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MAJOR ARTICLE

SARS-CoV-2 Cumulative Incidence and Period Seroprevalence: Results From a Statewide Population-Based Serosurvey in California

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Background. California has reported the largest number of coronavirus disease 2019 (COVID-19) cases of any US state, with more than 3.5 million confirmed as of March 2021. However, the full breadth of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission in California is unknown as reported cases only represent a fraction of all infections.

Methods. We conducted a population-based serosurvey, utilizing mailed, home-based SARS-CoV-2 antibody testing along with a demographic and behavioral survey. We weighted data from a random sample to represent the adult California population and estimated period seroprevalence overall and by participant characteristics. Seroprevalence estimates were adjusted for waning antibodies to produce statewide estimates of cumulative incidence, the infection fatality ratio (IFR), and the reported fraction.

Results. California's SARS-CoV-2 weighted seroprevalence during August–December 2020 was 4.6% (95% CI, 2.8%–7.4%). Estimated cumulative incidence as of November 2, 2020, was 8.7% (95% CrI, 6.4%–11.5%), indicating that 2 660 441 adults (95% CrI, 1 959 218–3 532 380) had been infected. The estimated IFR was 0.8% (95% CrI, 0.6%–1.0%), and the estimated percentage of infections reported to the California Department of Public Health was 31%. Disparately high risk for infection was observed among persons of Hispanic/Latinx ethnicity and people with no health insurance and who reported working outside the home.

Conclusions. We present the first statewide SARS-CoV-2 cumulative incidence estimate among adults in California. As of November 2020, ~1 in 3 SARS-CoV-2 infections in California adults had been identified by public health surveillance. When accounting for unreported SARS-CoV-2 infections, disparities by race/ethnicity seen in case-based surveillance persist.

Keywords. cumulative incidence; SARS-CoV-2; seroprevalence.

Since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection was first detected in California in January 2020, >3.5 million reported cases (8900 per 100 000 population) and 54 000 related deaths have been reported [1], making California the state with the largest number of reported cases in the United States. Like other US states, California relies on data from diagnosed infections, hospitalizations, and deaths that are reported to state and local health departments (eg, California Department of Public Health [CDPH]) to monitor the burden of SARS-CoV-2 infections. These data are critical for monitoring but, because undiagnosed infections are not reported, have limited utility for estimation of key epidemiologic indicators such as cumulative incidence, the infection fatality ratio (IFR), and the reported fraction of infections. These indicators require population-based estimates of the seroprevalence of antibodies to SARS-CoV-2.

Serosurveys, which pair SARS-CoV-2 antibody testing with surveys about demographic, behavioral, and clinical characteristics, are an effective tool for estimating the burden of diagnosed and undiagnosed infections alongside risk factors for infection [2, 3]. When conducted in population-based samples, serosurveys can provide relatively unbiased estimates of the burden of disease in a geographic area and of disparities in infection across population groups. To date, most California-based serosurveys have had limited geographic reach or were conducted in specific populations, such as blood donors or essential workers, who are likely not representative of the general population of the state [4–7]. Given California's diverse population of ~40 million, a representative statewide study was needed to capture data from people less likely to be included in convenience samples and to understand the full extent of SARS-CoV-2 burden in California and disparities that might exist by population characteristics and behaviors.

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We conducted a population-based serosurvey in California as part of the COVIDVu study, a longitudinal probability survey of US households using mailed at-home specimen collection for polymerase chain reaction (PCR) and serology testing [8]. In addition to period seroprevalence during August–December 2020, we estimated cumulative incidence, the IFR, and the percentage of infections that were reported. Given the common finding in serosurveys of waning detectable antibodies over time [9–11], we applied a model [12] to adjust the seroprevalence estimate for antibody waning.

METHODS

Sampling

We randomly sampled 8726 households in California from a frame derived from the USPS Computerized Delivery Sequence File, which has been used extensively for survey research [13–15] and represents nearly all housed, noninstitutionalized persons in the state. To account for suboptimal response among under-represented racial and ethnic groups in a pilot survey, we oversampled census blocks with >50% Black residents and households associated with surnames likely to signify Hispanic/Latinx ethnicity at a rate of 3 times the California general population.

Survey and Laboratory Procedures

Survey and laboratory procedures have been described elsewhere [8]. Briefly, during August–December 2020, we mailed an introductory letter followed a few days later by a kit for self-collecting specimens for SARS-CoV-2 PCR and antibody testing. The kit included an anterior nares (AN) swab, a dried blood spot (DBS) card and single-use lancet, and instructions for specimen self-collection using text and illustrations [16, 17]. An adult resident provided a list of all persons living in the household along with each person's age, and 1 adult aged ≥18 years was randomly selected for study participation by the study's electronic platform. Persons who consented were asked to respond to an online survey and to provide AN and DBS specimens, which were mailed back prepaid to a central laboratory.

PCR testing was performed as previously described [18] on AN specimens using the Thermo Emergency Use Authorization (EUA), Version 2, kit (Thermo Fisher Scientific, Waltham, MA, USA). DBS specimens were tested using the BioRAD Platelia Total Antibody test (ie, immunoglobulin [Ig] A, IgM, IgG; Biorad, Hercules, CA, USA; sensitivity, 92.2%; specificity, 99.6%), which was validated as a Laboratory-Developed Test (LDT) under Clinical Laboratory Improvement Amendments/College of American Pathologists protocols. Because the BioRAD test detects SARS-CoV-2 IgG targeting the nucleocapsid protein, which may wane more quickly than IgG targeting the spike protein [9, 19], we performed a sensitivity analysis by testing nonreactive samples with the EUROIMMUN IgG assay (EUROIMMUN, Lubeck, Germany), which targets the spike protein. Test results were returned to participants. Participants were compensated $60–$100 (depending on sampling group) for completing the survey and submitting specimens.

Patient Consent

COVIDVu was approved by the Emory University Institutional Review Board (STUDY00000695) and was deemed exempt public health surveillance by the California Committee for the Protection of Human Subjects (2020–124). Written consent was obtained from participants.

Sample Weights

We computed sample weights to estimate key epidemiologic parameters representing the noninstitutionalized, housed adult (aged ≥18) population of California. The first step was to ensure that participants had complete data for weighting variables, a process accomplished with hierarchical hot deck imputation for gender (replacing 0.1% missing data), education (1.6% missing), race (7.1% missing), ethnicity (2.5% missing), marital status (2.9% missing), and income (14.4% missing). The second step was to develop design weights, the reciprocal of the probability of being selected, which were adjusted for differential nonresponse using classification and regression tree analysis. This analysis identified characteristics distributed differently across responding and nonresponding households, which included homeownership status (rent vs own), residence in a household located in a census tract with >50% Black residents, presence of likely Hispanic/Latinx surname, and presence of household information about income or number of adults on the address-based sampling frame. The third step was to calibrate nonresponse-adjusted design weights to characteristics of adults residing in California using an iterative proportional fitting (raking) procedure to align the weights of California respondents simultaneously to bivariate distributions of gender nested with age, race/ethnicity, education, income, and marital status from US Census estimates for California [20]. In the final step, we examined weights to detect extreme outliers and trimmed at the 1st and 99th percentiles of the weight distribution.

Data Analysis

We used standard survey analytic procedures in SAS, version 9.4 (PROC SURVEY), to estimate statewide seroprevalence during August–December 2020. We estimated weighted seroprevalence overall and by participant characteristics and sampling month with accompanying 95% Modified Wilson score CIs. We assessed differences in seroprevalence across participant characteristics using prevalence ratios (PRs), which were computed using average marginal predictions from logistic regression in SUDAAN and associated CIs.

To estimate the cumulative incidence of SARS-CoV-2 infection through the median date of sampling (November 2,

2020), we adjusted the statewide seroprevalence estimate to account for antibody waning below a detectable level. In this analysis, we used a Bayesian model that has been previously described [12]. Briefly, it estimates the timing of infections based on (1) an external estimate of time from symptom onset to seroconversion [21], (2) estimated time from seroconversion to seroreversion from New York City [12], (3) time series data on COVID-19-related deaths reported to the CDPH through February 10, 2021, and (4) the distribution of timing of symptom onset to deaths in California. The model is calibrated with the statewide seroprevalence data estimated from this analysis. The model allowed us to directly estimate the IFR and derive a cumulative incidence estimate using the total number of modeled infections since the beginning of the epidemic in California. We estimated the reported fraction (the number of COVID-19 cases reported divided by the estimated number of total infections) as the ratio of PCR-confirmed COVID-19 cases reported to the CDPH to the estimated cumulative incidence as of November 2, 2020. Credible intervals (CrIs) for this ratio were derived using the Bayesian 95% credible intervals for the cumulative incidence estimate.

RESULTS

Of 8726 California households sampled, 357 (4.1%) were ineligible as evidenced by letters or kits returned undeliverable. Of 8369 eligible households, 1188 (14.2%) completed household enumeration, consent, and the online survey. Of those, 983 (83%) completed specimen self-collection and had a valid immunoglobulin result, representing 11.7% of eligible households (Figure 1). Unweighted and weighted distributions of the sample by characteristics are described in Table 1 with comparison to the adult California population.

Overall, weighted statewide SARS-CoV-2 seroprevalence among adults during August–December 2020 was 4.6% (95% CI, 2.8%–7.4%), with a median specimen collection date of November 2, 2020 (Table 2). Ninety-eight nonreactive samples were retested using the EUROIMMUN IgG assay targeting the spike protein; none were reactive for seropositivity. Seroprevalence was 7.5 times as high among Hispanic/Latinx persons compared with non-Hispanic/Latinx White persons (95% CI, 2.8%–20.2%) and higher among 35–44-year-olds compared with 55–64 year olds (PR, 3.3%; 95 CI, 1.0%–10.1%). Seroprevalence was also higher among people with no health insurance compared with people with private insurance (PR,

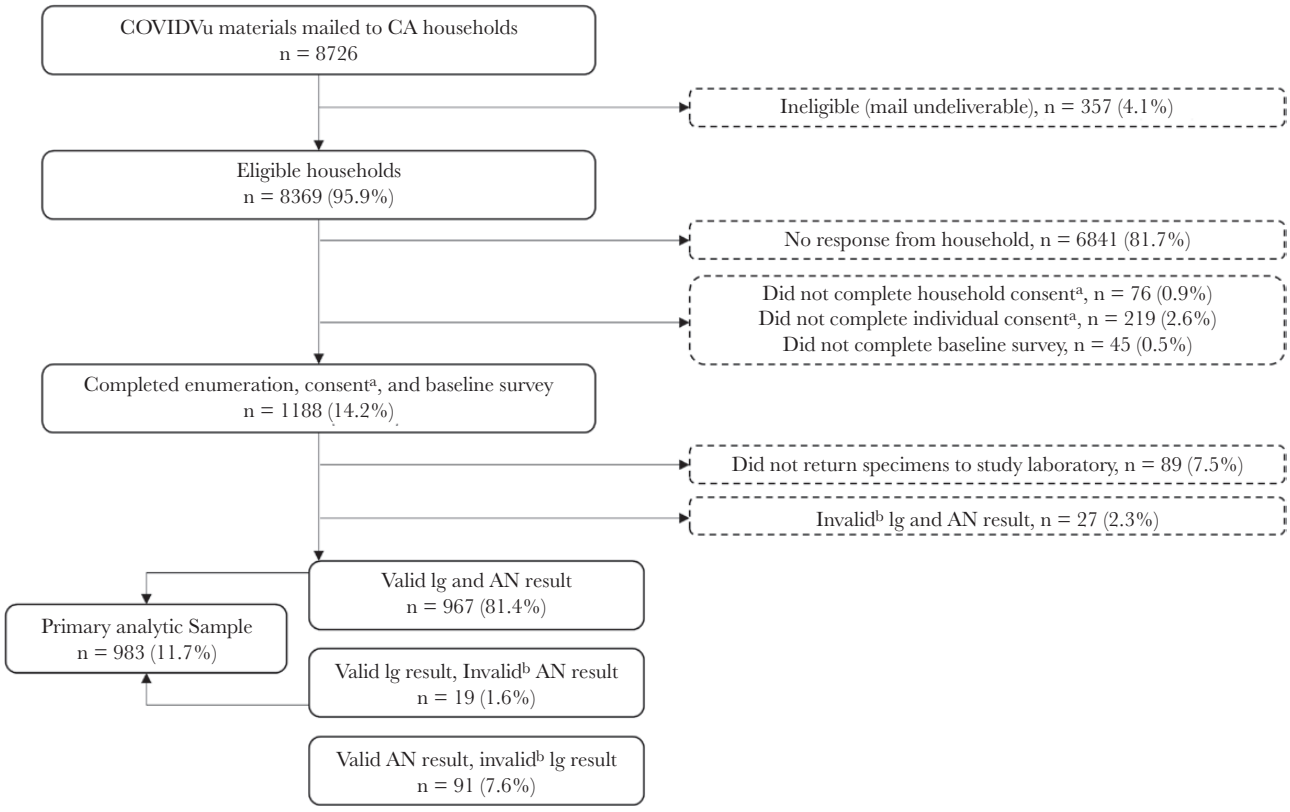

Figure 1. Flow diagram of probability sample of California households to estimate seroprevalence and cumulative incidence of SARS-CoV-2 infections among adults, August–December 2020. [a]Consent was required at the household level for household enumeration, and then at the individual level for the randomly selected member of an enumerated household. [b]Test results were considered invalid for the following reasons: sample not sufficient to process, processing incomplete by study closeout, sample collection date outside of the range 8/9/20–12/8/20. Abbreviations: AN, anterior nares; lg, immunoglobulin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Demographic Characteristics of Serosurvey Participants (n = 983) and Weighted Sample Size Compared With the California Population Aged ≥18 Years

	Sample		Weighted Sample		California Population (≥18 y)[a]	
Characteristic	No.	Column %	Weighted No.	Column %	No.	Column %
Overall	983	100.0	29 446 494	100.0	30 617 582	100.0
Sex						
Male	416	42.3	14 160 171	48.1	15 099 081	49.3
Female	567	57.7	15 286 322	51.9	15 518 501	50.7
Race/ethnicity						
Hispanic/Latinx	261	26.6	10 356 872	35.2	10 947 327	35.8
Non-Hispanic/Latinx White	549	55.8	12 079 332	41.0	12 470 678	40.7
Non-Hispanic/Latinx Black	35	3.6	1 424 280	4.8	1 903 134	6.2
Non-Hispanic/Latinx Asian	107	10.9	4 537 655	15.4	5 134 689	16.8
Non-Hispanic/Latinx other	31	3.2	1 048 355	3.6	161 754	0.5
Age						
18–34 y	236	24.0	8 930 380	30.3	9 730 987	31.8
35–44 y	156	15.9	5 322 270	18.1	5 282 100	17.3
45–54 y	167	17.0	4 737 818	16.1	4 979 745	16.3
55–64 y	188	19.1	4 776 294	16.2	4 786 635	15.6
65+ y	236	24.0	5 679 731	19.3	5 838 115	19.1

[a]2019 Bridged-Race Estimates (National Vital Statistics System).

4.5%; 95% CI, 1.2%–16.9%) and among people who left home for work vs those who did not (PR, 3.9%; 95% CI, 1.1%–14.0%). Having contact with someone with a confirmed COVID-19 infection and having a prior COVID-19 diagnosis were both associated with higher seroprevalence, but having COVID-19 symptoms was not associated with higher seroprevalence.

The estimated statewide cumulative incidence of SARS-CoV-2 infection among California adults as of November 2, 2020, adjusted for waning antibodies, was 8.7% (95% CrI, 6.4%–11.5%); an estimated 2 660 441 total infections (95% CrI, 1 959 218–3 532 380) had occurred among adults by that date. Based on these estimates and the number of PCR-confirmed COVID-19 cases reported to the CDPH by November 2, 2020, the estimated reported fraction was 31%, meaning that ~1 in 3 SARS-CoV-2 infections among adults was diagnosed and reported to the CDPH as a COVID-19 case through early November. The estimated IFR among California adults was 0.8% (95% CrI, 0.6%–1.0%).

DISCUSSION

We report the first representative statewide estimate of cumulative SARS-CoV-2 incidence using a population-based probability sampling approach for California, adjusted for waning antibodies. By early November 2020, nearly 9% of California adults had been infected with SARS-CoV-2, with ~1 in 3 infections diagnosed and reported to the state. By accounting for unreported infections, we estimated an IFR of 0.8% among adults in California.

Results from this study indicated large disparities in burden of infection among Californians, particularly among Hispanic/Latinx persons compared with non-Hispanic/Latinx White persons. These data support other findings in California, which have documented seroprevalence up to 3 times as high among Hispanic/Latinx persons compared with non-Hispanic/Latinx White persons [6, 22, 23]. We also reported differences in seroprevalence by insurance status and workplace. This is consistent with previous reports of varying seroprevalence by social determinants of health such as household income and housing status [2, 22] and parallels inequities seen among PCR-confirmed cases [24]. Socioeconomic factors including essential worker status and ability to physically distance from others while at work or home are associated with risk for SARS-CoV-2 infection; therefore, a continued focus on health equity in California's vaccine distribution is essential [23].

Population-level seroprevalence and cumulative incidence are critical indicators for monitoring the course of epidemics in populations. These indicators have been particularly challenging to estimate for SARS-CoV-2 because of the large number of asymptomatic infections and barriers to testing and diagnosis, particularly early in the pandemic [25]. Estimates of SARS-CoV-2 burden of disease are primarily derived from cases reported to health departments, and the Centers for Disease Control and Prevention's (CDC's) most recent estimate suggests that ~22% of infections are diagnosed and reported nationally [26]. Infections among racial or ethnic subgroups may be less likely to be detected through routine surveillance because of limited access to, or usage of, testing services [27]. This was evident in our findings, which show that racial and ethnic disparities observed among PCR-confirmed cases may be larger when accounting for undiagnosed infections. California surveillance data suggest that Hispanic/Latinx

Table 2. Unweighted and Weighted SARS-CoV-2 Antibody Prevalence Among Serosurvey Participants (n = 983) and Prevalence Ratios by Demographic and Epidemiologic Characteristics, California, August–December 2020

	Unweighted			Weighted						
Characteristic	n	N	%	n	N	%	95% CI[a]	PR	95% CI	*P* Value
Overall	33	983	3.4	1 338 730	29 446 494	4.5	2.8–7.4	n/a		
Sex										.64
Male	13	416	3.1	562 771	14 160 171	4.0	1.8–8.7	Reference		
Female	20	567	3.5	775 959	15 286 322	5.1	2.7–9.3	1.3	0.5–3.6	
Race/ethnicity										<.001
Hispanic/Latinx	21	261	8.0	1 069 853	10 356 872	10.3	5.8–17.8	7.5	2.8–20.2	
Non-Hispanic/Latinx White	10	549	1.8	166 116	12 079 332	1.4	0.6–3	Reference		
Non-Hispanic/Latinx Black	1	35	2.9	46 436	1 424 280	3.3	0.6–15.7	2.4	0.3–19.7	
Non-Hispanic/Latinx Asian	0	107	0.0	.	4 537 655	.	.	N/A		
Non-Hispanic/Latinx other	1	31	3.2	56 325	1 048 355	5.4	1–23.7	3.9	0.5–31.2	
Age										.07
18–34 y	14	236	5.9	461 821	8 930 380	5.2	2.8–9.5	2.7	0.9–8	
35–44 y	9	156	5.8	329 858	5 322 270	6.2	3–12.3	3.3	1.1–10.2	
45–54 y	3	167	1.8	410 604	4 737 818	8.7	2.5–25.6	4.6	1–21.5	
55–64 y	6	188	3.2	90 012	4 776 294	1.9	0.7–5	Reference		
65+ y	1	236	0.4	46 436	5 679 731	0.8	0.1–4.5	0.4	0.1–3.7	
Education										.009
High school/GED or less	9	121	7.4	797 929	10 161 577	7.9	3.7–16	2.3	0.8–6.6	
Some college/Associate's degree	10	309	3.2	296 372	9 422 451	3.1	1.6–6.2	0.9	0.3–2.5	
Bachelor's degree	10	317	3.2	216 239	6 313 350	3.4	1.7–6.8	Reference		
Graduate degree	4	236	1.7	28 190	3 549 116	0.8	0.2–3	0.2	0.1–0.8	
Annual income										.41
$0–$49 999	16	310	5.2	487 740	8 021 148	6.1	3.4–10.6	2.1	0.7–6.6	
$50 000–$99 999	7	286	2.4	231 462	8 118 641	2.9	1.1–7	Reference		
$100 000+	10	387	2.6	619 529	13 306 704	4.7	1.9–11	1.6	0.4–6.2	
Health insurance										.004
No health insurance	3	30	10.0	98 187	791 167	12.4	4.1–31.9	4.5	1.2–16.9	
Medicare/Medicaid/other government plan	7	281	2.5	223 129	7 902 141	2.8	1.2–6.3	1.0	0.4–2.9	
Private insurance/parent's plan	18	595	3.0	497 215	17 999 789	2.8	1.5–5	Reference		
Don't know	5	77	6.5	520 200	2 753 397	18.9	7.3–40.9	6.8	2.2–21	
Household size										.23
1–2 persons	12	585	2.1	451 298	14 808 778	3.0	1.2–7.5	Reference		
3–5 persons	17	359	4.7	714 877	13 063 378	5.5	2.8–10.4	1.8	0.6–5.8	
>5 persons	4	39	10.3	172 555	1 574 338	11.0	4–26.9	3.6	0.9–15.2	
Leave home for work[b]	14	357	3.9	598 873	11 766 211	5.1	2.4–10.6	3.9	1.1–14	.04
COVID-19 symptoms since January 1, 2020[b,c]	25	551	4.5	1 012 017	16 608 417	6.1	3.3–10.9	2.4	0.9–6.5	.09
Contact to a confirmed case[b]	20	139	14.4	792 062	4 868 147	16.3	8.9–27.8	7.3	2.6–20.1	<.001
Prior COVID-19 diagnosis[b,d]	13	20	65.0	750 595	1 025 953	73.2	46–89.7	35.4	18.4–67.8	<.001
Month of sample collection										.17

Table 2. Continued

Characteristic	Unweighted			Weighted						*P* Value
	n	N	%	n	N	%	95% CI[a]	PR	95% CI	
August/September	3	158	1.9	83 257	4 687 510	1.8	0.5–5.6	Reference		
October	3	259	1.2	255 757	8 176 650	3.1	0.7–12.2	1.8	0.2–12.9	
November/December	27	566	4.8	999 716	16 582 334	6.0	3.5–10.1	3.4	0.9–13.2	

Abbreviations: COVID-19, coronavirus disease 2019; PR, prevalence ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Confidence intervals were calculated using the modified Wilson method.

[b]Reference group is persons without characteristic.

[c]Symptoms include cold/flu, cough, shortness of breath, or loss of taste or smell.

[d]Provider told them they likely had COVID-19 or a positive COVID-19 test result.

persons have nearly 3 times the PCR-confirmed infections (per population size) of White persons [28]. We estimated that seroprevalence was 7.5 times higher among Hispanic/Latinx persons compared with non-Hispanic/Latinx White persons. Equitable access to SARS-CoV-2 testing will aid in identification and reporting of cases across racial and ethnic groups [29]. Because there is no evidence that antibody waning is differential by race, cross-sectional serosurveys will continue to be an important tool for monitoring disparities.

With nearly 40 million residents representing a geographically and demographically diverse population, conducting representative serosurveys generalizable to California's population has been an ongoing challenge. Seroprevalence estimates from several local and population-specific serosurveys in California have ranged from <1% to >21% and have varied greatly depending on the sampling period, geographic location, and population sampled [4–7, 22–24, 30–33]. CDC estimates for California using clinical laboratory residual specimens ranged from 4.1% in September 2020 to 18.1% in January 2021, with an estimated seroprevalence from mid-November 2020 of 6.6% [34]. This CDC estimate may be lower than our estimated cumulative incidence for a similar time period because it does not account for waning antibodies and excludes specimens specifically collected for COVID-19 testing. Statewide estimates based on electronic laboratory reporting to the CDPH from clinical laboratories and blood banks indicate 38% seropositivity during February 2021; these data include persons seeking clinical care, donating blood, and those who may have been vaccinated and may not be representative of all Californians [35].

This study has limitations. First, while our response rate was within the expected range for an address-based survey, it was suboptimal, with ~12% of sampled households providing a valid specimen for SARS-CoV-2 antibody testing. This study was the first in the United States to mail out self-collection kits to a randomly selected probability sample, but even household surveys employing door-to-door outreach methods have only reached response rates of ~24% [36, 37]. The need for ongoing monitoring of population-level infection burden and vaccine coverage will require improved and innovative methods for recruiting participants, particularly those who may be under-represented in surveillance data due to issues with testing access or usage. Monetary compensation for participation may have contributed to sampling bias by making it more likely that persons of lower socioeconomic status would participate. An advantage of the address-based approach is that we were able to account for differential nonresponse by comparing responding with nonresponding households by characteristics available at the census tract level (eg, racial distribution of census tract, Hispanic/Latinx surname, and home ownership status) and using predictors of nonresponse in weighting computation. However, we were not able to adjust for variables associated with individual nonresponse, such as variables not assessed by

or substantially associated with our weighting schema, such as essential worker status or prior infection history. Differential nonresponse according to factors associated with seropositivity, if unadjusted for, would contribute to bias in our estimates.

There are also 2 potential limitations regarding our cumulative incidence estimates. First, due to waning SARS-CoV-2 antibodies, previous infections may be undetected by antibody assays [9, 10]. This issue may be exacerbated when using laboratory assays targeting the nucleocapsid, vs spike, protein [19, 38]. We addressed this limitation in 2 ways: (1) by using a modeling approach to estimate cumulative incidence given the observed period seroprevalence and death data and (2) by retesting a sample of nonreactive specimens with an assay targeting the spike protein. Nevertheless, there may be some degree of misclassification in antibody positivity. Second, we used an estimate for duration of seropositivity from published data from New York City to parameterize the model. The New York estimate was generated using the CDC ELISA kit, which detects total SARS-CoV-2 Ig targeting the spike protein, while the assay used for our study detects total Ig targeting the nucleocapsid protein. However, the New York City estimate is the only available approximation of the timeline for population-level waning antibodies at this point. Comparisons to external estimates allay laboratory- and modeling-related concerns to some extent. For example, the estimated reported fraction from our study is similar to a previous CDC estimate for California suggesting that 24% of infections were reported statewide during July–August 2020 [34].

As part of the COVIDVu study, we will perform 2 rounds of follow-up with study participants: once in the first quarter of 2021 and again in the second quarter of 2021. We will collect DBS samples to estimate incident infections and to assess antibody waning among baseline participants. We will test for IgA, IgG, and IgM to nucleocapsid (BioRad Platelia Total Antibody test) and for potentially vaccine-associated IgG (ie, antibodies to Spike, EuroIMMUN IgG assay). We will also administer follow-up surveys at both time points, focusing on vaccination and ongoing infection risk. Our estimates provide an important baseline for ongoing efforts to monitor seroprevalence statewide using laboratory surveillance data and additional population-based serosurveys.

In this population-based study, we estimated California statewide SARS-CoV-2 seroprevalence in adults. Accounting for waning antibody response, we estimated a cumulative incidence of 8.7% as of November 2, 2020. The estimated IFR was 0.8% for adults, and we found that only 1 in 3 SARS-CoV-2 infections in adults was reported to the CDPH through early November 2020. Disparities documented in our study by ethnicity and insurance status may be larger than previously suggested by local seroprevalence studies [6, 23] and surveillance data [28]. Taken together, these data underscore the continued need to focus public health interventions, including access to testing and vaccination in socioeconomically vulnerable communities, which are the most heavily impacted. Serosurveys are an important tool for understanding the full extent of SARS-CoV-2 infections and will be critical for ongoing monitoring of population-level immunity in the vaccine era.

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