Clinical Infectious Diseases

BRIEF REPORT

Neutralizing Antibody Immune Correlates for a Recombinant Protein Vaccine in the COVAIL Trial

Youyi Fong,[1,2,3] Lauren Dang,[4] Bo Zhang,[1] Jonathan Fintzi,[4] Shiyu Chen,[1] Jing Wang,[5] Nadine G. Rouphael,[6] Angela R. Branche,[7] David J. Diemert,[8] Ann R. Falsey,[7] Cecilia Losada,[6] Lindsey R. Baden,[9] Sharon E. Frey,[10] Jennifer A. Whitaker,[11] Susan J. Little,[12] Satoshi Kamidani,[13,14] Emmanuel B. Walter,[15] Richard M. Novak,[16] Richard Rupp,[17] Lisa A. Jackson,[18] Chenchen Yu,[1] Craig A. Magaret,[1] Cindy Molitor,[1] Bhavesh Borate,[1] Tara M. Babu,[19] Angelica C. Kottkamp,[20] Anne F. Luetkemeyer,[21] Lilly C. Immergluck,[22,a] Rachel M. Presti,[23] Martín Bäcker,[24] Patricia L. Winokur,[25] Siham M. Mahgoub,[26] Paul A. Goepfert,[27] Dahlene N. Fusco,[28] Robert L. Atmar,[11] Christine M. Posavad,[29,30] Jinjian Mu,[31] Mat Makowski,[31] Mamodikoe K. Makhene,[32] Seema U. Nayak,[32] Paul C. Roberts,[32] Dean Follmann,[4] and Peter B. Gilbert[1,2,3]; Coronavirus Variant Immunologic Landscape Trial (COVAIL) Study Team

[1]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [2]Public Health Sciences Division, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [3]Department of Biostatistics, School of Public Health, University of Washington, Seattle, Washington, USA; [4]Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; [5]Frederick National Laboratory for Cancer Research, Clinical Monitoring Research Program Directorate, Frederick, Maryland, USA; [6]Hope Clinic, Department of Medicine, Division of Infectious Diseases, Emory University, Decatur, Georgia, USA; [7]Vaccine and Treatment Evaluation Unit, University of Rochester, Rochester, New York, USA; [8]George Washington Vaccine Research Unit, George Washington University, Washington, District of Columbia, USA; [9]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA; [10]Center for Vaccine Development, Saint Louis University, Saint Louis, Missouri, USA; [11]Department of Molecular Virology and Microbiology and Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; [12]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego, La Jolla, California, USA; [13]Center for Childhood Infections and Vaccines, Children's Healthcare of Atlanta, Atlanta, Georgia, USA; [14]Department of Pediatrics, Emory University, Atlanta, Georgia, USA; [15]Duke Human Vaccine Institute, Duke University School of Medicine, Durham, North Carolina, USA; [16]Project WISH, University of Illinois at Chicago, Chicago, Illinois, USA; [17]Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas, USA; [18]Department of Internal Medicine, Kaiser Permanente Washington Health Research Institute, Seattle, Washington, USA; [19]Division of Allergy and Infectious Diseases, Department of Medicine, University of Washington, Seattle, Washington, USA; [20]Vaccine and Treatment Evaluation Unit, Manhattan Research Clinic, New York University Grossman School of Medicine, New York, New York, USA; [21]Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San Francisco General Hospital, University of California, San Francisco, California, USA; [22]Clinical Research Center, Department of Microbiology, Biochemistry, and Immunology, Morehouse School of Medicine, Atlanta, Georgia, USA; [23]Department of Medicine, Washington University School of Medicine, St Louis, Missouri, USA; [24]Vaccine and Treatment Evaluation Unit, Long Island Research Clinic, New York University, Long Island School of Medicine, Mineola, New York, USA; [25]Department of Medicine, University of Iowa College of Medicine, Iowa City, Iowa, USA; [26]Howard University College of Medicine, Howard University Hospital, Washington, District of Columbia, USA; [27]Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama, USA; [28]Department of Medicine, Tulane University School of Medicine, New Orleans, Louisiana, USA; [29]Infectious Diseases Clinical Research Consortium (IDCRC) Laboratory Operations Unit, Fred Hutchinson Cancer Center, Seattle, Washington, USA; [30]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA; [31]Department of Biostatistics, The Emes Company, LLC, Rockville, Maryland, USA; and [32]Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

For COVAIL recipients of a coronavirus disease 2019 (COVID-19) Sanofi booster vaccine, neutralizing antibody titers were assessed as a correlate of risk (CoR) of COVID-19. Peak and exposure-proximal titers were inverse CoRs with covariate-adjusted hazard ratios (95% confidence intervals) 0.30 (0.11, 0.78) and 0.25 (0.07, 0.85) per 10-fold increase in weighted average titer.

Keywords. correlate of risk; COVID-19 booster; exposure-proximal titer; Omicron; variant vaccine booster.

The COVID-19 Variant Immunologic Landscape (COVAIL) trial (NCT05289037) in the United States assessed the safety and immunogenicity of second coronavirus disease 2019 (COVID-19) variant vaccine boosters [1]. COVAIL was reviewed and initially approved by the Advarra Central Institutional Review Board, with written informed consent obtained from all trial participants before enrollment. This report considers Stage 3, which from June 6 to 13, 2022, randomized 146 participants to 1 of 3 AS03-adjuvanted, pre-S dTM [transmembrane-deleted] recombinant protein vaccine products (Sanofi) differing by the Spike protein component(s): Prototype (ancestral), Beta, Beta + Prototype. From serum samples collected pre-vaccination (D1) and at Days 15 (D15), 29, 91, 181, 50% inhibitory dilution neutralizing antibody (nAb) titers were measured against D614G (B.1.D614G), Beta, Delta, Omicron BA.1, and Omicron BA.4/BA.5 using a validated pseudovirus neutralization assay (Monogram Biosciences). The nAb titers have arbitrary units/mL (AU/mL), where for D614G multiplying values by 0.0653 converts values to the International Standard scale [2].

For the Sanofi booster recipients, we assessed the 5 nAb titer markers measured at D15 as absolute level and as fold-rise from D1, as a correlate of risk (CoR) of COVID-19 between 7 and 188 days post D15 (~6-month period), referred to as "peak CoR" analysis. We also assessed a sixth marker: the maximum diversity weighted [3] geometric mean of the nAb titers against the 5 strains. We also assessed predicted-at-exposure values of each of the 6 markers as exposure-proximal CoRs of COVID-19. The COVID-19 endpoint was a self-reported or study-conducted positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test, with onset date the earliest positive test date [1]. Of the 146 participants, 142 were eligible for CoR analysis based on having D1 and D15 nAb data, not having a protocol-defined eligibility deviation [1], and not having an early COVID-19 endpoint by 6 days post D15.

All correlates analyses adjusted for baseline participant factors (detailed below) that could putatively confound the association of nAb titer with COVID-19. Cumulative incidence and peak CoR analyses fit models using a study time scale, with time origin being D15, and adjusted for a baseline risk score built by ensemble statistical learning (Statistical Analysis Plan Section 7.1 in

Received 06 May 2024; editorial decision 05 September 2024; published online 26 September 2024

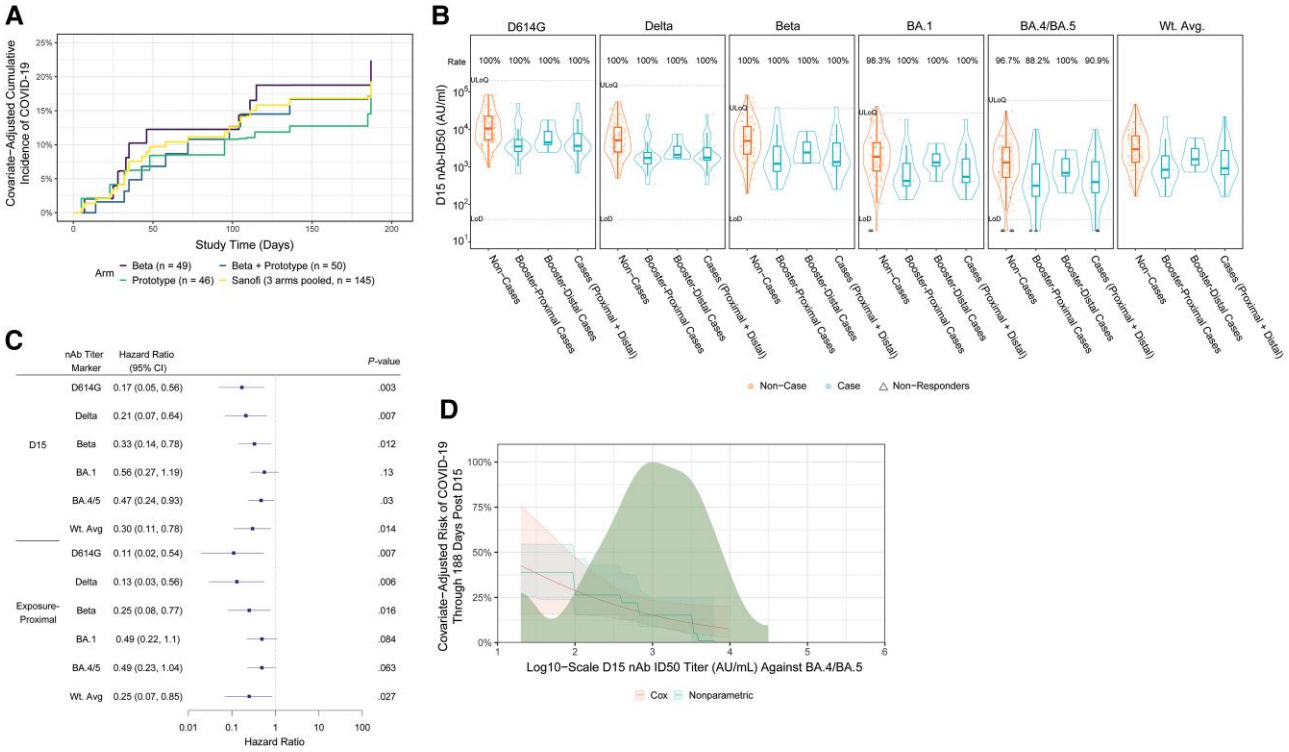

Figure 1. *A*, Covariate-adjusted cumulative incidence of COVID-19 from 7 through 188 d post D15 (last COVID-19 endpoint) for each booster arm (Beta, Prototype, Beta + Prototype) and for the three booster arms pooled. *B*, Violin box plots of D15 levels for the 6 nAb titer markers (D614G, Delta, Beta, BA.1, BA.4/BA.5, weighted average), shown by non-cases and COVID-19 endpoint cases (stratified by booster-proximal cases, booster-distal-cases, and proximal + distal cases). Non-cases: No evidence of SARS-CoV-2 infection after D1 through to the first event of (1) reaching 188 d post D15 visit without a COVID-19 event, (2) early termination, and (3) receiving an out-of-study boost. Booster-proximal cases: COVID-19 endpoint between 7 and 91 d post D15 visit; booster-distal cases: COVID-19 endpoint between 92 and 188 d post D15 visit; cases (proximal + distal): COVID-19 endpoint between 7 and 188 d post D15 visit. Rate: Percent with nAb titer above the limit of detection (LoD) = 40 AU/mL. *C*, Cox model covariate-adjusted hazard ratios of COVID-19 per 10-fold increase in each of the 6 nAb titer markers at D15 and exposure-proximal. Point estimates, 95% CIs, and 2-sided *P* values are shown. *D*, Covariate-adjusted controlled risk of COVID-19 by nAb ID50 titer against BA.4/BA.5 estimated using a Cox model (orange line) or a nonparametric method (turquoise line). Both curves were restricted to the middle 95% of the marker distribution. Shaded regions represent 95% CIs. The green shaded region is a kernel density estimate of $\log_{10}$ D15 nAb-ID50 BA.4/BA.5 titer (AU/mL). Panels *B*–*D* pool over the 3 booster arms. All analyses adjust for baseline factors defined in the text, where adjustment for FOI score had no influence on results. Wt. Avg. = Maximum diversity weighted geometric mean of the 5 nAb titers D614G reference, Beta, Delta, Omicron BA.1, and Omicron BA.4/BA.5. Abbreviations: AU/mL, arbitrary units/mL; CI, confidence interval; COVID-19, coronavirus disease 2019; FOI, force of infection, nAb, neutralizing antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULOQ, upper limit of quantitation.

Supplementary), baseline naive versus non-naive status defined by anti-nucleocapsid (N) seropositivity or self-reported previous infection (as in Branche et al [1]), and a force of infection (FOI) score calculated from the Coronavirus Resource Center's database [4] that measures the intensity of SARS-CoV-2 infection occurring in a participant's local temporal context. Each participant's FOI score is the average of daily COVID-19 incidence rates in the database in the participant's state (or District of Columbia) during their ∼6-month follow-up (Supplementary Figure 1). Exposure-proximal CoR analyses fit models using a calendar time scale and adjusted for baseline risk score and baseline anti-N serostatus. These analyses used linear mixed effects models to predict titers over time based on (1) nAb titers at D15, 29, 91, 181; (2) days since D15; and (3) baseline anti-N serostatus. The models were fit separately to the three vaccine arms including nAb titer values before any evidence of SARS-CoV-2 infection (details in Supplementary Materials). Supplementary Figure 2 shows measured versus predicted nAb titers over time.

[a]Current affiliation: Biological Sciences Division, The University of Chicago, Chicago, Illinois, USA.

Correspondence: P. B. Gilbert, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, 1100 Fairview Ave N PO Box 19024, Seattle, WA 98109 (pgilbert@fredhutch.org); D. Follmann, Biostatistics Research Branch, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 5601 Fishers Lane, MSC 9820 Rockville, MD 20892 (dfollmann@niaid.nih.gov).

Clinical Infectious Diseases®

https://doi.org/10.1093/cid/ciae465

Figure 1*A* shows covariate-adjusted cumulative incidence of COVID-19 by vaccine arm, with ~20% participants diagnosed with COVID-19. Of the 22 participants that acquired COVID-19, 17 occurred by 3 months post D15. Supplementary Table 1 shows the distribution of lineages of the 22 COVID-19 endpoints: 2 (13) were identified by sequencing as BA.4 (BA.5) and 7 were imputed from sequences in GISAID to be BA.5. Figure 1*B* and Supplementary Table 2 show distributions of the nAb titers at D15 for non-cases versus COVID-19 endpoint cases, indicating lower D15 titers in the latter (Branche et al [1] previously described nAb titer distributions for the three individual vaccines). Figure 1*B* also shows distributions of nAb titers at D15 for booster-proximal versus -distal cases, with nAb titers of the former appearing especially low.

Supplementary Figures 3 and 4 show the nAb titer distributions at D1 and as fold-rise from D1 to D15. Supplementary Figure 5 shows weighted average nAb titer trajectories across the time points, showing stable titers through 6 months. Supplementary Figures 6 and 7 show the intercorrelations of the 6 nAb titer markers across the antigens at D1 and at D15, demonstrating high correlations (median Spearman rank correlation between pairs of markers 0.93 at D1 and 0.90 at D15). Supplementary Figure 8 shows the inter-correlations of the weighted average nAb titer marker across time points.

Figure 1*C* shows covariate-adjusted hazard ratios for each of the 6 markers at peak and as predicted time-varying covariates for exposure-proximal Cox models, showing consistent inverse CoRs, with peak CoR hazard ratios ranging from 0.17 to 0.56 per 10-fold marker increase across the markers (median P value = .033) and exposure-proximal CoR hazard ratios ranging from 0.11 to 0.49 across the markers (median P value .022). The peak correlates analysis restricting to the COVID-19 endpoints through 3 months (booster-proximal) also showed significant inverse CoRs (Supplementary Table 3). The 6 D1 to D15 fold-rise nAb titer markers were also assessed and not found to be CoRs (P values ranging from .29 to .87, Supplementary Table 4). Fold-rise, stratified by naive status, was modestly lower in cases, thus aligning with the Cox model results (Supplementary Figures 9–15).

Based on controlled risk modeling by a Cox model or monotone-constrained nonparametric analysis [5] previously applied to phase 3 trials [2, 6–9], Figure 1*D* shows how the cumulative incidence of COVID-19 from 7 through 188 days post D15 changes with D15 BA.4/BA.5 nAb titer. Hypothesis tests for the cumulative incidence varying with the D15 marker yielded $P = .030$ for the Cox model and $P = .038$ for the nonparametric model; these results were $P = .014$ (Cox) and $P = .024$ (nonparametric) for weighted average titer. The probability of BA.4/BA.5 COVID-19 acquisition was about 40%–50% at undetectable nAb titer and decreased to about 15% and 7% at nAb titers of 1000 and 10,000, respectively (nonparametric model). The pattern of decreasing COVID-19 risk with increasing D15 nAb titer occurred for all nAb titer markers (Supplementary Figure 16).

The US Government COVID-19 Vaccine Correlates of Protection Program [10] showed that nAb titer against D614G was a consistent inverse CoR of COVID-19 [11] for the Moderna mRNA-1273 vaccine [7, 9], Janssen AD26.CoV.2S vaccine [2], Astra-Zeneca Chimp-AdOx vaccine [6], and Novavax NVX-CoV2373 vaccine [6]. The results presented here for COVAIL are the first results that assessed nAb titer as a correlate for the Sanofi recombinant protein vaccine, where nAb titer was measured using the same assay (Monogram) employed in 3 of the phase 3 trials listed above. Correlates analyses are ongoing for the Sanofi VAT0008 phase 3 trial [12, 13], which as 2 harmonized placebo-controlled trials will inform about correlates of protection as well as about CoR, and will provide results restricted to non-naïve individuals separately for the Prototype and Beta + Prototype vaccines. The COVAIL results showed that nAb titer is also an inverse CoR for the combined Sanofi recombinant protein pre-S dTM AS03 boosters, both measured at peak/D15 and predicted over time. Compared to the previous results, interesting features of COVAIL include assessment of CoR in the context of Omicron circulating strains and inclusion of nAb titers measured against Omicron strains, and a sizable fraction (41.5%) of the cohort was estimated to have prior infection with SARS-CoV-2. Point estimates of CoRs for the Sanofi vaccine were as strong as has been observed in any of the phase 3 trials, although there are insufficient data to venture inferences about whether the CoR strength differs in COVAIL versus the phase 3 trials.

A limitation of this study is that the COVID-19 endpoint was defined in some (7/22) cases as a self-reported positive test, differing from the definition in the phase 3 trials that required central lab virologic confirmation and meeting pre-specified symptoms criteria. For the majority (15/22), the COVID-19 endpoint was virologically confirmed. Another limitation is only 22 evaluable breakthrough COVID-19 endpoints, which curtailed the set of objectives that could be addressed. In particular, CoRs could not be assessed separately by history of infection, nor separately by the 3 vaccine product arms, precluding a correlate of protection (CoP) analysis comparing COVID-19 incidence among the randomized groups. Similarly, there is low precision for comparing CoRs for COVID-19 endpoints proximal versus distal to the booster, and for comparing CoRs against different antigens.

The limitations above notwithstanding, point estimates from the analyses suggest the following hypothesis-generating results: (1) the CoRs were stronger against booster-proximal COVID-19 over the first 3 months, an intriguing trend given that nAb titers were stable through 6 months, suggesting waning of protective components of the immune response not captured by nAb titers; and (2) BA.4/BA.5 titer, which best matched the circulating strains (majority BA.4/BA.5), was not a stronger CoR compared to nAb titer against the original

D614G reference strain. Overall, this study provides evidence that pseudovirus neutralizing antibody titer—measured with a consistent assay employed for other US Government program studies—constitutes a biomarker that can be used to predict risk of COVID-19 after a Sanofi pre-S dTM AS03 booster.

Supplementary Data

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

Notes

Acknowledgments. The authors thank the participants and site staff of the COVAIL trial. We also thank Lindsay Carpp for assistance in scientific writing and technical editing.

Data availability. All data were previously included with Branche et al [1].

Financial support. This research was supported in part by the National Institutes of Health (NIH). This work was funded in part by the National Institute of Allergy and Infectious Diseases (NIAID) of the NIH "COVAIL Correlates of Protection Project" and by NIAID award number R37AI054165 to P. B. G. The COVAIL trial was funded in part by federal funds from NIAID and the National Cancer Institute, NIH, under contract number 75N910D00024, task order number 75N91022F00007, and in part by the Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority, under Government Contract number 75A50122C00008 with Monogram Biosciences, LabCorp. This work was also supported in part with federal funds from the NIAID, NIH, under contract number 75N93021C00012, and by the Infectious Diseases Clinical Research Consortium (IDCRC) through the NIAID under award number UM1AI148684. Testing of neutralizing antibody titers by Monogram Biosciences, LabCorp has been funded in part with federal funds from the Department of Health and Human Services, the Administration for Strategic Preparedness and Response, Biomedical Advanced Research and Development Authority, under contract number. 75A50122C00008. Testing for anti-N-specific antibody was conducted by Cerba Research under contract number 75N93021D00021. The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIH—NIAID. The production of clinical material used in this study was funded by Sanofi and by federal funds from the Biomedical Advanced Research and Development Authority, part of the office of the Administration for Strategic Preparedness and Response at the US Department of Health and Human Services in collaboration with the US Department of Defense Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense under contract number W15QKN-16-9-1002. The views presented here are those of the authors and do not purport to represent those of the Department of the Army.

Potential conflicts of interest. L. D. received support from Novo Nordisk (NN) via a philanthropic gift to UC Berkeley that supported conference/meeting-related travel she took in 2021 and 2022, as well as supported her tuition during her PhD from 9/2020 to 5/2023. S. C. reports grant support to her institution from NIH/NIAID for the present manuscript. N. G. R. received NIH funding to her institution for the present manuscript and her institution received funds for her to conduct research in the past 36 months from Merck, Sanofi, Pfizer, Vaccine Company, Immorna, Quidel and Lilly. In the past 36 months, N. G. R. received consulting fees from Krog; payment for virology education; support from Sanofi and Moderna to attend meetings and/or travel; participated on Moderna, Sanofi, Seqirus, Pfizer advisory boards; served on EMMES, ICON, BARDA, CyanVac Micron Safety Committees; served in advisory roles on ARLG, TMRC, CDC-Pertussis challenge, served (and is currently) an Associate Editor at *Clinical Infectious Diseases*; and her institution received equipment, materials, drugs, medical writing, gifts or other services from the Georgia Research Alliance. A. R. B. received support for the present manuscript from Merck, and received grants or contracts from Moderna, Pfizer, Cyanvac, and Vaccitech in the past 36 months. In the past 36 months, she also received consulting fees from GSK, Moderna, Sanofi, and Novavax; and payment for a speaker role at learning lounges for IDWeek from Moderna and Sanofi.

D. J. D. received an award to his institution from Leidos Biomed/NIH to conduct the clinical trial reported in the manuscript. A. R. F. reports in the past 36 months research grants to her institution from Janssen, Merck, CyanVac, VaxCo, BioFire Diagnostics, Moderna, Pfizer, and AstraZeneca; consulting fees from ADMA Biologics, GSK, Sanofi Pasteur, and Merck; support for attending meetings and/or travel from GSK, Moderna, and Sanofi Pasteur; and participation on a Novavax Data Safety Monitoring Board or Advisory Board. L. R. B received an NIH grant to his institution for the present manuscript; reports grants from NIH, Harvard Medical School, Wellcome Trust, and the Gates Foundation to his institution in the past 36 months; and participated in an NIH DSMB meeting in the past 36 months and an FDA AMDAC Committee in the past 36 months. L. R. B. is involved in human immunodeficiency virus (HIV) and SARS-CoV-2 vaccine clinical trials conducted in collaboration with the NIH, HIV Vaccine Trials Network (HVTN), COVID Vaccine Prevention Network (CoVPN), International AIDS Vaccine Initiative (IAVI), Crucell/Janssen, Moderna, Military HIV Research Program (MHRP), the Gates Foundation, and Harvard Medical School.

S. E. F. reports funding from Leidos Biomed via a contract to support the present manuscript and participated on an HVTN SMB in the past 36 months. S. J. L. reports research grant funding from the NIH and from Gilead Sciences paid to her institution in the past 36 months. S. K. reports research support to his institution in the past 36 months from Pfizer, Moderna, Bavarian Nordic, Meissa, Sanofi, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH). In the past 36 months, he also received payment from the American Academy of Pediatrics for development of educational materials (related to vaccines). E. B. W. received support from Leidos Biomedical Research to his institution for the present manuscript. In the past 36 months, E. B. W. received payments to his institution from Pfizer, Moderna, Sequiris, Najit Technologies Inc, and Clinetic for the conduct of clinical trials and clinical research; received consulting fees from Iliad Biotechnologies; and received payment from Vaxcyte (for serving on a Scientific Advisory Board), Pfizer (for serving on an Advisory Board), and Shionogi (for serving on a DSMB). R. M. N. reports funding from the NIH for the present manuscript. In the past 36 months, he received payment from Moderna for serving in an advisory role for Moderna after this study enrolled and participated on an NIH DSMB or Advisory Board. R. M. N. reports grant funding to his institution from the NIH for the present manuscript. L. A. J. reports grant funding to her institution within the past 36 months from the NIH and the CDC. A. F. L. reports funding to her institution from COVAIL. In the past 36 months, her institution received grant support from Cepheid, Gilead, GSK, and Merck, as well as donation of lab kits and regents from Cepheid and Hologic, and donation of medication from Mayne Pharma, to support research projects. L. C. I. reports funding from NIH-NIAID-DMID for the present manuscript. In the past 36 months, her institution received funding from the NIH-NIMHD, NIH-NCATS, NIH-NHBL-NIMHD, DOE, Pediatric Emergency Medicine Associates, GSK, Merck, Novavax, Sanofi, Moderna, and Pfizer for vaccine trials; she received consulting fees from the CDC for reviewing grants, an honorarium from the National Medical Association for speaking, and payment from the American Academy of Pediatrics for attending meetings and/or travel; she participated (no payment for services) on an NIH-DMID- Data Safety Monitoring Board for an mpox vaccine trial, served on the American Academy of Pediatrics-Section on Infectious Diseases, Executive Board, and on the HIV Vaccine Trials Network- Co-Chair of HIV Vaccine Trial Protocol Development; served as a Board Member for the Georgia Institute of Technology, Center for Spatial Analytics, held a leadership or fiduciary role in the American Academy of Pediatrics, and served on the Education Committee of the Pediatric Infectious Diseases Society. M. B. reports

funding from the NIH via Leidos Biomedical Research to his institution to support the present manuscript. In the past 36 months, his institution received research funding from Pfizer. P. A. G. reports funding from the NIH in the past 36 months, as well as a patent planned, issued, or pending for a COVID monoclonal antibody with Aridis Pharmaceuticals. P. L. W. reports contract support to her institution from the NIH for the present manuscript, as well as clinical trials contract support to her institution from Pfizer in the past 36 months. In the past 36 months, she also participated on a Data Safety Monitoring Board or Advisory Board for Emmes Corporation and for Blue Lake. In the past 36 months, D. N. F. served on an Advisory Board for AXCELLA, as a speaker for Gilead Sciences, and as site PI for clinical trials sponsored by Gilead Sciences, Regeneron, MetroBiotech LLC, and the NIH (DMID COVAIL); consulted for Gilead Sciences; and received speaker honoraria from Gilead Sciences. R. L. A. reports funding to his institution from NIH/NIAID/DMID for the present manuscript. C. M. P. reports grant funding to her institution from NIH/NIAID to support the present manuscript. J. M. and M. M. report a contract to their institution from NIH/DMID to support the present manuscript. P. B. G. had NIH NIAID grant support for the present manuscript. In the past 36 months, P. B. G. participated on 3 Sanofi vaccine advisory boards for pertussis, RSV, and RSV/hMPV/PIV3, and was reimbursed for his time with contracts to his institution and with independent consulting. He also has received contracts to his institution from Sanofi Pasteur in the past 36 months.

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

References

1. Branche AR, Rouphael NG, Diemert DJ, et al. Comparison of bivalent and monovalent SARS-CoV-2 variant vaccines: the phase 2 randomized open-label COVAIL trial. Nat Med **2023**; 29:2334–46.
2. Fong Y, McDermott AB, Benkeser D, et al. Immune correlates analysis of the ENSEMBLE single Ad26.COV2.S dose vaccine efficacy clinical trial. Nat Microbiol **2022**; 7:1996–2010.
3. He Z, Fong Y. Maximum diversity weighting for biomarkers with application in HIV-1 vaccine studies. Stat Med **2019**; 38:3936–46.
4. Johns Hopkins Coronavirus Resource Center. Region—United States. Available at: https://coronavirus.jhu.edu/region/united-states. Accessed 12 March 2024. Last updated 10 March 2023.
5. Gilbert PB, Fong Y, Kenny A, Carone M. A controlled effects approach to assessing immune correlates of protection. Biostatistics **2023**; 24:850–65.
6. Benkeser D, Fong Y, Janes HE, et al. Immune correlates analysis of a phase 3 trial of the AZD1222 (ChAdOx1 nCoV-19) vaccine. NPJ Vaccines **2023**; 8:36.
7. Benkeser D, Montefiori DC, McDermott AB, et al. Comparing antibody assays as correlates of protection against COVID-19 in the COVE mRNA-1273 vaccine efficacy trial. Sci Transl Med **2023**; 15:eade9078.
8. Fong Y, Huang Y, Benkeser D, et al. Immune correlates analysis of the PREVENT-19 COVID-19 vaccine efficacy clinical trial. Nat Commun **2023**; 14:331.
9. Gilbert PB, Montefiori DC, McDermott AB, et al. Immune correlates analysis of the mRNA-1273 COVID-19 vaccine efficacy clinical trial. Science **2022**; 375:43–50.
10. Koup RA, Donis RO, Gilbert PB, Li AW, Shah NA, Houchens CR. A government-led effort to identify correlates of protection for COVID-19 vaccines. Nat Med **2021**; 27:1493–4.
11. Gilbert PB, Donis RO, Koup RA, Fong Y, Plotkin SA, Follmann D. A COVID-19 milestone attained—a correlate of protection for vaccines. N Engl J Med **2022**; 387:2203–6.
12. Dayan GH, Rouphael N, Walsh SR, et al. Efficacy of a bivalent (D614 + B.1.351) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, parallel, randomised, modified double-blind, placebo-controlled trial. Lancet Respir Med **2023**; 11:975–90.
13. Dayan GH, Rouphael N, Walsh SR, et al. Efficacy of a monovalent (D614) SARS-CoV-2 recombinant protein vaccine with AS03 adjuvant in adults: a phase 3, multi-country study. EClinicalMedicine **2023**; 64:102168.