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Assessment of public health interventions to mitigate SARS-CoV-2 transmission and risk factors for infection in California

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Assessment of public health interventions to mitigate SARS-CoV-2 transmission and risk factors for infection in California

by

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University of California, Berkeley

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Abstract

Assessment of public health interventions to mitigate SARS-CoV-2 transmission and risk factors for infection in California

by

Kristin Leigh Andrejko

Doctor of Philosophy in Epidemiology

University of California, Berkeley

Professor Joseph A Lewnard, Chair

Vaccination and non-pharmaceutical interventions (NPIs) have been of central importance to mitigate the ongoing COVID-19 pandemic. In collaboration with California Department of Public Health, I designed and managed a test-negative design case-control study to assess risk factors for SARS-CoV-2 infection and the effectiveness of various mitigation strategies including vaccination and the use of face masks. Throughout the study period, a team of trained interviewers placed over 40,000 telephone calls and enrolled over 4,000 total cases and controls, testing positive and negative for SARS-CoV-2, respectively. In Chapter 1, I present COVID-19 vaccine effectiveness estimates using data collected between February – April 2021 when Epsilon (B.1.427 and B.1.429) and Alpha (B.1.1.7) were the dominant SARS-CoV-2 variants of concern circulating in California. I demonstrate mRNA-based vaccines (BNT-162b2 [Pfizer] and mRNA-1273 [Moderna]) conferred substantial protection against documented SARS-CoV-2 infection. However, nearly one-third of participants expressed reluctance to initiate the COVID-19 vaccination series, primarily due to concerns about vaccine side effects or safety. In Chapter 2, I evaluate predictors of SARS-CoV-2 infection amongst a subset of participants who reported history of social contact with a person confirmed or suspected to have been infected with SARS-CoV-2 within 14 days of testing. Among the unvaccinated, participants had a significantly higher odds of testing SARS-CoV-2 positive when social contact was long-lasting ($\geq$3 hours), involved a household member, or occurred indoors. Additionally, in the context of these high-risk exposures, I demonstrate mask wearing was most protective among the unvaccinated or partially unvaccinated. Last, in Chapter 3, I estimate the real-world effectiveness of face masks in reducing the risk of acquiring a SARS-CoV-2 infection in public indoors settings. Participants self-reported their frequency of mask use and the type of mask typically worn in public indoor settings. I found that any mask use in public indoor settings reduced the odds the wearer acquired a SARS-CoV-2 infection and mask use exhibited additional protection with increasing frequency of use. Upgrading face masks to masks with higher filtration capacity (N95/KN95s) conferred additional protection. This work has demonstrated the value of case-control studies to rapidly

collect real-time data to address and monitor emerging issues in the COVID-19 pandemic and advance public health policy.

For Mom, Dad, Kelly, Sam, and Braeden

Contents

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INTRODUCTION

As of March 2022, in California (USA) there have been over 9 million recorded cases and over 86,000 deaths from SARS-CoV-2, the virus that causes COVID-19 [1]. Prior to widespread availability of COVID-19 vaccines, non-pharmaceutical interventions (NPIs) aiming to reduce close contact between susceptible and infectious individuals were implemented as the primary mitigation strategy [2,3]. In California, NPIs included physical distancing measures intending to limit contact in public settings including transitions to work-from-home, remote learning, prolonged closures of non-essential businesses, or limits on large events and gatherings. Use of fabric face coverings was initially recommended to limit shedding of SARS-CoV-2 by infected persons and reduce the likelihood an individual exposed to an infectious person may acquire an infection [4]. COVID-19 vaccinations became widely available to all Californians over the age of 12 in May 2021 [5,6], and efforts to monitor vaccine effectiveness against infection, hospitalization, and death became of central importance as novel SARS-CoV-2 variants potentially associated with immune escape began to emerge and circulate [7,8].

Amid implementation of strategies to mitigate the COVID-19 pandemic including non-pharmaceutical interventions and vaccination campaigns, various public health epidemiologic and surveillance activities emerged to provide an evidence base detailing the relative effectiveness and continued necessity of each intervention [9]. While the risk of infection associated with exposure to a household member or close contact was well established [10], defining exposures or risk factors for infection was needed to target prevention efforts in response to changes in the ongoing pandemic. Relatedly, it remained necessary to understand how preventative behaviors like mask-wearing or physical distancing modified the risk of acquiring an infection in various settings [11].

Case-control studies were rapidly implemented throughout the COVID-19 pandemic to assess risk factors for infection and generate estimates of vaccine effectiveness [12–15]. However, most case-control studies were underpowered to determine risk associated with exposures common among controls. Moreover, ecological studies compared differences in COVID-19 incidence before and after implementation of multiple non-pharmaceutical interventions, but by design could not isolate the effect of individual interventions, like use of face masks, on an individual-level clinical outcome [16,17]. This work seeks to build upon the existing literature by highlighting predictors of infection following SARS-CoV-2 exposure and to better understand mitigating factors that may alter the risk of SARS-CoV-2 infection including the use of face masks or vaccination.

In February 2021, the California Department of Public Health (CDPH) and UC Berkeley launched a test-negative design case-control study to evaluate risk factors for SARS-CoV-2 infection. Cases and controls were defined as persons testing positive or negative for SARS-CoV-2 infection, respectively. A random sample of cases and controls was obtained on a regular 48-hour interval throughout the study period from among all the molecular test results reported to the California Reportable Disease Registry. Cases and controls were individually matched by age category, sex, multi-county region in California, and SARS-CoV-2 test result window. Trained interviewers administered a structured, phone-based questionnaire to eligible participants which asked individuals to self-report, in the 14 days preceding their SARS-CoV-2 test, settings they have visited, history of a known or suspected contact with an individual infected with SARS-CoV-2, vaccination history, and sociodemographic variables.

The California COVID-19 Case Control (C4) Study was designed with the express purpose of answering emerging questions about the SARS-CoV-2 pandemic with relevance to public-health policy. Therefore, research questions ranged from estimating vaccine effectiveness amid circulation of new variants to estimating the real-world effectiveness of various types of face masks in indoor public settings.

In Chapter 1, I estimate vaccine effectiveness of mRNA-based vaccine products across a general population sample in California during the initial roll-out of COVID-19 vaccinations (February – April 2021). Generating estimate of vaccine effectiveness are important to understand performance under real-world conditions [18], evaluate alternative clinical end points or new dosing regimens [8], and monitor barriers to vaccine uptake [19]. Here, I assess vaccine effectiveness as the matched odds ratio of prior vaccination, comparing cases (testing SARS-CoV-2 positive) to controls (testing SARS-CoV-2 negative). Additionally, among participants unvaccinated at the time of the telephone survey, I assess predictors of vaccine hesitancy, defined as being unwilling or unsure to receive COVID-19 vaccination upon eligibility.

In Chapter 2, I evaluate predictors of SARS-CoV-2 infection following social contact with an individual known or suspected to have been infected with SARS-CoV-2. While risk of infection following SARS-CoV-2 exposure has been well established, the understanding of the relative effectiveness of various non-pharmaceutical interventions to reduce risk of infection remains poorly understood [20,21]. Among a sample of cases and controls who reported “high-risk exposures” defined as social contact with an individual infected with SARS-Co-V-2 within the 14 days of seeking a SARS-CoV-2 test, I estimated the adjusted odds ratios of case status comparing attributes of social contact within strata of vaccination status—indoors vs. outdoors; longer vs. shorter duration; mask use vs. no mask use; household vs. non-household member.

Last, in Chapter 3, I assess the effectiveness of face masks in public indoor settings. Despite public health recommendations to wear face masks to reduce the quantity of virus shed by infectious persons in public settings, evidence about the real-world effectiveness of face mask use remains limited [22]. While laboratory studies have demonstrated that face masks effectively filter viruses or virus-sized particles from inhaled and exhaled air, few studies have assessed the effectiveness of face masks at reducing the wearers odds of acquiring a SARS-CoV-2 infection [23,24]. This analysis was restricted to participants who did not report a history of social contact with an individual infected with SARS-CoV-2 and who reported attending at least one indoor public setting within the two weeks of SARS-CoV-2 testing. Mask effectiveness was estimated both by frequency of use (always, most times, sometimes versus none of the time) and type of mask worn (N95/KN95 respirator, surgical, fabric vs. no mask).

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Chapter 1

Prevention of COVID-19 by mRNA-based vaccines within the general population of California

1.1 ABSTRACT

Background: Estimates of COVID-19 vaccine effectiveness under real-world conditions, and understanding of barriers to uptake, are necessary to inform vaccine rollout.

Methods: We enrolled cases (testing positive) and controls (testing negative) from among the population whose SARS-CoV-2 molecular diagnostic test results from 24 February-29 April 2021 were reported to the California Department of Public Health. Participants were matched on age, sex, and geographic region. We assessed participants' self-reported history of mRNA-based COVID-19 vaccine receipt (BNT162b2 and mRNA-1273). Participants were considered fully vaccinated two weeks after second dose receipt. Among unvaccinated participants, we assessed willingness to receive vaccination. We measured vaccine effectiveness (VE) via the matched odds ratio of prior vaccination, comparing cases with controls.

Results: We enrolled 1023 eligible participants aged ≥18 years. Among 525 cases, 71 (13.5%) received BNT162b2 or mRNA-1273; 20 (3.8%) were fully vaccinated with either product. Among 498 controls, 185 (37.1%) received BNT162b2 or mRNA-1273; 86 (16.3%) were fully vaccinated with either product. Two weeks after second dose receipt, VE was 87.0% (95% confidence interval: 68.6-94.6%) and 86.2% (68.4-93.9%) for BNT162b2 and mRNA-1273, respectively. Fully vaccinated participants receiving either product experienced 91.3% (79.3-96.3%) and 68.3% (27.9-85.7%) VE against symptomatic and asymptomatic infection, respectively. Among unvaccinated participants, 42.4% (159/375) residing in rural regions and 23.8% (67/281) residing in urban regions reported hesitancy to receive COVID-19 vaccination.

Conclusions: Authorized mRNA-based vaccines are effective at reducing documented SARS-CoV-2 infections within the general population of California. Vaccine hesitancy presents a barrier to reaching coverage levels needed for herd immunity.

Chapter 1 is included here with the permission of my coauthors: Jake Pry, Jennifer Myers, John Openshaw, James Watt, Seema Jain, and Joseph Lewnard

1.2 INTRODUCTION

After being found safe and efficacious 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 under emergency use authorization. Two mRNA-based vaccines encoding the SARS-CoV-2 spike protein, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), have been the main products in use since December 2020. By early May, 2021, 40% of California residents were considered fully vaccinated [4].

Observational studies characterizing COVID-19 vaccine effectiveness (VE) are needed to understand performance under real-world conditions [5], for instance evaluating VE against clinical endpoints not addressed in trials, and defining VE for alternative dosing schedules [6]. While many studies of real-world VE have followed healthcare workers and other essential or frontline personnel [7–9], vaccine eligibility rapidly expanded to included broader population groups during in early 2021 throughout the United States. In California, vaccination was offered to healthcare workers beginning December 14, 2020, and expanded to persons at increased risk due to older age or occupation (including workers in emergency services, food and agriculture, or childcare and education) during January and February, 2021. Eligibility was extended to persons aged 16-64 years with high-risk medical conditions in March, 2021, and to all persons aged ≥16 years on April 15, 2021. To inform vaccination efforts, it is crucial to understand VE within the general population, and to identify reasons behind individuals' decisions to delay or defer vaccination.

In conjunction with epidemiologic surveillance, we initiated a test-negative case-control study design to monitor VE within the general population of California in real time. Over the study period (February 24, 2021 to April 29, 2021), sequenced SARS-CoV-2 isolates in California were predominantly identified as B.1.427/429 (50-60%) variants in February and March; by April, B.1.1.7 variant overtook other lineages and accounted for 49% of sequenced SARS-CoV-2 isolates, as compared to 6% in February, while the proportion of B.1.427/429 variants declined to ~20% [10]. Here we provide an assessment of VE for authorized mRNA-based COVID-19 vaccines, and report data on the intentions of unvaccinated participants to receive vaccination.

1.3 METHODS

Design

All diagnostic tests in California for SARS-CoV-2 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 with molecular SARS-CoV-2 test results (e.g., polymerase chain reaction [PCR]) between 24 February-April 29, 2021 and a telephone number were eligible for participation in this study. Cases were defined as persons with positive molecular

SARS-CoV-2 test results during the study timeframe. Controls were persons with negative SARS-CoV-2 molecular test results during the same period.

Each day during the study period, we prospectively selected cases with a telephone number and newly-reported positive molecular test result within each of nine regions of the state, sampling cases at random with intent to enroll equally across regions (**Table S1**). For each case who consented and completed the study interview, we attempted to enroll and interview one control from a sample of 30 controls randomly selected to match the case by age (18-39, 40-64, ≥65 years), sex, region, and week of SARS-CoV-2 test. Up to two call attempts were made for each case and control. Call shifts were scheduled to cover mornings, afternoons, and evenings each day.

To mitigate bias resulting from previous infection-derived immunity [6], participants who recalled receiving any previous positive test result for SARS-CoV-2 infection or seropositivity, prior to the reported test, were not eligible to continue the interview. This analysis excludes data from children aged 0-17 years, who were generally ineligible for COVID-19 vaccination over the study period; and participants who reported receiving COVID-19 vaccinations other than BNT162b2 or mRNA-1273 (due to limited coverage of a third authorized vaccine, Ad26.COV2.S, over the study period), or receipt of COVID-19 vaccination without knowledge of vaccination dates.

Exposures

We administered a standardized questionnaire via facilitated telephone interviews in English or Spanish collecting 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 eligible; if participants indicated they were not likely to receive a vaccine or unsure, we asked them to state reasons behind their hesitancy. Additionally, we asked participants to indicate reasons they sought a COVID-19 test, and presence of any COVID-19 symptoms within the 14 days prior to their test date (**Supplementary text S1**).

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

Our primary objective was to estimate VE of two doses of BNT162b2 or mRNA-1273 against documented SARS-CoV-2 infection, ≥2 weeks after receipt of the second dose of either vaccine. To estimate VE, we calculated the Mantel Haenszel (matched) odds ratio (OR_{MH}) of vaccination among cases relative to test-negative controls [5,6]. We used conditional logistic regression models defining match strata by age group, sex, region, and testing week to estimate the OR_{MH} (and accompanying 95% confidence interval [CI]). We defined fully-vaccinated status as receipt of two doses of BNT162b2 or mRNA-1273 ≥2 weeks before participants' date of testing; unvaccinated status was the reference exposure. We calculated adjusted VE as $(1–OR_{MH})×100\%$. We determined that analyses with 500 cases and 500 controls would provide 90% statistical power for estimating VE of ≥55% at the two-sided $p<0.05$ confidence threshold, assuming 10% of controls were fully vaccinated. We did analyses in R software (version 3.6.1; R Foundation for Statistical Computing; Vienna, Austria).

As secondary analyses, we also aimed to assess VE for incomplete vaccination series, VE for each product, and VE against SARS-CoV-2 infection endpoints corresponding to differing levels of clinical severity. To determine VE for incomplete vaccination series, we defined exposures as receipt of 1 dose or 2 doses of BNT162b2 or mRNA-1273 within 1-7 or 8-14 days before participants' testing date, or 1 dose of BNT162b2 or mRNA-1273 ≥15 days before participants' testing date. As described above, we used conditional logistic regression models to compute the OR_{MH} comparing cases to controls.

To determine product-specific VE, we restricted the vaccinated population to participants who received two doses of either BNT162b2 or mRNA-1273 ≥15 days before their date of testing. To determine VE against differing clinical endpoints, we conducted analyses restricting cases to participants testing positive with symptoms; without symptoms; who were hospitalized for COVID-19; who reported seeking healthcare or advice via outpatient or virtual interactions with healthcare providers; and who did not seek treatment or advice from a healthcare provider beyond receipt of a molecular SARS-CoV-2 diagnostic testing. Each of these groupings of cases was compared against match-eligible controls to compute the OR_{MH} of vaccination (defined as two doses received ≥15 days prior, versus no doses received), using the same conditional logistic regression framework described above. For these secondary analyses, sufficient counts were not available to further stratify VE estimates by doses received and time since receipt.

Last, to understand factors predicting vaccine hesitancy among participants who had not yet received COVID-19 vaccination, we fit logistic regression models defining hesitancy to receive vaccination as the outcome; covariates selected *a priori* for inclusion as potential causal factors were age group, region, sex, income, and race/ethnicity. Participants who reported being unwilling or unsure about receiving a COVID-19 vaccine when eligible were considered vaccine-hesitant. As missing data were present in participants' responses regarding income (189/656; 28.8%) and race (10/656; 1.5%), we conducted analyses of vaccine hesitancy across five datasets generated through multiple imputation by chained equations using the Amelia II package in R [11]. Under the assumption that data were missing conditionally at random, given observations of other covariates, all variables included in the analyses model were included in the imputation models. We compared measures of association to those resulting from complete-case analysis without imputation as a supplemental check.

1.4 RESULTS

From February 24 to April 29, 2021, 4,827,165 SARS-CoV-2 molecular test results were reported to CDPH with a telephone number and indication of individuals' age, sex, and region of residence (108,606 positive and 4,718,559 negative; **Figure 1**; **Figure S1**; **Figure S2**). We called 3847 cases and 5253 controls, among whom we enrolled 603 cases (15.7%) and 590 controls (11.2%). Among participants enrolled, 78 cases and 92 controls who were ineligible for the analyses reported here, including participants who were <18 years old, received COVID-19 vaccines other than BNT162b2 or mRNA-1273, or were unable to provide precise dates of COVID-19 vaccine receipt. Our final study population included 525 cases and 498 controls, among 477 cases and 472 controls had eligible matches and thus contributed to conditional logistic regression analyses for VE estimation. While most strata included 1:1 (case:control) matches, 25 strata matched multiple controls to one case, and 33 strata matched multiple cases to one control (**Table 1**; **Table S2**). Among participants enrolled, 20.9% (214/1023) and 98.3% (1006/1023) were contacted within ≤3 days and ≤7 of their test results being posted, respectively.

Among 525 cases, 288 (54.9%) indicated they were tested due to concerns about symptoms. Of these 288 symptomatic cases, 262 (91.0%) were unvaccinated and 26 (9.0%) received ≥1 vaccine dose (**Table 2**). Among 498 controls, 56 (11.2%) sought testing due to symptoms, among whom 43 (76.8%) were unvaccinated and 13 (23.2%) received ≥1 vaccine dose. The most common reason for testing among controls was routine screening required for work or school attendance (233/498; 46.8%), whereas the most common reasons for testing among cases were symptoms (288/525; 54.9%) and known contact with a positive case (173/525; 33.0%).

Among 525 cases, 43 (8.2%) and 28 (5.3%) reported receiving ≥1 dose of BNT162b2 and mRNA-1273, respectively (**Figure 2**; **Table 1**; **Table S3**). Among 498 controls, 98 (19.7%) and 87 (17.5%) received ≥1 dose of BNT162b2 and mRNA-1273, respectively. Twenty cases (3.8% of 525) and 86 (17.3% of 498) controls were fully vaccinated with either product, with ≥15 days passing from receipt of their second dose to their testing date. A majority of both vaccinated and unvaccinated participants agreed with the importance of masking and social distancing to prevent COVID-19, and vaccinated and unvaccinated participants were equally likely to report feeling anxious about COVID-19 (**Table S4**). For fully-vaccinated participants receiving either BNT162b2 or mRNA-1273, VE was 87.4% (95%CI: 77.2-93.1%).

We did not identify protection within the first 7 days after receipt of a first BNT162b or mRNA-1273 dose (VE: 18.8% [–74.9-61.7%]). Within the second week after receipt of a first dose for either vaccine, VE was 50.7% (–17.5-79.8%); ≥15 days after receipt of a first dose, and before receipt of a second dose, VE was 66.9% (28.7-84.6%). Following receipt of a second dose, VE was 78.3% (42.7-91.6%) at days 1-7, and 79.4% (39.0-92.9%) at days 8-14. VE estimates were similar in analyses that restricted or did not restrict the sample to participants who reported consulting their vaccination cards or calendars during the telephone interview to confirm dates of receipt of each dose (**Figure S3**).

Protection among fully-vaccinated participants did not differ according to the product received; among recipients of BNT162b and mRNA-1273, VE was 87.0% (68.6-94.6%) and 86.2% (68.4-93.9%), respectively (**Figure 2**).

Among fully vaccinated cases, 45.0% (9/20) reported experiencing ≥1 symptom, in contrast to 78.0% (354/454) of unvaccinated cases, 66.7% (34/41) of partially vaccinated cases, and 13.7% (68/498) of controls (**Table S5**). For symptomatic and asymptomatic infection endpoints, VE was 91.3% (79.3-96.3%) and 68.3% (27.9-85.7%), respectively, at ≥15 days after the second dose (**Figure 2**).

Eighteen (3.4%) of 525 cases were hospitalized by the time of our telephone interview, among whom 15 (83.3%) were unvaccinated, and three (16.7%) were partially vaccinated (**Table S5**). Among all 525 cases, 150 (28.6%) sought treatment, care, or advice via outpatient or virtual interactions with healthcare providers, among whom 132 (25.1%) were unvaccinated, 15 (2.9%) were incompletely vaccinated, and 3 (0.6%) were fully vaccinated. Among 128 cases who did not experience symptoms, 103 (80.4%) did not seek care. Considering these differing levels of care sought for SARS-CoV-2 infection, VE was 79.3% (61.3-89.1%) against episodes for which cases did not seek treatment or advice, 90.9% (63.2-97.9%) against episodes for which cases sought healthcare through outpatient or virtual interactions, and 100% (with undefined confidence limits) against hospitalized illness (**Figure 2**).

Overall, 226 (34.5%) of 656 unvaccinated participants (including 139/403 [34.5%] unvaccinated cases and 87/253 [34.4%] unvaccinated controls) indicated they were unlikely to receive or unsure about receiving COVID-19 vaccination when eligible (**Table 3; Table S6; Table S7).** Residents of rural regions had 2.42 (1.66-3.52) fold higher adjusted odds of reporting hesitancy to receive vaccination, when eligible, whereas hesitancy to receive vaccination was not independently associated with age or household income. Adjusted odds of reporting hesitancy to receive vaccination were 1.47 (1.04-2.08) fold higher among females than males. In comparisons by participants' race/ethnicity, adjusted odds of reporting hesitancy to receive vaccination were 2.54 (1.24-5.15) fold higher among non-Hispanic Black participants than non-Hispanic Whites; in contrast, adjusted odds of vaccine hesitancy were 0.72 (0.46-1.12) fold as high among Hispanic participants as among non-Hispanic whites. Point estimates of odds ratios were similar in complete-case analyses without imputation (**Table S8**). Fears over vaccine side effects (66/219 [30.1%]) or safety (60/219 [27.4%]) were the most common concerns among participants expressing hesitancy to receive vaccination (**Table 4**). No participants cited cost, inconvenience, or inability to access a COVID-19 vaccination site as a reason for not receiving vaccination.

1.5 DISCUSSION

Among a sample of the general population of Californians and during a period when 10,653,334 (27%) California residents became fully vaccinated, available mRNA-based COVID-19 vaccines demonstrated robust protection against documented SARS-CoV-2 infection under real-world conditions. While we identified partial protection before two weeks from receipt of the second dose, similar to other published estimates [7,9], the increase in VE from 67% following the first dose to 87% at $\geq$15 days after receipt of the second dose indicated a robust 59% incremental reduction in risk. We also found that mRNA-based COVID-19 vaccines elicited substantial protection against both symptomatic illness and infections for which participants reported healthcare-seeking, with 91% VE against each of these endpoints. No hospitalizations were observed among fully-vaccinated cases within our study, consistent with findings of other published studies demonstrating strong protection against clinically-severe COVID-19 endpoints [12]. Our results closely resemble estimated efficacy of mRNA-based COVID-19 vaccines in trials that monitored for symptomatic COVID-19 endpoints [1,2]. The low frequency of post-vaccination infections, and our estimate of 68% VE against infections for which participants did not report symptoms, together indicate vaccination may substantially reduce SARS-CoV-2 circulation within the community.

Our finding that 66% of as-yet unvaccinated participants in this early period of vaccine rollout were willing to receive COVID-19 vaccination align with national estimates of COVID-19 vaccine confidence [13]. We further identified rural-urban divides in vaccine enthusiasm, in addition to lower vaccine confidence among female and Black participants. Concerns over vaccine safety and side effects were reported by only a minority of all participants who expressed hesitancy about receiving COVID-19 vaccination (27-30%), but were the most commonly cited reasons for hesitancy. Recent studies have documented emerging differences in acceptance of COVID-19 vaccination associated with region of residence, educational background, employment status, and ideological factors [14–16]. Differing messaging and outreach strategies will thus be needed to address barriers to vaccine acceptance across communities, including people whose hesitancy to receive vaccination stems from mistrust or adverse experiences within US healthcare systems [17]. Prior studies have demonstrated that a provider's recommendation is a key determinant of vaccine acceptance [18]. As healthcare providers in California and other settings have generally reported high (although not universal) enthusiasm around receiving COVID-19 vaccination [19,20], they may serve as important advocates to encourage vaccine uptake in their communities.

Our study has limitations. While observational studies face risks of bias (due, for instance, to differences in risk behavior between vaccinated and unvaccinated individuals) similarity of our estimates to those of other studies, stepwise increases in VE with time since receipt of each dose, and the absence of apparent protection immediately following first-dose receipt each support external validity of our findings . Reliance on participants being available and willing to answer the phone is a limitation, although this applied to both cases and controls who received SARS-CoV-2 testing. Nonetheless, our study may have under-enrolled participants experiencing very severe illness (e.g. who were hospitalized, had died, or were unable to participate in the phone interview due to sickness), who would be unable to answer the phone. As such, our findings should be interpreted as estimates of VE against a primarily mild to moderate spectrum of illness. We did not identify differential willingness to participate in the study among persons who tested positive and negative, provided contact was made. While misclassification of self-reported vaccination is possible, we did not find significant differences in VE estimates between analyses that did or did not restrict data to include participants who referenced a vaccine card. We did not re-contact cases to verify that cases who reported no symptoms remained asymptomatic over the course of their infection, or to confirm that cases who were not hospitalized or had not sought advice from healthcare providers at the time of their interview did not subsequently receive such care. Last, it is possible that certain participants were unaware of prior SARS-CoV-2 infections they may have experienced, particularly if these infections were mildly symptomatic or asymptomatic. Immunity resulting from such infections could lead to lower estimates of VE under our study design [6,21].

Our findings indicate that vaccine rollout is preventing COVID-19 in the general population of California and significantly reducing the risk of both asymptomatic and symptomatic SARS-CoV-2 infection. Vaccine hesitancy among historically marginalized and rural populations, which account for a substantial proportion of all COVID-19 cases in California to date [4], presents a barrier to reaching coverage levels needed for herd immunity.

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1.7 TABLES AND FIGURES

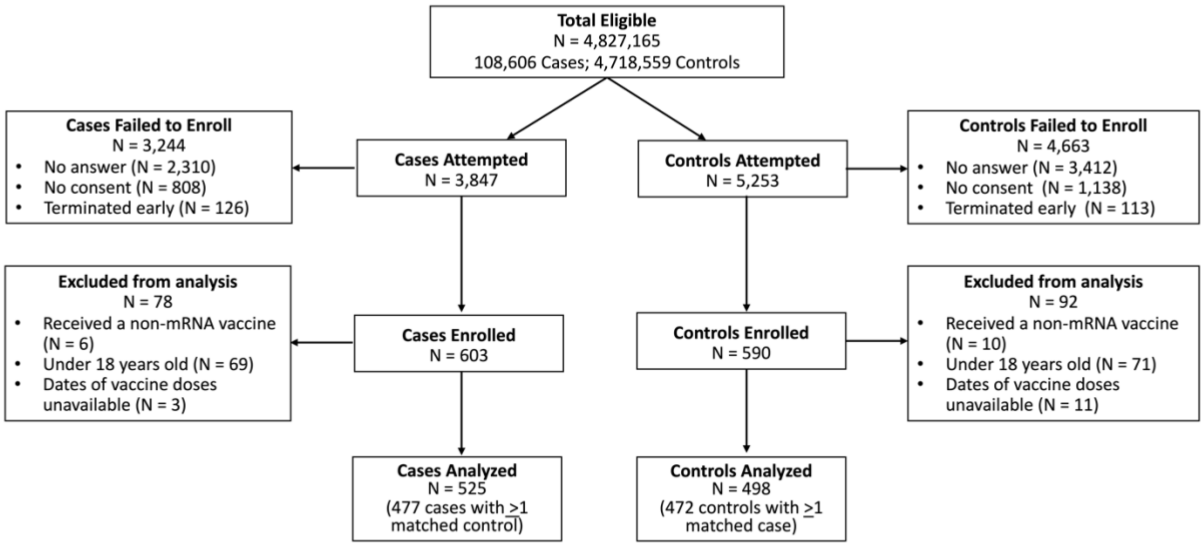

Figure 1: Enrollment of participants in the California COVID-19 Case-Control study. Data in the figure indicate numbers of tests reported, cases and controls for whom contact was attempted, and excluded and enrolled participants for this analysis.

By doses received & time of receipt	Vaccine Effectiveness (95% CI)	Cases (N)	Controls (N)
1 dose (1−7 days)	18.8 (−74.9, 61.7)	14	15
1 dose (8−14 days)	50.7 (−17.5, 79.8)	11	14
1 dose (15 + days)	66.9 (28.7, 84.6)	11	26
2 doses (1−7 days)	78.3 (42.7, 91.6)	6	18
2 doses (8−14 days)	79.4 (39.0, 92.9)	5	19
2 doses (15 + days)	87.4 (77.2, 93.1)	16	83
BNT162b2	87.0 (68.6, 94.6)	9	42
mRNA−1273	86.2 (68.4, 93.9)	7	41
By presence of symptoms			
No reported symptoms	68.3 (27.9, 85.7)	10	80
Symptomatic	91.3 (79.3, 96.3)	6	3
By level of care sought			
No Care	79.3 (61.3, 89.1)	14	74
Outpatient Care	90.9 (63.2, 97.9)	2	8
Hospitalization	100	0	1

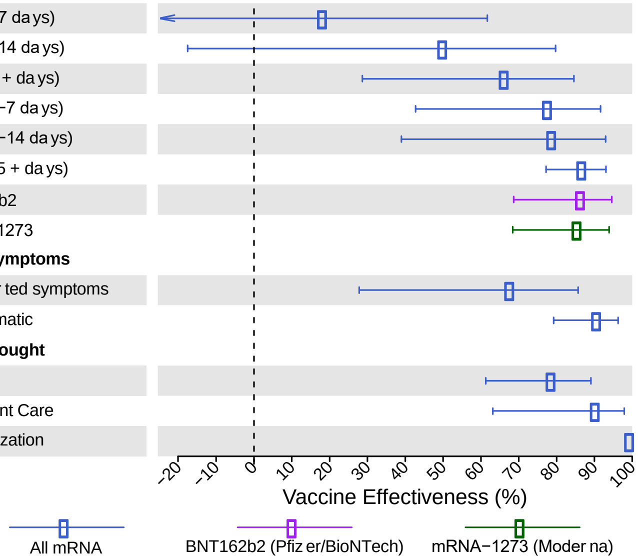

Figure 2: COVID-19 vaccine effectiveness, by doses received and time since last dose. Lines denote 95% confidence intervals, respectively, for estimates of vaccine effectiveness. Estimates were calculated via conditional logistic regression. Estimates for the presence of symptoms and level of care sought compare fully vaccinated versus unvaccinated participants only.

Table 1: Distribution of cases and controls.

		Overall *n* (%) *N* = 1023	Case *n* (%) *N* = 525	Control *n* (%) *N* = 498
Age				
	18-29	395 (38.6)	200 (38.1)	195 (39.2)
	30-49	363 (35.5)	188 (35.8)	175 (35.1)
	50-64	192 (18.8)	100 (19.0)	92 (18.5)
	65+	73 (7.1)	37 (7.0)	36 (7.2)
Region				
	Predominantly urban regions			
	San Francisco Bay Area	129 (12.6)	66 (12.6)	63 (12.7)
	Greater Los Angeles Area	91 (8.9)	48 (9.1)	43 (8.6)
	Greater Sacramento Area	115 (11.2)	58 (11.0)	57 (11.4)
	San Diego and southern Border	110 (10.8)	54 (10.3)	56 (11.2)
	Predominantly rural regions			
	Central Coast	140 (13.7)	74 (14.1)	66 (13.3)
	Northern Sacramento Valley	116 (11.3)	60 (11.4)	56 (11.2)
	San Joaquin Valley	106 (10.4)	54 (10.3)	52 (10.4)
	Northwestern California	108 (10.6)	55 (10.5)	53 (10.6)
	Sierras Region	108 (10.6)	56 (10.7)	52 (10.4)
Sex				
	Male	519 (50.7)	264 (50.3)	255 (51.2)
	Female	504 (49.3)	261 (49.7)	243 (48.8)
Household income				
	Under $50,000	272 (26.6)	153 (29.1)	119 (23.9)
	$50,000 to $100,000	220 (21.5)	113 (21.5)	107 (21.5)
	$100,000 to $150,000	121 (11.8)	45 (8.6)	76 (15.3)
	Over $150,000	135 (13.2)	64 (12.2)	71 (14.3)
	Refuse	154 (15.1)	86 (16.4)	68 (13.7)
	Not sure	121 (11.8)	64 (12.2)	57 (11.4)
Race/Ethnicity				
	White	444 (43.4)	217 (41.4)	227 (45.6)
	Hispanic	286 (28.0)	160 (30.5)	126 (25.3)
	Asian	115 (11.3)	58 (11.1)	57 (11.4)
	Black	47 (4.6)	30 (5.7)	17 (3.4)
	More than 1 race	89 (8.7)	36 (6.9)	53 (10.6)
	Native American	16 (1.6)	11 (2.1)	5 (1.0)
	Native Hawaiian	10 (1.0)	4 (0.8)	6 (1.2)
	Refuse	15 (1.5)	8 (1.5)	7 (1.4)
Vaccination				
	Unvaccinated	767 (75.0)	454 (86.5)	313 (62.9)
	Incompletely vaccinated	150 (14.7)	51 (9.7)	99 (19.9)
	Fully vaccinated[1]	106 (10.4)	20 (3.8)	86 (17.3)

[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: Reasons for testing.

Reasons*	Controls		Cases	
	Unvaccinated *N*=313	Vaccinated[1] *N*=185	Unvaccinated *N*=454	Vaccinated *N*=71
Contact with positive case	28 (8.9)	8 (4.3)	143 (31.5)	30 (42.3)
Contact with symptomatic individual	12 (3.8)	4 (2.2)	18 (4.0)	2 (2.8)
Told by public health worker to get tested	1 (0.3)	1 (0.5)	3 (0.7)	0 (0.0)
Routine screening for my work or school	120 (38.3)	113 (61.1)	29 (6.4)	17 (23.9)
Test required for medical procedure or hospital admittance	43 (13.7)	25 (13.5)	16 (3.5)	5 (7.0)
Someone in household had contact with a positive case	4 (1.3)	0 (0.0)	11 (2.4)	0 (0.0)
Test required to attend public event/ share public space	2 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)
I just wanted to see if I was infected	71 (22.7)	18 (9.7)	43 (9.5)	4 (5.6)
Concerned about symptoms	43 (13.7)	13 (7.0)	262 (57.7)	26 (36.6)
Pre or post-travel screening	21 (6.7)	7 (3.8)	17 (3.7)	4 (5.6)

*Since interviewers indicated all reasons listed by participants, reasons will not sum to the total sample size.
[1]An individual is considered vaccinated if they have had at least one dose of a SARS-CoV-2 mRNA vaccine.

Table 3: Predictors of vaccine hesitancy

Participant characteristics	Enthusiasm to receive vaccination		Odds ratio (95% CI)	
	Not willing/unsure, *n* (%) *N*=226	Willing, *n* (%) *N*=430	Unadjusted	Adjusted
Case status[1]				
Case with SARS-CoV-2 infection	139 (61.5)	264 (61.4)	N/A	N/A
Uninfected control	87 (38.5)	166 (38.6)	N/A	N/A
Age				
18-29	82 (36.3)	189 (44.0)	Ref.	Ref.
30-49	93 (41.2)	147 (34.2)	1.45 (1.01,2.10)	1.45 (0.97,2.16)
50-64	34 (15.0)	76 (17.7)	1.03 (0.64,1.66)	0.77 (0.46,1.28)
65+	17 (7.5)	18 (4.2)	2.20 (1.07,4.40)	1.66 (0.77,3.57)
Region				
Predominantly urban regions[2]	67 (29.6)	214 (49.8)	Ref.	Ref.
Predominantly rural regions[3]	159 (70.4)	216 (50.2)	2.35 (1.66,3.29)	2.42 (1.66,3.52)
Sex				
Male	107 (47.3)	236 (54.9)	Ref.	Ref.
Woman	119 (52.7)	194 (45.1)	1.35 (0.97,1.87)	1.47 (1.04,2.08)
Income[4]				
Under $50,000	55 (24.3)	132 (30.7)	Ref.	Ref.
$50,000 to $100,000	49 (21.7)	98 (22.8)	1.20 (0.76,1.91)	1.17 (0.73,1.86)
$100,000 to $150,000	28 (12.4)	39 (9.1)	1.72 (0.98,3.07)	1.4 (0.81,2.41)
Over $150,000	22 (9.7)	44 (10.2)	1.20 (0.66,2.18)	1.25 (0.7,2.28)
Race[5]				
White	104 (46.0)	163 (38.0)	Ref.	Ref.
Hispanic	53 (23.5)	146 (34.0)	0.57 (0.38,0.85)	0.72 (0.46,1.12)
Asian	7 (3.1)	58 (13.5)	0.19 (0.08,0.44)	0.24 (0.1,0.55)
Black	20 (8.8)	18 (4.2)	1.74 (0.88,3.44)	2.54 (1.24,5.15)
More than 1 race	26 (11.5)	36 (8.4)	1.13 (0.64,1.97)	1.4 (0.78,2.51)
Native American or Alaskan Native	6 (2.7)	4 (0.9)	2.34 (0.64,8.48)	2.02 (0.54,7.53)
Native Hawaiian or Pacific Islander	3 (1.3)	1 (0.2)	4.73 (0.48,42.82)	4.64 (0.46,45.74)

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]Case status is presented here for context but was not included in regression analyses as it could be considered an outcome of willingness to receive vaccination.

[2]Predominatly urban regions include San Francisco Bay Area, Greater Los Angeles Area, Greater Sacramento area, San Diego and the Southern border. We tabulate regions of residence for individuals who were hesitant or willing to receive vaccination in **Table S1**.

[3]Predominatly rural regions include Central Coast, Northern Sacramento valley, San Joaquin Valley, Northwestern California, and the Sierras region. We tabulate regions of residence for individuals who were hesitant or willing to receive vaccination in **Table S1**.

[4]For regression analyses, values were imputed for individuals who did share income data due to refusal (43 [19.0%] among hesitant and 66 [15.3%] among non-hesitant participants) or those who did not know their income (29 [12.8%] among hesitant and 51 [11.9%] among non-hesitant participants).

[5]For regression analyses, values were imputed for individuals who did not share race data (7 [3.1%] among hesitant and 3 [0.7%] among non-hesitant participants).

Table 4: Reasons for vaccine hesitancy among individuals not yet vaccinated.

Stated reason	*n* (%) among 219 respondents reporting hesitancy to receive vaccination
Concerned about any vaccine side effects	66 (30.0)
Concerned about long term vaccine side effects	60 (27.4)
Concerned about COVID-19 vaccine safety	60 (27.4)
Waiting to see more research on COVID-19 vaccines	40 (18.3)
I have not yet thought about whether I want the COVID-19 vaccine	24 (11.0)
Currently infected with SARS-CoV-2	23 (10.5)
Concerned about safety for vaccines generally	22 (10.0)
Do not believe vaccination against COVID-19 is important	20 (9.1)
Not at high risk for COVID-19	17 (7.8)
Currently pregnant	9 (4.1)
Do not trust the government	9 (4.1)
Negative reaction to prior vaccinations	5 (2.3)
Lack of trust in the medical system	5 (2.3)
Would only get vaccine if required by school/work	5 (2.3)
Contraindicated medical condition	5 (2.3)
Afraid of getting SARS-CoV-2 from the vaccine	3 (1.4)
Depends on the vaccine product offered	2 (0.9)
Object to vaccination due to religious reasons	2 (0.9)
Afraid of needles	1 (0.5)

[1]Calculated out of N=219 because 7 individuals declined to answer.

1.8 SUPPLEMENTAL INFORMATION

Table S1: Counties included in each 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

Table S2: Characteristics of total population eligible for inclusion

		Eligible		Attempted		Final analytic sample	
		Case n (%) N = 108,606	Control n (%) N = 4,718,559	Case n (%) N = 3,847	Control n (%) N = 5,253	Case n (%) N = 525	Control n (%) N = 498
Age							
	<18	16,535 (15.2)	650,959 (13.8)	438 (11.4)	540 (10.3)	--	--
	18-29	27584 (25.4)	1179240 (25.0)	1038 (27.0)	1724 (32.8)	200 (38.1)	195 (39.2)
	30-49	34640 (31.9)	1494701 (31.7)	1219 (31.7)	1584 (30.2)	188 (35.8)	175 (35.1)
	50-64	19918 (18.3)	887593 (18.8)	732 (19.0)	956 (18.2)	100 (19.0)	92 (18.5)
	65+	9929 (9.1)	506066 (10.7)	419 (10.9)	447 (8.5)	37 (7.0)	36 (7.2)
Region							
	Predominantly urban regions						
	San Francisco Bay Area	25354 (23.3)	1728944 (36.6)	432 (11.2)	694 (13.2)	66 (12.6)	63 (12.7)
	Greater Los Angeles Area	35706 (32.9)	1728944 (31.5)	537 (14.0)	519 (9.9)	48 (9.1)	43 (8.6)
	Greater Sacramento Area	6412 (5.9)	171474 (3.6)	316 (8.2)	576 (11.0)	58 (11.0)	57 (11.4)
	San Diego and southern Border	11190 (10.3)	430201 (9.1)	487 (12.7)	545 (10.4)	54 (10.3)	56 (11.2)
	Predominantly rural regions						
	Central Coast	4352 (4.0)	159802 (3.4)	433 (11.3)	778 (14.8)	74 (14.1)	66 (13.3)
	Northern Sacramento Valley	2334 (2.1)	107760 (2.3)	401 (10.4)	482 (9.2)	60 (11.4)	56 (11.2)
	San Joaquin Valley	18398 (16.9)	478466 (10.4)	453 (11.8)	596 (11.3)	54 (10.3)	52 (10.4)
	Northwestern California	1785 (1.6)	59791 (1.3)	345 (9.0)	449 (8.5)	55 (10.5)	53 (10.6)
	Sierras Region	3075 (2.8)	96366 (2.1)	443 (11.5)	614 (11.7)	56 (10.7)	52 (10.4)
Sex							
	Male	53185 (48.9)	2125671 (45.0)	1937 (50.3)	2705 (51.5)	264 (50.3)	255 (51.2)
	Female	55421 (51.1)	2592888 (55.0)	1910 (49.6)	2548 (48.5)	261 (49.7)	243 (48.8)

Table S3: Demographic attributes of vaccinated and unvaccinated cases and controls.

Characteristics	Controls		Cases	
	Unvaccinated, *n* (%) *N*=313	Vaccinated, *n* (%) *N*=185	Unvaccinated, *n* (%) *N*=454	Vaccinated, *n* (%) *N*=71
Age				
18-29	142 (45.4)	53 (28.6)	177 (39.0)	23 (32.4)
30-49	101 (32.3)	74 (40.0)	171 (37.7)	17 (23.9)
50-64	53 (16.9)	39 (21.1)	82 (18.1)	18 (25.4)
65+	17 (5.4)	19 (10.3)	24 (5.3)	13 (18.3)
Region				
Predominantly urban regions				
San Francisco Bay Area	35 (11.2)	28 (15.1)	54 (11.9)	12 (16.9)
Greater Los Angeles Area	34 (10.9)	9 (4.9)	40 (8.8)	8 (11.3)
Greater Sacramento Area	33 (10.5)	24 (13.0)	56 (12.3)	2 (2.8)
San Diego and southern border	37 (11.8)	19 (10.3)	49 (10.8)	5 (7.0)
Predominantly rural regions				
Central Coast	41 (13.1)	25 (13.5)	63 (13.9)	11 (15.5)
Northern Sacramento Valley	35 (11.2)	21 (11.4)	52 (11.5)	8 (11.3)
San Joaquin Valley	36 (11.5)	16 (8.6)	43 (9.5)	11 (15.5)
Northwestern California	34 (10.9)	19 (10.3)	46 (10.1)	9 (12.7)
Sierras Region	28 (8.9)	24 (13.0)	51 (11.2)	5 (7.0)
Sex				

Male	159 (50.8)	96 (51.9)	227 (50.0)	37 (52.1)
Female	154 (49.2)	89 (48.1)	227 (50.0)	34 (47.9)
Household income				
Under $50,000	79 (25.2)	40 (21.6)	138 (30.4)	15 (21.1)
$50,000 to $100,000	71 (22.7)	36 (19.5)	99 (21.8)	14 (19.7)
$100,000 to $150,000	45 (14.4)	31 (16.8)	34 (7.5)	11 (15.5)
Over $150,000	31 (9.9)	40 (21.6)	50 (11.0)	14 (19.7)
Refuse	49 (15.7)	19 (10.3)	79 (17.4)	7 (9.9)
Not sure	38 (12.1)	19 (10.3)	54 (11.9)	10 (14.1)
Race/Ethnicity				
White	128 (40.9)	99 (53.5)	178 (39.3)	39 (54.9)
Hispanic	86 (27.5)	40 (21.6)	143 (31.6)	17 (23.9)
Asian	33 (10.5)	24 (13.0)	50 (11.0)	8 (11.3)
Black	11 (3.5)	6 (3.2)	29 (6.4)	1 (1.4)
More than 1 race	43 (13.7)	10 (5.4)	32 (7.1)	4 (5.6)
Native American	4 (1.3)	1 (0.5)	10 (2.2)	1 (1.4)
Native Hawaiian	3 (1.0)	3 (1.6)	3 (0.7)	1 (1.4)
Refuse	5 (1.6)	2 (1.1)	8 (1.8)	0 (0.0)

Table S4: Perceptions of face mask and social distancing recommendations by vaccination status.

Statement	Response	Overall *N*=1023	Unvaccinated *N*=767		Vaccinated[1] *N*=256	
		n (%)	*n* (%)	95% CI	*n* (%)	95% CI
Face masks reduce risk of COVID-19[2]						
	Agree	895 (87.5)	652 (85.0)	82.3, 87.3	243 (94.9)	91.5, 97.0
	Neutral	64 (6.3)	57 (7.5)	5.8, 9.5	7 (2.8)	1.3, 5.5
	Disagree	56 (5.5)	52 (6.8)	5.2, 8.8	4 (1.6)	0.6, 3.9
Social distancing reduces risk of COVID-19[3]						
	Agree	883 (86.3)	642 (83.7)	80.9, 86.1	241 (94.1)	90.6, 96.4
	Neutral	75 (7.4)	69 (8.9)	7.2, 11.2	6 (2.3)	1.1, 5.0
	Disagree	55 (5.4)	47 (6.2)	4.6, 8.1	8 (3.1)	1.6, 6.0
I feel anxiety about getting COVID-19[4]						
	Anxious	511 (50.0)	385 (50.2)	46.7, 53.7	126 (49.2)	43.2, 55.3
	Not anxious/Neutral	512 (50.0)	382 (49.8)	46.3, 53.3	130 (50.8)	44.7, 56.8

[1] Vaccinated participants had received one or more doses of a COVID-19 vaccine product at the time of their SARS-CoV-2 test

[2] Participants were asked whether they strongly agree, are neutral, disagree, or strongly disagree that face masks reduce the risk of COVID-19. Individuals who agreed or strongly agreed to the statement were classified as “Agree”, and individuals who disagreed, or strongly disagreed were classified as “disagree”.

[3] Participants were asked whether social distancing measures like avoiding large crowds, travel, and maintaining 6 feet of distance in public places reduce the risk of COVID-19, using a Likert scale. Individuals who agreed or strongly agreed to the statement were classified as “Agree”, and individuals who disagreed or strongly disagreed were classified as “disagree”.

[4] Participants were asked about how worried they felt about getting COVID-19 in the two weeks prior to their COVID-19 test on a Likert scale with options: very worried, somewhat worried, neutral, or not worried at all. Participants who indicated they were very worried or somewhat worried are reclassified as anxious, while those who said they were either neutral or not worried at all were listed as “not anxious/ neutral”.

Table S5: Frequency of each reported symptom and level of care sought by outcome and vaccination status.

Outcome	Controls			Cases		
	Unvaccinated, *n* (%) *N*=313	Incompletely Vaccinated[1], *n* (%) *N*=99	Fully Vaccinated, *n* (%) *N*=86	Unvaccinated, *n* (%) *N*=454	Incompletely Vaccinated, *n* (%) *N*=51	Fully Vaccinated, *n* (%) *N*=20
Symptoms						
Fever	12 (3.8)	4 (4.0)	0 (0.0)	120 (26.4)	9 (17.6)	2 (10.0)
Cough	14 (4.5)	4 (4.0)	2 (2.3)	134 (29.5)	15 (29.4)	2 (10.0)
Headache	12 (3.8)	4 (4.0)	0 (0.0)	141 (31.1)	12 (23.5)	1 (5.0)
Loss of taste	2 (0.6)	1 (1.0)	0 (0.0)	69 (15.2)	4 (7.8)	1 (5.0)
Loss of smell	1 (0.3)	1 (1.0)	0 (0.0)	66 (14.5)	4 (7.8)	1 (5.0)
Chills	6 (1.9)	1 (1.0)	0 (0.0)	75 (16.5)	6 (11.8)	0 (0.0)
Muscle Pain	3 (1.0)	2 (2.0)	0 (0.0)	91 (20.0)	10 (19.6)	1 (5.0)
Fatigue	9 (2.9)	1 (1.0)	0 (0.0)	81 (17.8)	8 (15.7)	2 (10.0)
Shortness of breath	3 (1.0)	2 (2.0)	1 (1.2)	41 (9.0)	5 (9.8)	0 (0.0)
Sore throat	14 (4.5)	4 (4.0)	0 (0.0)	69 (15.2)	6 (11.8)	2 (10.0)
Blocked nose	8 (2.6)	2 (2.0)	0 (0.0)	42 (9.3)	7 (13.7)	0 (0.0)
Runny nose	10 (3.2)	5 (5.1)	1 (1.2)	57 (12.6)	6 (11.8)	2 (10.0)
Chest pain	3 (1.0)	0 (0.0)	1 (1.2)	19 (4.2)	1 (2.0)	0 (0.0)
Watery eyes	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	0 (0.0)
Nausea	3 (1.0)	1 (1.0)	0 (0.0)	22 (4.8)	0 (0.0)	0 (0.0)
Sweating	1 (0.3)	0 (0.0)	0 (0.0)	9 (2.0)	0 (0.0)	1 (5.0)
Loss of appetite	1 (0.3)	1 (1.0)	0 (0.0)	25 (5.5)	3 (5.9)	0 (0.0)
Throat tickle	1 (0.3)	0 (0.0)	0 (0.0)	8 (1.8)	1 (2.0)	0 (0.0)
Any symptoms	52 (16.6)	13 (13.1)	3 (3.5)	354 (78.0)	34 (66.7)	9 (45.0)
Level of care						
Hospital	5 (1.6)	3 (3.0)	1 (1.2)	15 (3.3)	3 (5.9)	0 (0.0)
Emergency room	9 (2.9)	3 (3.0)	4 (4.7)	37 (8.1)	5 (9.8)	1 (5.0)
Physician	14 (4.5)	2 (2.0)	3 (3.5)	16 (3.5)	1 (2.0)	0 (0.0)
Telehealth	17 (5.4)	4 (4.0)	1 (1.2)	67 (14.8)	10 (19.6)	1 (5.0)
Urgent care	3 (1.0)	2 (2.0)	2 (2.3)	23 (5.1)	2 (3.9)	0 (0.0)
Pharmacy	6 (1.9)	1 (1.0)	0 (0.0)	14 (3.1)	0 (0.0)	1 (5.0)
Any care[2]	41 (13.1)	11 (11.1)	8 (9.3)	132 (29.1)	15 (29.4)	3 (15.0)

[1]An individual was considered incompletely vaccinated if they had received one or more doses of a mRNA COVID-19 vaccine product, but got tested <14 days after their second dose.
[2] Numbers for any care sought will not sum to the column totals owing to individuals who sought multiple forms of care

Table S6: Vaccine confidence among cases and controls not yet vaccinated.

Characteristics	Controls		Cases		
	Not willing/unsure, *n* (%) *N*=87	Willing, *n* (%) *N*=166	Not willing/unsure, *n* (%) *N*=139	Willing, *n* (%) *N*=264	*p*
Age					0.021
18-29	29 (33.3)	86 (51.8)	53 (38.1)	103 (39.0)	
30-49	42 (48.3)	44 (26.5)	51 (36.7)	103 (39.0)	
50-64	10 (11.5)	29 (17.5)	24 (17.3)	47 (17.8)	
65+	6 (6.9)	7 (4.2)	11 (7.9)	11 (4.2)	
Region					< 0.001
Predominantly urban regions					
San Francisco Bay Area	4 (4.6)	19 (11.4)	7 (5.0)	40 (15.2)	
Greater Los Angeles area	7 (8.0)	20 (12.0)	9 (6.5)	27 (10.2)	
Greater Sacramento area	13 (14.9)	14 (8.4)	16 (11.5)	37 (14.0)	
San Diego and southern border region	4 (4.6)	24 (14.5)	7 (5.0)	33 (12.5)	
Predominantly rural regions					
Central Coast	11 (12.6)	22 (13.3)	21 (15.1)	34 (12.9)	
Northern Sacramento Valley	10 (11.5)	22 (13.3)	26 (18.7)	24 (9.1)	
San Joaquin Valley	15 (17.2)	14 (8.4)	11 (7.9)	28 (10.6)	
Northwestern California	13 (14.9)	16 (9.6)	22 (15.8)	16 (6.1)	
Sierras Region	10 (11.5)	15 (9.0)	20 (14.4)	25 (9.5)	
Sex					
Woman	44 (50.6)	76 (45.8)	75 (54.0)	118 (44.7)	0.182
Male	43 (49.4)	90 (54.2)	64 (46.0)	146 (55.3)	
Income					0.182
Under $50,000	16 (18.4)	49 (29.5)	39 (28.1)	83 (31.4)	
$50,000 to $100,000	22 (25.3)	33 (19.9)	27 (19.4)	65 (24.6)	
$100,000 to $150,000	16 (18.4)	22 (13.3)	12 (8.6)	17 (6.4)	
Over $150,000	7 (8.0)	17 (10.2)	15 (10.8)	27 (10.2)	
Refuse	14 (16.1)	25 (15.1)	29 (20.9)	41 (15.5)	
Not sure	12 (13.8)	20 (12.0)	17 (12.2)	31 (11.7)	
Race					<0.001
White	38 (43.7)	72 (43.4)	66 (47.5)	91 (34.6)	
Hispanic	21 (24.1)	51 (30.7)	32 (23.0)	95 (36.1)	
Asian	2 (2.3)	18 (10.8)	5 (3.6)	40 (15.2)	
Black	5 (5.7)	4 (2.4)	15 (10.8)	14 (5.3)	
More than 1 race	15 (17.2)	19 (11.4)	11 (7.9)	17 (6.5)	
Native American	2 (2.3)	0 (0.0)	4 (2.9)	4 (1.5)	
Native Hawaiian	2 (2.3)	0 (0.0)	1 (0.7)	1 (0.4)	
Refuse	2 (2.3)	2 (1.2)	5 (3.6)	1 (0.4)	

Table S7: Regions of residence among participants reporting hesitancy or willingness to receive vaccination.

Region of residence	Not willing/unsure, *n* (%)	Willing, *n* (%)
Predominantly urban regions	67 (29.6)	214 (49.8)
San Francisco Bay area	11 (4.9)	59 (13.7)
Greater Los Angeles area	16 (7.1)	47 (10.9)
Greater Sacramento area	29 (12.8)	51 (11.9)
San Diego and southern border region	11 (4.9)	57 (13.3)
Predominantly rural regions	159 (70.4)	216 (50.2)
Central Coast	32 (14.2)	56 (13.0)
Northern Sacramento Valley	36 (15.9)	46 (10.7)
San Joaquin Valley	26 (11.5)	42 (9.8)
Northwestern California	35 (15.5)	32 (7.4)
Sierras Region	30 (13.3)	40 (9.3)

Table S8: Complete case analysis of predictors of vaccine confidence.

Participant characteristics	**Enthusiasm to receive vaccination**		**Adjusted Odds Ratio** (95% CI)
	Not willing/unsure, *n* (%) *N*=226	Willing, *n* (%) *N*=430	
Case status			
Case with SARS-CoV-2 infection	139 (61.5)	264 (61.4)	N/A
Uninfected control	87 (38.5)	166 (38.6)	N/A
Age			
18-29	82 (36.3)	189 (44.0)	Ref.
30-49	93 (41.2)	147 (34.2)	1.22 (0.25,2.37)
50-64	34 (15.0)	76 (17.7)	1.26 (0.26,3.16)
65+	17 (7.5)	18 (4.2)	1.42 (0.29,3.47)
Region			
Predominantly urban regions	67 (29.6)	214 (49.8)	Ref.
Predominantly rural regions	159 (70.4)	216 (50.2)	1.21 (0.23,8.54)
Sex			
Male	107 (47.3)	236 (54.9)	Ref.
Woman	119 (52.7)	194 (45.1)	1.10 (0.26,8.2)
Income[4]			
Under $50,000	55 (24.3)	132 (30.7)	Ref.
$50,000 to $100,000	49 (21.7)	98 (22.8)	1.31 (0.20,3.24)
$100,000 to $150,000	28 (12.4)	39 (9.1)	1.63 (0.16,20.67)
Over $150,000	22 (9.7)	44 (10.2)	1.69 (0.11,7.53)
Race[5]			
White	104 (46.0)	163 (38.0)	Ref.
Hispanic	53 (23.5)	146 (34.0)	1.44 (0.24,11.0)
Asian	7 (3.1)	58 (13.5)	1.45 (0.27,7.08)
Black	20 (8.8)	18 (4.2)	1.28 (0.27,10.65)
More than 1 race	26 (11.5)	36 (8.4)	1.33 (0.14,3.61)
Native American or Alaskan Native	6 (2.7)	4 (0.9)	1.21 (0.27,3.14)
Native Hawaiian or Pacific Islander	3 (1.3)	1 (0.2)	1.36 (0.11,4.67)

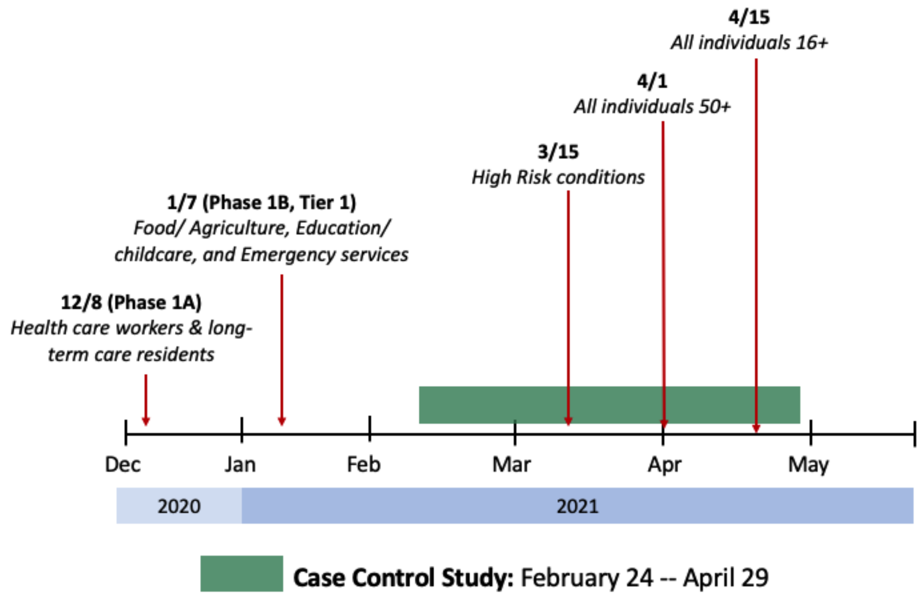

Figure S1: Timeline of COVID-19 vaccine availability in California. Red arrows denote key events in expansion of eligibility in the California population. Green bar represents the dates during which data was collected and presented for this study.

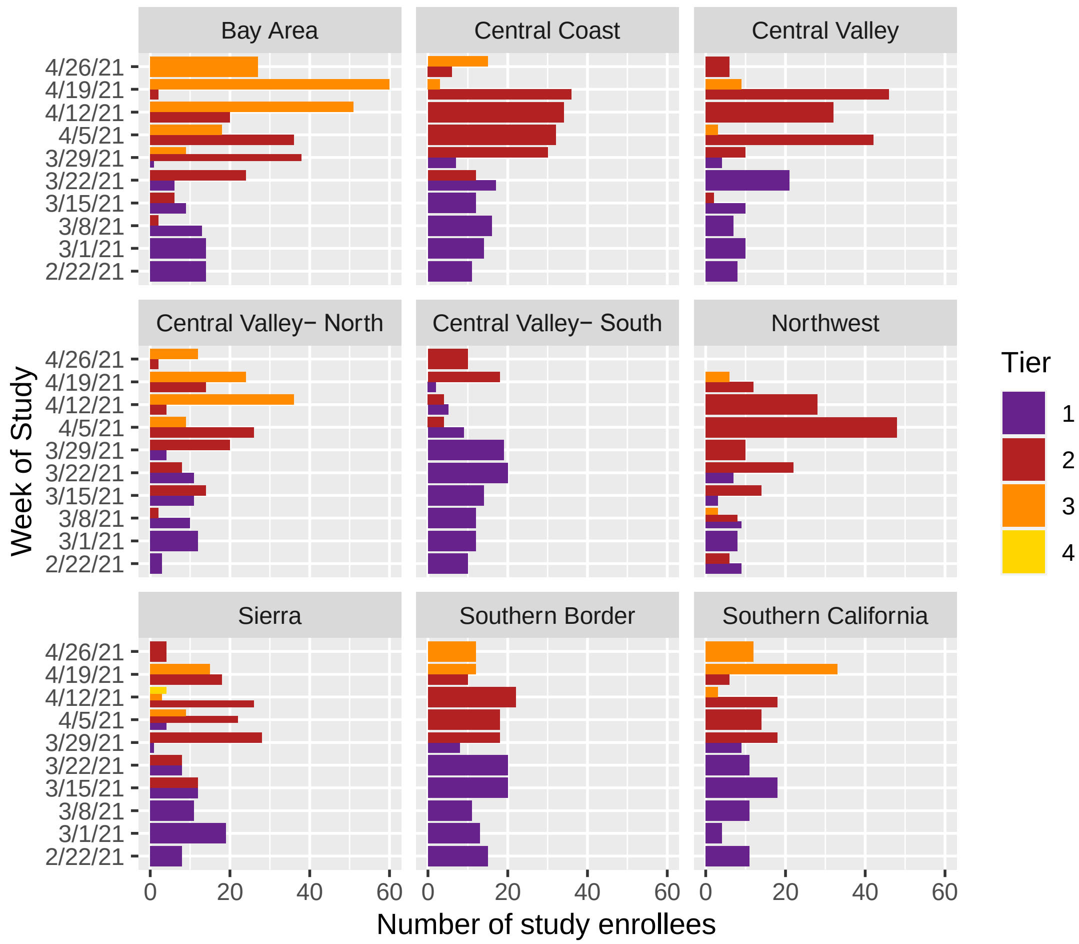

Figure S2: Tier of region by week of study. Tier 1 (purple) corresponds to the strictest restrictions, Tier 4 (yellow) corresponds to the loosest restrictions. As tiers are designated by county, bars are split in regions where participants within a region were enrolled from counties assigned to differing tiers.

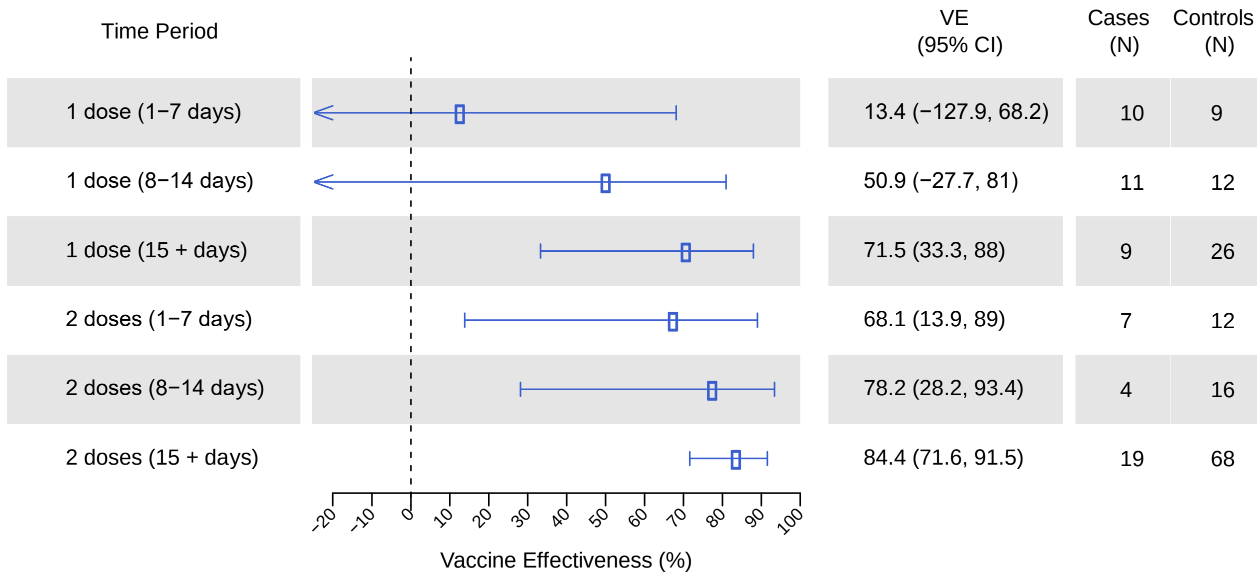

Figure S3: Sensitivity analyses of individuals (*N*=53) without access to vaccination cards. Lines denote 95% confidence intervals, respectively, for estimates of vaccine effectiveness for both mRNA vaccines poled. Estimates were calculated via conditional logistic regression.

Chapter 2

Predictors of SARS-Cov-2 infection following high-risk exposure

2.1 ABSTRACT

Background: Non-pharmaceutical interventions (NPIs) are recommended for COVID-19 prevention. However, the effectiveness of NPIs in preventing SARS-CoV-2 transmission remains poorly quantified.

Methods: We conducted a test-negative design case-control study enrolling cases (testing positive for SARS-CoV-2) and controls (testing negative) with molecular SARS-CoV-2 diagnostic test results reported to California Department of Public Health between 24 February-12 November, 2021. We used conditional logistic regression to estimate adjusted odds ratios (aORs) of case status among participants who reported contact with an individual known or suspected to have been infected with SARS-CoV-2 ("high-risk exposure") ≤14 days before testing.

Results: 751 of 1448 cases (52%) and 255 of 1443 controls (18%) reported high-risk exposures ≤14 days before testing. Adjusted odds of case status were 3.02-fold (95% confidence interval: 1.75-5.22) higher when high-risk exposures occurred with household members (vs. other contacts), 2.10-fold (1.05-4.21) higher when exposures occurred indoors (vs. outdoors only), and 2.15-fold (1.27-3.67) higher when exposures lasted ≥3 hours (vs. shorter durations) among unvaccinated and partially-vaccinated individuals; excess risk associated with such exposures was mitigated among fully-vaccinated individuals. Cases were less likely than controls to report mask usage during high-risk exposures (aOR=0.50 [0.29-0.85]). The adjusted odds of case status was lower for fully-vaccinated (aOR=0.25 [0.15-0.43]) participants compared to unvaccinated participants. Benefits of mask usage were greatest among unvaccinated and partially-vaccinated participants, and in interactions involving non-household contacts or interactions occurring without physical contact.

Conclusions: NPIs reduced the likelihood of SARS-CoV-2 infection following high-risk exposure. Vaccine effectiveness was substantial for partially and fully vaccinated persons.

Chapter 2 is included here with permission from my co-authors: Jake Pry, Jennifer Myers, John Openshaw, James Watt, Nozomi Birkett, Jennifer DeGuzman, Camilla Barbaduomo, Zheng Dong, Anna Fang, Paulina Frost, Timothy Ho, Mahsa Javadi, Sophia Li, Vivian Tran, Christine Wan, Seema Jain and Joseph Lewnard

2.2 INTRODUCTION

Strategies aimed at preventing SARS-CoV-2 transmission during contact between infectious and susceptible individuals have been critical to mitigating the COVID-19 pandemic. While vaccines effectively reduce individual risk of infection and severe disease [1–3], non-pharmaceutical interventions (NPIs) continue to be recommended in various circumstances; these include within populations ineligible for vaccination, in settings where vaccines remain inaccessible or under-utilized, and in response to emergence of SARS-CoV-2 variants with increased transmissibility. Efforts to prevent transmission include social distancing and avoiding direct physical contact with non-household members [4]; interacting with non-household members outdoors [5]; and use of face coverings to filter virus-containing droplets and aerosols [6,7].

However, evidence demonstrating the effectiveness of various NPIs in mitigating transmission risk remains limited [8,9]. Understanding of exposures mediating SARS-CoV-2 transmission stems largely from anecdotal reports with unknown generalizability [10]. Additionally, many assessments of the effectiveness of NPIs have been ecological studies comparing COVID-19 incidence before and after implementation of multiple interventions [11–13], making it difficult to distinguish independent effects of each strategy [14]. While numerous studies demonstrate that face masks limit the quantity of virus shed into the environment by infectious individuals [15,16], few have assessed real-world effectiveness of face masks in preventing SARS-CoV-2 infection [6]. Improved understanding of aspects of social contact that exacerbate or reduce risk of SARS-CoV-2 transmission are needed to guide intervention prioritization [17,18].

To mitigate transmission of SARS-CoV-2, California mandated social distancing and wearing of facial coverings in spring 2020, and implemented a tiered system for closure and reopening of public places based on community-level measures of SARS-CoV-2 transmission and hospital utilization [19]. Statewide social distancing and mask mandates among vaccinated people in most public places and the tiered system were relaxed on 15 June, 2021, when roughly 57% of eligible Californians were considered fully vaccinated [19,20]. However, amid rising incidence of COVID-19 and increases in hospitalizations following emergence of the Delta (B.1.617.2) variant [21,22], measures encouraging or requiring face masks in certain indoor settings regardless of vaccination status were reinstated on 17 July 2021 [23]. We initiated a retrospective, test-negative design case-control study to understand risk factors for SARS-CoV-2 infection in California and inform public health strategies [1]. Here, we address predictors of SARS-CoV-2 infection among participants who reported high-risk exposures, defined as social contact with an individual known or suspected to have been infected with SARS-CoV-2, within two weeks preceding participants' SARS-CoV-2 tests.

2.3 METHODS

Design

California residents with confirmatory, molecular SARS-CoV-2 diagnostic test results reported to the California Department of Public Health (CDPH) between 24 February, 2021 and 12 November, 2021 with a recorded phone number were eligible for inclusion. Each day, trained interviewers called potential participants selected at random from all individuals with test results reported in the preceding 48 hours. Cases were persons with a positive molecular SARS-CoV-2 test result while controls were persons with a negative result. We enrolled cases equally across nine regions of the state (**Table S1**). For each enrolled case, interviewers attempted to enroll one control matched to the case by age group, sex, region, and week of SARS-CoV-2 test from a list of ≥30 randomly selected controls meeting these criteria. Individuals were eligible to enroll if they provided informed consent in English or Spanish, and had not received a previous diagnosis of COVID-19 or positive test result for SARS-CoV-2 infection (molecular, antigen, or serological test). Additional sampling and enrollment details have been described elsewhere [1].

The study protocol was approved as public health surveillance by the State of California Health and Human Services Agency Committee for the Protection of Human Subjects.

Exposures

Trained interviewers administered a standardized phone-based questionnaire to assess exposures (**Text S1**). This analysis included participants who reported they were potentially exposed to SARS-CoV-2 $\leq$ 14 days prior to their test through social contact with an individual known or suspected by the participant to have been infected with SARS-CoV-2 at the time of their interaction ("high-risk exposure"). Participants were asked to specify if they were aware that one or more of these individuals had been a confirmed case, based on receipt of a positive diagnostic test result for SARS-CoV-2 infection.

Among participants reporting exposure to a confirmed or suspected COVID-19 case during the 14 days prior to their test, interviewers systematically collected characteristics of the exposure including setting (any indoor exposure versus outdoor exposure only); duration (whether contact lasted ≥3 hours); whether the participant and the contact had any physical contact; whether the contact was a member of the participant's household; and use of face coverings by the participant and the contact during the interaction(s).

Additionally, all study participants were asked to indicate their reasons for seeking SARS-CoV-2 testing, including any symptoms experienced in the 14 days preceding their test. Interviews also recorded participants' self-reported history of visiting other locations, including restaurants, bars, coffee shops, retail shops, public gyms, salons, movie theaters, or worship services; participating in social gatherings; and using ride share services, public transportation, or air travel. Interviewers recorded the COVID-19 vaccination status of participants, including the manufacturer and dates of all doses received, and asked participants to describe their level of concern about the COVID-19 pandemic in the 14 days prior to seeking SARS-CoV-2 testing.

Statistical analysis

To convey descriptive features of the enrolled sample, we summarized demographic attributes and exposure characteristics among participants enrolled in the study using proportions. Our primary inferential objective was to identify characteristics of high-risk exposure events associated with SARS-CoV-2 infection. We fit conditional logistic regression models to estimate adjusted odds ratios (aORs) and accompanying 95% confidence intervals (CIs) of various exposure attributes, comparing cases with controls. These included exposure setting (any indoor exposure versus outdoor-only exposure), exposure duration (any exposure ≥3 hours versus <3 hours), whether the exposure involved a potentially infectious household member(s) (versus non-household contact(s) only), the nature of exposure (any physical contact versus no physical contact), and mask usage by the participant or their contact during the entire interaction (versus mask usage by neither party). Models included interaction terms between each contact attribute and the vaccination history of the participant at the time of their test to assess effect modification. We considered participants tested >14 days after receipt of two doses of BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (National Institutes of Health/Moderna) or one dose of JNJ-78436735 (Janssen Pharmaceutical Companies) to be fully vaccinated. Others reporting receipt of any COVID-19 vaccine doses before their test date were considered partially vaccinated.

To correct for differences in infection prevalence over time and across regions, independent of the specific exposures being analyzed, regression strata (i.e., matching sets) were defined by the reopening tier of participants' county of residence at the time of testing, or, for the period after 15 June, 2021 (when the tiered reopening system was retired), by participants' month of SARS-CoV-2 testing. We further controlled for potential confounders including demographic variables (age, sex, and region), participants' self-reported level of anxiety about the COVID-19 pandemic prior to seeking SARS-CoV-2 testing, and participants' self-reported attendance at community settings (as listed above) which may have been associated with risk of SARS-CoV-2 exposure. As a sensitivity analysis, we repeated these primary analyses within only the subset of participants who reported contact with a confirmed case. To further verify that findings did not owe to confounding between risk-mitigating behaviors and test-seeking, we repeated the analyses within the subset of participants who cited contact with a COVID-19 case as a primary motivation for their decision to receive a test.

To identify determinants of the effectiveness or impact of mask usage in mitigating transmission, we also undertook secondary analyses estimating the aOR of mask usage among cases versus controls within subsets of participants who reported distinct types of high-risk exposures [24]. Consistent with our primary analyses, these included indoor and outdoor exposures, exposures lasting ≥3 hours and <3 hours, exposures to potentially infected individuals who were and were not members of participants' households, and exposures with and without physical contact. We further estimated the aOR of mask usage separately among fully-vaccinated and partially-vaccinated or unvaccinated participants. Conditional logistic regression models for these analyses followed the framework described above and included interaction terms between each exposure characteristic and mask usage by participants or their contacts.

Last, we aimed to test the hypothesis that attributes of high-risk exposure including face mask usage predicted the severity of illness among SARS-CoV-2 infected individuals [25–27]. Here, we restricted our analytic sample to cases testing positive for SARS-CoV-2. As a measure of severity, we considered whether participants reported any type of consultation with a health care provider (e.g., virtual or outpatient appointment, emergency room attendance, or hospitalization) in conjunction with testing. We estimated aORs of each exposure characteristic, comparing cases who received clinical care to those who did not, using conditional logistic regression models following the same framework described above.

We conducted analyses in R software (version 3.6.1).

2.4 RESULTS

Descriptive features of the enrolled sample

Between 24 February and 12 November, 2021, we enrolled 2891 participants, including 1448 cases and 1443 controls. In total, 1006 participants, including 751 cases (52% of 1448) and 255 controls (18% of 1443), reported high-risk exposure within 14 days before testing, including 833 (83% of 1006) with confirmed and 173 (17% of 1006) with suspected exposure (**Table 1; Table S2; Table S3**). Most participants reported their high-risk exposure occurred within their household (55% of 847) or workplace (14% of 847) (**Table S4**). A majority of these participants (788/1006; 78%) listed high-risk exposure as a motivation for testing. In total, 600 (60% of 1006) indicated that they experienced symptoms, and 319 (32% of 1006) cited symptoms as a primary motivation for testing (**Table S5**).

Among 1006 participants reporting high-risk exposure, 880 (87%) reported contact occurring indoors, 728 (72%) reported contact lasting ≥3 consecutive hours, 594 (59%) reported physical contact with the individual known or suspected to have been infected, and 559 (56%) indicated their contact was a household member. Participants who reported interactions occurring indoors, lasting ≥3 hours, or involving physical contact were generally more likely to have been enrolled after 15 June, or to have resided in counties within less-restrictive reopening tiers at the time of their test, than those who reported outdoor, shorter, or non-physical contact (**Table 2a; Table 2b**).

The majority (816/1006; 81%) of participants reporting high-risk exposure indicated both they and their contact did not wear a mask during the interaction (**Table 3**). Mask usage did not differ substantially among participants by age, region, income strata, or in association with vaccination status; however, a higher proportion of individuals who reported unmasked interactions were non-Hispanic whites (382/816; 47%) in comparison to participants reporting masked interactions (59/188; 31%). Most enrolled participants were unvaccinated (649/1006; 65%) at the time of testing; 8% (83/1006) and 22% (217/1006) were partially or fully vaccinated, respectively. Vaccination coverage varied over the study period, reflecting the continuous rollout of vaccination over time.

Predictors of infection

Among unvaccinated or partially-vaccinated participants, cases were more likely to report high-risk exposures involving a potentially-infected household member, occurring indoors, lasting ≥3 hours, or where either they or their contact did not wear a face mask (**Figure 1**; **Table S6**). Adjusted odds of contact having occurred indoors, having lasted ≥3 hours, and having occurred with a household member were 2.10 (95% CI: 1.05-4.20), 2.15 (1.27-3.57), and 3.02 (1.75-5.22) fold higher among cases than controls, respectively. In contrast, we did not identify an association between case status and whether participants reported physical contact with the individual known or suspected to being infected. The association of each of these exposures with case status was mitigated among fully-vaccinated participants, as indicated by lower point estimates of the aOR for each exposure among fully-vaccinated participants as compared to other participants. Estimated aORs were similar in models restricted to participants who specified that their contact was confirmed to have been infected with SARS-CoV-2 at the time of their interaction, and among individuals who indicated this exposure was a primary motivation for testing (**Table S7; Table S8; Figure S1**).

Among study participants, 14% of cases (101/749) and 34% of controls (87/255) reported mask usage during the high-risk interaction (aOR=0.50 [0.29-0.85]; **Figure 2**). Estimated effect size estimates did not differ appreciably according to whether masks were worn exclusively by participants or their contacts, although analyses were underpowered to demonstrate significant effects within each of these strata or to make comparisons across them; (**Figure S2).** However, mask usage was protective when both parties reported mask usage during the interaction (aOR=0.50 [0.26-0.96]). Adjusted odds of cases status were lower for both partially (aOR=0.30 [0.16-0.60]) and fully-vaccinated (aOR=0.25 [0.15-0.43]) participants relative to unvaccinated participants.

Protective effects of mask usage by either participants or their contacts differed according to several characteristics of exposure events. Mask usage was protective among participants reporting exposures to infected individuals outside their household (aOR=0.39 [0.22-0.70]), exposures that occurred without physical contact (aOR=0.37 [0.20-0.69]), and indoor exposures (aOR=0.51 [0.28-0.93]; **Figure 3**). In contrast, we did not identify significant protective effects of mask usage when exposure involved an infected household member, involved physical contact, or occurred outdoors. Among unvaccinated or partially-vaccinated participants, 13% of cases (80/600) and 36% of controls (47/130) reported mask usage during the interaction, and adjusted odds of mask usage were 0.47-fold (0.26-0.86) as high among cases as compared to controls. Among fully vaccinated participants, 12% of cases (15/123) and 32% of controls (30/94) reported mask usage during the interaction, and adjusted odds of mask usage were 0.60-fold (0.24-1.50) as high among cases as compared to controls.

Among 751 cases testing positive for SARS-CoV-2 who reported high-risk exposures, 187 (25%) indicated receiving healthcare beyond testing alone (**Table 4**). The aOR for mask usage during high-risk interactions was 0.69 (0.36-1.34) for cases who sought care with a medical provider, as compared to cases who did not. The proportion of cases experiencing symptoms likewise did not vary according to whether high-risk exposures involved a household member, involved physical contact, occurred indoors or outdoors, or lasted <3 hours or ≥3 hours. Similarly, neither the likelihood of experiencing symptoms nor the number of symptoms that participants reported experiencing differed according to these exposure attributes (**Table S9**, **Table S10**, **Table S11**).

2.5 DISCUSSION

Among participants in our study who reported recent high-risk exposures, use of face masks was associated with reduced odds of testing positive for SARS-CoV-2 infection. Interacting in an indoor setting, longer (≥3 hour) lengths of interaction, and exposures involving household members were each associated with increased odds of testing positive for SARS-CoV-2 infection among participants who were not fully vaccinated. Among fully vaccinated participants, excess infection risk associated with exposure characteristics including unmasked contact, indoor contact, physical contact, and contact with a household member was mitigated. While associations between risk-reducing behaviors and test-seeking may be of concern in test-negative design studies of SARS-CoV-2 infection, our analyses controlled for participants' self-reported levels of concern about the COVID-19 pandemic, and our findings held in sensitivity analyses restricted to individuals who reported that concerns about their high-risk exposure were a primary reason for test-seeking. These findings may inform the use of NPIs in populations with limited vaccine access or those ineligible to be vaccinated, and in response to changing epidemiologic conditions such as emergence of variants associated with enhanced infectiousness.

Whereas mask usage was protective in interactions where participants reported no physical contact with a potentially infectious individual, we did not identify protection in interactions where physical contact was made. Mask usage was also less clearly protective when participants were exposed to a potentially infected member of their own household. This finding may reflect the difficulty of adhering to stringent masking over periods of extended or repeated exposure, as may occur among household members [28,29]. Our analysis provided the strongest evidence of benefits of masking for unvaccinated participants, although we also estimated 40% lower odds of infection associated with mask wearing among fully vaccinated participants. While this estimate did not exclude the possibility of no effect, analyses within the fully-vaccinated stratum were underpowered due to the low numbers of participants experiencing post-vaccination infections.

Contrary to prevailing hypotheses [24], we did not identify strong evidence of associations between measures of infection severity and the likelihood for cases to report unmasked, indoor, long-lasting, or physical interactions with their potentially-infected contacts. While bias may have occurred if individuals' decision to wear masks was associated with their likelihood of seeking testing when asymptomatic or minimally symptomatic, receipt of care in a clinical setting provides a more objective indication of infection severity. Direct measurement of SARS-CoV-2 exposure intensity and clinical status was not possible under this design. However, based on our observations, real-world effects of masking and other non-pharmaceutical mitigation measures may have greater impact on individuals' risk of infection than their likelihood of experiencing symptoms, once infected. Studies in animal models have likewise provided inconsistent support for the hypothesis that reducing SARS-CoV-2 exposure dose may lower the risk of severe disease, given infection [26].

While the test-negative design we have employed in this analysis has historically been used primarily for studies of pathogen-specific interventions such as vaccines [30,31], several features of our study design make this design applicable for NPIs, despite their potential for effects on multiple respiratory pathogens. Restricting our analytic sample to individuals who came into contact with COVID-19 cases during the 14 days before testing supports our effort to assess how features of known or suspected SARS-CoV-2 exposure events affect transmission of SARS-CoV-2, specifically. Furthermore, because transmission of respiratory pathogens other than SARS-CoV-2 has remained at historically low levels in California and much of the United States throughout the COVID-19 pandemic [32,33], the likelihood for other infections to cause test-seeking within our study population is low.

Additional factors which may have modified the likelihood of transmission during high-risk exposure could include the vaccination status of infected contacts [34], the type of masks or face coverings used [35], the physical distance individuals maintained while interacting, and ventilation of indoor spaces where interactions occurred. Obtaining reliable information on these details of each interaction was not feasible through retrospective interviews with participants. While our sample size was not powered to distinguish between protection associated with masking by participants, their contacts, or both parties, confounding may also arise if the decision to wear masks was influenced by factors we did not measure, including contacts' vaccination status. This may bias effect size estimates from our study toward the null, along with several other factors including exposure misclassification resulting from our reliance on self-reported behaviors, imperfect knowledge of contacts' infection status, and the possibility that participants were infected through interactions other than the high-risk exposure events analyzed.

Our findings provide real-world evidence that NPIs including mask usage reduce risk of SARS-CoV-2 transmission when infectious and susceptible individuals come into contact. We also demonstrate substantial vaccine effectiveness against SARS-CoV-2 in the context of high-risk interactions, suggesting such exposures are not associated with heightened risk of vaccine failure. Study participants were mainly enrolled prior to the Delta variant becoming the predominant SARS-CoV-2 lineage in California. Nonetheless, multiple observational studies have confirmed persistence of vaccine protection against SARS-CoV-2 infection despite the emergence and circulation of new variants [36], and high vaccine effectiveness against severe outcomes including hospitalization and death when post-vaccination infections occur [37]. Amid efforts to increase vaccine uptake as a primary public health strategy, our findings indicate NPIs can protect unvaccinated persons and may also be valuable for vaccinated persons as measures to reduce SARS-CoV-2 transmission.

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2.7 TABLES AND FIGURES

Contact attribute		Total n (%)	Cases n (%)	Controls n (%)	aOR (95% CI)
Relationship to contact					
Fully vaccinated					
	Non−household member	144 (66.7)	67 (54.9)	77 (81.9)	ref.
	Household member	72 (33.3)	55 (45.1)	17 (18.1)	2.27 (1.10,4.77)
Unvaccinated/ partially vaccinated					
	Non−household member	371 (50.8)	270 (45.0)	101 (77.7)	ref.
	Household member	359 (49.2)	330 (55.0)	29 (22.3)	3.02 (1.75,5.22)
Nature of contact					
Fully vaccinated					
	Non−physical contact	70 (34.8)	35 (29.4)	35 (42.7)	ref.
	Any physical contact	131 (65.2)	84 (70.6)	47 (57.3)	0.78 (0.39,1.59)
Unvaccinated/ partially vaccinated					
	Non−physical contact	267 (38.0)	202 (34.8)	65 (53.3)	ref.
	Any physical contact	436 (62.0)	379 (65.2)	57 (46.7)	1.05 (0.64,1.72)
Exposure setting					
Fully vaccinated					
	No indoor exposure	24 (11.8)	10 (8.4)	14 (16.5)	ref.
	Any indoor exposure	180 (88.2)	109 (91.6)	71 (83.5)	0.97 (0.36,2.58)
Unvaccinated/ partially vaccinated					
	No indoor exposure	59 (8.4)	33 (5.7)	26 (21.5)	ref.
	Any indoor exposure	645 (91.6)	550 (94.3)	95 (78.5)	2.10 (1.05,4.20)
Duration					
Fully vaccinated					
	Under 3 hours	61 (28.9)	27 (22.1)	34 (38.2)	ref.
	Over 3 hours	150 (71.1)	95 (77.9)	55 (61.8)	1.51 (0.72,3.11)
Unvaccinated/ partially vaccinated					
	Under 3 hours	173 (24.2)	116 (19.6)	57 (46.3)	ref.
	Over 3 hours	541 (75.8)	475 (80.4)	66 (53.7)	2.15 (1.27,3.57)

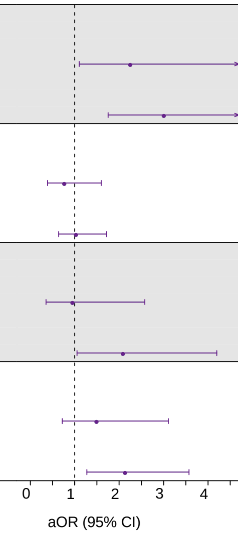

Figure 1. Predictors of infection following high-risk exposure. aOR: adjusted odds ratio, computed using conditional logistic regression models interacting vaccination status with each contact attribute, and adjusting for community exposures (listed in the main text), vaccination status (defined as fully vaccinated or unvaccinated/incompletely vaccinated) of the participant and mask-wearing by the participant and their contact, level of anxiety about COVID-19 prior to testing, and participants' age, sex, and region of residence. Regression strata were defined for county reopening tiers and, for the period after June 15th, the month of SARS-CoV-2 test. Further regression parameter estimates are presented in **Table S4**. Counts for cases and controls differ from **Table 1** due to some participants indicating they did not know these details about their known or suspected contact, and missing data on vaccination status among cases (*N*=8) and controls (*N*=18).

	Total n (%)	Cases n (%)	Controls n (%)	aOR (95% CI)
Mask usage at interaction				
No mask usage at interaction	816 (81.2)	648 (86.5)	168 (65.9)	ref.
Mask usage by either party	188 (18.7)	101 (13.5)	87 (34.1)	0.50 (0.29, 0.85)
Vaccination status of participant				
No vaccine doses	649 (68.4)	546 (75.3)	103 (46.0)	ref.
Incomplete vaccination series	83 (8.7)	56 (7.7)	27 (12.1)	0.30 (0.15, 0.60)
Full vaccination series	217 (22.9)	123 (17.0)	94 (42.0)	0.25 (0.15, 0.43)

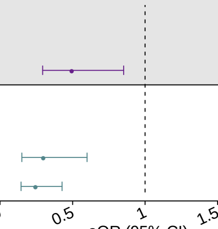

Figure 2. Protective effects of mask-wearing and vaccination in the context of high-risk exposure. aOR: adjusted odds ratio, computed using conditional logistic regression models adjusting for vaccination status, community exposures (listed in the main text), characteristics of high-risk contact, level of anxiety about COVID-19 prior to testing, and participants' age, sex, and region of residence. Regression strata were defined for county reopening tiers and week of SARS-CoV-2 test. An individual was considered fully vaccinated if their SARS-CoV-2 test date was more than 14 days after their second dose of a mRNA vaccine product (Pfizer/BioNTech [BNT-162b2] or Moderna [mRNA-1273]), or more than 14 days after their first dose of a single dose product (Jansen Pharmaceutical Companies [JNJ-78436735]). In sensitivity analyses limiting to those who received a mRNA vaccine product (excluding *N*=25 recipients of JNJ-78436735) the aORs (95% CI) for incompletely vaccinated and fully vaccinated individuals were 0.30 (0.14-0.63) and 0.26 (0.14-0.46), respectively.

Contact attribute	Masking	Cases n (%)	Controls n (%)	aOR (95% CI)
Relationship to contact				
Non−household member				
	Both parties unmasked	284 (80.0)	120 (59.1)	ref.
	Mask usage by either party	71 (20.0)	83 (40.9)	0.39 (0.22, 0.70)
Household member				
	Both parties unmasked	361 (92.3)	48 (92.3)	ref.
	Mask usage by either party	30 (7.7)	4 (7.7)	1.68 (0.42, 6.69)
Nature of contact				
Non−physical contact only				
	Both parties unmasked	185 (75.2)	57 (49.1)	ref.
	Mask usage by either party	61 (24.8)	59 (50.9)	0.37 (0.20, 0.69)
Any physical contact				
	Both parties unmasked	443 (93.1)	101 (86.3)	ref.
	Mask usage by either party	33 (6.9)	16 (13.7)	1.00 (0.37, 2.59)
Exposure setting				
Outdoor exposure only				
	Both parties unmasked	27 (60.0)	21 (48.8)	ref.
	Mask usage by either party	18 (40.0)	22 (51.2)	0.45 (0.15, 1.37)
Any indoor Exposure				
	Both parties unmasked	606 (89.1)	142 (73.6)	ref.
	Mask usage by either party	74 (10.9)	51 (26.4)	0.51 (0.28, 0.93)
Duration				
Under 3 hours				
	Both parties unmasked	100 (68.0)	60 (57.1)	ref.
	Mask usage by either party	47 (32.0)	45 (42.9)	0.52 (0.25, 1.04)
Over 3 hours				
	Both parties unmasked	538 (91.3)	104 (75.9)	ref.
	Mask usage by either party	51 (8.7)	33 (24.1)	0.47 (0.22, 1.05)
Vaccination status				
Unvaccinated/ partially vaccinated				
	Both parties unmasked	520 (86.7)	83 (63.8)	ref.
	Mask usage by either party	80 (13.3)	47 (36.2)	0.47 (0.26, 0.86)
Fully vaccinated				
	Both parties unmasked	108 (87.8)	64 (68.1)	ref.
	Mask usage by either party	15 (12.2)	30 (31.9)	0.60 (0.24, 1.50)

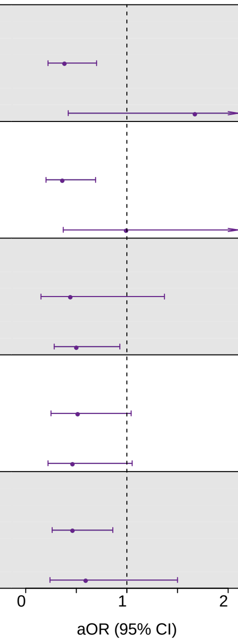

Figure 3. Protective effects of mask-wearing in differing high-risk exposure contexts. aOR: adjusted odds ratio, computed using conditional logistic regression models adjusting for vaccination status of respondent, community exposures (listed in main text), characteristics of the high-risk contact, level of COVID-19 anxiety prior to testing, and participants' age, sex, and region of residence. An interaction term was included between mask usage and the contact attribute in five separate models. Regression strata were defined for county reopening tiers and week of SARS-CoV-2 test. The aOR represents the adjusted odds ratio for case status comparing mask usage within each category (with respect to relationship, physical/non-physical nature of contact, indoor/outdoor exposure, duration, and participant vaccination status.

Table 1: Descriptive attributes of participants reporting high-risk exposures.

		All participants	**Cases**[1]	**Controls**[2]
		n (%)	*n* (%)	*n* (%)
		N=847	*N*=643	*N*=204
Age				
	0-6	30 (3.5)	28 (4.4)	2 (1.0)
	7-12	48 (5.7)	37 (5.8)	11 (5.4)
	13-17	53 (6.3)	41 (6.4)	12 (5.9)
	18-29	269 (31.8)	206 (32.0)	63 (30.9)
	30-49	291 (34.4)	202 (31.4)	89 (43.6)
	50-64	111 (13.1)	91 (14.2)	20 (9.8)
	65+	45 (5.3)	38 (5.9)	7 (3.4)
Sex				
	Male	388 (45.8)	295 (45.9)	93 (45.6)
	Female	459 (54.2)	348 (54.1)	111 (54.4)
Household income				
	Under $50,000	206 (24.3)	159 (24.7)	47 (23.0)
	$50,000 to $100,000	201 (23.7)	160 (24.9)	41 (20.1)
	$100,000 to $150,000	99 (11.7)	63 (9.8)	36 (17.6)
	Over $150,000	103 (12.2)	73 (11.4)	30 (14.7)
	Refuse	146 (17.2)	114 (17.7)	32 (15.7)
	Not sure	92 (10.9)	74 (11.5)	18 (8.8)
Race/ ethnicity				
	Non-Hispanic White	357 (43.9)	272 (44.2)	85 (43.1)
	Non-Hispanic Black	38 (4.7)	32 (5.2)	6 (3.0)
	Hispanic (any race)	230 (28.3)	176 (28.6)	54 (27.4)
	Asian	67 (8.2)	51 (8.3)	16 (8.1)
	Native American	17 (2.1)	15 (2.4)	2 (1.0)
	Native Hawaiian	5 (0.6)	5 (0.8)	0 (0.0)
	More than 1 race	99 (12.2)	65 (10.6)	34 (17.3)
	Refuse	34 (4.1)	27 (4.2)	7 (3.4)
Region of residence[3]				
	Predominantly urban regions			
	San Francisco Bay Area	87 (10.3)	73 (11.4)	14 (6.9)
	Greater Los Angeles Area	89 (10.5)	70 (10.9)	19 (9.3)
	Greater Sacramento Area	107 (12.6)	82 (12.8)	25 (12.3)
	San Diego and southern border	80 (9.4)	62 (9.6)	18 (8.8)
	Predominantly rural regions			
	Central Coast	113 (13.3)	79 (12.3)	34 (16.7)
	Northern Sacramento Valley	88 (10.4)	69 (10.7)	19 (9.3)
	San Joaquin Valley	92 (10.9)	65 (10.1)	27 (13.2)
	Northwestern California	96 (11.3)	68 (10.6)	28 (13.7)
	Sierras Region	95 (11.2)	75 (11.7)	20 (9.8)
Vaccination status[4]				
	Unvaccinated	591 (72.0)	502 (79.1)	89 (47.8)
	Partially vaccinated	72 (8.8)	49 (7.7)	23 (12.4)
	Fully vaccinated	158 (19.2)	84 (13.2)	74 (39.8)
County reopening tier[5]				
	Purple tier (most restrictive)	201 (23.7)	160 (24.9)	41 (20.1)
	Red tier	203 (24.0)	163 (25.3)	40 (19.6)
	Orange tier	200 (23.6)	165 (25.7)	35 (17.2)
	Yellow tier (least restrictive)	23 (2.7)	17 (2.6)	6 (2.9)
	After June 15th	220 (26.0)	138 (21.5)	82 (40.2)
Symptoms experienced				
	No symptoms			
	At least one symptom	336 (39.7)	178 (27.7)	158 (77.5)

Recent high-risk exposure is defined as reported contact with an individual known or suspected to have been infected with SARS-CoV-2 at any time within the 14 days before participants were tested.
[1]Cases reporting high-risk exposure represent 50% of 1280 cases who enrolled in and successfully completed the study.
[2]Controls reporting high-risk exposure represent 16% of 1263 controls who enrolled in and successfully completed the study.
[3]We list counties grouped into each region in **Table S1**.
[4]We defined participants as fully vaccinated at the time of their test if ≥14 days had passed following receipt of a second dose of BNT162b2 or mRNA-1273 (72 cases, 67 controls) or a single dose of JNJ-78436735 (12 cases, 7 controls). Participants who had received at least one dose of any COVID-19 vaccine, but did not meet these criteria for fully-vaccinated status, were considered partially vaccinated (46 cases and N=20 controls who received BNT162b2 or mRNA-1273; 3 cases and 3 controls who received JNJ-78436735). Participants who had not received any COVID-19 vaccine doses were considered unvaccinated.
[5]The State of California implemented a tiered system of reopening to reduce risk of SARS-CoV-2 transmission in community settings. On June 15, 2021, California discontinued the tiered system, relaxed facial masking requirements in certain indoor settings, and allowed businesses to reopen without physical distancing restrictions.

Table 2a. Attributes of contact reporting high-risk exposure with differing characteristics of contact

	Relationship to contact		Exposure setting	
	Non- household member	Household member	Outdoor exposure only	Any indoor exposure
	n (%)	*n* (%)	*n* (%)	*n* (%)
	N=460	*N*=385	*N*=79	*N*=743
Age				
0-6 years	9 (2.0)	21 (5.5)	1 (1.3)	28 (3.8)
7-12 years	20 (4.3)	28 (7.3)	3 (3.8)	43 (5.8)
13-17 years	23 (5.0)	30 (7.8)	6 (7.6)	44 (5.9)
18-29 years	164 (35.7)	104 (27.0)	25 (31.6)	235 (31.6)
30-49 years	161 (35.0)	130 (33.8)	30 (38.0)	254 (34.2)
50-64 years	60 (13.0)	50 (13.0)	8 (10.1)	100 (13.5)
≥65 years	23 (5.0)	22 (5.7)	6 (7.6)	39 (5.2)
Sex				
Male	215 (46.7)	173 (44.9)	40 (50.6)	333 (44.8)
Female	245 (53.3)	212 (55.1)	39 (49.4)	410 (55.2)
Household Income				
Under $50,000	118 (25.7)	87 (22.6)	18 (22.8)	183 (24.6)
$50,000 to $100,000	105 (22.8)	96 (24.9)	16 (20.3)	178 (24.0)
$100,000 to $150,000	64 (13.9)	35 (9.1)	8 (10.1)	90 (12.1)
Over $150,000	52 (11.3)	51 (13.2)	6 (7.6)	95 (12.8)
Refuse	75 (16.3)	71 (18.4)	18 (22.8)	123 (16.6)
Not sure	46 (10.0)	45 (11.7)	13 (16.5)	74 (10.0)
Race/ ethnicity				
Non-Hispanic White	199 (43.3)	158 (41.0)	25 (31.6)	319 (42.9)
Non-Hispanic Black	22 (4.8)	16 (4.2)	2 (2.5)	36 (4.8)
Hispanic (any race)	110 (23.9)	119 (30.9)	32 (40.5)	191 (25.7)
Asian	34 (7.4)	33 (8.6)	3 (3.8)	63 (8.5)
Native American	10 (2.2)	7 (1.8)	0 (0.0)	17 (2.3)
Native Hawaiian	4 (0.9)	1 (0.3)	1 (1.3)	4 (0.5)
More than 1 race	57 (12.4)	41 (10.6)	9 (11.4)	88 (11.8)
Refuse	24 (5.2)	10 (2.6)	7 (8.9)	25 (3.4)
Region				
Predominantly urban regions				
San Francisco Bay Area	36 (7.8)	51 (13.2)	8 (10.1)	78 (10.5)
Greater Los Angeles Area	44 (9.6)	43 (11.2)	12 (15.2)	74 (10.0)
Greater Sacramento Area	52 (11.3)	55 (14.3)	13 (16.5)	90 (12.1)
San Diego and southern border	52 (11.3)	28 (7.3)	8 (10.1)	70 (9.4)
Predominantly rural regions				
Central Coast	65 (14.1)	48 (12.5)	10 (12.7)	102 (13.7)
Northern Sacramento Valley	45 (9.8)	43 (11.2)	9 (11.4)	77 (10.4)
San Joaquin Valley	48 (10.4)	44 (11.4)	4 (5.1)	85 (11.4)
Northwestern California	61 (13.3)	35 (9.1)	8 (10.1)	83 (11.2)
Sierras Region	57 (12.4)	38 (9.9)	7 (8.9)	84 (11.3)
Vaccination status[1]				
Unvaccinated	295 (67.0)	294 (77.6)	51 (67.1)	528 (73.1)
Partially vaccinated	40 (9.1)	32 (8.4)	8 (10.5)	61 (8.4)
Fully vaccinated	105 (23.9)	53 (14.0)	17 (22.4)	133 (18.4)
Reopening Tier				
Purple tier (most restrictive)	102 (22.2)	98 (25.5)	23 (29.1)	174 (23.4)
Red tier	113 (24.6)	89 (23.1)	19 (24.1)	180 (24.2)
Orange tier	97 (21.1)	103 (26.8)	13 (16.5)	183 (24.6)
Yellow tier (least restrictive)	13 (2.8)	10 (2.6)	1 (1.3)	22 (3.0)
After June 15	135 (29.3)	85 (22.1)	23 (29.1)	184 (24.8)
Symptoms				
No symptoms	193 (42.0)	143 (37.1)	40 (50.6)	283 (38.1)
At least one symptom	267 (58.0)	242 (62.9)	39 (49.4)	460 (61.9)

[1]An individual was considered partially-vaccinated if their SARS-CoV-2 test date with less than 14 days before their second dose of a mRNA vaccine product (Pfizer/BioNTech [BNT-162b2] or Moderna [mRNA-1273]), or less than 14 days after

Table 2b. Attributes of contact reporting high-risk exposure with differing characteristics of contact, continued

	Duration		Nature of contact	
	<3 hours	≥3 hours	<3 hours	≥3 hours
	n (%)	*n* (%)	*n* (%)	*n* (%)
	N=215	*N*=613	*N*=215	*N*=613
Age				
0-6 years	3 (1.4)	27 (4.4)	3 (1.4)	27 (4.4)
7-12 years	6 (2.8)	42 (6.9)	6 (2.8)	42 (6.9)
13-17 years	4 (1.9)	45 (7.3)	4 (1.9)	45 (7.3)
18-29 years	72 (33.5)	188 (30.7)	72 (33.5)	188 (30.7)
30-49 years	83 (38.6)	204 (33.3)	83 (38.6)	204 (33.3)
50-64 years	34 (15.8)	75 (12.2)	34 (15.8)	75 (12.2)
≥65 years	13 (6.0)	32 (5.2)	13 (6.0)	32 (5.2)
Sex				
Male	102 (47.4)	280 (45.7)	102 (47.4)	280 (45.7)
Female	113 (52.6)	333 (54.3)	113 (52.6)	333 (54.3)
Household Income				
Under $50,000	53 (24.7)	149 (24.3)	53 (24.7)	149 (24.3)
$50,000 to $100,000	49 (22.8)	145 (23.7)	49 (22.8)	145 (23.7)
$100,000 to $150,000	30 (14.0)	69 (11.3)	30 (14.0)	69 (11.3)
Over $150,000	19 (8.8)	83 (13.5)	19 (8.8)	83 (13.5)
Refuse	39 (18.1)	106 (17.3)	39 (18.1)	106 (17.3)
Not sure	25 (11.6)	61 (10.0)	25 (11.6)	61 (10.0)
Race/ ethnicity				
Non-Hispanic White	85 (39.5)	262 (42.7)	85 (39.5)	262 (42.7)
Non-Hispanic Black	7 (3.3)	30 (4.9)	7 (3.3)	30 (4.9)
Hispanic (any race)	59 (27.4)	166 (27.1)	59 (27.4)	166 (27.1)
Asian	18 (8.4)	49 (8.0)	18 (8.4)	49 (8.0)
Native American	4 (1.9)	13 (2.1)	4 (1.9)	13 (2.1)
Native Hawaiian	2 (0.9)	3 (0.5)	2 (0.9)	3 (0.5)
More than 1 race	31 (14.4)	67 (10.9)	31 (14.4)	67 (10.9)
Refuse	9 (4.2)	23 (3.8)	9 (4.2)	23 (3.8)
Region				
Predominantly urban regions				
San Francisco Bay Area	15 (7.0)	72 (11.7)	15 (7.0)	72 (11.7)
Greater Los Angeles Area	18 (8.4)	70 (11.4)	18 (8.4)	70 (11.4)
Greater Sacramento Area	29 (13.5)	72 (11.7)	29 (13.5)	72 (11.7)
San Diego and southern border	22 (10.2)	56 (9.1)	22 (10.2)	56 (9.1)
Predominantly rural regions				
Central Coast	24 (11.2)	87 (14.2)	24 (11.2)	87 (14.2)
Northern Sacramento Valley	26 (12.1)	60 (9.8)	26 (12.1)	60 (9.8)
San Joaquin Valley	29 (13.5)	62 (10.1)	29 (13.5)	62 (10.1)
Northwestern California	31 (14.4)	61 (10.0)	31 (14.4)	61 (10.0)
Sierras Region	21 (9.8)	73 (11.9)	21 (9.8)	73 (11.9)
Vaccination status[1]				
Unvaccinated	125 (60.1)	453 (76.0)	125 (60.1)	453 (76.0)
Partially vaccinated	34 (16.3)	37 (6.2)	34 (16.3)	37 (6.2)
Fully vaccinated	49 (23.6)	106 (17.8)	49 (23.6)	106 (17.8)
Reopening Tier				
Purple tier (most restrictive)	59 (27.4)	140 (22.8)	59 (27.4)	140 (22.8)
Red tier	56 (26.0)	142 (23.2)	56 (26.0)	142 (23.2)
Orange tier	43 (20.0)	154 (25.1)	43 (20.0)	154 (25.1)
Yellow tier (least restrictive)	6 (2.8)	17 (2.8)	6 (2.8)	17 (2.8)
After June 15	51 (23.7)	160 (26.1)	51 (23.7)	160 (26.1)
Symptoms				
No symptoms	105 (48.8)	220 (35.9)	105 (48.8)	220 (35.9)
At least one symptom	110 (51.2)	393 (64.1)	110 (51.2)	393 (64.1)

[1]An individual was considered partially-vaccinated if their SARS-CoV-2 test date with less than 14 days before their second dose of a mRNA vaccine product (Pfizer/BioNTech [BNT-162b2] or Moderna [mRNA-1273]), or less than 14 days after

Table 3. Distribution of exposures among respondents reporting differing types of recent contact with an individual known or suspected to have SARS-CoV-2 infection.

	Mask usage		Vaccination[1]		
	No masks worn	Mask used by participant or contact	Unvaccinated	Partially vaccinated	Fully vaccinated
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
	N=694	*N*=151	*N*=591	*N*=72	*N*=158
Age					
0-6 years	28 (4.0)	2 (1.3)	30 (5.1)	0 (0.0)	0 (0.0)
7-12 years	37 (5.3)	11 (7.3)	48 (8.1)	0 (0.0)	0 (0.0)
13-17 years	42 (6.1)	10 (6.6)	45 (7.6)	1 (1.4)	5 (3.2)
18-29 years	228 (32.9)	41 (27.2)	189 (32.0)	32 (44.4)	38 (24.1)
30-49 years	236 (34.0)	54 (35.8)	190 (32.1)	19 (26.4)	72 (45.6)
50-64 years	86 (12.4)	25 (16.6)	67 (11.3)	12 (16.7)	29 (18.4)
≥65 years	37 (5.3)	8 (5.3)	22 (3.7)	8 (11.1)	14 (8.9)
Sex					
Male	309 (44.5)	78 (51.7)	283 (47.9)	36 (50.0)	59 (37.3)
Female	385 (55.5)	73 (48.3)	308 (52.1)	36 (50.0)	99 (62.7)
Household income					
Under $50,000	170 (24.5)	36 (23.8)	156 (26.4)	15 (20.8)	31 (19.6)
$50,000 to $100,000	169 (24.4)	32 (21.2)	147 (24.9)	12 (16.7)	34 (21.5)
$100,000 to $150,000	79 (11.4)	20 (13.2)	51 (8.6)	11 (15.3)	32 (20.3)
Over $150,000	93 (13.4)	10 (6.6)	61 (10.3)	7 (9.7)	33 (20.9)
Refuse	116 (16.7)	28 (18.5)	110 (18.6)	16 (22.2)	18 (11.4)
Not sure	67 (9.7)	25 (16.6)	66 (11.2)	11 (15.3)	10 (6.3)
Race/ ethnicity					
Non-Hispanic White	316 (45.5)	41 (27.2)	233 (39.4)	33 (45.8)	81 (51.3)
Non-Hispanic Black	31 (4.5)	7 (4.6)	31 (5.2)	1 (1.4)	5 (3.2)
Hispanic (any race)	174 (25.1)	55 (36.4)	166 (28.1)	23 (31.9)	35 (22.2)
Asian	48 (6.9)	19 (12.6)	42 (7.1)	6 (8.3)	17 (10.8)
Native American	17 (2.4)	0 (0.0)	15 (2.5)	0 (0.0)	2 (1.3)
Native Hawaiian	2 (0.3)	3 (2.0)	5 (0.8)	0 (0.0)	0 (0.0)
More than 1 race	80 (11.5)	19 (12.6)	73 (12.4)	8 (11.1)	13 (8.2)
Refuse	26 (3.7)	7 (4.6)	26 (4.4)	1 (1.4)	5 (3.2)
Region					
Predominantly urban regions					
San Francisco Bay Area	72 (10.4)	15 (9.9)	63 (10.7)	6 (8.3)	14 (8.9)
Greater Los Angeles Area	77 (11.1)	12 (7.9)	65 (11.0)	5 (6.9)	18 (11.4)
Greater Sacramento Area	77 (11.1)	30 (19.9)	78 (13.2)	10 (13.9)	15 (9.5)
San Diego and southern Border	67 (9.7)	13 (8.6)	55 (9.3)	8 (11.1)	15 (9.5)
Predominantly rural regions					
Central Coast	93 (13.4)	20 (13.2)	74 (12.5)	10 (13.9)	25 (15.8)
Northern Sacramento Valley	79 (11.4)	8 (5.3)	60 (10.2)	4 (5.6)	22 (13.9)
San Joaquin Valley	73 (10.5)	19 (12.6)	60 (10.2)	14 (19.4)	15 (9.5)
Northwestern California	81 (11.7)	15 (9.9)	67 (11.3)	5 (6.9)	20 (12.7)
Sierras Region	75 (10.8)	19 (12.6)	69 (11.7)	10 (13.9)	14 (8.9)
Reopening Tier					
Purple tier (most restrictive)	154 (22.2)	47 (31.1)	182 (30.8)	15 (20.8)	3 (1.9)
Red tier	164 (23.6)	38 (25.2)	145 (24.5)	31 (43.1)	25 (15.8)
Orange tier	177 (25.5)	22 (14.6)	150 (25.4)	16 (22.2)	28 (17.7)
Yellow tier (least restrictive)	22 (3.2)	1 (0.7)	14 (2.4)	2 (2.8)	5 (3.2)
After June 15th	177 (25.5)	43 (28.5)	100 (16.9)	8 (11.1)	97 (61.4)
Vaccination status[1]					
Unvaccinated	497 (73.5)	92 (64.3)	--	--	--
Partially vaccinated	54 (8.0)	18 (12.6)	--	--	--
Fully vaccinated	125 (18.5)	33 (23.1)	--	--	--
Symptoms					
No symptoms	260 (37.5)	75 (49.7)	204 (34.5)	37 (51.4)	79 (50.0)
Symptoms	434 (62.5)	76 (50.3)	387 (65.5)	35 (48.6)	79 (50.0)

Table 4: Comparison of infection severity among cases who reported high-risk exposures with and without mask usage.

	A. Symptoms experienced		
	No symptoms *n* (%) *N*=178	**Symptoms** *n* (%) *N*=465	**aOR (95% CI)**
Mask usage at interaction			
No mask usage at interaction	160 (90.0)	396 (85.2)	– –
Mask usage by either party	17 (9.6)	68 (14.6)	2.11 (1.01, 4.30)
Mask usage by participant and contact			
Mask usage by both parties	10 (5.6)	35 (7.5)	2.13 (0.83, 5.51)
Mask usage by participant only	3 (1.7)	20 (4.3)	1.73 (0.48, 6.30)
Mask usage by contact only	4 (2.3)	13 (2.8)	2.13 (0.83, 5.51)

	B. Level of care sought		
	No care *n* (%) *N*=499	**Care** *n* (%) *N*=144	**aOR (95% CI)**
Mask usage at interaction	428 (85.8)	128 (88.9)	– –
No mask usage at interaction	69 (13.8)	16 (11.1)	0.74 (0.36, 1.55)
Mask usage by either party			
Mask usage by participant and contact	37 (7.4)	8 (5.6)	0.95 (0.38, 2.42)
Mask usage by both parties	18 (3.6)	5 (3.5)	0.80 (0.22, 2.90)
Mask usage by participant only	14 (2.8)	3 (21)	0.36 (0.07, 1.78)

aOR: adjusted odds ratio, computed using logistic regression models restricted to cases who reported high-risk contact. We additionally adjusted adjusting for vaccination status of respondent, community exposures (listed in main text), characteristics of the high-risk exposure (as listed in **Figure 1**), and participants' age, sex, and region of residence. The aOR represents the adjusted odds ratio for experiencing symptoms or healthcare seeking according to mask usage during the high-risk exposure. We present the mean number of symptoms experienced among cases stratified by mask usage in **Table S7** during the high-risk exposure. **Table S8** and **Table S9** present the presence of symptoms and mean number of symptoms, respectively, according to other attributes of the high-risk exposure. Due to occasional missing data on mask usage, the denominators differ for the following counts: number of cases reporting no symptoms (*N*=178), number of cases reporting symptomatic infections (*N*=465), number of cases reporting no care was sought (*N*=499)

2.7 SUPPLEMENTAL MATERIAL

Table S1: Counties included in each 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

Table S2: Demographic attributes of study population, stratified by high-risk contact.

		Total	No High-risk contact		High-risk contact	
			Case	Control	Case	Control
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
		N=2541	*N*=617	*N*=1046	*N*=643	*N*=204
Age						
	0-6	70 (2.8)	6 (1.0)	34 (3.3)	28 (4.4)	2 (1.0)
	7-12	102 (4.0)	14 (2.3)	40 (3.8)	37 (5.8)	11 (5.4)
	13-17	128 (5.0)	21 (3.4)	50 (4.8)	41 (6.4)	12 (5.9)
	18-29	817 (32.2)	200 (32.4)	342 (32.7)	206 (32.0)	63 (30.9)
	30-49	887 (34.9)	231 (37.4)	353 (33.7)	202 (31.4)	89 (43.6)
	50-64	386 (15.2)	106 (17.2)	162 (15.5)	91 (14.2)	20 (9.8)
	65+	151 (5.9)	39 (6.3)	65 (6.2)	38 (5.9)	7 (3.4)
Sex						
	Male	1232 (48.5)	312 (50.6)	516 (49.3)	295 (45.9)	93 (45.6)
	Female	1309 (51.5)	305 (49.4)	530 (50.7)	348 (54.1)	111 (54.4)
Household income						
	Under $50,000	622 (24.5)	179 (29.0)	226 (21.6)	159 (24.7)	47 (23.0)
	$50,000 to $100,000	563 (22.2)	134 (21.7)	219 (20.9)	160 (24.9)	41 (20.1)
	$100,000 to $150,000	304 (12.0)	50 (8.1)	152 (14.5)	63 (9.8)	36 (17.6)
	Over $150,000	345 (13.6)	72 (11.7)	167 (16.0)	73 (11.4)	30 (14.7)
	Refuse	434 (17.1)	113 (18.3)	171 (16.3)	114 (17.7)	32 (15.7)
	Not sure	273 (10.7)	69 (11.2)	111 (10.6)	74 (11.5)	18 (8.8)
Race/ ethnicity						
	Non-Hispanic White	1061 (43.1)	249 (41.4)	440 (43.2)	272 (44.2)	85 (43.1)
	Non-Hispanic Black	118 (4.8)	44 (7.3)	35 (3.4)	32 (5.2)	6 (3.0)
	Hispanic (any race)	746 (30.3)	210 (34.9)	298 (29.3)	176 (28.6)	54 (27.4)
	Asian	237 (9.6)	51 (8.5)	116 (11.4)	51 (8.3)	16 (8.1)
	Native American	30 (1.2)	6 (1.0)	6 (0.6)	15 (2.4)	2 (1.0)
	Native Hawaiian	17 (0.7)	2 (0.3)	10 (1.0)	5 (0.8)	0 (0.0)
	More than 1 race	252 (10.2)	39 (6.5)	113 (11.1)	65 (10.6)	34 (17.3)
Region of residence[1]						
	Predominantly urban regions					
	San Francisco Bay Area	296 (11.6)	75 (12.2)	131 (12.5)	73 (11.4)	14 (6.9)
	Greater Los Angeles Area	283 (11.1)	76 (12.3)	118 (11.3)	70 (10.9)	19 (9.3)
	Greater Sacramento Area	285 (11.2)	55 (8.9)	117 (11.2)	82 (12.8)	25 (12.3)
	San Diego and southern Border	277 (10.9)	76 (12.3)	120 (11.5)	62 (9.6)	18 (8.8)
	Predominantly rural regions					
	Central Coast	304 (12.0)	74 (12.0)	113 (10.8)	79 (12.3)	34 (16.7)
	Northern Sacramento Valley	277 (10.9)	66 (10.7)	119 (11.4)	69 (10.7)	19 (9.3)
	San Joaquin Valley	281 (11.1)	73 (11.8)	110 (10.5)	65 (10.1)	27 (13.2)
	Northwestern California	272 (10.7)	68 (11.0)	106 (10.1)	68 (10.6)	28 (13.7)
	Sierras Region	266 (10.5)	54 (8.8)	112 (10.7)	75 (11.7)	20 (9.8)
Vaccination status[2]						
	Unvaccinated	1617 (66.7)	483 (80.2)	521 (53.7)	502 (79.1)	89 (47.8)
	Partially vaccinated	257 (10.6)	43 (7.1)	139 (14.3)	49 (7.7)	23 (12.4)
	Fully vaccinated	550 (22.7)	76 (12.6)	310 (32.0)	84 (13.2)	74 (39.8)
County reopening tier[3]						
	Purple tier (most restrictive)	599 (23.6)	141 (22.9)	245 (23.4)	160 (24.9)	41 (20.1)
	Red tier	649 (25.5)	164 (26.6)	270 (25.8)	163 (25.3)	40 (19.6)
	Orange tier	625 (24.6)	136 (22.0)	285 (27.2)	165 (25.7)	35 (17.2)
	Yellow tier (least restrictive)	75 (3.0)	20 (3.2)	32 (3.1)	17 (2.6)	6 (2.9)
	After June 15th	593 (23.3)	156 (25.3)	214 (20.5)	138 (21.5)	82 (40.2)
Symptoms experienced						
	No symptoms	1330 (52.3)	111 (18.0)	869 (83.1)	178 (27.7)	158 (77.5)
	At least one symptom	1211 (47.7)	506 (82.0)	177 (16.9)	465 (72.3)	46 (22.5)

Recent high-risk exposure is defined as reported contact with an individual known or suspected to have been infected with SARS-CoV-2 at any time within the 14 days before participants were tested.
[1]We list counties grouped into each region in **Table S1**.
[2]An individual was considered partially-vaccinated if their SARS-CoV-2 test date with less than 14 days before their second dose of a mRNA vaccine product (Pfizer/BioNTech [BNT-162b2] or Moderna [mRNA-1273]), or less than 14 days after their first dose of a single dose vaccine product (Jansen Pharmaceutical Companies [JNJ-78436735]). An individual was considered fully-vaccinated if their SARS-CoV-2 test date was more than 14 days after their second dose of a mRNA vaccine product (Pfizer/BioNTech [BNT-

162b2] or Moderna [mRNA-1273]), or more than 14 days after their first dose of a single dose product (Jansen Pharmaceutical Companies [JNJ-78436735])
[3]The State of California implemented a tiered system of reopening to reduce risk of SARS-CoV-2 transmission in community settings. On June 15, 2021, California discontinued the tiered system, relaxed facial requirements in certain indoor settings, and allowed businesses to reopen without physical distancing restrictions.

Table S3: Location(s) of confirmed or suspected contact among interviewed participants.

Location of contact	Total participants	Confirmed contact	Suspected contact
	n (%)	*n* (%)	*n* (%)
	N=847	*N*=694	*N*=153
Residence[a]	456 (53.8)	383 (55.2)	73 (47.7)
Same household	332 (72.8)	282 (73.6)	50 (68.5)
Outside of the household	80 (17.5)	64 (16.7)	16 (21.9)
Visits to multiple households	38 (8.3)	32 (8.4)	6 (8.2)
Unknown but related to a residence	6 (1.3)	5 (1.3)	1 (1.4)
Workplace	115 (13.6)	88 (12.7)	27 (17.6)
Public space or event[b]	96 (11.3)	78 (11.2)	18 (11.8)
In a vehicle, including public transportation	14 (1.7)	12 (1.7)	2 (1.3)
Multiple location types[c]	112 (13.2)	94 (13.5)	18 (11.8)
Unknown[d]	54 (6.4)	39 (5.6)	15 (9.8)

[a] Includes individuals who reported having contact with known or suspected case(s) from the same household, outside of the household, and during visits to multiple households (e.g., participant had contact with known cases from two separate residences)
[b] Excludes individuals who reported working at a public space (e.g., bar, restaurant, hospital) at the time of contact
[c] Includes individuals who reported having contact at any combination of the above location types (e.g., participant had contact with suspected cases at their workplace and at a relative's residence)
[d] Includes individuals who declined to answer or did not report a specific location

Table S4: Reasons for testing among participants who reported high-risk interactions.

Reasons*	Controls		Cases	
	Unvaccinated *N*=89	Vaccinated[1] *N*=97	Unvaccinated *N*=502	Vaccinated *N*=133
Contact with positive case	52 (58.4)	64 (66.0)	355 (70.7)	97 (72.9)
Contact with symptomatic individual, unknown whether confirmed positive	11 (12.4)	11 (11.3)	39 (7.8)	7 (5.3)
Told by public health worker to get tested	0 (0.0)	4 (4.1)	5 (1.0)	2 (1.5)
Routine screening	22 (24.7)	12 (12.4)	14 (2.8)	6 (4.5)
Test required for medical procedure or hospital admittance	2 (2.2)	0 (0.0)	5 (1.0)	0 (0.0)
Someone in household had contact with a positive case	2 (2.2)	2 (2.1)	27 (5.4)	6 (4.5)
I just wanted to see if I was infected	8 (9.0)	6 (6.2)	18 (3.6)	4 (3.0)
Concerned about symptoms	10 (11.2)	9 (9.3)	193 (38.4)	62 (46.6)
Pre or post-travel screening	1 (1.1)	6 (6.2)	4 (0.8)	4 (3.0)

*Since interviewers indicated all reasons listed by participants, and some participants refused to respond to the question, reasons will not sum to the total sample size.

[1]An individual is considered vaccinated if they have had at least one dose of any SARS-CoV-2 vaccine product.

Table S5: Regression parameter estimates.

Covariate	aOR (95% CI)
Restaurant	0.79 (0.37, 1.71)
Bar/ brewery/ winery	0.79 (0.37, 1.71)
Coffee shop	0.92 (0.55, 1.60)
Retail shop	0.87 (0.53, 1.44)
Gym	0.89 (0.44, 1.82)
Ride share service	0.97 (0.48, 2.03)
Public transport	1.06 (0.32, 3.46)
Salon	0.64 (0.33, 1.26)
Worship service	2.68 (0.76, 9.19)
Social gathering	1.15 (0.73, 1.82)

aOR: adjusted odds ratio, computed using conditional logistic regression models adjusting for vaccination status, community exposures (listed in the main text), vaccination status of the participant and mask-wearing by the participant and their contact (as listed in **Figure 2**), and participants' age, sex, and region of residence. Regression strata were defined for county reopening tiers and week of SARS-CoV-2 test.

Table S6: Predictors of infection following high-risk exposure among participants with confirmed SARS-CoV-2 contact.

Exposure and participant vaccination status			**Case** *n* (%)	**Control** *n* (%)	**aOR (95%CI)**
Relationship to contact					
	Fully vaccinated				
		Non-household member (ref.)	38 (7.1)	10 (7.1)	– –
		Household member	30 (5.6)	47 (33.3)	1.98 (0.72, 5.56)
	Unvaccinated				
		Non-household member (ref.)	199 (37.3)	16 (11.3)	– –
		Household member	266 (49.9)	68 (48.2)	3.41 (1.68, 6.87)
Nature of contact					
	Fully vaccinated				
		Non-physical contact only (ref.)	23 (4.5)	23 (17.2)	– –
		Any physical contact	42 (8.1)	30 (22.4)	0.60 (0.24, 1.52)
	Unvaccinated				
		Non-physical contact only (ref.)	149 (28.9)	48 (35.8)	– –
		Any physical contact	302 (58.5)	33 (24.6)	1.5 (0.79, 2.85)
Setting					
	Fully vaccinated				
		No indoor exposure (ref.)	7 (1.3)	6 (4.4)	– –
		Any indoor exposure	60 (11.5)	48 (35.6)	0.50 (0.12, 2.09)
	Unvaccinated				
		No indoor exposure (ref.)	25 (4.8)	19 (14.1)	– –
		Any indoor exposure	428 (82.3)	62 (45.9)	2.21 (0.96, 5.06)
Duration					
	Fully vaccinated				
		<3 hours (ref.)	14 (2.7)	23 (16.9)	– –
		≥3 hours	54 (10.2)	32 (23.5)	1.41 (0.54, 3.66)
	Unvaccinated				
		<3 hours (ref.)	77 (14.6)	46 (33.8)	– –
		≥3 hours	382 (72.5)	35 (25.7)	4.21 (2.18, 8.14)

aOR: adjusted odds ratio, computed using conditional logistic regression models restricted to 694 individuals (539 cases/ 155 controls) who reported they had confirmed recent contact with an individual infected with SARS-CoV-2. Models interacted vaccination status with each contact attribute, and additionally adjusted for community exposures (listed in the main text), characteristics of high-risk contact (as listed in **Figure 1**), and participants' age, sex, and region of residence. Regression strata were defined for county reopening tiers and, for the period after June 15th, the month of SARS-CoV-2 test.

Due to occasional missing data, the denominators differ for the following counts: relationship to contact among cases and controls (*N*=533, *N*=141), nature of contact among cases and controls (*N*=516, *N*=134), settings among cases and controls (*N*=520, *N*=135), duration among cases and controls (*N*=527, *N*=136)

Table S7: Protective effects of mask-wearing and vaccination in the context of high-risk exposure among participants with confirmed SARS-CoV-2 contact.

Exposure and participant vaccinations status	Case *n* (%) *N*=539	Control *n* (%) *N*=155	aOR (95% CI)
Mask usage at interaction			
No mask usage at interaction	473 (87.9)	103 (66.5)	ref.
Mask usage by either party	65 (12.1)	52 (33.5)	0.48 (0.24, 0.95)
Mask usage by participant and contact			
Mask usage by both parties	473 (87.9)	103 (66.5)	0.63 (0.28, 1.47)
Mask usage by participant only	65 (12.1)	52 (33.5)	0.13 (0.03, 0.63)
Mask usage by contact only	473 (87.9)	103 (66.5)	0.47 (0.15, 1.48)
Vaccination status of respondent			
No vaccine doses	424 (79.4)	66 (46.8)	ref.
Incomplete vaccination series	42 (7.9)	18 (12.8)	0.38 (0.15, 0.92)
Full vaccination series[1]	68 (12.7)	57 (40.4)	0.20 (0.09, 0.41)

aOR: adjusted odds ratio, computed using conditional logistic regression models restricted to 694 individuals (539 cases/ 155 controls) who reported they had confirmed recent contact with an individual infected with SARS-CoV-2 Models additionally adjusted for vaccination status, community exposures (listed in the main text), characteristics of high-risk contact (as listed in **Figure 1**), and participants' age, sex, and region of residence. Regression strata were defined for county reopening tiers and week of SARS-CoV-2 test.

Due to occasional missing data, the denominators differ for the following counts: mask usage at interaction among cases (*N*=538), vaccination status among cases and controls (*N*=534, *N*=141).

Table S8: Number of reported symptoms among cases by level of mask usage during high-risk exposures.

Mask usage	Mean number of reported symptoms (SD)
Mask usage at interaction	
No mask usage at interaction	2.44 (2.05)
Mask usage by either party	2.26 (2.21)
Mask usage by participant and contact	
Mask usage by both parties	2.58 (2.41)
Mask usage by participant only	2.61 (1.64)
Mask usage by contact only	1.82 (1.38)

Among cases who reported a high-risk interaction, we computed the mean number of reported symptoms within strata of reported mask usage by the participant and their contact during the interaction

Table S9: Presence of reported symptoms by attributes of high-risk contact among cases.

Contact Attribute	Symptoms *n* (%) *N*=465	No reported symptoms *n* (%) *N*=178
Relationship to contact		
Non-household member (ref.)	231 (49.7)	68 (38.2)
Household member	232 (49.9)	110 (61.8)
Nature of contact		
Non-physical contact only (ref.)	161 (34.62)	61 (34.3)
Any physical contact	289 (62.2)	109 (61.2)
Setting		
No indoor exposure (ref.)	33 (7.1)	11 (6.2)
Any indoor exposure	423 (91.0)	161 (90.5)
Duration		
<3 hours (ref.)	96 (20.7)	32 (18.0)
≥3 hours	362 (77.9)	143 (80.3)

Among cases who reported a high-risk interaction, we tabulated whether any symptoms were present at the time for SARS-CoV-2 testing within strata of attributes of contact reported by the participant.

Table S10: Number of reported symptoms among cases by attributes of the high-risk contact.

Contact Attribute	Mean number of reported symptoms (SD)
Relationship to contact	
Non-household member (ref.)	2.59 (2.22)
Household member	2.01 (2.14)
Nature of contact	
Non-physical contact only (ref.)	2.24 (2.24)
Any physical contact	2.33 (2.19)
Setting	
No indoor exposure (ref.)	2.41 (2.20)
Any indoor exposure	2.29 (2.20)
Duration	
<3 hours (ref.)	2.51 (2.49)
≥3 hours	2.23 (2.12)

Among cases who reported a high-risk interaction, we calculated the mean number of symptoms at the time of SARS-CoV-2 testing within strata of attributes of contact reported by the participant.

Chapter 3

Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for the Prevention of SARS-CoV-2 Infection

3.1 ABSTRACT

Background: The use of face masks or respirators (N95/KN95) is recommended to reduce transmission of SARS-CoV-2, the virus that causes COVID-19. Well-fitting face masks and respirators effectively filter virus-sized particles in laboratory conditions, though few studies have assessed their real-world effectiveness in preventing acquisition of SARS-CoV-2 infection.

Methods: A test-negative design case-control study enrolled randomly selected California residents who had received a test result for SARS-CoV-2 during February 18–December 1, 2021. Face mask or respirator use was assessed among 652 case-participants (residents who had received positive test results for SARS-CoV-2) and 1,176 matched control-participants (residents who had received negative test results for SARS-CoV-2) who self-reported being in indoor public settings during the 2 weeks preceding testing and who reported no known contact with anyone with confirmed or suspected SARS-CoV-2 infection during this time.

Results: Always using a face mask or respirator in indoor public settings was associated with lower adjusted odds of a positive test result compared with never wearing a face mask or respirator in these settings (adjusted odds ratio [aOR] = 0.44; 95% CI = 0.24–0.82). Among 534 participants who specified the type of face covering they typically used, wearing N95/KN95 respirators (aOR = 0.17; 95% CI = 0.05–0.64) or surgical masks (aOR = 0.34; 95% CI = 0.13–0.90) was associated with significantly lower adjusted odds of a positive test result compared with not wearing any face mask or respirator.

Conclusion: These findings reinforce that in addition to being up to date with recommended COVID-19 vaccinations, consistently wearing a face mask or respirator in indoor public settings reduces the risk of acquiring SARS-CoV-2 infection. Using a respirator offers the highest level of personal protection against acquiring infection, although it is most important to wear a well-fitting mask or respirator that is comfortable and can be used consistently.

Chapter 3 is included here with permission from my co-authors: Jake Pry, Jennifer Myers, John Openshaw, James Watt, Joseph Lewnard, and Seema Jain

3.2 INTRODUCTION

Wearing face coverings is recommended to reduce transmission and acquisition of SARS-CoV-2 infection [1]. In laboratory settings, well-fitting face masks effectively filter viruses or viral size particles from exhaled or inhaled air [2,3]. However, laboratory studies can only evaluate the efficacy of mask use under circumstances where fit is optimized, and do not measure the efficacy of masks against a clinical outcome. To better understand the impact of face-mask use in real-world settings, ecological studies have assessed the reductions in population-level incidence rates associated with implementation of masking requirements in communities or schools [4]. However, in ecological study designs, it is difficult to disentangle the effect masking requirements from other interventions concurrently implemented (vaccinations, physical distancing) which may confound the effect demonstrated with a population-level outcome. As such, there has been to our knowledge, few studies that have assessed the real-world effectiveness of face mask use in a general population sample using a clinical outcome, SARS-CoV-2 infection.

We sought to estimate the real-world effectiveness of face masks or respirators using self-reported data on face mask use from a sample of Californians' who reported attending indoor, public settings within 14 days of seeking a SARS-CoV-2 test.

3.3 METHODS

This study used a test-negative case-control design, enrolling persons who received a positive (case-participants) or negative (control-participants) SARS-CoV-2 test result, from among all California residents, without age restriction, who received a molecular test result for SARS-CoV-2 during February 18–December 1, 2021 [5]. Potential case-participants were randomly selected from among all persons who received a positive test result during the previous 48 hours and were invited to participate by telephone. For each enrolled case-participant, interviewers enrolled one control-participant matched by age group, sex, and state region; thus, interviewers were not blinded to participants' SARS-CoV-2 infection status. Participants who self-reported having received a previous positive test result (molecular, antigen, or serologic) or clinical diagnosis of COVID-19 were not eligible to participate. During February 18–December 1, 2021, a total of 1,528 case-participants and 1,511 control-participants were enrolled in the study among attempted calls placed to 11,387 case- and 17,051 control-participants (response rates were 13.4% and 8.9%, respectively).

After obtaining informed consent from participants, interviewers administered a telephone questionnaire in English or Spanish. All participants were asked to indicate whether they had been in indoor public settings (e.g., retail stores, restaurants or bars, recreational facilities, public transit, salons, movie theaters, worship services, schools, or museums) in the 14 days preceding testing and whether they wore a face mask or respirator all, most, some, or none of the time in those settings. Interviewers recorded participants' responses regarding COVID-19 vaccination status, sociodemographic characteristics, and history of exposure to anyone known or suspected to have been infected with SARS-CoV-2 in the 14 days before participants were tested. Participants enrolled during September 9–December 1, 2021, (534) were also asked to indicate the type of face covering typically worn (N95/KN95 respirator, surgical mask, or cloth mask) in indoor public settings.

The primary analysis compared self-reported face mask or respirator use in indoor public settings 14 days before SARS-CoV-2 testing between case- (652) and control- (1,176) participants. Secondary analyses accounted for consistency of face mask or respirator use all, most, some, or none of the time. To understand the effects of masking on community transmission, the analysis included the subset of participants who, during the 14 days before they were tested, reported visiting indoor public settings and who reported no known exposure to persons known or suspected to have been infected with SARS-CoV-2. An additional analysis assessed differences in protection against SARS-CoV-2 infection by the type of face covering worn, and was limited to a subset of participants enrolled after September 9, 2021, who were asked to indicate the type of face covering they typically wore; participants who indicated typically wearing multiple different mask types were categorized as wearing either a cloth mask (if they reported cloth mask use) or a surgical mask (if they did not report cloth mask use). Adjusted odds ratios comparing history of mask-wearing among case- and control-participants were calculated using conditional logistic regression. Match strata were defined by participants' week of SARS-CoV-2 testing and by county-level SARS-CoV-2 risk tiers as defined under California's Blueprint for a Safer Economy reopening scheme. Adjusted models accounted for self-reported COVID-19 vaccination status (fully vaccinated with ≥2 doses of BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna] or 1 dose of Ad.26.COV2.S [Janssen (Johnson & Johnson)] vaccine ≥14 days before testing versus zero doses), household income, race/ethnicity, age, sex, state region, and county population density. Statistical significance was defined by two-sided Wald tests with p-values <0.05. All analyses were conducted using R software (version 3.6.1; R Foundation). This activity was approved as public health surveillance by the State of California Health and Human Services Agency Committee for the Protection of Human Subjects.

3.4 RESULTS

A total of 652 case- and 1,176 control-participants were enrolled in the study equally across nine multi-county regions in California (**Table 1**). The majority of participants (43.2%) identified as non-Hispanic White; 28.2% of participants identified as Hispanic (any race). A higher proportion of case-participants (78.4%) was unvaccinated compared with control-participants (57.5%).

Overall, 44 (6.7%) case-participants and 42 (3.6%) control-participants reported never wearing a face mask or respirator in indoor public settings and 393 (60.3%) case-participants and 819 (69.6%) control-participants reported always wearing a face mask or respirator in indoor public settings (**Table 2**).

Any face mask or respirator use in indoor public settings was associated with significantly lower odds of a positive test result compared with never using a face mask or respirator (aOR = 0.51; 95% CI = 0.29–0.93). Always using a face mask or respirator in indoor public settings was associated with lower adjusted odds of a positive test result compared with never wearing a face mask or respirator (aOR = 0.44; 95% CI = 0.24–0.82); however, adjusted odds of a positive test result suggested stepwise reductions in protection among participants who reported wearing a face mask or respirator most of the time (aOR = 0.55; 95% CI = 0.29–1.05) or some of the time (aOR = 0.71; 95% CI = 0.35–1.46) compared with participants who reported never wearing a face mask or respirator.

Wearing an N95/KN95 respirator (aOR = 0.17; 95% CI = 0.05–0.64) or wearing a surgical mask (aOR = 0.34; 95% CI = 0.13–0.90) was associated with lower adjusted odds of a positive test result compared with not wearing a mask (**Table 3**). Wearing a cloth mask (aOR = 0.44; 95% CI = 0.17–1.17) was associated with lower adjusted odds of a positive test compared with never wearing a face covering but was not statistically significant.

3.5 DISCUSSION

During February–December 2021, using a face mask or respirator in indoor public settings was associated with lower odds of SARS-CoV-2 infection, with protection being highest among those who reported wearing a face mask or respirator all of the time. Although consistent use of any face mask or respirator indoors was protective, the adjusted odds of infection were lowest among persons who reported typically wearing an N95/KN95 respirator, followed by wearing a surgical mask. These data from real-world settings reinforce the importance of consistently wearing face masks or respirators to reduce the risk of acquisition of SARS-CoV-2 infection among the general public in indoor community settings.

These findings are consistent with existing research demonstrating that face masks or respirators effectively filter viruses in laboratory settings and with ecological studies showing reductions in SARS-CoV-2 incidence associated with community-level masking requirements [6,7]. In a previous evaluation, wearing face masks or respirators in the context of exposure to a person with confirmed SARS-CoV-2 infection was associated with similar reductions in risk for infection [8]. Strengths of the current study include use of a clinical endpoint of SARS-CoV-2 test result, and applicability to a general population sample.

The findings in this report are subject to at least eight limitations. First, this study did not account for other preventive behaviors that could influence risk for infection, including adherence to physical distancing recommendations. In addition, generalizability of this study is limited to persons seeking SARS-CoV-2 testing and who were willing to participate in a telephone interview, who might otherwise exercise other protective behaviors. Second, this analysis relied on an aggregate estimate of self-reported face mask or respirator use across, for some participants, multiple indoor public locations. However, the study was designed to minimize recall bias by enrolling both case- and control-participants within a 48-hour window of receiving a SARS-CoV-2 test result. Third, small strata limited the ability to differentiate between types of cloth masks or participants who wore different types of faces masks in differing settings, and also resulted in wider CIs and statistical nonsignificance for some estimates that were suggestive of a protective effect. Fourth, estimates do not account for face mask or respirator fit or the correctness of face mask or respirator wearing; assessing the effectiveness of face mask or respirator use under real-world conditions is nonetheless important for developing policy. Fifth, data collection occurred before the expansion of the SARS-CoV-2 B.1.1.529 (Omicron) variant, which is more transmissible than earlier variants. Sixth, face mask or respirator use was self-reported, which could introduce social desirability bias. Seventh, small strata limited the ability to account for reasons for testing in the adjusted analysis, which may be correlated with face mask or respirator use. Finally, this analysis does not account for potential differences in the intensity of exposures, which could vary by duration, ventilation system, and activity in each of the various indoor public settings visited.

These findings of this report reinforce that in addition to being up to date with recommended COVID-19 vaccinations, consistently wearing face masks or respirators while in indoor public settings protects against the acquisition of SARS-CoV-2 infection [9,10]. This highlights the importance of improving access to high-quality masks to ensure access is not a barrier to use. Using a respirator offers the highest level of protection from acquisition of SARS-CoV-2 infection, although it is most important to wear a well-fitting mask or respirator that is comfortable and can be used consistently.

3.6 REFERENCES

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3.7 TABLES

TABLE 1. Characteristics of case- and control-participants included in analysis of the effectiveness of mask-wearing in indoor public settings, by SARS-CoV-2 test result — California,* February–December 2021

	No (%)	
	Case-participants (SARS-CoV-2 Positive)	**Control-participants (SARS-CoV-2 negative)**
Characteristic	N = 652	N = 1,176
Age category (years)		
0–6	8 (1.2)	43 (3.7)
7–12	15 (2.3)	49 (4.2)
13–17	25 (3.8)	57 (4.8)
18–29	210 (32.2)	359 (30.5)
30–49	237 (36.3)	409 (34.8)
50–64	109 (16.7)	180 (15.3)
≥65	48 (7.4)	79 (6.7)
Sex		
Male	321 (49.2)	581 (49.4)
Female	331 (50.8)	595 (50.6)
Annual Household Income		
Under $50,000	191 (29.3)	258 (21.9)
$50,000 to $100,000	147 (22.5)	254 (21.6)
$100,000 to $150,000	60 (9.2)	171 (14.5)
Over $150,000	77 (11.8)	197 (16.8)
Refused	106 (16.3)	184 (15.6)
Not sure	71 (10.9)	112 (9.5)
Region†		
San Francisco Bay Area	79 (12.1)	147 (12.5)
Greater Los Angeles Area	77 (11.8)	130 (11.1)
Greater Sacramento Area	53 (8.1)	131 (11.1)
San Diego and southern border	73 (11.2)	142 (12.1)
Central Coast	87 (13.3)	132 (11.2)
Northern Sacramento Valley	69 (10.6)	134 (11.4)
San Joaquin Valley	79 (12.1)	130 (11.1)
Northwestern California	78 (12.0)	113 (9.6)
Sierras	57 (8.7)	117 (9.9)
Race/Ethnicity		
Non-Hispanic White	288 (44.2)	502 (42.7)
Non-Hispanic Black	39 (6.0)	42 (3.6)
Hispanic (any race)	201 (30.8)	315 (26.8)
Non-Hispanic Asian	56 (8.6)	134 (11.4)
Non-Hispanic American Indian	9 (1.4)	10 (0.9)
Non-Hispanic Native Hawaiian	2 (0.3)	12 (1.0)
Non-Hispanic Middle Eastern	4 (0.6)	4 (0.3)
More than one race	40 (6.1)	131 (11.1)
Refuse	13 (2.0)	26 (2.2)
COVID-19 Vaccination Status§		
Unvaccinated or incompletely vaccinated	511 (78.4)	676 (57.5)
Fully Vaccinated	115 (17.6)	377 (32.1)
Unknown	26 (4.0)	123 (10.5)
Reopening tier of California¶		
Tier 1 (most restrictive)	125 (19.2)	237 (20.2)
Tier 2	152 (23.3)	255 (21.7)
Tier 3	119 (18.3)	272 (23.1)
Tier 4 (least restrictive)	18 (2.8)	32 (2.7)
After June 15, 2021	238 (36.5)	380 (32.3)
Reasons for SARS-CoV-2 testing**		
Experiencing symptoms	508 (77.9)	196 (16.7)
Testing required for medical procedure	40 (6.1)	199 (16.9)
Routine screening through work or school	71 (10.9)	507 (43.1)
Pre-travel test	33 (5.1)	120 (10.2)
Just wanted to see if I was infected	65 (10.0)	172 (14.6)
Test required for admission to an event or gathering	3 (0.5)	21 (1.8)

* A random sample of California residents with a molecular SARS-CoV-2 test result were invited to participate in a phone-based questionnaire to document frequency of face mask or respirator use and type of face mask or respirator typically worn in indoor public settings 2 weeks before testing. For each enrolled case patient (person with a positive SARS-CoV-2 test result), interviewers attempted to enroll one control (person with a negative SARS-CoV-2 test result) matched by age

category, sex, region, and whose test result was posted to the reportable disease registry in the 48 hours preceding the call. Among 1947 case- and control-participants who visited indoor public settings and did not report a known or suspected exposure to SARS-CoV-2 in the 14 days before getting a SARS-CoV-2 test, 6% (119/1,947) of participants were unable to report face mask use and were excluded from analysis. Parents or guardians served as proxy respondents and answered questions throughout the telephone survey on behalf of children aged under 13 years old.

† California counties were divided into nine geographic regions. Counties included in each geographic region are listed in Andrejko KL, Pry J, Myers JF, et al. Predictors of SARS-CoV-2 infection following high-risk exposure. Clin Infect Dis. 2021 Dec 21;ciab1040.

§ Vaccination status was defined using self-reported dates and manufacturers of doses received. Participants were asked to reference their COVID-19 vaccination card while providing vaccination history. Participants who could not provide a complete vaccination history (dates of doses received and manufacturers) were coded as unknown. Fully vaccinated was defined as receipt of 2 doses of BNT-162b2 [Pfizer/BioNTech] or mRNA-1273 [Moderna], or receipt of one dose of Ad26.COV2.S [Janssen] ≥14 days before SARS-CoV-2 testing. Of the 492 participants who were fully-vaccinated, 4.1% (22/492) had received a booster dose at the time of enrollment. All other participants were considered unvaccinated.

¶ Reopening tiers in California were determined by the Blueprint for a Safer Economy the State of California implemented from February 24 to June 15, 2021. This was a tiered system of public health restrictions tied to county level positive test results and incidence. On June 15, 2021, California retired the tiered reopening system and removed most restrictions on public gatherings, while in some counties maintaining guidelines for guests and workers to show proof of vaccination or a negative test result to gather in certain types of venues and workplaces. The tier of a given participant was determined by using the date that occurred 14 days before the SARS-Cov-2 specimen collection date recorded for each participant in the California Reportable Disease Registry.

** Reasons for testing may sum to numbers greater than the total number of case-participants or control-participants because participants could indicate more than one reason for seeking a SARS-CoV-2 test.

TABLE 2. Face mask or respirator use in indoor public settings among persons with positive (case-participants) and negative (control-participants) SARS-CoV-2 test results — California, February–December 2021

	SARS-CoV-2 infection status, No. (%)		Odds Ratio (95% CI)	
Mask type and use*	**Cases N = 652**	**Controls N = 1,176**	**Unadjusted†**	**Adjusted§**
No face mask or respirator (ref.)	44 (6.7)	42 (3.6)	—	—
Any face mask or respirator use†	608 (93.3)	1,134 (96.4)	0.57 (0.37–0.90)	0.51 (0.29–0.93)
– Some of the time	62 (9.5)	76 (6.5)	0.81 (0.47–1.41)	0.71 (0.35–1.46)
– Most of the time	153 (23.5)	239 (20.3)	0.64 (0.40–1.05)	0.55 (0.29–1.05)
– All of the time	393 (60.3)	819 (69.6)	0.49 (0.31–0.78)	0.44 (0.24–0.82)

Abbreviation: ref = referent

*Trained interviewers administered a structured telephone-based questionnaire and asked participants to indicate whether they attended indoor public spaces in the 2 weeks before seeking a SARS-CoV-2 test. Participants who indicated attending these settings were further asked to specify whether they typically wore a face mask or respirator all, most, some, or none of the time while in these settings.

† Conditional logistic regression models were used to estimate the unadjusted odds of mask use by type of face mask or respirator worn in indoor public settings in the 2 weeks before testing. Models included matching strata defined by (for the period before June 15, 2021) the reopening tier of California in the county of residence, and the week of SARS-CoV-2 testing

§ Conditional logistic regression models were used to estimate the odds of face mask or respirator use in indoor public settings in the 2 weeks before testing, adjusting for COVID-19 vaccination status, household income, race/ethnicity, age category, sex, region, and county population density. All models included matching strata defined by (for the period before June 15, 2021) the reopening tier of California in the county of residence, and the week of SARS-CoV-2 testing. To understand effect of masking in community settings, this analysis was restricted to a subset of persons who did not indicate a known or suspected exposure to a SARS-CoV-2 case within 14 days of seeking a SARS-CoV-2 test. Adjusted models used a complete case analysis (454 case-participants and 789 control-participants). A sensitivity analysis using multiple imputation of missing covariate values obtained results similar to those reported in the table: adjusted odds ratios were 0.54 (95% CI = 0.33–0.89) for any mask use, 0.44 (95% CI = 0.27–0.73) for mask use all of the time, 0.62 (95% CI = 0.37–1.04) for mask use most of the time, and 0.77 (95% CI = 0.43–1.40) for mask use some of the time.

TABLE 3. Types of face mask or respirator worn in indoor public settings among persons with positive (case-participants) or negative (control-participants) SARS-CoV-2 test results — California, September–December 2021

Mask type*	SARS-CoV-2 infection status, No. (%)		Odds Ratio (95% CI)			
	Case-participant (SARS-CoV-2 positive) N = 259	Control-participant (SARS-CoV-2 negative) N = 275	Unadjusted[§]	*p* value	Adjusted[†]	*p* value
No face mask or respirator (ref.)	24 (9.3)	11 (4.0)	—		—	
Cloth mask	112 (43.2)	104 (37.8)	0.50 (0.23–1.06)	0.071	0.44 (0.17–1.17)	0.101
Surgical mask	113 (43.6)	139 (50.5)	0.28 (0.18–0.81)	0.012	0.34 (0.13–0.90)	0.029
N95/KN95 respirator	10 (3.9)	21 (7.6)	0.22 (0.08–0.62)	< 0.01	0.17 (0.05–0.64)	< 0.01

Abbreviation: ref = referent

*Among all participants enrolled after September 9, 2021, trained interviewers administered a structured telephone-based questionnaire and asked participants to identify the type of face covering typically worn in indoor public settings in the 2 weeks before seeking a SARS-CoV-2 test. Persons who reported that the type of face covering worn varied by setting were recoded as wearing the least protective type of facial covering (ex. A person who reported wearing a N95/KN95 respirator at work and a cloth mask while grocery shopping was recoded as typically wearing a cloth mask).

§ Conditional logistic regression models were used to estimate the unadjusted odds of mask use by type of face mask or respirator worn in indoor public settings in the 2 weeks before testing. Models included matching strata defined by the week of SARS-CoV-2 testing.

† This analysis was not restricted to individuals with no self-reported known or suspected SARS-CoV-2 contact given that this secondary analysis was underpowered upon exclusion of these participants (N = 316) as adjusted models did not converge. Instead, models adjusted for history of known or suspected contact as a covariate. In a sensitivity analysis restricting to (N = 316) participants who did not report known or suspected contact, conditional logistic regression models were used to estimate that the unadjusted odds ratios of face mask use by type of face mask with matching strata defined by the week of SARS-CoV-2 testing: 0.13 (95% CI= 0.03–0.61), 0.32 (95% CI = 0.12–0.89), 0.36 (95% CI = 0.13–1.00) for N95/KN95 respirators, surgical masks, or cloth masks, respectively, relative to no face mask or respirator use.

Conclusion

From these three chapters, I have demonstrated that: (1) mRNA-based COVID-19 vaccines conferred significant protection against SARS-CoV-2 infection and hospitalization during the period in which Epsilon and Alpha were the dominant circulating variants of concern, yet vaccine hesitancy among rural Californians presents a barrier to achieving herd immunity thresholds, (2) in settings of social contact with an individual known or suspected to have been infected with SARS-CoV-2, unvaccinated individuals are at higher risk of acquiring a SARS-CoV-2 infection when social contact was unmasked, occurred with household members or indoors, or lasted >3 hours in duration and (3), consistent use of high-quality face masks reduces the odds the wearer will acquire SARS-CoV-2 infection. Each of these findings contributes to the growing body of evidence detailing SARS-CoV-2 epidemiology throughout the COVID-19 pandemic.

There are several future research directions which can leverage data that was collected as part of the C4 study. One feature of this work is that it has relied on self-reported vaccination status; however, history COVID-19 vaccination is now additionally recorded in the Californian Immunization Registry (CAIR). Future work can evaluate the accuracy of self-reported vaccination status in comparison to immunization registry to help inform the extent of misclassification of this self-reported variable in future observational studies. Additionally, since the study began prior to the widespread availability of COVID-19 vaccinations, further work could assess predictors of vaccine uptake over time by comparing the willingness to receive a COVID-19 vaccination at the time of the telephone interview to an individual's ultimate decision of whether to vaccinate as recorded in CAIR. This work can additionally be extended to provide estimates of waning protection of two-dose vaccine-induced immunity against symptomatic SARS-CoV-2 infection and understand the risk of bias introduced by depletion-of-suspectable. Lastly, given the interest in relating mask mandates and polices to an individuals' vaccination status, future efforts to stratify the estimates of the protective benefits of masks by vaccination status may advance public health policy.

Conducting an observational study amid a global pandemic was fraught with many challenges but also presented a series of unparalleled, timely opportunities to advance our collective understanding of the effectiveness of various public health interventions throughout the COVID-19 era. What began as a relatively ambitious project to investigate risk factors for SARS-CoV-2 infection in community settings spiraled into a dynamic platform to ask and answer emerging questions relevant to California's public health policies. Use of the test-negative case-control design allowed us to be flexible with our research question and therefore vary our exposure of interest, whilst also retaining robust statistical methods.

Beyond the research outputs presented throughout these chapters, the study also provided an opportunity for over 30 students in public health undergraduate or graduate programs to expand the breadth of their public health experience by serving as interviewers and collecting the study data. Though not discussed in detail throughout these chapters, but was a critical component of this projects' success, is the phenomenal team of student interviewers we hired and supported to collect the study data. Hiring motivated and empathetic students, I learned, was critical to our success, as we would not have collected any useful data without the small army of dedicated students. In short, placing cold calls is hard and often demoralizing work. Our interviewers placed cold calls under clouds of uncertainty- they did not even know whether some cases had survived their COVID-19 condition prior to calling. Critical to this study was creating a supporting and welcoming environment for interviewers to share stories, vent, and grieve on a weekly basis. For the entire study duration, all active interviewers met weekly over Zoom with the study team, forming a quasi-support group. During these sessions, we also tried to provide additional enrichment series to support the interviewers in their public health career. We invited speakers at various stages of their career in a "Path to Public Health" series to demonstrate the myriad of ways one can establish a career in Public Health. Additionally, we used these sessions as platforms for basic trainings in Epidemiology and statistical programming.

In summary, our work exemplifies how the case-control study design can be leveraged to provide rapid answers to a range of emerging questions and hypotheses during an outbreak. We demonstrate the use of this study design in providing estimates of the effectiveness of masks, vaccines, and risk factors for SARS-CoV-2 infection. We believe the case-control study has been an example of a successful collaboration between public health and academics, leveraging the strengths of both partners to produce high quality, policy-relevant science.