Clinical Infectious Diseases

BRIEF REPORT

Severe Acute Respiratory Syndrome Coronavirus 2 (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] and Joseph DeRisi[2,5]

[1]University of California, Berkeley—University of California, San Francisco Graduate Program in Bioengineering, Berkeley, California, USA; [2]Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, California, USA; [3]Division of HIV, Infectious Diseases, and Global Medicine, University of California, San Francisco, San Francisco, California, USA; [4]Department of Medicine, Diabetes Center, University of California, San Francisco, San Francisco, California, USA; [5]Chan Zuckerberg Biohub, San Francisco, California, USA; [6]The Public Health Company, Oakland, California, USA; [7]Unidos en Salud, San Francisco, California, USA; [8]Fungal Pathogenesis Section, Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; [9]Division of Biostatistics, University of California, Berkeley, Berkeley, California, USA; and [10]Department of Laboratory Medicine, University of California, San Francisco, San Francisco, California, USA

While SARS-CoV-2 vaccines prevent severe disease effectively, postvaccination "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 type 1 interferon in the presumptive index case.

Keywords. SARS-CoV-2; antibody neutralization; breakthrough infection; anti-interferon autoantibody; autoimmunity.

Coronavirus disease 2019 (COVID-19) has caused over 230 million cases of infection worldwide, leading to more than 4.7 million deaths due to COVID-19 [1]. Global vaccination efforts have so far administered 6.1 billion vaccine doses [2]. In the United States, 3 Food and Drug Administration (FDA)–authorized vaccines have been widely distributed: BNT162b2 by Pfizer/BioNTech, mRNA-1273 by Moderna, and JNJ-78436735 by Johnson & Johnson/Janssen. Each has demonstrated, through clinical trials and retrospective studies, the capacity to prevent symptomatic infection and severe disease [3].

Approximately 50% of the US population is considered fully vaccinated. Many households have mixed populations of adults and children with variable completion of COVID-19 vaccination [2]. Furthermore, most severe acute respiratory syndrome coronavirus 2 (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 (ie, 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 the rapidly emerging literature on SARS-CoV-2 transmission dynamics within households of vaccinated persons.

METHODS

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 1 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 the BNT162b2/Pfizer vaccine on 20 April and 10 May 2021. On 13 May, malaise, myalgia, and diarrhea developed. On 19 May, a SARS-CoV-2 polymerase chain reaction (PCR) test was positive, and on 20 May, 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,

Received 18 October 2021; editorial decision 11 January 2022; published online 17 January 2022.

Correspondence: J. DeRisi, Department of Biochemistry and Biophysics, University of California, San Francisco, 1700 4th Street, San Francisco, CA 94158 (joe@derisilab.ucsf.edu).

Clinical Infectious Diseases® 2022;75(1):e303–6

https://doi.org/10.1093/cid/ciac029

and tociluzimab and improved, was weaned from the ventilator, and was discharged home on 2 June.

Individual 2 is a 36-year-old woman who received the JNJ-78436735/Janssen vaccine on 10 April 2021. On 16 May, she had onset of fever, cough, rhinorrhea, and headache. On 19 May, a PCR test was positive. On 23 May, 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 the mRNA-1273/Moderna vaccine on 9 March and 6 April 2021. On 19 May, she had onset of fever, chills, cough, and rhinorrhea. On 20 May, a SARS-CoV-2 PCR test was positive, and on 23 May, 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 the mRNA-1273/Moderna vaccine on 25 February and 26 March 2021. After members of her family tested positive for COVID-19, she began home-based quarantine on 20 May. On 23 May, 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 24 July 2020. At that time, he isolated with Individual 6. Individual 5 received the JNJ-78436735/Janssen vaccine on 10 April 2021. Although he did not quarantine separately from family members who tested positive, a SARS-CoV-2 PCR test on 22 May 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 17 May 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 23 May, 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 quantitative PCR (qPCR) amplification of the nasal swab samples corroborated the BinaxNOW results for each household member. Viral genome sequences were recovered from the 3 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 5 household members were analyzed for SARS-CoV-2 neutralizing antibodies using a pseudo-virus neutralization assay [9]. Sera from members of this household demonstrated a wide range of neutralization (Figure 1B). Individual 1 had a much lower neutralizing antibody titer compared with the fully vaccinated individuals (D614G 50% neutralization titer [NT_{50}] = 4.4× lower, Gamma NT_{50} = 6.3× 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} = 4.5× higher, Gamma NT_{50} = 5.0× 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 immunoglobulin G (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 pseudo-type 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, 7].

Additionally, we tested for anti–interferon (IFN)-α2 autoantibodies, a marker correlated with severe COVID-19 and poor patient outcomes [10, 11]. 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 IFN autoimmunity, we measured for anti–IFN-α2 antibody presence using a radioligand binding assay (RLBA) [10]. 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 1 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

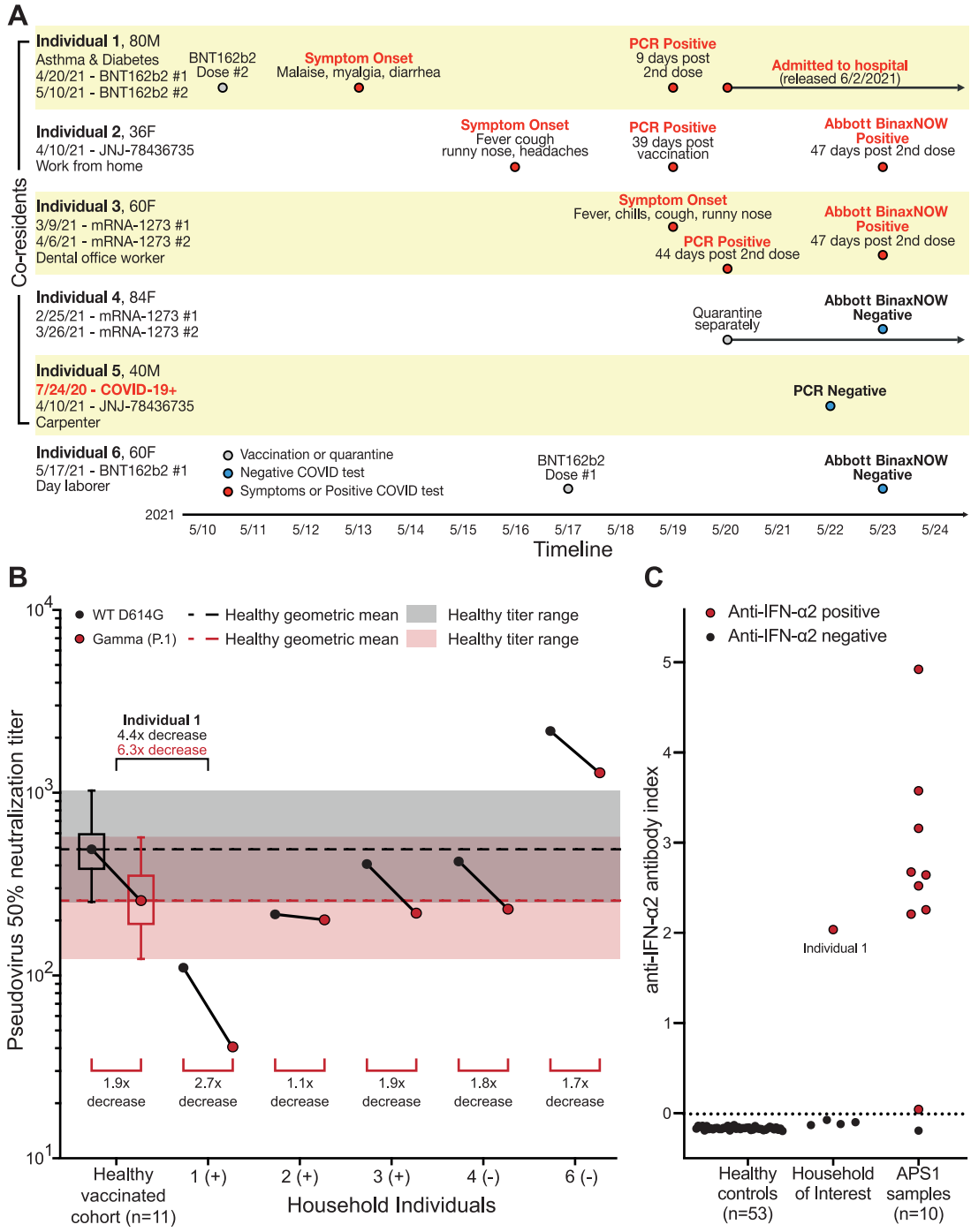

Figure 1. Serum samples from household individuals reveal diverse neutralization capabilities as well as presence of anti–IFN-α2 auto-antibodies in Individual 1. (*A*) Timeline illustrating the order of events experienced by individuals in the study household, including vaccination, symptom onset, and test results. Additional details are available in Supplementary Table 1. (*B*) Plot of 50% pseudo-virus neutralization titers (NT_{50}) of serum samples from healthy vaccinated controls (n = 11) collected 12–60 days post–second dose (average = 26.4 days; details of serum collection timing relative to vaccination and positive COVID-19 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) are shown for D614G (black) and Gamma (red) pseudo-viruses. NT_{50} values for Gamma variant pseudo-virus were approximately 2-fold lower than D614G pseudo-virus 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 those in healthy controls, respectively. (*C*) Detection by radioligand binding assay reveals that anti–IFN-α2 autoantibodies are absent from all assayed prepandemic healthy controls (n = 42) and vaccinated healthy controls (n = 11) [7]. In this household, only Individual 1 demonstrated the presence of anti–IFN-α2 auto-antibodies. Autoimmune polyglandular syndrome type 1 (APS1) patient sera are used as positive controls [8]; negative controls are from pre-COVID healthy blood donor plasma or the healthy vaccinated donor cohort. Abbreviations: COVID-19, coronavirus disease 2019; F, female; IFN, interferon; M, male; PCR, polymerase chain reaction.

Gamma variant sequences from this time period had 3–32 (mean = 13, median = 14) nucleotide substitutions compared with 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 autoantibodies 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 [11]. Although the presence of such autoantibodies can be clinically silent, they appear to play an influential role in patient outcomes for SARS-CoV-2 infection [12].

Comorbidities such as autoimmune disease caused by anti-IFN autoantibodies can lead to decreased protection against circulating variants with spike mutations conferring neutralization escape and thus raise the risk of breakthrough infections [11]. With household exposure to COVID-19, even fully vaccinated individuals with typical levels of neutralizing antibodies are at risk of infection. These data are strongly consistent with intrahousehold transmission among 3 vaccinated household members in this study, and these data highlight the inherent complexities of individuals, including unrealized underlying autoimmunity, that may contribute to transmission dynamics. These data support the urgency for continued vaccination, boosters, and next-generation vaccines that contain mutations known to confer immune escape potential.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. The authors thank Dr. Chuka Didigu; Dorothy Park, CRNA; Salu Ribeiro; and Bay Area Phlebotomy and Laboratory Services for performing blood draws of study subjects. The authors thank Dr. Andreas Puschnik for providing the engineered cell line used in this study. They also thank Drs. Peter Kim, Don Ganem, Sandy Schmidt, and Cori Bargmann for technical assistance and discussion.

Financial support. This work was supported by the University of California San Francisco COVID fund (to J. D., M. T. 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 National Institute of Allergy and Infectious Diseases (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 of interest. J. D. is a member of the scientific advisory board of The Public Health Company, Inc, and is a scientific advisor for Allen & Co. J. D. 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; and is a member of the board of the Chan Zuckerberg Biohub, a nonprofit 501c3 scientific research organization affiliated with University of California San Francisco (UCSF), Stanford, and University of California Berkeley. None of the other authors have any potential conflicts. C. M. reports grants or contracts from the National Institutes of Health (NIH), Stupski Foundation, and J. P. McGovern Foundation paid to the institution outside of the submitted work, and Chan Zuckerberg Biohub honoraria for panel discussion on vaccine hesitancy. D. H. reports grants or contracts from NIH outside of the submitted work. M. A. reports grants or contracts NIH/NIAID R37AI097457 (NIH grant to UCSF); consulting fees to self from Aboleris, Inc, Sana, Inc, Rubius, Inc, and NGM Bio, Inc; is a member of the scientific advisory board for Imcyse, Inc; is President, Federation of Clinical Immunology Societies (FOCIS), which is a not-for-profit immunology society; and owns stock in Medtronic, Inc, and Merck, Inc. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Johns Hopkins University. 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**; 70:1088–93.
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**; 592:616–22.
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**; 27:2673–6.
7. Laurie MT, Liu J, Sunshine S, et al. SARS-CoV-2 variant exposures elicit antibody responses with differential cross-neutralization of established and emerging strains including Delta and Omicron. J Infect Dis **2022**; jiab635.
8. 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.
9. 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.
10. 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.
11. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science **2020**; 370:eabd4585.
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.