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Title: ***Factors associated with SARS-CoV-2 transmission in setting of high COVID-19 vaccination coverage: a case-control study***

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Despite availability of effective vaccines, community exposures continue to drive the coronavirus disease 2019 (COVID-19) pandemic across the Unites States. Though vaccination coverage is high in some regions, uptake has lagged elsewhere.[1] Characterizing risk factors remains critically important to inform policies on non-pharmaceutical interventions that target highest risk activities and reduce SARS-CoV-2 transmission, while preserving economic and societal structures.

While prior case-control studies have identified diverse risk factors for SARS-CoV-2 transmission[2–4], there is critical need to understand how increasing vaccination coverage impacts risk of SARS-CoV-2 transmission, particularly with the increased spread of the Delta (B.1.617.2) variant.[5,6] We determined risk factors of SARS-CoV-2 transmission in the City and County of San Francisco from April to June 2021, when the proportion of fully vaccinated residents increased from 27.4% to 62.6%.[7]

METHODS

Our objective was to identify factors associated with transmission of SARS-CoV-2 in San Francisco between April 7th, 2021, and June 8th, 2021. We used an unmatched case control design, recruiting individuals ≥18 years of age. We recruited cases from individuals reported to the San Francisco Department of Public Health

who tested positive for SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR) and controls from those who tested negative. Given the narrow time window, we did not match for date of test result.

Ineligibility criteria included residing outside of San Francisco County, living in a congregate setting (e.g. long-term care facility or homeless shelter), or being unable to confirm birth date or test date. Cases were also ineligible if they were unaware of their status or had not yet been interviewed by the case investigation team. Participants were contacted within three weeks of their test dates.

Both cases and controls who were fully or partially vaccinated at the time of the testing were also ineligible due to their different risk for infection. Moreover, we only included individuals who were unvaccinated at the time of testing in the final analysis.

All eligible study participants completed a telephone interviewer-led, close-ended questionnaire focused on exposures and activities during the two-week period prior to their test date. Interviews assessed for demographic factors; household exposures (number of persons and bedrooms in the home); occupational exposures (job category, workplace setting, and mask use at work); frequency of outdoor and indoor dining and visits to bars; and community and travel exposures. For travel exposures, we defined the San Francisco Bay Area as the nine-county Bay Area, including Alameda, Contra Costa, Marin, Napa, San Francisco, San Mateo, Santa Clara, Solano and Sonoma counties. Interviews were conducted in English, Spanish, Mandarin and Tagalog.

We constructed a logistic regression model to assess differences in community exposures between cases and controls. Because the number of participants in the control group was low (n=27), we used Firth's penalized maximum likelihood regression method, which yields yield more accurate point estimates and confidence intervals for sparse data compared with standard maximum likelihood methods.[8,9] All results were adjusted for age quartile and self-reported Latinx ethnicity. Statistical analyses were conducted using R.[10]

This study was approved by the University of California San Francisco Committee Human Research. Informed consent was obtained from all study participants.

RESULTS

Among 258,026 records, 1,202 cases (SARS-CoV-2 positive) and 193,137 controls (SARS-CoV-2 negative) were sampled. Of these, 957 cases and 1,358 controls were reached by 'phone and of those reached by 'phone, 184 cases and 44 controls were screened eligible, consented and interviewed, (see Web Figure 1). Fifty-one cases and 17 controls enrolled early in the study were excluded due to vaccination at the time of

testing (eligibility criteria were subsequently changed), leading to the final analytic sample of 133 cases and 27 controls.

Overall, cases were younger than the controls (38.3% cases aged 18-29 vs. 18.5% controls), more likely to be female (49.6% vs. 37.0%) and more likely to identify as Latinx (37.6% vs. 14.8%) (**Table 1**). Controls were more likely to identify as LGBTQ (18.5% controls vs. 6.8% cases) and white (40.7% vs. 15.8%). The odds of testing positive were higher in Latinx participants (adjusted OR [aOR]: 6.04, 95% CI: 1.89, 22.52 [vs. white, adjusted only for age]).

Housing status was not associated with testing positive. Regarding workplace exposures, 74.4% of cases and 77.8% of controls were employed, 24.8% of cases and 22.2 % of controls were unemployed, retired, or students, (see Web Table 1).

Participants who traveled outside of the nine-county San Francisco Bay Area (within the rest of California, within the USA, or internationally) in the two weeks prior to testing were at higher adjusted odds of testing positive (aOR: 7.07, 95% CI: 2.05, 37.41 [vs. no travel or travel only within the Bay Area]). Participants who traveled and had an overnight stay (aOR: 3.09, 95% CI: 1.05, 10.96 [vs. no travel]) were at higher adjusted odds of testing positive.

DISCUSSION

In this setting of COVID-19 high vaccination coverage, before the Delta (B.1.617.2) SARS-CoV-2 variant was widespread, the odds of testing positive were significantly greater among those who had recently traveled outside of the San Francisco Bay Area or had an overnight stay during such travel. At the end of study data collection, the nine-county San Francisco Bay Area population was highly vaccinated, with the proportion of the entire population having completed a full series ranging from 41.6% in Solano County to 66.9% in Marin County.[7] While travel has been identified as a risk factor for SARS-CoV-2 infection in other studies,[2,4,11] our findings illustrate the importance of travel as a risk factor when local vaccination coverage was high. San Francisco has been successful in implementing population-level interventions and has experienced low COVID-19 case rates compared to other US cities;[7] nonetheless, these findings underscore how local efforts may be ineffective in preventing imported cases.

We did not find an increased transmission risk associated with restaurant or bar dining (indoors or outdoors) or working in congregate environments, such as stores, offices or schools. While transmission in these settings might have been reduced because of high local vaccination coverage, we interpret these negative findings with caution, given the small sample size, especially as prior studies have identified these factors to be associated with transmission. Consistent with the findings of other studies, we found an increased risk of SARS-CoV-2 transmission among Latinx populations.[12]

Our study has several limitations. The rapid vaccine uptake in the community during our study's recruitment phase was a meaningful challenge, resulting in a small number of eligible controls. We recommend that investigators planning similar case-control attempt to foresee major changes to the epidemiological landscape and respond quickly and appropriately. The small number of controls in this study also limit our statistical power. We further note that the high vaccine uptake likely exhausted the pool of protection-seeking individuals in the community, such that the remaining unvaccinated controls during the study period likely had more frequent, and riskier, risk behaviors than the excluded controls. The differences in risk between our exposure comparisons were thus probably effectively diminished (compared to if we had conducted the study prior to vaccine rollout. While all of our analyses were restricted to unvaccinated individuals, we note that the larger pool of our data is suggestive of vaccine effectiveness. Finally, we acknowledge that our findings are susceptible to selection bias, as persons who did not seek testing, did not respond, or did not want to participate in the study may have differed from the study sample. Interviewees may have been prone to recall bias; awareness of their COVID-19 test result may have influenced their responses.

Public Health Implications

This case-control study examined factors associated with SARS-CoV-2 transmission in San Francisco, a city with high COVID-19 vaccination coverage, and found that infection was strongly associated with recent travel outside of the San Francisco Bay Area. These findings suggest that introduction of infection from high incidence, low vaccination coverage areas may remain a major source of transmission in low incidence, high vaccination coverage areas such as San Francisco. Increasing public awareness of the risk of travel and nationally mandated negative testing or vaccination prior to air travel could be considered to reduce the risk of SARS-CoV-2 transmission.

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Table 1: Demographic and transmission risk factors among cases and controls

Characteristic	Cases (*n* = 133)		Controls (*n* = 27)		Adjusted Odds Ratio[a]	95% CI
	No.	%	No.	%		
Age, years[b]						
18-29	51	38.3	5	18.5	2.62	0.99, 8.00
30-54	68	51.1	19	70.4	1.00	Referent
55 and over	14	10.5	3	11.1	1.09	0.32, 4.61
Gender identity						
Male	65	48.9	17	63.0	1.00	Referent
Female	66	49.6	10	37.0	1.60	0.69, 3.87
Genderqueer or non-binary	1	0.8	0	0.0		
Sexual orientation						
Heterosexual or straight	123	92.5	20	74.1	1.00	Referent
Gay, lesbian, bisexual, identity not listed	9	6.8	5	18.5	0.29	0.09, 1.05
Race/ ethnicity[c]						
Asian	16	12.0	4	14.8	1.99	0.56, 8.04
Black or African American	25	18.8	5	18.5	2.82	0.88, 10.01
Latinx	50	37.6	4	14.8	6.04	1.89, 22.52
White	21	15.8	11	40.7	1.00	Referent
Bi-/Multi-racial, other	14	10.5	2	7.4	3.17	0.76, 18.59
Housing						
Apartment	86	64.7	12	44.4	1.00	Referent
Single family home	36	27.1	12	44.4	0.42	0.16, 1.05
SRO, multi-family home, other	11	8.3	3	11.1	0.30	0.08, 1.39
Employment status						
Unemployed, retired or student	33	24.8	6	22.2	1.00	Referent
Employed	99	74.4	21	77.8	0.96	0.32, 2.58
Dining-related exposures						
No dining	70	53.4	14	51.9	1.00	Referent
Outdoor only	21	15.8	8	29.6	0.51	0.18, 1.46
Indoor only	17	12.8	1	3.7	2.85	0.59, 28.36
Both outdoor & indoor	23	17.3	4	14.8	1.15	0.37, 4.21
Travel exposures						
Travel outside San Francisco County						
No	75	56.8	18	66.7	1.00	Referent
Yes	57	43.2	9	33.3	1.71	0.72, 4.36
Distance travelled						
Did not travel/Traveled within the San Francisco Bay	87	65.4	25	92.6	1.00	Referent

Area[d]						
Traveled outside of the San Francisco Bay Area (rest of California, USA, Internationally)	46	34.6	2	7.4	7.07	2.05, 37.41
Overnight stay						
Did not travel	75	56.4	18	66.7	1.00	Referent
No	11	8.3	5	18.5	0.59	0.19, 2.05
Yes	46	34.6	4	14.8	3.09	1.05, 10.96

[a]Adjusted for age and Latinx ethnicity

[b]Age which was not adjusted for age

[c]Latinx ethnicity which was not adjusted for Latinx ethnicity

[d]We defined the San Francisco Bay Area as the nine-county Bay Area, including Alameda, Contra Costa, Marin, Napa, San Francisco, San Mateo, Santa Clara, Solano and Sonoma counties.

Abbreviations: CI, confidence interval; SRO, single room occupancy.