Household transmission of SARS-CoV-2 in the United States: living density, viral load, and disproportionate impact on communities of color

Carla Cerami[1,2], Zachary R. Popkin-Hall[1], Tyler Rapp[1], Kathleen Tompkins[1], Haoming Zhang[3], Meredith S. Muller[1], Christopher Basham[1], Maureen Whittelsey[1], Srijana B. Chhetri[1], Judy Smith[1], Christy Litel[1], Kelly D. Lin[1], Mehal Churiwal[1], Salman Khan[4], Rebecca Rubinstein[3], Faith Claman[1], Katie Mollan[3], David Wohl[1], Lakshmanane Premkumar[4], Kimberly A. Powers[3], Jonathan J. Juliano[1], Feng-Chang Lin[3], Jessica T. Lin[1]

1 Institute of Global Health and Infectious Diseases, University of North Carolina School of Medicine, Chapel Hill, NC USA

2 Medical Research Council Unit The Gambia at the London School of Hygiene & Tropical Medicine, Fajara, The Gambia

3 Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC USA

4 Department of Microbiology and Immunology, University of North Carolina School of Medicine, Chapel Hill, NC USA

Corresponding author:
Jessica T. Lin, MD MSCR
111 Mason Farm Rd
2336 MBRB, CB#7036
Chapel Hill, NC 27599, USA
jessica_lin@med.unc.edu

Summary: Households are hotspots for SARS-CoV-2 transmission. In the US, the COVID-19 pandemic has had a disproportionate impact on communities of color. Household crowding in the context of high-inoculum infections may amplify the spread of COVID-19, potentially contributing to disproportionate impact on communities of color.

ABSTRACT

Background Households are hotspots for SARS-CoV-2 transmission. In the US, the COVID-19 pandemic has had a disproportionate impact on communities of color.

Methods Between April-October 2020, the CO-HOST prospective cohort study enrolled 100 COVID-19 cases and 208 of their household members in North Carolina, including 44% who identified as Hispanic or non-white. Households were enrolled a median of 6 days from symptom onset in the index case. Incident secondary cases within the household were detected by quantitative PCR of weekly nasal swabs (days 7, 14, 21) or by seroconversion at day 28.

Results Excluding 73 household contacts who were PCR-positive at baseline, the secondary attack rate among household contacts was 32% (33/103, 95% CI 22%-44%). The majority of cases occurred by day 7, with later cases confirmed as household-acquired by viral sequencing. Infected persons in the same household had similar nasopharyngeal viral loads (ICC=0.45, 95% CI 0.23-0.62). Households with secondary transmission had index cases with a median viral load that was 1.4 $\log_{10}$ higher than households without transmission (p=0.03) as well as higher living density (>3 persons occupying <6 rooms) (OR 3.3, 95% CI 1.02-10.9). Minority households were more likely to experience high living density and had a higher risk of incident infection than did white households (SAR 51% vs. 19%, p=0.01).

Conclusions Household crowding in the context of high-inoculum infections may amplify the spread of COVID-19, potentially contributing to disproportionate impact on communities of color.

INTRODUCTION

Households are hotspots for SARS-CoV2 transmission [1]. Person-to-person transmission is difficult to control in shared living spaces. For those isolating at home with young children in small living spaces, following guidelines to physically distance and use separate sleeping, eating, and lavatory facilities is difficult [2]. Because the period of peak infectiousness starts prior to the onset of symptoms, spread can occur before these measures are taken [3–5].

Meta-analyses of secondary household attack rates (SAR) in the first six months of the pandemic range from 15-20% [6,7], but these analyses incorporated both retrospective and prospective analyses [6,7]. Prospective testing of household contacts regardless of symptom status is required to capture all secondary cases. Previously identified risk factors associated with increased transmission include the presence of symptoms [6–8] and high viral load in the index case [9]. Among household contacts, spouses and those over age 18 (i.e. adults compared to children) are more likely to acquire infection [6,7,10]. Measuring secondary household attack rates in vulnerable communities and identifying risk factors for transmission in these communities is critical.

The UNC CO-HOST (COVID-19 Household Transmission Study) is the largest, single-site observational household cohort in the US to date and the most ethnically and racially diverse. Weekly sampling for quantitative viral loads combined with SARS-CoV-2 antibody testing at baseline and at one month provided an extended period to evaluate transmission. The objective of this study was to measure the incident SAR in a setting where infected individuals were asked to quarantine at home and given standard guidance. Household and individual demographics as well as daily symptoms and weekly viral loads were collected to identify risk factors and timing of household transmission.

METHODS

Study design and enrollment

The CO-HOST Study evaluated SARS-CoV-2 acquisition among persons undergoing quarantine in their home after a care-seeking household member (the index case) tested positive for SARS-CoV-2. The study was approved by the Institutional Review Board at the University of North Carolina. Recruitment occurred between April-October 2020, prior to the introduction of SARS-CoV-2 vaccines in the US. Inclusion criteria for the index cases were >18 years with a positive qualitative nasopharyngeal (NP) swab for SARS-CoV-2 RNA using PCR performed at the UNC Hospitals clinical laboratory, willingness to self-isolate at home for a 14-day period, living with at least one household contact who was also willing to participate, and living within driving distance (<1 hour) from study site. Inclusion criteria for household contacts of index patients included age > 1 year, and currently living in the same home as the index case without plans to live elsewhere during the 28-day study. All participants (or their parents/guardians) gave written, informed consent. Minors over the age of 7 provided assent.

As shown in Figure S1, all households were visited on Day 1 by a study team. NP and nasal mid-turbinate (NMT) swabs were collected for SARS-CoV-2 PCR and blood samples were collected for serology. All study participants received instruction on self-collection of NMT swabs and completed baseline questionnaires that included basic demographic and household information, abbreviated medical history, symptoms, recent travel history, and exposure to confirmed cases of COVID-19.

All participants received a daily symptom questionnaire via email until no symptoms were reported for two consecutive days. Household contacts who remained asymptomatic received the questionnaire for 21 days to monitor for new symptoms. On Days 7, 14 and 21, a study staff member conducted home visits to collect self-collected NMT swabs. At the final study visit (Day 28), participants were asked about COVID-related care-seeking and underwent serologic testing.

Laboratory analyses

Details for all laboratory methods are found in the Supplementary Material. Quantitative PCR testing for SARS-CoV-2 was performed using a Centers for Disease Control (CDC) RT-qPCR protocol authorized by the Food and Drug Administration (FDA) for emergency use, as previously described [11]. Serology was performed using an enzyme linked immunoassay assay (ELISA) that detects antibodies to the receptor binding domain (RBD) of the spike protein with high sensitivity and specificity [17, 18]. When ELISA results were not available (i.e. in kids who did not undergo venipuncture), results from a BioMedomics COVID-19 IgM/IgG Rapid Test [12–14] were used.

To evaluate the prevalence of the 614G variant, which predominated in North Carolina at the time of the study, in our study samples, we developed a real-time PCR assay targeting a 107 bp region encompassing the D614G mutation in the S1 segment of the SARS-CoV-2 spike protein.

Finally, to help determine whether secondary cases were acquired outside the household rather than due to household transmission, we performed high density amplicon sequencing on NP/NMT swab samples from households with late secondary cases to assign SARS-CoV-2 clades and determine the genetic relatedness of viral isolates within and between households.

Statistical analysis

We summarized baseline demographic characteristics and underlying conditions of index cases and household contacts, as well as their household demographics. We evaluated if baseline NP SARS-CoV-2 viral loads were correlated within households by the intraclass correlation coefficient (ICC), which compares within versus between household variation.

We evaluated the secondary household attack rate among household members of persons who tested positive for SARS-CoV-2. For each household, if multiple participants were positive at enrollment, the index case was defined as the person with the earliest onset of infection based on reported onset of symptoms and known date(s) of PCR test positivity. If this was ambiguous, then baseline antibody positivity was used as evidence of less recent infection. We calculated the SAR as the risk of incident infection among household contacts, defined as the proportion of contacts who were PCR-negative at baseline, but then developed SARS-CoV-2 infection during the 28-day study follow-up, confirmed by either PCR or antibody seroconversion. Those with evidence of prior infection (antibody-positive and PCR-negative) or household contacts who reported the same COVID exposure outside the household as the index case were excluded from the analysis. To avoid misclassification of asymptomatic infection, household contacts who tested PCR-negative at weekly nasal swabs (D7, D14, D21) but without D28 antibody results were also excluded. A 95% CI for the SAR was calculated using a robust variance estimation for the intercept term in a logistic regression model to account for outcome dependence within a household.

Potential risk factors for secondary transmission within the household, including characteristics of index cases, households, and household contacts were examined. These risk factors and details of symptom severity evaluation are described in the Supplementary Material. Statistical significance was tested by either Fisher's exact or chi-square test for categorical variables and Mann-Whitney test for continuous variables. To explore if the association between index race-ethnicity and SAR was related to housing density or viral load (which were correlated with race/ethnicity and/or transmission in unadjusted analyses), we calculated the odds ratio of the race-ethnicity specific SAR, with 95% CI estimated using the same robust variance estimation described above, then added the other risk factors as covariates in the logistic regression model to calculate adjusted odds ratios.

Analyses were performed using R 4.0.2 (R Core Team, Vienna, Austria). All hypothesis tests were two-sided at a significance level of 0.05 with no adjustments for multiple comparisons.

RESULTS

Study enrollment

Between April-October 2020, the UNC CO-HOST study enrolled 102 households across the central Piedmont Region of North Carolina, US (Figure S2). After excluding participants who did not complete follow-up, had evidence of prior infection, or those who were possibly infected at the same time as the index case based on a common exposure, 91 households were included in the baseline analysis (Figure 1). Households were enrolled a median of 6 (IQR 4-7) days after symptom onset of the designated index case, which was reassigned in 11 households. Baseline characteristics of the 91 index cases and 176 household contacts (HCs) are shown in Table 1. The median index case age was 37 years (IQR 23-49 years), while HCs ranged from 2 to 77 years of age with 34% under 18

years. Overall, 44% of participants identified as other than White, non-Hispanic race-ethnicity and 33% of adults were obese (BMI >30 kg/m^2) (Table 1, other comorbidities in Table S1).

Household characteristics

The median size of households was 4 persons (Table S2), though in 38% of households, at least one household member chose not to participate. Households with a non-white index case were more likely to live in a home <2,000 square feet (71% versus 43%, p=0.01). This led to a higher "living density" for non-white households: 43% had >3 household members living in a home with fewer than 6 rooms, compared to 8% of white households (p<0.001).

SARS-CoV-2 viral burden was correlated within households (Figure 2). When comparing the baseline nasopharyngeal viral load within versus between households, viral burden showed significant clustering within households (ICC=0.45, 95% CI 0.23-0.62, p<0.001). Differences in viral load are not attributable to D614G mutation in the viral spike protein that has been associated with increased viral load and infectivity [15], as 90/92 (98%) of genotyped SARS-CoV-2 isolates contained the 614G mutant, while only 2/92 were wild-type at this locus.

Secondary attack rate among household contacts

The incident SAR among household contacts was 32% (33/103, 95% CI 22%-44%). Among 91 households, 73/176 (41%) household contacts tested PCR positive at baseline and were excluded from the primary SAR analysis (Figure 1, Table S3 for demographics of baseline infected cases). Among the remaining 103 household contacts of 51 index cases, 33 incident SARS-CoV-2 infections were observed during the 28-day study follow-up (SAR=32% (33/103)). Of these 33 secondary cases, 22 were identified by both PCR and seroconversion from Day 1 to Day 28, 4 were identified by PCR only, and 7 were identified on seroconversion alone. The majority of secondary cases in the household experienced symptoms (27/33), while 18% (n=6) remained asymptomatic.

Secondary household transmission occurred early, within the first week following enrollment for the majority of cases (n=21/26 for those identified by PCR) (Figure 1). Five cases were detected by PCR after the first week

of enrollment, at Day 14 or 21. Four of these late secondary cases occurred in households of 5 or more (including two from the same household), which suggests the possibility of sequential transmission within the household. High density amplicon sequencing of viral isolates from these late secondary cases and others in their household confirmed that 4/5 were indeed due to household transmission (1 isolate failed sequencing), and not community-acquired (Figure 3).

Risk factors for household transmission

At the household level, 44% of households (40/91) had at least one infected household member at enrollment besides the index case, rising to 69% (63/91) of households one month later. Sixty households contained susceptible HCs at enrollment and were thus included in the risk factor analysis.

Secondary transmission in the household was associated with a higher nasopharyngeal viral load in index cases at enrollment. The median NP viral load among index cases was 1.4 $\log_{10}$ higher in households with secondary cases detected during the study versus those with no incident cases in the household (p=0.03) (Table 2). This difference persisted when the analysis was restricted to index cases who were still antibody-negative, and thus more recently infected [14,16] (Figure 4). Symptom severity was not associated with household transmission, though secondary transmission did occur in households of the 4 index cases that were hospitalized (Table 2).

Households with non-white index cases were more likely to experience incident transmission in the household (Table 2), despite there being no difference in index case viral loads by race/ethnicity (median NP viral load for white vs. non-white: 8.3 vs. 8.3 log10 copies/mL). This corresponds to a SAR of 51% (95% CI 33%-69%) in households with a non-white or Hispanic index case compared to 19% (95% CI 10%-35%) in white, non-Hispanic households (p=0.008). Higher living density, defined as greater than 3 household members living in a home with fewer than 6 rooms, was associated with a greater odds of transmission (OR 3.3, 95% CI 1.02-10.9, p=0.047) (Table 3), and a greater proportion of non-white/Hispanic households met this definition of high living density (42%, 11/26) compared to white, non-Hispanic households (12%, 4/34) (p=0.01). However, after adjusting for viral load and living density, Hispanic/non-white race-ethnicity remained associated with secondary household transmission (Table 4).

Among susceptible household contacts, those sharing a bathroom with the index case were at higher risk of acquiring infection (Table S4). Obesity and being female were also associated with a higher risk of incident infection, though these associations were not statistically significant. Though a slightly greater percentage of participants in households without secondary transmission reported wearing a mask at home in the week prior to enrollment (22% vs 13% for index cases and 30% vs 20% in household contacts), these differences were not statistically significant.

DISCUSSION

Household transmission is one of the main drivers of the SARS-CoV-2 pandemic. By incorporating timely recruitment of index cases, prospective sampling to 21 days regardless of symptom status, and confirmatory viral sequencing in a subset of households, we show that household transmission occurs in a substantial proportion of COVID-positive households, with racial-ethnic disparities in

secondary attack rates and higher risk of infection in more crowded households. Our data also suggest that those infected with a high viral load are not only more likely to transmit virus to other household members, but that they may seed other high-viral load infections, putting the entire household at higher risk for more severe illness.

The incident SAR in this study was 32%, rising to 51% in minority households. While a meta-analysis of household transmission studies conducted in the first six months of the pandemic (prior to circulation of new variants) found a much lower overall household SAR of 17% (95% CI 14%-19%), it noted significant heterogeneity between studies (ranging 4-45%) and combined both retrospective studies based on contact tracing data and prospective analyses [6]. As expected, prospective studies with increased frequency of testing regardless of symptom status generally show higher infection rates [7]. In the US, a retrospective study in New York that included household testing offered regardless of symptom status reported a SAR of 38% [17], while two prospective studies following households in Utah and Wisconsin (58 households, SAR 29%)[18], and Tennessee and Wisconsin (101 households, SAR 53%) [10] also reported higher SARs. Altogether, these studies document high secondary household attack rates within US households.

To our knowledge, this is the first study to show increased transmission in non-white US households. Though they experience similar case fatality rates, African American/Black and Hispanic populations in the US experience disproportionately higher rates of SARS-CoV-2 infection [19–21]. These racial disparities are likely due to differences in health care access and exposure risk that are driven by systemic societal inequities rather than individual biological or behavioral characteristics [22–25]. Our limited findings are consistent with this explanation. While the sample size precluded full investigation of drivers of increased transmission in minority households, we found that high living density/household crowding was more common in non-white households, while viral load and reported masking in the home did not differ by race-ethnicity.

We also found that SARS-CoV-2 viral burden was correlated within households. Increased viral load increases infectivity *in vivo [26]*, and a study of 282 clusters in Spain showed an increased risk of transmission with shorter time to onset of symptoms among contacts as viral load of the index cases increased [9]. Since greater viral burden (high viral load or lower Ct values by PCR) is associated with disease severity [27–30], our findings imply that when a person is hospitalized, others in the same household may be at a higher risk for a similar outcome than would be predicted based on their individual risk factors alone. An inoculum effect may underlie this finding [31] and also explain why secondary cases in households appear to be overdispersed, with either most or all members infected, or none at all [6,32,33].

This study has several limitations. First, although we enrolled most households within 24-48 hours of a positive SARS-CoV-2 test result, delays in testing meant that it was common for others in the household to be PCR-positive at enrollment. While 33 household contacts met our endpoint as

incident SARS-CoV-2 cases, 73 household contacts were infected at study baseline and hence could not be categorized definitively as due to household transmission and were excluded from the analysis. Thus, we likely underestimated the true SAR, and the resultant small sample size was not sufficient to investigate all drivers of household transmission. We were similarly limited in our ability to do adjusted analyses beyond a simplistic exploration of whether living density might account for the observed racial disparity in SAR. In the households with multiple infected household members at baseline, we cannot be certain that the designated index case was the source of infection for all infected household members. This may have affected our evaluation of index case risk factors associated with transmission.

Additionally, we were unable to adequately assess the effects of age, mask-wearing, and the presence of symptoms on transmission. We recruited adult index cases, and in 38% of households, at least one household member (most often young children) declined to participate. While mask use was queried, mask use prior to any COVID diagnosis in the household was not specifically elicited. All index cases except one were tested because they were symptomatic.

In conclusion, SARS-CoV-2 transmits early and often among household members. While masking, physical distancing, and quarantining the whole household may reduce or prevent transmission beyond the household, these strategies are less effective within the household, especially in the setting of high viral load infections and crowded living spaces. Frequent point-of-care testing and post-exposure prophylaxis in those at-risk for severe illness [34], and ultimately widespread and equitable distribution of vaccines [35], are needed to lessen the impact of COVID-19 within households and vulnerable communities.

NOTES

ACKNOWLEDGEMENTS

We thank our wonderful CO-HOST study participants, Moby and the Chapel Hill CRS, and the UNC RDC team. Thanks to Michelle Berrey, JoAnn Kuruc, and Dania Munson for help with protocol writing and submission; to Oksana Kharabora, Maureen Furlong, Amy James Loftis, Tia Belvin, and Dana Swilley for help with study preparation and implementation; and to Joe Eron, Billy Fischer, and Ada Adimora for their input and support.

FUNDING

Research was supported by funds and charitable contributions from the UNC Department of Medicine (emergency funds to PI Jessica Lin, UNC School of Medicine), UNC COVID-19 Response Fund/Health Foundation (via UNC Health Foundation to PI Jessica Lin, UNC School of Medicine), a Gillings Innovations Laboratory Award funded by the 2007 Gillings Gift to UNC-Chapel Hill's Gillings School of Global Public Health (to co-PIs Kim Powers and Jessica Lin), and the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number UL1TR002489 (NC TrACs Pilot Funding Award to PI, Jessica Lin). LP reports grants as the co-investigator for NCI-U54 CA260543 and NC Collaboratory Fund. Trainees were supported by the National Institute of Allergy and Infectious Diseases (T32A1007151, K.T.) and the Infectious Diseases Society of America (T.R.). Rapid antibody tests were provided by Biomedomics Inc, Morrisville, NC.

CONFLICT OF INTEREST

KRM received grant support from Ridgeback Biotherapeutics LP (2020-2021) and has HIV collaborations, unrelated to this study, with Gilead Sciences (ongoing). LP reports grants or contracts as co-investigator for NIAID U01AI151788. All other authors declare no conflicts of interest related to the content of this manuscript.

REFERENCES

1. who-china-joint-mission-on-covid-19-final-report.pdf. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf.

2. CDC. Public Health Guidance for Community-Related Exposure. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/php/public-health-recommendations.html. Accessed 16 February 2021.

3. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nat Med **2020**; 26:672–675.

4. Tindale LC, Stockdale JE, Coombe M, et al. Evidence for transmission of COVID-19 prior to symptom onset. Elife **2020**; 9. Available at: http://dx.doi.org/10.7554/eLife.57149.

5. Benefield AE, Skrip LA, Clement A, Althouse RA, Chang S, Althouse BM. SARS-CoV-2 viral load peaks prior to symptom onset: a systematic review and individual-pooled analysis of coronavirus viral load from 66 studies. bioRxiv. 2020; Available at: http://medrxiv.org/lookup/doi/10.1101/2020.09.28.20202028.

6. Madewell ZJ, Yang Y, Longini IM Jr, Halloran ME, Dean NE. Household Transmission of SARS-CoV-2: A Systematic Review and Meta-analysis. JAMA Netw Open **2020**; 3:e2031756.

7. Fung HF, Martinez L, Alarid-Escudero F, et al. The Household Secondary Attack Rate of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Rapid Review. Clin Infect Dis **2020**; Available at: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa1558/5921151. Accessed 21 February 2021.

8. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med **2020**; 17:e1003346.

9. Marks M, Millat-Martinez P, Ouchi D, et al. Transmission of COVID-19 in 282 clusters in Catalonia, Spain: a cohort study. Lancet Infect Dis **2021**; Available at: http://dx.doi.org/10.1016/S1473-3099(20)30985-3.

10. Grijalva CG, Rolfes MA, Zhu Y, et al. Transmission of SARS-COV-2 Infections in Households - Tennessee and Wisconsin, April-September 2020. MMWR Morb Mortal Wkly Rep **2020**; 69:1631–1634.

11. Muller MS, Chhetri SB, Basham C, et al. Practical strategies for SARS-CoV-2 RT-PCR testing in resource-constrained settings. medRxiv **2021**; Available at: http://dx.doi.org/10.1101/2021.02.18.21251999.

12. Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol **2020**; 92:1518–1524.

13. COVID-19 IgM/IgG Rapid Test – BioMedomics Inc. Available at:

https://www.biomedomics.com/products/infectious-disease/covid-19-rt/. Accessed 17 February 2021.

14. Naranbhai V, Chang CC, Beltran WFG, et al. High Seroprevalence of Anti-SARS-CoV-2 Antibodies in Chelsea, Massachusetts. J Infect Dis **2020**; 222:1955–1959.

15. Korber B, Fischer WM, Gnanakaran S, et al. Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell **2020**; 182:812–827.e19.

16. Premkumar L, Segovia-Chumbez B, Jadi R, et al. The receptor binding domain of the viral spike protein is an immunodominant and highly specific target of antibodies in SARS-CoV-2 patients. Sci Immunol **2020**; 5. Available at: http://dx.doi.org/10.1126/sciimmunol.abc8413.

17. Rosenberg ES, Dufort EM, Blog DS, et al. COVID-19 Testing, Epidemic Features, Hospital Outcomes, and Household Prevalence, New York State—March 2020. Clin Infect Dis **2020**; Available at: https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciaa549/5831986. Accessed 13 September 2020.

18. Lewis NM, Chu VT, Ye D, et al. Household Transmission of SARS-CoV-2 in the United States. Clin Infect Dis **2020**; Available at: http://dx.doi.org/10.1093/cid/ciaa1166.

19. Mackey K, Ayers CK, Kondo KK, et al. Racial and Ethnic Disparities in COVID-19-Related Infections, Hospitalizations, and Deaths : A Systematic Review. Ann Intern Med **2020**; Available at: http://dx.doi.org/10.7326/M20-6306.

20. Lopez CA, Cunningham CH, Pugh S, et al. Disparities in SARS-CoV-2 seroprevalence among individuals presenting for care in central North Carolina over a six-month period. medRxiv **2021**; Available at: http://dx.doi.org/10.1101/2021.03.25.21254320.

21. Brandt K, Goel V, Keeler C, et al. SARS-CoV-2 testing in North Carolina: Racial, ethnic, and geographic disparities. Health Place **2021**; 69:102576.

22. Karmakar M, Lantz PM, Tipirneni R. Association of Social and Demographic Factors With COVID-19 Incidence and Death Rates in the US. JAMA Netw Open **2021**; 4:e2036462.

23. Poteat T, Millett GA, Nelson LE, Beyrer C. Understanding COVID-19 risks and vulnerabilities among black communities in America: the lethal force of syndemics. Ann Epidemiol **2020**; 47:1–3.

24. Holmes L, Enwere M, Williams J, et al. Black--White risk differentials in COVID-19 (SARS-COV2) transmission, mortality and case fatality in the United States: translational epidemiologic perspective and challenges. Int J Environ Res Public Health **2020**; 17:4322.

25. Rogers TN, Rogers CR, VanSant-Webb E, Gu LY, Yan B, Qeadan F. Racial Disparities in COVID-19 Mortality Among Essential Workers in the United States. World medical & health policy **2020**; 12:311–327.

26. Hou YJ, Chiba S, Halfmann P, et al. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. Science **2020**; 370:1464–1468.

27. Maltezou HC, Raftopoulos V, Vorou R, et al. Association between upper respiratory tract viral load, comorbidities, disease severity and outcome of patients with SARS-CoV-2 infection. J Infect Dis **2021**; Available at: http://dx.doi.org/10.1093/infdis/jiaa804.

28. Magleby R, Westblade LF, Trzebucki A, et al. Impact of SARS-CoV-2 Viral Load on Risk of Intubation and Mortality Among Hospitalized Patients with Coronavirus Disease 2019. Clin Infect Dis **2020**; Available at: http://dx.doi.org/10.1093/cid/ciaa851.

29. Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis **2020**; 20:656–657.

30. Fajnzylber J, Regan J, Coxen K, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat Commun **2020**; 11:5493.

31. Silvia Munoz-Price L, Rivera F, Ledeboer N. Air contamination of households versus hospital inpatient rooms occupied by SARS-CoV-2 positive patients. Infect Control Hosp Epidemiol :1–14.

32. Ladhani SN, Andrews N, Aiano F, et al. Secondary attack rate and family clustering of SARS-CoV-2 infection in children of healthcare workers with confirmed COVID-19. Clin Infect Dis **2020**; Available at: http://dx.doi.org/10.1093/cid/ciaa1737.

33. Paul LA, Daneman N, Brown KA, et al. Characteristics associated with household transmission of SARS-CoV-2 in Ontario, Canada: A cohort study. Clin Infect Dis **2021**; Available at: http://dx.doi.org/10.1093/cid/ciab186.

34. Hurt AC, Wheatley AK. Neutralizing Antibody Therapeutics for COVID-19. Viruses **2021**; 13. Available at: http://dx.doi.org/10.3390/v13040628.

35. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of Vaccination on Household Transmission of SARS-CoV-2 in England. N Engl J Med **2021**; Available at: http://dx.doi.org/10.1056/NEJMc2107717.

Table 1. Demographics of study participants

INDIVIDUALS	Index cases (n)	Index cases (%)	Household contacts (n)	Household contacts (%)
	91	%	176	%
Male	43	47	87	49
Female	48	53	89	51
Race/Ethnicity				
White, non-Hispanic	52	57	96	55
Non-White	39	43	77	44
Black or African American	10	11	17	9.7
Hispanic/Latinx	26	29	58	33
Other, non-Hispanic	3	3.3	2	1.1
Unknown	0	0.0	3	1.7
Language				
Spanish speaking (yes)	13	14	28	16
Spanish speaking (no)	78	86	148	84
Age				
0-12y	2	2.2	38	22
13-17y	6	6.6	22	13

18-24y	20	22	23	13
25-49y	41	45	56	32
50-64y	18	20	27	15
>65y	4	4.4	10	5.7
Education (excluding <18y)				
Total Responses for Adults >18y	*80*	%	*113*	%
High school or lower	36	45	54	48
College degree	23	29	34	30
Graduate degree	21	26	25	22
Occupation (excluding <18y)				
Total Responses for Adults >18y	*83*	%	*116*	%
Education	3	3.6	6	5.2
Healthcare worker	11	13	9	7.8
Retail/hospitality/other frontline worker	19	23	22	19
Student	7	8.4	12	10
White collar worker	23	28	34	29
Other (trade and arts)	6	7.2	6	5.2
Not working outside the home	14	17	27	23
Co-Morbidities (excluding <18y)				
Diabetes	4	4.8	9	7.8
High blood pressure	12	15	24	21
BMI >30	28	34	38	33

BMI 25-29.9	24	29	31	27
BMI >30 and one or more co-morbidity				
Adults >18y (n = 83 index, 116 HC)	16	19	22	19
Adults >50y (n = 22 index, 37 HC)	7	32	12	32

Table 2. Potential risk factors for SARS-CoV-2 transmission from index cases

INDEX CASES	All Indexes (n, %)	Household transmission (n, %)	No transmission (n, %)	p-value
	60 (100%)	32 (53%)	28 (47%)	-
Age				
<18y	7 (12%)	4 (13%)	3 (11%)	
18-50y	45 (75%)	25 (78%)	20 (71%)	NS
>50y	8 (13%)	3 (9%)	5 (18%)	
Sex				
Female	33 (55%)	15 (47%)	18 (64%)	NS
Male	27 (45%)	17 (53%)	10 (36%)	
Mask wearing prior to enrollment (missing n = 3)				
Mask wearing at home	10 (18%)	4 (13%)	6 (22%)	NS
Race/Ethnicity				
White, non-Hispanic	34 (57%)	13 (41%)	21 (75%)	0.01*
Black or African American	7 (12%)	5 (16%)	2 (7%)	
Other, non-Hispanic	4 (7%)	4 (12%)	0 (0%)	
Hispanic/Latinx	15 (25%)	10 (31%)	5 (18%)	
Symptom severity				
Mild	12 (21%)	4 (14%)	8 (29%)	0.07

Moderate/Severe	41 (72%)	21 (72%)	20 (71%)	
Hospitalized	4 (7%)	4 (14%)	0 (0%)	
Duration of symptoms at enrollment				
Median days (IQR)	5 (4-7)	5 (4-7)	6 (4-7)	NS
Nasopharyngeal viral load (log10 copies/mL) at enrollment (missing n = 6)				
Median (IQR)	8.3 (5.9-9.5)	8.8 (7.3-10.1)	7.4 (5.3-8.7)	0.03
Co-Morbidities for adults >18y (missing n = 1 for diabetes, n = 3 for obesity)				
Diabetes	0 (0%)	0 (0%)	0 (0%)	NS
Obesity, BMI >30	21 (42%)	13 (50%)	8 (33%)	NS
Education for adults >18y (missing n = 3)				
High school or lower	21 (42%)	13 (52%)	8 (32%)	
College degree	17 (34%)	9 (36%)	8 (32%)	NS
Graduate degree	12 (24%)	3 (12%)	9 (36%)	

p-values only reported if ≤ 0.10, otherwise noted as not significant (NS)

*compares white, non-Hispanic versus all other categories

Table 3. Potential household-level risk factors for SARS-CoV-2 transmission

HOUSEHOLDS	All Households (n, %)	Infected (n, %)	Uninfected (n, %)	p-value
	60 (100%)	32 (53%)	28 (47%)	-
Household size				
Mean	3.8	4.2	3.4	0.03
Living space (missing n = 3)				
<2000 sq ft	29 (51%)	18 (60%)	11 (41%)	NS
>2000 sq ft	28 (49%)	12 (40%)	16 (59%)	
Number of rooms*				
2 or fewer rooms	5 (8%)	2 (6%)	3 (10%)	0.06
3-5 rooms	27 (45%)	19 (59%)	8 (29%)	
6 or more rooms	28 (47%)	11 (34%)	17 (61%)	
Living density				
>3 people and <6 rooms	15 (25%)	13 (41%)	2 (7%)	0.003
Home ownership (missing n = 1)				
Renting apartment	4 (7%)	2 (7%)	2 (7%)	NS
Renting home	17 (29%)	11 (36%)	6 (21%)	NS
Own home	38 (64%)	18 (58%)	20 (71%)	NS

*Number of rooms includes bedrooms, kitchen, and common rooms, but not bathrooms or garage

p-values only reported if ≤ 0.10, otherwise noted as not significant (NS)

Table 4. Risk factors for SARS-CoV-2 transmission in the household

Index or household risk factors	Susceptible HCs	Incident secondary cases	SAR (95% CI)	OR (95% CI)	aOR (95% CI)
All	103	33	32% (22-44%)		
Non-white	41	21	51% (33-69%)	4.4 (1.5-13.0)	4.8 (1.5-15.4)
White, non-Hispanic	62	12	19% (10-35%)	-	
Higher index NP viral load*	-	-	-	3.5 (1.5-8.1)	3.6 (1.5-8.5)
High living density**	29	15	52% (27%-75%)	3.3 (1.02-10.9)	1.4 (0.4-4.6)
Not high living density	74	18	24% (15%-37%)	-	

*OR for 3 log10 increase in index viral load. For example, the odds of transmission in a household where index VL is 1x10^9 copies/mL is 3.5 times greater than in a household where index VL is 1x10^6 copies/mL.

**Defined as >3 people occupying <6 rooms

aOR adjusts for viral load as a continuous variable and racial-ethnicity and living density as dichotomous variables

FIGURE LEGENDS

Figure 1. CO-HOST enrollment and secondary household attack rate (SAR). Among 100 households that completed the 28-day follow-up, household contacts were excluded if they had evidence of prior infection (negative PCR and positive antibody test at enrollment), were possibly infected at the same time as the index case based on a common exposure event, or negative PCR testing could not be confirmed with a negative antibody test at Day 28. Of the remaining 176 household contacts of 91 index cases, 41% (73) were already PCR-positive at baseline and thus excluded from the primary SAR analysis. During study follow-up, 33 incident SARS-CoV-2 cases were identified, yielding a SAR of 32% (33/103). Among the 33 secondary cases, 22 were identified by both PCR and seroconversion from Day 1 to Day 28, 4 were identified by PCR only, and 7 were identified based on seroconversion.

Figure 2. SARS-CoV-2 viral burden is correlated within families. The viral load obtained at enrollment from nasopharyngeal swabs in households with multiple COVID-positive household members are shown (n=42 households). Each vertical row in red depicts an individual household, with circles delineating the log viral load of each member within the household. Circles shaded in gray represent values derived from a nasal mid-turbinate swab if NP sampling was not performed. This was based on a linear regression equation generated from >100 study participants with positive viral load from both NP and NMT swabs [11]. Households are depicted across the x-axis in order of decreasing viral load. Data drawn from 148 participants. The intraclass correlation coefficient ICC = 0.45, 95% CI (0.23, 0.62), p-value < 0.001.

Figure 3. Bayesian phylogeny showing high relatedness within household infections, indicating household transmission. High density amplicon sequencing was performed on all available viral isolates from ten households with secondary infections to assess relatedness between infections. Whole genome sequences were assembled according to the Wuhan reference genome, assigned to major clades, and then used for Bayesian phylogeny reconstruction. Index cases within each numbered household are written in bold. Household contacts are numbered sequentially starting with the index case number, i.e. X-1, X-2, etc. Minors are indicated with a c prior to the case number. Each asterisk indicates one study week preceding a positive qPCR test, i.e. * indicating a D7 positive test, ** indicating a D14 positive test, and *** indicating a D21 positive test. Household contacts without asterisks were PCR-positive at baseline.

Figure 4. Association of index nasopharyngeal viral load and transmission in the household. Households with secondary cases were more likely to have index cases with high nasopharyngeal viral load compared to households without secondary transmission (median NP viral load log 8.8 vs 7.4 copies/mL, respectively p=0.03). Index cases that were not yet antibody-positive at enrollment, as a marker of more recent infection, are depicted to the right in gray.

Figure 1

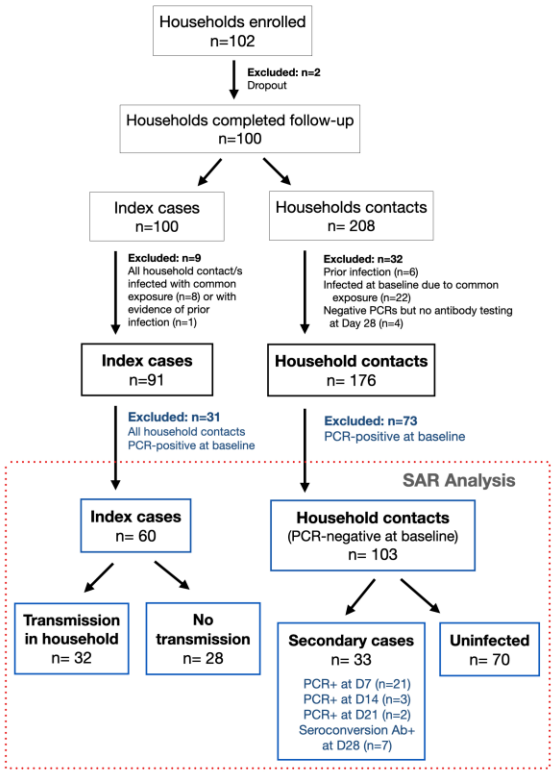

Figure 2

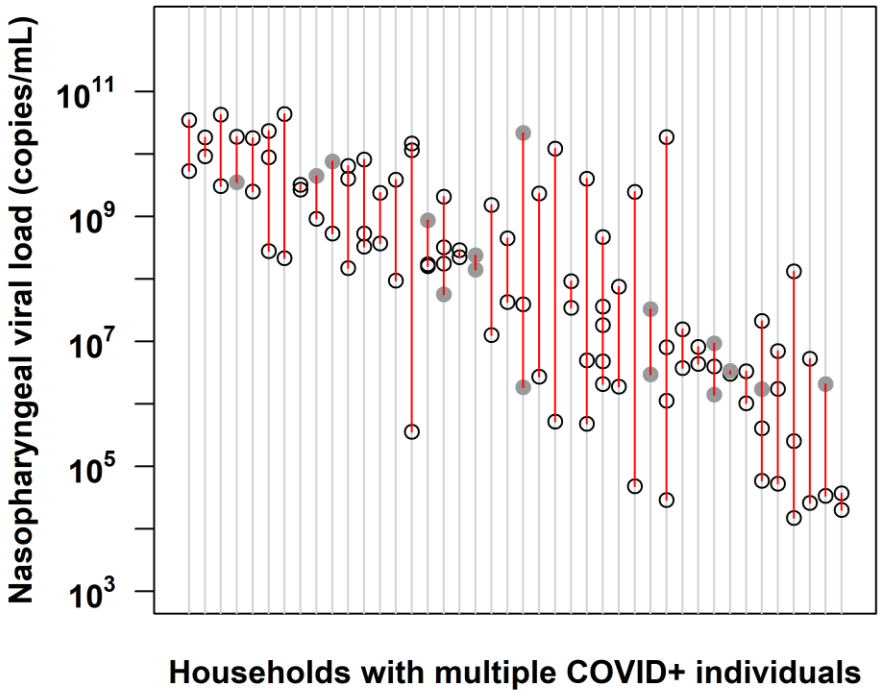

Figure 3

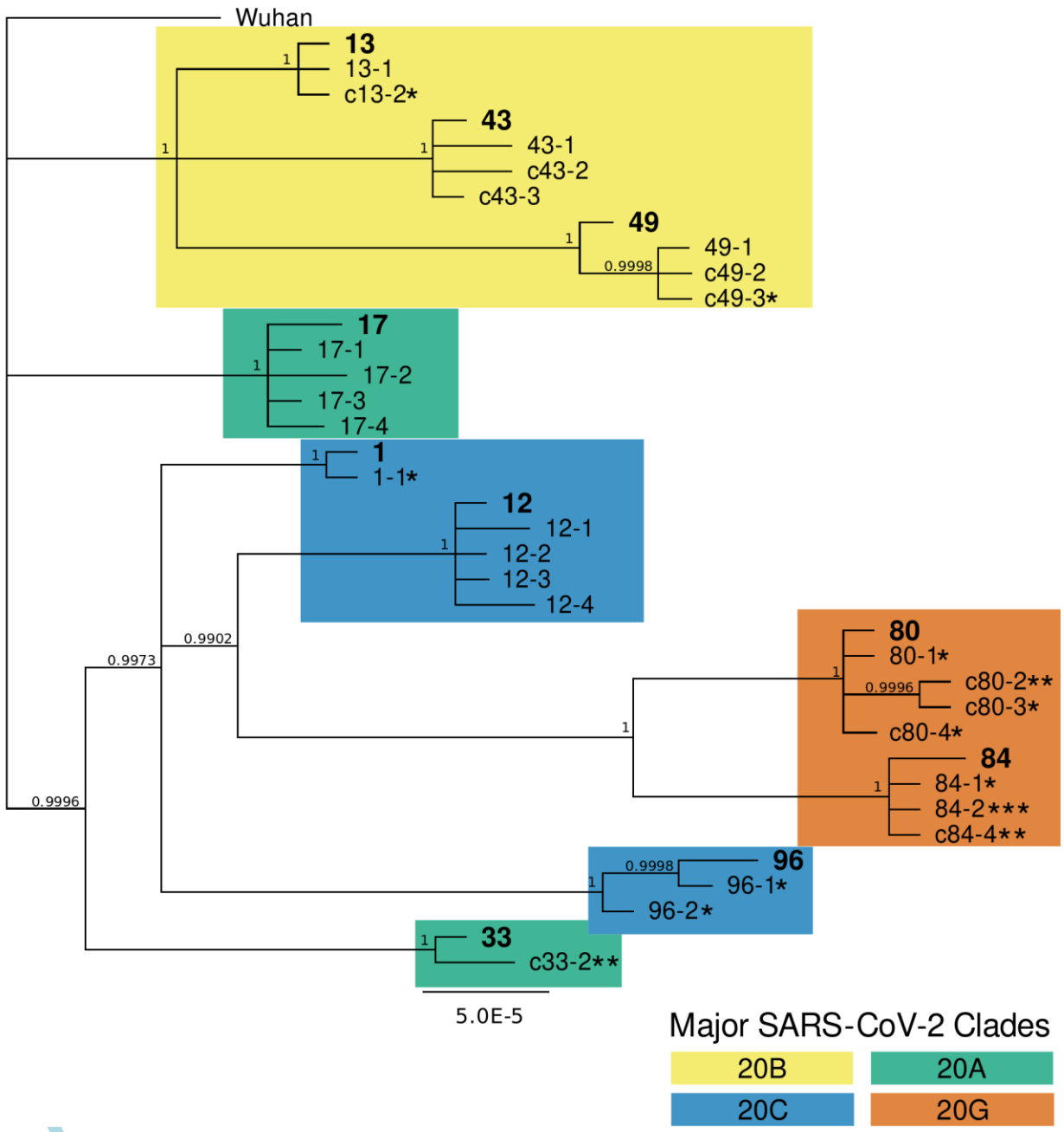

Figure 4