

Effect of Immunosuppression on the Immunogenicity of mRNA Vaccines to SARS-CoV-2

A Prospective Cohort Study

Parakkal Deepak, MBBS, MS*; Woeseob Kim, PhD*; Michael A. Paley, MD, PhD*; Monica Yang, MD; Alexander B. Carvidi, BA; Emanuel G. Demissie, BS; Alia A. El-Qunni, BS; Alem Haile, BS; Katherine Huang, BA; Baylee Kinnett, BS; Mariel J. Liebeskind, BA; Zhuoming Liu, PhD; Lily E. McMorrow, BA; Diana Paez, BS; Niti Pawar, BA; Dana C. Perantie, MPH; Rebecca E. Schrieffer, BA; Shannon E. Sides, BA; Mahima Thapa, BS; Maté Gergely, MD; Suha Abushamma, MD; Sewuese Akuse, MBBS, MPH; Michael Klebert, PhD, RN, ANP-BC; Lynne Mitchell, MA, MS; Darren Nix; Jonathan Graf, MD; Kimberly E. Taylor, PhD, MPH; Salim Chahin, MD, MSCE; Matthew A. Ciorba, MD; Patricia Katz, PhD; Mehrdad Matlobian, MD, PhD; Jane A. O'Halloran, MD, PhD; Rachel M. Presti, MD, PhD; Gregory F. Wu, MD, PhD; Sean P.J. Whelan, PhD; William J. Buchser, PhD; Lianne S. Gensler, MD; Mary C. Nakamura, MD; Ali H. Ellebedy, PhD†; and Alfred H.J. Kim, MD, PhD†

Background: Patients with chronic inflammatory disease (CID) treated with immunosuppressive medications have increased risk for severe COVID-19. Although mRNA-based SARS-CoV-2 vaccination provides protection in immunocompetent persons, immunogenicity in immunosuppressed patients with CID is unclear.

Objective: To determine the immunogenicity of mRNA-based SARS-CoV-2 vaccines in patients with CID.

Design: Prospective observational cohort study.

Setting: Two U.S. CID referral centers.

Participants: Volunteer sample of adults with confirmed CID eligible for early COVID-19 vaccination, including hospital employees of any age and patients older than 65 years. Immunocompetent participants were recruited separately from hospital employees. All participants received 2 doses of mRNA vaccine against SARS-CoV-2 between 10 December 2020 and 20 March 2021. Participants were assessed within 2 weeks before vaccination and 20 days after final vaccination.

Measurements: Anti-SARS-CoV-2 spike (S) IgG⁺ binding in all participants, and neutralizing antibody titers and circulating S-specific plasmablasts in a subset to assess humoral response after vaccination.

Results: Most of the 133 participants with CID (88.7%) and all 53 immunocompetent participants developed antibodies in response to mRNA-based SARS-CoV-2 vaccination, although some with CID developed numerically lower titers of anti-S IgG. Anti-S IgG antibody titers after vaccination were lower in participants with CID receiving glucocorticoids ($n = 17$) than in those not receiving them; the geometric mean of anti-S IgG

antibodies was 357 (95% CI, 96 to 1324) for participants receiving prednisone versus 2190 (CI, 1598 to 3002) for those not receiving it. Anti-S IgG antibody titers were also lower in those receiving B-cell depletion therapy (BCDT) ($n = 10$). Measures of immunogenicity differed numerically between those who were and those who were not receiving antimetabolites ($n = 48$), tumor necrosis factor inhibitors ($n = 39$), and Janus kinase inhibitors ($n = 11$); however, 95% CIs were wide and overlapped. Neutralization titers seemed generally consistent with anti-S IgG results. Results were not adjusted for differences in baseline clinical factors, including other immunosuppressant therapies.

Limitations: Small sample that lacked demographic diversity, and residual confounding.

Conclusion: Compared with nonusers, patients with CID treated with glucocorticoids and BCDT seem to have lower SARS-CoV-2 vaccine-induced antibody responses. These preliminary findings require confirmation in a larger study.

Primary Funding Source: The Leona M. and Harry B. Helmsley Charitable Trust, Marcus Program in Precision Medicine Innovation, National Center for Advancing Translational Sciences, and National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Ann Intern Med. 2021;174:1572-1585. doi:10.7326/M21-1757 **Annals.org**
For author, article, and disclosure information, see end of text.

This article was published at Annals.org on 31 August 2021.

* Drs. Deepak, Kim, and Paley contributed equally to this work and share first authorship.

† Drs. Ellebedy and Kim contributed equally to this work and share senior authorship.

The global COVID-19 pandemic, caused by SARS-CoV-2, has infected an estimated 177 million people worldwide, causing 3.8 million deaths and widespread

See also:

Web-Only
Supplement

economic devastation (1). Three vaccines against SARS-CoV-2 using either a novel liposomal mRNA-based delivery platform or an adenovirus-based approach have been authorized for emergency use by the U.S. Food and Drug Administration (2-5). The goal of vaccination is to generate long-lasting protection against infection, and most vaccines in clinical use achieve this at least in part through generation of pathogen-specific antibody responses. Ending the COVID-19 pandemic will depend greatly on vaccine effectiveness. An important clinical question is whether vaccine responses are altered in

patients with immune disorders who are receiving immunomodulatory medications.

Current management of various chronic inflammatory diseases (CIDs), including inflammatory bowel disease (IBD), rheumatoid arthritis (RA), spondyloarthritis, systemic lupus erythematosus, and multiple sclerosis (MS), typically requires immunosuppressive medications. These include glucocorticoids, antimetabolites, tumor necrosis factor inhibitors (TNFis), B-cell depleting therapy (BCDT), and Janus kinase inhibitors (JAKis) to achieve and maintain disease response and remission (6–10). Patients with CID receiving immunosuppressive medications can be compromised when encountering infectious diseases, and certain medications, such as BCDT, glucocorticoids, and the antimetabolite sulfasalazine, have been associated with increased hospitalization and death due to COVID-19 (11–13). Consequently, vaccination is recommended for patients with CID. Nevertheless, prior studies have shown that certain immunosuppressive medications can blunt influenza and pneumococcal vaccine responses (14), which can sow doubt in providers and patients about the effectiveness of SARS-CoV-2 vaccination in this population. Guidance from medical organizations, such as the American College of Rheumatology (15), provides clinicians critical instructions on vaccinating this vulnerable population, but initial recommendations are challenging to implement because of the absence of data specifically on vaccination in patients with CID.

Emerging data show reduced antibody responses in some immunosuppressed persons after mRNA vaccination. Organ transplant recipients using antimetabolite therapy and older recipients were less likely to develop an antibody response, even after receiving 2 doses of the BNT162b2 or mRNA-1273 vaccine, suggesting the need for an additional vaccine dose in this population (16, 17). Furthermore, studies with small numbers of patients with CID have found blunted anti-spike (S) IgG levels after mRNA-based vaccination, with some showing modestly reduced *in vitro* viral neutralization compared with immunocompetent participants (18–21). Anti-SARS-CoV-2 antibody reactivity after COVID-19 infection has been reported to be attenuated in TNFi (infliximab)-treated patients with IBD compared with those treated with vedolizumab, and it was further blunted in those with concomitant thiopurine or methotrexate treatment (15, 19–22).

These early observations in small groups of patients have heightened suspicions that immunosuppression in patients with CID receiving medications may reduce antibody responses after SARS-CoV-2 vaccination. This led to a recommendation from the Advisory Committee on Immunization Practices that persons with moderately to severely compromised immune systems due to immunosuppressive therapies should receive an additional dose of SARS-CoV-2 mRNA vaccine at least 28 days after a second dose of BNT162b2 or mRNA-1273 vaccine (23). In this article, we report immunogenicity data from a cohort of 133 patients with CID and 53 immunocompetent participants from 2 U.S. university hospitals after completion of the 2-dose mRNA SARS-CoV-2 vaccination series.

METHODS

Study Design

The COVaRiPAD (COVID-19 Vaccine Responses in Patients with Autoimmune Disease) study is a longitudinal observational study seeking to elucidate the magnitude, quality, and evolution of the immune response to SARS-CoV-2 vaccines. The initial phase of COVaRiPAD specifically examined the magnitude and quality of the acute humoral response.

Setting and Participants

We recruited participants with confirmed CID and immunocompetent participants from among hospital employees (any age) and clinic patients (aged >65 years) at Washington University School of Medicine and the BJC HealthCare system (St. Louis, Missouri, metropolitan area) and at the University of California San Francisco (UCSF), UCSF Health, and Zuckerberg San Francisco General Hospital (San Francisco, California, metropolitan area) from 10 December 2020 to 20 March 2021. Participants with CID and immunocompetent participants were passively recruited using on-campus posters distributed across each university and affiliated hospital systems, university newsletters sent as blast e-mails to employees of the 2 medical centers, and word of mouth. To actively recruit vaccine-eligible persons with CID during the study period, blast messages were sent to select patients with CID through each health care system's patient portal. For this recruitment group, participants with CID were identified via lists generated by searches of the electronic medical record for patients seen in university or affiliated hospital rheumatology, MS, or IBD clinics regardless of specific CID diagnosis and medication used. This refined list of potential participants was then screened for vaccine eligibility by identifying 1) hospital employees, based on either membership in the hospital insurance plan or presence of an employee designation in the electronic medical record (Washington University); 2) possession of an e-mail domain (@ucsf.edu) to confirm university employee status (UCSF); or 3) age over 65 years according to each state's vaccine prioritization. Diagnoses of CID were provided by the participant and were confirmed via chart review by study physicians. Immunocompetent participants had their medical history and medication use reviewed at the time of screening by study physicians (J.A.O. and R.M.P.) to ensure that those with any acquired or inherited immunocompromised condition or use of systemic immunosuppression were excluded. Detailed inclusion and exclusion criteria are provided in **Appendix 1** (available at [Annals.org](#)).

All participants provided written informed consent. Participants were assessed within 2 weeks before initial vaccination and 20 days after final vaccination, with 96% of blood samples collected within 14 days after vaccination. Medications, including dose and last administration date, were confirmed at each study visit using surveys administered on paper or an electronic tablet, and data were stored in the Research Electronic Data Capture (REDCap) system (24). Medications classified as antimetabolites and BCDT are listed in **Appendix 1**. Daily audits of the participant-provided data were performed by the

Table. Demographic and Clinical Characteristics of Study Participants

Characteristics	Participants With CID (n = 133)	Immunocompetent Participants (n = 53)
Mean age (SD), y	45.5 (16.0)	43.4 (14.1)
Age, n (%)		
<65 y	114 (85.7)	46 (86.8)
≥65 y	19 (14.3)	7 (13.2)
Gender, n (%)*		
Female	99 (74.4)	29 (54.7)
Male	34 (25.6)	24 (45.3)
Hispanic or Latinx ethnicity, n (%)*		
Yes	6 (4.5)	4 (7.5)
No	127 (95.5)	49 (92.5)
Racial/ethnic group, n (%)*		
White	117 (88.0)	42 (79.2)
Asian	9 (6.8)	7 (13.2)
Black or African American	4 (3.0)	1 (1.9)
Other	3 (2.3)	3 (5.7)
Mean body mass index (SD), kg/m²	26.6 (6.3)	27.9 (7.6)
Mean time after second immunization for blood sample (SD), d	8.5 (2.8)	7.1 (1.8)
Immunologic diagnosis, n (%)†		
IBD	42 (31.6)	-
Crohn disease	22 (16.5)	-
Ulcerative colitis	18 (13.5)	-
Other	2 (1.5)	-
Rheumatoid arthritis	38 (28.6)	-
Spondyloarthritis	20 (15)	-
Axial spondyloarthritis	6 (4.5)	-
Psoriatic arthritis/psoriasis	10 (7.5)	-
IBD-associated arthritis	4 (3.0)	-
Uveitis	5 (3.8)	-
Systemic lupus erythematosus	15 (11.3)	-
Other connective tissue disease‡	4 (3.0)	-
Sjögren syndrome	8 (6.0)	-
Vasculitis	5 (3.8)	-
Autoinflammatory syndrome	2 (1.5)	-
Multiple sclerosis	9 (6.8)	-
Neuromyelitis optica	1 (0.8)	-
IgG4-related disease	2 (1.5)	-
Hidradenitis suppurativa	1 (0.8)	-
HIV	1 (0.8)	-
Antiphospholipid syndrome	1 (0.8)	-
Additional diagnosis, n (%)		
Hypertension	20 (15.0)	9 (17.0)
Diabetes mellitus	9 (6.8)	0 (0.0)
Coronary artery disease	1 (0.8)	0 (0.0)
Asthma	15 (11.3)	3 (5.7)
Chronic obstructive pulmonary disease	1 (0.8)	1 (1.9)
Chronic kidney disease	3 (2.3)	0 (0.0)
Chronic liver disease	4 (3.0)	0 (0.0)
Medication exposure, n (%)		
Prednisone	17 (12.8)	-
Mean dose (SD), mg/d	6.5 (5.8)	-
Range of doses, mg/d	1-20	-

Continued on following column

Table—Continued

Characteristics	Participants With CID (n = 133)	Immunocompetent Participants (n = 53)
Disease-modifying antirheumatic drugs		
Methotrexate	29 (21.8)	-
Mean dose (SD), mg/wk	17.1 (5.4)	-
Range of doses, mg/wk	7.5-25	-
Hydroxychloroquine	30 (22.6)	-
Mycophenolate mofetil	9 (6.8)	-
Azathioprine	4 (3.0)	-
Leflunomide	2 (1.5)	-
Sulfasalazine	7 (5.3)	-
Teriflunomide	1 (0.8)	-
6-Mercaptopurine	2 (1.5)	-
Janus kinase inhibitors		
Tofacitinib	10 (7.5)	-
Upadacitinib	1 (0.8)	-
Biologic therapies		
Tumor necrosis factor inhibitors§	38 (28.6)	-
B-cell depleting therapies	10 (7.5)	-
Belimumab	3 (2.3)	-
Vedolizumab	12 (9.0)	-
Interleukin-12/23 or interleukin-23 inhibitors¶	10 (7.5)	-
Abatacept	2 (1.5)	-
Tocilizumab	1 (0.8)	-
Fingolimod	1 (0.8)	-
Ibrutinib	1 (0.8)	-
Nonsteroidal anti-inflammatory drugs	27 (20.3)	-
No immunosuppression	9 (6.8)	-

CID = chronic inflammatory disease; IBD = inflammatory bowel disease.

* Gender, race, and ethnicity were reported by participants.

† Patients could be diagnosed with >1 condition, so the sum of diagnoses is greater than the number of participants.

‡ Includes undifferentiated connective tissue disease and mixed connective tissue disease.

§ Includes adalimumab (n = 13), certolizumab pegol (n = 5), etanercept (n = 13), golimumab (n = 2), and infliximab (n = 6).

|| Includes rituximab (n = 8) and ocrelizumab (n = 4).

¶ Includes the interleukin-12/23 inhibitor ustekinumab (n = 9) and the interleukin-23 inhibitor guselkumab (n = 1).

study coordinators or investigators to ensure accuracy of results. Any discrepancies were reconciled via a telephone conversation with the participant. All patients continued use of their immunosuppressive medications per their treating physician, except for 3 who held methotrexate within 1 week of immunization.

Sample Collection and Storage

Serum, plasma, and peripheral blood mononuclear cells (PBMCs) were collected using Vacutainer CPT tubes (BD Biosciences), with identical protocols and reagents used at each medical center. Serum and plasma were immediately used or frozen at -80°C ; PBMCs were isolated using Ficoll density gradient centrifugation and were immediately used or cryopreserved in 10% dimesylsulfoxide in fetal bovine serum (FBS).

Assessment of Humoral Responses

As previously described (25), anti-S IgG quantification from plasma to assess the magnitude of systemic virus-

specific antibodies was performed using enzyme-linked immunosorbent assay (ELISA). Optical density measurements were taken at 490 nm. The half-maximal binding dilution for each serum or plasma sample was calculated using nonlinear regression (GraphPad Prism 9). The limit of detection was defined as 1:30. Antibodies were validated by their respective manufacturers per their associated data sheets and titrated for ELISA by serial dilution.

Direct ex vivo enzyme-linked immunosorbent spot (ELISpot) assays were performed to quantify recombinant S protein-binding IgG-secreting cells, which provide the source of vaccine-induced circulating antibodies. Notably, only certain participants at Washington University had the ELISpot assay performed because of the need to use freshly isolated, unfrozen PBMCs (the excluded participants either were from UCSF and were unable to provide fresh, unfrozen samples or had insufficient assay plates due to manufacturer shortages).

Neutralization assays on sera to determine the magnitude of functional S-specific antibodies that prevent the in vitro infectivity of virus were performed using a fluorescence-based platform, which leveraged a chimeric vesicular stomatitis virus (VSV) pseudotyped with the common variant strain (D614G) of the S protein of SARS-CoV-2 and was modified for high-throughput processing (26, 27). Assay validation with native SARS-CoV-2 was performed as described previously (26, 27). Half-maximal inhibitory concentrations (IC_{50} s) were generated using logistic regression and applying plateau and baseline thresholds. Only samples from Washington University were used for neutralization studies because serum was not initially collected at UCSF.

All assays were performed at Washington University School of Medicine by the laboratories of Dr. Ellebedy (ELISA and ELISpot) and Dr. Buchser (neutralization). Additional details are provided in **Appendix 1**.

Data Analysis

Data analyses were performed using Prism 9.1.0 (GraphPad Software) and R, version 4.0.3 (R Foundation for Statistical Computing). UpSet plots were generated using the R package UpSetR v1.4.0.

Ethics Approval

This study was approved by the Washington University School of Medicine Institutional Review Board (protocol #201105110, approved 1 June 2011; protocol #202012081, approved 21 December 2020; and protocol #202012084, approved 23 December 2020) and the UCSF Institutional Review Board (protocol #17-21898, approved 22 April 2017, and protocol #20-33078, approved 4 January 2021).

Role of the Funding Source

The Leona M. and Harry B. Helmsley Charitable Trust, the Marcus Program in Precision Medicine Innovation, the National Institutes of Health (NIH)/National Center for Advancing Translational Sciences, and the NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases (UCSF) had no role in the study's design, conduct, or analysis or the decision to submit the manuscript for publication.

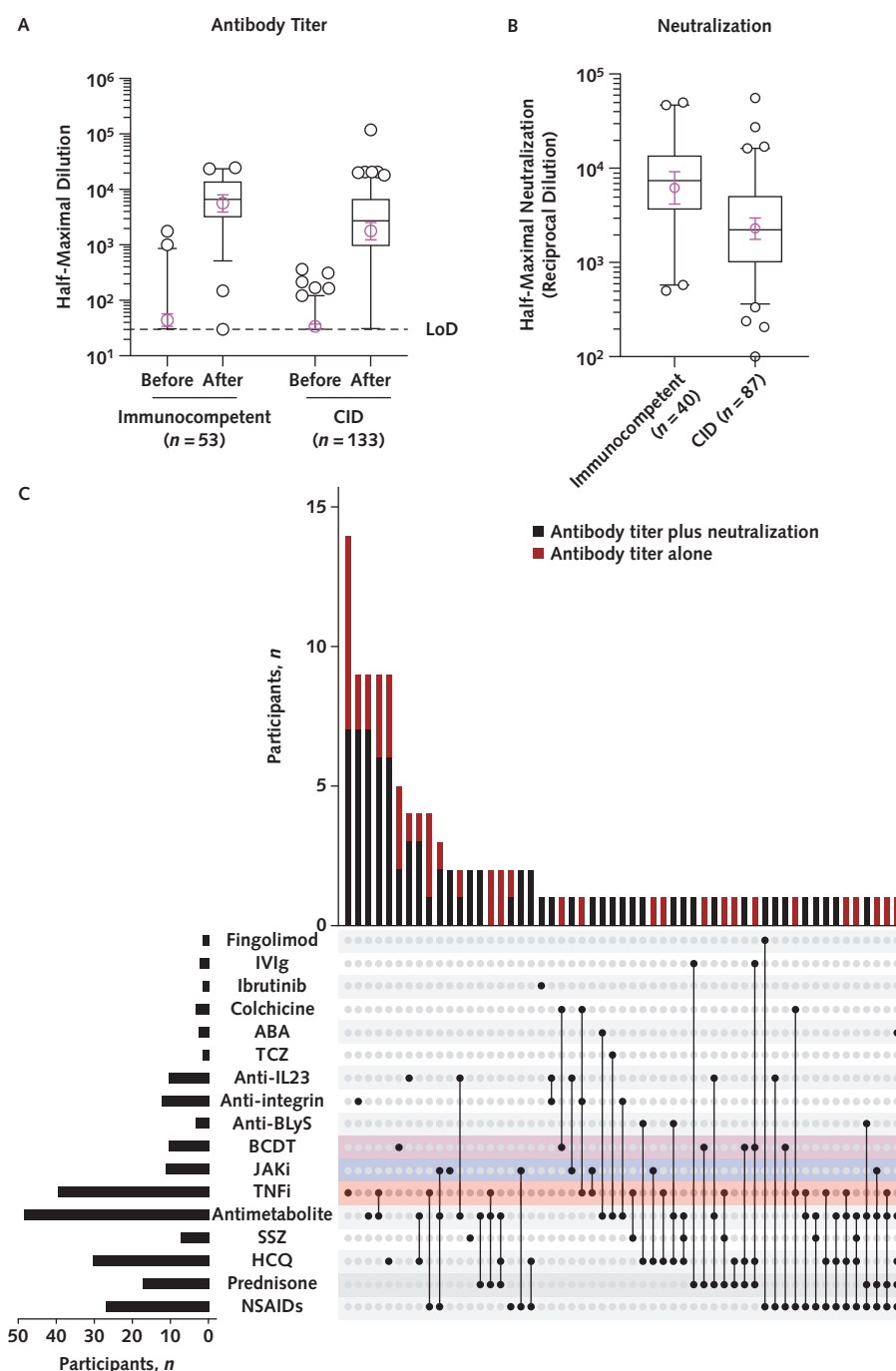
RESULTS

Between December 2020 and March 2021, 133 patients with CID and 53 immunocompetent participants underwent serologic testing at the 2 study sites (**Table**). The study team screened 577 eligible participants with CID; of these, 30 chose not to participate, and 199 did not qualify because they had already been vaccinated before enrollment (**Appendix Figure 1**, available at [Annals.org](#)). A total of 348 participants with CID consented; however, 17 withdrew and 198 were excluded from the analysis because they lacked a baseline blood draw ($n=57$) or had not yet reached the postbooster time point ($n=141$). The majority of the 133 patients with CID were female (74.4%) and White (88.0%) (**Table**). The most common CID diagnoses were IBD (31.6%) and RA (28.6%), and the most common immunosuppressive medications were TNFis (28.6%) and methotrexate (21.8%). Most participants with CID were receiving monotherapy (42.9%) or dual therapy (31.6%) (**Appendix Table**, available at [Annals.org](#); **Figure 1,C**).

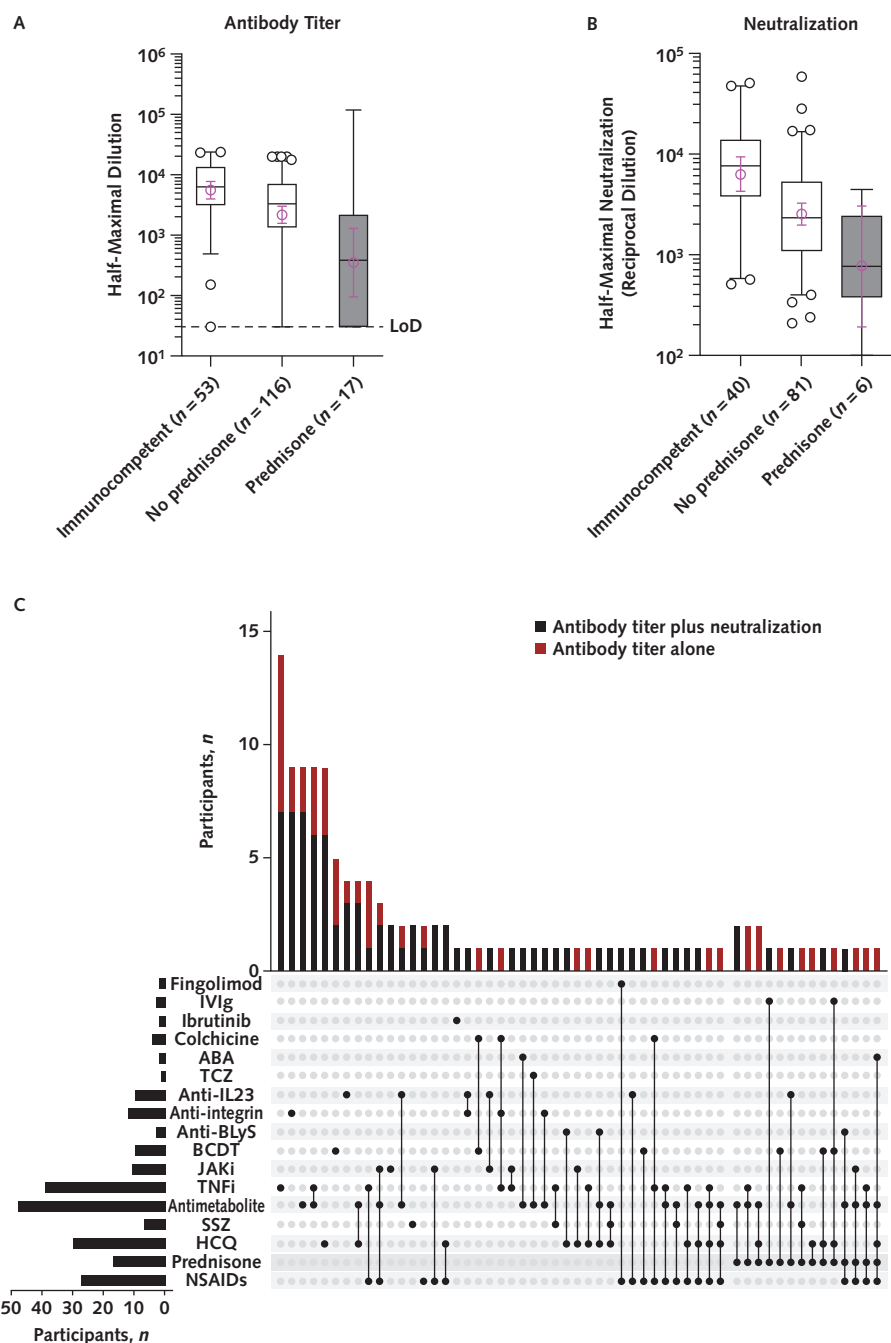
All immunocompetent participants and 88.7% of participants with CID (118 of 133) had seroconversion, with an anti-SARS-CoV-2 S IgG half-maximal titer above the limit of detection of 1:30. The geometric mean at half-maximal dilution was 5542 (95% CI, 3926 to 7823) among immunocompetent participants and 1737 (CI, 1248 to 2418) among those with CID (**Figure 1, A**); the geometric means at half-maximal neutralization were 6261 (CI, 4218 to 9293) and 2312 (CI, 1795 to 2978) (**Figure 1, B**), respectively. Circulating plasmablasts were higher among immunocompetent persons than among those with CID (geometric mean of spot-forming units per 10^6 PBMCs, 179 [CI, 100 to 318] vs. 48 [CI, 24 to 95], respectively) (**Appendix Figure 2, A**, available at [Annals.org](#)).

To examine the association between immunosuppressive medication exposure and the immunogenicity of mRNA-based SARS-CoV-2 vaccination in participants with CID, we first stratified the antibody titers in participants with CID receiving or not receiving glucocorticoids. The geometric mean of anti-S IgG antibodies was 357 (CI, 96 to 1324) in prednisone users and 2190 (CI, 1598 to 3002) in nonusers; respective neutralization results were 767 (CI, 196 to 3003) and 2509 (CI, 1947 to 3233), and respective circulating plasmablast levels were 5 (CI, 0.02 to 874) and 58 (CI, 28 to 120) (**Figure 2; Appendix Figure 2, B**). Within this subgroup, there was no association between prednisone dose and antibody response to the vaccine. Only 65% (11 of 17) of participants with CID were seropositive after vaccination (defined as any anti-S IgG titer above the limit of detection) compared with 92% (107 of 116) among participants with CID who were not using prednisone.

We next stratified immunogenicity of mRNA-based vaccination in patients with CID receiving antimetabolites (methotrexate, mycophenolate, azathioprine, leflunomide, teriflunomide, or 6-mercaptopurine) and found no clear difference compared with those not using antimetabolites. The geometric mean of anti-S antibody titers was 1371 (CI, 809 to 2323) for those using antimetabolites and 1985 (CI, 1293 to 3047) for those not using them; respective neutralization titers were 2391 (CI, 1537 to 3719) and 2270 (CI, 1650 to 3121), and respective circulating plasmablast

Figure 1. Immunogenicity among participants with CID and immunocompetent participants.

ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; S = spike; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Quantification of circulating anti-S IgG for immunocompetent participants and those with CID after immunization. **B.** Neutralization of pseudotyped vesicular stomatitis virus with SARS-CoV-2 S protein by serum of immunocompetent participants and those with CID after vaccination. In panels **A** and **B**, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. **C.** UpSet plot of immunomodulatory therapy combinations for participants with CID. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

Figure 2. Immunogenicity among participants with CID receiving glucocorticoids (prednisone).

ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; S = spike; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Quantification of anti-SARS-CoV-2 antibodies in participants with CID receiving or not receiving prednisone. **B.** Neutralization of pseudotyped vesicular stomatitis virus with SARS-CoV-2 S protein by serum for participants with CID receiving or not receiving prednisone. In panels **A** and **B**, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. **C.** UpSet plot of immunomodulatory therapy combinations for participants with CID, stratified by prednisone use. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

levels were 34 (CI, 5 to 241) and 67 (CI, 32 to 142) (Appendix Figure 2, C; Appendix Figure 3, available at [Annals.org](#)).

Given previous reports of targeted therapies impairing vaccine responses (14), we examined the immunogenicity of mRNA-based vaccination in patients with CID exposed to 3 additional drug classes (BCDT, TNFis, and JAKis). Although measures of immunogenicity were numerically different between patients receiving TNFis and JAKis and those who were not, 95% CIs were wide and overlapped. The geometric mean of anti-S IgG titers was 2478 (CI, 1360 to 4516) in those receiving any TNFi and 1499 (CI, 1005 to 2234) in those who were not; respective neutralization titers were 1956 (CI, 1093 to 3500) and 2415 (CI, 1811 to 3220) (Figure 3). The geometric means of anti-S IgG titers were 1056 (CI, 413 to 2705) for participants receiving any JAKi and 1816 (CI, 1277 to 2584) for those who were not; respective neutralization titers were 1951 (CI, 956 to 3982) and 2415 (CI, 1811 to 3220) (Figure 4). In contrast, immunogenicity seemed substantially lower (60%) in the 10 participants receiving BCDT. The geometric mean of anti-S IgG was 152 (CI, 36 to 652) in the 10 patients using BCDT versus 2117 (CI, 1539 to 2912) in those not using it ($n = 123$). The neutralization titers were 723 (CI, 233 to 2246) in the 4 participants using BCDT compared with 2445 (CI, 1890 to 3164) in the 83 who were not (Figure 5), and circulating plasmablasts were absent in 1 participant where PBMCs were available (Appendix Figure 2, D). The association between BCDT exposure and seroconversion was most striking in participants who had more recently (within 6 months) received BCDT (Appendix Figure 4, available at [Annals.org](#)). Removal of 2 participants with prior SARS-CoV-2 infection based on anti-S seropositivity before vaccination had no appreciable effect on the association between biologic therapy and anti-S antibody responses (seropositivity in 4 of 8 [50%]).

DISCUSSION

In a cohort of 133 participants with CID and 53 immunocompetent participants recruited from 2 academic medical centers in the United States, we found that 88.7% (118 of 133) of patients with CID had antibody responses after 2 doses of the BNT162b2 or mRNA-1273 vaccine; however, in many cases, antibody levels were lower than in immunocompetent participants. We observed that some patients with CID receiving BCDT and glucocorticoids had absent or numerically lower antibody titers after both vaccinations, which correlated with low in vitro neutralization responses. Although overall seroconversion after vaccination was 88.7% in patients with CID, only 6 of 10 (60%) patients with CID receiving BCDT and 11 of 17 (65%) patients with CID receiving glucocorticoids showed seroconversion after mRNA-based SARS-CoV-2 vaccination. In the BCDT-treated patients, the absence of seroconversion was seen primarily in those with recent administration of therapy.

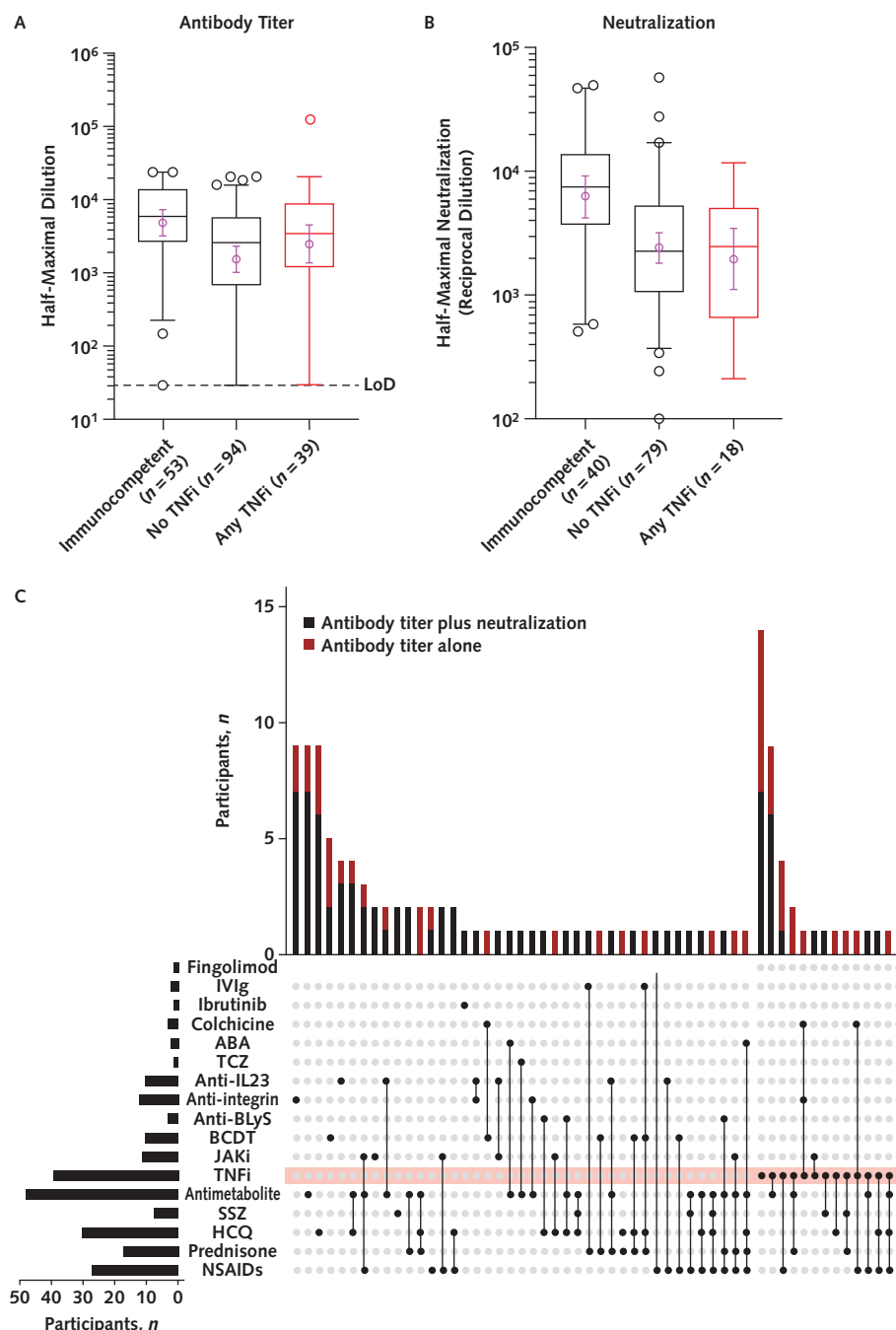
Our results build on data sets confirming that most patients with CID can mount humoral responses after SARS-CoV-2 vaccination, with a small proportion generating poor or no response (18, 22, 28). Although our study sample is

larger than some others, we were nonetheless unable to adjust for other differences between the immunocompetent participants and those with CID or across subgroups of participants receiving different immunosuppressant therapies. Thus, our findings should be interpreted with caution and as hypothesis generating. Nevertheless, other groups have also reported that some patients with CID receiving immunosuppressants mounted reduced humoral responses compared with immunocompetent participants (18, 19, 29).

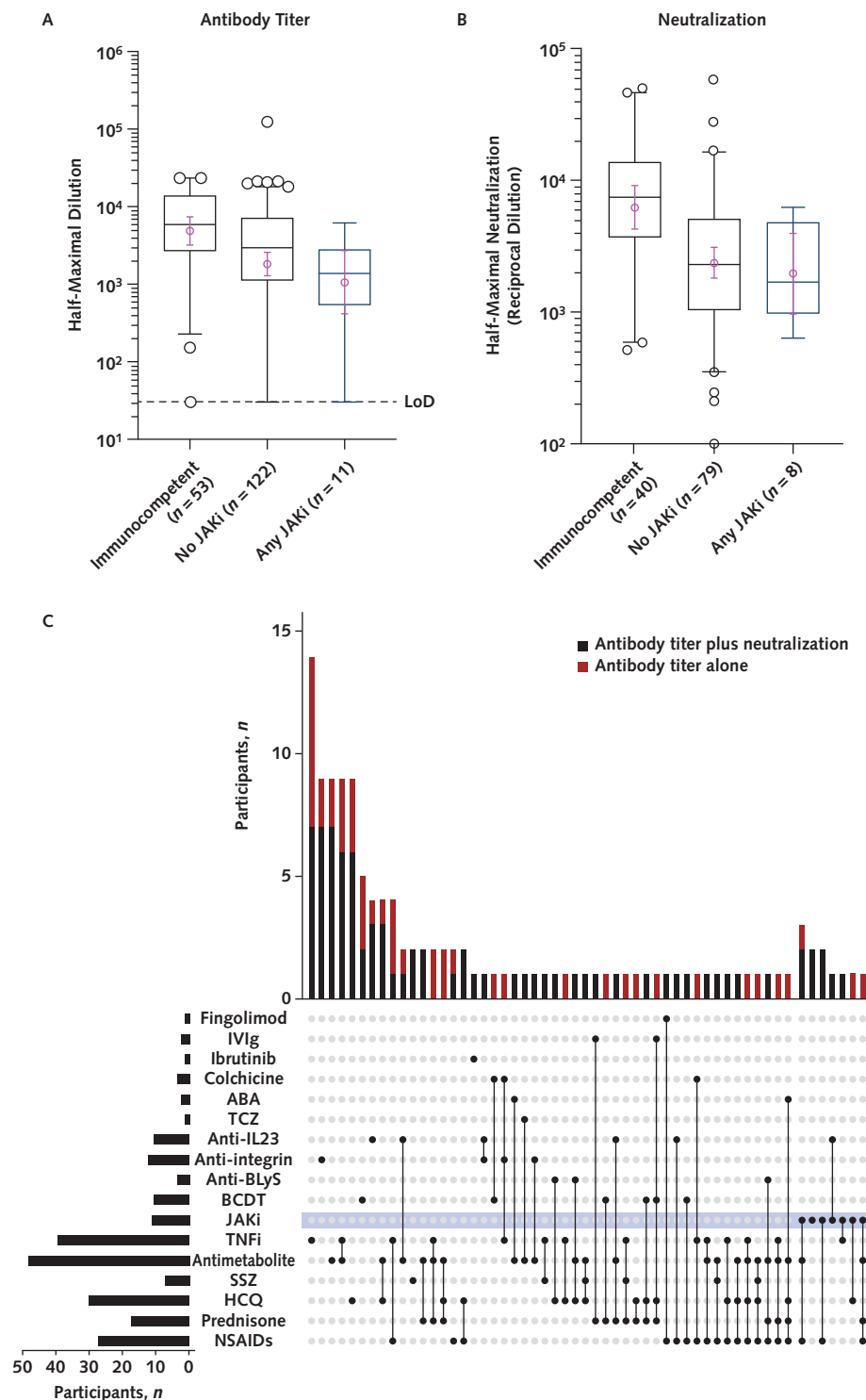
Patients receiving BCDT had numerically low titers of anti-S IgG as well as neutralizing antibodies similar to the decrease in observed antibody responses after influenza and pneumococcal vaccination in these patients (20, 21, 29–34). In the BCDT-treated patients in our study, the lack of seroconversion was seen primarily in those receiving vaccination within 6 months of BCDT administration, with gradual recovery of antibody response to vaccination 9 months after treatment with rituximab. All 4 participants in our study receiving ocrelizumab every 6 months had undetectable antibodies, and it is unclear whether they will have recovery of an antibody response to vaccination with a longer postmedication interval, as we observed in a few patients receiving rituximab. Ocrelizumab has improved antibody-dependent cellular cytotoxicity compared with rituximab, which may prolong its effect on SARS-CoV-2 immunization (35). Notably, a prior study of ocrelizumab found that a 3-immunization series did elicit antibody responses, albeit with reduced titers (36). Thus, additional studies are needed to determine whether vaccine responses can be improved either by a longer interval between BCDT and vaccine administration or by adding vaccine booster doses.

We also found that participants receiving glucocorticoids had lower antibody titers after SARS-CoV-2 vaccination. Similar observations of reduced antibody responses in glucocorticoid users were previously reported (20, 29), and the contribution of potential confounders, including additional immunosuppression (BCDT and mycophenolate use), was noted (20). In previous reports of patients with systemic lupus erythematosus, high-dose prednisone (>20 mg daily) was associated with a decline in seroconversion after influenza vaccination, but a dose-independent effect on seroconversion was observed after vaccination against pneumococcus, tetanus toxoid, *Haemophilus influenzae* type B, or hepatitis B (37–39). In contrast, glucocorticoids at high doses in the setting of asthma or low doses in patients with RA or spondyloarthritis had minimal effect on seroconversion after influenza vaccination (40–42). The explanation for the variable effects of glucocorticoids on response to COVID-19 vaccination remains unclear, although disease-specific factors or concomitant immunosuppressive medication use, which have not yet been adjusted for, may be important contributors. Indeed, most prednisone users were also using other immunosuppressants in this study. Thus, future studies are needed to determine whether tapering of prednisone, with or without initiation of additional therapies, can promote optimal antibody responses from mRNA-based vaccines.

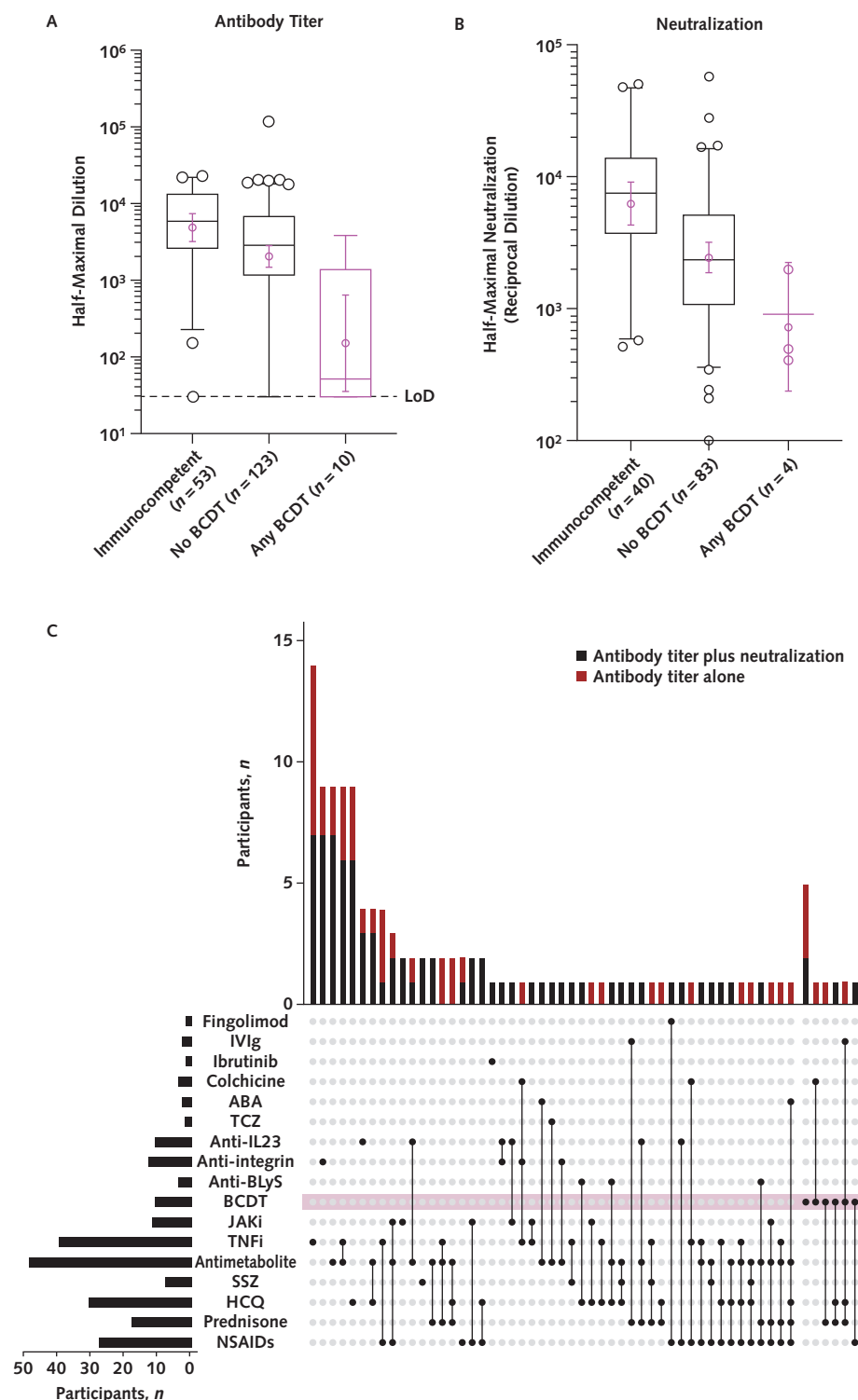
We were not able to draw conclusions about immunogenicity associated with use of antimetabolites, TNFis, or JAKis because CIs around our estimates in these

Figure 3. Immunogenicity among participants with CID receiving TNFis.

ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; S = spike; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Quantification of circulating anti-S IgG for participants with CID receiving or not receiving TNFis. **B.** Neutralization of pseudotyped vesicular stomatitis virus with SARS-CoV-2 S protein by participants with CID receiving or not receiving TNFis. In panels **A** and **B**, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. **C.** UpSet plot of immunomodulatory therapy combinations for participants with CID, stratified by TNFi use. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

Figure 4. Immunogenicity among participants with CID receiving JAKis.

ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; S = spike; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Quantification of circulating anti-S IgG for participants with CID receiving JAKis. **B.** Neutralization of pseudotyped vesicular stomatitis virus with SARS-CoV-2 S protein for participants with CID receiving JAKis. In panels A and B, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. **C.** UpSet plot of immunomodulatory therapy combinations for participants with CID, stratified by JAKi use. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

Figure 5. Immunogenicity among participants with CID receiving BCDT.

ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; S = spike; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Quantification of circulating anti-S IgG for participants with CID receiving BCDT. **B.** Neutralization of pseudotyped vesicular stomatitis virus with SARS-CoV-2 S protein for participants with CID receiving BCDT. In panels A and B, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. **C.** UpSet plot of immunomodulatory therapy combinations for participants with CID receiving BCDT. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

groups were wide and overlapped with estimates among participants not using these therapies. In contrast, the SAGA (Serologic Testing and Genomic Analysis of Autoimmune, Immune-Mediated and Rheumatic Patients with COVID-19) study observed that seropositivity was lower in methotrexate users (28 of 45 [62%]) than in non-users (including some using anticytokine therapies) (34 of 37 [91.9%]) and immunocompetent participants (204 of 208 [98.1%]) (19). However, an Israeli cohort showed similar seropositivity rates in TNFi monotherapy users ($n = 121$; 98% seropositivity rate) and those taking it with other treatments ($n = 172$; 97% seropositivity rate) (20, 28, 29). In the same study, most participants using JAKis became seropositive ($n = 21$; 90% seropositivity rate), even those with concomitant methotrexate use ($n = 24$; 92% seropositivity rate) (29). These observations highlight the complexities of these patients when examining medication effects due to other variables that may further influence antibody responses, such as disease state or concomitant immunosuppressive medication use (22).

Before any evaluation of mRNA-based vaccines in patients with CID, professional societies were pressed to provide guidance on use of immunosuppression in these patients. Current guidelines for IBD, psoriasis, and MS do not suggest holding biologics, small-molecule drugs, or antimetabolites before vaccination against SARS-CoV-2 (43–45). In contrast, the COVID-19 Vaccine Clinical Guidance Summary from the American College of Rheumatology has a moderate-level consensus in holding certain immunosuppressants, such as methotrexate and JAKis, for 1 week after each vaccine dose for those with well-controlled disease (15). It is important to note that our study was done before these recommendations were released, and only 3 participants in our cohort held any medications (all methotrexate).

Because a cutoff titer that is most strongly associated with protection has not been defined, the effect of reduced antibody levels on protection from SARS-CoV-2 infection remains unclear. In addition, our data did not directly evaluate subsequent SARS-CoV-2 infection or prevention of hospitalization. We note that S-specific antibody titers observed in patients with CID (particularly those using TNFis and JAKis) are similar to those in patients with rapid recovery from COVID-19 and may, therefore, provide sufficient humoral protection (46–48).

Limitations of this study include the inability to adjust for confounding from concomitant use of multiple immunosuppressive therapies due to small sample sizes for many of our subgroups. Use of specific medications is also highly associated with CID diagnosis; thus, it is difficult to disentangle whether the underlying disease or individual immunosuppressant therapies contribute to diminished vaccine immunogenicity. Notably, prior studies suggest that the presence of CID alone (in the absence of immunosuppressive medications) may be associated with lower antibody titers than in immunocompetent controls (49). In addition, potential unmeasured selection bias due to missing data (neutralization titers and ELISpot) limits interpretability. Also, we could not evaluate differences between the 2 mRNA vaccines or versus the adenovirus delivery platform. Finally, our

cohort had limited racial and ethnic diversity due to selection bias (most participants were employees of academic teaching hospitals); we continue to recruit from among nonemployee patients with CID to address this. Despite these limitations, our findings contribute important data to this nascent field, and we used assays that have been rigorously developed and used to generate other critical findings related to SARS-CoV-2 antibody responses (25–27, 50).

In summary, this initial analysis of the COVaRiPAD study, focusing on the magnitude and quality of antibody responses after 2 doses of the BNT162b2 or mRNA-1273 vaccine, reveals that most patients with CID receiving immunosuppressive treatment were able to mount antibody responses, which provides justification for current recommendations for this population to be vaccinated. We observed that patients with CID receiving glucocorticoids and BCDT developed numerically low or absent anti-S IgG and neutralizing antibody titers in contrast to other participants with CID. Further studies are needed to determine the importance of contributions of specific medications, exposure to multiple immunosuppressive medications, CID diagnosis, disease state, and additional comorbidities to better understand the critical factors in SARS-CoV-2 vaccine responses.

From Washington University School of Medicine, St. Louis, Missouri (P.D., W.K., M.A.P., A.A.E., A.H., K.H., B.K., M.J.L., Z.L., L.E.M., D.C.P., R.E.S., S.E.S., M.T., M.G., S.A., S.A., M.K., L.M., D.N., S.C., M.A.C., J.A.O., R.M.P., G.F.W., S.P.W., W.J.B., A.H.E., A.H.K.); University of California San Francisco, San Francisco, California (M.Y., A.B.C., E.G.D., D.P., N.P., J.G., K.E.T., P.K., M.M.); and University of California San Francisco and San Francisco VA Health Care System, San Francisco, California (L.S.G., M.C.N.).

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the views of the NIH.

Acknowledgment: The authors thank the study participants for their generous and enthusiastic participation; the entire COVaRiPAD team (see **Appendix 2**, available at [Annals.org](#)), including the treating clinicians for their support of the study recruitment process, the staff of the Washington University School of Medicine Infectious Diseases Clinical Research Unit, the Clinical Trials Research Unit, the Center for Clinical Studies, and the Digestive Diseases Research Core Center for their assistance with study visits; the Siteman Tissue Procurement Core for processing and storage of the blood specimens; and Grace L. Paley for constructive comments on the manuscript. Dr. Alfred Kim thanks Jinoos Yazdany for constructive conversations.

Grant Support: This research was funded and supported by The Leona M. and Harry B. Helmsley Charitable Trust, the Washington University Digestive Disease Research Core Center (NIDDK P30DK052574), the Washington University Rheumatic Diseases Research Resource-Based Center (NIAMS P30AR073752), The Judy Miniace Research Fund for the Washington University Lupus Clinic, the Washington University Institute of Clinical and Translational Sciences (ICTS) grant UL1TR002345 from the

National Center for Advancing Translational Sciences (NCATS), and NIAID Collaborative Influenza Vaccine Innovation Centers contract 75N93019C00051 for the Washington University Infectious Diseases Clinical Research Unit COVID sample collection. The UCSF investigators were funded by a Seeding Bold Ideas Grant from the Marcus Program in Precision Medicine Innovation, PREMIER, a NIAMS P30 Center (P30AR070155), and the Russell/Engleman Rheumatology Research Center. This study utilized samples obtained from the Washington University School of Medicine's COVID-19 biorepository, which is supported by the Barnes-Jewish Hospital Foundation, the Siteman Cancer Center grant P30CA091842 from the National Cancer Institute of the NIH, and the Washington University ICTS grant UL1TR002345 from the NCATS of the NIH. Dr. Deepak is supported by a Junior Faculty Development Award from the American College of Gastroenterology and IBD Plexus of the Crohn's & Colitis Foundation. Dr. Paley is supported by the Rheumatology Research Foundation. Dr. Ciorba is supported by R01DK109384 and by the Lawrence C. Pakula MD IBD Education and Innovation Fund and Pfizer (IIS #61798927). Dr. Wu is supported by the National Institute of Neurological Disorders and Stroke (R01NS106289) and the National Multiple Sclerosis Society (RG-1802-30253). Drs. Nakamura and Gensler are supported by the San Francisco VA Health Care System. Drs. O'Halloran, Presti, and Ellebedy are supported by NIAID Collaborative Influenza Vaccine Innovation Centers contract 75N93019C00051. Dr. Ellebedy is also supported by NIAID grant U01AI141990, NIAID Centers of Excellence for Influenza Research and Surveillance contracts HHSN272201400006C and HHSN272201400008C, and NIAID Collaborative Influenza Vaccine Innovation Centers contract 75N93019C00051. Dr. Alfred Kim is supported by the Rheumatology Research Foundation, NIH/NIAMS P30 AR073752, and PCORI SDM2017C28224.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-1757.

Reproducible Research Statement: Study protocol, statistical code, and data set: Available from Dr. Alfred Kim (e-mail, akim@wustl.edu).

Corresponding Author: Alfred H.J. Kim, MD, PhD, Division of Rheumatology, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8045, St. Louis, MO 63110; e-mail, akim@wustl.edu.

Previous Posting: This manuscript was posted as a preprint on medRxiv on 9 April 2021. doi:10.1101/2021.04.05.21254656

Current author addresses and author contributions are available at Annals.org.

References

1. Johns Hopkins Coronavirus Resource Center. Global Map. Accessed at <https://coronavirus.jhu.edu> on 18 June 2021.
2. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383:2603-15. [PMID: 33301246] doi:10.1056/NEJMoa2034577

3. Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384:403-16. [PMID: 33378609] doi:10.1056/NEJMoa2035389
4. Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S Covid-19 vaccine. *N Engl J Med*. 2021;384:1824-35. [PMID: 33440088] doi:10.1056/NEJMoa2034201
5. Voysey M, Clemens SAC, Madhi SA, et al; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397:99-111. [PMID: 33306989] doi:10.1016/S0140-6736(20)32661-1
6. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68:1-26. [PMID: 26545940] doi:10.1002/art.39480
7. Singh JA, Guyatt G, Ogdie A, et al. Special article: 2018 American College of Rheumatology/National Psoriasis Foundation guideline for the treatment of psoriatic arthritis. *Arthritis Care Res (Hoboken)*. 2019;71:2-29. [PMID: 30499259] doi:10.1002/acr.23789
8. Hahn BH, McMahon MA, Wilkinson A, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)*. 2012;64:797-808. [PMID: 22556106] doi:10.1002/acr.21664
9. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-88. [PMID: 29686116] doi:10.1212/WNL.0000000000005347
10. Chang JT. Pathophysiology of inflammatory bowel diseases. *N Engl J Med*. 2020;383:2652-64. [PMID: 33382932] doi:10.1056/NEJMra2002697
11. Brenner EJ, Ungaro RC, Gearry RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. *Gastroenterology*. 2020;159:481-491.e3. [PMID: 32425234] doi:10.1053/j.gastro.2020.05.032
12. Strangfeld A, Schäfer M, Gianfrancesco MA, et al; COVID-19 Global Rheumatology Alliance. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*. 2021;80:930-42. [PMID: 33504483] doi:10.1136/annrheumdis-2020-219498
13. Salter A, Fox RJ, Newsome SD, et al. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. *JAMA Neurol*. 2021;78:699-708. [PMID: 33739362] doi:10.1001/jamaneurol.2021.0688
14. Day AL, Winthrop KL, Curtis JR. The effect of disease-modifying antirheumatic drugs on vaccine immunogenicity in adults. *Cleve Clin J Med*. 2020;87:695-703. [PMID: 33139263] doi:10.3949/ccjm.87a.20056
15. Curtis JR, Johnson SR, Anthony DD, et al. American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 2. *Arthritis Rheumatol*. 2021;73:e30-e45. [PMID: 34128356] doi:10.1002/art.41877
16. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. *JAMA*. 2021;325:2204-6. [PMID: 33950155] doi:10.1001/jama.2021.7489
17. Werbel WA, Boyarsky BJ, Ou MT, et al. Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series [Letter]. *Ann Intern Med*. 2021;174:1330-2. [PMID: 34125572] doi:10.7326/L21-0282
18. Geisen UM, Berner DK, Tran F, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic

- inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis*. 2021. [PMID: 33762264] doi:10.1136/annrheumdis-2021-220272
19. Haberman RH, Herati R, Simon D, et al. Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. *Ann Rheum Dis*. 2021. [PMID: 34035003] doi:10.1136/annrheumdis-2021-220597
 20. Ruddy JA, Connolly CM, Boyarsky BJ, et al. High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases [Letter]. *Ann Rheum Dis*. 2021. [PMID: 34031032] doi:10.1136/annrheumdis-2021-220656
 21. Connolly CM, Boyarsky BJ, Ruddy JA, et al. Absence of humoral response after two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases: a case series [Letter]. *Ann Intern Med*. 2021;174:1332-4. [PMID: 34029488] doi:10.7326/M21-1451
 22. Wong SY, Dixon R, Martinez Pazos V, et al; ICARUS-IBD Working Group. Serologic response to messenger RNA coronavirus disease 2019 vaccines in inflammatory bowel disease patients receiving biologic therapies. *Gastroenterology*. 2021;161:715-718.e4. [PMID: 33887219] doi:10.1053/j.gastro.2021.04.025
 23. Centers for Disease Control and Prevention. COVID-19 Vaccines for Moderately to Severely Immunocompromised People. Updated 16 August 2021. Accessed at www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html on 16 August 2021.
 24. Harris PA, Taylor R, Minor BL, et al; REDCap Consortium. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208. [PMID: 31078660] doi:10.1016/j.jbi.2019.103208
 25. Turner JS, Kim W, Kalaidina E, et al. SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. *Nature*. 2021;595:421-5. [PMID: 34030176] doi:10.1038/s41586-021-03647-4
 26. Case JB, Rothlauf PW, Chen RE, et al. Replication-competent vesicular stomatitis virus vaccine vector protects against SARS-CoV-2-mediated pathogenesis in mice. *Cell Host Microbe*. 2020;28:465-474.e4. [PMID: 32798445] doi:10.1016/j.chom.2020.07.018
 27. Liu Z, VanBlargan LA, Bloyet LM, et al. Identification of SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization. *Cell Host Microbe*. 2021;29:477-488.e4. [PMID: 33535027] doi:10.1016/j.chom.2021.01.014
 28. Kennedy NA, Lin S, Goodhand JR, et al; Contributors to the CLARITY IBD study. Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. *Gut*. 2021. [PMID: 33903149] doi:10.1136/gutjnl-2021-324789
 29. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis*. 2021. [PMID: 34127481] doi:10.1136/annrheumdis-2021-220647
 30. van Assen S, Holvast A, Benne CA, et al. Humoral responses after influenza vaccination are severely reduced in patients with rheumatoid arthritis treated with rituximab. *Arthritis Rheum*. 2010;62:75-81. [PMID: 20039396] doi:10.1002/art.25033
 31. Crnkic Kapetanovic M, Saxne T, Jönsson G, et al. Rituximab and abatacept but not tocilizumab impair antibody response to pneumococcal conjugate vaccine in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2013;15:R171. [PMID: 24286269] doi:10.1186/ar4358
 32. Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other anti-rheumatic therapies, is associated with impaired serological response to SARS-CoV-2 vaccination in patients with rheumatic diseases [Letter]. *Ann Rheum Dis*. 2021. [PMID: 33975857] doi:10.1136/annrheumdis-2021-220604
 33. Achiron A, Mandel M, Dreyer-Alster S, et al. Humoral immune response to COVID-19 mRNA vaccine in patients with multiple sclerosis treated with high-efficacy disease-modifying therapies. *Ther Adv Neurol Disord*. 2021;14:17562864211012835. [PMID: 34035836] doi:10.1177/17562864211012835
 34. Rincon-Arevalo H, Choi M, Stefanski AL, et al. Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients. *Sci Immunol*. 2021;6. [PMID: 34131023] doi:10.1126/sciimmunol.abj1031
 35. Kappos L, Li D, Calabresi PA, et al. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. *Lancet*. 2011;378:1779-87. [PMID: 22047971] doi:10.1016/S0140-6736(11)61649-8
 36. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. *Neurology*. 2020;95:e1999-e2008. [PMID: 32727835] doi:10.1212/WNL.00000000000010380
 37. Borba EF, Saad CG, Pasoto SG, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy. *Rheumatology (Oxford)*. 2012;51:1061-9. [PMID: 22298793] doi:10.1093/rheumatology/ker427
 38. Battafarano DF, Battafarano NJ, Larsen L, et al. Antigen-specific antibody responses in lupus patients following immunization. *Arthritis Rheum*. 1998;41:1828-34. [PMID: 9778224]
 39. Aytac MB, Kasapcopur O, Aslan M, et al. Hepatitis B vaccination in juvenile systemic lupus erythematosus. *Clin Exp Rheumatol*. 2011;29:882-6. [PMID: 22011373]
 40. Hanania NA, Sockrider M, Castro M, et al; American Lung Association Asthma Clinical Research Centers. Immune response to influenza vaccination in children and adults with asthma: effect of corticosteroid therapy. *J Allergy Clin Immunol*. 2004;113:717-24. [PMID: 15100679]
 41. Elkayam O, Bashkin A, Mandelboim M, et al. The effect of infliximab and timing of vaccination on the humoral response to influenza vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. *Semin Arthritis Rheum*. 2010;39:442-7. [PMID: 19246078] doi:10.1016/j.semarthrit.2008.12.002
 42. Kuruma KA, Borba EF, Lopes MH, et al. Safety and efficacy of hepatitis B vaccine in systemic lupus erythematosus. *Lupus*. 2007;16:350-4. [PMID: 17576737]
 43. Siegel CA, Melmed GY, McGovern DP, et al; International Organization for the Study of Inflammatory Bowel Disease (IOIBD). SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut*. 2021;70:635-40. [PMID: 33472895] doi:10.1136/gutjnl-2020-324000
 44. National Psoriasis Foundation. COVID-19 Task Force Guidance Statements. Updated 1 April 2021. Accessed at www.psoriasis.org/covid-19-task-force-guidance-statements on 7 April 2021.
 45. National Multiple Sclerosis Society. COVID-19 Vaccine Guidance for People Living with MS. Updated 30 March 2021. Accessed at www.nationalmssociety.org/coronavirus-covid-19-information/multiple-sclerosis-and-coronavirus/covid-19-vaccine-guidance on 7 April 2021.
 46. Rodda LB, Netland J, Shehata L, et al. Functional SARS-CoV-2-specific immune memory persists after mild COVID-19. *Cell*. 2021;184:169-183.e17. [PMID: 33296701] doi:10.1016/j.cell.2020.11.029
 47. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*. 2020;181:1489-1501.e15. [PMID: 32473127] doi:10.1016/j.cell.2020.05.015
 48. Prendecki M, Clarke C, Brown J, et al. Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine [Letter]. *Lancet*. 2021;397:1178-81. [PMID: 33640037] doi:10.1016/S0140-6736(21)00502-X

49. Simon D, Tascilar K, Fagni F, et al. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis*. 2021. [PMID: 33958324] doi:10.1136/annrheumdis-2021-220461

50. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nat Med*. 2021;27:717-26. [PMID: 33664494] doi:10.1038/s41591-021-01294-w

ANNALS OF INTERNAL MEDICINE JUNIOR INVESTIGATOR AWARDS

Annals of Internal Medicine and the American College of Physicians recognize excellence among internal medicine trainees and junior investigators with annual awards for original research and scholarly review articles published in *Annals* in each of the following categories:

- Most outstanding article with a first author in an internal medicine residency program or general medicine or internal medicine subspecialty fellowship program
- Most outstanding article with a first author within 3 years following completion of training in internal medicine or one of its subspecialties

Selection of award winners will consider the article's novelty; methodological rigor; clarity of presentation; and potential to influence practice, policy, or future research. Judges will include *Annals'* Editors and representatives from *Annals'* Editorial Board and the American College of Physicians' Education/Publication Committee.

Papers published in the year following submission are eligible for the award in the year of publication. First author status at the time of manuscript submission will determine eligibility. Authors should indicate that they wish to have their papers considered for an award when they submit the manuscript, and they must be able to provide satisfactory documentation of their eligibility if selected for an award. Announcement of awards for a calendar year will occur in January of the subsequent year. Winners will receive a framed certificate, a letter documenting the award, and complimentary registration for the American College of Physicians' annual meeting.

Please direct questions to Jill Jackson at JJackson@acponline.org or visit www.acpjournals.org/journal/aim/junior-investigator-awards.

Current Author Addresses: Drs. Deepak, Gergely, Abushamma, Akuse, and Ciorba; Ms. Huang; Ms. Kinnett; and Mr. Nix: Division of Gastroenterology, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8124, St. Louis, MO 63110.

Drs. Woeseob Kim and Ellebedy and Ms. Thapa: Division of Immunobiology, Department of Pathology & Immunology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8118, St. Louis, MO 63110.

Drs. Paley and Alfred Kim, Ms. El-Qunni, Ms. McMorrow, Ms. Schriefer, and Ms. Mitchell: Division of Rheumatology, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8045, St. Louis, MO 63110.

Ms. Haile: Clinical Trials Unit, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8051, St. Louis, MO 63110.

Ms. Liebeskind and Dr. Buchser: Department of Genetics, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8232, St. Louis, MO 63110.

Ms. Perantie; Ms. Sides; and Drs. Klebert, Chahin, and Wu: Neuroimmunology Section, Department of Neurology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8232, St. Louis, MO 63110.

Drs. O'Halloran and Presti: Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8051, St. Louis, MO 63110.

Drs. Liu and Whelan: Department of Molecular Microbiology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8230, St. Louis, MO 63110.

Mr. Demissie and Ms. Pawar: University of California San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143.

Dr. Taylor: University of California San Francisco, 513 Parnassus Avenue, MSB 859, San Francisco, CA 94117.

Mr. Carvidi and Drs. Graf and Katz: University of California San Francisco, 1001 Potrero Avenue, San Francisco, CA 94110.

Dr. Matloubian: University of California San Francisco, 533 Parnassus Avenue, San Francisco, CA 94117.

Drs. Yang and Gensler and Ms. Paez: University of California San Francisco, 400 Parnassus Avenue, San Francisco, CA 94143-0326.

Dr. Nakamura: San Francisco VA Health Care System, 4150 Clement Street, 111R, San Francisco, CA 94121.

Author Contributions: Conception and design: P. Deepak, M.A. Paley, M. Yang, A.A. El-Qunni, B. Kinnett, M.A. Ciorba, P. Katz, M. Matloubian, R.M. Presti, S.P.J. Whelan, W.J. Buchser, L.S. Gensler, M.C. Nakamura, A.H. Ellebedy, A.H.J. Kim.

Analysis and interpretation of the data: P. Deepak, W. Kim, M.A. Paley, M. Yang, M.J. Liebeskind, K.E. Taylor, S. Chahin, M.A. Ciorba, P. Katz, J.A. O'Halloran, G.F. Wu, S.P.J. Whelan, W.J. Buchser, L.S. Gensler, M.C. Nakamura, A.H.J. Kim.

Drafting of the article: P. Deepak, W. Kim, M.A. Paley, M. Yang, J. Graf, S. Chahin, R.M. Presti, G.F. Wu, L.S. Gensler, M.C. Nakamura, A.H.J. Kim.

Critical revision of the article for important intellectual content: P. Deepak, M.A. Paley, M. Yang, Z. Liu, J. Graf, M.A. Ciorba, P. Katz, G.F. Wu, L.S. Gensler, M.C. Nakamura, A.H.J. Kim.

Final approval of the article: P. Deepak, W. Kim, M.A. Paley, M. Yang, A.B. Carvidi, E.G. Demissie, A.A. El-Qunni, A. Haile, K. Huang, B. Kinnett, M.J. Liebeskind, Z. Liu, L.E. McMorrow,

D. Paez, N. Pawar, D.C. Perantie, R.E. Schriefer, S.E. Sides, M. Thapa, M. Gergely, S. Abushamma, S. Akuse, M. Klebert, L. Mitchell, D. Nix, J. Graf, K.E. Taylor, S. Chahin, M.A. Ciorba, P. Katz, M. Matloubian, J.A. O'Halloran, R.M. Presti, G.F. Wu, S.P.J. Whelan, W.J. Buchser, L.S. Gensler, M.C. Nakamura, A.H. Ellebedy, A.H.J. Kim.

Provision of study materials or patients: P. Deepak, M. Yang, E.G. Demissie, A.A. El-Qunni, B. Kinnett, Z. Liu, L.E. McMorrow, D. Paez, M. Gergely, S. Abushamma, M. Klebert, J. Graf, M.A. Ciorba, M. Matloubian, J.A. O'Halloran, G.F. Wu, S.P.J. Whelan, L.S. Gensler, M.C. Nakamura, A.H.J. Kim.

Statistical expertise: K.E. Taylor, W.J. Buchser, A.H.J. Kim.

Obtaining of funding: P. Deepak, M. Yang, M. Matloubian, M.C. Nakamura, A.H. Ellebedy, A.H.J. Kim.

Administrative, technical, or logistic support: M. Yang, E.G. Demissie, A.A. El-Qunni, A. Haile, K. Huang, B. Kinnett, L.E. McMorrow, N. Pawar, R.E. Schriefer, S.E. Sides, M. Gergely, S. Abushamma, S. Akuse, M. Klebert, L. Mitchell, D. Nix, M.A. Ciorba, R.M. Presti, G.F. Wu, S.P.J. Whelan, A.H.J. Kim.

Collection and assembly of data: P. Deepak, W. Kim, M.A. Paley, M. Yang, A.B. Carvidi, A.A. El-Qunni, K. Huang, B. Kinnett, M.J. Liebeskind, Z. Liu, L.E. McMorrow, D. Paez, N. Pawar, D.C. Perantie, R.E. Schriefer, S.E. Sides, M. Thapa, M. Gergely, S. Abushamma, S. Akuse, D. Nix, J. Graf, S. Chahin, J.A. O'Halloran, R.M. Presti, S.P.J. Whelan, W.J. Buchser, L.S. Gensler, M.C. Nakamura, A.H.J. Kim.

APPENDIX 1: ADDITIONAL STUDY DETAILS

Inclusion Criteria

- Able to understand and give informed consent
 - Capable of attending all mandatory study visits according to the study schedule
 - Males or females older than 18 years
 - Participants in the CID cohort had to have CID documented by a health care provider and be patients seen in university or affiliated hospital rheumatology, MS, or IBD clinics, regardless of specific CID diagnosis or medication used. Any discrepancies in CID diagnosis or medication use identified by study physician chart review and participant-provided data were resolved by conversation between the treating provider and the participant.
 - Immunocompetent control participants had to be in good health as determined by medical history and physical examination and could not be using any immunomodulatory or immunosuppressive medication.
 - All participants who contributed data reported in this manuscript were faculty, staff, or employees of Washington University School of Medicine or BJC HealthCare system in St. Louis, Missouri, or UCSF, UCSF Health, or Zuckerberg San Francisco General Hospital in San Francisco, California.

Exclusion Criteria

- Prior SARS-CoV-2 vaccination or participation in an investigational study of SARS-CoV-2 vaccines in the previous 2 years (history of suspected or confirmed SARS-CoV-2 infection was not exclusionary)
 - History of allergy to vaccination
 - History of Guillain-Barré syndrome after vaccination
 - Acute illness or fever within 72 hours before vaccination

- History of uncontrolled HIV infection or cancer (particularly leukemia, lymphoma, use of antineoplastic drugs, or x-ray treatment). Persons with previous skin cancer or cured nonlymphatic tumors were not excluded from the study. HIV infection was considered controlled if there was documentation of a stable antiretroviral regimen for the previous 6 months and the current CD4 count was above 0.300×10^9 cells/L with undetectable viral load.

- History of any chronic medical conditions that were considered progressive or uncontrolled and had required hospitalization in the previous 3 months (such as diabetes, heart disease, lung disease, liver disease, kidney disease, or uncontrolled hypertension)

- History of excessive alcohol consumption, drug misuse, psychiatric conditions, social conditions, or occupational conditions that, in the opinion of the investigator, would have precluded adherence to the study

- Receipt of blood products within 90 days of the vaccination visit, excluding intravenous immunoglobulin

- Receipt of any licensed live vaccine within 30 days or any licensed inactivated vaccine within 14 days before SARS-CoV-2 vaccination

- Planned vaccination with any other vaccine during the first 60 days of study participation

- Had donated blood or blood products within 30 days before study vaccination, planned to donate blood at any time during study participation, or planned to donate blood within 30 days after the last blood draw

- Any condition that, in the opinion of the investigator, would have interfered with proper conduct of the trial

Detailed Methods

Data Collection Instruments

The case report form containing the data collection instruments is provided in the **Supplement** (available at [Annals.org](#)). Data were collected by clinical research coordinators with Collaborative Institutional Training Initiative program and Good Clinical Practice training managed by nurses who have Certified Clinical Research Coordinator status from the Association of Clinical Research Professionals.

Classification of Medications

Methotrexate, leflunomide, azathioprine, mycophenolate mofetil, teriflunomide, and 6-mercaptopurine were classified as antimetabolites. Rituximab and ocrelizumab were categorized together as BCDT.

Sample Collection and Storage

Serum, plasma, and PBMCs were collected by certified phlebotomists using Vacutainer CPT tubes (BD Biosciences). Serum and plasma were used immediately or frozen at -80°C ; PBMCs were isolated using Ficoll density gradient centrifugation and were used immediately or cryopreserved in 10% dimethylsulfoxide in FBS.

Enzyme-Linked Immunosorbent Assay

Ninety-six-well plates (MaxiSorp [Thermo Fisher]) were coated with 100 μL of recombinant S protein diluted to 1 $\mu\text{g}/\text{mL}$ in phosphate-buffered saline (PBS) and were incubated at 4°C overnight. Plates were then blocked with 10% FBS

and 0.05% polysorbate 20 in PBS. Serum or plasma was serially diluted in blocking buffer and added to the plates. Plates were incubated for 90 minutes at room temperature and then washed 3 times with 0.05% polysorbate 20 in PBS. Goat anti-human IgG-HRP (Jackson ImmunoResearch; 1:2500) was diluted in blocking buffer before being added to wells and incubating for 60 minutes at room temperature. Plates were washed 3 times with 0.05% polysorbate 20 in PBS and then washed 3 times with PBS before the addition of peroxidase substrate (SIGMAFAST o-Phenylenediamine dihydrochloride [Sigma-Aldrich]). Reactions were stopped by the addition of 1 M hydrochloric acid. Optical density measurements were taken at 490 nm. The half-maximal binding dilution for each serum or plasma sample was calculated using nonlinear regression (GraphPad Prism 9). The limit of detection was defined as 1:30. Antibodies were validated by their respective manufacturers per their associated data sheets and titrated for ELISA by serial dilution.

Enzyme-Linked Immunosorbent Spot

Direct ex vivo ELISpot was performed to determine the number of total vaccine-binding or recombinant S-binding IgG-secreting cells present in PBMC samples using IgG/IgA double-color ELISpot kits (Cellular Technology Limited) according to the manufacturer's instructions. Plates were coated overnight at 4°C with either Flucelvax Quadrivalent 2019/2020 seasonal influenza virus vaccine (diluted 1:100) or 5 $\mu\text{g}/\text{mL}$ recombinant S proteins, anti-human Ig. ELISpot plates were analyzed using an ELISpot counter (Cellular Technology Limited).

Antigens

Recombinant soluble SARS-CoV-2 S protein was expressed as previously described (51). Briefly, mammalian cell codon-optimized nucleotide sequence coding for the soluble ectodomain of the S protein of SARS-CoV-2 (GenBank: MN908947.3, amino acids 1-1213), including a C-terminal thrombin cleavage site, T4 foldon trimerization domain, and hexahistidine tag, was cloned into mammalian expression vector pCAGGS. The S protein sequence was modified to remove the poly basic cleavage site (RRAR to A), and 2 stabilizing mutations were introduced (K986P and V987P [wild-type numbering]). Recombinant proteins were produced in Expi293F cells (Thermo Fisher) by transfection with purified DNA using the ExpiFectamine 293 Transfection Kit (Thermo Fisher). Supernatants from transfected cells were harvested 3 days after transfection, and recombinant protein was purified using Ni-NTA Agarose (Thermo Fisher), then buffer-exchanged into PBS and concentrated using Amicon Ultracel centrifugal filters (EMD Millipore).

High-Throughput Assay Using Recombinant VSV-SARS-CoV-2

Recombinant VSV-SARS-CoV-2 was produced as described previously (26). The neutralization and assay validation with native SARS-CoV-2 was done as described previously (27). Briefly, serial dilutions of patient sera, beginning with a 1:10 initial dilution, were performed in 384-well plates and were incubated with 104 plaque-forming units of VSV-SARS-CoV-2 common variant for 1 hour at 37°C . Vero E6 cells were added to the human serum-virus

complexes in 384-well plates at 2.5×10^3 cells per well and incubated at 37, C for 16 hours. Cells were fixed at room temperature in 4% formaldehyde and then rinsed with PBS. Cells were stained at room temperature with NucRed Live 647 (Invitrogen) for 30 minutes. Images were acquired using an IN Cell 6500 confocal imager (Cytiva) to visualize nuclei and infected cells and were then segmented using IN Carta (Cytiva). Virus-infected cells were identified by comparison with the uninfected threshold in Spotfire (TIBCO). IC₅₀s were generated using logistic regression and applying plateau and baseline thresholds.

Web Reference

51. Stadlbauer D, Amanat F, Chromikova V, et al. SARS-CoV-2 seroconversion in humans: a detailed protocol for a serological assay, antigen production, and test setup. *Curr Protoc Microbiol.* 2020;57: e100. [PMID: 32302069] doi:10.1002/cpmc.100

APPENDIX 2: COVARIAPAD STUDY FULL ROSTER

Suha Abushamma, MD*; Sewuese Akuse, MBBS, MPH*; Megan Arb, BS†; Teresa Arb, BSN, RN, CCRC†; Joel Brune, RN, BSN†; Jennifer Bruns, RN†; William J. Buchser, PhD*; Samantha L. Burdess, MS†; Alexander B. Carvidi, BA*; Salim Chahin, MSCE, MD*; Matthew A. Ciorba, MD*; PeChaz L. Clark, BA†; Rachel Cody, BSN, RN, CCRC†; Parakkal Deepak, MBBS, MS*; Emanuel G. Demissie, BS*; Ali H. Ellebedy, PhD*; Alia A. El-Qunni, BS*; Lacey Feigl†; Lianne S. Gensler, MD*; Maté Gergely, MD*; Jonathan Graf, MD*; Alem Haile, BS*; Katherine (Lulu) Huang, BA*; Patricia Katz, PhD*; Alfred H.J. Kim, MD, PhD*; Wooseob Kim, PhD*; Baylee Kinnett, BS*; Michael Klebert, PhD, RN, ANP-BC*; Mariel J. Liebeskind, BA*; Zhuoming Liu, PhD*; Mehrdad Matloubian, MD*; Lily E. McMorrow, BA*; Lynne Mitchell, MA, MS*; Mary Nakamura, MD*; Tina Nolte, BA†; Darren Nix*; Jane A. O'Halloran, MD, PhD*; Diana Paez, BS*; Michael A. Paley, MD, PhD*; Niti Pawar, BA*; Dana C. Perantie, MPH*; Mackenzie Poole, BA†; Rachel M. Presti, MD, PhD*; Liz Reimer, RN, BSN†; Abbey Rose†; Shea M. Roesel-Wakeland, BA†; Rebecca E. Schriefer, BA*; Shannon E. Sides, BA*; Kelly Streckfuss, RN, BSN, CCRC†; Alyssa M. Spurling, MA†; Kimberly E. Taylor, PhD, MPH*; Mahima Thapa, BS*; Sean P.J. Whelan, PhD*; Gregory F. Wu, MD, PhD*; Monica Yang, MD*; and Brittany Zwijack, RN, BSN, CCRC†.

* Author.

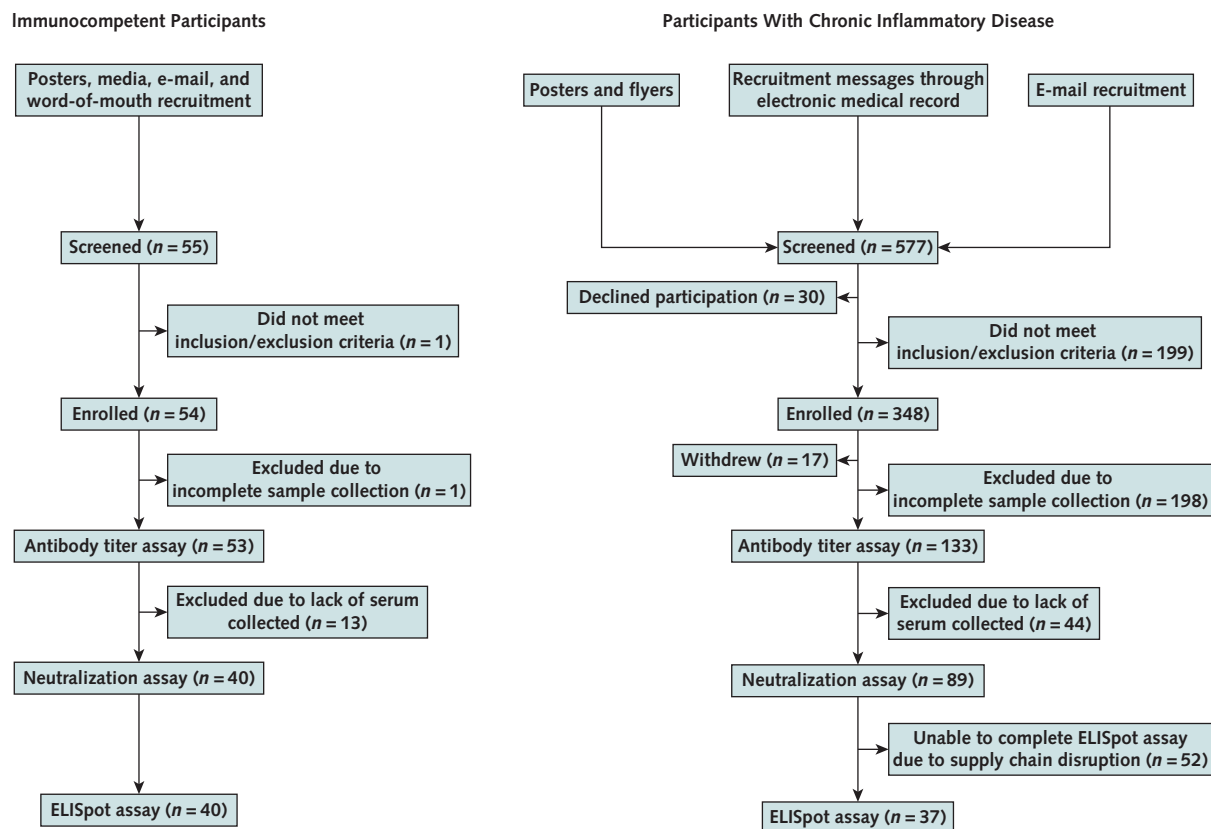
† Nonauthor contributor.

Appendix Table. Number of Immunomodulatory Medications Among Participants With CID

Medications, <i>n</i>	Participants With CID, <i>n</i> (%)
0	11 (8.2)
1	57 (42.9)
2	42 (31.6)
3	16 (12.0)
4	6 (4.5)
5	1 (0.8)

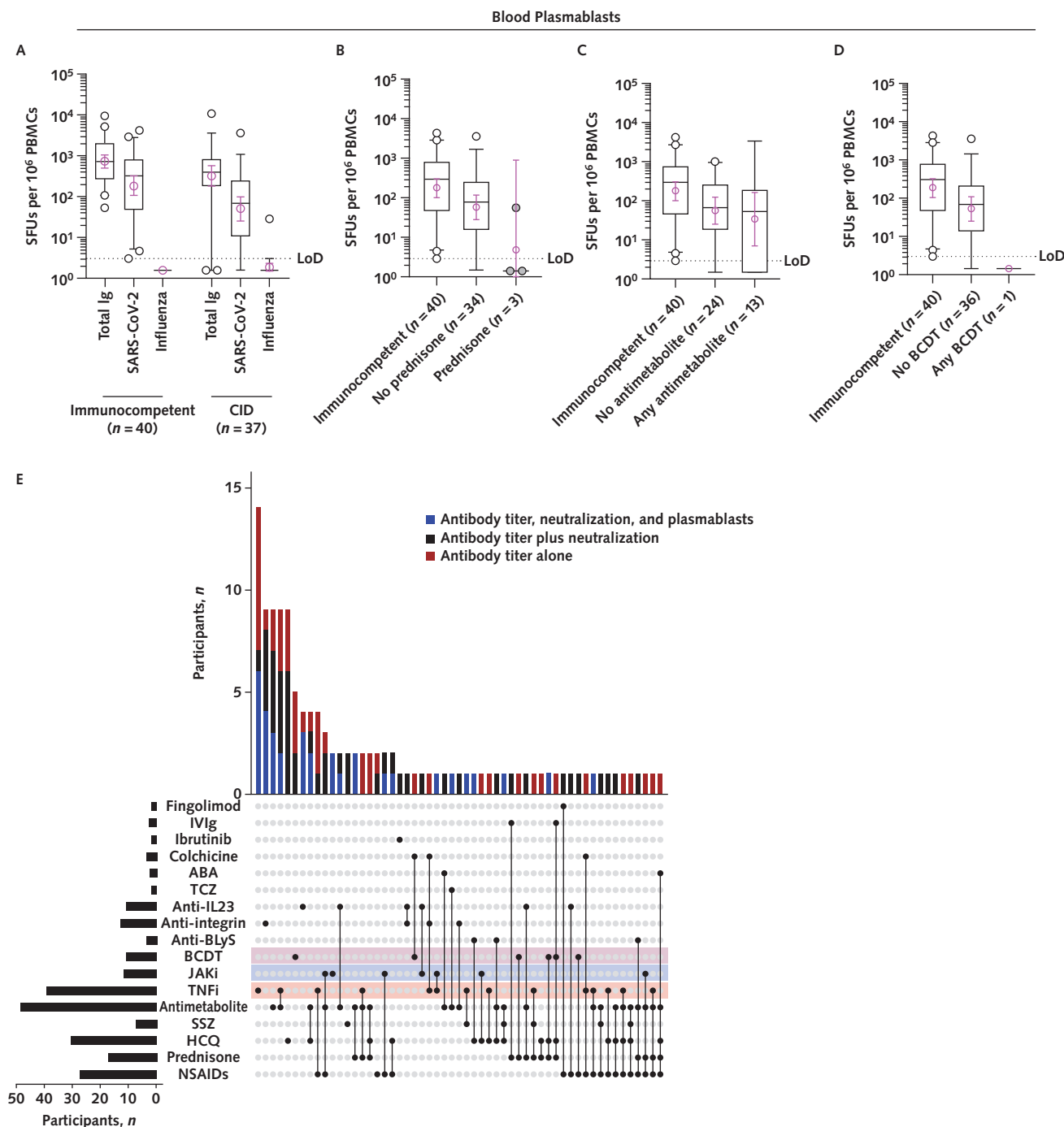
CID = chronic inflammatory disease.

Appendix Figure 1. Flow chart of inclusion, exclusion, and selection of participants.



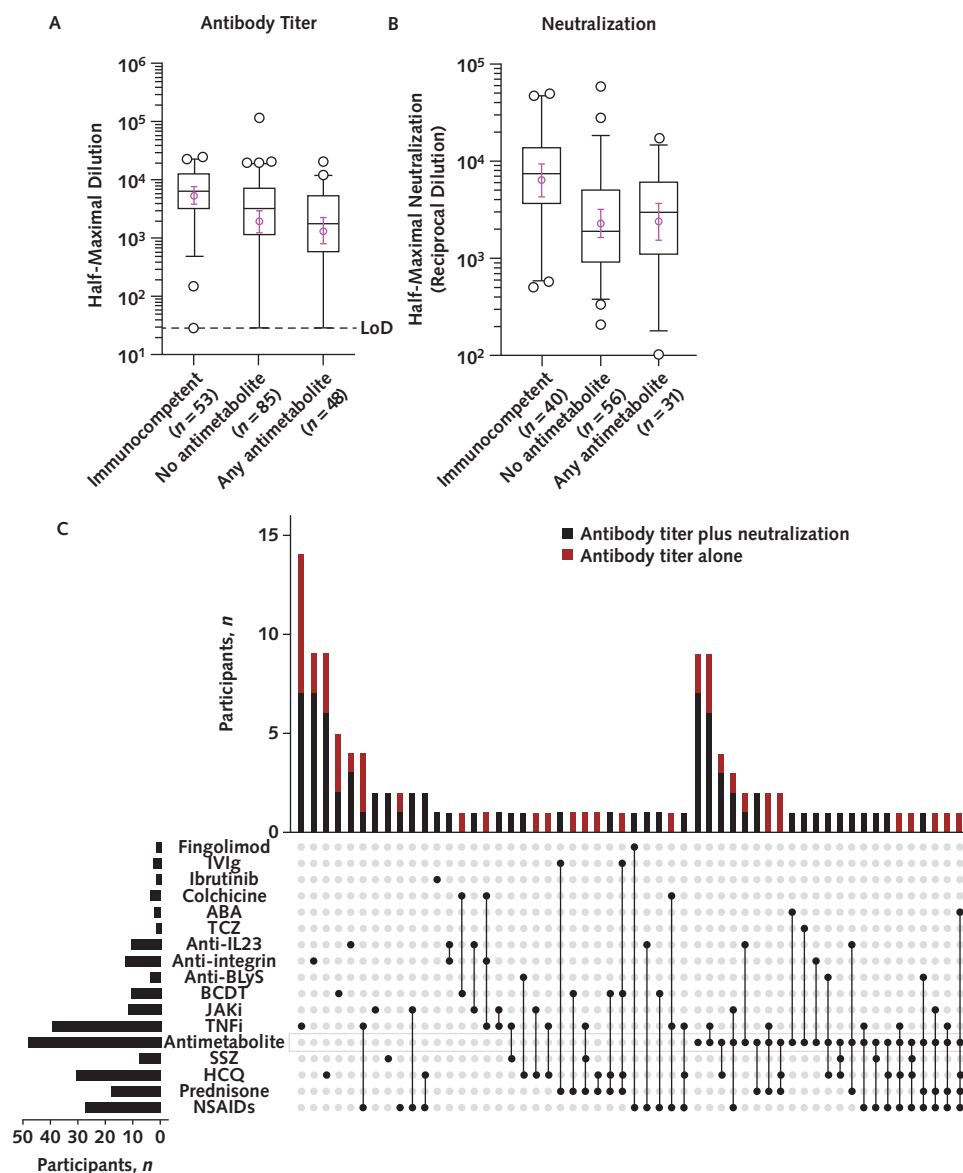
ELISpot = enzyme-linked immunosorbent spot.

Appendix Figure 2. Plasmablast formation among immunocompetent participants and those with CID.



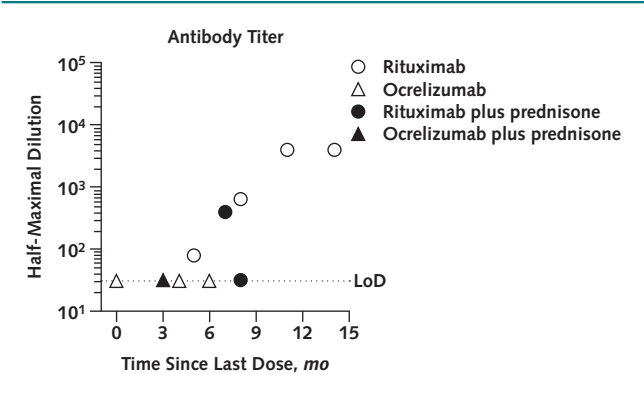
ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; ELISpot = enzyme-linked immunosorbent spot; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; PBMC = peripheral blood mononuclear cell; S = spike; SFU = spot-forming unit; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Frequency of circulating plasmablasts for immunocompetent participants and those with CID before and after immunization. Total Ig, SARS-CoV-2 S-binding Ig, and influenza virus vaccine-binding Ig are shown. **B.** Frequency of anti-S Ig circulating plasmablasts in participants with CID receiving or not receiving glucocorticoids (prednisone). **C.** Frequency of anti-S Ig circulating plasmablasts in participants with CID receiving or not receiving antimetabolites. **D.** Frequency of anti-S Ig circulating plasmablasts in participants with CID receiving or not receiving BCDT. In panels A through D, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. Plasmablast frequency was measured as SFUs per 10⁶ PBMCs via ELISpot assay. **E.** UpSet plot of immunomodulatory therapy combinations for participants with CID. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

Appendix Figure 3. Immunogenicity among participants with CID receiving antimetabolites.



ABA = abatacept; BCDT = B-cell depletion therapy; BLyS = B-lymphocyte stimulator; CID = chronic inflammatory disease; HCQ = hydroxychloroquine; IL23 = interleukin-23; IVIg = intravenous immunoglobulin; JAKi = Janus kinase inhibitor; LoD = limit of detection; NSAID = nonsteroidal anti-inflammatory drug; S = spike; SSZ = sulfasalazine; TCZ = tocilizumab; TNFi = tumor necrosis factor inhibitor. **A.** Quantification of anti-SARS-CoV-2 antibodies in participants with CID receiving or not receiving antimetabolites. In panels **A** and **B**, the boxes span the 25th to 75th percentiles, lines indicate the median, and whiskers denote the 5th and 95th percentiles. Magenta circles are at the geometric means, with error bars showing the 95% CIs. Circles represent outliers. **C.** UpSet plot of immunomodulatory therapy combinations for participants with CID, stratified by antimetabolite use. Dots with connecting lines indicate medication combinations. Combinations with no participants are omitted.

Appendix Figure 4. Anti-S IgG titers versus time since the last dose of B-cell depletion therapy.



Symbols represent individual participants. LoD = limit of detection; S = spike.