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Title: Monitoring SARS-CoV-2 incidence and seroconversion in a university cohort in California, June to August 2020

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Abstract

Objective: To inform effective SARS-CoV-2 mitigation strategies in university settings, we piloted an integrated symptom and exposure monitoring and testing system among a cohort of university students and employees.

Methods: We aimed to identify incident SARS-CoV-2 infections in a longitudinal cohort of 2,180 students and 738 employees of a public university in California from June to August 2020. At baseline and endline, we tested participants for active SARS-CoV-2 infection via quantitative polymerase chain reaction (qPCR) test and collected blood for antibody testing. Participants received notifications to complete additional qPCR tests throughout the study if they reported symptoms or exposures in daily surveys or were selected for surveillance testing. Viral whole genome sequencing was performed on positive qPCR samples, and phylogenetic trees were constructed with these genomes and external genomes retrieved from GISAID.

Results: Over the study period, 57 students (2.6%) and 3 employees (0.3%) were diagnosed with SARS-CoV-2 infection via qPCR test. Phylogenetic analyses revealed that a super-spreader event among undergraduates in congregate housing accounted for at least 48% of cases but did not spread beyond campus. Test positivity was higher among participants who self-reported symptoms (incidence rate ratio [IRR]: 12.4; 95% confidence interval [CI]: 7.3, 21.3) or had household exposures (IRR: 12.3; 95% CI: 5.6, 26.9) which triggered notifications to test. Most (91%) participants with newly identified antibodies at endline had been diagnosed with incident infection via qPCR test during the study.

Conclusions: Our findings suggest that integrated monitoring systems can successfully identify and link at-risk students to SARS-CoV-2 testing. Building upon such systems may prove key in the next stage of the pandemic, as universities grapple with highly transmissible variants, incomplete vaccine coverage and breakthrough infections, and reduced reliance on prevention strategies such as masking and remote learning.

Strengths and limitations of this study

- The study is strengthened by rich longitudinal data including more than 117,000 daily symptom surveys; 17,000 weekly exposure surveys; 7,600 qPCR tests to detect active SARS-CoV-2 infection; and 4,900 antibody tests to detect previous infection collected from 2,918 university students and employees over three months.
- Using seroconversion data from serial antibody tests and phylogenetic analyses comparing viral genome sequences to a broader database, we were able to evaluate the extent to which the study system identified incident cases and contained an outbreak among university students. However, our identification of participants who seroconverted between baseline and endline may be incomplete due to loss-to-follow up and imperfect sensitivity of SARS-CoV-2 antibody testing.
- A high proportion of identified cases were traced to one outbreak, limiting the generalizability of our exploratory assessment of risk factors for incident infection. While self-referral into the study in the context of the outbreak is likely to induce selection bias, it also illustrates the utility of implementing non-stigmatizing, incentivized testing approaches to increase testing uptake among at-risk students.
- As the study took place before the development of highly transmissible variants and vaccine rollout, further research is necessary to adapt and evaluate similar systems in the context of both heightened transmissibility and more prevalent natural and vaccine-induced immunity.

Background

Universities have been identified as hotspots for SARS-CoV-2 transmission in the United States,[1] where SARS-CoV-2 incidence is highest among young adults.[2] Young adults may be less likely to adhere to social distancing guidelines and more likely to experience workplace exposure (for example, at food service or retail jobs).[2] Their risk may be heightened in university settings where many live in congregate housing, interact with wide social networks, or attend large gatherings.[3] Although young adults are at low risk of serious acute illness or death from COVID-19 (the disease caused by SARS-CoV-2),[4] the higher likelihood of asymptomatic or mildly symptomatic infection in this age group makes young adults a key population through which SARS-CoV-2 may be spread to other, more vulnerable groups.[2,5] Indeed, there is evidence that transmission among university students may lead to increased COVID-19-related mortality in the surrounding counties.[6–8] Although widespread vaccination has enabled most campuses to return to in-person activities, the elimination of SARS-CoV-2 transmission in campus populations may be stymied by vaccine hesitancy among students and employees and breakthrough infection and subsequent transmission by vaccinated persons, particularly in the context of waning immunity and viral variants which reduce vaccine efficacy.[9,10] Therefore, rapid and resource-efficient identification of incident cases in university populations is a critical first step of outbreak investigation and control, followed by isolation, case investigation, and contact tracing, to minimize transmission within campus and to the broader community.

Universities have adopted a wide range of approaches for testing and outbreak mitigation.[11–13] While a number of well-resourced universities have scaled up testing capacity in order to frequently test all students and employees accessing campus or living in university-affiliated housing,[13] many other universities do not have well-defined testing strategies or restrict testing to those with symptoms or known exposure.[12] Beyond investing in testing programs, some universities have sought to reduce on-campus transmission by mandating the completion of self-administered symptom screening tools by students and employees. However, such tools

have primarily been used to regulate daily access to campus (i.e., deny entry to those who report COVID-19-like symptoms), rather than to detect emergent outbreaks among university populations. As universities resume normal operations and discontinue mitigation strategies such as masking, non-punitive, resource-efficient strategies which can both identify those who are at highest risk of infection *and* expediently link them to low-barrier testing services may play a key role in transitioning from a "one-size-fits-all" approach of uniform testing to a sustainable monitoring paradigm.

In 2020, we piloted an integrated symptom and exposure monitoring and testing system designed to identify incident SARS-CoV-2 infections among a cohort of university students and employees.[14] Here we describe the incidence and seroprevalence of SARS-CoV-2 infection within this cohort to evaluate the extent to which incident infections were successfully detected and contained over the study period, identify sociodemographic factors associated with incident infection, and ascertain which self-reported symptoms and exposures tracked by the monitoring system were predictive of test positivity, with the ultimate objective of informing monitoring and testing strategies in university settings.

Methods

Study design and setting

The study comprised three prospective cohorts of University of California, Berkeley affiliates followed from June to August 2020: students, essential workers (i.e., employees working on campus in health, facilities, or key student services), and other employees (hereafter, "faculty/staff"). We report the findings according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies.[15]

Throughout the study period, UC Berkeley did not offer in-person classes, and on-campus work was restricted to essential workers and a small subset of faculty, staff, and student researchers. Although few students were living in on-campus residence halls, many

students continued to live in congregate living settings off campus, such as fraternities, sororities, and co-operative housing.

Participant recruitment and eligibility

The study was promoted through targeted messages from university officials to campus email listservs and social media platforms from early June to mid-July 2020. To increase reach to students expected to be at higher risk of COVID-19, we also placed flyers in congregate living settings and conducted in-person recruitment for student athletes who had resumed training on campus. Participants were eligible to enroll in the study if they were at least 18 years of age, were a current student or employee at UC Berkeley, and planned to live in or near Berkeley during summer 2020. Specific eligibility criteria and enrollment windows varied by cohort (Supplementary Table 1, Supplementary Figure 1).

Upon enrollment, participants were linked to an online baseline survey that collected sociodemographic data and information about their COVID-19-related health history. Participants were then referred to a baseline testing appointment at University Health Services (UHS) which included a SARS-CoV-2 quantitative polymerase chain reaction (qPCR) test and blood collection for antibody testing (procedures described below). To facilitate daily temperature monitoring, study staff also provided participants with free oral thermometers upon request at testing appointments. Participants who completed this appointment or a non-study qPCR test at UHS by July 20th were eligible to remain in the study. We pre-specified a maximum sample size of 4,000 participants across cohorts but did not reach this limit before the final day of baseline data collection.

Symptom and exposure surveys

Participants received daily text messages or emails, depending on their preference specified in the baseline survey, which linked to short symptom surveys through which they

reported their daily body temperature and any symptoms of illness. Once per week, the daily survey included a longer exposure module, which asked about recent symptoms of illness among their household member(s), potential exposure(s) to COVID-19, and activities related to potential COVID-19 risk. All surveys were administered via REDCap.[16,17]

Endline survey and testing

In early August, participants were sent an endline survey which collected updated information on their COVID-19 history to identify any diagnoses outside of the study. Participants in the student and essential worker cohorts were also invited to complete endline testing appointments by August 18th, including a final qPCR test and blood collection.

qPCR testing

Midturbinate nasal and oral swabs were collected by UHS clinical staff and tested for SARS-CoV-2 by qPCR at the Innovative Genomics Institute (IGI).[18] qPCR tests were performed at baseline for all three cohorts and at endline for the student and essential worker cohorts. Between baseline and endline testing, additional qPCR tests were performed for the following reasons:

- **Symptom- or exposure-based tests triggered based on participants' responses in daily surveys**: Participants who reported COVID-19-like signs or symptoms[1] (in themselves or household member(s)) or who reported a suspected or confirmed COVID-19 case in their household were automatically notified to sign up for a qPCR test.

[1] Signs or symptoms which triggered a testing notification when reported were: temperature of ≥100.4°F, dry cough (without mucus), coughing up mucus, feeling feverish, unusual pain or pressure in the chest, difficulty breathing, shortness of breath, unexplained trouble thinking or concentrating, loss of sense of taste, or loss of sense of smell.

- **Random surveillance testing**: A subset of participants in the student and faculty/staff cohorts who had not had a qPCR test within a week were randomly selected and emailed notifications to come in for surveillance testing in July.
- **Address-based surveillance testing**: Participants who lived at the same address as another participant who tested positive for SARS-CoV-2 were immediately emailed surveillance testing notifications. Following an outbreak among group-housed students in early July, surveillance testing notifications were also emailed to all participants who had not been tested within the week and who reported living in fraternities, sororities, or co-operative housing.
- **Participant-initiated testing**: Participants could self-schedule study testing appointments on demand, with or without consulting a healthcare provider and regardless of exposure history.

Participants with positive qPCR test results were informed by phone by UHS clinical staff, who provided guidance on isolation and performed case investigation to identify potential contacts. Participants with negative qPCR test results were informed of their results via the UHS online patient portal.

SARS-CoV-2 sequencing and phylogenetic analyses

Viral whole genome sequencing was performed on a set of positive samples at the IGI, using previously described procedures.[19] Briefly, SARS-CoV-2 RNA extracted from swabs was reverse transcribed using SuperScript IV (Invitrogen), and the viral genome was amplified from the resulting cDNA in four separate qPCR reactions using distinct primer sets tiling the SARS-CoV-2 genome. The four qPCR reactions were pooled 1:1:1:1 and diluted 1:50 in H_2O. A second qPCR reaction was set up to add Nextera Unique Dual Indexing (UDI) sequences to either end of the amplicons. The resulting qPCR reaction was cleaned up using 0.7x AMPureXP beads (Beckman Coulter) and quantified using a Qubit dsDNA HS Assay Kit (Thermo Fisher).

The libraries were then pooled to an equimolar ratio and sequenced with a 10% PhiX spike in using a MiSeq v3 kit at 300bp PE reads.

Fastq sequencing files were processed through a custom pipeline using publicly available software. The reads were preprocessed by quality trimming, removing adaptors, and PhiX cleaning with BBTools,[20] and then aligned to the Wuhan reference sequence (NC_045512.2) with minimap2 v2.16-r922. ARTICv3 primers were trimmed, and the consensus sequence was built with iVar v1.3.1, where an 'N' is called if the depth is less than 10 reads at any nucleotide. The genomes were then processed through the Nextstrain Auger pipeline with other genomes from GISAID to construct a maximum likelihood tree.[21,22] Several phylogenies were constructed for this analysis: a tree of 7,091 genomes subsampled from the worldwide genomes in GISAID at the time (approximately 200,000 genomes as of October 2020) was used to place the IGI genomes in the larger tree; a tree with all IGI genomes sequenced at the time of analysis (356 genomes); and a tree containing 500 genomes (from 1 million genomes as of April 2021) was constructed using UShER.[23]

Antibody testing

Up to 10 mL of blood was collected by phlebotomists via venipuncture at baseline from participants in all three cohorts and again at endline from participants in the student and essential worker cohorts. Blood was centrifuged and serum was stored at -20°C for 2 to 4 months before being tested at Vitalant Research Institute using the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack, which detects IgA, IgG, and IgM antibodies and has an estimated clinical specificity of 100% and unreported sensitivity.[24]

Participant compensation

Participants in the student cohort received a $50 gift card after completing baseline testing and 10 daily surveys; this incentive was conditional on daily survey completion to

encourage early habit formation.[25] Student participants received a second $50 gift card at their endline testing appointment. To facilitate travel to and from UHS for testing appointments, student participants were also offered pre-paid car rides via a ride-sharing app.

Participants in the essential worker cohort received a gift card worth $1 per daily survey completed (to a maximum of $70) after the study ended. Participants in the faculty/staff cohort were not compensated.

Statistical analyses

To identify sociodemographic factors associated with incident infection, we used Poisson regression to estimate unadjusted incidence rate ratios (IRRs) for SARS-CoV-2 infection by study cohort and within strata of sociodemographic variables self-reported in the baseline survey (e.g., age, gender, housing type), setting person-months of enrollment as an offset term to account for differing lengths of follow-up.

We also calculated IRRs comparing test positivity by recent signs/symptoms, exposures, and activities reported in the daily and weekly surveys. We estimated IRRs for several temperature thresholds (i.e., ≥100.4°F, ≥100.0°F, ≥99.0°F) to compare to symptom-specific IRRs; however, continuous associations between temperature and positivity have been previously explored in this cohort.[26] We accounted for clustered observations due to repeated tests per participant using a generalized estimating equation approach with Huber-White standard error estimates and an exchangeable working correlation structure.[27]

Finally, to assess the extent to which the testing and monitoring system captured incident infections, we identified participants who seroconverted from having non-reactive (no antibodies detected) to reactive (antibodies detected) blood samples between baseline and endline and calculated the proportion of these participants who were also diagnosed with incident SARS-CoV-2 infection via positive qPCR test during the study period. Analyses were conducted in R version 4.0.4.[28]

Ethical approvals

All study activities were approved by the University of California, Berkeley Committee for the Protection of Human Subjects (#2020-06-13349, #2020-05-13261, #2020-04-13238).

Patient and public involvement

The study's target population comprised university students and employees. While the study was conducted by faculty, staff, and graduate students from the UC Berkeley School of Public Health, University Health Services, and the Innovative Genomics Institute, the broader student body and university workforce were not involved in designing the study or selecting the research question, outcome measures, or method of disseminating results.

Results

Participant recruitment and retention

Between June 1 and July 20th, 2020, we enrolled 2,180 students, 268 essential workers, and 470 faculty/staff who completed at least one qPCR test or antibody test (Table 1, Supplementary Figure 1). The student cohort was split between undergraduate (52%) and graduate (48%) students. Nearly half (44%) of essential workers worked in health services. While 85% of essential workers were working on campus at the time of enrollment, most (81%) faculty/staff were working entirely remotely. At the time of enrollment, only 12 (0.4%) participants reported a previous COVID-19 diagnosis.

Participants provided a total of 5,545 person-months of follow-up from enrollment to the end of the study (mean person-days per participant: 57, range: 32-78). Participants completed a mean of 40 daily symptom surveys and 6 weekly exposure surveys over the study period, for a total of 117,235 symptom and 17,172 exposure surveys. A subset of participants did not complete any daily symptom surveys (1.7%) or weekly exposure surveys (4.2%).

Table 1. Baseline characteristics of participants in the Berkeley COVID-19 Safe Campus Initiative by study cohort, June-August 2020.

	All	Students	Essential Workers	Faculty/Staff
N (row %)	2,918 (100)	2,180 (74.7)	268 (9.2)	470 (16.1)
Age, mean ± SD	29.4 ± 11.6	24.3 ± 5.4	42.5 ± 12.3	45.2 ± 12.3
Gender, n (column %)				
Man	1,177 (40.3)	911 (41.8)	103 (38.4)	163 (34.7)
Woman	1,653 (56.6)	1,187 (54.4)	164 (61.2)	302 (64.3)
Non-binary/other	51 (1.7)	46 (2.1)	1 (0.4)	4 (0.9)
Race/ethnicity, n (column %)*				
American Indian/Alaska Native	39 (1.3)	29 (1.3)	2 (0.7)	8 (1.7)
Asian/Pacific Islander	833 (28.5)	703 (32.2)	66 (24.6)	64 (13.6)
Black/African American	103 (3.5)	83 (3.8)	16 (6.0)	4 (0.9)
Hispanic/Latine/Spanish origin	420 (14.4)	346 (15.9)	39 (14.6)	35 (7.4)
White	1,814 (62.2)	1,261 (57.8)	160 (59.7)	393 (83.6)
Other	280 (9.6)	223 (10.2)	31 (11.6)	26 (5.5)
Program level, n (column %)				
Undergraduate	-	1,114 (51.7)	-	-
Graduate	-	1,039 (48.2)	-	-
Living at fraternity/sorority, n (column %)	-	125 (5.7%)	-	-
Education, n (column %)				
High school diploma/GED	-	-	6 (2.2)	0 (0)
Some college or trade school	-	-	59 (22.0)	13 (2.8)
Bachelor's degree	-	-	78 (29.1)	119 (25.3)
Graduate/professional degree	-	-	121 (45.1)	337 (71.7)
Department, n (column %)				
Health services	-	-	129 (48.1)	-
Facilities/building services	-	-	61 (22.8)	-
Student services/other	-	-	77 (28.7)	-
Job title, n (column %)				
Faculty	-	-	-	110 (23.4)
Staff	-	-	-	311 (66.2)
Postdoctoral scholar/other	-	-	-	49 (10.4)
Currently working outside the home, n (column %)	748 (25.6)	418 (19.2)	228 (85.1)	102 (21.7)
Pre-enrollment COVID-19 diagnosis, n (column %)	12 (0.4)	8 (0.4)	1 (0.4)	3 (0.6)

*Categories not mutually exclusive.

SARS-CoV-2 incidence

During the study period, participants underwent 7,638 qPCR tests for active SARS-CoV-2 infection, with a mean of 2.6 tests per participant (range: 0-9). Almost all (99.9%) participants completed at least one qPCR test. Overall, 60 participants (2.0%) tested positive: 57 students, 2 essential workers, and 1 faculty/staff.

Among cohorts, students were at highest risk of incident infection over the study period (IRR students vs. faculty/staff: 5.83; 95% confidence interval [CI]: 1.28, 102.99). Due to the low number of cases outside of the student cohort, we examined additional risk factors for infections among students only (Table 2), finding higher rates of infection among students who were 18-19 years old (IRR vs. students ≥22 years: 8.34; 95% CI: 4.17, 17.48) and undergraduates (IRR vs. graduate students: 4.12; 95% CI: 2.17, 8.66). We also observed a higher incidence among white students (IRR: 2.80 vs. non-white students; 95% CI: 1.53, 5.54). These associations were largely driven by an outbreak among participants living in fraternities or sororities. Nearly one-quarter of participants living in fraternities or sororities were infected with SARS-CoV-2 during the study period (IRR vs. other students: 20.86; 95% CI: 12.27, 35.54), and these participants accounted for 49% of cases observed among student participants.

Table 2. Bivariate associations between sociodemographic characteristics and SARS-CoV-2 incidence among student participants in the Safe Campus Initiative, June-August 2020.

	Cases, N (row %)	Non-Cases, N (row %)	IRR (95% CI)
Overall*	57 (2.6)	2,120 (97.4)	-
Age			
18-19 years	21 (8.0)	243 (92.0)	8.34 (4.17, 17.48)
20-21 years	24 (3.8)	607 (96.2)	4.15 (2.11, 8.58)
≥22 years	12 (0.9)	1,270 (99.1)	Reference
Gender			
Woman	37 (3.1)	1,147 (96.9)	1.45 (0.85, 2.58)
Man	19 (2.1)	892 (97.9)	Reference
Non-binary/other	0 (0)	46 (100)	-
Race/ethnicity**			
American Indian/Alaska Native	0 (0)	29 (100)	-
Asian/Pacific Islander	11 (1.6)	691 (98.4)	0.49 (0.24, 0.91)
Black/African American	1 (1.2)	82 (98.8)	0.45 (0.03, 2.03)
Hispanic/Latine/Spanish origin	8 (2.3)	337 (97.7)	0.88 (0.39, 1.76)
White	45 (3.6)	1,216 (96.4)	2.80 (1.53, 5.54)
Other	4 (1.8)	217 (98.2)	0.65 (0.20, 1.58)
Program level			
Undergraduate	46 (4.1)	1,067 (95.9)	4.12 (2.17, 8.66)
Graduate	10 (1.0)	1,027 (99.0)	Reference
Living at fraternity/sorority	28 (22.4)	97 (77.6)	20.86 (12.27, 35.54)
Currently working outside the home	6 (1.4)	410 (98.6)	0.51 (0.20, 1.11)

IRR: incidence rate ratio, CI: confidence interval.
*N=2,177 students with at least one qPCR test for SARS-CoV-2 during the study period.
**Not mutually exclusive; all participants not included in specified racial/ethnic category served as reference for each comparison.

Phylogenetic analysis

We retrieved whole viral genome sequences for 35 of the 60 positive cases from this study, 29 (83%) of which were found to be part of a campus super-spreader event involving a total of 57 campus-affiliated individuals with samples sequenced by IGI (Figure 1A). Most (69%) study participants within this cluster lived at one of two residences, with likely a single participant originating the super-spreader event. The cluster of genomes was defined by three mutations (A6360G, C24502A and G110083T), two of which were extremely rare at the time of the outbreak. The combination of the three variants was only found in four genomes outside of

this cluster (two in the UK and two in Florida) by October 2020, making it a strong phylogenetic signature.

Phylogenetic analysis demonstrated that the cluster remained confined to campus, as this signature was not observed in any genomes from samples in the surrounding communities or California state in the months following the super-spreader event. When the trio of mutations was searched in a phylogeny constructed from over 1.2 million genomes worldwide using UShER in April 2021,[23] no descendent leaves were found in the tree under the cluster (Figure 1B), indicating that the lineage died out after the super-spreader event.

Factors associated with test positivity

At least one symptom survey was completed in the 7 days before sample collection for 90% of tests (n=6,864), including 72% of tests (n=5,469) that had symptom data from the day of sample collection. Of the 54 cases who completed at least one survey during the week before their positive sample was collected (mean: 4 surveys), 23 cases (43%) had reported at least one of the nine COVID-19 symptoms that triggered a notification for them to test. Test positivity was 12.4 times higher among participants who had a recent symptom-triggered notification (95% CI: 7.3, 21.3) (Table 3). Notification-triggering symptoms most strongly associated with test positivity included loss of sense of taste or smell and feeling feverish. Weakness, sweats or chills, and swollen glands were the non-triggering symptoms most strongly associated with test positivity.

Table 3. Bivariate associations between prospectively monitored symptoms and exposures and SARS-CoV-2 qPCR test positivity among participants in the Safe Campus Initiative, June-August 2020.

	Test Positivity, % (+ Tests / All Tests)	IRR (95% CI)
Overall*	0.8 (60 / 7,629)	-
Signs/symptoms within 7 days of test		
No	0.4 (21 / 5,704)	Reference
Yes (any)	3.2 (31 / 971)	8.6 (5.0, 14.9)
- Temperature ≥100.4°F †	0.0 (0 / 8)	0.0 (0.0, 0.0)
- Temperature ≥100.0°F	11.8 (2 / 17)	15.6 (4.1, 60.4)
- Temperature ≥99.0°F	2.6 (9 / 346)	4.1 (1.9, 8.7)
- Feeling feverish †	14.9 (11 / 74)	23.7 (12.7, 44.3)
- Dry cough †	5.5 (7 / 128)	7.9 (3.6, 17.2)
- Coughing up mucus †	5.5 (5 / 91)	7.6 (3.1, 18.8)
- Unusual chest pain or pressure †	9.7 (6 / 62)	13.8 (6.1, 31.1)
- Difficulty breathing †	5.6 (1 / 18)	7.2 (1.1, 48.7)
- Shortness of breath †	8.7 (4 / 46)	11.9 (4.4, 31.9)
- Trouble thinking/concentrating †	7.6 (5 / 66)	10.6 (4.3, 25.7)
- Loss of sense of taste †	42.9 (3 / 7)	57.6 (23.5, 141)
- Loss of sense of smell †	33.3 (4 / 12)	45.8 (19.0, 110)
- Any notification-triggering symptom †	5.8 (23 / 397)	12.4 (7.3, 21.3)
- Loss of appetite	10.0 (6 / 60)	14.3 (6.3, 32.5)
- Fatigue	3.5 (13 / 373)	5.6 (3.0, 10.4)
- Trouble sleeping	5.1 (7 / 137)	7.4 (3.4, 16.1)
- Headache	4.6 (14 / 302)	7.7 (4.2, 14.1)
- Runny, blocked, or painful sinuses	5.2 (14 / 268)	8.8 (4.8, 16.0)
- Sneezing	1.9 (2 / 104)	2.5 (0.6, 10.0)
- Swollen, red, or painful eyes	8.6 (5 / 53)	12.1 (4.9, 29.7)
- Sore throat	3.1 (8 / 259)	4.5 (2.1, 9.4)
- Stomach pain	5.8 (5 / 86)	8.1 (3.3, 19.8)
- Diarrhea	4.8 (4 / 83)	6.6 (2.4, 17.8)
- Nausea or vomiting	3.3 (3 / 92)	4.4 (1.4, 13.6)
- Body aches or muscle pain	8.1 (12 / 149)	13.0 (7.0, 24.4)
- Sweats or chills	11.3 (10 / 89)	17.5 (9.0, 34.0)
- Swollen glands	11.9 (5 / 42)	16.6 (7.0, 39.7)
- Weakness	13.2 (10 / 76)	20.5 (10.6, 39.4)
Exposures within 14 days before test		
No	0.3 (14 / 4,179)	Reference
Yes (any)	3.4 (17 / 499)	10.1 (5.0, 20.4)
- Suspected or confirmed COVID-19 case in household †	6.7 (6 / 89)	14.7 (6.0, 35.9)
- Close contact with suspected or confirmed case outside household	2.9 (4 / 138)	6.3 (2.2, 18.2)
- Household member with new COVID-19-like symptoms †	4.4 (5 / 114)	7.6 (3.0, 19.6)
- Household member with any new symptoms of illness	2.4 (8 / 336)	4.7 (2.1, 10.4)

- Any notification-triggering exposure †	5.2 (9 / 173)	12.3 (5.6, 26.9)
Activities within 14 days before test		
No	0.5 (3 / 630)	Reference
Yes (any)	0.7 (29 / 4,142)	1.5 (0.5, 4.8)
- Spent time at another residence	1.1 (26 / 2,330)	4.6 (1.9, 11.1)
- Had visitors at own residence	1.0 (22 / 2,203)	2.5 (1.2, 5.4)
- Attended gathering >10 people	2.8 (19 / 672)	9.0 (4.4, 18.1)
- Worked outside of home	0.5 (10 / 2,132)	0.6 (0.3, 1.2)
- Used public restroom	0.7 (12 / 1,830)	1.0 (0.5, 2.0)
- Used public transportation	0.6 (5 / 695)	0.8 (0.3, 2.3)
- Participated in group sports	1.6 (4 / 255)	2.6 (0.9, 7.3)

qPCR: quantitative polymerase chain reaction, IRR: incidence rate ratio, CI: confidence interval.
*Excluding resamples and repeated positives; includes N=2,914 participants with at least one qPCR test for SARS-CoV-2 during the study period.
† Reporting triggered notification to test.

Participants completed at least one weekly exposure survey in the 14 days before sample collection for 61% of tests (n=4,678). Of the 31 cases who had recently completed an exposure survey at the time of sample collection, 9 (29%) reported a potential household exposure that triggered a notification for them to test (Table 3). Test positivity was 12.3 times higher among participants who had a recent exposure-triggered notification (95% CI: 5.6, 26.9). Test positivity was also significantly higher among participants who reported recent engagement in 'higher risk' social activities, most notably attending a gathering of more than 10 people (IRR: 9.0; 95% CI: 4.4, 18.1).

SARS-CoV-2 seroprevalence

Only 18 (0.6%) of 2,877 participants who provided blood samples at baseline had SARS-CoV-2 antibodies (Table 4), all but one of them students. Most participants with antibodies at baseline either suspected past infection (28%), had been previously diagnosed (22%), or had a positive qPCR test the day blood was drawn (11%). Most (85%) participants in the student and essential worker cohorts provided blood samples at both baseline and endline (mean interval between samples: 48 days). Among 2,076 participants with baseline and endline blood samples, 33 (1.6%) seroconverted from non-reactive at baseline to reactive at endline, 30

of whom (91%) were also diagnosed via qPCR test during the study. Of the three participants who seroconverted without a positive qPCR test, two self-reported suspected past infection (one before baseline, one during the study period), while the third did not suspect past infection and had four negative qPCR tests over 40 days of study participation.

Of the 60 participants with incident SARS-CoV-2 infection during the study period, 41 (68%) provided an endline blood sample at least one week after the date of their first positive qPCR test (mean time between positive qPCR test and blood sample: 36 days; range 13-52 days). Of these, 34 (83%) were reactive (Table 4).

Table 4. Seroprevalence of SARS-CoV-2 antibodies among participants in the Safe Campus Initiative, June-August 2020.

	Baseline, N (%)	Endline, N (%)	Both, N (%)
Serostatus – Cross-sectional*			
Reactive	18 (0.6)	48 (2.3)	-
Non-reactive	2,859 (99.4)	2,039 (97.7)	-
Serostatus – Longitudinal**			
Non-Reactive → Non-Reactive	-	-	2,029 (97.7)
Non-Reactive → Reactive	-	-	33 (1.6)
Reactive → Non-Reactive	-	-	0 (0)
Reactive → Reactive	-	-	14 (0.7)
Serostatus – Previous qPCR Positive†			
Reactive	-	34 (82.9)	-
Non-reactive	-	7 (17.1)	-

qPCR: quantitative polymerase chain reaction.
*N=2,888 participants who provided at least one blood sample.
**N=2,076 participants who provided blood samples at baseline and endline.
†N=41 participants who provided an endline blood sample ≥7 days *after* infection with SARS-CoV-2 identified via positive qPCR test.

Discussion

This study provides a model of a voluntary, incentivized system to identify and link at-risk students to SARS-CoV-2 testing. While the incidence and seroprevalence of SARS-CoV-2 were generally low in this cohort of university students and employees in the summer of 2020, we

observed the highest incidence among undergraduate students living in congregate settings, with nearly half of cases found to be associated with a super-spreader event.

Within this cohort, we previously demonstrated the acceptability of our low-barrier SARS-CoV-2 mitigation approach and the limitations of temperature monitoring as a tool for case identification.[14,26] The present analysis builds upon these contributions by triangulating prospective qPCR testing data with phylogenetic analyses of positive samples and serial antibody testing to evaluate whether case identification and containment were achieved. In doing so, we found evidence that the system successfully identified a high proportion of incident SARS-CoV-2 cases among participants and may have mitigated community transmission after an outbreak. Specifically, 91% of participants with newly-identified antibodies for SARS-CoV-2 at the end of the study had also been diagnosed with incident infection via qPCR test during the study period. While a sizeable cluster of cases among participants was traced to a single super-spreader event, the associated cluster lineage was successfully contained without spreading beyond campus. As the outbreak unfolded, the system also allowed for rapid real-time response (i.e., surveillance testing notifications to students living in congregate housing) and offered a readily accessible, incentivized entry point for testing for students concerned about potential exposure.

Although some universities have adopted punitive measures intended to prevent transmission by controlling student behavior (for example, suspending students for hosting gatherings),[29–31] this approach has been criticized for its potential to reduce students' trust and cooperation.[32–34] Instead of punishing or shaming students who fail to adhere to public health guidance, some epidemiologists have called for a harm-reduction approach which supports and engages students as part of the solution.[32–34] The present study reinforces the potential to integrate voluntary testing and risk monitoring systems to support targeted case identification, as evidenced by the significantly higher positivity rates found among participants whose self-reported symptoms and exposures triggered notifications to test. Our findings also support

increased outreach to groups of students at highest risk, particularly younger students in congregate housing.

This study is strengthened by rich longitudinal data, including symptom and exposure tracking, qPCR testing, and seroprevalence data from more than 2,000 participants. The study population comprised of a broad sample of university affiliates, both students and employees, with strong representation of university subpopulations perceived to be at higher risk of infection (e.g., undergraduates, essential healthcare workers). As on-campus activities were severely restricted throughout the study period (all classes were held online, and few students were living in residence halls), this study cannot provide insight into SARS-CoV-2 transmission risks related to on-campus student activities. Nevertheless, as 73% of UC Berkeley undergraduate students lived off campus *before* the pandemic,[35] systems to detect off-campus (i.e., community and household) transmission remain important for SARS-CoV-2 monitoring efforts among students. Additionally, all participants in the essential workers cohort and a subset of participants in the faculty/cohort were working on campus during the study period, further motivating efforts to monitor incidence in this population.

There remain several limitations. We observed relatively few SARS-CoV-2 cases during the study period, which took place before the development of highly transmissible variants, such as Delta and Omicron, and before vaccine rollout. Further research is necessary to adapt and evaluate similar systems in the context of both heightened transmissibility and more prevalent natural and vaccine-induced immunity. Observed associations between symptoms and positivity may also differ among those who have been infected by more recent variants and/or vaccinated. Additionally, a high proportion of identified cases were traced to one outbreak, limiting the generalizability of our exploratory assessment of risk factors for incident infection. There was also anecdotal evidence that the outbreak prompted exposed students to enroll as study participants.[14] While this self-referral into the study is likely to increase selection bias, it also illustrates the utility of implementing non-stigmatizing, incentivized testing approaches to

increase testing uptake among at-risk students. Finally, our identification of participants who seroconverted between baseline and endline may be incomplete due to loss-to-follow up and imperfect sensitivity of SARS-CoV-2 antibody testing.

By integrating symptom and exposure monitoring systems with low-barrier testing, we identified incident SARS-CoV-2 infections to reduce transmission within a university setting. While there have been seismic shifts in the SARS-CoV-2 pandemic since 2020, universities continue to grapple with how best to mitigate on-campus spread in the face of emerging variants, incomplete vaccination coverage, breakthrough infections, and decreased reliance on other mitigation strategies (e.g., masking, remote learning).[36,37] The lessons learned through this study may inform the design of future adaptive strategies, ideally building beyond symptom/exposure monitoring and qPCR testing to integrate complementary interventions such as rapid antigen self-testing and vaccination promotion.

Keywords: COVID-19, SARS-CoV-2, United States, young adults, students, universities, essential workers, seroprevalence

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Data sharing: De-identified data sets used in analyses and accompanying R Markdown script files will be publicly available at the time of publication at the following link: https://github.com/lauren-hunter/bcsci

Ethical approvals: All study activities were approved by the University of California, Berkeley Committee for the Protection of Human Subjects (#2020-06-13349, #2020-05-13261, #2020-04-13238).

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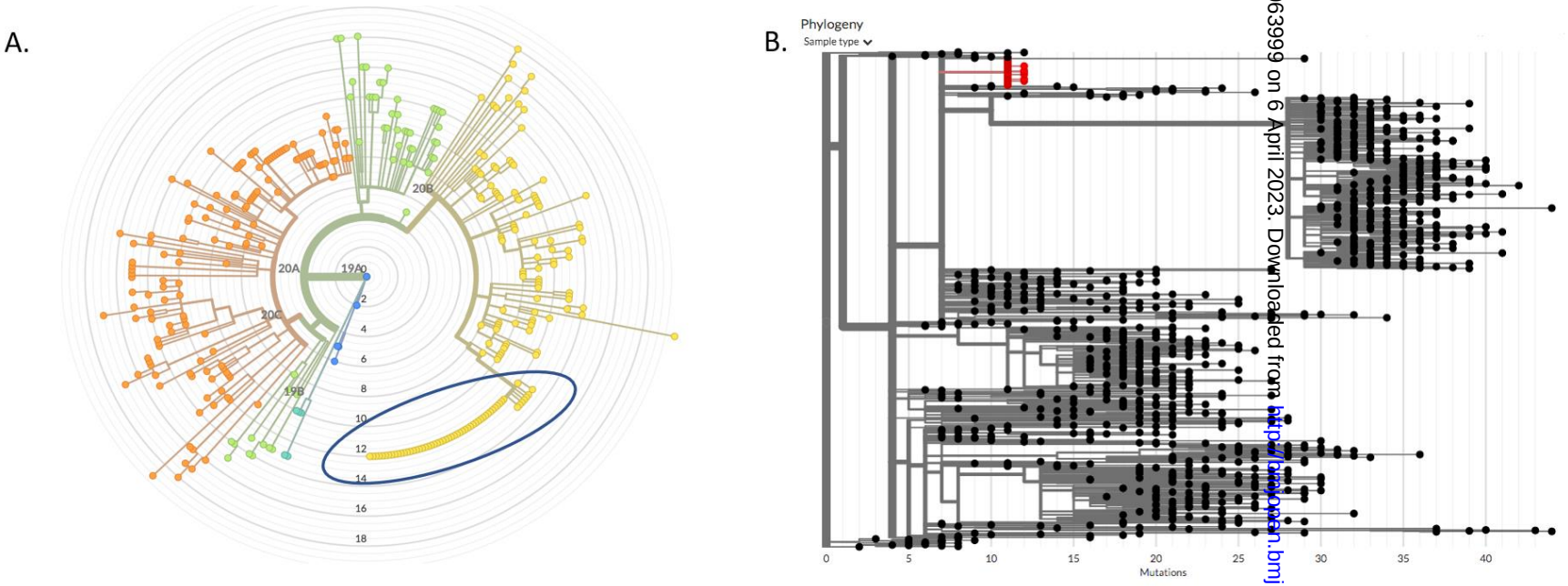
Figure 1. Phylogeny of outbreak-associated strain of SARS-CoV-2 among participants in the Safe Campus Initiative.



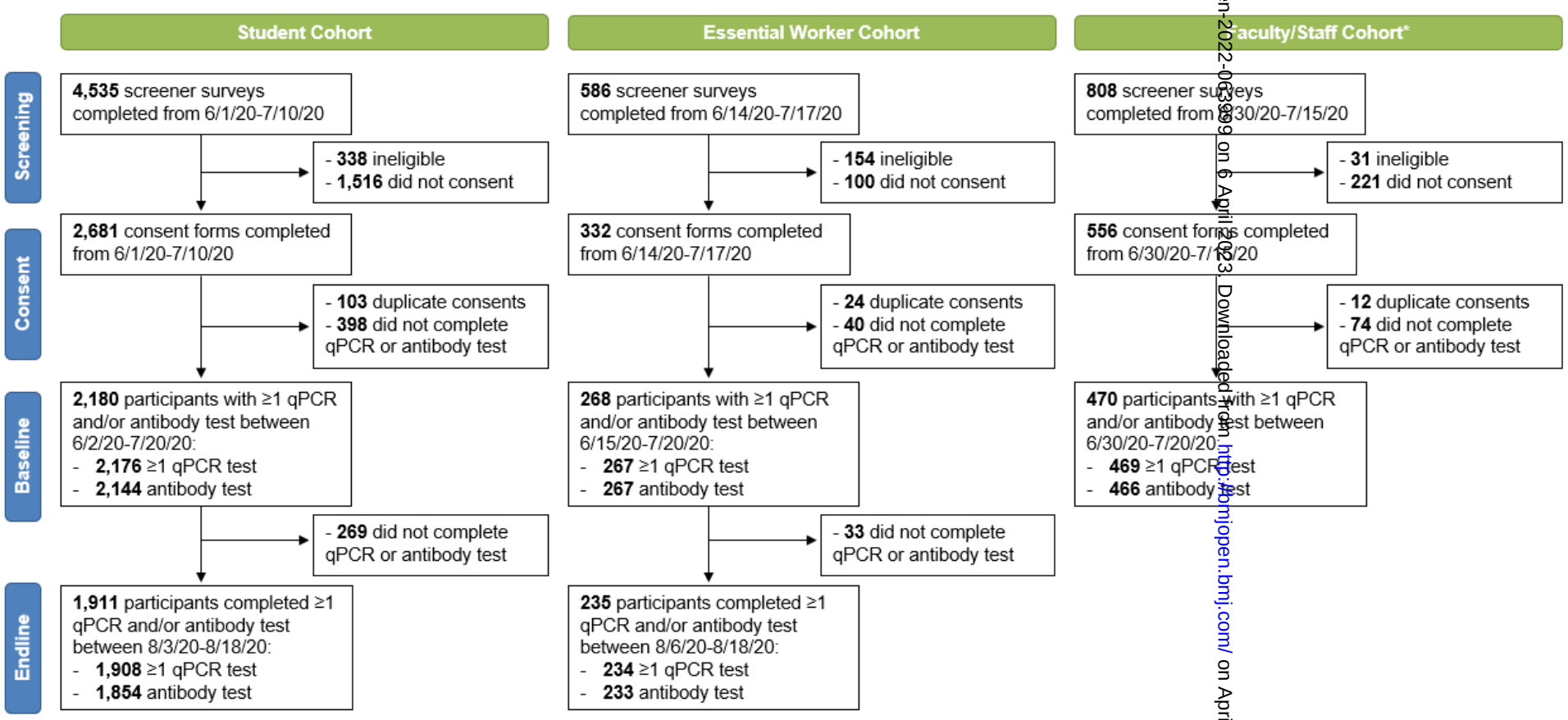
A. A maximum likelihood phylogeny constructed from 357 genomes sequenced by the Innovative Genomics Institute between May and July 2020 constructed using Nextstrain. Branch lengths represent divergence from Wuhan reference genome at center. Blue circle marks cluster of identical genomes from a campus super-spreader event.

B. A 1,057 node subtree of a neighbor-joining tree constructed with all SARS-CoV-2 sequences to date (constructed using UShER with over 1 million genomes in April 2021), showing the most similar genomes to the super-spreader event cluster (in red). There are no descendant branches from the cluster, demonstrating that the outbreak was contained and the lineage died out.

Supplementary Table 1. Eligibility criteria across Berkeley COVID-19 Safe Campus Study cohorts.

	Student Cohort	Essential Worker Cohort	Faculty/Staff Cohort
Eligibility Criteria	- At least 18 years of age	- At least 18 years of age	- At least 18 years of age
	- Currently enrolled as an undergraduate or graduate student at UC Berkeley (i.e., not graduated in Spring 2020 or incoming for Fall 2020)	- Currently employed in one of the following departments at UC Berkeley: health services, police, facility services or other building management, environmental health and safety, laboratory animal care, athletics, dining, childcare, other residential or student services - Currently working on campus at UC Berkeley *or* expected to return to work during June 2020	- Currently employed as a faculty member, staff member, or postdoctoral scholar at UC Berkeley - Not already enrolled in the essential workers cohort
	- Primarily residing in Alameda County or Contra Costa Country between 6/1/20-8/31/20	N/A	- Primarily residing in Alameda County or Contra Costa Country between 6/1/20-8/31/20
	- Willing to sign release of information for COVID-19-related medical records	- Willing to sign release of information for COVID-19-related medical records	- Willing to sign release of information for COVID-19-related medical records

Supplementary Figure 1. Flow diagram for Berkeley COVID-19 Safe Campus Study cohorts.



qPCR: quantitative polymerase chain reaction.
*Faculty/staff cohort not invited for endline testing appointments but could complete follow-up qPCR tests through 8/18/20.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9, Supplementary Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-9, Supplementary Table 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary Figure 1
		(b) Give reasons for non-participation at each stage	Supplementary Figure 1
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	11-13
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14, Tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	10, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Title: Monitoring SARS-CoV-2 incidence and seroconversion among university students and employees: a longitudinal cohort study in California, June to August 2020

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Abstract

Objectives: To identify incident SARS-CoV-2 infections and inform effective mitigation strategies in university settings, we piloted an integrated symptom and exposure monitoring and testing system among a cohort of university students and employees.

Design: Prospective cohort study.

Setting: A public university in California from June to August 2020.

Participants: 2,180 university students and 738 university employees.

Primary outcome measures: At baseline and endline, we tested participants for active SARS-CoV-2 infection via quantitative polymerase chain reaction (qPCR) test and collected blood samples for antibody testing. Participants received notifications to complete additional qPCR tests throughout the study if they reported symptoms or exposures in daily surveys or were selected for surveillance testing. Viral whole genome sequencing was performed on positive qPCR samples, and phylogenetic trees were constructed with these genomes and external genomes.

Results: Over the study period, 57 students (2.6%) and 3 employees (0.4%) were diagnosed with SARS-CoV-2 infection via qPCR test. Phylogenetic analyses revealed that a super-spreader event among undergraduates in congregate housing accounted for at least 48% of cases but did not spread beyond campus. Test positivity was higher among participants who self-reported symptoms (incidence rate ratio [IRR]: 12.7; 95% confidence interval [CI]: 7.4, 21.8) or had household exposures (IRR: 10.3; 95% CI: 4.8, 22.0) that triggered notifications to test. Most (91%) participants with newly identified antibodies at endline had been diagnosed with incident infection via qPCR test during the study.

Conclusions: Our findings suggest that integrated monitoring systems can successfully identify and link at-risk students to SARS-CoV-2 testing. As the study took place before the evolution of highly transmissible variants and widespread availability of vaccines and rapid antigen tests, further research is necessary to adapt and evaluate similar systems in the present context.

Strengths and limitations of this study

- The study is strengthened by rich longitudinal data including more than 117,000 daily symptom surveys; 17,000 weekly exposure surveys; 7,600 qPCR tests to detect active SARS-CoV-2 infection; and 4,900 antibody tests to detect previous infection collected from 2,918 university students and employees over three months.
- We used seroconversion data from serial antibody tests and phylogenetic analyses comparing viral genome sequences to a broader database to evaluate the extent to which the study system identified incident cases and contained an outbreak among university students.
- Our identification of participants who seroconverted between baseline and endline may be incomplete due to loss-to-follow up and imperfect sensitivity of SARS-CoV-2 antibody testing.
- A high proportion of identified cases were traced to one outbreak, limiting the generalizability of our exploratory assessment of risk factors for incident infection. .

Background

Universities have been identified as hotspots for SARS-CoV-2 transmission in the United States,[1] where SARS-CoV-2 incidence is highest among young adults.[2] Young adults may be less likely to adhere to social distancing guidelines and more likely to experience workplace exposure (for example, at food service or retail jobs).[2] Their risk may be heightened in university settings where many live in congregate housing, interact with wide social networks, or attend large gatherings.[3] Although young adults are at low risk of serious acute illness or death from COVID-19 (the disease caused by SARS-CoV-2),[4] the higher likelihood of asymptomatic or mildly symptomatic infection in this age group makes young adults a key population through which SARS-CoV-2 may spread to other, more vulnerable groups.[2,5] Indeed, there is evidence that transmission among university students may lead to increased COVID-19-related mortality in the surrounding counties.[6–8] Although widespread vaccination has enabled campuses to return to in-person activities, the elimination of SARS-CoV-2 transmission in campus populations may be stymied by vaccine hesitancy among students and employees and breakthrough infection and subsequent transmission by vaccinated persons, particularly in the context of waning immunity and viral variants which reduce vaccine efficacy.[9,10] Therefore, rapid and resource-efficient identification of incident cases in university populations is a critical first step of outbreak investigation and control, followed by isolation, case investigation, and contact tracing, to minimize transmission within campus and to the broader community.

Universities have adopted a wide range of approaches for testing and outbreak mitigation.[11–13] While a number of well-resourced universities have scaled up testing capacity in order to frequently test all students and employees accessing campus or living in university-affiliated housing,[13] many other universities do not have well-defined testing strategies or restrict testing to those with symptoms or known exposure.[12] Beyond investing in testing programs, some universities have sought to reduce on-campus transmission by mandating the

completion of self-administered symptom screening tools by students and employees. However, such tools have primarily been used to regulate daily access to campus (i.e., deny entry to those who report COVID-19-like symptoms), rather than to detect emergent outbreaks among university populations. As universities resume normal operations and discontinue mitigation strategies such as masking, non-punitive, resource-efficient strategies which can both identify those who are at highest risk of infection *and* expediently link them to low-barrier testing services may play a key role in transitioning from a "one-size-fits-all" approach of uniform testing to a sustainable monitoring paradigm.

In 2020, we piloted an integrated symptom and exposure monitoring and testing system designed to identify incident SARS-CoV-2 infections among a cohort of university students and employees.[14] Here we describe the incidence and seroprevalence of SARS-CoV-2 infection within this cohort to evaluate the extent to which incident infections were successfully detected and contained over the study period, identify sociodemographic factors associated with incident infection, and ascertain which self-reported symptoms and exposures tracked by the monitoring system were predictive of test positivity, with the ultimate objective of informing monitoring and testing strategies in university settings.

Methods

Study design and setting

The study comprised three prospective cohorts of University of California, Berkeley affiliates followed from June to August 2020: students, essential workers (i.e., employees working on campus in health, facilities, or student services), and other employees (hereafter, "faculty/staff"). We report the findings according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies.[15]

Throughout the study period, public health orders mandated the use of face coverings in public and upheld many restrictions set forth by earlier shelter-in-place orders, while allowing

phased reopening of certain businesses and activities.[16] UC Berkeley did not offer in-person classes, and on-campus work was restricted to essential workers and a small subset of faculty, staff, and student researchers. Although few students were living in on-campus residence halls, many students continued to live in congregate living settings off campus, such as fraternities, sororities, and co-operative housing. From June to August 2020, daily case counts in Alameda County ranged from approximately 50 to 350 (0 to 17 within the city of Berkeley).[17]

Participant recruitment and eligibility

The study was promoted through targeted messages from university officials to campus email listservs and social media platforms from early June to mid-July 2020. To increase reach to students expected to be at higher risk of COVID-19, we also placed flyers in congregate living settings and conducted in-person recruitment for student athletes who had resumed training on campus. Participants were eligible to enroll in the study if they were at least 18 years of age, were a current student or employee at UC Berkeley, and planned to live in or near Berkeley during the summer of 2020. Specific eligibility criteria and enrollment windows varied by cohort (Supplementary Table 1, Supplementary Figure 1).

Upon enrollment, participants were linked to an online baseline survey that collected sociodemographic data and information about their COVID-19-related health history. Participants were then referred to a baseline testing appointment at University Health Services (UHS) which included a SARS-CoV-2 quantitative polymerase chain reaction (qPCR) test and blood collection for antibody testing (procedures described below). To facilitate daily temperature monitoring, study staff also provided participants with free oral thermometers upon request at testing appointments. Participants who completed this appointment or a non-study qPCR test at UHS by July 20 were eligible to remain in the study. We pre-specified a maximum sample size of 4,000 participants across cohorts but did not reach this limit before the final day of baseline data collection.

Symptom and exposure surveys

Participants received daily text messages or emails, depending on their preference specified in the baseline survey, which linked to short symptom surveys through which they reported their body temperature and any symptoms of illness. Once per week, the daily survey included a longer exposure module, which asked about recent symptoms of illness among their household member(s), potential exposure(s) to COVID-19, and activities related to potential COVID-19 risk. All surveys were administered via REDCap.[18,19]

Endline survey and testing

In early August, participants were sent an endline survey which collected updated information on their COVID-19 history to identify any diagnoses outside of the study. Participants in the student and essential worker cohorts were also invited to complete endline testing appointments by August 18, including a final qPCR test and blood collection.

qPCR testing

Midturbinate nasal and oral swabs were collected by UHS clinical staff and tested for SARS-CoV-2 by qPCR at the Innovative Genomics Institute (IGI).[20] qPCR tests were performed at baseline for all three cohorts and at endline for the student and essential worker cohorts. Between baseline and endline testing, additional qPCR tests were performed for the following reasons:

- **Symptom- or exposure-based tests triggered based on participants' responses in daily surveys**: Participants who reported COVID-19-like signs or symptoms[1] (in

[1] Signs or symptoms which triggered a testing notification when reported were: temperature of ≥100.4°F, dry cough (without mucus), coughing up mucus, feeling feverish, unusual pain or pressure in the chest, difficulty breathing, shortness of breath, unexplained trouble thinking or concentrating, loss of sense of taste, or loss of sense of smell.

themselves or household member(s)) or who reported a suspected or confirmed COVID-19 case in their household were automatically notified to sign up for a qPCR test.

- **Random surveillance testing**: A subset of participants in the student and faculty/staff cohorts who had not had a qPCR test within a week were randomly selected and emailed notifications to come in for surveillance testing in July.
- **Address-based surveillance testing**: Participants who lived at the same address as another participant who tested positive for SARS-CoV-2 were immediately emailed surveillance testing notifications. Following an outbreak among group-housed students in early July, surveillance testing notifications were also emailed to all participants who had not been tested within the week and who reported living in fraternities, sororities, or co-operative housing.
- **Participant-initiated testing**: Participants could self-schedule study testing appointments on demand, with or without consulting a healthcare provider and regardless of exposure history.

Participants with positive qPCR test results were informed by phone by UHS clinical staff, who provided guidance on isolation and performed case investigation to identify potential contacts. Participants with negative qPCR test results were informed of their results via the UHS online patient portal.

SARS-CoV-2 sequencing and phylogenetic analyses

Viral whole genome sequencing was performed on a set of positive samples at the IGI, using previously described procedures.[21] Briefly, SARS-CoV-2 RNA extracted from swabs was reverse transcribed using SuperScript IV (Invitrogen), and the viral genome was amplified from the resulting cDNA in four separate qPCR reactions using distinct primer sets tiling the SARS-CoV-2 genome. The four qPCR reactions were pooled 1:1:1:1 and diluted 1:50 in H_2O. A second qPCR reaction was set up to add Nextera Unique Dual Indexing (UDI) sequences to

either end of the amplicons. The resulting qPCR reaction was cleaned up using 0.7x AMPureXP beads (Beckman Coulter) and quantified using a Qubit dsDNA HS Assay Kit (Thermo Fisher). The libraries were then pooled to an equimolar ratio and sequenced with a 10% PhiX spike in using a MiSeq v3 kit at 300bp PE reads.

Fastq sequencing files were processed through a custom pipeline using publicly available software. The reads were preprocessed by quality trimming, removing adaptors, and PhiX cleaning with BBTools,[22] and then aligned to the Wuhan reference sequence (NC_045512.2) with minimap2 v2.16-r922. ARTICv3 primers were trimmed, and the consensus sequence was built with iVar v1.3.1, where an 'N' is called if the depth is less than 10 reads at any nucleotide. The genomes were then processed through the Nextstrain Auger pipeline with other genomes from GISAID to construct a maximum likelihood tree.[23,24] Several phylogenies were constructed for this analysis: a tree of 7,091 genomes subsampled from the worldwide genomes in GISAID at the time (approximately 200,000 genomes as of October 2020) was used to place the IGI genomes in the larger tree; a tree with all IGI genomes sequenced at the time of analysis (356 genomes); and a tree containing 500 genomes (from 1 million genomes as of April 2021) was constructed using UShER.[25]

Antibody testing

Up to 10 mL of blood was collected by phlebotomists via venipuncture at baseline from participants in all three cohorts and again at endline from participants in the student and essential worker cohorts. Blood was centrifuged and serum was stored at -20°C for 2 to 4 months before being tested at Vitalant Research Institute using the VITROS Immunodiagnostic Products Anti-SARS-CoV-2 Total Reagent Pack, which detects IgA, IgG, and IgM antibodies against the SARS-CoV-2 spike protein S1 antigen and has an estimated clinical specificity of 100% and unreported sensitivity.[26]

Participant compensation

Participants in the student cohort received a $50 gift card after completing baseline testing and 10 daily surveys; this incentive was conditional on daily survey completion to encourage early habit formation.[27] Student participants received a second $50 gift card at their endline testing appointment. To facilitate travel to and from UHS for testing appointments, student participants were also offered pre-paid car rides via a ride-sharing app.

Participants in the essential worker cohort received a gift card worth $1 per daily survey completed (to a maximum of $70) after the study ended. Participants in the faculty/staff cohort were not compensated.

Statistical analyses

To identify sociodemographic factors associated with incident infection, we used Poisson regression to estimate unadjusted incidence rate ratios (IRRs) for SARS-CoV-2 infection by study cohort and within strata of sociodemographic variables self-reported in the baseline survey (e.g., age, gender, housing type), setting person-months of enrollment as an offset term to account for differing lengths of follow-up.

We also calculated IRRs comparing test positivity by recent signs/symptoms, exposures, and activities reported in the daily and weekly surveys. We estimated IRRs for several temperature thresholds (i.e., ≥100.4°F, ≥100.0°F, ≥99.0°F) to compare to symptom-specific IRRs; however, continuous associations between temperature and positivity have been previously explored in this cohort, finding that temperature screening has low sensitivity to SARS-CoV-2 infection and, thus, limited efficacy as a primary means of detection.[28] While it was not possible to isolate participants' specific reason(s) for testing over the study period (e.g., participants could receive symptom- and/or exposure-triggered testing notifications over the same time window in which they completed baseline or endline testing), we linked qPCR test results to recently-completed symptom and exposure surveys to identify testing appointments

that took place in the days or weeks following symptom- and exposure-triggered testing notifications (Supplementary Figure 2). We accounted for clustered observations due to repeated tests per participant using a generalized estimating equation approach with Huber-White standard error estimates and an exchangeable working correlation structure.[29]

Finally, to assess the extent to which the testing and monitoring system captured incident infections, we identified participants who seroconverted from having non-reactive (no antibodies detected) to reactive (antibodies detected) blood samples between baseline and endline and calculated the proportion of these participants who were also diagnosed with incident SARS-CoV-2 infection via positive qPCR test during the study period. Analyses were conducted in R version 4.2.1.[30]

Ethical approvals

All study activities were approved by the University of California, Berkeley Committee for the Protection of Human Subjects (#2020-06-13349, #2020-05-13261, #2020-04-13238).

Patient and public involvement

The study's target population comprised university students and employees. While the study was conducted by faculty, staff, and graduate students from the UC Berkeley School of Public Health, University Health Services, and the Innovative Genomics Institute, the broader student body and university workforce were not involved in designing the study or selecting the research question, outcome measures, or method of disseminating results.

Results

Participant recruitment and retention

Between June 1 and July 20, 2020, we enrolled 2,180 students, 268 essential workers, and 470 faculty/staff who completed at least one qPCR test or antibody test (Table 1,

Supplementary Figure 1). The student cohort was split between undergraduate (52%) and graduate (48%) students. Nearly half (44%) of essential workers worked in health services. While 85% of essential workers were working on campus at the time of enrollment, most (81%) faculty/staff were working entirely remotely. At the time of enrollment, only 12 (0.4%) participants reported a previous COVID-19 diagnosis.

Participants provided a total of 5,545 person-months of follow-up from enrollment to the end of the study (mean person-days per participant: 57, range: 32-78). Participants completed a mean of 40 daily symptom surveys and 6 weekly exposure surveys over the study period, for a total of 117,239 symptom and 17,162 exposure surveys. A subset of participants did not complete any daily symptom surveys (1.7%) or weekly exposure surveys (4.2%).

Table 1. Baseline characteristics of participants in the Berkeley COVID-19 Safe Campus Initiative by study cohort, June-August 2020.

	All	Students	Essential Workers	Faculty/Staff
N (row %)	2,918 (100)	2,180 (74.7)	268 (9.2)	470 (16.1)
Age, mean ± SD	29.4 ± 11.6	24.3 ± 5.4	42.5 ± 12.3	45.2 ± 12.3
Gender, n (column %)				
Man	1,177 (40.3)	911 (41.8)	103 (38.4)	163 (34.7)
Woman	1,653 (56.6)	1,187 (54.4)	164 (61.2)	302 (64.3)
Non-binary/other	51 (1.7)	46 (2.1)	1 (0.4)	4 (0.9)
Race/ethnicity, n (column %)*				
American Indian/Alaska Native	39 (1.3)	29 (1.3)	2 (0.7)	8 (1.7)
Asian/Pacific Islander	833 (28.5)	703 (32.2)	66 (24.6)	64 (13.6)
Black/African American	103 (3.5)	83 (3.8)	16 (6.0)	4 (0.9)
Hispanic/Latine/Spanish origin	420 (14.4)	346 (15.9)	39 (14.6)	35 (7.4)
White	1,814 (62.2)	1,261 (57.8)	160 (59.7)	393 (83.6)
Other	280 (9.6)	223 (10.2)	31 (11.6)	26 (5.5)
Program level, n (column %)				
Undergraduate	-	1,114 (51.7)	-	-
Graduate	-	1,039 (48.2)	-	-
Living at fraternity/sorority, n (column %)	-	125 (5.7%)	-	-
Education, n (column %)				
High school diploma/GED	-	-	6 (2.2)	0 (0)
Some college or trade school	-	-	59 (22.0)	13 (2.8)
Bachelor's degree	-	-	78 (29.1)	119 (25.3)
Graduate/professional degree	-	-	121 (45.1)	337 (71.7)

Department, n (column %)				
Health services	-	-	129 (48.1)	-
Facilities/building services	-	-	61 (22.8)	-
Student services/other	-	-	77 (28.7)	-
Job title, n (column %)				
Faculty	-	-	-	110 (23.4)
Staff	-	-	-	311 (66.2)
Postdoctoral scholar/other	-	-	-	49 (10.4)
Currently working outside the home, n (column %)	748 (25.6)	418 (19.2)	228 (85.1)	102 (21.7)
Pre-enrollment COVID-19 diagnosis, n (column %)	12 (0.4)	8 (0.4)	1 (0.4)	3 (0.6)

*Categories not mutually exclusive.

SARS-CoV-2 incidence

During the study period, participants underwent 7,638 qPCR tests for active SARS-CoV-2 infection, with a mean of 2.6 tests per participant (range: 0-9). Almost all (99.9%) participants completed at least one qPCR test. Overall, 60 participants (2.0%) tested positive: 57 students, 2 essential workers, and 1 faculty/staff.

Among cohorts, students were at highest risk of incident infection over the study period (IRR students vs. faculty/staff: 5.8; 95% confidence interval [CI]: 1.3, 103.0). Due to the low number of cases outside of the student cohort, we examined additional risk factors for infections among students only (Table 2), finding higher rates of infection among students who were 18-19 years old (IRR vs. students ≥22 years: 8.3; 95% CI: 4.2, 17.5) and undergraduates (IRR vs. graduate students: 4.1; 95% CI: 2.2, 8.7). We also observed a higher incidence among white students (IRR: 2.8 vs. non-white students; 95% CI: 1.5, 5.5). These associations were largely driven by an outbreak among participants living in fraternities or sororities. Nearly one-quarter of participants living in fraternities or sororities were infected with SARS-CoV-2 during the study period (IRR vs. other students: 20.9; 95% CI: 12.3, 35.5), and these participants accounted for 49% of cases observed among student participants.

Table 2. Bivariate associations between sociodemographic characteristics and SARS-CoV-2 incidence among student participants in the Safe Campus Initiative, June-August 2020.

	Cases, N (row %)	Non-Cases, N (row %)	IRR (95% CI)
Overall*	57 (2.6)	2,120 (97.4)	-
Age			
18-19 years	21 (8.0)	243 (92.0)	8.3 (4.2, 17.5)
20-21 years	24 (3.8)	607 (96.2)	4.2 (2.1, 8.6)
≥22 years	12 (0.9)	1,270 (99.1)	Reference
Gender			
Woman	37 (3.1)	1,147 (96.9)	1.5 (0.9, 2.6)
Man	19 (2.1)	892 (97.9)	Reference
Non-binary/other	0 (0)	46 (100)	-
Race/ethnicity**			
American Indian/Alaska Native	0 (0)	29 (100)	-
Asian/Pacific Islander	11 (1.6)	691 (98.4)	0.5 (0.2, 0.9)
Black/African American	1 (1.2)	82 (98.8)	0.5 (0.03, 2.0)
Hispanic/Latine/Spanish origin	8 (2.3)	337 (97.7)	0.9 (0.4, 1.8)
White	45 (3.6)	1,216 (96.4)	2.8 (1.5, 5.5)
Other	4 (1.8)	217 (98.2)	0.7 (0.2, 1.6)
Program level			
Undergraduate	46 (4.1)	1,067 (95.9)	4.1 (2.2, 8.7)
Graduate	10 (1.0)	1,027 (99.0)	Reference
Living at fraternity/sorority	28 (22.4)	97 (77.6)	20.9 (12.3, 35.5)
Currently working outside the home	6 (1.4)	410 (98.6)	0.5 (0.2, 1.1)

IRR: incidence rate ratio, CI: confidence interval.
*N=2,177 students with at least one qPCR test for SARS-CoV-2 during the study period.
**Not mutually exclusive; all participants not included in specified racial/ethnic category served as reference for each comparison.

Phylogenetic analysis

We retrieved whole viral genome sequences for 35 of the 60 positive cases from this study, 29 (83%) of which were found to be part of a campus super-spreader event involving a total of 57 campus-affiliated individuals with samples sequenced by IGI (Figure 1A). Most (69%) study participants within this cluster lived at one of two residences, with likely a single participant originating the super-spreader event. The cluster of genomes was defined by three mutations (A6360G, C24502A and G110083T), two of which were extremely rare at the time of the outbreak. The combination of the three variants was only found in four genomes outside of

this cluster (two in the UK and two in Florida) by October 2020, making it a strong phylogenetic signature.

Phylogenetic analysis demonstrated that the cluster remained confined to campus, as this signature was not observed in any genomes from samples in the surrounding communities or California state in the months following the super-spreader event. When the trio of mutations was searched in a phylogeny constructed from over 1.2 million genomes worldwide using UShER in April 2021,[25] no descendent leaves were found in the tree under the cluster (Figure 1B), indicating that the lineage died out after the super-spreader event.

Factors associated with test positivity

At least one symptom survey was completed in the 7 days before sample collection for 88% of tests (n=6,668), including 72% of tests (n=5,465) that had symptom data from the day of sample collection. Of the 52 cases who completed at least one survey during the week before their positive sample was collected (mean: 4 surveys), 23 cases (44%) had reported at least one of the nine COVID-19 symptoms that triggered a notification for them to test. Test positivity was 12.7 times higher among participants who had a recent symptom-triggered notification (95% CI: 7.4, 21.8) (Table 3). Notification-triggering symptoms most strongly associated with test positivity included loss of sense of taste or smell and feeling feverish. Weakness, sweats or chills, and swollen glands were the non-triggering symptoms most strongly associated with test positivity.

Table 3. Bivariate associations between prospectively monitored symptoms and exposures and SARS-CoV-2 qPCR test positivity among participants in the Safe Campus Initiative, June-August 2020.

	Test Positivity, % (+ Tests / All Tests)	IRR (95% CI)
Overall*	0.8 (60 / 7,615)	-
Signs/symptoms within 7 days of test		
No	0.3 (18 / 5,489)	Reference**
Yes (any)	2.9 (34 / 1,179)	8.8 (5.0, 15.5)
- Temperature ≥100.4°F †	0.0 (0 / 10)	0.0 (0.0, 0.0)
- Temperature ≥100.0°F	10.5 (2 / 19)	13.2 (3.4, 50.9)
- Temperature ≥99.0°F	2.9 (12 / 417)	4.3 (2.2, 8.2)
- Feeling feverish †	15.3 (11 / 72)	24.6 (13.2, 45.8)
- Dry cough †	5.6 (7 / 126)	8.1 (3.7, 17.7)
- Coughing up mucus †	5.5 (5 / 91)	7.7 (3.1, 19.0)
- Unusual chest pain or pressure †	9.7 (6 / 62)	13.9 (6.1, 31.6)
- Difficulty breathing †	5.6 (1 / 18)	7.2 (1.0, 49.8)
- Shortness of breath †	8.9 (4 / 45)	12.3 (4.6, 32.9)
- Trouble thinking/concentrating †	7.6 (5 / 66)	10.7 (4.4, 26.1)
- Loss of sense of taste †	42.9 (3 / 7)	58.3 (23.7, 143)
- Loss of sense of smell †	33.3 (4 / 12)	46.2 (19.2, 111)
- Any notification-triggering symptom †	5.9 (23 / 393)	12.7 (7.4, 21.8)
- Loss of appetite	10.3 (6 / 58)	14.8 (6.5, 33.9)
- Fatigue	3.5 (13 / 371)	5.4 (3.0, 10.6)
- Trouble sleeping	5.1 (7 / 136)	7.5 (3.4, 16.4)
- Headache	4.7 (14 / 300)	7.8 (4.3, 14.3)
- Runny, blocked, or painful sinuses	5.2 (14 / 267)	8.8 (4.8, 16.2)
- Sneezing	1.9 (2 / 106)	2.5 (0.6, 10.1)
- Swollen, red, or painful eyes	8.6 (5 / 58)	12.1 (4.9, 30.0)
- Sore throat	3.1 (8 / 258)	4.5 (2.1, 9.5)
- Stomach pain	5.8 (5 / 86)	8.1 (3.3, 20.1)
- Diarrhea	4.9 (4 / 82)	6.7 (2.5, 18.2)
- Nausea or vomiting	3.3 (3 / 90)	4.5 (1.4, 14.2)
- Body aches or muscle pain	8.2 (12 / 146)	13.4 (7.2, 25.2)
- Sweats or chills	11.5 (10 / 87)	18.0 (9.2, 35.2)
- Swollen glands	12.2 (5 / 41)	17.3 (7.2, 41.2)
- Weakness	13.5 (10 / 74)	21.2 (11.0, 40.9)
Exposures within 14 days before test		
No	0.3 (15 / 4,319)	Reference**
Yes (any)	3.4 (17 / 506)	9.6 (4.8, 19.2)
- Suspected or confirmed COVID-19 case in household †	7.4 (7 / 95)	13.9 (6.1, 31.8)
- Close contact with suspected or confirmed case outside household	3.5 (5 / 144)	6.0 (2.3, 15.4)
- Household member with new COVID-19-like symptoms †	4.4 (5 / 114)	7.6 (3.0, 19.6)
- Household member with any new symptoms of illness	2.6 (9 / 347)	5.0 (2.3, 10.8)

- Any notification-triggering exposure †	5.1 (9 / 177)	10.3 (4.8, 22.09)
Activities within 14 days before test		
No	0.4 (3 / 678)	Reference**
Yes (any)	0.7 (29 / 4,145)	1.6 (0.5, 5.1)
- Spent time at another residence	1.1 (26 / 2,327)	4.6 (1.9, 11.3)
- Had visitors at own residence	1.0 (22 / 2,205)	2.6 (1.2, 5.5)
- Attended gathering >10 people	2.8 (19 / 672)	9.0 (4.5, 18.1)
- Worked outside of home	0.5 (10 / 2,152)	0.6 (0.3, 1.2)
- Used public restroom	0.7 (12 / 1,821)	1.0 (0.5, 2.0)
- Used public transportation	0.6 (4 / 699)	0.8 (0.3, 2.4)
- Participated in group sports	1.6 (4 / 257)	2.5 (0.9, 7.2)

qPCR: quantitative polymerase chain reaction, IRR: incidence rate ratio, CI: confidence interval.
*Excluding resamples, same-day re-tests, and repeated positives; includes N=2,914 participants with at least one qPCR test for SARS-CoV-2 during the study period.
**Reference group for "Yes (any)" comparisons; reference groups for specific symptoms/exposures/activities were those who did not report that symptom/exposure/activity.
† Reporting triggered notification to test.

Participants completed at least one weekly exposure survey in the 14 days before sample collection for 63% of tests (n=4,825). Of the 32 cases who had recently completed an exposure survey at the time of sample collection, 9 (29%) reported a potential household exposure that triggered a notification for them to test (Table 3). Test positivity was 10.3 times higher among participants who had a recent exposure-triggered notification (95% CI: 4.8, 22.0). Test positivity was also significantly higher among participants who reported recent engagement in 'higher risk' social activities, most notably attending a gathering of more than 10 people (IRR: 9.0; 95% CI: 4.5, 18.1).

SARS-CoV-2 seroprevalence

Only 18 (0.6%) of 2,877 participants who provided blood samples at baseline had SARS-CoV-2 antibodies (Table 4), all but one of them students. Most participants with antibodies at baseline either suspected past infection (28%), had been previously diagnosed (22%), or had a positive qPCR test the day blood was drawn (11%). Most (85%) participants in the student and essential worker cohorts provided blood samples at both baseline and endline (mean interval between samples: 48 days). Among 2,076 participants with baseline and endline

blood samples, 33 (1.6%) seroconverted from non-reactive at baseline to reactive at endline, 30 of whom (91%) were also diagnosed via qPCR test during the study. Of the three participants who seroconverted without a positive qPCR test, two self-reported suspected past infection (one before baseline, one during the study period), while the third did not suspect past infection and had four negative qPCR tests over 40 days of study participation.

Of the 60 participants with incident SARS-CoV-2 infection during the study period, 41 (68%) provided an endline blood sample at least one week after the date of their first positive qPCR test (mean time between positive qPCR test and blood sample: 36 days; range 13-52 days). Of these, 34 (83%) were reactive (Table 4).

Table 4. Seroprevalence of SARS-CoV-2 antibodies among participants in the Safe Campus Initiative, June-August 2020.

	Baseline, N (%)	Endline, N (%)	Both, N (%)
Serostatus – Cross-sectional*			
Reactive	18 (0.6)	48 (2.3)	-
Non-reactive	2,859 (99.4)	2,039 (97.7)	-
Serostatus – Longitudinal**			
Non-Reactive → Non-Reactive	-	-	2,029 (97.7)
Non-Reactive → Reactive	-	-	33 (1.6)
Reactive → Non-Reactive	-	-	0 (0)
Reactive → Reactive	-	-	14 (0.7)
Serostatus – Previous qPCR Positive†			
Reactive	-	34 (82.9)	-
Non-reactive	-	7 (17.1)	-

qPCR: quantitative polymerase chain reaction.
*N=2,888 participants who provided at least one blood sample.
**N=2,076 participants who provided blood samples at baseline and endline.
†N=41 participants who provided an endline blood sample ≥7 days *after* infection with SARS-CoV-2 identified via positive qPCR test.

Discussion

This study provides a model of a voluntary, incentivized system to identify and link at-risk students to SARS-CoV-2 testing. While the incidence and seroprevalence of SARS-CoV-2 were

generally low in this cohort of university students and employees in the summer of 2020, we observed the highest incidence among undergraduate students living in congregate settings, with nearly half of cases found to be associated with a super-spreader event.

At the time of the study, many infection control strategies centered on symptomatic testing, reducing the likelihood of identifying asymptomatic, mildly symptomatic, and pre-symptomatic infections. Our approach sought to integrate symptom-based monitoring with exposure monitoring, random surveillance testing, and targeted surveillance testing in the context of an outbreak. Within this cohort, we previously demonstrated the acceptability of our low-barrier SARS-CoV-2 mitigation approach and the limitations of temperature monitoring as a tool for case identification.[14,28] The present analysis builds upon these contributions by triangulating prospective qPCR testing data with phylogenetic analyses of positive samples and serial antibody testing to evaluate whether case identification and containment were achieved. In doing so, we found evidence that the system successfully identified a high proportion of incident SARS-CoV-2 cases among participants and may have mitigated community transmission after an outbreak. Specifically, 91% of participants with newly-identified antibodies for SARS-CoV-2 at the end of the study had also been diagnosed with incident infection via qPCR test during the study period. While a sizeable cluster of cases among participants was traced to a single super-spreader event, the associated cluster lineage was successfully contained without spreading beyond campus. As the outbreak unfolded, the system also allowed for rapid real-time response (i.e., surveillance testing notifications to students living in congregate housing) and offered a readily accessible, incentivized entry point for testing for students concerned about potential exposure.

Although some universities have adopted punitive measures intended to prevent transmission by controlling student behavior (for example, suspending students for hosting gatherings),[31–33] this approach has been criticized for its potential to reduce students' trust and cooperation.[34–36] Instead of punishing or shaming students who fail to adhere to public

health guidance, some epidemiologists have called for a harm-reduction approach which supports and engages students as part of the solution.[34–36] The present study reinforces the potential to integrate voluntary testing and risk monitoring systems to support targeted case identification, as evidenced by the significantly higher positivity rates found among participants whose self-reported symptoms and exposures triggered notifications to test. Our findings also support increased outreach to groups of students at highest risk, particularly younger students in congregate housing.

This study is strengthened by rich longitudinal data, including symptom and exposure tracking, qPCR testing, and seroprevalence data from more than 2,000 participants. The study population comprised of a broad sample of university affiliates, both students and employees, with strong representation of university subpopulations perceived to be at higher risk of infection (e.g., undergraduates, essential healthcare workers). As on-campus activities were severely restricted throughout the study period (all classes were held online, and few students were living in residence halls), this study cannot provide insight into SARS-CoV-2 transmission risks related to on-campus student activities. Nevertheless, as 73% of UC Berkeley undergraduate students lived off campus *before* the pandemic,[37] systems to detect off-campus (i.e., community and household) transmission remain important for SARS-CoV-2 monitoring efforts among students. Additionally, all participants in the essential workers cohort and a subset of participants in the faculty/cohort were working on campus during the study period, further motivating efforts to monitor incidence in this population.

There remain several limitations. We observed relatively few SARS-CoV-2 cases during the study period. Accordingly, although many associations are statistically significant, our estimates are imprecise (i.e., have wide confidence intervals) and must be interpreted with caution. This study took place before the development of highly transmissible variants, such as Delta and Omicron, and before vaccine rollout. Observed associations between symptoms and positivity may also differ among those who have been infected by more recent variants and/or

vaccinated. Further research is necessary to adapt and evaluate similar systems in the context of both heightened transmissibility and more prevalent natural and vaccine-induced immunity. Additionally, a high proportion of identified cases were traced to one outbreak, limiting the generalizability of our exploratory assessment of risk factors for incident infection. There was also anecdotal evidence that the outbreak prompted exposed students to enroll as study participants.[14] While this self-referral into the study is likely to increase selection bias, it also illustrates the utility of implementing non-stigmatizing, incentivized testing approaches to increase testing uptake among at-risk students. Finally, our identification of participants who seroconverted between baseline and endline may be incomplete due to loss-to-follow up and imperfect sensitivity of SARS-CoV-2 antibody testing.

By integrating symptom and exposure monitoring systems with low-barrier testing, we identified incident SARS-CoV-2 infections to reduce transmission within a university setting. Our study contributes to a growing body of literature on novel, integrated SARS-CoV-2 surveillance strategies in university settings.[38–44] While there have been seismic shifts in the SARS-CoV-2 pandemic since 2020, universities continue to grapple with how best to mitigate on-campus spread in the face of emerging variants, incomplete vaccination coverage, breakthrough infections, and decreased reliance on other mitigation strategies (e.g., masking, remote learning).[45,46] In light of universities' resource constraints and persistently high case counts, incentivized approaches may not be feasible or sustainable in many settings. Thus, further research is needed to identify and test non-monetary incentives and other behavioral nudge strategies that encourage students and other campus community members to actively participate in public health efforts to combat the pandemic. The lessons learned through this study may inform the design of future adaptive strategies, ideally building beyond symptom/exposure monitoring and qPCR testing to integrate complementary interventions such as rapid antigen self-testing and vaccination promotion.

Keywords: COVID-19, SARS-CoV-2, United States, young adults, students, universities, essential workers, seroprevalence

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Data sharing: De-identified data sets used in analyses and accompanying R Markdown script files will be publicly available at the time of publication at the following link: https://github.com/lauren-hunter/bcsci

Ethical approvals: All study activities were approved by the University of California, Berkeley Committee for the Protection of Human Subjects (#2020-06-13349, #2020-05-13261, #2020-04-13238).

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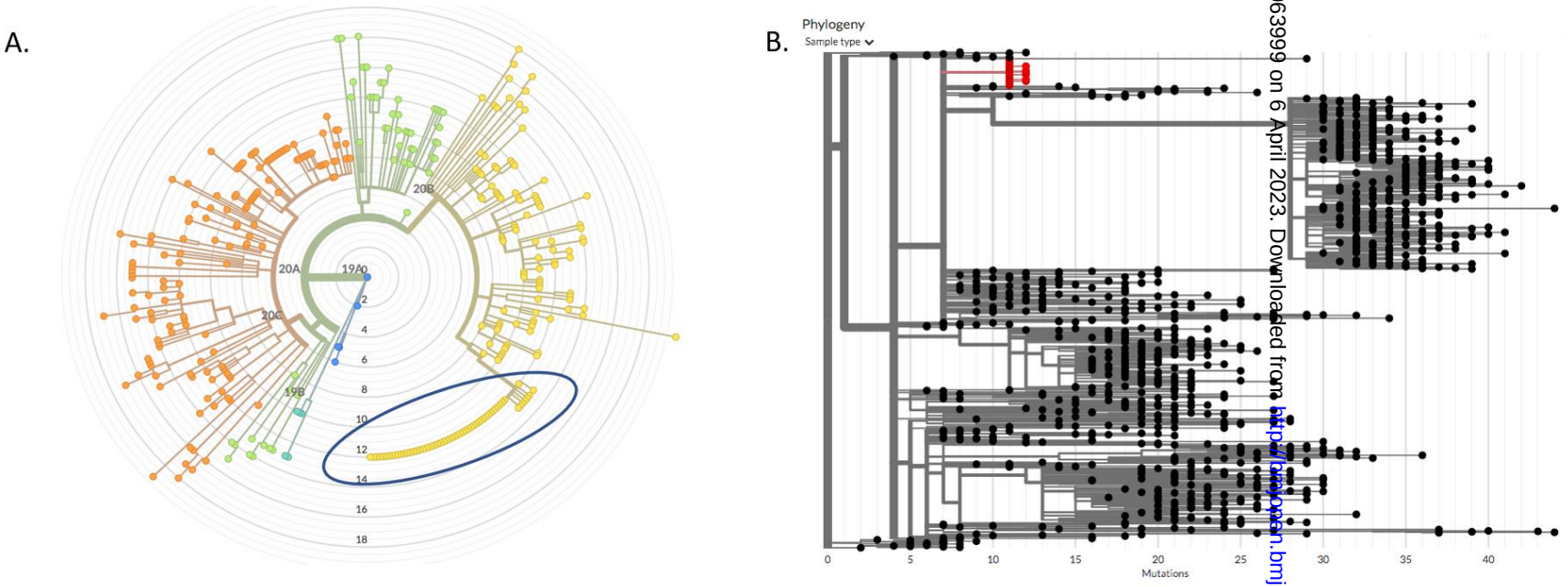
Figure 1. Phylogeny of outbreak-associated strain of SARS-CoV-2 among participants in the Safe Campus Initiative.



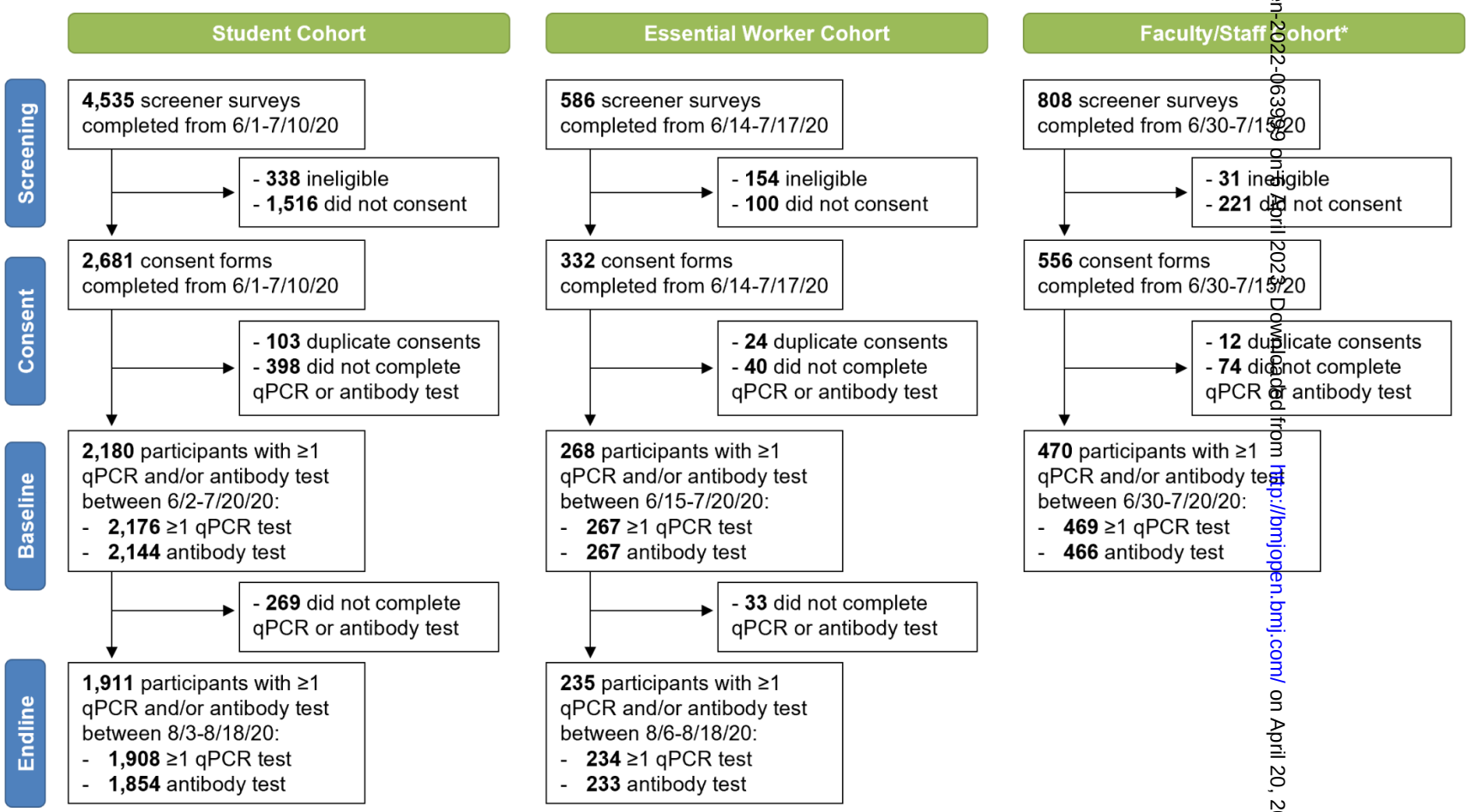
A. A maximum likelihood phylogeny constructed from 357 genomes sequenced by the Innovative Genomics Institute between May and July 2020 constructed using Nextstrain. Branch lengths represent divergence from Wuhan reference genome at center. Blue circle marks cluster of identical genomes from a campus super-spreader event.

B. A 1,057 node subtree of a neighbor-joining tree constructed with all SARS-CoV-2 sequences to date (constructed using UShER with over 1 million genomes in April 2021), showing the most similar genomes to the super-spreader event cluster (in red). There are no descendant branches from the cluster, demonstrating that the outbreak was contained and the lineage died out.

Supplementary Table 1. Eligibility criteria across the Berkeley COVID-19 Safe Campus Study cohorts.

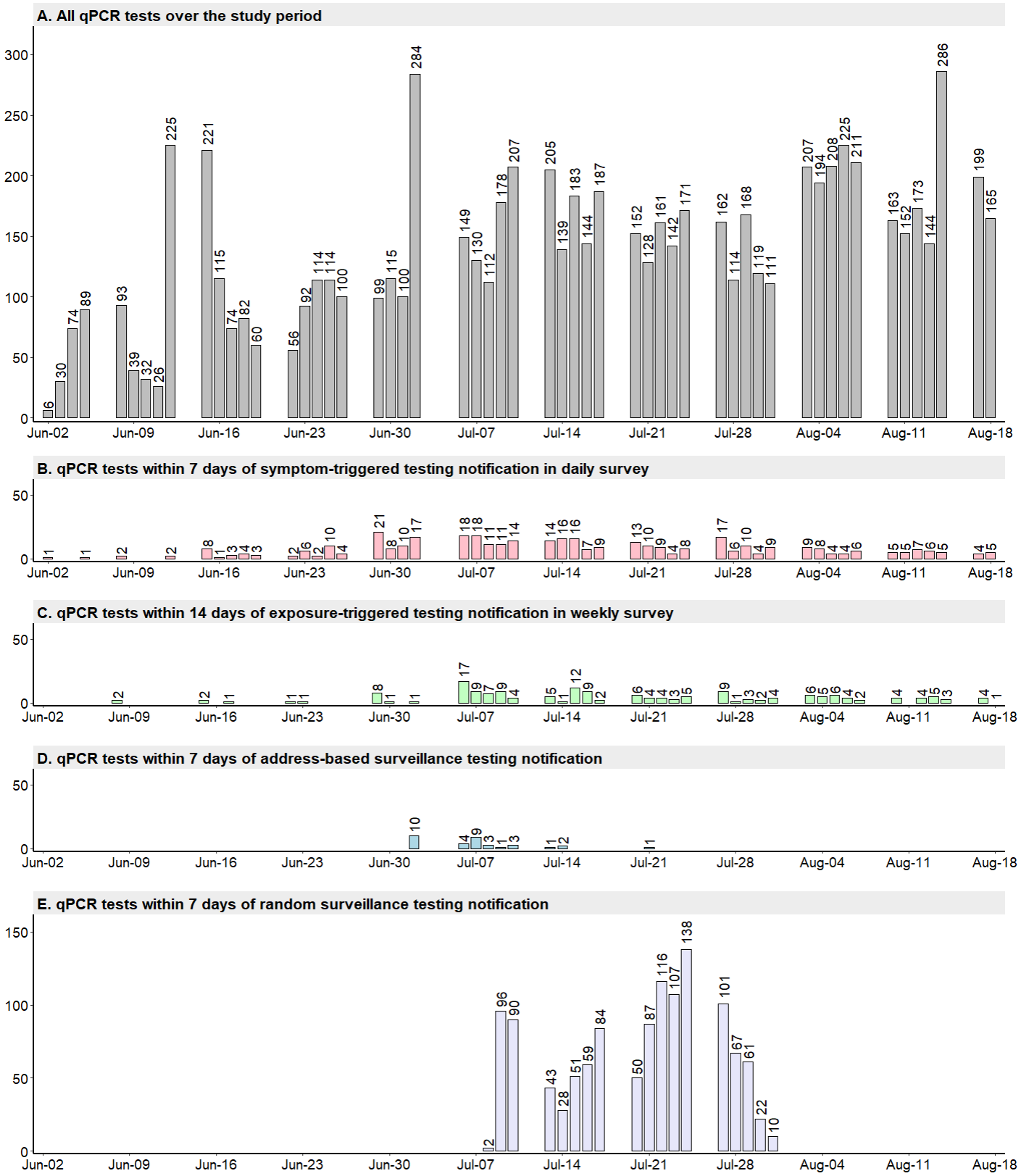
	Student Cohort	Essential Worker Cohort	Faculty/Staff Cohort
Eligibility Criteria	- At least 18 years of age	- At least 18 years of age	- At least 18 years of age
	- Currently enrolled as an undergraduate or graduate student at UC Berkeley (i.e., not graduated in Spring 2020 or incoming for Fall 2020)	- Currently employed in one of the following departments at UC Berkeley: health services, police, facility services or other building management, environmental health and safety, laboratory animal care, athletics, dining, childcare, other residential or student services - Currently working on campus at UC Berkeley *or* expected to return to work during June 2020	- Currently employed as a faculty member, staff member, or postdoctoral scholar at UC Berkeley - Not already enrolled in the essential workers cohort
	- Primarily residing in Alameda County or Contra Costa Country between 6/1/20-8/31/20	N/A	- Primarily residing in Alameda County or Contra Costa Country between 6/1/20-8/31/20
	- Willing to sign release of information for COVID-19-related medical records	- Willing to sign release of information for COVID-19-related medical records	- Willing to sign release of information for COVID-19-related medical records

Supplementary Figure 1. Flow diagram for the Berkeley COVID-19 Safe Campus Study cohorts.



qPCR: quantitative polymerase chain reaction.
*Faculty/staff cohort not invited for endline testing appointments but could complete follow-up qPCR tests through 8/18/20.

Supplementary Figure 2. qPCR testing over time across the Berkeley COVID-19 Safe Campus Study cohorts.



qPCR: quantitative polymerase chain reaction.
Note: Panels are not mutually exclusive.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1-2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-9, Supplementary Figure 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-9, Supplementary Table 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-10
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Supplementary Figure 1
		(b) Give reasons for non-participation at each stage	Supplementary Figure 1
		(c) Consider use of a flow diagram	Supplementary Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	11-13
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12-14, Tables 2-3
		(*b*) Report category boundaries when continuous variables were categorized	10, Table 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.