Index Cases First Identified by Nasal-Swab Rapid COVID-19 Tests Had More Transmission to Household Contacts Than Cases Identified by Other Test Types

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ABSTRACT

Importance: At-home rapid COVID-19 tests utilize nasal-swab specimens and require high viral loads to reliably give positive results. Longitudinal studies from the onset of infection have found infectious virus can present in oral specimens days before nasal. Detection and initiation of infection-control practices may therefore be delayed when nasal-swab rapid tests are used, resulting in greater exposure and transmission to contacts. **Objective:** We assessed whether index cases first identified by rapid nasal-swab COVID-19 tests had more transmission to household contacts than index cases who used other test types (tests with higher analytical sensitivity but longer turnaround times, and/or that utilize non-nasal specimen types). **Design:** In this observational cohort study, members of households with a recent COVID-19 case were screened for infection at least daily by RT-qPCR on one or more self-collected upper-respiratory specimen types. Participants reported demographic/medical information (including COVID-19 testing), symptom and exposure information, and household infection-control practices. A two-level random intercept model was used to assess the association between the infection outcome of household contacts and each covariable (household size, race/ethnicity, age, vaccination status, viral variant, infection-control practices, and whether a rapid nasal-swab test was used to initially identify the household index case). **Setting:** Southern California, September 2020—June 2021 and November 2021—March 2022. **Participants:** Cohort of 370 individuals from 85 households. **Main Outcome(s) and Measure(s):** Transmission was quantified by adjusted secondary attack rates (aSAR) and adjusted odds ratios (aOR). **Results:** An aSAR of 53.6% (95% CI 38.8–68.3%) was observed among households where the index case first tested positive by a rapid nasal-swab COVID-19 test, which was significantly higher than the aSAR for households where the index case utilized another test type (27.2% 95% CI 19.5–35.0%, P=0.003 pairwise comparisons of predictive margins). We observed an aOR of 4.90 (95% CI 1.65–14.56) for transmission to household contacts when a nasal-swab rapid test was used to identify the index case, compared to other test types. **Conclusions and Relevance:** Use of nasal-swab rapid COVID-19 tests for initial detection of infection and initiation of infection control may not limit transmission as well as other test types.

Keywords: Household, Transmission, Rapid, Nasal, Antigen, Swabs, Omicron, Secondary Attack Rate, Delta, Southern California variant, association

Key Points:

1. Question: Does identification of index cases by rapid nasal-swab tests limit household transmission of SARS-CoV-2 as well as other test types?

2. Finding: Significantly higher adjusted secondary attack rates and adjusted odds ratios for transmission were observed in households where the index case used a nasal rapid COVID-19 test for initial detection versus other test types.

3. Meaning: The use of nasal-swab rapid COVID-19 tests for initial detection of infection and initiation of infection control may not limit transmission as well as other test types.

Introduction

The majority of SARS-CoV-2 transmission events occur among household contacts.[1,2] Numerous studies have characterized household transmission of SARS-CoV-2[3-8] and identified factors that modulate the risk of transmission within households, such as larger household size being associated with higher risk.[9-12] Similarly, disparities by race and ethnicity have been observed, while controlling for socioeconomic differences.[11,13] Age of both the index case (first person in the household to become infected) and at-risk household contacts (who either remain uninfected or become infected secondary cases) has also been implicated in SARS-CoV-2 household-transmission patterns.[6,14-16] Furthermore, although vaccination does not fully prevent breakthrough infections,[17] vaccination has been shown to be protective and decrease the risk of infection[8,18-22]. Specific infection-control practices, such as wearing a mask around infected contacts, physical distancing, and quarantining sick individuals have also shown protective effects.[14,18,23-25] Lastly, SARS-CoV-2 variants such as Delta and Omicron have been shown in large studies to have greater transmissibility compared with ancestral variants.[8,18,19,26-33]

Early identification of an infectious individual is a critical step to reduce subsequent transmission, including within households. Because transmission of SARS-CoV-2 occurs during both the asymptomatic and symptomatic periods of infection,[34-37] diagnostic testing to quickly prompt infection control practices has been effective to limit additional exposures and transmission.[38] Conversely, infectious individuals that go unidentified or delay identification allow for greater exposure to contacts and thereby more transmission. [12,39,40]

Delayed detection can occur due to test turnaround times or when a test yields a false-negative result. Rapid tests (e.g., antigen and some molecular tests) offer fast turnaround times, but require higher levels of virus to reliably result positive; e.g., ~100,000 times more virus is needed to yield a positive result by the LumiraDx SARS-CoV-2 Ag Test than the PerkinElmer New Coronavirus Nucleic Acid Detection Kit[41,42]. Additionally, SARS-CoV-2 can infect different upper-respiratory compartments, so numerous specimen types are used to detect infection (e.g., anterior-nares nasal swab, mid-turbinate nasal swab, nasopharyngeal swab, oropharyngeal swab, tonsillar swab, buccal swab, lingual swab, gingival crevicular fluid, saliva). The rise and fall of viral loads in each specimen type throughout infection affects whether SARS-CoV-2 is detectable in that specimen type at the time of testing. A diagnostic test successfully detects infection when the viral load in the tested specimen type is above the limit of detection (LOD) of the test.

In our recent analysis[43] of viral loads from three specimen types (anterior-nares swab, oropharyngeal swab, and saliva) prospectively collected daily before or at the incidence of infection with the Omicron variant, we observed that longitudinal

viral-load timecourses in different specimen types from the same person often exhibit extreme differences and do not correlate. Further, most people in that study[43] and our prior study of ancestral variants[44] had delayed accumulation of virus in nasal swabs compared with oral specimens. A delayed rise in nasal-swab viral loads has been observed in many studies,[45-48] including among participants in a SARS-CoV-2 human challenge study who received intra-nasal inoculation.[49] We[50] and others[43,46,48,51,52] found that this delayed rise in nasal viral loads, in combination with the high levels of virus required for detection by tests with low analytical sensitivity, leads to delayed detection of infected and infectious individuals by nasal-swab rapid antigen tests. Non-nasal upper respiratory specimen types and/or tests with high-analytical-sensitivity could detect these individuals earlier in the infection.[43]

In this study, we aimed to investigate whether test analytical sensitivity and differences in viral-load patterns among different specimen types may have implications for household transmission. We specifically tested whether the type of test (rapid nasal-swab vs all other COVID-19 tests) used to first identify household index cases was correlated with higher rates of transmission to household contacts. Data were collected from a 2-year COVID-19 household transmission study in Southern California. We applied a two-level random intercept model, clustering by household and controlling for potential confounders[53] to assess the relationship between the use of a nasal-swab rapid COVID-19 tests to first identify the household index case, and subsequent transmission to household contacts (**Fig 1**).

Methods

Participant Enrollment and Metadata

We conducted a case-ascertained COVID-19 household transmission observational cohort study in Southern California in two phases: between September 2020 and June 2021,[44,54] prior to the predominance of the Delta variant[55], and between November 2021 and March 2022,[43] during the emergence and subsequent predominance of the Omicron variant[55] (**Table S1A**). The study was approved by the California Institute of Technology IRB (protocol #20-1026). Participants aged 8 years and older provided written informed consent, and all minors additionally provided verbal assent accompanied by written parental permission.

Upon enrollment, participants completed a questionnaire to provide information about demographics (see Supplementary Information). At the conclusion of their participation, participants were asked to complete another questionnaire to report any SARS-CoV-2 test results from outside of the study, updated infection status of each household member (including those unenrolled), and infection-control practices performed.

Laboratory Screening Testing

Specimens (saliva, anterior nares swabs, oropharyngeal swabs, **Fig 1A,B**) from participants underwent laboratory testing for SARS-CoV-2 infection, as previously described (Supplementary Information).[43,44,54] Participants reported COVID-19-like symptoms at each specimen collection timepoint. At least one specimen from most households underwent viral sequencing as previously described,[43,44] to ascertain the infecting SARS-CoV-2 variant of household members. For one household enrolled in early December 2022, sequencing was not performed but Delta variant was inferred based on the dominating variants circulating at the time[55] and for 5 households enrolled after mid-January 2022, sequencing was not performed, but Omicron variant was inferred based on local predominance.[55]
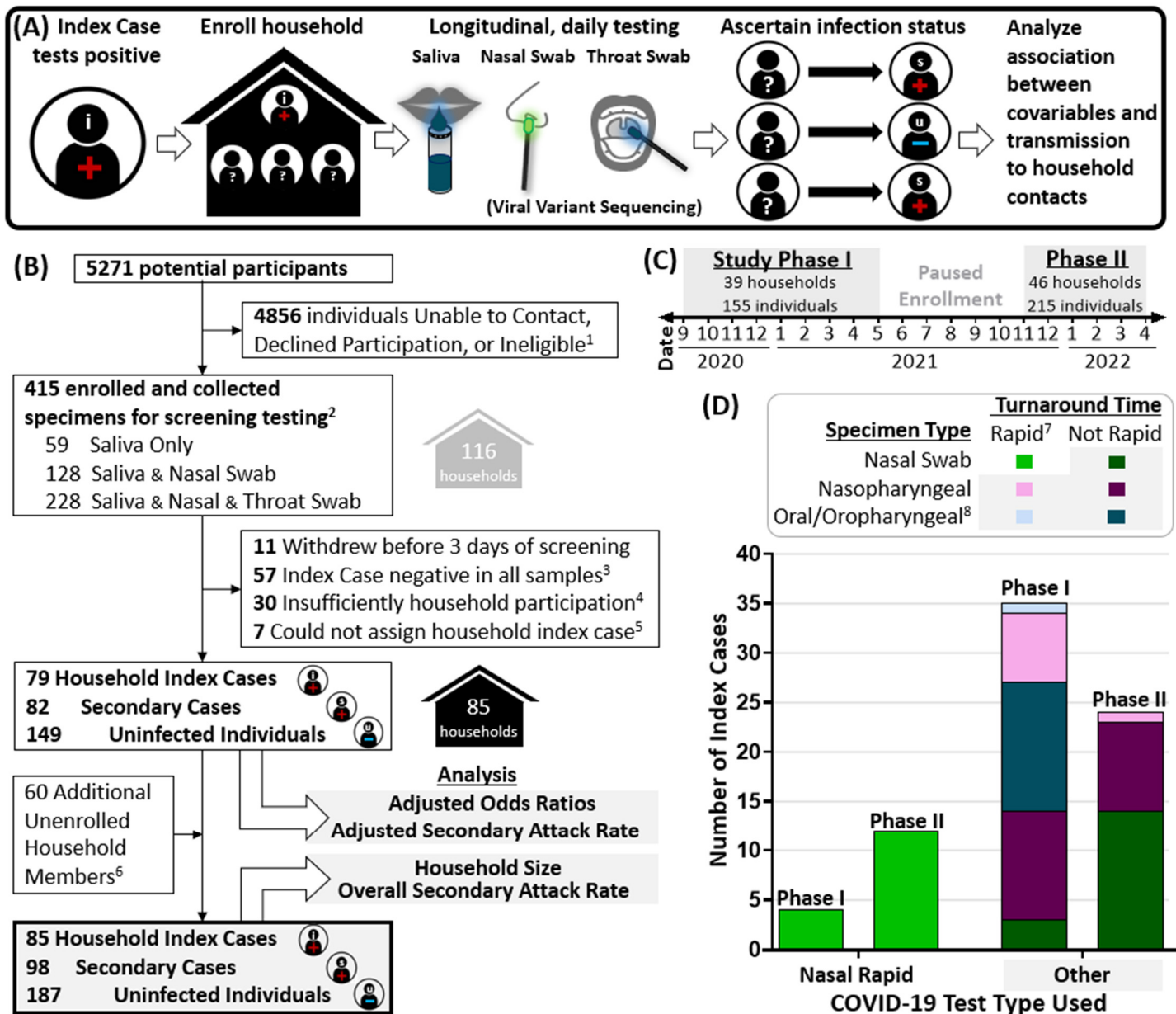
FIGURE 1 Overview of study design and analysis. (A) Study design beginning with recording the COVID-19 test type first used to identify index cases at study enrollment, enrollment of household contacts for daily, high-analytical-sensitivity laboratory screening, and analysis of potential factors modulating transmission. **(B)** CONSORT diagram for study enrollment. **(C)** Timeline of participant enrollment in study Phase I (September 2020—June 2021) and Phase II (November 2021—March 2022). Date is listed as numeric month over year. **(D)** Breakdown of self-reported COVID-19 test types (specimen type, and rapid or not) utilized to first identify household index cases. Test type was not reported by 10 of 85 index cases.

1. Individuals were ineligible for enrollment if they resided outside study jurisdiction, lived alone, or were more than 7 days from positive result or symptom onset. 2. Participants in Phase I collected either saliva only, or paired saliva and nasal swabs; participants in Phase II collected paired saliva, nasal swabs, and throat swabs. 3. Households were considered not at risk if no member including the suspected index case had detectable SARS-CoV-2 in any sample tested upon enrollment. 4. Households in which a majority of unenrolled household members were considered to have insufficient information. 5. Households in which a single household index case could not be assigned. 6. Information about unenrolled household members was reported by enrolled participants. 7. Test type was defined as 'Rapid' if the participant reported receiving results either within an hour or on the same day as the specimen was collected. Longer turnaround times were classified as 'Not Rapid' tests. 8. Oral/oropharyngeal specimen type category included participants who self-reported that saliva, buccal swabs, or oropharyngeal swabs were collected for testing.

Statistical Analyses

We utilized the questionnaire data and laboratory testing data to investigate SARS-CoV-2 transmission within households. Households were included in this analysis if laboratory testing confirmed at least one household member was acutely infected with SARS-CoV-2 and more than a third of reported household members were enrolled in the study. Three households were excluded because they withdrew before three days of screening, 22 households were excluded because all members were negative for SARS-CoV-2 in all tested specimens, five households were excluded because of insufficient information about unenrolled household contacts, and one household was excluded because of inability to determine index case (**Fig 1B**). See Supplemental Information for details.

For each household, an index case was defined as the first member of the household (enrolled in the study or not) to test positive for SARS-CoV-2 infection, usually prior to enrollment. In one case where multiple members had the same first test date, the member with earlier self-reported onset of symptoms was considered the household index case. In five cases where symptom onset of household members was within 1 day of each other, we defined the index case as the individual with a known exposure to a non-household contact with laboratory-confirmed SARS-CoV-2 infection. In three cases with similar timing of exposure to infected, non-household contacts, the index case was defined as the individual whose viral load peaked first. All other members of the household who tested positive for SARS-CoV-2 prior to or during household enrollment in the study were considered secondary cases. Household members who never tested positive for SARS-CoV-2 prior to or while the household was enrolled in the study were considered uninfected. 143 of 149 (96%) participants classified as uninfected were enrolled and screened for at least 5 days; most (53%) were enrolled for at least 9 days.

The test type of the household index case was interpreted as a "nasal-swab rapid test" when the household index case self-reported "shallow nasal swab (anterior nares or mid turbinate nasal swab)" as the specimen type and a result turnaround time of "within an hour" or "same day." Participants were not asked to report the specific test name, laboratory platform, or viral target (e.g., molecular, antigen), due to concerns that laypersons would not be aware of these terms (especially if the test was run by a clinic rather than direct-to-consumer). However, rapid tests (both antigen and molecular) have characteristically low analytical sensitivity because they forego the time-consuming and technically challenging extraction steps to purify and concentrate viral targets. Because our hypothesis was related to low-analytical-sensitivity rapid tests performed on specimens from nasal swabs, we simply distinguish rapid tests from those with longer turnaround times and presumably higher analytical sensitivity (**Fig 1D**).

We calculated unadjusted odds ratios (ORs) for *a priori* confounders,[56] infection-control practices, the use of nasal-swab rapid tests by index cases, and the risk of SARS-CoV-2 transmission to household contacts using mixed-effect logistic regression (**Fig 2**, **Table S2**). We also used a two-level mixed-effects logistic regression model with random intercepts by household to account for clustering of individuals within households and including all covariables to estimate adjusted odds ratios (aOR) (**Fig 2, Table S3**). This type of model[57] was chosen to estimate the effects of predictors at both individual and household levels. The model adjusted for a sufficient set of the following potentially confounding variables: household size,[10-12] age,[6,15,16] race/ethnicity,[11,13] and vaccination status.[18-22] We also accounted for infecting SARS-CoV-2 viral variant.[18-20,28,32,33] Observations with missing data were omitted from respective analyses.

We used this model to assess the effect of household prevention practices and the COVID-19 test type used to first identify the household index case. An aOR >1.0 was associated with increased likelihood of household transmission, and deemed statistically significant if its associated *P*-value was ≤0.05 by Wald and likelihood ratio tests.

Predictive margins based on the results of the regression models were used to estimate unadjusted and adjusted secondary attack rates (SAR and aSAR). Binomial confidence intervals (CIs) were calculated as recommended by the Clinical Laboratory Standards Institute EP12-A guidance.[58] Differences among SARs and aSARs were assessed across strata.[59]

We separately assessed the conditional direct effects of viral variant and test type used to identify the household index case by modifying the model with or without each of these covariables (**Fig 3**). Calculations were performed in STATA/BE 17.0.

Table 1. Demographics, COVID-19 Vaccination Status, Viral Variant, and Smoking History of the 85-Household Cohort Used for Analyses.

	Index Case N= 85		Secondary Case N= 98		Uninfected N= 187		Total N= 370	
Self-Reported Gender Identity*	n	(%)	n	(%)	n	(%)	n	(%)
Male	31	36.5	50	51.0	91	48.7	172	46.5
Female	52	61.2	45	45.9	96	51.3	193	52.2
Non-Binary/Other	0	0.0	0	0.0	0	0.0	0	0.0
Unknown	2	2.4	3	3.1	0	0.0	5	1.4
Age Category (years)	n	(%)	n	(%)	n	(%)	n	(%)
<10	4	4.7	19	19.4	33	17.6	56	15.1
10 to 60	78	91.8	75	76.5	133	71.1	286	77.3
>60	2	2.4	2	2.0	21	11.2	25	6.8
Unknown	1	1.2	2	2.0	0	0.0	3	0.8
Self-Reported Race/Ethnicity**	n	(%)	n	(%)	n	(%)	n	(%)
Asian or Pacific Islander	14	16.5	10	10.2	23	12.3	47	12.7
Biracial	4	4.7	4	4.1	8	4.3	16	4.3
Black/African American	2	2.4	3	3.1	11	5.9	16	4.3
Native American/Alaska Native	4	4.7	1	1.0	7	3.7	12	3.2
Unknown	20	23.5	39	39.8	68	36.4	127	34.3
White, Hispanic	22	25.9	20	20.4	26	13.9	68	18.4
White, Non-Hispanic	19	22.4	21	21.4	44	23.5	84	22.7
Vaccination Status***	n	(%)	n	(%)	n	(%)	n	(%)
Unvaccinated	43	50.6	40	40.8	65	34.8	148	40.0
Partial	0	0.0	2	2.0	3	1.6	5	1.4
Complete	19	22.4	23	23.5	36	19.3	78	20.6
Boosted	17	20.0	17	17.3	45	24.1	79	21.4
Unknown	6	7.1	16	16.3	38	20.3	60	16.2
Household Viral Variant	n	(%)	n	(%)	n	(%)	n	(%)
Ancestral	39	45.9	37	37.8	79	42.2	155	41.9
Delta	12	14.1	14	14.3	22	11.8	48	13.0
Omicron	28	32.9	45	45.9	64	34.2	137	37.0
Unknown	6	7.1	2	2.0	22	11.8	30	8.1
Smoking/Vaping History History	n	(%)	n	(%)	n	(%)	n	(%)
Never	60	70.6	58	59.2	105	56.1	223	60.3
Former	13	15.3	14	14.3	24	12.8	51	13.8
Current	5	5.9	4	4.1	6	3.2	15	4.1
Unknown	7	8.2	22	22.4	52	27.8	81	21.9

*Both sex assigned at birth and current gender identity were self-reported by participants. One participant reported male assignment at birth and current gender identity of woman. Reported gender is listed.

**63 individuals currently listed as 'Unknown' did not select a race category but wrote-in "Latino"/"Latina"/"Latinx."

***Participants reported date and manufacturer of each vaccine dose received; vaccination status was defined only by doses received at least 7 days prior to enrollment in the study. Unvaccinated was defined as having received no COVID-19 vaccine doses. Partial vaccination was defined as receiving one dose of a multiple-dose series (e.g., Pfizer-BioNTech, Moderna). Complete vaccination was defined as receiving all doses of an initial COVID-19 vaccine series. Boosted was defined as the participant receiving any dose beyond an initial COVID-19 vaccine series. Vaccination and viral variant distributions varied by Study Phase; demographics by Study Phase are shown in **Table S1**.
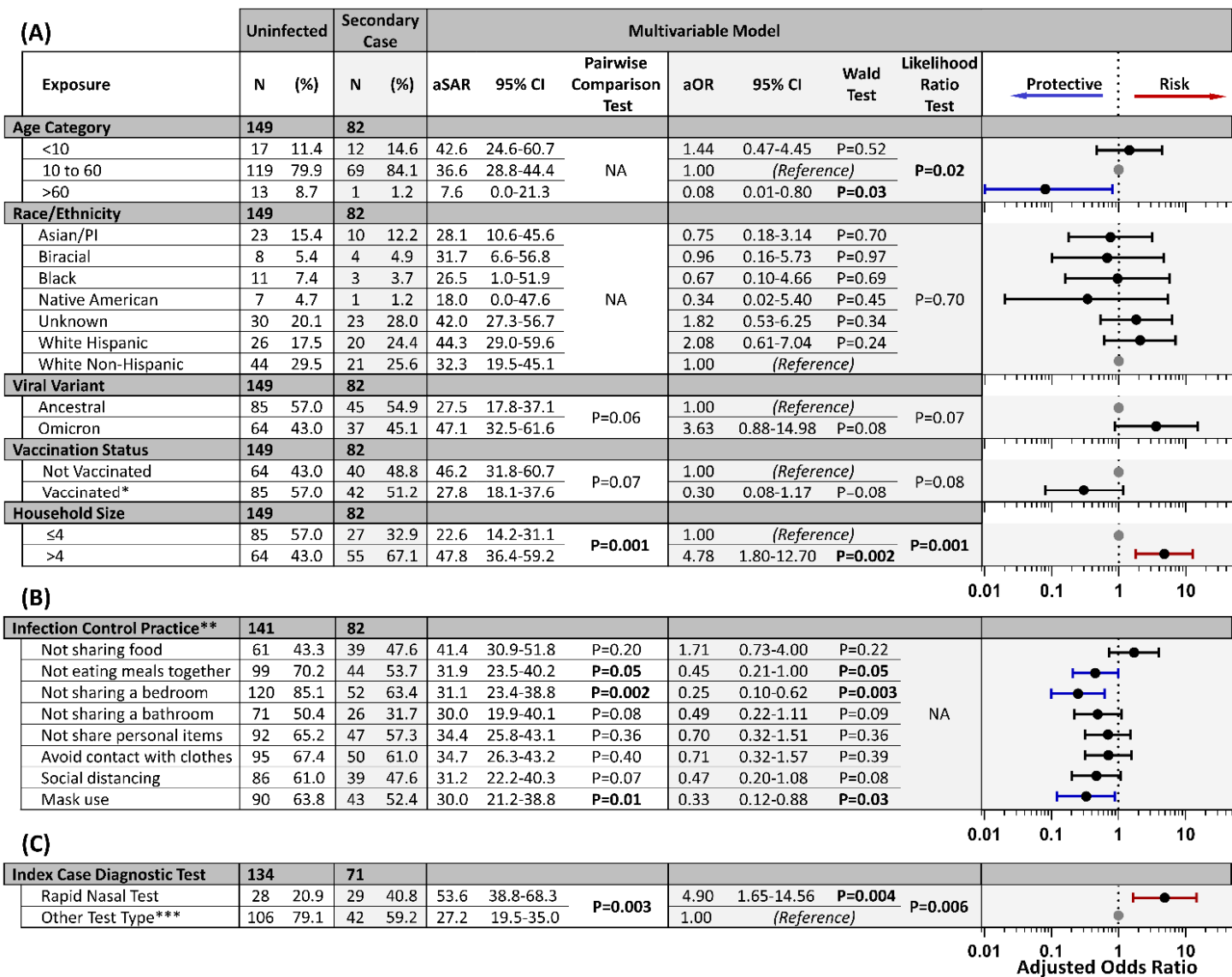
Results

We analyzed data from 370 individuals (enrolled and unenrolled participants) of which 85 were defined as household index cases (**Table 1**). Among index cases, nasal-swab rapid test use more than tripled from the first to second study phase (**Fig 1D**). Only 3 of 16 index cases first identified by a rapid nasal-swab rapid tests had a prior negative rapid nasal-test within three days of their positive result, suggesting repeat rapid nasal testing.[60] Across both study phases, we observed an overall, unadjusted SAR of 34.4% (95% CI 28.9%–40.2%, 98 of 285 household contacts) in this population.

Without accounting for index case testing, we observed several covariables associated with SARS-CoV-2 transmission in households (**Fig 2**). Household size greater than four members was associated with nearly a 5-fold increase in the odds of infection (aOR=4.78, 95% CI 1.80–12.70). Whether a household contact had received at least one dose of a COVID-19 vaccine was found to reduce the odds of infection by 70% (aOR=0.30, 95% CI 0.08–1.17). Most infection-control practices were associated with reduced risk, such as not sharing a bedroom with (aOR=0.25, 95% CI 0.10–0.62) and wearing masks around (aOR=0.33, 95% CI 0.12-0.88) infected individuals.

Our results were also consistent with previous observations that infection with the Omicron variant is associated with greater transmission than ancestral variants.[8,18,19,31-33] Increased transmissibility of the Omicron variant compared to ancestral variants was observed in our study by both aOR (3.64, 95% CI 0.88–15.07), as well as aSAR stratified by whether the index case was infected with the Omicron variant (46.9%, 95% CI 32.3%-61.6%) or an ancestral variant (27.3%, 95% CI 17.7%-36.9%). Increased transmissibility of the Omicron variant was not observed in the univariable model (**Table S2**), likely because this model does not correct for a compensating, protective effect of vaccination, which was more prevalent among individuals from households infected with the Omicron variant (76.7%) than ancestral variants (17.5%, **Table S1**).

Identification of index cases by nasal-swab rapid tests was associated with higher transmission to household contacts than other test types, both when aggregated (**Fig 2C**) and for all other test type subgroups (**Table S3**), and in both univariable (OR=2.64, 95% CI 1.41–4.95, *P*=0.003, **Table S2**) and multivariable models (aOR=4.93, 95% CI 1.65–14.69, *P*=0.004, **Fig 2**). The multivariable model suggests that nasal-swab rapid test use by index cases increased the odds of transmission relative to other test types by almost five-fold (though both smaller and larger increases are also compatible with the data). Index cases who used nasal-swab rapid tests also had a higher aSAR of 53.5% (95% CI 38.7%–68.3%) compared to other test types (27.0%, 95% CI 19.3%–34.8%).

Because the use of nasal-swab rapid test use has increased in parallel with SARS-CoV-2 variants shown to have increased transmissibility, we examined the relationship of these two covariables on risk of transmission to household contacts. The use of a nasal-swab rapid test to identify the index case was associated with a similar increased risk of transmission to household contacts) as infection with the Omicron variant (**Fig 3**). Introducing adjustment in the model for nasal-swab rapid test use by the index case decreased the aOR for infection with the Omicron variant from 3.63 (95% CI 0.88-15.0) to 2.40 (95% CI 0.63–9.22) (**Fig 3A**). The aOR of rapid nasal-swab test use also decreased from 5.50 (95% CI 1.78–17.04) to 4.90 (95% CI 1.65–14.59) without or with adjustment for viral variant, but nasal-swab rapid tests remained associated with at least a 1.5-fold increase in the odds of household contact infection (**Fig 3B**).

(A)

Exposure	Uninfected N	(%)	Secondary Case N	(%)	aSAR	95% CI	Pairwise Comparison Test	aOR	95% CI	Wald Test	Likelihood Ratio Test
Age Category	149		82								
<10	17	11.4	12	14.6	42.6	24.6-60.7		1.44	0.47-4.45	P=0.52	
10 to 60	119	79.9	69	84.1	36.6	28.8-44.4	NA	1.00	(Reference)		P=0.02
>60	13	8.7	1	1.2	7.6	0.0-21.3		0.08	0.01-0.80	P=0.03	
Race/Ethnicity	149		82								
Asian/PI	23	15.4	10	12.2	28.1	10.6-45.6		0.75	0.18-3.14	P=0.70	
Biracial	8	5.4	4	4.9	31.7	6.6-56.8		0.96	0.16-5.73	P=0.97	
Black	11	7.4	3	3.7	26.5	1.0-51.9		0.67	0.10-4.66	P=0.69	
Native American	7	4.7	1	1.2	18.0	0.0-47.6	NA	0.34	0.02-5.40	P=0.45	P=0.70
Unknown	30	20.1	23	28.0	42.0	27.3-56.7		1.82	0.53-6.25	P=0.34	
White Hispanic	26	17.5	20	24.4	44.3	29.0-59.6		2.08	0.61-7.04	P=0.24	
White Non-Hispanic	44	29.5	21	25.6	32.3	19.5-45.1		1.00	(Reference)		
Viral Variant	149		82								
Ancestral	85	57.0	45	54.9	27.5	17.8-37.1	P=0.06	1.00	(Reference)		P=0.07
Omicron	64	43.0	37	45.1	47.1	32.5-61.6		3.63	0.88-14.98	P=0.08	
Vaccination Status	149		82								
Not Vaccinated	64	43.0	40	48.8	46.2	31.8-60.7	P=0.07	1.00	(Reference)		P=0.08
Vaccinated*	85	57.0	42	51.2	27.8	18.1-37.6		0.30	0.08-1.17	P–0.08	
Household Size	149		82								
≤4	85	57.0	27	32.9	22.6	14.2-31.1	P=0.001	1.00	(Reference)		P=0.001
>4	64	43.0	55	67.1	47.8	36.4-59.2		4.78	1.80-12.70	P=0.002	

Protective ← / → Risk
0.01 0.1 1 10

(B)

Infection Control Practice**	141		82		aSAR	95% CI		aOR	95% CI	Wald/LRT	
Not sharing food	61	43.3	39	47.6	41.4	30.9-51.8	P=0.20	1.71	0.73-4.00	P=0.22	
Not eating meals together	99	70.2	44	53.7	31.9	23.5-40.2	P=0.05	0.45	0.21-1.00	P=0.05	
Not sharing a bedroom	120	85.1	52	63.4	31.1	23.4-38.8	P=0.002	0.25	0.10-0.62	P=0.003	
Not sharing a bathroom	71	50.4	26	31.7	30.0	19.9-40.1	P=0.08	0.49	0.22-1.11	P=0.09	NA
Not share personal items	92	65.2	47	57.3	34.4	25.8-43.1	P=0.36	0.70	0.32-1.51	P=0.36	
Avoid contact with clothes	95	67.4	50	61.0	34.7	26.3-43.2	P=0.40	0.71	0.32-1.57	P=0.39	
Social distancing	86	61.0	39	47.6	31.2	22.2-40.3	P=0.07	0.47	0.20-1.08	P=0.08	
Mask use	90	63.8	43	52.4	30.0	21.2-38.8	P=0.01	0.33	0.12-0.88	P=0.03	

0.01 0.1 1 10

(C)

Index Case Diagnostic Test	134		71		aSAR	95% CI		aOR	95% CI	Wald	LRT
Rapid Nasal Test	28	20.9	29	40.8	53.6	38.8-68.3	P=0.003	4.90	1.65-14.56	P=0.004	P=0.006
Other Test Type***	106	79.1	42	59.2	27.2	19.5-35.0		1.00	(Reference)		

0.01 0.1 1 10
Adjusted Odds Ratio

FIGURE 2 Results of Modeled Risk of Transmission to Household Contacts. Counts (N) of enrolled individuals who did not become infected during enrollment (uninfected) or became infected after the index case (secondary case) are provided for each covariable included in the multivariable model (**Fig 1C**). The adjusted secondary attack rate (aSAR) and adjusted odds ratio (aOR) point estimates with 95% confidence intervals from multivariable analysis are listed for each covariable and visualized to the right. Results of univariable analysis are provided in **Table S2**. The Wald test *P*-values for the analyses likelihood ratio test is shown. Covariates with an aOR 95% CI >1 are shown in red, and those <1 are shown in blue. Reference groups are shown as a grey point. **(A)** Data for the five covariables included in the sufficient set. **(B)** Covariables related to infection-control practices controlling for the sufficient set. The aOR represents the conditional effect of the covariable in the model. **(C)** Association between COVID-19 test type used to identify the household index case, and subsequent transmission to household contacts. Unenrolled household index cases' test type was unknown, resulting in a lower total count for this category.

Vaccinated is defined as having received at least one dose of a COVID-19 vaccine at least 7 days prior to enrollment.

**Participants were asked to respond whether or not they performed each action during interactions data coded. Data on infection control practices was not available for some participants. Observations with missing data were omitted, resulting in a lower total count for this category of covariables.*

***Analysis by Other Test Type subgroups is shown in **Table S3**.*
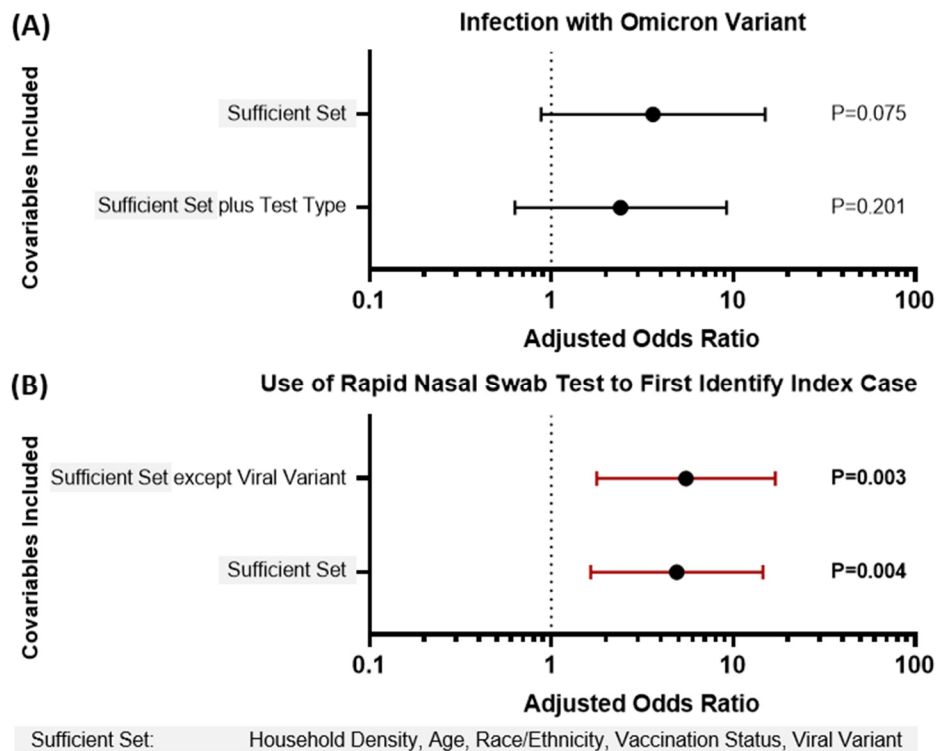
FIGURE 3. Effect Size Interactions of COVID-19 Test Type and Viral Variant on Transmission to Household Contacts. (A) The adjusted odds ratios (aOR) for infection with the Omicron variant (with ancestral SARS-CoV-2 variants as reference). Analysis was performed while controlling for the sufficient set of covariables in the model (grey box), as well as when additionally controlling for whether the index case was first identified using a nasal-swab rapid test or other COVID-19 test type. **(B)** The aOR for the use of nasal-swab rapid tests to first identify index cases, as opposed to other COVID-19 test type. Analysis was performed while controlling for the sufficient set of covariables in the model (shown in grey box), and with all covariables in the sufficient set except for viral variant. Wald test P-values are shown for each estimate of effect size. All error bars are 95% CI. Vertical dotted black line indicates an aOR of 1.0.

Discussion

Household contacts of index cases who used nasal-swab rapid antigen COVID-19 tests for primary infection detection had an increased risk of becoming infected compared with household contacts of index cases who used other test types. Greater transmission of SARS-CoV-2 to household contacts by individuals first identified by nasal-swab rapid tests is supported mechanistically by studies of SARS-CoV-2 viral load and nasal swab rapid test performance. First, a gradual rise in viral loads, as we[43,44,50,61] and others[52,62-64] have observed, often creates a several-day delay between when an individual likely becomes infectious and when viral loads reach levels detectable by low-analytical-sensitivity, rapid tests. Second, a delay in the rise of nasal viral loads relative to oral specimen types, as we [43,44,50] and others[45,49] have observed, renders nasal-swab rapid tests less able to detect individuals during the early phase of the infection.[46,50] During this early period of low nasal viral loads, we[43,50] and others[46] find that individuals exhibited high, presumably infectious viral loads in oral specimens. Relatedly, among data from a SARS-CoV-2 human challenge study,[49] we see that the majority of infected participants had

replication-competent virus present in throat swabs at least one day prior to nasal-swabs. Therefore, nasal-swab rapid tests may only yield positive results after exposure and transmission to contacts has occurred. These results together suggest that nasal-swab rapid tests are not as effective at identifying index cases to limit subsequent transmission as other test types.

Several additional findings from our model and dataset were consistent with prior studies. Household size was a significant risk factor for household transmission,[9-12] whereas vaccination[8,18-22] and infection-control practices[14,18,23-25] were protective. The overall SAR (34.4%) we observed was similar to what others have reported.[5,12,18,31,65,66] Relatedly, in one of those studies[5], household transmission was monitored by daily high-analytical-sensitivity screening testing and the SAR calculated using only nasal-swab test data was lower than when both saliva and nasal-swab test data were used, which supports that even high-analytical-sensitivity nasal-swab testing may miss some infected individuals, and that the specimen type used for evaluation can impact estimates of transmission.

We also observed, as other epidemiological studies have,[8,18,19,31-33] that infection with the Omicron variant was associated with increased transmission compared with ancestral viral variants. However, the use of rapid nasal-swab tests (as opposed to other test types) to detect index cases had a similar conditional direct effect on transmission to household contacts as infection with the Omicron variant. Because the effect size of the Omicron variant association with transmission to household contacts decreased when controlling for nasal-swab rapid test use in our study, we speculate that a portion of the increased transmissibility attributed to the Omicron variant in published epidemiological studies may be partially attributable to the increased use of rapid nasal-swab tests in the U.S. that coincided with the predominance of this variant.[10,67] Although our results do not invalidate studies that conclude an increased transmissibility of the Omicron variant, they emphasize the potential impact of COVID-19 test type on estimates of transmissibility from epidemiological data.

Limitations

Our findings are subject to limitations. First, vaccination status, demographic information, and infection-control practices are self-reported and may be subject to recall bias. Second, although questionnaires were written in simple terms (e.g. "shallow nasal swab" and "deep nasal swab"), participants could have misinterpreted test type. Third, age, gender, and infection status of each unenrolled household member was independently reported by each enrolled household member, which could lead to inaccurate reporting. Fourth, our potential misclassification of which household member was the index case may impact the analysis,[53] although in almost all (79 of 85) households, the index case was confirmed by timing of self-reported positive tests. Fifth, in our transmission model, we did not analyze ordinal levels of contact among household

members (all household members were assumed to have equal contact). Instead, mitigating factors, including infection-control practices, were assessed for protective effects against transmission. Sixth, it is possible that high-analytical-sensitivity tests could have turnaround times which we classify as rapid. However, such misclassification would bias toward the null. Finally, evidence suggests[52,68] and the CDC[60] recommends repeating rapid antigen tests over several days to improve clinical sensitivity. Although some index cases reported a negative test result in the days prior to their first positive result, most participants in our study did not use repeated rapid testing.

Conclusion

Rapid COVID-19 tests, such as antigen tests, are less expensive, portable, and offer faster results than high-analytical-sensitivity molecular tests. However, results from this observational study suggest that the use of nasal-swab rapid COVID-19 tests to first identify infection do not limit household transmission as well as other test types. The use of tests with low analytical sensitivity by an infected individual can have two effects on transmission: (i) a true-positive result can change behavior to increase infection-control practices in a timely manner, thus reducing transmission, or (ii) a false-negative result can result in a health certificate effect,[69] where individuals falsely assume they are not infected/infectious and reduce precautions, thereby increasing transmission. While imperfect testing may be better than no testing, understanding the optimal use and limitations of rapid tests is important not only for SARS-CoV-2, but other pathogens for which timely infection control and/or early treatment is critical.

DATA SHARING STATEMENT

Raw data is available at CaltechDATA: https://doi.org/10.22002/csh5w-rf132.#

DISCLOSURE

R.F.I. is a cofounder, consultant, and a director and has stock ownership of Talis Biomedical Corp. All other co-authors report no competing interests.

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Supplemental Information for:

Index Cases First Identified by Nasal Swab Rapid COVID-19 Tests Had More Transmission to Household Contacts Than Cases Identified by Other Test Types

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Table S1. Participant Demographics by (A) Study Phase and (B) Infecting SARS-CoV-2 Variant Demographics, vaccination status, and index case testing type of the 85-household cohort divided by (**A**) study phase and (**B**) infecting viral variant.

	(A) Study Phase				(B) Viral Variant			
	Phase I		Phase II		Omicron		Ancestral Variants	
	N= 155		N= 215		N= 163		N= 207	
Self-Reported Gender Identity*	n	(%)	n	(%)	n	(%)	n	(%)
Man	70	45.2	104	48.4	78	47.9	96	46.4
Woman	85	54.8	111	51.6	85	52.1	111	53.6
Third Gender	0	0.0	0	0.0	0	0.0	0	0.0
Age Category	n	(%)	n	(%)	n	(%)	n	(%)
<10	29	18.7	28	13.0	20	12.3	37	17.9
10 to 60	115	74.2	173	80.5	129	79.1	159	76.8
>60	11	7.1	14	6.5	14	8.6	11	5.3
Self-Reported Race/Ethnicity**	n	(%)	n	(%)	n	(%)	n	(%)
Asian or Pacific Islander	11	7.1	36	16.7	31	19.0	16	7.7
Biracial	8	5.2	8	3.7	6	3.7	10	4.8
Black/African American	9	5.8	7	3.3	7	4.3	9	4.3
Native American/Alaska	0	0.0	12	5.6	8	4.9	4	1.9
Unknown	61	39.4	66	30.7	44	27.0	83	40.1
White, Hispanic	38	24.5	30	14.0	22	13.5	46	22.2
White, Non-Hispanic	28	18.1	56	26.0	45	27.6	39	18.8
Vaccination Status** *	n	(%)	n	(%)	n	(%)	n	(%)
Unvaccinated	133	85.8	15	7.0	4	2.5	144	69.6
Partial	3	1.9	2	0.9	2	1.2	3	1.4
Complete	1	0.6	77	35.8	52	31.9	26	12.6
Boosted	0	0.0	79	36.7	71	43.6	8	3.9
Unknown	18	11.6	42	19.5	34	20.9	26	12.6
Household Size	n	(%)	n	(%)	n	(%)	n	(%)
<= 4	97	62.6	85	39.5	65	39.9	117	56.5
> 4	58	37.4	130	60.5	98	60.1	90	43.5
Index Case Test Type	n	(%)	n	(%)	n	(%)	n	(%)
Rapid Nasal	17	11.0	72	33.5	62	38.0	27	13.0
Not Rapid Nasal	134	86.5	111	51.6	73	44.8	172	83.1
Unknown	4	2.6	32	14.9	28	17.2	8	3.9

Both sex assigned at birth and current gender identity were self-reported by participants. One participant reported male assignment at birth and current gender identity of woman. Reported gender is listed.

**63 individuals currently listed as 'Unknown' did not select a race category but wrote-in "Latino"/"Latina"/"Latinx."*

***Participants reported date and manufacturer of each vaccine dose received; vaccination status was defined only by doses received at least 7 days prior to enrollment in the study. Unvaccinated was defined as having received no COVID-19 vaccine doses. Partial vaccination was defined as receiving one dose of a multiple-dose series (e.g., Pfizer-BioNTech, Moderna). Complete vaccination was defined as receiving all doses of an initial COVID-19 vaccine series. Boosted was defined as the participant receiving any dose beyond an initial COVID-19 vaccine series.*

Table S2. Univariable Model. Simple Odds Ratios (OR) for covariables included in the models in Fig 2.

Exposure	SAR (%)	95% CI (%)	Pairwise Comparison Test	OR	95% CI	Wald Test
Age Category						
<10	41.4	23.5-59.3		1.22	0.55-2.70	P=0.63
10 to 60	36.7	29.8-43.6		1.00	(Reference)	
>60	7.1	0.0-20.6	NA	0.13	0.02-1.04	P=0.05
Race/Ethnicity						
Asian/PI	30.3	14.6-46.0		0.91	0.37-2.25	P=0.84
Biracial	33.3	6.66-60.0		1.05	0.28-3.87	P=0.94
Black	21.4	0.0-42.9		0.57	0.14-2.27	P=0.43
Native American	12.5	0.0-35.4		0.30	0.03-2.59	P=0.27
Unknown	43.4	30.1-56.7		1.61	0.76-3.41	P=0.22
White Hispanic	43.5	29.2-57.8		1.61	0.74-3.52	P=0.23
White Non-Hispanic	32.3	20.9-43.7	NA	1.00	(Reference)	
Viral Variant						
Ancestral	34.6	26.4-42.8		1.00	(Reference)	
Omicron	36.6	27.2-46.0	P=0.75	1.09	0.63-1.88	P=0.75
Vaccination Status						
Not Vaccinated	38.5	29.1-47.8		1.00	(Reference)	
Vaccinated*	33.1	24.9-41.3	P=0.40	0.79	0.46-1.36	P=0.40
Household Density						
≤4	24.1	16.2-32.0		1.00	(Reference)	
>4	46.2	37.3-55.2	**P<0.001**	2.71	1.54-4.75	**P=0.001**
Infection Control Practice**						
Not sharing food	39.0	29.4-48.6	P=0.53	1.19	0.69-2.05	P=0.53
Not eating meals together	30.8	23.2-38.3	**P=0.01**	0.49	0.28-0.86	**P=0.01**
Not sharing a bedroom	30.2	23.4-37.1	**P<0.001**	0.30	0.16-0.58	**P<0.001**
Not sharing a bathroom	26.8	18.0-35.6	**P=0.005**	0.46	0.26-0.81	**P=0.007**
Not share personal items	33.8	25.9-41.7	P=0.24	0.72	0.41-1.25	P=0.24
Avoid contact with clothes	34.5	26.7-42.2	P=0.34	0.76	0.43-1.33	P=0.33
Social distancing	31.2	23.1-39.3	P=0.05	0.58	0.33-1.01	P=0.05
Mask use	32.3	24.4-40.3	P=0.10	0.62	0.36-1.09	P=0.10
Index Case Diagnostic Test						
Rapid Nasal Test	50.9	37.9-63.9		2.61	1.39-4.91	**P=0.003**
Other Test Type	28.4	21.1-35.6	**P=0.003**	1.00	(Reference)	

Table S3. Association of Test Type Subcategories with SARS-CoV-2 Transmission Among Household Contacts. Provides data and Odds Ratios (OR) on the association between COVID-19 test type used to identify the household index case and subsequent transmission to household contacts.

Exposure	Uninfected N	(%)	Secondary Case N	(%)	aSAR	95% CI	aOR	95% CI	Wald Test	Likelihood Ratio Test
Test Type	149		82							
Nasal Rapid	28	18.8	31	37.8	48.1	32.6-63.5	1.00	(Reference)		
Nasal Not Rapid	37	24.8	7	8.5	16.2	4.59-27.8	0.13	0.03-0.51	P=0.003	
Nasopharyngeal Rapid	17	11.4	4	4.9	19.5	0.25-38.7	0.17	0.03-1.06	P=0.06	
Nasopharyngeal Not Rapid	31	20.8	15	18.3	33.1	18.0-48.2	0.43	0.11-1.61	P=0.21	P=0.05
Oral Rapid	1	0.7	3	3.7	43.9	0.0-98.4	0.80	0.04-18.01	P=0.89	
Oral Not Rapid	17	11.4	10	12.2	43.4	20.7-66.1	0.78	0.15-3.88	P=0.76	
Unknown	18	12.1	12	14.6	45.9	26.9-64.9	0.89	0.24-3.28	P=0.86	

Supplemental Methods

Participants

Individuals fluent in English or Spanish aged 6 years and older from households of two or more persons were eligible for participation if at least one household member had tested positive, developed COVID-19-like symptoms,[1] or had a known exposure with a SARS-CoV-2 infected individual within 7 days, and at least one other household member had either negative or unknown infection status during screening.

Upon enrollment, participants completed a questionnaire to provide information about demographics (based on the 2019 California Health Interview Survey tool)[2], medical information, and COVID-19 history (e.g., COVID-19-like symptoms[1], positive and negative test results, and COVID-19 vaccination information). For participants enrolled prior to February 22, 2021, vaccination was not asked, but unvaccinated status was inferred based on local vaccine availability.[3] Vaccination status was defined only by doses received at least 7 days prior to enrollment. The questionnaire also asked about household size, the age and gender of other household members and their SARS-CoV-2 infection status, as well as current and anticipated infection-control practices (e.g., shared items and spaces, disinfection, distancing, and masking).

Sample collection

In Phase I of the study, participants self-collected either saliva or paired saliva and anterior-nares nasal swabs every morning upon waking and in the evening before bed in Spectrum SDNA 1000 devices.[4] In Phase II, participants self-collected paired saliva, anterior-nares nasal swabs, and oropharyngeal swabs in Zymo Research's SafeCollect devices[5,6] once daily (upon enrollment and thereafter each morning upon waking).

Supplemental References

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DETAILED AUTHOR CONTRIBUTION STATEMENTS

Listed alphabetically by surname

Saharai Caldera (SC)- Study coordinator; recruited, enrolled and maintained study participants with NS, JAR, HD and NWS; study-data quality control; validated data provided by participants in study instruments.

Hannah Davich (HD)- Lead study coordinator; recruited, enrolled and maintained study participants with NS, JAR, SC and NWS; developed recruitment strategies and did outreach with NS; study-data quality control; validated data provided by participants in study instruments; Compiled data from screening with NS for use in Fig 1B. Compiled data for household size and density metrics.

Matthew Feaster (MF)- Co-investigator; contributed to overall study design and recruitment strategies; provided guidance and expertise on SARS-CoV-2 epidemiology and local trends. Contributed to design of biostatistical analysis, particularly conceptualization of causal model represented in Fig 1C and parameterization/coding of covariables. Technical guidance on analysis method and interpretation. Reviewed manuscript.

Ying-Ying Goh (YYG)- Co-investigator; contributed to overall study design and recruitment strategies; provided guidance and expertise on SARS-CoV-2 epidemiology and local trends.

Rustem F. Ismagilov (RFI)- Principal investigator; provided leadership, technical guidance, oversight of all analyses, and was responsible for obtaining the primary funding for the study.

Jenny Ji (JJ)- Conceptualization of study with AVW and RFI. Performed extensive literature search on household transmission and co-wrote enrollment questionnaire with AW and NS. Data curation. Performed preliminary analyses. Coded and cleaned data from participant questionnaires. Validated underlying data. Parameterization of participant data for analysis. Assigned index case with AVW, NS, and NWS. Performed analyses in STATA. Prepared Figure 1, 2 and 3 with AVW. Prepared Table 1 with AVW. Study-specific literature review with AVW. Outlined manuscript with AVW. Revised manuscript with AVW.

Jessica A. Reyes (JAR)- Lead study coordinator; recruited, enrolled and maintained study participants with NS, HD, SC, and NWS; study-data quality control; validated data provided by participants in study instruments.

Natasha Shelby (NS)- Study administrator; contributed to initial study design and recruitment strategies; co-wrote enrollment questionnaire with AW and JJ; hired, trained, and supervised the study-coordinator team; recruited, enrolled and maintained study participants with JAR, JAR, NWS, HD and SC; study-data quality control; validated data provided by participants in study instruments; data curation; organized archiving of participant data; helped assemble CONSORT diagram (Fig 1B); assisted with assignment of household index cases with JJ, AVW, and NWS; managed reference library; reviewed and edited the manuscript.

Noah W. Schlenker (NWS)- Study coordinator; recruited, enrolled and maintained study participants with NS, JAR, HD and SC; study-data quality control; validated data provided by participants in study instruments; major role in assignment of household index cases with JJ, AVW, and NS.

Colten Tognazzini (CT)- Coordinated the recruitment efforts at PPHD with case investigators and contact tracers; provided guidance and expertise on SARS-CoV-2 epidemiology and local trends.

Alexander Viloria Winnett (AVW)- Conceptualization of study with JJ and RFI. Contributed to overall study design and recruitment strategies. Co-wrote enrollment questionnaire with NS and JJ; Data curation and analysis. Assigned vaccination status for each participant. Assigned infection status from viral load data. Assigned index case with JJ, NS, and NWS. Prepared Figure 1, 2 and 3 with JJ. Prepared Table 1 with JJ. Verified underlying data and analyses performed by JJ. Study-specific literature review with JJ. Outlined manuscript with JJ. Drafted initial manuscript. Revised manuscript with JJ.

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