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1 **Magnitude and determinants of SARS-CoV-2 household transmission: a longitudinal**
2 **cohort study**

3
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30
31 **Running title:** SARS-CoV-2 household transmission

1 **Abstract**

2 **Background:** Households have emerged as important venues for SARS-CoV-2 transmission.

3 Little is known, however, regarding the magnitude and determinants of household transmission
4 in increasingly vaccinated populations.

5 **Methods:** From September 2020 to January 2022, symptomatic non-hospitalized individuals
6 with SARS-CoV-2 infection by RNA detection were identified within 5 days of symptom onset; all
7 individuals resided with at least one other SARS-CoV-2-uninfected household member. These
8 infected persons (cases) and their household members (contacts) were subsequently followed
9 with questionnaire-based measurement and serial nasal specimen collection. The primary
10 outcome was SARS-CoV-2 infection among contacts.

11 **Results:** We evaluated 42 cases and their 74 household contacts. Among the contacts, 32
12 (43%) became infected, of whom 5/32 (16%) were asymptomatic; 81% of transmissions
13 occurred by 5 days after the case's symptom onset. From 21 unvaccinated cases, 14-day
14 cumulative incidence of SARS-CoV-2 infection among contacts was 18/40 (45%; 95% CI: 29,
15 62), most of whom were unvaccinated. From 21 vaccinated cases, 14-day cumulative incidence
16 of SARS-CoV-2 infection was 14/34 (41%; 95% CI: 25, 59) among all contacts and 12/29 (41%;
17 95% CI: 24, 61) among vaccinated contacts. At least one co-morbid condition among cases and
18 10 or more days of RNA detection in cases were associated with increased risk of infection
19 among contacts.

20 **Conclusions:** Among households including individuals with symptomatic SARS-CoV-2
21 infection, both vaccinated-to-vaccinated and unvaccinated-to-unvaccinated transmission of
22 SARS-CoV-2 to household contacts was common. Because vaccination alone did not notably
23 reduce risk of infection, household contacts will need to employ additional interventions to avoid
24 infection.

25 **Presentations at meetings:** This work has not been presented.

26
27 **Keywords:** SARS-CoV-2; household transmission; epidemiology; infectious viral shedding
28

Introduction

The reported magnitude of SARS-CoV-2 transmission from index cases to household members has varied, depending on multiple factors including viral variant, vaccination status of both the index case and household contacts, and diagnostic procedures.[1] Prior to the introduction of Delta variant, fully vaccinated index cases had a lower proportion of transmission events (cumulative incidence, or secondary attack rates) to household members compared to unvaccinated index cases.[2-4] Studies focused on Delta infections, however, found that there was no difference in the proportion of transmission events between vaccinated and unvaccinated index cases.[5-7] It should be noted that most of these Delta-focused transmission studies did not perform longitudinal specimen collection more than weekly, and as a result, may have missed cases in the household. Very few studies have taken the additional step of generating qualitative and quantitative viral culture data from specimens to assess the effect of infectious viral shedding of cases on infection of contacts.

Without rigorous descriptions of transmission events in households from and between vaccinated and unvaccinated individuals, we have a limited understanding of the causal determinants of SARS-CoV-2 transmission and host susceptibility of infection. We developed a rigorous set of criteria, using viral, epidemiological, and genetic data, to identify primary cases. Then, we sought to assess the host and viral determinants and magnitude of SARS-CoV-2 household transmission, stratifying cases and contacts by vaccination status.

Methods

Overall Design

This was a longitudinal cohort study enrolling vaccinated and unvaccinated individuals (index cases) at the time of SARS-CoV-2 infection and their household contacts. The study was reviewed by the UCSF Institutional Review Board and given a designation of public health

1 surveillance according to federal regulations as summarized in 45 CFR 46.102(d)(1)(2). Written
2 informed consent was obtained from all participants.

3

4 **Participants**

5 From September 2020 to January 2022, we identified individuals of all ages who were
6 positive for SARS-CoV-2 via provider-ordered molecular testing at UCSF-affiliated testing sites.
7 Individuals were screened for study eligibility by review of available data or by telephone
8 interview. Individuals were eligible for inclusion as index cases if they were non-hospitalized,
9 resided with at least one other individual, and lived in non-congregate settings in the San
10 Francisco Bay Area. Symptomatic individuals were eligible if they could be enrolled within 5
11 days of symptom onset. To reliably identify asymptomatic index cases early in infection,
12 asymptomatic individuals were only eligible as index cases if they could be enrolled within 10
13 days of a known high-risk exposure (unprotected exposure within 6 feet for greater than 15
14 minutes over 24-hour period).

15 A household contact was defined as any individual who had spent at least one night in
16 the household during the 2 days before illness onset of the index case through to enrollment. If
17 the index case was eligible and at least one household member was willing to participate, then
18 household eligibility was assessed. Households were not eligible for the study if household
19 contacts ever had a history of confirmed or probable SARS-CoV-2 infection or had suspected
20 SARS-CoV-2 infection in the 14 days preceding symptom onset of the index case,[8] unless the
21 first study visit could occur within 5 days of symptom onset of all individuals living in the
22 household.

23

1 **Measurements**

2 *Questionnaire-based*

3 Our interviewers administered questionnaires to cases and contacts by telephone to
4 collect data on sociodemographics, exposure and medical history, symptom status and onset,
5 and clinical course of acute COVID-19. Our symptom checklist included 32 symptoms derived
6 from the U.S. Centers for Disease Control (CDC) list of COVID-19 symptoms[9] and the Patient
7 Health Questionnaire Somatic Symptom Scale.[10] We also recorded any other self-reported
8 symptom. Any symptoms were recorded as present if they were new or worsened since the time
9 of SARS-CoV-2 infection. Interviewers reviewed documentation of SARS-CoV-2 infection and
10 vaccination status during study visits. Participants were also assessed for receipt of vaccine
11 boosters. Questionnaires were completed on day (d) of enrollment (dE), and at d9, 14, 21, and
12 28 after symptom onset of the index case.

13
14 *Laboratory-based*

15 Study staff also visited participants in their households on the same days as the
16 telephone questionnaires (dE, d9, d14, d21, d28). Detailed operational methods are described
17 in the **Supplemental Material**. Anterior nasal specimens were self-collected daily from dE
18 through d14 and then on d17, d19, d21, and d28. Biospecimens were collected relative to the
19 symptom onset of the index case (or day of first positive test in asymptomatic index cases).
20 These specimens were stored in households at -20 °C for up to one week, until the next in-
21 person study visit by the investigators, and subsequently transported on dry ice to laboratories
22 at UCSF. To provide participants with timely clinical results, additional oropharynx (OP)
23 specimens were collected at enrollment for molecular testing at UCSF clinical laboratories. All
24 specimens tested by clinical and research laboratories were used to measure SARS-CoV-2
25 infection. We also measured infectious virus and viral lineage. Details of the laboratory assays
26 have been previously reported.[11]

1 *RT-PCR*

2 In brief, the research laboratory used all anterior nasal specimens to quantify SARS-
3 CoV-2 RNA through RT-PCR targeting nucleocapsid (N) and envelope (E) genes on a CFX
4 Connect Real-Time PCR detection system (Biorad).

5
6 *Whole genome sequencing of SARS-CoV-2*

7 Viral sequencing was done using RNA from nasal specimens with the highest RNA level
8 for each SARS-CoV-2-infected individual. The ARTIC Network amplicon-based sequencing
9 protocol for SARS-CoV-2 (using primer versions 3 and 4.1) was followed and sequencing was
10 done on a MinION sequencer (Oxford Nanopore Technologies). The nCoV-2019 novel
11 coronavirus bioinformatics protocol was used to assemble viral genomes and generate
12 consensus sequences.[12] Full consensus genomes were submitted to GISAID and NCBI. Viral
13 lineages were assigned using the PANGOLIN (Phylogenetic Assignment of Named Global
14 Outbreak Lineages) version 3.0.2.

15
16 *Phylogenetic analyses*

17 A dataset was compiled consisting of all available high-quality whole genome sequences
18 deposited to GISAID from San Francisco and Alameda counties collected between September
19 2020 and January 2021 (N=5,212) together with 72 genomes generated from our study cohort.
20 Sequence alignment was done using MAFFT v7.388 implemented in CIPRES Science
21 Gateway.[13] Aligned sequences were used as input for the Nextstrain bioinformatic pipeline
22 Augur version 13.0.2 [14] and maximum likelihood phylogenetic trees were inferred using
23 IQTREE v1.6 and a discrete traits model. Phylogenies were visualized using Auspice.

24

1 *Cytopathic effect assay*

2 Anterior nasal specimens were used to detect infectious virus on Vero-hACE2-
3 TMPRSS2 cells. All specimens up to 14 days after symptom onset were assayed for cytopathic
4 effect (CPE), which allows for a qualitative (yes/no) determination of infectious virus. In cases
5 where CPE was observed within days 11-14, testing was continued until there were three
6 consecutive negative results. Viral cultures with evidence of CPE underwent RT-PCR to confirm
7 the presence of SARS-CoV-2.

8

9 *Viral plaque assay*

10 Based on qRT-PCR data, the specimen with maximum RNA load for each participant
11 was selected for evaluation of quantitative infectious virus. Conventional plaque assays were
12 performed and plaques were counted to determine infectious viral titers (expressed as plaque
13 forming units/mL).[11]

14

15 **Analyses**

16 *Analytical definitions*

17 The index case for each household was the individual identified by the study team from
18 the overall list of individuals with positive SARS-CoV-2 PCR testing. For analyses, we defined
19 the single primary case as the first SARS-CoV-2-infected individual in the household, based on
20 the first illness onset or, if asymptomatic, the first individual with a positive test. Hereinafter,
21 single primary cases will be referred to as primary cases. Co-primary cases occurred when the
22 first SARS-CoV-2-infected individual was not able to be determined from two or more infected
23 individuals in the household (see next section for more details). A household case was any
24 household contact infected by SARS-CoV-2 after the primary case and not considered a co-
25 primary case. Serial interval was defined as the number of days between the symptom onsets
26 (or date of first positive test in asymptomatic cases) of the primary case and any household

1 case. Shared exposure was broadly defined as having had a high-risk exposure in the same
2 contextual setting (e.g., hospital, indoor dining, family gathering) within 14 days prior to
3 symptom onset of the index case. We created a decision algorithm with serial intervals, shared
4 exposures, and phylogenetic analyses to identify primary versus co-primary cases from index
5 cases. Details describing the decision algorithm can be found in the **Supplemental Material**.

6

7 *Statistical analyses*

8 We described the entire cohort and whether infected individuals self-reported the
9 presence or absence of any symptom over the infectious period. We restricted analyses to
10 households that had primary cases who were symptomatic. Our primary outcome was SARS-
11 CoV-2 infection among household contacts, defined as the identification of SARS-CoV-2 RNA in
12 any nasal or oropharyngeal specimen longitudinally obtained over the infectious period. All
13 household contacts who developed SARS-CoV-2 infection during the study had positive testing
14 within 10 days of symptom onset of the primary case in the household; we assumed that all
15 infections identified in these households represented transmission from the primary case.

16 We estimated 14-day cumulative incidence of SARS-CoV-2 infection among household
17 contacts and determined which host and viral factors were associated with household
18 transmission. We stratified cumulative incidence by vaccination status and by variant of the
19 primary case. Participants were considered vaccinated if participants completed a primary
20 series of a COVID-19 vaccine ≥ 14 days prior to enrollment; those who had received booster
21 dose were also included as vaccinated. Partial vaccination was defined as having received the
22 first mRNA dose in a 2-dose series > 14 days earlier but were either missing a second dose or
23 < 14 days had elapsed since the receipt of the second dose.[15]

24 We next performed analyses to assess risk factors for infection among household
25 contacts accounting for characteristics of primary cases and household contacts. Host factors
26 included age, sex, race/ethnicity, BMI (< 25 , $25-30$, > 30), vaccination status at baseline, and

1 presence of any comorbidities (autoimmunity, cancer, diabetes, HIV/AIDS, heart disease,
2 hypertension, lung disease, kidney disease). Viral factors included variant, maximum RNA load
3 (log copies/mL), maximum infectious viral load (log plaque forming units [log pfu]/mL), and
4 duration of RNA and infectious viral shedding (days after symptom onset until last positive test).
5 If no RNA or live virus was detected, we assigned that individual a duration of zero. In our
6 analyses of maximum RNA level or infectious viral load, we did not include individuals with a
7 value of zero because of the lack of a valid assumption for use of bins.

8 We used generalized estimating equations (GEE) with modified Poisson regression (log
9 link), clustering by household, to generate marginal estimates of risk ratios (cumulative
10 incidence ratios) and 95% confidence intervals (CIs). We performed a series of unadjusted
11 analyses examining each host and viral factor for primary cases and then each host factor for
12 household contacts. We performed a series of adjusted analyses that included factors for both
13 the primary cases and household contacts. To determine the relevant covariates, we created an
14 adjustment set of covariates in a Directed Acyclic Graph to assess potential confounders,
15 mediators, and colliders (**Suppl. Figure 1**). We considered the literature, expert consultation,
16 and the results of our unadjusted analyses in the determination of final covariate adjustment set.
17 We repeated this process in the assessment of each factor. Details of each model can be found
18 in the footnote of the tables.

19 Confidence intervals for cumulative incidence were calculated using Agresti-Coull
20 interval. We used GEE to compare cumulative incidence estimates and generated p-values,
21 considering any p-value of less than 0.05 as statistically significant. In the analyses involving
22 statistical modeling, we used confidence intervals to determine statistical significance and
23 considered intervals that did not include the null value to be significant. All analyses were
24 performed using STATA/BE 17.0 (StataCorp, College Station, Texas, USA). As a sensitivity
25 analysis of the cumulative incidence estimate, we repeated the analyses with the entire cohort,
26 inclusive of primary and co-primary cases (**Suppl. Table 1**).

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Results

From September 2020 to January 2022, we enrolled 65 index cases and their 115 household contacts in the total study cohort (180 participants) (**Figure 1**). Among these 180 participants, 72 (57%) of 126 infected participants had sufficient RNA levels for viral sequencing (**Figure 2**). There were 21 index cases that had no infected household contacts and were classified as primary cases. Among the remaining 44 index cases, we assessed the serial interval and shared exposures and identified 24 additional possible primary cases. From phylogenetic analyses of available genomic data, 24 contacts had viral sequences that could be paired to an index case and assessed as potentially related sequences. Based on these phylogenetic analyses, we reclassified one of the 45 households thought to have a single primary case as having co-primary cases (**Figure 3**). Among the remaining 44 single primary cases, two were asymptomatic. We excluded asymptomatic primary cases to focus on an analysis cohort of 42 symptomatic primary cases and their 74 household contacts (116 participants) (**Figure 4**).

Description of primary cases and household contacts

Primary cases were enrolled a median of 4 days (range: 1 to 5) from symptom onset. Among the 42 primary cases included in this analysis, half (50%) were unvaccinated and half (50%) vaccinated, with 1 having a full primary series and booster vaccine (no partially vaccinated primary cases). Almost all (20/21, 95%) vaccinated primary cases received an mRNA vaccine (3 received Moderna and 17 received Pfizer); one received the viral vector vaccine (Janssen). All vaccinated primary cases were enrolled from June 2021 through January 2022 during the Delta or Omicron periods. Among the 74 household contacts of these 42 primary cases, 40 (54%) were unvaccinated, 4 (5%) were partially vaccinated, and 30 (41%)

1 were vaccinated. Households had a median size of 3 participants (IQR: 2, 4), inclusive of
2 primary cases.

3 A median of 14 specimens (total of 552; IQR: 12, 15) were collected per primary case.
4 Based on viral sequencing results of the 42 primary cases, 12 (29%) were infected by non-
5 VOI/VOC, 18 (43%) by Delta variant, 3 (7%) by Omicron, 3 (7%) by Epsilon, 1 (2%) by Alpha,
6 and 5 (12%) by unclassified variants. Primary cases had a median maximum RNA viral load of
7 6.7 log copies/mL (IQR: 5.1, 8.2; n=40), median duration of RNA detection of 9.5 days since
8 symptom onset (IQR: 7, 11; n=42), median maximum infectious viral titers of 8.3 log pfu/mL
9 (IQR: 6.6, 12.3; n=32), and median duration of infectious viral shedding of 5 days since
10 symptom onset (IQR: ≤ 3 , 7; n=39). See **Table 1** for more characteristics of the primary cases
11 and their contacts, and see **Table 2** for virologic characteristics of the infected participants.

12 13 *Cumulative incidence of SARS-CoV-2 infection*

14 Among the 74 household contacts of the 42 primary cases, a median of 14 specimens
15 (total of 924; IQR 12, 15) were collected per household contact. 32/74 (43%) household
16 contacts were SARS-CoV-2 positive (e.g., household cases). Of 32 household cases, five (16%)
17 were asymptomatic (none were vaccinated), and none were hospitalized. Among household
18 contacts exposed to 21 vaccinated primary cases, cumulative incidence of SARS-CoV-2
19 infection was 14/34 (41%; 95% CI: 25, 59); among household contacts exposed to 21
20 unvaccinated primary cases, cumulative incidence was 18/40 (45%; 95% CI: 29, 62; p=0.60).

21 Most (29/34) household contacts of vaccinated primary cases were also vaccinated, and
22 cumulative incidence among these vaccinated household contacts was 12/29 (41%; 95% CI: 24,
23 61). Likewise, almost all (34/40) household contacts of unvaccinated primary cases were also
24 unvaccinated, and cumulative incidence among these unvaccinated household contacts was
25 16/34 (47%; 95% CI: 30, 65). (**Table 3**). Almost all (26/32, 81%) transmission events occurred

1 within 5 days since day of symptom onset of the primary case, with a median serial interval of 3
2 days (IQR: 2, 4; range: 0, 12) (**Suppl. Table 2**).

3 Stratifying by viral variant of 42 primary cases, cumulative incidence of SARS-CoV-2
4 infection was as follows: by Delta variant, 12/29 (41%; 95% CI: 24, 61) contacts from 18 cases;
5 by Omicron variant, 2/5 (40%; 95% CI: 5.3, 84) contacts from 3 cases; by Epsilon, 1/8 (13%;
6 95% CI 0, 53) contacts from 3 cases; and by non-VOI/VOC, 12/22 (55%; 95% CI: 32, 76)
7 contacts from 12 cases (**Table 4**).

8

9 *Host and viral determinants of SARS-CoV-2 infection*

10 In unadjusted analyses, household contacts had increased risk of infection when
11 exposed to primary cases who were female, or with at least one comorbidity, and 10 or more
12 days of RNA viral shedding. After adjustment, increased risk of infection among contacts
13 remained associated with primary cases who had at least one comorbidity and RNA viral
14 shedding for ≥ 10 days. Among these determinants, the greatest risk of infection was seen from
15 primary cases with at least one co-morbidity (adjusted risk ratio [aRR]: 2.1; 95% CI: 1.2, 3.8).
16 Although duration of infectious viral shedding was not statistically significant, household
17 contacts of primary cases with longer duration of infectious viral shedding had 1.05 times the
18 adjusted risk of infection than household contacts of primary cases with shorter duration of
19 shedding (95% CI: 0.96, 1.2) (**Table 5**).

20 Host susceptibility factors associated with infection were assessed among household
21 contacts, and we found that after adjustment, household contacts of White race had higher risk
22 of infection than other races (**Table 6**). We did not find any statistically significant associations
23 between risk of infection and the following characteristics of household contacts: age, sex, BMI,
24 vaccination status, or comorbidity status.

25

Discussion

1
2 In this cohort longitudinally sampled for evidence of SARS-CoV-2, we identified a
3 significant amount of onward transmission from both vaccinated-to-vaccinated and
4 unvaccinated-to-unvaccinated individuals within households. When comparing vaccination
5 status of primary cases, we did not observe a difference in cumulative incidence among
6 household contacts. We used phylogenetic analyses to strengthen evidence of transmission
7 events from and between vaccinated individuals in a similar way as other studies, which have
8 described high-confidence events.[5, 6] Although vaccination prevents severe illness[16],
9 SARS-CoV-2 transmission commonly occurs in vaccinated households, serving as a public
10 health reminder of the ongoing value in masking and other mitigating measures, particularly
11 when community transmission increases.

12 Although we did not detect associations between infection of household contacts and
13 most household contact characteristics, we did detect associations with host and viral
14 determinants of the primary case, despite small numbers. Increased risk of infection was
15 notably high among household contacts of primary cases with underlying conditions; this finding
16 may inform public health strategies, including targeted case and contact investigations. We also
17 identified an association between household contact infection and duration of viral RNA
18 shedding (10 or more days) in the primary case; we did not detect an association with maximum
19 viral RNA load, controlling for vaccination status, though previous studies have found maximum
20 viral RNA load was associated with the risk of onward transmission[6, 17]. Our study extends
21 the literature with its inclusion of infectious viral data. We did not find that risk of infection was
22 associated with maximum infectious viral titer or maximum viral RNA load, though may have
23 been underpowered to detect such associations. These two virological parameters (maximum
24 loads) have been correlated in previous work.[18] It is possible that duration of RNA and
25 infectious viral shedding are also correlated and may be important virological parameters of
26 transmissibility.

1 Our study has limitations. Although we attempted to reach infected participants as early as
2 possible, some of our primary cases were negative for infectious virus, meaning that we may
3 have missed the presence of viral shedding, which could have possibly left-censored our data.
4 Furthermore, we assessed maximum viral load available for each individual, but this may not
5 have reflected the true peak viral load in most primary cases. Low levels of RNA limited our
6 ability to sequence virus for some primary cases. Among the viruses sequenced, we had a
7 different distribution of variants among the vaccinated versus unvaccinated primary cases,
8 potentially biasing the difference in cumulative incidence among these groups to the null. Our
9 phylogenetic analyses depicted whether participants were from similar clades but were unable
10 to decipher the transmission chain with individual-level resolution. The magnitude of exposure
11 and mitigating factors during the isolation and quarantine periods likely varied and were not
12 considered in our analyses. We also lacked detailed symptom data for the characterization of
13 infected household contacts. This sample may have been enriched for characteristics specific to
14 non-hospitalized index cases who were symptomatic and diagnosed with rapid access to the
15 health system and thus limit the external validity or generalizability of the study. Our sample size
16 was small, however, so we may have been underpowered to detect some associations, such as
17 differences in cumulative incidence by variant or duration of infectious viral shedding. Because
18 of the small sample size, we also were not able to reliably assess the effects of time since
19 vaccination or booster vaccinations.

20 Although vaccination may reduce severity, it did not significantly reduce transmission from
21 June 2021 to January 2022, which was a period when household transmission was common
22 among vaccinated-to-vaccinated individuals. As new variants emerge and vaccines are
23 updated, we expect that the impact of vaccination on transmission may continue to change and
24 that there will be potential for unrecognized transmission despite widespread COVID-19
25 vaccination. It will be critical to characterize viral shedding and transmission dynamics through
26 ongoing active surveillance and natural history studies.

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12 The findings and conclusions in this report are those of the authors and do not
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20 **Conflicts of Interest**

21 MBH reports funding support from the Centers for Disease Control and Prevention. All authors
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23

24

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1 **Table 1:** Description of sociodemographic, epidemiological, clinical, and household
 2 characteristics of total cohort (N=180) and analysis cohort (N=116). We stratified the analysis
 3 cohort by primary cases (N=42) and their household contacts (N=74).
 4

| | Total cohort (N=180) | Household cohort with primary cases who were included in this analysis (N=116) | Primary cases (N=42) | Household contacts of primary cases (N=74) |
|------------------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------|-------------------------|-----------------------------------------------------|
| Age, median (IQR) | 33.5 (21.5 to 44) ¹ | 34 (24.5 to 44.5) | 34 (27 to 42) | 34 (23 to 46) |
| Age categories, n (%) | | | | |
| <18 | 13 (7.2%) | 7 (6.0%) | 4 (9.5%) | 3 (4.1%) |
| 18-44 | 113 (62.8%) | 79 (68.1%) | 33 (78.6%) | 46 (62.2%) |
| ≥45 | 19 (10.6%) | 11 (9.5%) | 1 (2.4%) | 10 (13.5%) |
| Female sex, n (%) | 94 (52.2%) | 58 (50.0%) | 20 (47.6%) | 38 (51.4%) |
| Race/ethnicity ² | | | | |
| Hispanic/Latino | 41 (22.8%) | 17 (14.7%) | 6 (14.3%) | 11 (14.9%) |
| White | 97 (53.9%) | 68 (58.6%) | 24 (57.1%) | 44 (59.5%) |
| Black/African American | 6 (3.3%) | 6 (5.2%) | 2 (4.8%) | 4 (5.4%) |
| Asian | 24 (13.3%) | 18 (15.5%) | 8 (19.0%) | 10 (13.5%) |
| Pacific Islander/Native Hawaiian | 3 (1.7%) | 2 (1.7%) | 0 (0.0%) | 2 (2.7%) |
| American Indian or Alaska Native | 2 (1.1%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| BMI - 3 Categories ^{2,3} | | | | |
| <25 | 90 (50.0%) | 61 (52.6%) | 22 (52.4%) | 39 (52.7%) |
| 25 to 30 | 44 (24.4%) | 29 (25.0%) | 10 (23.8%) | 19 (35.7%) |
| > 30 | 34 (18.9%) | 20 (17.2%) | 9 (21.4%) | 11 (14.9%) |
| Education ^{2,3} | | | | |
| At least some HS | 32 (17.8%) | 18 (15.5%) | 7 (16.7%) | 11 (14.9%) |
| At least some college | 71 (39.4%) | 49 (42.2%) | 17 (40.5%) | 32 (43.2%) |
| At least some graduate school | 40 (22.2%) | 28 (24.1%) | 13 (31.0%) | 15 (20.3%) |
| Annual household income ^{2,3,4} | | | | |
| \$50,000 or less | 7 (12.1%) | 4 (11%) | | |
| \$50,000 to \$100,000 | 10 (17.2%) | 9 (24%) | | |
| \$100,000 to \$300,000 | 21 (36.2%) | 11 (30%) | | |
| More than \$300,000 | 5 (8.6%) | 4 (11%) | | |
| Any comorbidity | 36 (20.0%) | 24 (20.7%) | 11 (26.2%) | 13 (17.6%) |
| Autoimmune disease | 4 (2.2%) | 3 (2.6%) | 0 (0%) | 3 (4.1%) |
| Cancer treated within past 2 years | 5 (2.8%) | 3 (2.6%) | 2 (4.8%) | 1 (1.4%) |
| Diabetes | 5 (2.8%) | 4 (3.4%) | 4 (9.5%) | 0 (0.0%) |
| Heart attack or heart failure | 1 (0.6%) | 1 (0.9%) | 1 (2.4%) | 0 (0.0%) |
| Hypertension or high blood pressure | 11 (6.1%) | 5 (4.3%) | 3 (7.1%) | 2 (2.7%) |

| | | | | |
|-----------------------------------------------------------------|------------|------------|-----------|------------|
| Lung disease | 22 (12.2%) | 14 (12.1%) | 5 (11.9%) | 9 (12.2%) |
| Vaccination status | | | | |
| No vaccination | 107 (59.4) | 60 (51.7%) | 21 (50%) | 39 (52.7%) |
| Partially vaccinated | 5 (2.8%) | 4 (3.4%) | 0 (0%) | 4 (5.4%) |
| Fully vaccinated | 56 (31.1%) | 44 (37.9%) | 20 (48%) | 24 (32.4) |
| Booster | 12 (6.7%) | 8 (6.9%) | 1 (2.4%) | 7 (9.5%) |
| Household size | | | | |
| Participating members per household ⁵ | 3 (2 to 4) | 3 (2 to 4) | | |
| 2 | 33 (52.4%) | 23 (54.8%) | | |
| 3 | 15 (23.8%) | 9 (21.4%) | | |
| 4 | 11 (17.5%) | 7 (16.7%) | | |
| 5 | 4 (6.35%) | 3 (7.14%) | | |
| Total members per household (including unenrolled) ⁵ | 3 (2 to 4) | 3 (2 to 4) | | |
| 2 | 25 (39.7%) | 17 (40.5%) | | |
| 3 | 16 (25.4%) | 11 (26.2%) | | |
| 4 | 14 (22.2%) | 8 (19.1%) | | |
| 5 | 7 (11.1%) | 5 (11.9%) | | |
| 10 | 1 (1.6%) | 1 (2.38%) | | |

- 1 ¹Median (Interquartile range) unless otherwise specified.
2 ²Missing and nonresponse. Race/ethnicity: 7 missing; BMI: 8 missing; Education: 35 missing, 2 prefer not
3 to answer; Annual household income: 7 missing, 24 prefer not to answer.
4 ³Categories limited to adult respondents,
5 ⁴Annual household income reported from N=65 total index cases and N=42 primary cases.
6 ⁵Among the 42 households with primary cases, 34 (81%) had full enrollment. Household size was
7 inclusive of cases.
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Table 2: Description of virologic characteristics of total infected cohort (N=126) and analysis cohort (N=74). We stratified the analysis cohort by primary cases (N=42) and their household contacts (N=32).

| | Total cohort (N=126) | Household cohort with primary cases who were included in this analysis (N=74) | Primary cases (N=42) | Household contacts of primary cases (N=32) |
|---------------------------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------|
| Maximum RNA viral load (log copies/mL) ¹ | 6.03 (3.60 to 8.22) | 5.44 (3.26 to 8.14) | 6.73 (5.07 to 8.21) | 3.81 (3.02 to 8.13) |
| Duration of RNA detection (days post-symptom onset) ¹ | 8 (5 to 11) Range: 0 to 28 | 8 (5 to 11) Range: 0 to 28 | 9.5 (7 to 11) Range: 0 to 19 | 7.5 (4 to 9.5) Range: 0 to 28 |
| Maximum infectious viral load (log plaque forming units/mL * 10 ³) ¹ | 12.00 (7.537 to 14.00) | 11.29 (6.824 to 13.85) | 8.33 (6.633 to 12.28) | 13.77 (9.378 to 14.44) |
| Duration of infectious viral shedding (days post-symptom onset) ¹ | 5 (0 to 7) Range: 0 to 13 | 5 (0 to 7) Range: 0 to 13 | 5 (0 to 7) Range: 0 to 13 | 2.5 (0 to 7) Range: 0 to 10 |
| Variant | | | | |
| Alpha | 1 (0.8%) | 1 (1.4.0%) | 1 (24%) | 0 (0.0%) |
| Delta | 43 (34.1%) | 30 (40.5%) | 18 (42.9%) | 12 (37.5%) |
| Epsilon | 4 (3.2%) | 4 (5.4%) | 3 (7.1%) | 1 (3.1%) |
| Omicron | 18 (14.3%) | 5 (6.8%) | 3 (7.1%) | 2 (66.%) |
| Non-VOI/VOC | 42 (33.3%) | 24 (32.4%) | 12 (28.6%) | 12 (37.5%) |
| Unknown | 18 (14.3%) | 10 (13.5%) | 5 (11.9%) | 5 (15.6.0%) |

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¹Laboratory values: maximum RNA load, 147 participants (40 primary cases and their 51 household contacts); duration of RNA and infectious shedding, 180 participants (all cases and contacts); infectious viral titers, 56 participants (32 primary cases and their 24 household contacts).

1 **Table 3:** SARS-CoV-2 infection among household contacts, stratified by vaccination status
 2 (Primary cases: N=42; household contacts: N=74). Note: p-values were estimated from
 3 unadjusted models using generalized estimating equations, which accounted for clustering by
 4 household.
 5

| | Vaccinated Primary Cases (n = 21) | Unvaccinated Primary Cases (n = 21) | P-values |
|------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------|-----------------|
| Proportion of household contacts who were SARS-CoV-2 positive | 14/34 (41%, 25 to 59%)* | 18/40 (45%, 29 to 62%) | 0.60 |
| Proportion of vaccinated household contacts who were SARS-CoV-2 positive | 12/29 (41%, 24 to 61%) | 0/2 (0%, 0 to 84%) | NA |
| Proportion of partially vaccinated household contacts who were SARS-CoV-2 positive | NA | 2/4 (50%, 7 to 93%) | NA |
| Proportion of unvaccinated household contacts who were SARS-CoV-2 positive | 2/5 (40%, 5.3 to 85%) | 16/34(47%, 30 to 65%) | 0.88 |

6 *proportion (95% CI)

7 NA: not applicable due to the inability of a statistical model to converge with a zero-value cell of
 8 a strata.
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1 **Table 4:** SARS-CoV-2 infection among all household contacts and vaccinated household
 2 contacts, stratified by viral variant of the primary case (Primary cases: N=42; household
 3 contacts: N=74). Unvaccinated and partially vaccinated primary cases and household contacts
 4 are not presented. Missing were unknown or Alpha variant (not shown because only one
 5 primary case).

| | Number of primary cases | Proportion of household contacts who were SARS-CoV-2 positive | Number of vaccinated primary index cases | Proportion of vaccinated household contacts who were SARS-CoV-2 positive |
|--------------------|-------------------------|---------------------------------------------------------------|------------------------------------------|--------------------------------------------------------------------------|
| Non-VOI/VOC | 12 | 12/22 (55%, 32 to 76%)* | 0 | NA |
| Delta | 18 | 12/29 (41%, 15 to 51%) | 18 | 10/24 (42%, 22 to 63%) |
| Epsilon | 3 | 1/8 (13%, 0.0 to 53%) | 0 | NA |
| Omicron | 3 | 2/5 (40%, 5.3 to 85%) | 3 | 2/5 (40%, 5.3 to 85%) |
| Alpha | 1 | 1/2 (50%, 1.3 to 99%) | 0 | NA |
| Unknown | 5 | 5/15 (33%, 12 to 62%) | 0 | NA |

6 *proportion (95% CI)
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1 **Table 5:** Host and viral determinants of cases associated with infection among household
 2 contacts* (Primary cases: N=42; household contacts: N=74). Note: risk ratios indicate
 3 cumulative incidence ratios. Confidence interval = CI.

| Characteristics of the primary case | Household cumulative incidence risk | Unadjusted | | Adjusted#* | |
|---------------------------------------------------------------|-------------------------------------|------------|------------|------------|------------|
| | n/N (%) | Risk Ratio | 95% CI | Risk Ratio | 95% CI |
| Age | | | | | |
| <18 | 2/12 (17) | Ref | Ref | Ref | Ref |
| 18-44 | 19/43 (44) | 2.15 | 0.58, 8.04 | 1.67 | 0.41, 6.72 |
| ≥45 | 11/19 (58) | 3.05 | 0.80, 11.6 | 1.91 | 0.46, 7.97 |
| Female | 24/41 (59) | 2.21 | 1.07, 4.55 | 1.57 | 0.71, 3.46 |
| Race/ethnicity | | | | | |
| Hispanic/Latino | 6/11 (55) | Ref | Ref | Ref | Ref |
| White | 20/46 (44) | 0.81 | 0.38, 1.75 | 0.47 | 0.19, 1.16 |
| Black/African American | 1/2 (50) | 0.92 | 0.19, 4.36 | 0.33 | 0.13, 0.89 |
| Asian | 2/12 (17) | 0.36 | 0.08, 1.59 | 0.34 | 0.09, 1.35 |
| BMI | | | | | |
| <25 | 11/35 (31) | Ref | Ref | Ref | Ref |
| 25-30 | 11/18 (61) | 1.75 | 0.90, 3.42 | 1.60 | 0.67, 3.86 |
| >30 | 7/17 (41) | 1.19 | 0.51, 2.81 | 0.93 | 0.37, 2.35 |
| Vaccinated cases at baseline | 14/34 (41) | 0.85 | 0.47, 1.55 | 1.29 | 0.52, 3.21 |
| At least one comorbidity | 15/18 (83) | 2.71 | 1.66, 4.43 | 2.11 | 1.16, 3.84 |
| Greater maximum RNA viral load (log copies/mL)** | 39/60 (65) | 1.10 | 0.97, 1.25 | 1.08 | 0.96, 1.23 |
| Longer duration of RNA detection (days) ** | 18/41 (44) | 1.02 | 0.94, 1.10 | 1.01 | 0.96, 1.07 |
| 10 or more days of RNA detection | 18/41 (44) | 1.05 | 1.03, 1.06 | 1.05 | 1.04, 1.08 |
| Greater maximum infectious viral load (log pfu/mL)** | 10/20 (50) | 0.96 | 0.87, 1.06 | 0.99 | 0.87, 1.11 |
| Longer duration of infectious virus detection (days)** | 25/46 (54) | 1.09 | 0.99, 1.20 | 1.05 | 0.96, 1.16 |
| Variant | | | | | |

| | | | | | |
|--------------------|------------|------|------------|------|------------|
| Delta | 11/22 (50) | Ref | Ref | Ref | Ref |
| Omicron | 2/5 (40) | 0.84 | 0.32, 2.21 | 0.98 | 0.33, 2.92 |
| Epsilon | 1/8 (13) | 0.36 | 0.05, 2.81 | 0.56 | 0.08, 4.13 |
| Non-VOI/VOC | 12/22 (55) | 1.08 | 0.56, 2.10 | 0.93 | 0.45, 1.93 |
| Alpha | 1/2 (50) | 1.01 | 0.64, 1.60 | 1.28 | 0.75, 2.18 |
| Unknown | 5/15 (33) | 0.69 | 0.27, 1.77 | 0.87 | 0.34, 2.22 |

1 *Each cell in this table represents the output of a generalized estimating equation with modified Poisson
2 regression, accounting for clustering by household.

3 #Each adjusted model includes factors of case and contact and was developed with a Directed Acyclic
4 Graph (DAG) of potential confounders, mediators, and colliders (age, sex, race/ethnicity, etc.). Please
5 see the **Supplemental Material** for a listing of the variables included in each model.

6 **Relative values for greater viral load and longer duration of shedding determined as upper 50th
7 percentile of observed values from primary cases

8

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1 **Table 6:** Host susceptibility factors associated with infection among household contacts*
 2 (Primary cases: N=42; household contacts: N=74). Note: risk ratios indicate cumulative
 3 incidence ratios. Confidence interval = CI.
 4

| Characteristics of the household contact | Household cumulative incidence risk | Unadjusted | | Adjusted#* | |
|------------------------------------------|-------------------------------------|------------|------------|------------|------------|
| | n/N (%) | Risk Ratio | 95% CI | Risk Ratio | 95% CI |
| Age | | | | | |
| <18 | 7/15 (47) | Ref | Ref | Ref | Ref |
| 18-44 | 17/38 (45) | 0.92 | 0.57, 1.50 | 1.02 | 0.59, 1.78 |
| ≥45 | 8/21 (38) | 0.79 | 0.43, 1.46 | 0.86 | 0.45, 1.63 |
| Female | 17/38 (45) | 0.91 | 0.56, 1.49 | 1.05 | 0.65, 1.71 |
| Race/ethnicity | | | | | |
| Hispanic/Latino | 5/11 (45) | Ref | Ref | Ref | Ref |
| White | 21/44 (48) | 1.18 | 0.59, 2.37 | 1.15 | 0.59, 2.23 |
| Black/African American | 2/4 (50) | 0.84 | 0.26, 2.69 | 0.83 | 0.28, 2.43 |
| Asian | 2/10 (20) | 0.47 | 0.13, 1.76 | 0.46 | 0.13, 1.60 |
| BMI | | | | | |
| <25 | 15/39 (39) | Ref | Ref | Ref | Ref |
| 25-30 | 9/19 (47) | 0.96 | 0.53, 1.75 | 0.88 | 0.46, 1.69 |
| >30 | 5/11 (45) | 0.95 | 0.42, 2.18 | 0.98 | 0.40, 2.36 |
| Vaccinated contacts at baseline | 12/31 (39) | 0.77 | 0.44, 1.36 | 0.90 | 0.37, 2.19 |
| At least one comorbidity | 5/13 (38) | 0.92 | 0.48, 1.79 | 0.72 | 0.36, 1.48 |

5 *Each cell in this table represents the output of a generalized estimating equation with modified Poisson
 6 regression, accounting for clustering by household.

7 #Each adjusted model includes factors of case and contact and was developed with a Directed Acyclic
 8 Graph (DAG) of potential confounders, mediators, and colliders (age, sex, race/ethnicity, etc.). Please
 9 see the **Supplemental Material** for a listing of the variables included in each model.
 10

1 **Figure 1:** Flow diagram of household cohort. Households from the initially enrolled cohort were
2 excluded if index cases were determined to have co-primary cases criteria or if single primary
3 cases were asymptomatic. Note: We identified 42 households with single primary cases, also
4 referred to as primary cases. For analysis, we excluded 21 households with co-primary cases
5 and 2 households with asymptomatic primary cases.

6

7 **Figure 2:** Phylogenetic tree situating SARS-CoV-2 associated genomes (colored dots) identified
8 over time from household clusters in the local pandemic of San Francisco and Alameda
9 Counties, California (N=72 participants). Inset, colors represent Pango lineages reflected in the
10 tree.

11

12 **Figure 3:** Phylogenetic sub-tree of a household cluster determined to be co-primary cases. The
13 index case and household contact reported symptoms two days apart (serial interval = 2) as
14 well as a shared exposure, but genomic epidemiology showed the SARS-CoV-2 sequences
15 belonged to distinct monophyletic clades. These participants were classified as having had
16 unrelated sequences.

17

18 **Figure 4:** Flow diagram of determination of single primary cases from the decision algorithm.
19 Determination of single primary or co-primary cases from 65 households (65 index cases). Note:
20 We identified 42 households with single primary cases, also referred to as primary cases.

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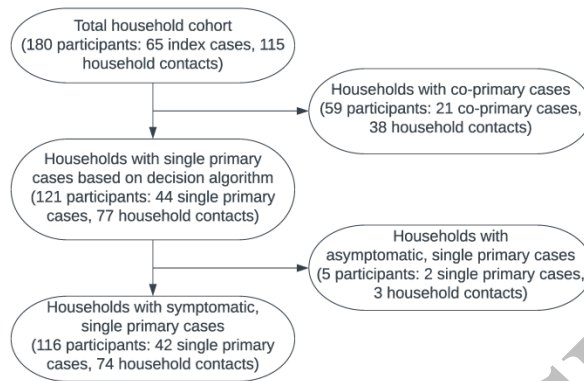


Figure 1
279x216 mm (x DPI)

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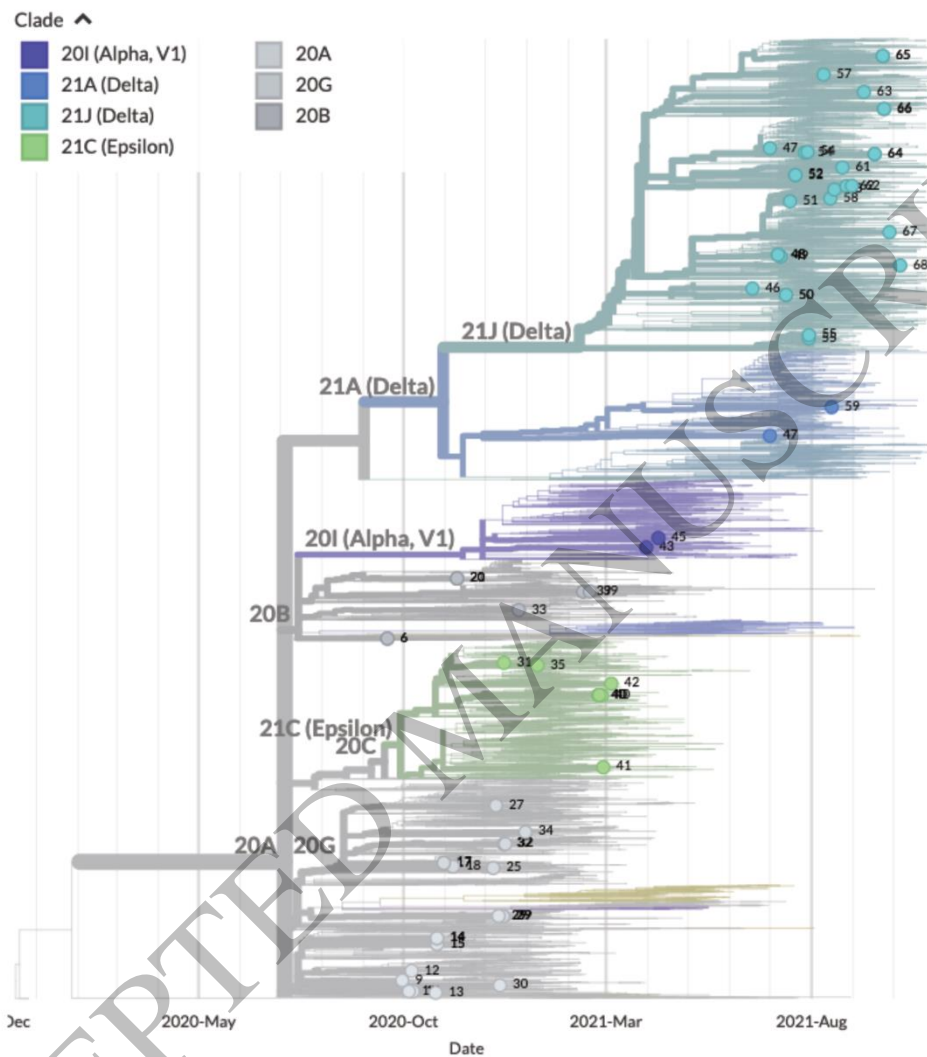
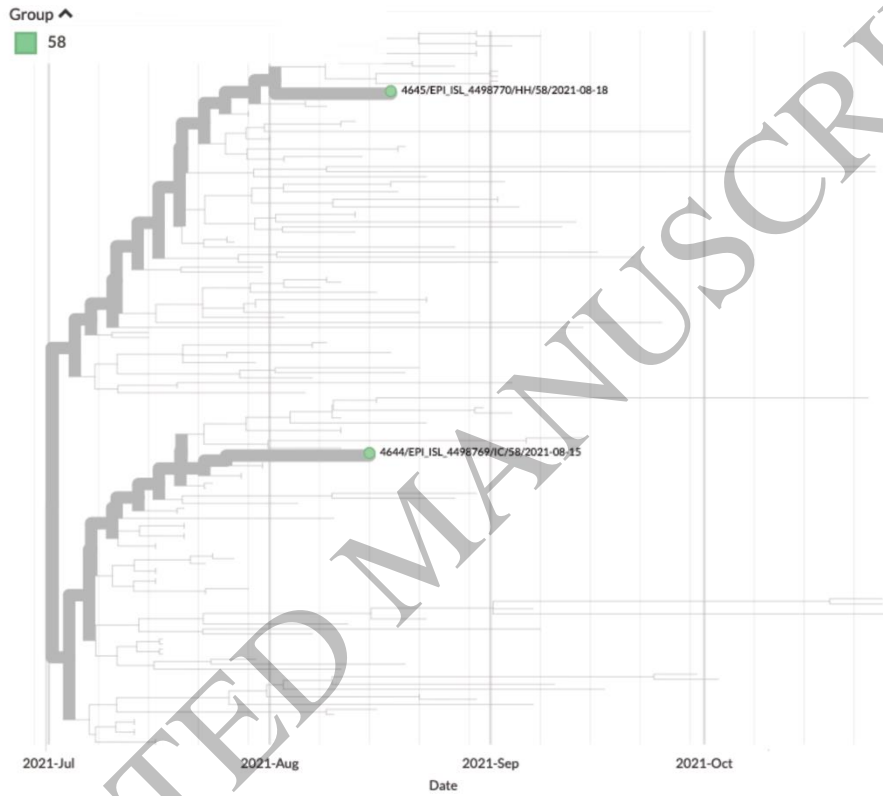


Figure 2
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Figure 3
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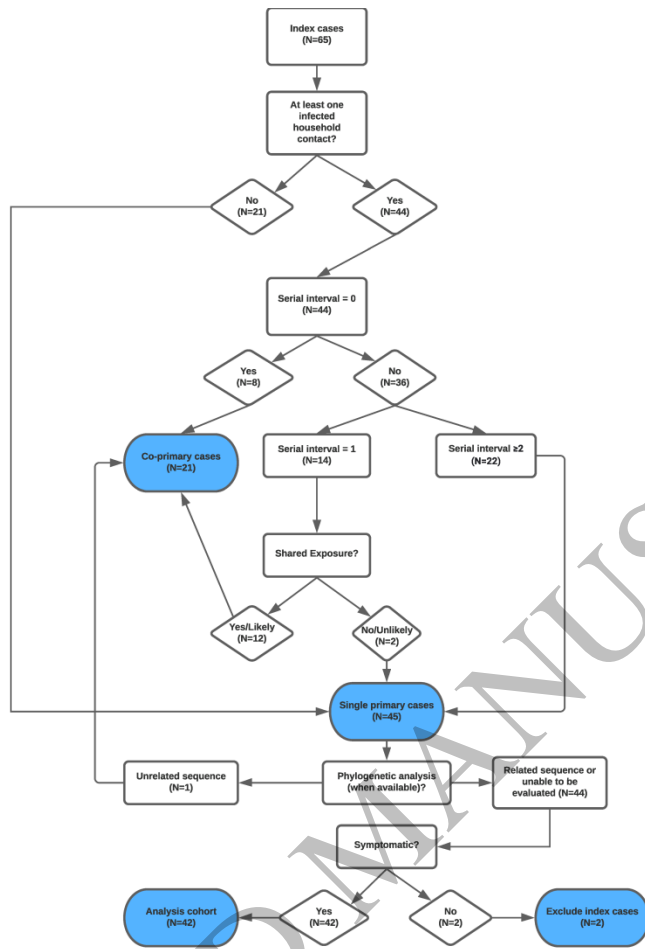


Figure 4
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