Title

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Transmission Dynamics and Immune Responses in a Household of Vaccinated Persons

Journal

Clinical Infectious Diseases, 75(1)

ISSN

1058-4838

Authors

Liu, Jamin
Laurie, Matthew T
Rubio, Luis
et al.

Publication Date

2022-08-24

DOI

10.1093/cid/ciac029

SARS-CoV-2 transmission dynamics and immune responses in a household of vaccinated persons

Jamin Liu[1,2], Matthew T. Laurie[2], Luis Rubio[3], Sara E. Vazquez[2,4], Sara Sunshine[2], Anthea M. Mitchell[2,5], Matthias Hapte-Selassie[2,5], Sabrina A. Mann[2,5], Genay Pilarowski[6,7], Douglas Black[3], Carina Marquez[3], Susana Rojas[7], Michail S. Lionakis[8], Maya Petersen[9], Jeffrey D. Whitman[10], Vivek Jain[3], Mark Anderson[4], Diane Havlir[3], Joseph DeRisi[2,5]*

[1]University of California, Berkeley-University of California, San Francisco Graduate Program in Bioengineering, Berkeley, CA 94720, USA

[2]Department of Biochemistry and Biophysics, University of California, San Francisco, CA 94143, USA

[3]Division of HIV, Infectious Diseases, and Global Medicine, University of California, San Francisco, San Francisco, CA 94143, USA

[4]Department of Medicine, Diabetes Center, University of California, San Francisco, San Francisco, CA 94143, USA

[5]Chan Zuckerberg Biohub, San Francisco, CA 94158, USA

[6]The Public Health Company, Oakland, CA 94609, USA

[7]Unidos en Salud, San Francisco CA, 94143, USA

[8]Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy & Infectious Diseases, National Institutes of Health, Bethesda, MD 20892 USA

[9]Division of Biostatistics, University of California, Berkeley, Berkeley, CA 94720, USA

[10]Department of Laboratory Medicine, University of California, San Francisco, San Francisco, CA 94143, USA

*Corresponding Author:

Joseph DeRisi, Ph.D.

Department of Biochemistry and Biophysics

University of California San Francisco

1700 4th St., San Francisco, CA 94158 USA

Email: joe@derisilab.ucsf.edu

ABSTRACT

While SARS-CoV-2 vaccines prevent severe disease effectively, post-vaccination 'breakthrough' COVID-19 infections and transmission among vaccinated individuals remain ongoing concerns. We present an in-depth characterization of transmission and immunity among vaccinated individuals in a household, revealing complex dynamics and unappreciated comorbidities, including autoimmunity to type1 interferon in the presumptive index case.

Keywords: SARS-CoV-2; antibody neutralization; breakthrough infection; anti-interferon auto-antibody; autoimmunity

INTRODUCTION

COVID-19 has caused over 230 million cases of infection worldwide, leading to more than 4.7 million deaths due to coronavirus disease (COVID-19)[1]. Global vaccination efforts have so far administered 6.1 billion vaccine doses[2]. In the United States, three FDA-authorized vaccines have been widely distributed: BNT162b2 by Pfizer/BioNTech, mRNA-1273 by Moderna, and JNJ-78436735 by J&J/Janssen. Each has demonstrated, through clinical trials and retrospective studies, the capacity to prevent symptomatic infection and severe disease[3].

Approximately 50% of the United States population is considered fully vaccinated. Many households have mixed populations of adults and children with variable completion of COVID-19 vaccination[2]. Furthermore, most SARS-CoV-2 lineages have been outcompeted and replaced by newer variants of concern including the Delta and Gamma variants. Further, many spike protein mutations associated with neutralizing antibody escape (K417N/T, R346K, L452R, T478K, E484K/Q, N501Y) have emerged[4,5]. Given these factors, COVID-19 infections in fully vaccinated people (i.e., breakthrough) are well documented[6]. However, there have been relatively few detailed studies to date of household transmission trajectories, especially in households with individuals who received different vaccines, or who have different vaccine completion statuses.

Here, we describe a household cluster of Gamma variant COVID-19 cases occurring in vaccinated family members living in co-residence that resulted in mixed clinical outcomes. A detailed inspection of the epidemiological and clinical features of these cases, together with serology testing and genomic sequencing, suggest complex factors including partial immunity and unrecognized underlying autoimmunity, as potential contributors to breakthrough infections. Our data add to

rapidly emerging literature on SARS-CoV-2 transmission dynamics within households of vaccinated persons.

Description of individuals in the study household

Individuals 1-5 lived together in the same residence, where they ate, slept, and socialized with one another in an unmasked setting. Individual 6 lived separately but frequented the home of Individuals 1-5. Together, these individuals also attended weekly community events, such as religious services, together as one large group. Each individual was thus exposed to one another either through co-residence or frequent visitation.

Individual 1 is an 80-year-old man with diabetes and asthma who received BNT162b2/Pfizer vaccine on April 20 and May 10, 2021. On May 13, malaise, myalgia and diarrhea developed. On May 19, a SARS-CoV-2 PCR test was positive and on May 20, he presented to a local hospital, had hypoxia, and was admitted for inpatient management. Due to severe COVID-19, acute respiratory distress syndrome (ARDS), and respiratory failure, he required mechanical ventilation. He received remdesivir, dexamethasone and tociluzimab and improved, was weaned from ventilator, and was discharged home on June 2.

Individual 2 is a 36-year-old woman who received JNJ-78436735/Janssen vaccine on April 10, 2021. On May 16, she had onset of fever, cough, rhinorrhea, and headache. On May 19, a PCR test was positive. On May 23, a BinaxNOW (Abbott) rapid antigen test was positive. She did not require care at a health facility and improved with self-monitoring at home.

Individual 3 is a 60-year-old woman who received mRNA-1273/Moderna vaccine on March 9 and April 6, 2021. On May 19, she had onset of fever, chills, cough and rhinorrhea. On May 20, a SARS-CoV-2 PCR test was positive and on May 23, a BinaxNOW test was positive. She also did not require care at a health facility and improved with self-monitoring at home.

Individual 4 is an 84-year-old woman who received mRNA-1273/Moderna vaccine on February 25 and March 26, 2021. After members of her family tested positive for COVID-19, she began home-based quarantine on May 20th. On May 23, a BinaxNOW test was negative.

Individual 5 is a 40-year-old man who had tested positive for SARS-CoV-2 the previous year on July 24, 2020. At that time, he isolated with Individual 6. Individual 5 received the JNJ-78436735/Janssen vaccine on April 10, 2021. Although he did not quarantine separately from family members who tested positive, a SARS-CoV-2 PCR test on May 22 was negative.

Individual 6 is a 60-year-old woman who directly cared for Individual 5 when he tested positive for SARS-CoV-2 in July 2020. Despite being unable to quarantine, she tested negative for SARS-CoV-2 and did not develop any COVID-like symptoms. On May 17, 2021, she received the first dose of BNT162b2/Pfizer vaccine. Although she lived apart from Individuals 1-5, she visited their home frequently and attended community events with them. When her BinaxNOW test was negative on May 23, she had not yet received a second dose of the vaccine.

Timelines of vaccination, COVID-19 symptom onset, and testing history are summarized in **Figure 1A** and **Supplementary Table 1**.

RESULTS

SARS-CoV-2 positivity as determined by qPCR amplification of the nasal swab samples corroborated the BinaxNOW results for each household member. Viral genome sequences were recovered from the three individuals who tested positive. Sequences consistent with the Gamma variant were recovered from Individual 2 (90% genome coverage; GISAID: EPI_ISL_2508365) and Individual 3 (98% genome coverage; GISAID: EPI_ISL_2508366). (**Supplementary Figure 1**, BioProject PRJNA790937) Despite incomplete recovery, the partial sequence from Individual 1 (17%) contained mutations consistent with the Gamma variant (**Supplementary Table 2**). Characteristic mutations of concern (K417T, E484K, and N501Y) were observed[4,5]. Analysis of the consensus genomes from Individuals 2 and 3 revealed only a single nucleotide difference (G17122T, leading to a ORF1b:A1219S amino acid substitution).

Serum samples from the five household members were analyzed for SARS-CoV-2 neutralizing antibodies using a pseudovirus neutralization assay[7]. Sera from members of this household demonstrated a wide range of neutralization (**Figure 1B**). Individual 1 had a much lower neutralizing antibody titer compared to the fully vaccinated individuals (D614G NT_{50}=4.4x lower, Gamma NT_{50}=6.3x lower), despite being measured 14 days post-symptom onset, and 17 days after his second vaccine dose. Conversely, despite only partial vaccination, Individual 6 had a very high neutralizing antibody titer (D614G NT_{50}=4.5x higher, Gamma NT_{50}=5.0x higher) versus the healthy vaccinated cohort. Although this may have been related to caring for Individual 5 a year prior, Individual 6 had negative serology on the anti-SARS-CoV-2-N IgG Abbott Architect test. Finally, while

Individuals 2, 3, and 4 had neutralizing antibody titers in the typical range of fully vaccinated individuals, Individuals 2 and 3 ultimately tested positive for COVID-19. Taken together, our observations indicate that fully vaccinated individuals may be at risk of breakthrough infection when living in households with sustained close contact with infected individuals.

The neutralization efficacy of patients' sera against the Gamma variant pseudotype was approximately 2-fold lower than the measured NT_{50} against wild-type virus (D614G spike mutation only). This observation is consistent with previously described decreases in neutralization against variants, especially those harboring mutations at E484K[4,5,8].

Additionally, we tested for anti-IFN-α2 auto-antibodies, a marker correlated with severe COVID-19 and poor patient outcomes[9,10]. Using serum from patients with Autoimmune Polyglandular Syndrome Type 1 (APS1), an autoimmune syndrome where patients frequently develop an abundance of anti-IFN-α2 antibodies, as a benchmark for verified interferon autoimmunity, we measured for anti-IFN-α2 antibody presence using a radioligand binding assay (RLBA)[9]. Serum from Individual 1, who had the most severe response to infection, exhibited positive anti-IFN-α2 antibody signal while the other family members had negative titers (**Figure 1C**).

DISCUSSION

We describe a family of mixed vaccination statuses who experienced various clinical trajectories after a Gamma variant COVID-19 exposure in the household. Although coverage of the recovered SARS-CoV-2 genome from Individual 1 is incomplete, and Individuals 2 and 3 differ by one

amino acid substitution, the rarity of the Gamma variant (6.5% of all sequences submitted to GISAID from San Francisco County from April to June) supports the conjecture that infection of this household is derived from a common source. Furthermore, all other Gamma variant sequences from this time period had 3-32 (mean=13; median=14) nucleotide substitutions compared to this household, strongly suggesting direct transmission between household individuals as opposed to coincidental, simultaneous infection outside the home.

Clinical trajectories experienced by household individuals ranged from severe illness requiring hospitalization to mild symptomatic illness to avoiding COVID-19 infection altogether. Individual 1, who had low titers of neutralizing antibodies following vaccination, still developed severe COVID-19 infection. Testing for anti-IFN-α2 auto-antibodies revealed that serum from Individual 1 contained high levels of antibodies against IFN-α2, a trait enriched among patients with life-threatening COVID-19 pneumonia[10]. Although the presence of such auto-antibodies can be clinically silent, they appear to play an influential role in patient outcomes for SARS-CoV-2 infection[12].

Comorbidities such as autoimmune caused by anti-IFN auto-antibodies can lead to decreased protection against circulating variants with spike mutations conferring neutralization escape and thus raise the risk of breakthrough infections[10]. With household exposure to COVID-19, even fully vaccinated individuals with typical levels of neutralizing antibodies are at risk of infection. This data is strongly consistent with intrahousehold transmission amongst three vaccinated household members in this study, and this data highlights the inherent complexities of individuals, including unrealized underlying autoimmunity, that may contribute to transmission dynamics. This data supports the urgency for continued vaccination, boosters, and next-generation vaccines that contain mutations known to confer immune escape potential.

NOTES

ACKNOWLEDGEMENTS

We would like to thank Dr. Chuka Didigu, Dorothy Park CRNA, Salu Ribeiro, and Bay Area Phlebotomy and Laboratory services for performing blood draws of study subjects. We thank Dr. Andreas Puschnik for providing the engineered cell line used in this study. We thank Drs. Peter Kim, Don Ganem, Sandy Schmidt, and Cori Bargmann for technical assistance and discussion.

FUNDING

This work was supported by the University of California San Francisco COVID fund [to J.D., M.L., J.L., and S.S.]; the National Institutes of Health [grant number UM1AI069496 to D.H.; and grant number F31AI150007 to S.S.]; the Division of Intramural Research of the NIAID [ZIA number AI001175 to M.S.L.]; the Chan Zuckerberg Biohub [to J.D. and D.H.]; and the Chan Zuckerberg Initiative [to J.D. and D.H.].

POTENTIAL CONFLICTS

Dr. DeRisi is a member of the scientific advisory board of The Public Health Company, Inc., and is a scientific advisor for Allen & Co. Dr. DeRisi also reports stock options granted for service on the Scientific Advisory Board of The Public Health Company; reports payment or honoraria for various small invited academic lectures at university, approximately 10 of these over the past 36 months; is a member of the board of the Chan Zuckerberg Biohub, and non-profit 501c3 medical research organization affiliated with UCSF, Stanford, and UCB. None of the other authors have any potential conflicts. Dr. Marquez reports grants or contracts from NIH, Stupski Foundation, J.P

McGovern Foundation paid to the institution outside of the submitted work and CZ Biohub honoraria for panel discussion on vaccine hesitancy. Dr. Havlir reports grants or contracts from NIH outside of the submitted work. Dr. Anderson reports grants or contracts NIH/NIAID R37AI097457 (NIH grant to UCSF); consulting fees to self from Aboleris, Inc., Sana, Inc., Rubius, Inc., NGM Bio, Inc.; member of scientific advisory board for Imcyse, Inc.; President, Federation of Clinical Immunology Societies (FOCIS) which is a not for profit immunology society; and owns stock for Medtronic, Inc. and Merck, Inc.

REFERENCES

1. COVID-19 Dashboard. Available at: https://coronavirus.jhu.edu/map.html. Accessed 11 September 2021.

2. Ritchie H, Mathieu E, Rodés-Guirao L, et al. Our World in Data: Coronavirus Pandemic (COVID-19). Our World in Data **2020**; Available at: https://ourworldindata.org/covid-vaccinations. Accessed 11 September 2021.

3. Moline HL, Whitaker M, Deng L, et al. Effectiveness of COVID-19 Vaccines in Preventing Hospitalization Among Adults Aged ≥65 Years - COVID-NET, 13 States, February-April 2021. MMWR Morb Mortal Wkly Rep **2021**; 70:1088–1093.

4. Garcia-Beltran WF, Lam EC, St Denis K, et al. Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity. Cell **2021**; 184:2372-2383.e9.

5. Wang Z, Schmidt F, Weisblum Y, et al. mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants. Nature **2021**; 592:616–622.

6. Vignier N, Bérot V, Bonnave N, et al. Breakthrough Infections of SARS-CoV-2 Gamma Variant in Fully Vaccinated Gold Miners, French Guiana, 2021. Emerg Infect Dis **2021**; 27:2673–2676.

7. Hoffmann M, Kleine-Weber H, Pöhlmann S. A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells. Mol Cell **2020**; 78:779-784.e5.

8. Laurie MT, Liu J, Sunshine S, et al. Exposures to different SARS-CoV-2 spike variants elicit neutralizing antibody responses with differential specificity towards established and emerging strains. medRxiv **2021**; :2021.09.08.21263095.

9. van der Wijst MGP, Vazquez SE, Hartoularos GC, et al. Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. Sci Transl Med **2021**; 13:eabh2624.

10. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science **2020**; 370:eabd4585.

11. Ferre EMN, Rose SR, Rosenzweig SD, et al. Redefined clinical features and diagnostic criteria in autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. JCI Insight **2016**; 1:e88782.

12. Bastard P, Gervais A, Le Voyer T, et al. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Sci Immunol **2021**; 6:eabl4340.

Figure 1. Serum from household individuals reveal diverse neutralization capabilities as well as presence of anti-IFN-α2 auto-antibodies in Individual 1. (**A**) Timeline illustrating the order of events experienced by individuals in the study household, including vaccination, symptom onset, and test results. Additional details are available in **Supplementary Table 1**. (**B**) Plot of 50% pseudovirus neutralization titers (NT_{50}) of serum samples from healthy vaccinated controls (n=11) collected 12-60 days post-second dose (avg. = 26.4 days; details of serum collection timing relative to vaccination and positive COVID tests are described in **Supplementary Table 3**). For the healthy vaccinated donor cohort, geometric mean titer (dashed lines), interquartile range (boxes), and full range (shaded region) and shown for D614G (black) and Gamma (red) pseudoviruses. NT_{50} values for Gamma variant pseudovirus were approximately 2-fold lower than D614G pseudovirus for the healthy vaccinated cohort and most household members sera, apart from Individual 2. All household member serum neutralization titers were within or above the range of healthy donor titers except for Individual 1, whose neutralization titers for D614G and Gamma were 4.4-fold and 6.3-fold lower than healthy controls, respectively. (**C**) Detected by radioligand binding assay reveals that Anti-IFN-α2 auto-antibodies are absent from all assayed pre-pandemic healthy controls (n=42) and vaccinated healthy controls (n=11)[8]. In this household, only Individual 1 demonstrated presence of anti-IFN-α2 auto-antibodies. Autoimmune Polyglandular Syndrome Type 1 (APS1) patient sera are used as positive controls[11]; negative controls are from pre-COVID healthy blood donor plasma or the healthy vaccinated donor cohort.

Figure 1