The primary endpoint was a positive SARS-CoV-2 molecular test result. For unvaccinated participants, we assessed willingness to receive vaccination, when eligible. We measured vaccine effectiveness via the matched odds ratio of prior vaccination, comparing cases with controls.

Results: Among 325 cases, 23 (7%) and 13 (4%) received BNT162b2 and mRNA-1273, respectively; 8 (2%) were fully vaccinated with either product. Among 260 controls, 49 (19%) and 49 (19%) received BNT162b2 and mRNA-1273, respectively; 42 (16%) were fully vaccinated with either product. Among fully vaccinated individuals, vaccine effectiveness was 86% (95% confidence interval: 67-94%). Vaccine effectiveness was 66% (–69-93%) and 78% (23-94%) one week following a first and second dose, respectively. Among unvaccinated participants, 39% of those residing in rural regions and 23% of those residing in urban regions reported hesitancy to receive COVID-19 vaccines, when eligible. In contrast, vaccine hesitancy did not significantly differ by age, sex, household income, or race/ethnicity.

Conclusions and Relevance: Ongoing vaccination efforts are preventing SARS-CoV-2 infection in the general population in California. Vaccine hesitancy presents a barrier to reaching coverage levels needed for herd immunity.

INTRODUCTION

Following demonstrations of efficacy in preventing coronavirus disease 2019 (COVID-19) in randomized controlled trials,[1–3] vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are being administered to the general public. Two mRNA-based vaccines encoding the SARS-CoV-2 spike protein, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), have been used since December 2020, and were administered to 24% of California residents by early April 2021.[4]

Observational studies characterizing COVID-19 vaccine effectiveness (VE) are needed to understand performance under real-world conditions and to inform implementation programs.[5] Such studies allow VE assessment against alternative clinical endpoints, as novel SARS-CoV-2 variants emerge and circulate, and under dosing schedules that differ from those assessed in randomized trials.[6] To date, most studies of real-world VE have enrolled healthcare workers and other essential or frontline personnel, and have been undertaken in settings without substantial circulation of SARS-CoV-2 variants of concern. However, as of March, 2021, variants B.1.1.7, B.1.427, and B.1.429 accounted for 69% of all sequenced SARS-CoV-2 isolates in California.[7] In conjunction with epidemiologic surveillance, we initiated a test-negative design case-control study to monitor VE within the general population of California. Here we provide an early assessment of VE for authorized mRNA-based COVID-19 vaccines based on experience with implementation within the general population. Additionally, to inform future vaccination strategies, we assessed the intention of unvaccinated participants to receive vaccination once eligible.

METHODS

Design

All diagnostic tests in California for SARS-CoV-2 infection are reported by laboratories and medical providers to their local health jurisdiction (LHJ). Sixty of 61 LHJs report data directly to the California Department of Public Health (CDPH) via a web-based reporting system, while Los Angeles County transmits data daily via an electronic file. California residents receiving molecular SARS-CoV-2 tests with results posted between 24 February-7 April, 2021 were eligible for participation in this study. Cases were individuals with positive molecular test results for SARS-CoV-2 infection, reported over the study timeframe, while controls were individuals with negative molecular test results during the same period. Individuals reporting a positive test for SARS-CoV-2 infection prior to the study period were not eligible to participate. This analysis excludes data from children aged 0-17 years, who were generally ineligible for COVID-19 vaccination over the study period.

Each day during the study period, we randomly selected from among all individuals with a telephone number and a positive or negative SARS-CoV-2 test result within nine regions of the state, with intent to enroll equally across each region (regions and the counties comprising them are listed in **Table S4**). For each case who consented and completed the study interview, we attempted to enroll and interview one control matched on age group (18-39, 40-64, ≥65 years), sex, region, and week of SARS-CoV-2 test.

Exposures

We designed and implemented a standardized questionnaire to be delivered via facilitated telephone interviews in English or Spanish including data on participant demographics, symptoms, and vaccination status. We asked participants to indicate whether they had received any COVID-19 vaccine, and to reference their COVID-19 vaccination card to report the manufacturer, number, and dates of doses received. We also asked unvaccinated participants whether they would be willing to receive a COVID-19 vaccine, when it was available to them; if participants indicated they were not likely to receive a vaccine or unsure about receiving a vaccine, we asked for their reasons for vaccine hesitancy.

The study protocol was granted a non-research determination by the State of California Health and Human Services Agency Committee for the Protection of Human Subjects (project number: 2021-034).

Statistical analysis

We measured VE as one minus the matched odds ratio of prior vaccination among cases relative to controls within strata defined by age group, sex, region, and testing week. We defined the vaccine exposure as receipt of BNT162b2 or mRNA-1273, within differing numbers of days since receipt of the first or second dose. We estimated effects using conditional logistic regression models (R version 3.6.1; R Foundation for Statistical Computing; Vienna, Austria).

We also conducted Chi-Square tests for differences in the: proportion of individuals testing positive for SARS-CoV-2 infection among those who received BNT162b2 or mRNA-1273; proportion of cases reporting any symptoms in the two weeks before their testing date among vaccine recipients and non-recipients; and proportion of unvaccinated individuals

reporting hesitancy to receive vaccination across differing demographic groups. We conducted hypothesis testing with two-sided $p<0.05$.

RESULTS

Our study recruited 325 cases and 320 controls. Among cases, 23 (7%) and 13 (4%) reported receiving at least one dose of BNT162b2 or mRNA-1273, respectively. Eight cases (2%) were considered to be fully vaccinated at the time of testing based on self-reported vaccination status (**Figure 1**; **Table S1**). Among fully vaccinated individuals, VE was 86% (67-94%) (**Figure 1**). Case status was not significantly associated with vaccine product received ($\chi^2_{\mathrm{df}=1} = 0.149; p = 0.7$). Presence of symptoms did not differ significantly among vaccinated and unvaccinated cases ($\chi^2_{\mathrm{df}=1} = 1.315; p = 0.3$); 26% of cases did not report symptoms. Thirteen (4%, 13/325) cases were hospitalized; of these, eleven were unvaccinated, and two were incompletely vaccinated.

Within the second week after receipt of a first dose, VE was 66% (–69-93%). Within the second week after receipt of a second dose, VE was 78% (23-94%).

Overall, 133 (32%) of 415 unvaccinated participants (including 78/242 [32%] unvaccinated cases and 55/173 [32%] unvaccinated controls) indicated they were unlikely or unsure about receiving a COVID-19 vaccine when eligible (**Table 2; Table S2**). Residents of rural regions ($\chi^2_{\mathrm{df}=1} = 24.0; p = 0.002$) were over-represented among those reporting vaccine hesitancy, whereas differences in vaccine hesitancy by age, sex, household income, and race/ethnicity were not evident (**Table S3**). Fears over vaccine safety (30/127 [24%]) or side effects (33/127 [26%]) were the most common concerns.

DISCUSSION

We find that authorized mRNA-based COVID-19 vaccines confer robust protection against COVID-19 under real-world conditions in the general population. Moreover, we identify partial protection before two weeks after receipt of the second dose, in agreement with previous estimates.[8] While our point estimate of 86% VE is lower than efficacy findings in earlier randomized trials[1,2] and marginally below that of a recent observational study,[7] several considerations should inform comparison of findings. Primary trial endpoints were COVID-19 diagnoses involving new-onset acute symptoms and SARS-CoV-2 detection, whereas 26% of cases in our study reported no symptoms. The majority of sequenced SARS-CoV-2 isolates in California over the study period represented B.1.427/B.1.429 variants associated with immune escape, which may reduce VE.[9,10] Importantly, though, our results indicate substantial protection despite widespread circulation of these variants.

We identified rural-urban divides in vaccine enthusiasm. Whereas concerns over vaccine safety and side effects were the most common reasons for hesitancy, these concerns were reported by only a minority of all participants who expressed hesitancy about receiving COVID-19 vaccination, when eligible. Differing messaging and outreach strategies will thus be needed to address barriers to vaccine acceptance across communities.

While observational studies face risks of bias, similarity of our estimates to those of other studies and stepwise increases in VE with time since receipt of each dose support external validity.[7,8,11] While the current sample size offered limited statistical power for first-dose VE estimation, enrollment in this study is ongoing. Analyses including larger samples will enable comparison of estimates across products and population subgroups. Meanwhile, our findings indicate that vaccine rollout is preventing COVID-19 in the general population of California.

CALIFORNIA COVID-19 CASE-CONTROL STUDY TEAM

Members of the California COVID-19 Case-Control Study Team include: Helia Samani, Sophia S. Li, Camilla M. Barbaduomo, Nikolina Walas, Christine Wan, Anna Fang, Timothy Ho, Vivian H. Tran, Erin Xavier, Mahsa H. Javadi, Diana J. Poindexter, Najla Dabbagh, Michelle M. Spinosa, Nozomi Birkett, Paulina M. Frost, Zheng Dong, Shrey Saretha, Adrian F. Cornejo, Jennifer L. DeGuzman, Miriam Bermejo, Hye Min Park

ACKNOWLEDGMENTS

The study was supported by the California Department of Public Health. JAL and NPJ received support from NIH/NIAID grant R01-AI14812701. JAL discloses receipt of grants and honoraria from Pfizer, Inc. unrelated to this study.

REFERENCES

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *NEJM* 2020; doi:10.1056/NEJMoa2034577.

2. Spector SA, Rouphael N, Creech CB, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *NEJM* 2020; doi:10.1056/NEJMoa2035389.

3. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1–2a trial of Ad26.COV2.S Covid-19 vaccine. *NEJM* 2021; doi:10.1056/nejmoa2034201.

4. State of California. Tracking COVID-19 in California - Coronavirus COVID-19 Response. https://covid19.ca.gov/state-dashboard/. Accessed 8 April 2021.

5. Patel MM, Jackson ML, Ferdinands J. Postlicensure evaluation of Covid-19 vaccines. *JAMA* 2020; doi:10.1001/jama.2020.19328.

6. Lewnard JA, Patel MM, Jewell NP, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. *Epidemiology* 2021; doi:10.1101/2021.01.21.21250258.

7. Thompson MG, Burgess JL, Naleway AL, et al. Interim estimates of vaccine effectiveness of BNT162b2 and mRNA-1273 COVID-19vaccines in preventing SARS-CoV-2 infection among health care personnel, first responders, and other essential and frontline workers — Eight US locations, December 2020–March 2021. *MMWR* 2021;70(13). doi:10.15585/mmwr.mm7013e3.

8. Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients. *Lancet* 2021;397(10277):875-877. doi:10.1016/S0140-6736(21)00448-7.

9. Deng X, Garcia-Knight MA, Khalid MM, et al. Transmission, infectivity, and antibody neutralization of an emerging SARS-CoV-2 variant in California carrying a L452R spike protein mutation. *medRxiv* 2021; doi:10.1101/2021.03.07.21252647.

10. McCallum M, Bassi J, Marco AD, et al. SARS-CoV-2 immune evasion by variant B.1.427/B.1.429. *bioRxiv* 2021; doi:10.1101/2021.03.31.437925.

11. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *NEJM* 2021; doi:10.1056/NEJMoa2101765.

Table 1: Distribution of cases and controls.

		Overall *n* (%) *N* = 645	Case *n* (%) *N* = 325	Control *n* (%) *N* = 320
Age				
	18-29	243 (37.7)	119 (36.6)	124 (38.8)
	30-49	228 (35.3)	118 (36.3)	110 (34.4)
	50-64	131 (20.3)	67 (20.6)	64 (20.0)
	65+	43 (6.7)	21 (6.5)	22 (6.9)
Region				
	Predominantly urban regions			
	San Francisco Bay Area	69 (10.7)	36 (11.1)	33 (10.3)
	Greater Los Angeles Area	59 (9.1)	30 (9.2)	29 (9.1)
	Greater Sacramento Area	63 (9.8)	32 (9.8)	31 (9.7)
	San Diego and southern Border	82 (12.7)	39 (12.0)	43 (13.4)
	Predominantly rural regions			
	Central Coast	90 (14.0)	47 (14.5)	43 (13.4)
	Northern Sacramento Valley	74 (11.5)	37 (11.4)	37 (11.6)
	San Joaquin Valley	74 (11.5)	37 (11.4)	37 (11.6)
	Northwestern California	69 (10.7)	34 (10.5)	35 (10.9)
	Sierras Region	65 (10.1)	33 (10.2)	32 (10.0)
Sex				
	Male	316 (49.0)	158 (48.6)	158 (49.4)
	Female	327 (50.7)	167 (51.4)	160 (50.0)
	Other	2 (0.3)	0 (0.0)	2 (0.6)
Household income				
	Under $50,000	172 (26.7)	95 (29.2)	77 (24.1)
	$50,000 to $100,000	140 (21.7)	66 (20.3)	74 (23.1)
	$100,000 to $150,000	72 (11.2)	28 (8.6)	44 (13.8)
	Over $150,000	91 (14.1)	43 (13.2)	48 (15.0)
	Refuse	97 (15.0)	57 (17.5)	40 (12.5)
	Not sure	73 (11.3)	36 (11.1)	37 (11.6)
Race/Ethnicity				
	White	294 (45.6)	141 (43.4)	153 (47.8)
	Hispanic	187 (29.0)	105 (32.3)	82 (25.6)
	Asian	64 (9.9)	30 (9.2)	34 (10.6)
	Black	21 (3.3)	15 (4.6)	6 (1.9)
	More than 1 race	53 (8.2)	20 (6.2)	33 (10.3)
	Native American	11 (1.7)	8 (2.5)	3 (0.9)
	Native Hawaiian	7 (1.1)	3 (0.9)	4 (1.2)
	Refuse	8 (1.2)	3 (0.9)	5 (1.6)
Vaccination				
	Unvaccinated	511 (79.2)	289 (88.9)	222 (69.4)
	Incompletely vaccinated	84 (13.0)	28 (8.6)	56 (17.5)
	Fully vaccinated[1]	50 (7.8)	8 (2.5)	42 (13.1)

[1]An individual was considered "fully-vaccinated" $\geq$ 14 days after two doses of Pfizer/BioNTech BNT162b2 or Moderna mRNA-1273, and "incompletely-vaccinated" if they received only one dose or two doses <14 days after second dose

Table 2: Vaccine hesitancy among individuals not yet vaccinated.

		Willingness to receive COVID-19 vaccination when eligible		
		No or unsure, *n* (%) *N*=133	Yes, *n* (%) *N*=282	*p*
Test outcome				1
	Case with SARS-CoV-2 infection	78 (58.6)	164 (58.2)	
	Uninfected control	55 (41.4)	118 (41.8)	
Age				0.234
	18-29	45 (33.8)	119 (42.2)	
	30-49	58 (43.6)	96 (34.0)	
	50-64	23 (17.3)	55 (19.5)	
	65+	7 (5.3)	12 (4.3)	
Sex				0.136
	Male	61 (45.9)	153 (54.3)	
	Female	72 (54.1)	129 (45.7)	
Household income				0.119
	Under $50,000	31 (23.3)	88 (31.2)	
	$50,000 to $100,000	27 (20.3)	63 (22.3)	
	$100,000 to $150,000	13 (9.8)	31 (11.0)	
	Over $150,000	16 (12.0)	32 (11.3)	
	Refuse	30 (22.6)	34 (12.1)	
	Not sure	16 (12.0)	34 (12.1)	
Race				0.036
	White	63 (47.4)	120 (42.6)	
	Hispanic	38 (28.6)	90 (31.9)	
	Asian	5 (3.8)	33 (11.7)	
	Black	7 (5.3)	11 (3.9)	
	More than 1 race	12 (9.0)	22 (7.8)	
	Native American	3 (2.3)	3 (1.1)	
	Native Hawaiian	3 (2.3)	0 (0.0)	
	Refuse	2 (1.5)	3 (1.1)	
Region				0.001
	Predominantly urban regions	39 (29.3)	132 (46.8)	
	San Francisco Bay area	6 (4.5)	35 (12.4)	
	Greater Los Angeles area	11 (8.3)	28 (9.9)	
	Greater Sacramento area	17 (12.8)	26 (9.2)	
	San Diego and southern border region	5 (3.8)	43 (15.2)	
	Predominantly rural regions	94 (70.7)	150 (53.2)	
	Central Coast	20 (15.0)	40 (14.2)	
	Northern Sacramento Valley	19 (14.3)	35 (12.4)	
	San Joaquin Valley	16 (12.0)	30 (10.6)	
	Northwestern California	19 (14.3)	21 (7.4)	
	Sierras Region	20 (15.0)	24 (8.5)	
Reasons for vaccine hesitancy[1]				
	Concerned about long term vaccine side effects	--	33 (26.9)	
	Concerned about any vaccine side effects	--	32 (25.2)	
	Concerned about COVID-19 vaccine safety	--	30 (23.6)	
	Waiting to see more research on COVID-19 vaccines	--	16 (12.6)	
	Currently infected with SARS-CoV-2	--	13 (10.2)	
	I have not yet thought about whether I want the COVID-19 vaccine	--	13 (10.2)	
	Do not believe vaccination against COVID-19 is important	--	12 (9.4)	
	Concerned about safety for vaccines generally	--	12 (9.4)	
	Not at high risk for COVID-19	--	9 (7.1)	
	Currently pregnant	--	6 (4.7)	
	Negative reaction to prior vaccinations	--	4 (3.1)	
	Do not trust the government	--	3 (2.3)	
	Would only get vaccine if required by school/work	--	2 (1.6)	
	Depends on the vaccine product offered	--	2 (1.6)	
	Object to vaccination due to religious reasons	--	2 (1.6)	
	Contraindicated medical condition	--	1 (0.84)	
	Afraid of needles	--	1 (0.84)	

[1]Calculated out of N=127 because 6 individuals declined to answer.

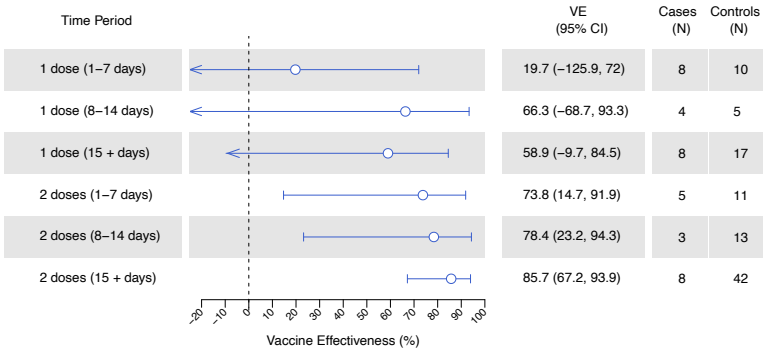

Figure 1: COVID-19 vaccine effectiveness, by doses received and time since last dose. Lines denote 95% confidence intervals, respectively, for estimates of vaccine effectiveness. Estimates were calculated via conditional logistic regression.

Table S1: Demographic attributes of vaccinated and unvaccinated cases and controls.

Characteristics	Controls		Cases	
	Unvaccinated, *n* (%) *N*=222	Vaccinated, *n* (%) *N*=98	Unvaccinated, *n* (%) *N*=289	Vaccinated, *n* (%) *N*=36
Age				
18-29	99 (44.6)	25 (25.5)	107 (37.0)	12 (33.3)
30-49	70 (31.5)	40 (40.8)	109 (37.7)	9 (25.0)
50-64	41 (18.5)	23 (23.5)	60 (20.8)	7 (19.4)
65+	12 (5.4)	10 (10.2)	13 (4.5)	8 (22.2)
Region				
Predominantly urban regions				
San Francisco Bay Area	24 (10.8)	9 (9.2)	32 (11.1)	4 (11.1)
Greater Los Angeles Area	22 (9.9)	7 (7.1)	26 (9.0)	4 (11.1)
Greater Sacramento Area	20 (9.0)	11 (11.2)	30 (10.4)	2 (5.6)
San Diego and southern border	30 (13.5)	13 (13.3)	36 (12.5)	3 (8.3)
Predominantly rural regions				
Central Coast	30 (13.5)	13 (13.3)	43 (14.9)	4 (11.1)
Northern Sacramento Valley	26 (11.7)	11 (11.2)	31 (10.7)	6 (16.7)
San Joaquin Valley	25 (11.3)	12 (12.2)	32 (11.1)	5 (13.9)
Northwestern California	25 (11.3)	10 (10.2)	27 (9.3)	7 (19.4)
Sierras Region	20 (9.0)	12 (12.2)	32 (11.1)	1 (2.8)
Sex				
Male	112 (50.5)	46 (46.9)	137 (47.4)	21 (58.3)
Female	109 (49.1)	51 (52.0)	152 (52.6)	15 (41.7)
Other	1 (0.5)	1 (1.0)	0 (0.0)	0 (0.0)
Household income				
Under $50,000	59 (26.6)	18 (18.4)	86 (29.8)	9 (25.0)
$50,000 to $100,000	54 (24.3)	20 (20.4)	58 (20.1)	8 (22.2)
$100,000 to $150,000	29 (13.1)	15 (15.3)	25 (8.7)	3 (8.3)
Over $150,000	26 (11.7)	22 (22.4)	36 (12.5)	7 (19.4)
Refuse	27 (12.2)	13 (13.3)	52 (18.0)	5 (13.9)
Not sure	27 (12.2)	10 (10.2)	32 (11.1)	4 (11.1)
Race/Ethnicity				
White	98 (44.1)	55 (56.1)	121 (41.9)	20 (55.6)
Hispanic	61 (27.5)	21 (21.4)	95 (32.9)	10 (27.8)
Asian	25 (11.3)	9 (9.2)	27 (9.3)	3 (8.3)
Black	3 (1.4)	3 (3.1)	15 (5.2)	0 (0.0)
More than 1 race	26 (11.7)	7 (7.1)	19 (6.6)	1 (2.8)
Native American	3 (1.4)	0 (0.0)	7 (2.4)	1 (2.8)
Native Hawaiian	3 (1.4)	1 (1.0)	2 (0.7)	1 (2.8)
Refuse	3 (1.4)	2 (2.0)	3 (1.0)	0 (0.0)

Table S2: Vaccine hesitancy among cases and controls.

Characteristics	Controls		Cases		
	Not willing/unsure, *n* (%) *N*=55	Willing, *n* (%) *N*=118	Not willing/unsure, *n* (%) *N*=78	Willing, *n* (%) *N*=164	*p*
Age					0.203
18-29	19 (34.5)	58 (49.2)	26 (33.3)	61 (37.2)	
30-49	27 (49.1)	32 (27.1)	31 (39.7)	64 (39.0)	
50-64	6 (10.9)	23 (19.5)	17 (21.8)	32 (19.5)	
65+	3 (5.5)	5 (4.2)	4 (5.1)	7 (4.3)	
Region					0.012
Predominantly urban regions					
San Francisco Bay Area	2 (3.6)	13 (11.0)	4 (5.1)	22 (13.4)	
Greater Los Angeles area	6 (10.9)	11 (9.3)	5 (6.4)	17 (10.4)	
Greater Sacramento area	8 (14.5)	8 (6.8)	9 (11.5)	18 (11.0)	
San Diego and southern border region	2 (3.6)	19 (16.1)	3 (3.8)	24 (14.6)	
Predominantly rural regions					
Central Coast	7 (12.7)	17 (14.4)	13 (16.7)	23 (14.0)	
Northern Sacramento Valley	8 (14.5)	17 (14.4)	11 (14.1)	18 (11.0)	
San Joaquin Valley	10 (18.2)	8 (6.8)	6 (7.7)	22 (13.4)	
Northwestern California	6 (10.9)	14 (11.9)	13 (16.7)	7 (4.3)	
Sierras Region	6 (10.9)	11 (9.3)	14 (17.9)	13 (7.9)	
Sex					
Woman	28 (50.9)	52 (44.1)	44 (56.4)	77 (47.0)	0.907
Male	27 (49.1)	66 (55.9)	34 (43.6)	87 (53.0)	
Income					0.186
Under $50,000	10 (18.2)	38 (32.2)	21 (26.9)	50 (30.5)	
$50,000 to $100,000	14 (25.5)	25 (21.2)	13 (16.7)	38 (23.2)	
$100,000 to $150,000	7 (12.7)	17 (14.4)	6 (7.7)	14 (8.5)	
Over $150,000	6 (10.9)	13 (11.0)	10 (12.8)	19 (11.6)	
Refuse	9 (16.4)	10 (8.5)	21 (26.9)	24 (14.6)	
Not sure	9 (16.4)	15 (12.7)	7 (9.0)	19 (11.6)	
Race					0.05
White	23 (41.8)	58 (49.2)	40 (51.3)	62 (37.8)	
Hispanic	16 (29.1)	33 (28.0)	22 (28.2)	57 (34.8)	
Asian	2 (3.6)	13 (11.0)	3 (3.8)	20 (12.2)	
Black	2 (3.6)	1 (0.8)	5 (6.4)	10 (6.1)	
More than 1 race	8 (14.5)	11 (9.3)	4 (5.1)	11 (6.7)	
Native American	1 (1.8)	0 (0.0)	2 (2.6)	3 (1.8)	
Native Hawaiian	2 (3.6)	0 (0.0)	1 (1.3)	0 (0.0)	
Refuse	1 (1.8)	2 (1.7)	1 (1.3)	1 (0.6)	

Table S3: Adjusted models evaluating the likelihood an individual is unwilling or unsure of whether they will receive the COVID-19 vaccine.

Characteristics	aOR (95% CI)
Age	
18-29	Ref.
30-49	1.64 (0.98,2.75)
50-64	0.77 (0.4,1.47)
65+	1.22 (0.42,3.55)
Region	
Predominantly urban regions[1]	Ref.
Predominantly rural regions[2]	2.29 (1.41,3.69)
Sex	
Male	Ref.
Woman	1.53 (0.98,2.38)
Income	
Under $50,000	Ref.
$50,000 to $100,000	1.1 (0.57,2.09)
$100,000 to $150,000	1.37 (0.59,3.25)
Over $150,000	1.18 (0.55,2.46)
Race	
White	Ref.
Hispanic	0.91 (0.52,1.6)
Asian	0.29 (0.11,0.81)
Black	1.63 (0.58,4.49)
More than 1 race	1.22 (0.55,2.69)
Native American	1.33 (0.26,7.14)
Native Hawaiian	6.65 (0,Inf)

Logistic regression models adjusting for age, region, sex, income, and race predicted the likelihood an individual was vaccine hesitant. Missing values of income and race were multiply imputed using the Amelia II package.

[1]Predominatly urban regions include San Francisco Bay Area, Greater Los Angeles Area, Greater Sacramento area, San Diego and the Southern border.

[2]Predominatly rural regions include Central Coast, Northern Sacramento valley, San Joaquin Valley, Northwestern California, and the Sierras region.

Table S4: Counties by geographic region

County	Region
Alameda County	San Francisco San Francisco Bay Area
Alpine County	Sierras Region
Amador County	Sierras Region
Butte County	Northern Sacramento Valley
Calaveras County	Sierras Region
Colusa County	Northern Sacramento Valley
Contra Costa County	San Francisco Bay Area
Del Norte County	Northwestern California
El Dorado County	Sierras Region
Fresno County	San Joaquin Valley
Glenn County	Northern Sacramento Valley
Humboldt County	Northwestern California
Imperial County	San Diego and southern border
Inyo County	Sierras Region
Kern County	San Joaquin Valley
Kings County	San Joaquin Valley
Lake County	Northwestern California
Lassen County	Sierras Region
Los Angeles County	Greater Los Angeles area
Madera County	San Joaquin Valley
Marin County	San Francisco Bay Area
Mariposa County	Sierras Region
Mendocino County	Northwestern California
Merced County	San Joaquin Valley
Modoc County	Sierras Region
Mono County	Sierras Region
Monterey County	Central Coast
Napa County	San Francisco Bay Area
Nevada County	Sierras Region
Orange County	Greater Los Angeles area
Placer County	Sierras Region
Plumas County	Sierras Region
Riverside County	Greater Los Angeles area
Sacramento County	Central Valley
San Benito County	San Francisco Bay Area
San Bernardino County	Greater Los Angeles area
San Diego County	San Diego and southern border
San Francisco County	San Francisco Bay Area
San Joaquin County	San Joaquin Valley
San Luis Obispo County	Central Coast
San Mateo County	San Francisco Bay Area
Santa Barbara County	Central Coast
Santa Clara County	San Francisco Bay Area
Santa Cruz County	San Francisco Bay Area
Shasta County	Northwestern California
Sierra County	Sierras Region
Siskiyou County	Northwestern California
Solano County	San Francisco Bay Area
Sonoma County	San Francisco Bay Area
Stanislaus County	San Joaquin Valley
Sutter County	Northern Sacramento Valley
Tehama County	Northern Sacramento Valley
Trinity County	Northwestern California
Tulare County	San Joaquin Valley
Tuolumne County	Sierras Region
Ventura County	Greater Los Angeles area
Yolo County	Northern Sacramento Valley
Yuba County	Northern Sacramento Valley

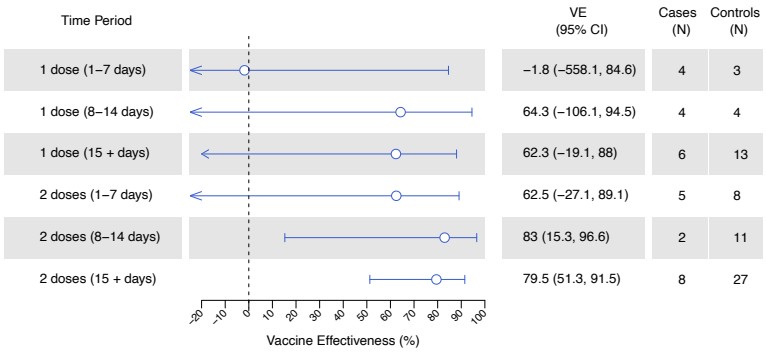

Figure S1: Sensitivity analyses excluding individuals (*N*=39) without access to vaccination cards.
Lines denote 95% confidence intervals, respectively, for estimates of vaccine effectiveness. Estimates were calculated via conditional logistic regression.