

Understanding “Hybrid Immunity”: Comparison and Predictors of Humoral Immune Responses to Severe Acute Respiratory Syndrome Coronavirus 2 Infection (SARS-CoV-2) and Coronavirus Disease 2019 (COVID-19) Vaccines

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Background. Comparison of humoral responses in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinees, those with SARS-CoV-2 infection, or combinations of vaccine/ infection (“hybrid immunity”) may clarify predictors of vaccine immunogenicity.

Methods. We studied 2660 US Military Health System beneficiaries with a history of SARS-CoV-2 infection-alone (n = 705), vaccination-alone (n = 932), vaccine-after-infection (n = 869), and vaccine-breakthrough-infection (n = 154). Peak anti-spike-immunoglobulin G (IgG) responses through 183 days were compared, with adjustment for vaccine product, demography, and comorbidities. We excluded those with evidence of clinical or subclinical SARS-CoV-2 reinfection from all groups.

Results. Multivariable regression results indicated that vaccine-after-infection anti-spike-IgG responses were higher than infection-alone ($P < .01$), regardless of prior infection severity. An increased time between infection and vaccination was associated with greater post-vaccination IgG response ($P < .01$). Vaccination-alone elicited a greater IgG response but more rapid waning of IgG ($P < .01$) compared with infection-alone ($P < .01$). BNT162b2 and mRNA-1273 vaccine-receipt was associated with greater IgG responses compared with JNJ-78436735 vaccine-receipt ($P < .01$), regardless of infection history. Those with vaccine-after-infection or vaccine-breakthrough-infection had a more durable anti-spike-IgG response compared to infection-alone ($P < .01$).

Conclusions. Vaccine-receipt elicited higher anti-spike-IgG responses than infection-alone, although IgG levels waned faster in those vaccinated (compared to infection-alone). Vaccine-after-infection elicits a greater humoral response compared with vaccine or infection alone; and the timing, but not disease severity, of prior infection predicted these post-vaccination IgG responses. While differences between groups were small in magnitude, these results offer insights into vaccine immunogenicity variations that may help inform vaccination timing strategies.

Keywords. SARS-CoV-2; IgG; antibody response; vaccine; vaccine breakthrough.

Coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccines induce severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein expression in vaccine recipients, resulting in robust humoral and T-cell responses [1]. In the United States, two mRNA vaccines were authorized in December 2020 [2–4]. Since their widespread use in the United States and elsewhere, these mRNA vaccines proved highly effective in prevention and reduced hospitalization, morbidity,

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and death [5–7]. The US Food and Drug Administration (FDA) also authorized use of a viral vectored vaccine using an adenovirus-26 backbone in February 2021 [8].

While there is strong evidence of COVID-19 vaccines' effectiveness and safety [2, 3, 6, 9, 10], full characterization of the durability of vaccine-induced humoral immunity and predictors of a durable vaccine immune response remains important to investigate. Comparison of humoral immune responses of SARS-CoV-2 vaccine recipients with and without a history of SARS-CoV-2 infection to immunity induced by SARS-CoV-2 infection alone helps to identify such predictors of vaccine immune response and potentially inform vaccination timing strategies.

Prior studies noted that infection-induced and vaccine-induced immunity were durable for at least 6 months, but those vaccinated with prior infection (ie, vaccine after infection) mounted a greater and more durable level of humoral response [11–13]. While these studies emphasized the value of vaccination following a prior infection, additional data that replicate these findings add to consensus for vaccination regardless of infection history. However, several questions surround SARS-CoV-2 “hybrid immunity” that is induced by infection and subsequent vaccination. It is unclear whether initial illness severity or time between infection and subsequent vaccination modifies this post-infection vaccine immunoglobulin G (IgG) “boost.” The emergence of the Omicron variant underscores the importance of understanding predictors of durable and robust vaccine immunity, particularly as a rapidly growing proportion of the population with a history of vaccination before or after infection develops hybrid immunity.

Here, we sought to compare the magnitude and durability of vaccine-induced humoral immunity against humoral immune response elicited by SARS-CoV-2 infection, adjusting for vaccine product and vaccine recipient baseline health and age. We then confirmed whether vaccine-induced immunity following prior infection (hybrid immunity) offered more robust humoral response than that afforded by prior infection/vaccination alone and whether this was affected by host characteristics (age and comorbidities), severity or timing of the prior infection, specific product vaccine received, or number of vaccine doses received.

METHODS

Study Population and General Study Design

The Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study is a longitudinal cohort study of US Military Health System (MHS) beneficiaries with a history of SARS-CoV-2 infection and/or vaccination (see [Supplementary Materials](#) for extended details). Briefly, eligibility criteria for enrollment include those MHS beneficiaries who present to a military treatment facility (MTF) for SARS-CoV-2 polymerase chain reaction (PCR) testing. In early 2021,

eligibility for EPICC was expanded to enroll those who receive an FDA-authorized SARS-CoV-2 vaccine, that is, BNT162b2 (Pfizer/BioNTech), mRNA-1273 (Moderna), or JNJ-78436735 (Janssen) within the MHS, with enrollment on the day of vaccination.

EPICC enrollment occurs at 10 MTFs: Brooke Army Medical Center, Fort Belvoir Community Hospital, Madigan Army Medical Center, Naval Medical Center Portsmouth, Naval Medical Center San Diego, Tripler Army Medical Center, Walter Reed National Military Medical Center, Carl R. Darnall Army Medical Center, William Beaumont Army Medical Center, and Womack Army Medical Center. To permit scalability of enrollment across other geographic areas (including non-US locations) and to enhance convenience to participants, beginning on 19 October 2020, MHS beneficiaries who were either tested for SARS-CoV-2 and/or vaccinated were also eligible for enrollment and followed remotely via an online pathway ([Supplementary Table 1](#)).

The EPICC study therefore enrolls and follows participants who are SARS-CoV-2 test-positive, SARS-CoV-2 test-negative, and those vaccinated with or without a history of SARS-CoV-2 infection. MHS beneficiaries enrolled in EPICC who were diagnosed with SARS-CoV-2 and/or vaccinated against SARS-CoV-2 from 20 March 2020 through 15 November 2021 were included in this analysis.

We excluded those participants who tested SARS-CoV-2-negative and had not received any vaccination. We also excluded those who received a vaccine as part of a clinical trial. In addition, children (aged <18 years) were excluded from the analysis due to later implementation of vaccines in pediatric populations ([Supplementary Figure 1](#)).

Diagnosis of SARS-CoV-2 Infection and Case Definition

SARS-CoV-2 infection was determined using a positive PCR clinical laboratory test performed at the enrolling MTF or follow-up positive upper respiratory swab collected as part of the EPICC study by day 17 post-enrollment and tested by PCR [2] and/or supplemented with self-reported testing history in online-enrolled participants (see [Supplementary Materials](#)).

Ascertainment and Definitions of COVID-19 Vaccine History

Vaccination status was established, including the date and product of vaccine receipt, through the Military Health System Data Repository (MDR) in addition to a case report form and supplemented by questionnaire self-report (see [Supplementary Materials](#)). We defined “completed primary vaccine series” by 14 days after a 2-dose series of mRNA vaccine administered 21 days (ie, BNT162b2) or 28 days (ie, mRNA-1273) apart or a single dose of viral vector vaccine (ie, JNJ-78436735).

Measurement of SARS-CoV-2 Anti-Spike-IgG Response

Anti-spike-IgG responses were measured using a multiplex microsphere-based immunoassay, described in detail previously [14, 15], which has been used in concurrent testing with the Mt. Sinai emergency use authorization enzyme-linked immunosorbent assay and performed with 99% concordance [16] (see [Supplementary Materials](#)). Antigen-specific SARS-CoV-2 spike and nucleocapsid protein (NP) reactive IgG levels were reported as a median fluorescence intensity (MFI).

Comparisons of Anti-Spike-IgG Responses to SARS-CoV-2 Infection and Vaccines

The primary outcome of interest in this analysis was peak observed SARS-CoV-2 anti-spike-IgG MFI assessed out to 183 days post-vaccine/infection exposure (ie, final vaccine date or symptom onset date, respectively). This period was constrained by the duration of post-vaccine follow-up time available. \log_{10} transformations were applied to anti-spike-IgG MFI values to normalize the data, and exponentiated coefficients were used to interpret the results. We compared 4 groups for anti-spike-IgG responses to SARS-CoV-2 infection and/or vaccines: infection alone (those who tested SARS-CoV-2-positive and did not receive any subsequent vaccination), vaccination alone (completed primary vaccination series without a known history of SARS-CoV-2 infection), vaccination after infection (those who tested SARS-CoV-2-positive and then received complete primary vaccination series), and vaccine breakthrough infection (those who were infected by SARS-CoV-2 two or more weeks after complete primary vaccination series). Given the small number of participants who received booster doses and limited follow-up time, these participants were excluded from analysis. We retained a subset of participants classified as vaccine after infection who received only 1 dose of mRNA vaccine (compared with 2 doses) to examine humoral immune response (see [Supplementary Materials](#) for extended details).

Adjusted Comparisons of Anti-Spike-IgG Responses to SARS-CoV-2 Infection and Vaccines and Identification of Predictors of Humoral Immune Response

We performed unadjusted and adjusted comparisons of peak observed SARS-CoV-2 anti-spike-IgG MFI between 4 groups using univariable and multivariable linear regression. These models considered other potential predictors of vaccine and/or infection humoral response, including serum specimen sampling time, that is, time between date of serum specimen collection of peak anti-spike-IgG and date of final dose of vaccine receipt or SARS-CoV-2 infection symptom onset date (whichever was latest); comorbidities; sex; age; and vaccine product received. We examined post-vaccination anti-spike-IgG response in participants with a prior infection history with a multivariable regression model to examine how severity of initial infection changed peak post-vaccination anti-spike-IgG. We

conducted a Spearman correlation (ρ) to determine whether increasing time from infection to vaccination correlated with increased peak post-vaccination IgG.

We used the Charlson comorbidity index (CCI) [17] to quantify comorbidities measured in MDR or self-reported by participant. Age, sex, race and ethnicity were reported by participants. We categorized infection severity by the need for hospitalization for COVID-19. Descriptive statistics were calculated for demographic characteristics, comorbidities, and illness severity by 4 groups, with *P* values computed using the Fisher exact test. The nonparametric Mann-Whitney *U* test and Kruskal-Wallis variance analysis were used to evaluate the data. Figures were generated and statistical analyses were performed using RStudio version 4.0.2 software [18].

Repeated Measures Sensitivity Analysis

We extended the above analyses (which used a single time point anti-spike-IgG value with adjustment for sampling time after latest antigenic exposure) and confirmed findings with a repeated measures model that incorporated within-participant changes in anti-spike-IgG over time and restricted to those with two or more sera specimens collected. For this mixed linear model, we used anti-spike-IgG as the dependent variable while controlling for random effects of participants and the fixed effect of time since infection to vaccination. The coefficients derived from this estimate indicated whether vaccination alone, vaccine after infection, and vaccine breakthrough infection were associated with larger peak IgG response compared with SARS-CoV-2 infection alone. We fit an interaction term of sampling time by group to estimate whether IgG quantity waned faster by group.

Ethics

The Uniformed Services University of the Health Sciences Institutional Review Board (under protocol IDCRP-085) approved this study. All participants or their legally authorized representative provided informed consent to participate.

RESULTS

Demographic, Clinical, and Antigenic Exposure Characteristics of EPICC Participants

Among 3475 SARS-CoV-2-tested and/or vaccinated participants who were enrolled in EPICC, 2660 (84%) had sera or dried blood spot collected and were included in this analysis: SARS-CoV-2 infection alone ($n = 705$), SARS-CoV-2 vaccinated alone ($n = 932$), vaccine after infection ($n = 869$), and vaccine breakthrough infection ($n = 154$; [Supplementary Figure 1](#)). This total number of participants included 189 and 217 participants who received 1 dose of vaccine in the vaccination-alone and vaccine-after-infection groups, respectively, at the time of data cutoff for analysis. These participants were not used for 4-group comparison but were used for

supplemental analyses. This analysis set excluded ($n = 209$) clinically apparent infections and ($n = 502$) subclinical reinfections across all 4 groups (Supplementary Figure 1). Most (79.9%) vaccinees received the BNT162b2 vaccine, 18.9% received the mRNA-1273 vaccine, and 1.2% received the JNJ-78436735 vaccine.

More than half of these participants were male (59.4%), 66.2% were aged 18–44 years, and 81% had no comorbidities at enrollment (Table 1). The median age of these enrolled participants was 38 years (interquartile range, 20.7). The median sampling time for each group was evaluated based on the latest antigenic exposure (SARS-CoV-2 infection/vaccination) and is presented in Table 1.

Unadjusted and Adjusted Comparison of Anti-Spike-IgG Response to SARS-CoV-2 Infection and/or Vaccination

The observed maximum (peak) SARS-CoV-2 anti-spike-IgG levels by sampling time are presented in Figure 1. The mean unadjusted peak anti-spike-IgG level was higher in vaccine-after-infection participants compared with infection-alone or vaccination-alone participants ($P < .01$) and highest in those with vaccine breakthrough infection (Figure 2). Age group stratification revealed similar findings related to peak anti-spike-IgG responses (Supplementary Figure 2A). Even after a single dose of mRNA vaccine following prior infection, peak anti-spike-IgG response was greater than peak anti-spike-IgG response after infection alone ($P < .01$; Supplementary Figure 2B).

To account for differences in post-infection/post-vaccine sera sampling time and host characteristics between groups (Table 1), we examined the differences in peak anti-spike-IgG between groups and demonstrated that vaccination-alone status was associated with a 1.07 MFI increase in peak anti-spike-IgG compared with those with SARS-CoV-2 infection alone, after adjusting for host characteristics (ie, age, sex, CCI, and sampling time; $P < .01$; Table 2). We confirmed that SARS-CoV-2 vaccination after infection is associated with a larger peak anti-spike-IgG response (increase of 1.13 MFI compared with SARS-CoV-2 infection alone, adjusting for group and host characteristics; $P < .01$; Table 2) and that vaccine breakthrough infection is associated with the highest peak anti-spike-IgG (1.2 MFI; $P < .01$; Table 2).

Comparison of Vaccine Product Responses, Accommodating Infection History, and Host Characteristics

When stratified by each vaccine product, we consistently noted the highest median anti-spike-IgG response in the vaccine-breakthrough-infection group (Supplementary Figure 2C). The vaccination-after-infection group had a higher peak anti-spike-IgG response compared with the vaccination-alone group (Supplementary Figure 2C).

When directly compared between vaccine types (unadjusted), a receipt of an mRNA vaccine (BNT162b2, mRNA-1273)

induced a higher peak anti-spike-IgG compared with JNJ-78436735 ($P < .01$; Supplementary Figure 2D). Even after adjusting for differences in host characteristics and prior infection history between vaccine recipient groups, JNJ-78436735 receipt produced lower peak response compared with BNT162b2 and mRNA-1273 (Table 3). These adjusted comparisons also noted a statistically significant difference in the magnitude of peak responses between BNT162b2 and mRNA-1273, but the magnitude of this difference was small (Table 3, Supplementary Table 2).

Correlation of Severity and Timing of Initial Infection With Post-Vaccine Anti-Spike-IgG Response

We examined predictors of vaccine-after-infection anti-spike-IgG responses, specifically whether this was dependent on severity of initial infection. We fit a multivariable regression model restricted to vaccine-after-infection participants (Table 4). The result indicated that being hospitalized for COVID-19 (compared with outpatient COVID-19 infection history) was not associated with higher observed post-vaccine peak anti-spike-IgG \log_{10} ($P = .88$). However, we noted an increasing post-vaccine IgG peak with increasing time since infection to vaccination (Supplementary Figure 3).

Estimation of Anti-Spike-IgG Waning Rates by Vaccination and/or Infection

A mixed effects model derived from longitudinally collected sera compared within-participant changes of anti-spike-IgG levels among groups. The findings confirmed prior single time point analyses, that is, that vaccination alone was associated with a higher peak IgG than infection alone, that vaccine breakthrough infection was associated with the highest peak spike IgG response, and that vaccination after infection was associated with a higher peak anti-spike-IgG response than vaccine alone or infection alone (Supplementary Table 3).

To better understand anti-spike-IgG durability, we included a regression model interaction term of vaccine/infection history and sampling time to specifically estimate the rate of anti-spike-IgG waning. These longitudinal time-varying interaction coefficients permitted valid estimation of waning rates that weighted moving averages of cross-sectional data (Figure 1) could not provide. The coefficient estimates indicated that anti-spike-IgG waned faster in those who only received a vaccine compared with SARS-CoV-2 infection (Table 5, Figure 3). Post-vaccination anti-spike-IgG waned slowest in those with vaccine breakthrough infection and those who received vaccine after infection (Table 5, Figure 3). We performed 2 sensitivity analyses: removing potentially influential data points and compared standardized differences between regression coefficients (using the *dfbeta* command) and restricting to nonsevere (ie, outpatients) SARS-CoV-2 infections. The findings from both

Table 1. Clinical and Demographic Characteristics of 2660 Military Health System Beneficiaries by SARS-CoV-2 Infection and/or Vaccination History

Characteristic	SARS-CoV-2 Infection Alone (N = 705)	Vaccination Alone (N = 932)	Vaccine After Infection (N = 869)	Vaccine Breakthrough Infection (N = 154)	Total (N = 2660)	P Value ^a
Vaccine						<.01
Pfizer/BioNTech-BNT162b2		727 (78.0%)	701 (80.7%)	134 (87.0%)	1562 (79.9%)	
Moderna/mRNA-1273		200 (21.5%)	150 (17.3%)	19 (12.3%)	369 (18.9%)	
Janssen/JNJ-78436735		5 (0.5%)	18 (2.1%)	1 (0.6%)	24 (1.2%)	
Sex						.81
Female	284 (40.3%)	390 (41.8%)	347 (39.9%)	60 (39.0%)	1081 (40.6%)	
Male	421 (59.7%)	542 (58.2%)	522 (60.1%)	94 (61.0%)	1579 (59.4%)	
Age group, years						< .01
18–44	448 (63.5%)	726 (77.9%)	492 (56.6%)	94 (61.0%)	1760 (66.2%)	
45–64	203 (28.8%)	169 (18.1%)	283 (32.6%)	41 (26.6%)	696 (26.2%)	
≥65	54 (7.7%)	37 (4.0%)	94 (10.8%)	19 (12.3%)	204 (7.7%)	
Race/ethnicity						< .01
White	314 (44.5%)	593 (63.6%)	468 (53.9%)	90 (58.4%)	1465 (55.1%)	
Hispanic or Latino	200 (28.4%)	125 (13.4%)	192 (22.1%)	30 (19.5%)	547 (20.6%)	
Black	102 (14.5%)	64 (6.9%)	109 (12.5%)	19 (12.3%)	294 (11.1%)	
Asian	21 (3.0%)	49 (5.3%)	28 (3.2%)	3 (1.9%)	101 (3.8%)	
Others	68 (9.6%)	101 (10.8%)	72 (8.3%)	12 (7.8%)	253 (9.5%)	
Charlson comorbidity index						< .01
≥5	23 (3.3%)	3 (0.3%)	34 (3.9%)	4 (2.6%)	64 (2.4%)	
3–4	28 (4.0%)	11 (1.2%)	44 (5.1%)	5 (3.2%)	88 (3.3%)	
1–2	124 (17.6%)	37 (4.0%)	180 (20.7%)	17 (11.0%)	358 (13.5%)	
0	530 (75.2%)	881 (94.5%)	611 (70.3%)	128 (83.1%)	2150 (80.8%)	
Severity						< .01
Inpatient	168 (23.8%)		142 (16.3%)	9 (5.8%)	319 (18.5%)	
Outpatient	537 (76.2%)		727 (83.7%)	145 (94.2%)	1409 (81.5%)	
Sampling time^b						
Time since infection	32 (20)					
Time since latest antigenic exposure ^c		76 (79)	78 (70)	89 (63)		

Vaccination status determined through Military Health System Data Repository record, case report form, and/or self-report questionnaire.

^an × k Fisher exact test.

^bMedian (interquartile range).

^cTime since final dose of vaccine or infection, whatever is latest.

sensitivity analyses were similar to the findings from the overall analysis (Supplementary Tables 4, 5).

DISCUSSION

Our findings confirm that hybrid immunity arising from COVID-19 vaccine-induced immunity after prior infection offers greater humoral immunogenicity than either vaccination or prior infection alone. Furthermore, humoral immune response to prior infection is substantially augmented by even a single dose of vaccine, corroborating the findings from other studies [19–24]. These findings are particularly relevant as the Delta and Omicron variants have led to a large proportion of the population having hybrid immunity. Our findings expand on those from prior studies on this topic and show that increasing infection to vaccine time, but not initial infection severity, correlates

with a greater post-vaccination response. This finding may help guide strategies on timing of mRNA vaccine dosing after initial SARS-CoV-2 infection, although this requires further study. In addition, we noted that vaccine breakthrough infections offer the highest peak IgG response (even as breakthrough infections were noted to be milder than pre-vaccine infections), emphasizing that repeated exposures to SARS-CoV-2 antigens leads to higher IgG responses. This latter finding is consistent with recent data that show that mRNA vaccine booster doses lead to significant increases in immunogenicity [25]. Importantly, these analyses only refer to antibody kinetics and do not measure cellular immune response or vaccine effectiveness directly.

Our results indicate that receipt of an mRNA vaccine (in those without a history of infection) offers higher short- to medium-term peak humoral responses compared with

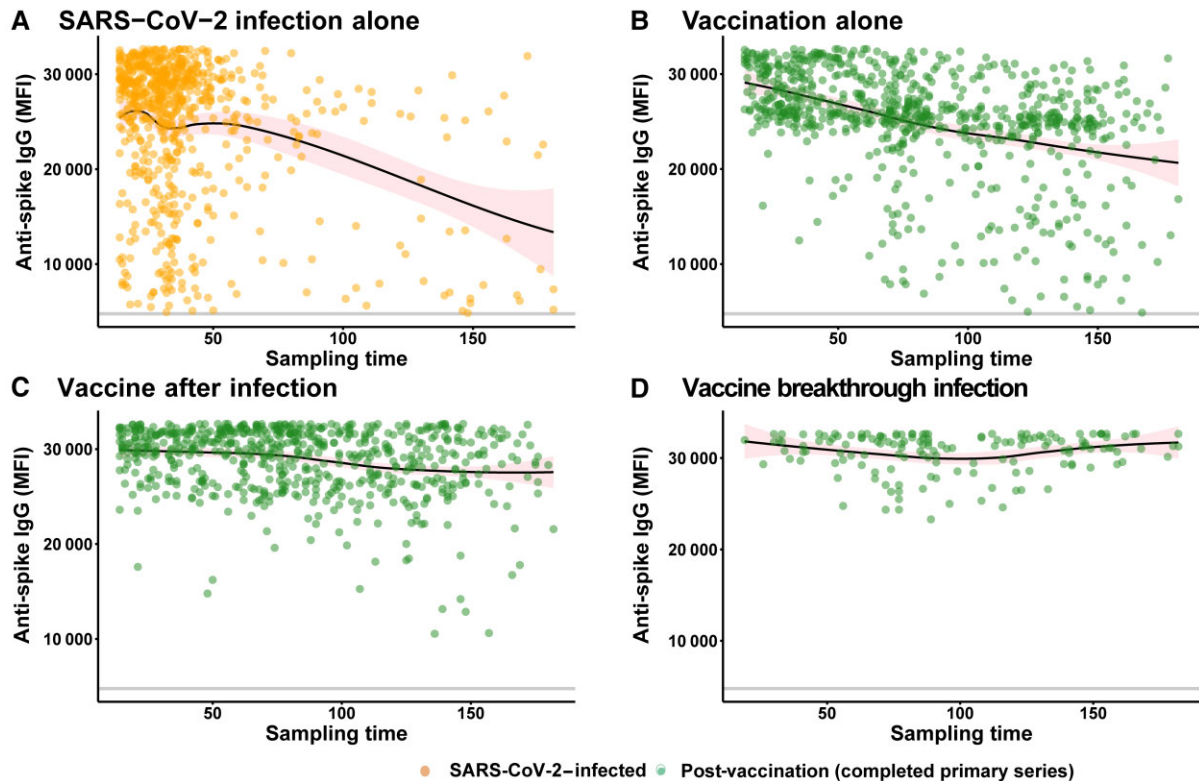


Figure 1. Peak anti-spike-IgG MFI by sampling time (sampling time defined as time since vaccination or infection, whatever is latest). The y-axis depicts anti-spike-IgG MFI values, and the x-axis depicts sampling time (days). Each data point represents a single participant with a single peak humoral response. The locally estimated scatterplot smoothing (LOESS) curves were fit to SARS-CoV-2 infection alone (those who tested SARS-CoV-2-positive and did not receive any subsequent vaccination) (A), vaccination alone without a known history of SARS-CoV-2 infection (B), vaccine after infection (those who tested SARS-CoV-2-positive and then received a complete series of vaccination) (C), and vaccine breakthrough infection (those who were infected by SARS-CoV-2 after complete doses of vaccination) (D). These curves report moving averages but are not adjusted rates of decay; 95% confidence intervals are shaded in pink. Orange dots depict pre-vaccination samples, and green data points depict sampling greater than 2 weeks after complete vaccination. Abbreviations: IgG, immunoglobulin G; MFI, median fluorescence intensity; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

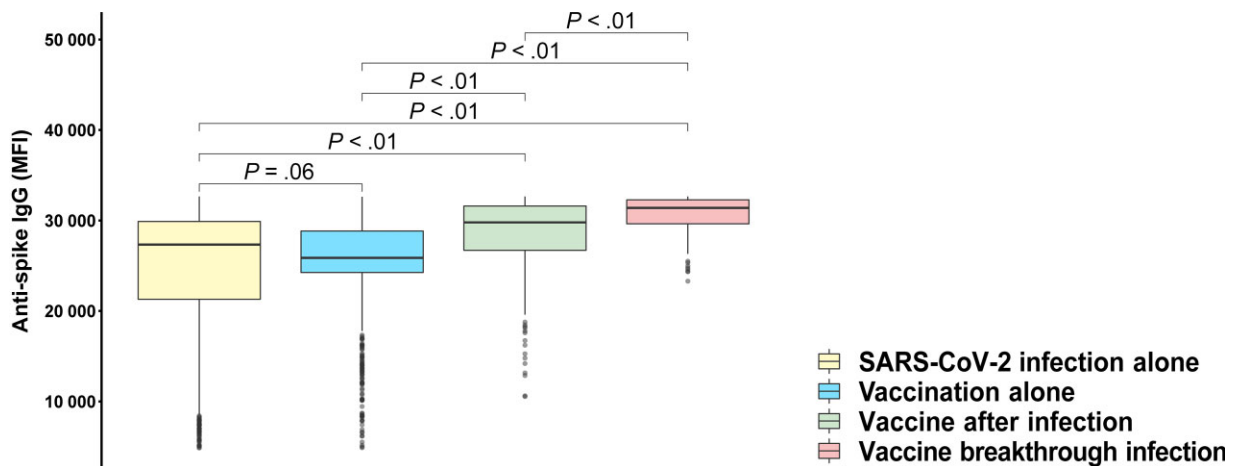


Figure 2. Unadjusted comparison of peak observed anti-spike-IgG MFI by category of infection and/or vaccination. *P* value determined using the Mann-Whitney *U* test. These comparisons do not adjust for sampling time, which varies by group. Box plots denote median, first quartile (25th percentile), and third quartile (75th percentile) of anti-spike-IgG MFI levels (y-axis) and each group (x-axis) representing SARS-CoV-2 infection alone (yellow), vaccination alone (blue), vaccine after infection (light green), and vaccine breakthrough infection (coral). SARS-CoV-2 infection alone and vaccination alone did not portray any statistically significant difference, but vaccination after vaccine-breakthrough SARS-CoV-2 infection shows greater humoral response compared with infection alone or vaccination alone. Abbreviations: IgG, immunoglobulin G; MFI, median fluorescence intensity; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Univariable and Multivariable Models to Compare Adjusted Anti-Spike Log₁₀ Median Fluorescence Intensity Response in Different Categories of Infection and Vaccination

Covariates	Coefficient (95% CI)	P Value	Adjusted Coefficient ^a (95% CI)	P Value
Age group, years				
45–64	0.03 (.02 to .05)	<.01	0.02 (.01 to .04)	<.01
≥65	0.06 (.04 to .08)	<.01	0.03 (.01 to .05)	.01
Sex, male	<0.01 (–.01 to .01)	.81	<0.01 (–.01 to .01)	.5
Charlson comorbidity index				
≥5	0.04 (<0.01 to .08)	.04	<0.01 (–.04 to .03)	.91
3–4	0.05 (.01 to .08)	.01	0.02 (–.01 to .05)	.25
1–2	0.05 (.03 to .07)	<.01	0.03 (.01 to .04)	<.01
Group				
Vaccination after infection ^b	0.1 (.08 to .11)	<.01	0.13 (.12 to .15)	<.01
Vaccine breakthrough infection ^b	0.13 (.1 to .15)	<.01	0.18 (.16 to .21)	<.01
Vaccination alone ^b	0.03 (.01 to .04)	<.01	0.07 (.06 to .09)	<.01
Sampling time	<<0.01 (<<.01 to <<.01)	<.01	<<0.01 (<<.01 to <<.01)	<.01

Number of observations, 2254. Sampling time refers to last antigenic exposure, that is, time since final dose of vaccine or infection, whatever is latest. Log₁₀ median fluorescence intensity coefficients are exponentiated in the text for interpretability.

Abbreviation: CI, confidence interval.

^aAdjusted for age group, sex, CCI, group, and sampling time.

^bRef: SARS-CoV-2 infection alone.

Table 3. Univariable and Multivariable Models to Identify Correlates of Peak Post-Vaccine Anti-Spike Log₁₀ IgG Among Those Vaccinated With and Without a History of Infection

Covariates	Coefficient (95% CI)	P Value	Adjusted Coefficient ^a (95% CI)	P Value
Age group, years				
45–64	<0.01 (–.01 to .02)	.65	–0.01 (–.02 to 0)	.09
≥65	0.03 (.01 to .05)	.01	<<0.01 (–.02 to .02)	.89
Sex, male	<0.01 (–.01 to .01)	.8	<<0.01 (–.01 to .01)	.49
Charlson comorbidity index				
≥5	0.04 (0 to .08)	.04	–0.01 (–.05 to .03)	.66
3–4	0.06 (.02 to .09)	<.01	0.03 (0 to .06)	.04
1–2	0.04 (.02 to .06)	<.01	0.01 (–.01 to .03)	.26
Sampling time	<<0.01 (<<.01 to <<.01)	<.01	<<0.01 (<<.01 to <.01)	<.01
Vaccine				
Pfizer/BioNTech BNT162b2 ^b	0.06 (.01 to .11)	.01	0.09 (.05 to .13)	<.01
Moderna/mRNA-1273 ^b	0.08 (.03 to .12)	<.01	0.11 (.07 to .16)	<.01
History of SARS-CoV-2 infection ^c	0.07 (.06 to .08)	<.01	0.08 (.06 to .09)	<.01

Number of observations 1395. Sampling time refers to last antigenic exposure, that is, time since final dose of vaccine or infection, whatever is latest.

Abbreviation: CI, confidence interval.

^aAdjusted for age group, sex, CCI, sampling time, vaccine product, and prior SARS-CoV-2 infection.

^bRef: Janssen/JNJ-78436735.

^cRef: No history of SARS-CoV-2 infection.

SARS-CoV-2 infection alone, after adjustment for other predictors (Table 2). However, we noted that the vaccine-alone group had more rapid waning of IgG compared with those with SARS-CoV-2 infection alone and those who received vaccine after infection. The difference in waning rates between groups was small, and their clinical significance is unclear [26]. These data contribute to the discussion about the significance of recent comparisons of infection frequency and clinical outcomes among vaccinees when compared with infection-alone

participants and those with a history of both infection and vaccination [27–32]. These findings also contribute to our understanding of how vaccine-induced immunity compares with SARS-CoV-2 infection and optimal timing of vaccine boosting.

Our study also permitted a head-to-head comparison of COVID-19 vaccines. As with other studies, we noted a greater peak anti-spike-IgG response in those who received an mRNA vaccine (mRNA-1273, BNT162b2) compared with the JNJ-78436735 vaccine when adjusting for host characteristics

Table 4. Univariable and Multivariable Models to Identify Correlates of Peak Anti-Spike log₁₀ Median Fluorescence Intensity Response in Those Vaccinated With Prior Infection History

Covariates	Coefficient (95% CI)	P Value	Adjusted Coefficient ^a (95% CI)	P Value
Age group, years				
45–64	<0.01 (–.01 to .01)	.66	<0.01 (–.01 to .01)	.72
65+	0.01 (–.01 to .03)	.18	0.01 (–.01 to .02)	.52
Sex, male	0.01 (–.01 to .01)	.3	<0.01 (–.01 to .01)	.41
Charlson comorbidity index				
≥5	0.01 (–.01 to .04)	.33	<0.01 (–.02 to .03)	.86
3–4	0.02 (–.01 to .04)	.03	0.02 (0 to .04)	.06
1–2	0.01 (–.01 to .02)	.38	<0.01 (–.01 to .02)	.67
Severity of prior infection Inpatient ^b	<0.01 (–.01 to .02)	.46	<0.01 (–.01 to .01)	.88
Sampling time ^c	–<0.01 (–<.01 to –<.01)	<.01	–<0.01 (–<.01 to –<.01)	<.01

Number of observations, 653. Vaccination refers to messenger RNA vaccine.

Abbreviation: CI, confidence interval.

^aAdjusted for age, sex, CCI, severity, sampling time.

^bRef: Outpatient.

^cSampling time refers to time since final dose of vaccination.

and infection history. Among mRNA vaccinees, we also noted that mRNA-1273 vaccine showed a higher peak IgG compared with BNT162b2 (Table 3, Supplementary Table 2) [33–35]. This is consistent with published findings that show a greater humoral immune response from mRNA-1273 and, in some studies, apparent increased effectiveness of the mRNA-1273 vaccine.

This analysis has several limitations. First, these results refer only to binding antibody assays due to prohibitive logistics for performing neutralizing antibody assays on these many specimens. However, this binding assay (and other binding anti-spike–IgG assays) has moderate to high correlation with neutralizing antibody titers previously performed on a small number of EPICC participants [15]. Second, quantitative differences of anti-spike–IgG binding responses, measured as MFI at a single blood specimen dilution (1:400), between groups were small overall, which may reflect upper limits of assay quantification and anti-spike–IgG MFI saturation in blood samples collected after multiple immunogen stimulations. Third, follow-up time did not exceed 183 days, yet the study spanned a period of sequential dominant variants in the United States. Finally, our understanding of how antibody responses serve as a correlate of clinical protection is still developing [36]. While a landmark meta-analysis estimated a neutralizing antibody titer that could protect against infection [37], definition of a protective titer remains challenging and is subject to assay-to-assay comparability and the particular clinical end point of interest. Further, there is increasing evidence on the protective role of T-cell immune responses against infection and severity, further complicating estimations of a protective antibody titer [38, 39]. These limitations are important to acknowledge before inference is undertaken of relative protection between those with different antigenic exposure

Table 5. Longitudinal Linear Mixed Modeling to Estimate Decay Kinetics of Log₁₀ Anti-Spike IgG Response to Antigenic Exposure

Covariates	Coefficient	P Value
Sampling time	–<0.01 (–<0.01 to –<0.01)	<.01
Vaccination after infection ^a	0.13 (0.09 to 0.16)	<.01
Vaccine breakthrough infection ^a	0.1 (0.06 to 0.14)	<.01
Vaccination alone ^a	0.15 (0.09 to 0.21)	<.01
Sampling time * Vaccine after infection	<0.01 (<0.01 to <0.01)	.03
Sampling time * Vaccine breakthrough infection	<0.01 (<0.01 to <0.01)	<.01
Sampling * Vaccination alone	–<0.01 (–<0.01 to –<0.01)	.02

Number of observations, 1160. Sampling time refers to last antigenic exposure, that is, time since final dose of vaccine or infection, whatever is latest. Model fit to all longitudinal data and including group, sampling time, and an interaction term of sampling time and group. The asterisk (*) is used to indicate interactions among the variables that it joins.

^aRef: SARS-CoV-2 infection alone.

histories. They also underscore the need for further study in this and other cohorts to include integration of clinical outcomes with a range of immune readout data from B-cell, T-cell, and innate arms of the immune system, as well as in pediatric age groups and booster recipients, which were not part of this analysis.

The strengths of this study include a large sample size, measurement of a broad range of participant and illness characteristics to account for confounding between 4 groups, and careful ascertainment of subclinical repeat infections that could have biased comparisons. Taken together, these findings provide additional data on the importance of antiviral immunogenicity by vaccination beyond that afforded by prior SARS-CoV-2 infection and offer further insights into host responses to sequential SARS-CoV-2 antigenic exposure that may inform future

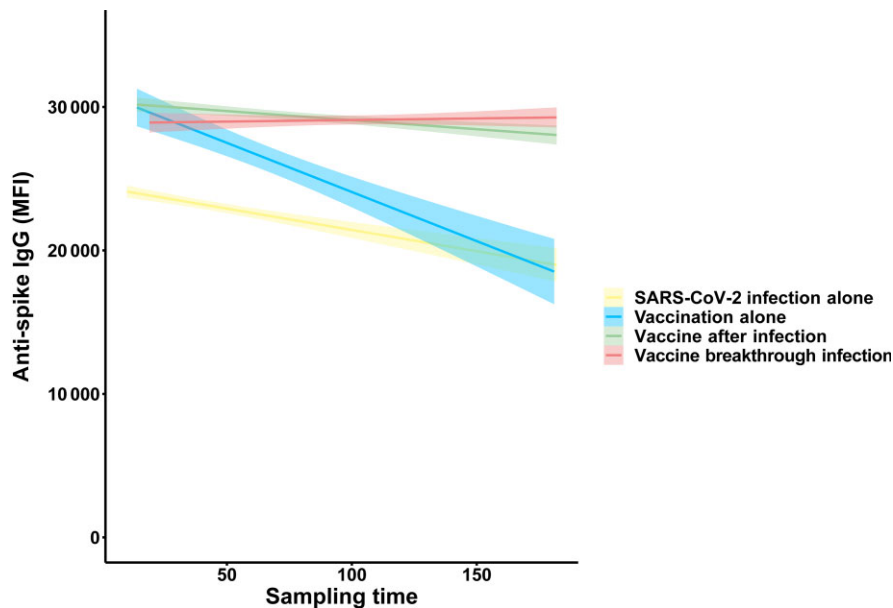


Figure 3. Anti-spike-IgG MFI by sampling time (time since vaccination or infection, whatever is latest), restricted to longitudinal analysis using at least 2 sera samples per participant, stratified by SARS-CoV-2 infection alone (yellow), vaccination alone (blue), vaccine after infection (light green), and vaccine breakthrough infection (coral). The y-axis depicts anti-spike-IgG MFI values, and the x-axis depicts sampling time. Each data point represents a sera sample. The solid line is the estimated slope derived from mixed-effects regression models in Table 5; shaded area depicts confidence interval. Abbreviations: IgG, immunoglobulin G; MFI, median fluorescence intensity; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

vaccination strategies and their development, including evaluation on timing of post-infection vaccine administration.

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

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