RESOURCE REPORT

PARIS and SPARTA: Finding the Achilles' Heel of SARS-CoV-2

Viviana Simon,[a,b,c,s,t] Vamsi Kota,[j] Ryan F. Bloomquist,[k] Hannah B. Hanley,[d] David Forgacs,[d] Savita Pahwa,[l] Suresh Pallikkuth,[l] Loren G. Miller,[f,g] Joanna Schaenman,[f] Michael R. Yeaman,[f,g] David Manthei,[p] Joshua Wolf,[r] Aditya H. Gaur,[r] Jeremie H. Estepp,[r] Komal Srivastava,[a] Juan Manuel Carreño,[a] Frans Cuevas,[a] PARIS/SPARTA Study Group, Ali H. Ellebedy,[m,n,o] Aubree Gordon,[p] Riccardo Valdez,[u] Sarah Cobey,[q] Elaine F. Reed,[h] Ravindra Kolhe,[i,j,k] Paul G. Thomas,[r] Stacey Schultz-Cherry,[r] Ted M. Ross,[d,e] Florian Krammer[a,s,t]

[a]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[b]Division of Infectious Diseases, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[c]The Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[d]Center for Vaccine and Immunology, University of Georgia, Athens, Georgia, USA
[e]Department of Infectious Diseases, University of Georgia, Athens, Georgia, USA
[f]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[g]Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, California, USA
[h]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[i]Department of Pathology, Medical College of Georgia, Augusta University, Augusta, Georgia, USA
[j]Department of Medicine, Medical College of Georgia, Augusta University, Augusta, Georgia, USA
[k]Department of Restorative Sciences, Dental College of Georgia, Augusta University, Augusta, Georgia, USA
[l]Department of Microbiology and Immunology, University of Miami Miller School of Medicine, Miami, Florida, USA
[m]Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, Missouri, USA
[n]Andrew M. and Jane M. Bursky Center for Human Immunology and Immunotherapy Programs, Washington University School of Medicine, St. Louis, Missouri, USA
[o]Center for Vaccines and Immunity to Microbial Pathogens, Washington University School of Medicine, St. Louis, Missouri, USA
[p]Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA
[q]Department of Ecology and Evolution, University of Chicago, Chicago, Illinois, USA
[r]Department of Infectious Diseases, St Jude Children's Research Hospital, Memphis, Tennessee, USA
[s]Department of Pathology, Molecular and Cell-Based Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA
[t]Center for Vaccine Research and Pandemic Preparedness (C-VARPP), Icahn School of Medicine at Mount Sinai, New York, New York, USA
[u]Department of Pathology, University of Michigan, Ann Arbor, Michigan, USA

ABSTRACT To understand reinfection rates and correlates of protection for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we established eight different longitudinal cohorts in 2020 under the umbrella of the PARIS (Protection Associated with Rapid Immunity to SARS-CoV-2)/SPARTA (SARS SeroPrevalence And Respiratory Tract Assessment) studies. Here, we describe the PARIS/SPARTA cohorts, the harmonized assays and analysis that are performed across the cohorts, as well as case definitions for SARS-CoV-2 infection and reinfection that have been established by the team of PARIS/SPARTA investigators.

IMPORTANCE Determining reinfection rates and correlates of protection against SARS-CoV-2 infection induced by both natural infection and vaccination is of high significance for the prevention and control of coronavirus disease 2019 (COVID-19). Furthermore, understanding reinfections or infection after vaccination and the role immune escape plays in these scenarios will inform the need for updates of the current SARS-CoV-2 vaccines and help update guidelines suitable for the postpandemic world.

KEYWORDS COVID-19, SARS-CoV-2, antibodies, cohort study, reinfection

Editor Angela L. Rasmussen, University of Saskatchewan

Address correspondence to Ted M. Ross, tedross@uga.edu, or Florian Krammer, florian.krammer@mssm.edu.

The authors declare a conflict of interest. The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays (inventors named FK, VS) and NDV-based SARS-CoV-2 vaccines (inventor named FK). FK would also like to note the following, which could be perceived as a conflict of interest: He has previously published work on influenza virus vaccines with S. Gilbert (University of Oxford), has consulted for Curevac, Merck and Pfizer (before 2020), is currently consulting for Pfizer, Seqirus, Third Rock Ventures and Avimex, his laboratory is collaborating with Pfizer on animal models of SARS-CoV-2, his laboratory is collaborating with N. Pardi at the University of Pennsylvania on mRNA vaccines against SARS-CoV-2, his laboratory was working in the past with GlaxoSmithKline on the development of influenza virus vaccines and two of his mentees have recently joined Moderna. RK reports consulting fees, honoraria, travel funding, and research support from Illumina, QIAGEN, and Perkin Elmer which manufactures SARS-CoV-2 testing and sequencing kits.

Received 2 April 2022
Accepted 13 April 2022
Published 19 May 22

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 in China and has since caused the coronavirus disease 2019 (COVID-19) pandemic. Early reports from the Wuhan Institute of Virology indicated that individuals infected with this virus mounted antibody responses against it (1). Assays to measure these antibody responses were swiftly developed (2), and the general assumption was that antibodies, especially neutralizing antibodies, would correlate with protection and prevent reinfection. These assumptions were backed up by the detection of neutralizing antibodies after infection (3, 4) and the findings that prior infection protects nonhuman primates from reinfection (5, 6). Importantly, SARS-CoV-2 spike antibodies provided a correlate of protection in the nonhuman primate model (7, 8). However, reports of reinfections (9, 10), reports about waning of antibody within 8 weeks (11) (which turned out to be misleading), and studies suggesting reinfection with human seasonal coronaviruses (hCoVs) (12–14) highlight the need for large longitudinal observational studies to test these assumptions in a rigorous manner.

We established several longitudinal cohorts under the umbrella of the PARIS (Protection Associated with Rapid Immunity to SARS-CoV-2) and SPARTA (SARS SeroPrevalence And Respiratory Tract Assessment) studies to address the question of SARS-CoV-2 antibody durability and efficacy (e.g., protection against reinfection). These human cohorts were initially designed to compare the frequency of SARS-CoV-2 infection in seropositive to seronegative participants, thus pinpointing correlates of protection in the context of natural infection. With the rapid SARS-CoV-2 vaccine rollouts starting in mid-December 2020 in the United States, many of our cohorts also now track immune responses to vaccination in both seronegative and seropositive individuals at the time of immunization. These natural infection/vaccine cohorts will help to establish correlates of protection after natural infection and vaccination and inform about vaccine-induced immunity to newly emerging SARS-CoV-2 variants of interest/concern (15–20) (Fig. 1).

CONCEPT

The original PARIS cohort was planned and established at the Icahn School of Medicine at Mount Sinai in New York, NY, with the first participants being enrolled on 27 April 2020. During the following months, seven other cohorts were added to provide geographic diversity and achieve more statistical power (Table 1, Fig. 1). These cohorts were either preexisting (St. Jude, Washington University) or newly initiated. The overall concept for all cohorts was to follow individuals with and without prior COVID-19 by collecting data as well as biospecimens to measure immune responses (e.g., antibody responses to the spike protein of SARS-CoV-2) at least every 2 months. Molecular SARS-CoV-2 testing of symptomatic individuals to identify SARS-CoV-2, akin to phase III vaccine trials, was also included in each of the cohorts.

A shared theme of all eight cohorts was to enroll individuals who were at greater risk of COVID-19 in order to accumulate new infections faster. The initial PARIS study focused on health care workers (HCWs) in New York City, one of the early epicenters of the pandemic in the United States, but the other cohorts targeted other populations, including communities of color, first responders, and students. All cohorts used the same serological assay, which had originally been developed at Mount Sinai, to measure SARS-CoV-2 spike IgG antibodies (3, 21). This assay is an orthogonal enzyme-linked immunosorbent assay with high specificity and sensitivity which measures immune responses to the SARS-CoV-2 spike protein and therefore captures both infection- and vaccine-induced serum antibody responses (21). A detailed protocol for this assay has been published (21). However, as described below, many sites also collect saliva samples and perform molecular testing for not only SARS-CoV-2 but also other respiratory pathogens using multiplex diagnostic panels, and some cohorts sample and collect data at shorter (e.g., 2- or 4-week) intervals.

The eight PARIS/SPARTA cohorts are geographically distributed across the United States, covering the coasts (New York, NY, Los Angeles, CA, Miami, FL, Augusta, GA, Athens, GA) as well as the heartland (Memphis, TN, St. Louis, MO, Ann Arbor, MI). Collectively, these eight cohorts provide COVID-19-specific

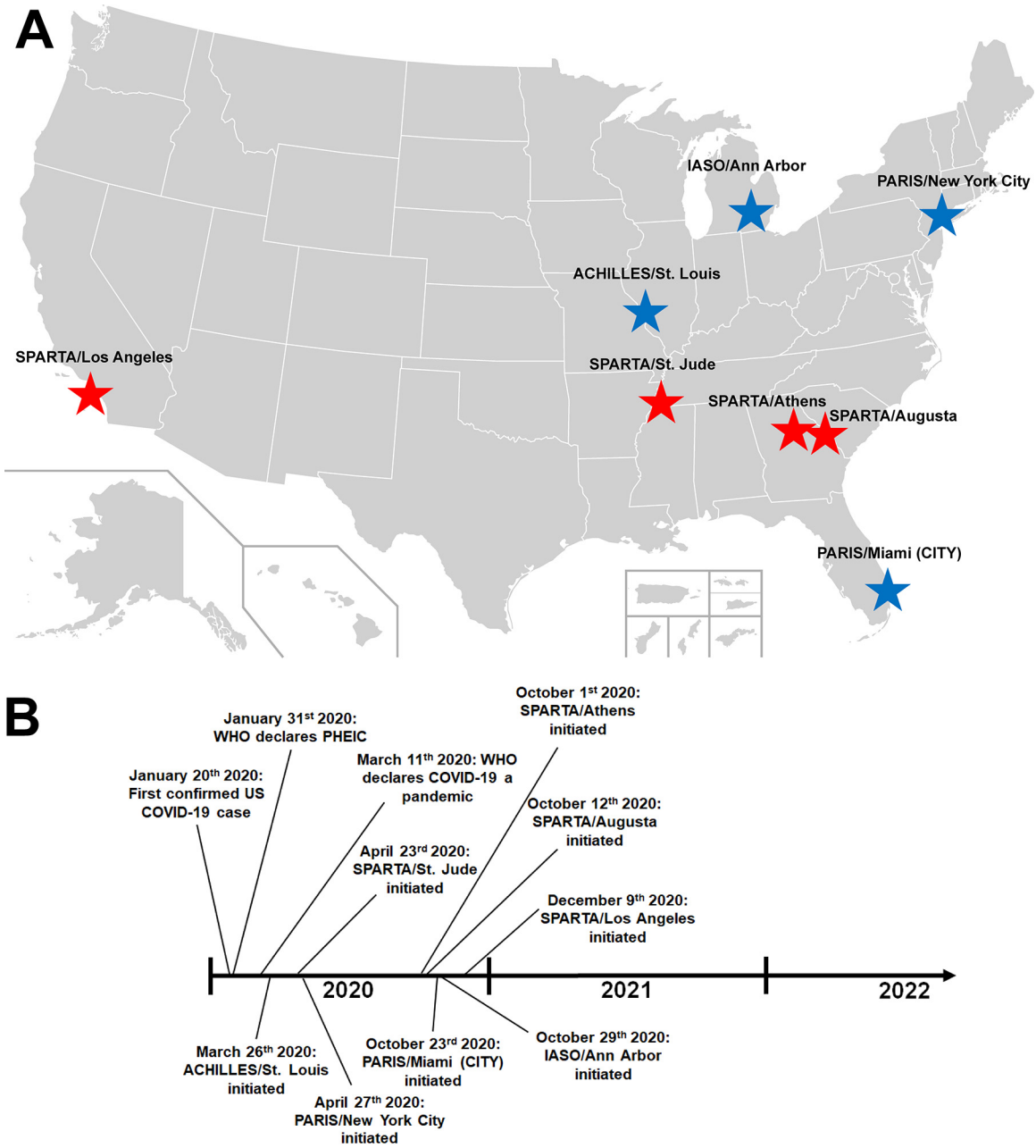

FIG 1 Overview of the PARIS/SPARTA cohorts. (A) Geographic location of the different sites in the United States. Blue stars indicate sites supported by 75N93019C00051, red stars indicate sites supported by 75N93019C00052. (B) Timeline of the pandemic in the United States and the establishment of the different cohorts. The U.S. map in panel A was used as permitted under a CC0 license (source: https://commons.wikimedia.org/wiki/File:Blank_USA,_w_territories.svg).

information and biospecimens, at minimum, every 2 months for a total of 8,741 participants. While the primary analysis of antibody responses specific for each cohort is conducted by each site, a secondary analysis of the immune response data generated by the eight cohorts using the harmonized collection time points and assays will be performed by the common data analysis site established for the purpose of cross-cohort analysis and data modeling.

DETAILED COHORT DESCRIPTIONS

PARIS (NYC). This cohort follows health care workers from the Mount Sinai Health System in New York City (NYC). Immediate household members were also eligible for

TABLE 1 Overview of the PARIS/SPARTA cohorts, status as of 28 February 2022[a]

Cohort/ location	Target enrollment (current enrollment)	Date of first enrollment	Sex, age, ethnicity distribution	Specimen and sampling intervals	Percent vaccinated	Percent boosted	No. of breakthrough infections after full vaccination	Principal investigator	Studies published
ACHILLES/St. Louis, MO	800 (671)	26 March 2020	49% female Avg age, 54.5 yrs (range, 18.9–93.6) 49% white, 48% African-American	Serum, saliva, PBMCs 1/8 wks	NA	NA	NA	Ali Ellebedy	22, 35, 41–44
SPARTA/St. Jude	1,315 (1,316)	23 April 2020	73% female Avg age, 43.7 yrs (range, 20–83 yrs) 80% white	Plasma, PBMCs 2 and 4 wks post event, then every 3 mo	91	NA	NA	Paul Thomas	36, 45–48
PARIS/New York City	400 (500)	27 April 2020	67% female Avg age, 39 yrs (range, 18–74 yrs) 55% white	Saliva, serum, plasma, PBMCs 2/4 wks	92	81	90	Viviana Simon, Florian Krammer	32–34, 37, 39, 40, 49–51
SPARTA/ Athens, GA	1,500 (1,833)	1 October 2020	69% female Avg age, 44.7 yrs (range, 18–86) 86% white	Saliva, serum, PBMCs 2/4 wks	74	42.9	236	Ted M. Ross	31, 52–54
SPARTA/ Augusta, GA[b]	1,500 (637)	12 October 2020	62% female Avg age, 45 yrs (range, 18–85) 49% white, 38% African-American	Saliva, serum, PBMCs 2/4 wks	55	15	NA	Ravindra Kolhe	55–59
PARIS/Miami, FL (CITY)	200 (228)	23 October 2020	60% female Avg age, 48.2 yrs (range, 20–92) 84% white, 6.6% African-American, 38.5% Hispanic/LatinX	Serum, plasma, PBMCs 4/8 wks	87.2	50.8	31	Savita Pahwa	
IASO/Ann Arbor, MI	5,000 (3,356)	29 October 2020	78.1% female Avg age, 44.3 yrs (range, 18–94) 85.9% white	Serum, PBMCs 8 wks	96.4	85.7	385	Aubree Gordon, Riccardo Valdez	60, 61
SPARTA/Los Angeles, CA	200 (200)	9 December 2020	70% female Avg age, 40.2 yrs (range, 19–77) 16.5% white, 29% Asian, 40.5% Hispanic/ LatinX	Saliva, serum, PBMCs 2/4 wks	83	32	23	Elaine Reed	

[a]NA, Not applicable.
[b]Status as of 1 April 2022, not 28 February 2022.

participation. The first participants were enrolled on 27 April 2020. A total of 500 participants completed at least one study visit as of 28 February 2022, with 412 currently active participants (withdrawal rate, 18%). In total, 67% of participants are female, and the average age is 39 years (range: minimum [min], 18; maximum [max], 74 years); 55% of the participants self-identify as white, 14% as Asian, and 6% as African-American. In addition, 13% identify as Hispanic/LatinX. A total of 36% of the participants were seropositive at enrollment, with the majority having been infected with SARS-CoV-2 in March/April of 2020 during the first pandemic wave when New York City emerged as one of the early epicenters of the pandemic in the United States. A total of 92% of the cohort has been fully vaccinated with mRNA vaccines (BNT162b2 [Pfizer] or mRNA-1273 [Moderna]), and 81% have received a booster vaccination (as of February 2022). A total of 90 PARIS participants tested positive for SARS-CoV-2 after being fully vaccinated (two doses of mRNA vaccines). At each study visit, saliva, serum, plasma, and peripheral blood mononuclear cells (PBMCs) are collected and cryopreserved. Nasopharyngeal swabbing is performed when participants report signs and symptoms suggestive of upper respiratory tract infections. Full-length spike binding IgG antibody concentrations are measured at each study visit.

IASO (PARIS/Ann Arbor, MI). The Immunity Associated with SARS-COV-2 (IASO) study follows staff and student employees at the University of Michigan, Ann Arbor. The first participant was enrolled on 29 October 2020, and as of 28 February 2021, 2,541 participants were active in the study, and enrollment is ongoing. To date, a total of 3,356 participants have ever been enrolled, 300 have withdrawn from the study (withdrawal rate, 8.9%), and 515 (15.3%) participants chose not to enroll in year 2. The average age of participants is 44.3 years (range: min., 18; max., 94 years), and 78.1% are female; 85.9% of the participants self-identify as white, 7.3% as Asian, 2.7% as African-American, 0.01% as Native Hawaiian or other Pacific Islander, 0.1% as American Indian or Alaska Native, and 2.0% as multiracial. In addition, 3.7% identified as Hispanic/LatinX. A total of 96.4% of the cohort was fully vaccinated as of 28 February 2021, and 85.7% had received a booster. Prior to vaccination, 62.8% of participants were SARS-CoV-2 naive, 9.6% were infected, 12.2% were vaccinated with an unknown infection history, and 3.0% were both vaccinated and infected, with timing of infection unknown; 0.5% of vaccinated participants were infected during the course of vaccination (between doses 1 and 2 or $<$14 days after dose 2), while 11.9% of vaccinated participants experienced a breakthrough infection (positive $\geq$14 days after dose 2). Of the 385 reported breakthrough infections, 284 (73.8%) were confirmed by PCR. Of study participants that are currently unvaccinated, 30.3% have no infection history and 69.7% have a history of at least one infection with SARS-CoV-2. At each study visit, serum is collected and cryopreserved. Asymptomatic serial respiratory samples and/or and peripheral blood mononuclear cells and plasma are collected from a subset of the cohort.

ACHILLES (PARIS/St. Louis, MO). The ACHILLES cohort comprises two study protocols enrolling participants at the Barnes-Jewish Hospital system and at the Infectious Disease Clinical Research Unit at Washington University School of Medicine. The first is the WU-350 study, which is a sample collection study that enrolled participants who were being tested for SARS-CoV-2, and thus, baseline samples consist of both SARS-CoV-2-positive and -negative participants. Participants who test positive for SARS-CoV-2 are subsequently followed at 3, 7, 14, and 28 days and then 3, 6, 9, and 12 months after infection. Blood, saliva, and other biospecimens are collected from these participants where possible. In total, 500 participants were enrolled in WU-350. This cohort consists of 233 women and 267 men, with 314 African-American 177 white, and 9 Asian participants. The second study, WU-353, enrolled participants with PCR-confirmed SARS-CoV-2 infection who were convalescent and had been tested positive at least 14 days prior to the baseline visit. These participants are also followed every 3 months for 2 years. A total of 171 participants were enrolled in this study. Current demographics are 97 women and 73 men and 1 undisclosed, with 154 white participants, 7 Asian, 6 African-American, and 4 with more than one race or unreported. These participants provided samples every 3

months for up to 2 years. We have also enrolled several of these participants in substudies, which collect lymph node or bone marrow biopsy specimens. Information is being collected from both cohorts about symptoms, recurrent infections, and vaccinations (22).

CITY (PARIS/Miami, FL). The COVID Immunity Study (CITY) cohort follows high-risk groups such as health care workers and participants from the community, with a target enrollment of 200 participants divided between those with confirmed prior SARS-CoV-2 infection or self-reported as uninfected. The first participant was enrolled on 23 October 2020, and enrollment is complete. As of 18 November 2021, we have recruited 228 participants (39.9% males and 60.1% females) with an average age of 48.2 years (range: min., 20; max., 92 years). A total of 84% of the participants self-identified as white, 6.6% as African-American, 5.2% as Asian, and 3.9% as other. Overall, 38.5% identified as Hispanic/LatinX. SARS-CoV-2 infection status is well matched, with 49.5% (113) having had SARS-CoV-2 infection and 50.5% (115) not ever being SARS-CoV-2 infected. A total of 87.2% (199) of the cohort has received at least one dose of an mRNA-vaccine (BNT162b2 or mRNA-1273) or vectored vaccine (J&J). Based on their real-time study status, only 6% of the SARS-CoV-2-uninfected group and 21.2% of those with past COVID-19 diagnosis have not yet been vaccinated. Participants are followed monthly for the first 6 visits, including baseline, and then every other month for each subsequent visit up to 2 years; 118 participants have completed year 1 and are continuing into year 2. At each visit, serum, plasma, and peripheral blood mononuclear cells are collected and cryopreserved. Overall study withdrawal occurred in 20.2% (46) of participants; of these, 45.6% (21) were in the noninfected and 54.3% (25) in the previously infected group. In addition to the regular follow-ups, we are collecting samples after COVID-19 vaccine and booster doses at two additional time points (1 week and 1 month post-last vaccine dose and booster) to collect plasma, serum, and PBMCs. At present, we have these samples collected from 84 participants.

SPARTA/Athens. The SPARTA/Athens study follows university employees and students at the University of Georgia, hospital workers from Piedmont Athens Regional and St. Mary's Hospitals, first responders, and residents from the local Atlanta, GA, and Athens, GA, communities. The first participant was enrolled on 1 October 2020. As of 28 February 2022, 1,833 participants were enrolled in the study, and enrollment is ongoing. Of the potential participants that completed a study screening call, 1,833 enrolled, 60 declined enrollment, and the enrollment process is ongoing for 10 participants. To date, 114 participants have withdrawn from the study (withdrawal rate, 6.5%). A total of 69% of participants are female, 31% are male, and 0.3% identify as other. The average age is 44.7 years (range: min., 18; max., 86 years); 86% of the participants self-identify as white, 4% as Asian, 7% as African-American, and 2% as other or multiple. In addition, 6% identified as Hispanic/LatinX. A total of 13% of participants were previously infected at enrollment, and 61% were SARS-CoV-2 naive; 74% of the cohort was vaccinated as of 28 February 2022, and 61% were vaccinated without history of infection. A total of 931 participants received the BNT162b2 (Pfizer)vaccine, 383 participants received the mRNA-1273 (Moderna) vaccine, 3 participants received the AZD1222 (AstraZeneca) vaccine, and 29 participants received the Ad26.COV2.S (J&J) vaccine; 42.9% of the entire Athens cohort (786 out of 1,833 total participants) received a vaccine booster. A total of 236 breakthrough infections occurred as of February 2022 in the Athens cohort. Of the Athens/SPARTA participants, 11% (175) are currently antibody negative and 89% (1,559) are antibody positive, largely due to vaccination. There are 33 participants that have tested positive for viral RNA following nasal swab/saliva collection, which amounts to 2% of the Athens/SPARTA cohort. At each visit, saliva, serum, plasma, and peripheral blood mononuclear cells are collected and cryopreserved.

SPARTA/Augusta. The SPARTA/Augusta study follows Augusta University Medical Center health care workers and students at the Augusta University, hospital workers from the Dental College of Georgia, and residents from the regional Central Savannah River Area communities. The first participant was enrolled on 12 October 2020. As of 1 April 2022, 637 participants were enrolled in the study, and enrollment is ongoing. To date, 108 participants have formally withdrawn or transferred to another study site. Of

all subjects enrolled, 62.1% are female and 37.9% are male. The average age is ~45 years (range, 18 to 85). A total of 49.1% self-identify as white, 10.7% as Asian, 38.2% as African-American, and 2.6% as other or multiple, and 5.2% identify as Hispanic/LatinX. In addition, 49.9% were previously infected or vaccinated at enrollment, and 51.1% were SARS-CoV-2 naive. 177 participants tested positive at enrollment for viral RNA following nasal swab/saliva collection, which is 30% of the cohort. Currently, 25.4% are antibody negative and 74.1% are antibody positive, largely due to vaccination. At each visit, saliva, serum, plasma, and peripheral blood mononuclear cells are collected and cryopreserved.

SPARTA/St. Jude. The SPARTA/St. Jude (SJTRC) study follows hospital employees, with both direct and indirect patient contact, at St. Jude Children's Research Hospital (SJCRH) in Memphis, TN. The first participant was enrolled on 23 April 2020, and of the potential participants who received the study participation email, 1,316 had enrolled as of 28 February 2022. Enrollment is closed for the naive arm of the study but is ongoing for infected individuals. To date, 80 participants have withdrawn from the study, mostly because they no longer work at SJCRH (withdrawal rate, 6%). In all, 73.4% of participants are female, and 26.3% are male. The average age is 43.7 years (range: min., 20; max., 83 years). A total of 80% of the participants self-identified as white, 9% as Asian, 8.1% as African-American, 0.1% as American Indian/Alaska Native, and 2.6% as other or declined to answer. In addition, 3.6% identified as Hispanic/LatinX, and 94.7% identified as non-Hispanic. As of 28 February 2022, of the unvaccinated participants, 6.7% (88) had no infection history, and 2.4% (31) have infection history. Of the vaccinated participants, 77.9% (1,025) have no infection history, 10.6% (139) were infected prior to vaccination, 1.0% (13) were infected during vaccination or $<$14 days following the full course of vaccination, and 1.9% (25) were infected $\geq$14 days following the full course of vaccination. A total of 1,049 participants received BNT162b2 (Pfizer), 135 participants received mRNA-1273 (Moderna), 17 participants received Ad26.COV2.S (J&J), and 1 participant received multiple vaccines. Of the SJTRC participants with serological tests run, 926 individuals are SARS-CoV-2 receptor binding domain (RBD)- and spike IgG antibody-positive, largely due to vaccination. There are 192 participants that have tested positive for viral RNA following nasal swab/saliva collection, which is 14.6% of the SJTRC cohort. Subjects are routinely swabbed as part of an employee screening program and have consented to have those results and their swabs used for study purposes. Symptomatic screening is also performed. For baseline enrollment, plasma and peripheral blood mononuclear cells are collected and cryopreserved. Following a positive PCR test, plasma and peripheral blood mononuclear cells are collected and cryopreserved at acute ($<$day 14), convalescent (~day 28,) and post-convalescent (every subsequent 3 months) time points. Postvaccine time points (approximately day 14 after completion) are also collected for plasma and peripheral blood mononuclear cells.

SPARTA/Los Angeles, CA. The Los Angeles-SPARTA (SPARTA/LA) component of the program is the western-most site of the PARIS/SPARTA network. SPARTA/LA is based at the Lundquist Institute on the Harbor-UCLA Medical Center Campus in southwest Los Angeles County. Participant enrollment was focused on individuals at the intersection of a real-world situation of great concern—high COVID-19 risk and high vaccine hesitancy. In this respect, the recruitment goal was to engage participants likely to have a high risk of SARS-CoV-2 exposure but who represent populations less likely to be vaccinated, including Hispanic/LatinX, Pacific Islanders, and African-American and other underrepresented groups. Participants were enrolled based on results of viral nucleic acid and/or antibody testing and then followed in one of two parallel study cohorts; cohort A followed individuals with documented acute SARS-CoV-2 infection (PCR positive for SARS-CoV-2 RNA) at time of enrollment, and cohort B followed individuals found to be antibody positive due to prior infection or vaccination. The first participant was enrolled on 9 December 2020. As of 28 February 2022, 200 participants were enrolled in the study, and enrollment is complete. To date, 12 participants (6%) have withdrawn from the study. Among enrolled participants, 70%

are female and 30% are male. The mean age of participants is 40.2 years (range, 19 to 77). Racial/ethnic background was 40.5% Hispanic/LatinX, 29% Asian, 16.5% non-Hispanic white, 6.5% African-American, 4% mixed race, 2% Native Hawaiian/Pacific Islander, 0.5% American Indian/Alaskan Native, and 1% other/declined to answer. The vaccination rate in our cohort was 83% as of 28 February 2022; 83% of vaccinated participants received the BNT162b2 (Pfizer) vaccine, 15% received the mRNA-1273 (Moderna) vaccine, and 2% received the Ad26.COV2.S (J&J) vaccine. At enrollment, 18% were antibody negative and 82% were antibody positive (65.5% due to vaccination and 16.5% due to prior SARS-CoV-2 infection). At each study visit, saliva, serum, plasma, and peripheral blood mononuclear cells are collected and cryopreserved.

PARIS/SPARTA INFECTION AND REINFECTION CLASSIFICATION

An important aspect of the PARIS and SPARTA cohorts is the common unified definitions of infection and reinfection, which are applicable both in the pre- as well as postvaccine era. Of note, these temporary working definitions will be continuously refined as we obtain more data from our longitudinal cohorts and as understanding of the immunological and virological dynamics of SARS-CoV-2 infections grows. Our current classification includes distinct categories for seronegative versus seropositive individuals. Factors taken into account are the reliability of diagnostic molecular and serological tests, the time between potential initial infection and reinfection, complete viral genome sequence information, and consistent increase in serum antibody responses. Missing/unobserved data will be taken into account in the future.

SARS-COV-2 infection in a previously seronegative individual. (i) Possible infection. One positive test including any of the following: nucleic acid amplification test (NAAT), rapid antigen test, or serological test (e.g., SARS-CoV-2 IgM/IgG).

(ii) Confirmed infection. A combination of any two positive tests completed, including molecular tests (NAAT), rapid antigen tests, complete viral genome sequencing, clinical diagnosis of COVID-19, or serological assays used in the study (3, 21). With the exception of complete viral genome sequencing, diagnostic tests must be completed on a different biospecimen.

SARS-COV-2 infection in a seropositive individual. (established seroconverted due to infection or vaccination). (i) Possible reinfection. Possible reinfections need to meet one of the following scenarios: (i) Two positive molecular tests (NAAT) at least 90 days apart. (ii) A stable (two measurements at a lower level followed by two measurements at a higher level) 4-fold increase in serum spike antibody titer in individuals who are seropositive. (iii) The combination of a documented positive NAAT for the primary infection and evidence for the second infection being caused by a viral strain that did not exist/circulate in a given region at the time of the first infection (and an unlikely within-host descendant of the previously infecting strain) is also considered as representing a likely reinfection.

(ii) Possible breakthrough infection after vaccination. One positive test including any of the following: NAAT, rapid antigen test, or serological test against nucleoprotein.

(iii) Confirmed reinfection. Two NAAT-confirmed SARS-CoV-2 infections in which both viruses were isolated, sequenced, and determined to be phylogenetically distinct to constitute separate infection events.

(iv) Confirmed breakthrough infection after vaccination. A combination of any two positive tests, including molecular tests (NAAT), rapid antigen tests, complete viral genome sequencing conducted on a different biospecimen, serological test against nucleoprotein, or clinical diagnosis of COVID-19. A change in antibody levels after the infection is also indicative of an infection. Of note, individuals who are seropositive exclusively due to vaccination, will not develop antibodies to regions other than spike (e.g., N protein).

DISCUSSION

We established the PARIS and SPARTA cohorts to study infection with SARS-CoV-2 in seropositive and seronegative participants at high risk for infection. In addition to

defining the durability and variability of antibody responses, we seek to obtain data on the attack rates in both groups, which will inform about the risk of reinfection and help identify the spike antibody titers that correlate with protection in individuals with different histories of exposure to SARS-CoV-2.

The data collected across the studies (some of which started as early as March/April 2020) will provide insights into infection and reinfection with SARS-CoV-2 (23–30) in naive and vaccinated participants, including by variants of concern, once the ongoing analysis is completed.

Many of the PARIS/SPARTA participants are health care workers, who were first in line to be eligible for SARS-CoV-2 vaccination starting in December 2020 and who were also first in line for booster doses in 2021. Thus, vaccination rates in several of the cohorts increased rapidly leading to the conversion of the initial natural infection studies to studies that are suited to characterize the protective effects of vaccines, including immune responses mounted to vaccination in naive individuals and individuals who previously had COVID-19, immune responses to booster doses and breakthrough infections as well as vaccine-induced correlates of protection (31, 32). With the emergence of viral variants of interest/concern, the PARIS/SPARTA cohorts started also to characterize viruses isolated from participants infected after vaccination to determine if viral variants carrying mutations indicative of immune escape are present. To date, data and samples from PARIS/SPARTA have already been used in several studies, including work that determined that only one SARS-CoV-2 mRNA vaccine shot may be necessary in individuals previously infected with COVID-19 (see references to PARIS/SPARTA manuscripts in Table 1). The data collected from PARIS/SPARTA participants also have value as a healthy control group, which can be used as a reference when analyzing immune responses observed in patient populations with specific immunemodulatory comorbidities (e.g., posttransplant patients, patients with B cell malignancies, or patients receiving treatment with biologicals) (33, 34). In addition, cohort samples have been a rich source to study the longevity of infection-induced B-cells in the bone marrow, to study affinity maturation of B-cells after COVID-19 vaccination, to characterize the T-cell response to SARS-CoV-2, etc., and similar studies using PARIS/SPARTA samples are ongoing (22, 35, 36). Currently, samples from PARIS/SPARTA are being extensively used to determine immune responses after booster doses and after breakthrough infections, and assessment of mucosal immune responses in the cohorts is also ongoing (37). Furthermore, samples from the PARIS/SPARTA cohorts have been shared with and used extensively by the SARS-CoV-2 Assessment of Viral Evolution (SAVE) program (38), which was established by the National Institutes of Health to track and characterize variants of concern (39, 40). SAVE investigators have used these samples to track immune escape of different variants from neutralizing antibodies (38).

This study design is unique in that it encompasses eight geographically distinct cohorts exploring specific aspects of viral infections and vaccination using harmonized assays and analysis, which allows for pooling of data from many study participants for robust secondary analysis. However, one limitation is, that the study population consists of mostly health care workers and is in general healthy and younger, with individuals with comorbidities being underrepresented. In the near future, the PARIS/SPARTA cohorts will be uniquely suited to track the kinetics of and protection afforded by vaccine-induced immunity over time, including against novel viral variants, and to investigate how vaccination influences postacute sequelae of COVID-19 (PASC, long COVID-19).

ACKNOWLEDGMENTS

We thank the study participants for their continued generosity and willingness to support COVID-19 research. We thank Teresa Hauguel, Stacy Ferguson, Debbie Bratt, and Diane Post at NIAID for their scientific input and encouragement during these challenging times.

This work is part of the PARIS/SPARTA studies funded by the NIAID Collaborative Influenza Vaccine Innovation Centers (CIVIC) contracts 75N93019C00051 and 75N93019C00052. T.M.R. is

supported by the Georgia Research Alliance as an eminent scholar. We also thank the University of Georgia Clinical and Translational Research Unit (CTRU) for assistance. The CTRU is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR002378. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. SPARTA LA was also supported by the UCLA W. M. Keck Foundation COVID 19 Research Award Program.

The Icahn School of Medicine at Mount Sinai has filed patent applications relating to SARS-CoV-2 serological assays (named inventors, F.K. and V.S.) and Newcastle disease virus-based SARS-CoV-2 vaccines (named inventor, F.K.). F.K. also notes the following, which could be perceived as a conflict of interest: He has previously published work on influenza virus vaccines with S. Gilbert (University of Oxford), has consulted for Curevac, Merck, and Pfizer (before 2020), is currently consulting for Pfizer, Seqirus, Third Rock Ventures, and Avimex; his laboratory is collaborating with Pfizer on animal models for SARS-CoV-2, his laboratory is collaborating with N. Pardi at the University of Pennsylvania on mRNA vaccines against SARS-CoV-2, his laboratory was working in the past with GlaxoSmithKline on the development of influenza virus vaccines, and three of his mentees have recently joined Moderna. R.K. reports consulting fees, honoraria, travel funding, and research support from Illumina, Qiagen, and Perkin Elmer, which manufactures SARS-CoV-2 testing and sequencing kits.

The PARIS/SPARTA study group is ACHILLES (PARIS/St. Louis, MO): Michael K. Klebert, Jackson S. Turner Wooseob, Kim Elizaveta Kalaidina, Rachel M. Presti, Jane A. O'Halloran, Alem Haile, Charles W. Goss, Adriana M. Rauseo, Aaron Schmitz, Tingting Lei; CITY (PARIS/Miami, FL): Erin Williams, Michael Hoffer; PARIS/NYC: Hala Alshammary, Angela A. Amoako, Dalles Andre, Mahmoud H. Awawda, Katherine Beach, Carolina Bermúdez-González, Dominika Bielak, Gianna Y. Cai, Ilaria Ceglia, Christian Cognigni, Charles Gleason, Hisaaki Kawabata, Giulio Kleiner, Neko Lyttle, Wanni Mendez, Lubbertus CF Mulder, Annika Oostenink, Jose Polanco, Ariel Raskin, Aria Rooker, Ashley Salimbangon, Miti Saksena, Gagandeep Singh, Levy Sominsky, Johnstone Tcheou; IASO (PARIS/Ann Arbor, MI): Theresa Kowalski-Dobson, Carmen Gherasim, Emily Stoneman, Yoshihiro Kawaoka, Peter Halfman, Kevin Bakker, Victoria Blanc, Savanna Sneeringer, Joe Paulauskis, Jamie Bird, Lauren Warsinske, Mahboob Chowdhury, Dawson Davis, Alyssa Meyers, Kathleen Lindsey, Rebecca Tutino; SPARTA/Athens, GA: Brittany Baker, Charlotte Bolle, Debbie Bratt, Courtney Briggs, Lillian Buescher, Jasmine Burris, Jordan Byrne, Michael Carlock, Patrick Fagan, Jasper Gattiker, Naveen Gokanapudi, Omar Hamwy, Tejal Hill, Lauren Howland, Hana Ji, Katie Mailloux, Brad Phillips, Kimberly Schmitz, Hua Shi, Cleopatria Smith, Terrie Waits, Emma Whitesell; SPARTA/St. Jude: E. Kaitlynn Allen, Kim Allison, Hana Hakim, Randall T. Hayden, Diego R. Hijano, James Hoffman, Maureen A McGargill, Tomi Mori, Li Tang, Elaine Tuomanen, Richard Webby, Resha Bajracharya, Sean Cherry, Brandi L Clark, Ronald H. Dallas, Thomas Fabrizio, Jason Hodges, Ashleigh Gowen, Chun-Yang Lin, Jamie Russell-Bell, James Sparks, David E. Wittman, Lee-Ann Van de Velde, Taylor L Wilson, Ericka Kirkpatrick Roubidoux, Valerie Cortez, Pamela Freiden, Nicholas Wohlgemuth, Kendall Whitt; SPARTA/Augusta, GA: Jaspreet Farmaha, Jeffrey N James, Caroline Marie Carlock, Drew Fransoso, Ashis Mondal, Nikhil Sahajpal, Lara Churchwell, Kimya Jones, Sudha Ananth, Colin Williams, Reeya Patel, Patty Ray, Bradshaw Danielle, Justin Moore; SPARTA/Los Angeles, CA: Evelyn Flores, Deborah Kupferwasser, Prudencio Merino, Donna Phan Tran, Meagan M. Jenkins; PARIS/Chicago, IL: Qifang Bi.

REFERENCES

1. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 588:E6. https://doi.org/10.1038/s41586-020-2951-z.
2. Krammer F, Simon V. 2020. Serology assays to manage COVID-19. Science 368:1060–1061. https://doi.org/10.1126/science.abc1227.
3. Amanat F, Stadlbauer D, Strohmeier S, Nguyen THO, Chromikova V, McMahon M, Jiang K, Arunkumar GA, Jurczyszak D, Polanco J, Bermudez-Gonzalez M, Kleiner G, Aydillo T, Miorin L, Fierer DS, Lugo LA, Kojic EM, Stoever J, Liu STH, Cunningham-Rundles C, Felgner PL, Moran T, García-Sastre A, Caplivski D, Cheng AC, Kedzierska K, Vapalahti O, Hepojoki JM, Simon V, Krammer F. 2020. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nat Med 26:1033–1036. https://doi.org/10.1038/s41591-020-0913-5.

4. Okba NMA, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, Lamers MM, Sikkema RS, de Bruin E, Chandler FD, Yazdanpanah Y, Le Hingrat Q, Descamps D, Houhou-Fidouh N, Reusken CBEM, Bosch BJ, Drosten C, Koopmans MPG, Haagmans BL. 2020. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease 2019 patients. Emerg Infect Dis 26:1478–1488. https://doi.org/10.3201/eid2607.200841.
5. Deng W, Bao L, Liu J, Xiao C, Liu J, Xue J, Lv Q, Qi F, Gao H, Yu P, Xu Y, Qu Y, Li F, Xiang Z, Yu H, Gong S, Liu M, Wang G, Wang S, Song Z, Liu Y, Zhao W, Han Y, Zhao L, Liu X, Wei Q, Qin C. 2020. Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. Science 369:818–823. https://doi.org/10.1126/science.abc5343.
6. Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, Tostanoski LH, Yu J, Maliga Z, Nekorchuk M, Busman-Sahay K, Terry M, Wrijil LM, Ducat S, Martinez DR, Atyeo C, Fischinger S, Burke JS, Slein MD, Pessaint L, Van Ry A, Greenhouse J, Taylor T, Blade K, Cook A, Finneyfrock B, Brown R, Teow E, Velasco J, Zahn R, Wegmann F, Abbink P, Bondzie EA, Dagotto G, Gebre MS, He X, Jacob-Dolan C, Kordana N, Li Z, Lifton MA, Mahrokhian SH, Maxfield LF, Nityanandam R, Nkolola JP, Schmidt AG, Miller AD, Baric RS, Alter G, Sorger PK, Estes JD, et al. 2020. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science 369:812–817. https://doi.org/10.1126/science.abc4776.
7. McMahan K, Yu J, Mercado NB, Loos C, Tostanoski LH, Chandrashekar A, Liu J, Peter L, Atyeo C, Zhu A, Bondzie EA, Dagotto G, Gebre MS, Jacob-Dolan C, Li Z, Nampanya F, Patel S, Pessaint L, Van Ry A, Blade K, Yalley-Ogunro J, Cabus M, Brown R, Cook A, Teow E, Andersen H, Lewis MG, Lauffenburger DA, Alter G, Barouch DH. 2021. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature 590:630–634. https://doi.org/10.1038/s41586-020-03041-6.
8. Yu J, Tostanoski LH, Peter L, Mercado NB, McMahan K, Mahrokhian SH, Nkolola JP, Liu J, Li Z, Chandrashekar A, Martinez DR, Loos C, Atyeo C, Fischinger S, Burke JS, Slein MD, Chen Y, Zuiani A, Lelis FJN, Travers M, Habibi S, Pessaint L, Van Ry A, Blade K, Brown R, Cook A, Finneyfrock B, Dodson A, Teow E, Velasco J, Zahn R, Wegmann F, Bondzie EA, Dagotto G, Gebre MS, He X, Jacob-Dolan C, Kirilova M, Kordana N, Lin Z, Maxfield LF, Nampanya F, Nityanandam R, Ventura JD, Wan H, Cai Y, Chen B, Schmidt AG, Wesemann DR, Baric RS, et al. 2020. DNA vaccine protection against SARS-CoV-2 in rhesus macaques. Science 369:806–811. https://doi.org/10.1126/science.abc6284.
9. Tillett RL, Sevinsky JR, Hartley PD, Kerwin H, Crawford N, Gorzalski A, Laverdure C, Verma SC, Rossetto CC, Jackson D, Farrell MJ, Van Hooser S, Pandori M. 2021. Genomic evidence for reinfection with SARS-CoV-2: a case study. Lancet Infect Dis 21:52–58. https://doi.org/10.1016/S1473-3099(20)30764-7.
10. To KK, Hung IF, Ip JD, Chu AW, Chan WM, Tam AR, Fong CH, Yuan S, Tsoi HW, Ng AC, Lee LL, Wan P, Tso E, To WK, Tsang D, Chan KH, Huang JD, Kok KH, Cheng VC, Yuen KY. 2020. Coronavirus disease 2019 (COVID-19) re-infection by a phylogenetically distinct severe acute respiratory syndrome coronavirus 2 strain confirmed by whole genome sequencing. Clin Infect Dis 73:e2946–e2951. https://doi.org/10.1093/cid/ciaa1275.
11. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, Hu JL, Xu W, Zhang Y, Lv FJ, Su K, Zhang F, Gong J, Wu B, Liu XM, Li JJ, Qiu JF, Chen J, Huang AL. 2020. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med 26:1200–1204. https://doi.org/10.1038/s41591-020-0965-6.
12. Edridge AWD, Kaczorowska J, Hoste ACR, Bakker M, Klein M, Loens K, Jebbink MF, Matser A, Kinsella CM, Rueda P, Ieven M, Goossens H, Prins M, Sastre P, Deijs M, van der Hoek L. 2020. Seasonal coronavirus protective immunity is short-lasting. Nat Med 26:1691–1693. https://doi.org/10.1038/s41591-020-1083-1.
13. Petrie JG, Bazzi LA, McDermott AB, Follmann D, Esposito D, Hatcher C, Mateja A, Narpala SR, O'Connell SE, Martin ET, Monto AS. 2021. Coronavirus occurrence in the household influenza vaccine evaluation (HIVE) cohort of Michigan households: reinfection frequency and serologic responses to seasonal and severe acute respiratory syndrome coronaviruses. J Infect Dis 224:49–59. https://doi.org/10.1093/infdis/jiab161.
14. Eguia RT, Crawford KHD, Stevens-Ayers T, Kelnhofer-Millevolte L, Greninger AL, Englund JA, Boeckh MJ, Bloom JD. 2021. A human coronavirus evolves antigenically to escape antibody immunity. PLoS Pathog 17:e1009453. https://doi.org/10.1371/journal.ppat.1009453.
15. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, Doolabh D, Pillay S, San EJ, Msomi N, Mlisana K, von Gottberg A, Walaza S, Allam M, Ismail A, Mohale T, Glass AJ, Engelbrecht S, Van Zyl G, Preiser W, Petruccione F, Sigal A, Hardie D, Marais G, Hsiao M, Korsman S, Davies M-A, Tyers L, Mudau I, York D, Maslo C, Goedhals D, Abrahams S, Laguda-Akingba O, Alisoltani-Dehkordi A, Godzik A, Wibmer CK, Sewell BT, Lourenço J, Alcantara LCJ, Pond SLK, Weaver S, Martin D, Lessells RJ, Bhiman JN, Williamson C, de Oliveira T. 2020. Emergence and rapid spread of a new severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) lineage with multiple spike mutations in South Africa. medRxiv https://doi.org/10.1101/2020.12.21.20248640.
16. Public Health England. 2021. Investigation of novel SARS-CoV-2 variant: variant of concern 202012/01. Technical briefing 5. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/959426/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5.pdf.
17. Davies NG, Abbott S, Barnard RC, Jarvis CI, Kucharski AJ, Munday JD, Pearson CAB, Russell TW, Tully DC, Washburne AD, Wenseleers T, Gimma A, Waites W, Wong KLM, van Zandvoort K, Silverman JD, Diaz-Ordaz K, Keogh R, Eggo RM, Funk S, Jit M, Atkins KE, Edmunds WJ, CMMID COVID-19 Working Group, COVID-19 Genomics UK (COG-UK) Consortium. 2021. Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. Science 372:eabg3055. https://doi.org/10.1126/science.abg3055.
18. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, Crispim MAE, Sales FCS, Hawryluk I, McCrone JT, Hulswit RJG, Franco LAM, Ramundo MS, de Jesus JG, Andrade PS, Coletti TM, Ferreira GM, Silva CAM, Manuli ER, Pereira RHM, Peixoto PS, Kraemer MUG, Gaburo N, Camilo CDC, Hoeltgebaum H, Souza WM, Rocha EC, de Souza LM, de Pinho MC, Araujo LJT, Malta FSV, de Lima AB, Silva JDP, Zauli DAG, Ferreira ACS, Schnekenberg RP, Laydon DJ, Walker PGT, Schlüter HM, Dos Santos ALP, Vidal MS, Del Caro VS, Filho RMF, Dos Santos HM, Aguiar RS, Proença-Modena JL, Nelson B, Hay JA, Monod M, Miscouridou X, et al. 2021. Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science 372:815–821. https://doi.org/10.1126/science.abh2644.
19. Viana R, Moyo S, Amoako DG, Tegally H, Scheepers C, Althaus CL, Anyaneji UJ, Bester PA, Boni MF, Chand M, Choga WT, Colquhoun R, Davids M, Deforche K, Doolabh D, Engelbrecht S, Everatt J, Giandhari J, Giovanetti M, Hardie D, Hill V, Hsiao N-Y, Iranzadeh A, Ismail A, Joseph C, Joseph R, Koopile L, Pond SLK, Kraemer MU, Kuate-Lere L, Laguda-Akingba O, Lesetedi-Mafoko O, Lessells RJ, Lockman S, Lucaci AG, Maharaj A, Mahlangu B, Maponga T, Mahlakwane K, Makatini Z, Marais G, Maruapula D, Masupu K, Matshaba M, Mayaphi S, Mbhele N, Mbulawa MB, Mendes A, Mlisana K, Mnguni A, et al. 2021. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. medRxiv 603:679–686. https://doi.org/10.1038/s41586-022-04411-y.
20. Liu Y, Rocklöv J. 2021. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med 28:taab124. https://doi.org/10.1093/jtm/taab124.
21. Stadlbauer D, Amanat F, Chromikova V, Jiang K, Strohmeier S, Arunkumar GA, Tan J, Bhavsar D, Capuano C, Kirkpatrick E, Meade P, Brito RN, Teo C, McMahon M, Simon V, Krammer F. 2020. SARS-CoV-2 seroconversion in humans: a detailed protocol for a serological assay, antigen production, and test setup. Curr Protoc Microbiol 57:e100. https://doi.org/10.1002/cpmc.100.
22. Turner JS, Kim W, Kalaidina E, Goss CW, Rauseo AM, Schmitz AJ, Hansen L, Haile A, Klebert MK, Pusic I, O'Halloran JA, Presti RM, Ellebedy AH. 2021. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. Nature 595:421–425. https://doi.org/10.1038/s41586-021-03647-4.
23. Hall V, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, Wellington E, Cole MJ, Saei A, Oguti B, Munro K, Wallace S, Kirwan PD, Shrotri M, Vusirikala A, Rokadiya S, Kall M, Zambon M, Ramsay M, Brooks T, Brown CS, Chand MA, Hopkins S. 2021. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020. medRxiv https://doi.org/10.1101/2021.01.13.21249642.
24. Pilz S, Chakeri A, Ioannidis JP, Richter L, Theiler-Schwetz V, Trummer C, Krause R, Allerberger F. 2021. SARS-CoV-2 re-infection risk in Austria. Eur J Clin Invest 51:e13520. https://doi.org/10.1111/eci.13520.
25. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A, Hatch SB, Marsden BD, Cox S, James T, Warren F, Peck LJ, Ritter TG, de Toledo Z, Warren L, Axten D, Cornall RJ, Jones EY, Stuart DI, Screaton G, Ebner D, Hoosdally S, Chand M, Crook DW, O'Donnell A-M, Conlon CP, Pouwels KB, Walker AS, Peto TEA, Hopkins S, Walker TM, Jeffery K, Eyre DW, Oxford University Hospitals Staff Testing Group. 2021. Antibody status and incidence of SARS-CoV-2 infection in health care workers. N Engl J Med 384:533–540. https://doi.org/10.1056/NEJMoa2034545.
26. Letizia AG, Ge Y, Vangeti S, Goforth C, Weir DL, Kuzmina NA, Chen HW, Ewing D, Soares-Schanoski A, George M-C, Graham WD, Jones F, Bharaj P, Lizewski RA, Lizewski SA, Marayag J, Marjanovic N, Miller C, Mofsowitz S,

Nair VD, Nunez E, Parent DM, Porter CK, Ana ES, Schilling M, Stadlbauer D, Sugiharto V, Termini M, Sun P, Tracy RP, Krammer F, Bukreyev A, Ramos I, Sealfon SC. 2021. SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study. medRxiv https://doi.org/10.1101/2021.01.26.21250535.
27. Sheehan MM, Reddy AJ, Rothberg MB. 2021. Reinfection rates among patients who previously tested positive for coronavirus disease 2019: a retrospective cohort study. Clinical Infectious Diseases 73:1882–1886. https://doi.org/10.1093/cid/ciab234.
28. Hansen CH, Michlmayr D, Gubbels SM, Mølbak K, Ethelberg S. 2021. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet 397:P1204–P1212. https://doi.org/10.1016/S0140-6736(21)00575-4.
29. Harvey RA, Rassen JA, Kabelac CA, Turenne W, Leonard S, Klesh R, Meyer WA, Kaufman HW, Anderson S, Cohen O, Petkov VI, Cronin KA, Van Dyke AL, Lowy DR, Sharpless NE, Penberthy LT. 2021. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. JAMA Intern Med 181:672. https://doi.org/10.1001/jamainternmed.2021.0366.
30. Addetia A, Crawford KHD, Dingens A, Zhu H, Roychoudhury P, Huang ML, Jerome KR, Bloom JD, Greninger AL. 2020. Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with a high attack rate. J Clin Microbiol 58:e02107-20. https://doi.org/10.1128/JCM.02107-20.
31. Forgacs D, Jang H, Abreu RB, Hanley HB, Gattiker JL, Jefferson AM, Ross TM. 2021. Functional characterization of SARS-CoV-2 vaccine elicited antibodies in immunologically naïve and pre-immune humans. bioRxiv https://doi.org/10.1101/2021.05.29.445137.
32. Krammer F, Srivastava K, Alshammary H, Amoako AA, Awawda MH, Beach KF, Bermúdez-González MC, Bielak DA, Carreño JM, Chernet RL, Eaker LQ, Ferreri ED, Floda DL, Gleason CR, Hamburger JZ, Jiang K, Kleiner G, Jurczyszak D, Matthews JC, Mendez WA, Nabeel I, Mulder LCF, Raskin AJ, Russo KT, Salimbangon AT, Saksena M, Shin AS, Singh G, Sominsky LA, Stadlbauer D, Wajnberg A, Simon V. 2021. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. N Engl J Med 384:1372–1374. https://doi.org/10.1056/NEJMc2101667.
33. Aleman A, Upadhyaya B, Tuballes K, Kappes K, Gleason CR, Beach K, Agte S, Srivastava K, PVI/Seronet Study Group, Van Oekelen O, Barcessat V, Bhardwaj N, Kim-Schulze S, Gnjatic S, Brown B, Cordon-Cardo C, Krammer F, Merad M, Jagannath S, Wajnberg A, Simon V, Parekh S. 2021. Variable cellular responses to SARS-CoV-2 in fully vaccinated patients with multiple myeloma. Cancer Cell 39:1442–1444. https://doi.org/10.1016/j.ccell.2021.09.015.
34. Van Oekelen O, Gleason CR, Agte S, Srivastava K, Beach KF, Aleman A, Kappes K, Mouhieddine TH, Wang B, Chari A, Cordon-Cardo C, Krammer F, Jagannath S, Simon V, Wajnberg A, Parekh S, PVI/Seronet team. 2021. Highly variable SARS-CoV-2 spike antibody responses to two doses of COVID-19 RNA vaccination in patients with multiple myeloma. Cancer Cell 39:1028–1030. https://doi.org/10.1016/j.ccell.2021.06.014.
35. Turner JS, O'Halloran JA, Kalaidina E, Kim W, Schmitz AJ, Zhou JQ, Lei T, Thapa M, Chen RE, Case JB, Amanat F, Rauseo AM, Haile A, Xie X, Klebert MK, Suessen T, Middleton WD, Shi PY, Krammer F, Teefey SA, Diamond MS, Presti RM, Ellebedy AH. 2021. SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. Nature 596:109–113. https://doi.org/10.1038/s41586-021-03738-2.
36. Minervina AA, Pogorelyy MV, Kirk AM, Allen EK, Allison KJ, Lin C-Y, Brice DC, Zhu X, Vegesana K, Wu G, Crawford JC, Schultz-Cherry S, Estepp JH, McGargill MA, Wolf J, Thomas PG, SJTRC Study Team. 2021. Convergent epitope-specific T cell responses after SARS-CoV-2 infection and vaccination. medRxiv https://doi.org/10.1101/2021.07.12.21260227.
37. Sano K, Bhavsar D, Singh G, Floda D, Srivastava K, Gleason C, Carreño JM, Simon V, Krammer F, PARIS Study Group. 2021. Efficient mucosal antibody response to SARS-CoV-2 vaccination is induced in previously infected individuals. medRxiv https://doi.org/10.1101/2021.12.06.21267352.
38. DeGrace MM, Ghedin E, Frieman MB, Krammer F, Grifoni A, Alisoltani A, Alter G, Amara RR, Baric RS, Barouch DH, Bloom JD, Bloyet L-M, Bonenfant G, Boon ACM, Boritz EA, Bratt DL, Bricker TL, Brown L, Buchser WJ, Carreño JM, Cohen-Lavi L, Darling TL, Davis-Gardner ME, Dearlove BL, Di H, Dittmann M, Doria-Rose NA, Douek DC, Drosten C, Edara V-V, Ellebedy A, Fabrizio TP, Ferrari G, Florence WC, Fouchier RAM, Franks J, García-Sastre A, Godzik A, Gonzalez-Reiche AS, Gordon A, Haagmans BL, Halfmann PJ, Ho DD, Holbrook MR, Huang Y, James SL, Jaroszewski L, Jeevan T, Johnson RM, Jones TC, et al. 2022. Defining the risk of SARS-CoV-2 variants on immune protection. Nature https://doi.org/10.1038/s41586-022-04690-5.
39. Carreño JM, Alshammary H, Singh G, Raskin A, Amanat F, Amoako A, Gonzalez-Reiche AS, van de Guchte A, Study Group P, Srivastava K, Sordillo EM, Sather DN, van Bakel H, Krammer F, Simon V. 2021. Evidence for retained spike-binding and neutralizing activity against emerging SARS-CoV-2 variants in serum of COVID-19 mRNA vaccine recipients. EBioMedicine 73:103626. https://doi.org/10.1016/j.ebiom.2021.103626.
40. Carreño JM, Alshammary H, Tcheou J, Singh G, Raskin AJ, Kawabata H, Sominsky LA, Clark JJ, Adelsberg DC, Bielak DA, Gonzalez-Reiche AS, Dambrauskas N, Vigdorovich V, Alburquerque B, Amoako AA, Banu R, Beach KF, Bermúdez-González MC, Cai GY, Ceglia I, Cognigni C, Farrugia K, Gleason CR, van de Guchte A, Kleiner G, Khalil Z, Lyttle N, Mendez WA, Mulder LCF, Oostenink A, Rooker A, Salimbangon AT, Saksena M, Paniz-Mondolfi AE, Polanco J, Srivastava K, Sather DN, Sordillo EM, Bajic G, van Bakel H, Simon V, Krammer F, PSP-PARIS Study Group. 2022. Activity of convalescent and vaccine serum against SARS-CoV-2 Omicron. Nature 602:682–688. https://doi.org/10.1038/d41586-021-03846-z.
41. Kim W, Zhou JQ, Sturtz AJ, Horvath SC, Schmitz AJ, Lei T, Kalaidina E, Thapa M, Alsoussi WB, Haile A, Klebert MK, Suessen T, Parra-Rodriguez L, Mudd PA, Middleton WD, Teefey SA, Pusic I, O'Halloran JA, Presti RM, Turner JS, Ellebedy AH. 2021. Germinal centre-driven maturation of B cell response to SARS-CoV-2 vaccination. bioRxiv https://doi.org/10.1101/2021.10.31.466651.
42. Schmitz AJ, Turner JS, Liu Z, Zhou JQ, Aziati ID, Chen RE, Joshi A, Bricker TL, Darling TL, Adelsberg DC, Altomare CG, Alsoussi WB, Case JB, VanBlargan LA, Lei T, Thapa M, Amanat F, Jeevan T, Fabrizio T, O'Halloran JA, Shi PY, Presti RM, Webby RJ, Krammer F, Whelan SPJ, Bajic G, Diamond MS, Boon ACM, Ellebedy AH. 2021. A vaccine-induced public antibody protects against SARS-CoV-2 and emerging variants. Immunity 54:2159–2166.e6. https://doi.org/10.1016/j.immuni.2021.08.013.
43. Deepak P, Kim W, Paley MA, Yang M, Carvidi AB, Demissie EG, El-Qunni AA, Haile A, Huang K, Kinnett B, Liebeskind MJ, Liu Z, McMorrow LE, Paez D, Pawar N, Perantie DC, Schriefer RE, Sides SE, Thapa M, Gergely M, Abushamma S, Akuse S, Klebert M, Mitchell L, Nix D, Graf J, Taylor KE, Chahin S, Ciorba MA, Katz P, Matloubian M, O'Halloran JA, Presti RM, Wu GF, Whelan SPJ, Buchser WJ, Gensler LS, Nakamura MC, Ellebedy AH, Kim AHJ. 2021. Effect of immunosuppression on the immunogenicity of mRNA vaccines to SARS-CoV-2: a prospective cohort study. Ann Intern Med 174:1572–1585. https://doi.org/10.7326/M21-1757.
44. Reynolds D, Vazquez Guillamet C, Day A, Borcherding N, Vazquez Guillamet R, Choreño-Parra JA, House SL, O'Halloran JA, Zúñiga J, Ellebedy AH, Byers DE, Mudd PA. 2021. Comprehensive immunologic evaluation of bronchoalveolar lavage samples from human patients with moderate and severe seasonal influenza and severe COVID-19. J Immunol 207:1229–1238. https://doi.org/10.4049/jimmunol.2100294.
45. Lin CY, Wolf J, Brice DC, Sun Y, Locke M, Cherry S, Castellaw AH, Wehenkel M, Crawford JC, Zarnitsyna VI, Duque D, Allison KJ, Allen EK, Brown SA, Mandarano AH, Estepp JH, Taylor C, Molina-Paris C, Schultz-Cherry S, Tang L, Thomas PG, McGargill MA, SJTRC Study Team. 2021. Pre-existing humoral immunity to human common cold coronaviruses negatively impacts the protective SARS-CoV-2 antibody response. Cell Host Microbe 30:83–96.e4. https://doi.org/10.1016/j.chom.2021.12.005.
46. Tang L, Cherry S, Tuomanen EI, Roubidoux EK, Lin CY, Allison KJ, Gowen A, Freiden P, Allen EK, Su Y, Gaur AH, Estepp JH, McGargill MA, Krammer F, Thomas PG, Schultz-Cherry S, Wolf J, St. Jude Investigative Team. 2021. Host predictors of broadly cross-reactive antibodies against SARS-CoV-2 variants of concern differ between infection and vaccination. Clin Infect Dis https://doi.org/10.1093/cid/ciab996.
47. Schultz-Cherry S, McGargill MA, Thomas PG, Estepp JH, Gaur AH, Allen EK, Allison KJ, Tang L, Webby RJ, Cherry SD, Lin CY, Fabrizio T, Tuomanen EI, Wolf J, SJTRC Investigative Team. 2021. Cross-reactive antibody response to mRNA SARS-CoV-2 vaccine after recent COVID-19-specific monoclonal antibody therapy. Open Forum Infect Dis 8:ofab420. https://doi.org/10.1093/ofid/ofab420.
48. Wohlgemuth N, Whitt K, Cherry S, Kirkpatrick Roubidoux E, Lin CY, Allison KJ, Gowen A, Freiden P, Allen EK, Gaur AH, Estepp JH, Tang L, Mori T, Hijano DR, Hakim H, McGargill MA, Krammer F, Whitt MA, Wolf J, Thomas PG, Schultz-Cherry S, St. Jude Investigative Team. 2021. An assessment of serological assays for SARS-CoV-2 as surrogates for authentic virus neutralization. Microbiol Spectr 9:e0105921. https://doi.org/10.1128/Spectrum.01059-21.
49. Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, Grifoni A, Ramirez SI, Haupt S, Frazier A, Nakao C, Rayaprolu V, Rawlings SA, Peters B, Krammer F, Simon V, Saphire EO, Smith DM, Weiskopf D, Sette A, Crotty S. 2021. Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 371:eabf4063. https://doi.org/10.1126/science.abf4063.

50. Jangra S, Ye C, Rathnasinghe R, Stadlbauer D, Krammer F, Simon V, Martinez-Sobrido L, García-Sastre A, Schotsaert M, Personalized Virology Initiative study group. 2021. SARS-CoV-2 spike E484K mutation reduces antibody neutralisation. Lancet Microbe 2:e283–e284. https://doi.org/10.1016/S2666-5247(21)00068-9.
51. Frieman M, Harris AD, Herati RS, Krammer F, Mantovani A, Rescigno M, Sajadi MM, Simon V. 2021. SARS-CoV-2 vaccines for all but a single dose for COVID-19 survivors. EBioMedicine 68:103401. https://doi.org/10.1016/j.ebiom.2021.103401.
52. Forgacs D, Jang H, Abreu RB, Hanley HB, Gattiker JL, Jefferson AM, Ross TM. 2021. SARS-CoV-2 mRNA vaccines elicit different responses in immunologically naïve and pre-immune humans. Front Immunol 12:728021. https://doi.org/10.3389/fimmu.2021.728021.
53. Tang J, Grubbs G, Lee Y, Huang C, Ravichandran S, Forgacs D, Golding H, Ross TM, Khurana S. 2021. Antibody affinity maturation and cross-variant activity following SARS-CoV-2 mRNA vaccination: impact of prior exposure and sex. EBioMedicine 74:103748. https://doi.org/10.1016/j.ebiom.2021.103748.
54. Forgacs D, Moraes VS, Hanley HB, Gattiker JL, Jefferson AM, Ross TM. 2022. The effect of waning on antibody levels and memory B cell recall following SARS-CoV-2 infection or vaccination. bioRxiv https://doi.org/10.1101/2022.03.16.484099.
55. Sahajpal NS, Mondal AK, Njau A, Petty Z, Chen J, Ananth S, Ahluwalia P, Williams C, Ross TM, Chaubey A, DeSantis G, Schroth GP, Bahl J, Kolhe R. 2021. High-throughput next-generation sequencing respiratory viral panel: a diagnostic and epidemiologic tool for SARS-CoV-2 and other viruses. Viruses 13:2063. https://doi.org/10.3390/v13102063.
56. Sahajpal NS, Mondal AK, Ananth S, Njau A, Fulzele S, Ahaluwalia P, Chaubey A, Hegde M, Rojiani AM, Kolhe R. 2021. Making a difference: adaptation of the clinical laboratory in response to the rapidly evolving COVID-19 pandemic. Acad Pathol 8:23742895211023948. https://doi.org/10.1177/23742895211023948.
57. Sahajpal NS, Mondal AK, Ananth S, Njau A, Ahluwalia P, Kota V, Caspary K, Ross TM, Farrell M, Shannon MP, Fulzele S, Chaubey A, Hegde M, Rojiani AM, Kolhe R. 2021. Clinical validation of a sensitive test for saliva collected in healthcare and community settings with pooling utility for severe acute respiratory syndrome coronavirus 2 mass surveillance. J Mol Diagn 23:788–795. https://doi.org/10.1016/j.jmoldx.2021.04.005.
58. Moore JX, Gilbert KL, Lively KL, Laurent C, Chawla R, Li C, Johnson R, Petcu R, Mehra M, Spooner A, Kolhe R, Ledford CJW. 2021. Correlates of COVID-19 vaccine hesitancy among a community sample of African Americans living in the southern United States. Vaccines (Basel) 9:879. https://doi.org/10.3390/vaccines9080879.
59. Sahajpal NS, Mondal AK, Ananth S, Njau A, Ahluwalia P, Newnam G, Lozoya-Colinas A, Hud NV, Kota V, Ross TM, Reid MD, Fulzele S, Chaubey A, Hegde M, Rojiani AM, Kolhe R. 2021. SalivaSTAT: direct-PCR and pooling of saliva samples collected in healthcare and community setting for SARS-CoV-2 mass surveillance. Diagnostics (Basel) 11:904. https://doi.org/10.3390/diagnostics11050904.
60. Imai M, Halfmann PJ, Yamayoshi S, Iwatsuki-Horimoto K, Chiba S, Watanabe T, Nakajima N, Ito M, Kuroda M, Kiso M, Maemura T, Takahashi K, Loeber S, Hatta M, Koga M, Nagai H, Yamamoto S, Saito M, Adachi E, Akasaka O, Nakamura M, Nakachi I, Ogura T, Baba R, Fujita K, Ochi J, Mitamura K, Kato H, Nakajima H, Yagi K, Hattori SI, Maeda K, Suzuki T, Miyazato Y, Valdez R, Gherasim C, Furusawa Y, Okuda M, Ujie M, Lopes TJS, Yasuhara A, Ueki H, Sakai-Tagawa Y, Eisfeld AJ, Baczenas JJ, Baker DA, O'Connor SL, O'Connor DH, Fukushi S, Fujimoto T, et al. 2021. Characterization of a new SARS-CoV-2 variant that emerged in Brazil. Proc Natl Acad Sci U S A 118:e2106535118. https://doi.org/10.1073/pnas.2106535118.
61. Halfmann PJ, Kuroda M, Armbrust T, Accola M, Valdez R, Kowalski-Dobson T, Rehrauer W, Gordon A, Kawaoka Y. 2022. Long-term, infection-acquired immunity against the SARS-CoV-2 Delta variant in a hamster model. Cell Rep 38:110394. https://doi.org/10.1016/j.celrep.2022.110394.