Comparison of Symptoms and Antibody Response Following Administration of Moderna or Pfizer SARS-CoV-2 Vaccines

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• ***Context.***—**Moderna (mRNA-1272) and Pfizer (BNT162b2) SARS-CoV-2 vaccines demonstrate favorable safety and efficacy profiles, but direct comparison data are lacking.**

Objective.—**To determine the vaccines' side effect profiles and expected antibody responses. These data may help personalize vaccine selection and identify individuals with a suboptimal vaccine response.**

Design.—**One hundred forty-nine healthy, largely seronegative adults were assigned Moderna (n = 79) or Pfizer (n = 70). Following the second dose, participants completed a survey documenting their side effects. Serum was collected 0 to 4 days prior to dose 2, and 14 ± 4 days, 30 ± 4 days, 90 ± 10 days, and 180 ± 20 days after dose 2. Convalescent serum specimens were collected 32 to 54 days from donors after a polymerase chain reaction–confirmed SARS-CoV-2 infection (n = 20). Anti-spike antibodies were measured using the Roche Diagnostics Elecys Anti–SARS-CoV-2 S assay on a Roche cobas e801 instrument.**

Results.—**Participants receiving the Moderna vaccine experienced side effects with greater frequency and severity. Both vaccines elicited a robust antibody response, but median signal was higher in Moderna recipients. Symptom severity decreased with age. Antibody response in Pfizer recipients negatively correlated with age. Antibody response decreased after 6 months (84% reduction in Moderna, 79% Pfizer), but values remained greater than for convalescent donors. Antibody response did not correlate with gender or symptom severity.**

Conclusions.—**Moderna may be preferred in individuals in need of greater immune stimulation (eg, older individuals), whereas Pfizer may be preferred in those concerned about vaccine reactions. Anti-spike antibody signal varies by vaccine, so specific reference intervals will be needed to identify individuals with a suboptimal response.**

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Since its identification as the cause of a novel respiratory pneumonia first documented in Wuhan, China, in December 2019, SARS-CoV-2 has spread rapidly throughout the globe, causing 221 million confirmed infections and 4.5 million deaths as of September 2021.[1,2] Although many infected persons experience only mild symptoms, others experience critical illness or death due to septic shock, multiorgan failure, or respiratory failure.[3] The elderly and those with preexisting medical conditions are at highest risk for poor outcomes. Postmortem evaluation firmly implicates SARS-CoV-2 as the cause of death, whereas preexisting conditions play only a minor contributory role.[4]

Public health efforts advocating the wearing of masks, social distancing, contact tracing, isolation, and surveillance testing limited transmission, but they did not eliminate the spread of SARS-CoV-2. To put an end to this global pandemic, substantial effort was dedicated to SARS-CoV-2 vaccine development, resulting in emergency use authorization of 2 novel mRNA-based vaccines by the US Food and Drug Administration in December 2020. Both BNT162b2 (Pfizer-BioNTech) and mRNA-1272 (Moderna) consist of a lipid nanoparticle-encapsulated RNA encoding the full-length SARS-CoV-2 spike protein stabilized in the prefusion conformation.[5,6] Individuals receiving either vaccine are considered to be protected from infection 14 days after administration of the second dose. Spike and neutralizing antibody signals were equivalent to or greater than those observed in SARS-CoV-2–infected individuals at a similar time point after exposure.[5,7,8] Previous work described the safety profiles following vaccination with either Moderna[6] or Pfizer[9,10] independently, and follow-up research found that the reactogenicity of Moderna was greater than for Pfizer, and symptoms were more common after dose 2 of the vaccine.[11–13] However, there is still ongoing concern for side

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effects and adverse reactions following mRNA vaccine administration.

Many commercially available, automated immunoassays have been granted emergency use authorization for the measurement of spike antibodies. These assays may be routinely used in the future to confirm immune status following viral infection or vaccination, although they are currently not approved for this purpose. Others have described the spike antibody response at defined time points following administration of BNT162b2 or mRNA-1272, but it is unknown whether these observations would extend to other commercially available test methods.[5–7,14] Because trends in nucleocapsid antibody signal vary substantially depending on the analytical platform used, differences in assay design may also lead to markedly different patterns of spike antibody response following vaccination.[15] If future work demonstrates that serum antibody values measured shortly after vaccination predict the duration of seropositivity, assay-specific reference intervals may be required to identify individuals with a suboptimal response who may benefit from more frequent reimmunization. The International Standard and Reference Panel for Anti–SARS-CoV-2 antibody testing was established in December 2020 by the World Health Organization Expert Committee on Standardization to facilitate assay standardization across different platforms.[16]

New data on the efficacy of mRNA vaccines against SARS-CoV-2 are rapidly becoming available. One study found that Pfizer vaccine efficacy peaked at 96.2% between 7 days and 2 months following the second dose and then gradually declined to 83.7% efficacy after 4 months.[17] The US Centers for Disease Control and Prevention (CDC) also released a study showing vaccine efficacy in preventing hospitalization is higher for Moderna (93%) relative to Pfizer (88%) and Johnson & Johnson (71%).[18] Median antibody response was also substantially higher in individuals receiving mRNA vaccines (Moderna and Pfizer) 2 to 6 weeks following administration of the complete vaccine series; the response was greatest in individuals receiving the Moderna vaccine.[18] However, many questions still remain about mRNA vaccine efficacy and duration of protection. It is unclear if antibody response at later time points ever becomes equivalent between the 2 mRNA vaccines. It is also unknown whether the 2 vaccines elicit equivalent side effects, and whether the severity of symptoms predicts an individual's antibody response. It is possible that distinctly different postvaccine profiles might help select the optimal vaccine for individuals of a given age or sex. Here, we directly compare symptoms and spike antibody response during 6 months as measured by the Roche Elecsys Anti-SARS-CoV-2 S automated immunoassay in predominantly seronegative individuals following administration of either the Moderna or Pfizer vaccine.

MATERIALS AND METHODS

Institutional Review

This study was approved by the medical center institutional review board.

Volunteer Participation and Sample Collection

Participants were randomly assigned the Moderna or Pfizer vaccine based on the day of their appointment and were unable to indicate vaccine preference. After providing informed consent, 154 healthy adults aged 19 to 74 years recorded their preferred gender, date of birth, vaccine manufacturer, date of vaccination, and completed a survey regarding side effects (severity scale 0–5; Supplemental Digital Content at https://meridian.allenpress.com/aplm in the June 2022 table of contents) experienced following vaccination. Demographic information can be found in Supplemental Table 1. All participants received the complete, 2-dose series of either the Moderna or Pfizer vaccine.

Serum samples were collected prior to vaccination from 8 participants who received Moderna and 6 who received Pfizer. Participants receiving Moderna (n = 81) or Pfizer (n = 72) had samples collected at target dates of 0 to 4 days before dose 2 (relative to dose 1: 27 days Moderna, 20 days Pfizer), 14 ± 4 days after dose 2 (42 days Moderna, 35 days Pfizer), 30 ± 4 days after dose 2 (58 days Moderna, 51 days Pfizer), 90 ± 10 days after dose 2 (118 days Moderna, 111 days Pfizer), and 180 ± 20 days after dose 2 (208 days Moderna, 201 days Pfizer). After serum was allowed to clot, samples were centrifuged and either analyzed immediately or stored at 4°C for up to 6 days prior to analysis.

Participants who self-identified as immunocompromised and those who did not receive the second dose of vaccine within 7 days of the manufacturer-recommended interval were excluded from the study (Supplemental Figure 1). After exclusion, 79 participants given the Moderna vaccine and 70 participants given the Pfizer vaccine remained in the study. Any samples drawn outside the target collection dates were excluded from analyses of antibody response. One pre–dose 2 specimen with undetectable antibody signal was removed from further analysis because of incompatibility with log transformation. One participant did not complete the survey and was excluded from analyses involving symptom severity.

Convalescent Donors

Serum specimens were collected in gel separator tubes 32 to 54 days after a polymerase chain reaction (PCR)–confirmed SARS-CoV-2 infection from 20 unique individuals with a documented positive SARS-CoV-2 molecular diagnostic result, aliquoted into sealed plastic tubes, and frozen at −80°C until further use.

Detection of Antibodies to the SARS-CoV-2 Nucleocapsid and Spike Proteins

Samples were analyzed on a Roche cobas e801 instrument (Roche Diagnostics, Indianapolis, Indiana) using the Elecsys Anti–SARS-CoV-2 S (spike; 09289267190) and Anti–SARS-CoV-2 (nucleocapsid; 09203079190) electrochemiluminescence immunoassays.

The Roche Anti–SARS-CoV-2 S is a total antibody assay that predominantly quantifies Anti–SARS-CoV-2 immunoglobulin (Ig) G, but also detects IgA and IgM antibodies to the spike protein. It uses a double-antigen sandwich principle similar to the Roche Anti–SARS-CoV-2 nucleocapsid total antibody assay previously described.[15] Spike antibody results were reported quantitatively (U/mL) with a cutoff for positivity of ≥0.8 U/mL. Linearity was confirmed up to 250 U/mL, and a 2- to 100-fold dilution with Diluent Universal was conducted as necessary to expand the reportable range to 25 000 U/mL. One sample >25 000 U/mL underwent 2 sequential dilution steps to achieve a quantitative result. Assay imprecision was 4.6%, 2.5%, and 2.9% for a negative patient pool (0.61 U/mL), positive patient pool (17.2 U/mL), and quality control (8.7 U/mL), respectively, after performing 5 replicates of each per day for 5 days. Nucleocapsid antibody results were reported qualitatively with a cutoff index for positivity of ≥1.0. Cutoff index and test performance characteristics were described previously.[15]

Statistical Analysis

For each dose and vaccine manufacturer, the prevalence of symptoms (severity >0) was reported as percentages. The significance of prevalence and severity associations was interpreted using the effect estimates and 95% credible intervals estimated

through multivariable regression modeling procedures. Additional details may be found in the Supplemental Digital Content.

Several ordinal, binomial, and continuous-response multivariable regression models were used to estimate the relationships between symptom severity (0–5; overall and symptom-specific) and antibody signal. Dose number, vaccine manufacturer, age, gender, and use of pain relief medication were incorporated in the multivariable models to account for their association with symptom severity. Spike antibody response was log transformed prior to modeling. Nonlinear associations with age were evaluated by binning age into 3 categories (19–35, 36–59, and 60–74 years). Bayesian hierarchical models were employed to control for potential bias that may arise from a small sample size and repeat measurements by participant.

All multivariable statistical models were fit using *brms* and *RStan* via the R statistical software language v3.6.[19,20] Antibody response reference intervals for each manufacturer were established using the *ReferenceIntervals* package as the central 95% of values generated at each time point.[21]

The directionality and statistical significance of all associations may be found in Supplemental Tables 2 through 10, as can the greater details of all the statistical methods.

RESULTS

Participant Demographic Information

More women (n = 113) than men (n = 36) participated in this study, but the percentage of women within the Moderna group (57 of 79; 72.2%) did not significantly differ from that in the Pfizer group (56 of 70; 80.0%; Supplemental Table 1). The mean age of participants in the Moderna (45 years) group was skewed slightly older than the Pfizer (41 years) group ($P = .06$; Supplemental Table 1).

Three participants tested positive for antibodies to the nucleocapsid protein. The first participant (Pfizer) had detectable nucleocapsid antibodies prior to receiving vaccine dose 1 but did not have any detectable spike antibodies and did not report a previous infection. This person retained detectable nucleocapsid antibodies at all subsequent collections and displayed a spike antibody concentration near the median at each time point. The second participant had a known exposure to COVID-19 1 month prior to the start of the study. This participant (Pfizer) was positive for nucleocapsid antibodies at all time points examined and had the highest spike antibody response after dose 1 (1253 U/mL). A third participant (Moderna) was nucleocapsid antibody negative before dose 2 and 14 days after dose 2 but nucleocapsid antibody positive at 30 days after dose 2. At the 90- and 180-day post–dose 2 collection, this participant was negative for nucleocapsid antibodies. This participant's spike antibody response was near the 25th percentile at all time points and did not show a notable increase following the detection of nucleocapsid antibodies, suggesting this was a false-positive nucleocapsid result. Nucleocapsid antibody results were negative for all other participants throughout the study and were interpreted to indicate an absence of previous infection. Because of the low incidence of nucleocapsid antibody positivity, no comparisons were made between nucleocapsid-positive and nucleocapsid-negative participants.

Side Effects After Vaccine Administration

Side effects began within 1 day after vaccination for most participants after both doses 1 and 2 (data not shown). Symptoms noted after vaccination, ordered from most to least common, are shown in Figure 1. Overall, participants who received the Moderna vaccine had a more severe reaction than those who received Pfizer (Figure 1). Of the specific symptoms, sore arm, swelling at the injection site, chills, and fever were more severe in those receiving Moderna (Figure 1).

There was no statistical difference in overall symptom severity between the Pfizer and Moderna groups after dose 1 (Figure 1; Supplemental Table 2). However, swelling at the injection site (Moderna, 19 of 79; 24.1%; Pfizer, 7 of 69; 10.1%), rash at the injection site (Moderna, 10 of 79; 12.7%; Pfizer, 0 of 69; 0%; data not shown), and fever (Moderna, 2 of 79; 2.5%; Pfizer, 0 of 69; 0%) were reported more frequently and with a higher severity rating in those who received Moderna (Figure 1). After dose 2, 75 of 79 participants (94.9%) receiving Moderna reported a reaction compared with 60 of 69 (87.0%) of those who received Pfizer, and overall symptom severity was significantly greater for Moderna (Figure 1). Sore arm (Moderna, 77 of 79; 97.5%; Pfizer, 61 of 69; 88.4%), swelling at the injection site (Moderna, 26 of 79; 32.9%; Pfizer, 6 of 69; 8.7%), rash at the injection site (Moderna, 9 of 79; 11.4%; Pfizer, 2 of 69; 2.9%; data not shown), body aches (Moderna, 53 of 79; 67.1%; Pfizer, 28 of 69; 40.6%), chills (Moderna, 38 of 79; 48.1%; Pfizer, 18 of 69; 26.1%), and fever (Moderna, 36 of 79; 45.6%; Pfizer, 10 of 69; 14.5%) occurred more frequently and were rated more severely in participants who received Moderna compared with those who received Pfizer (Figure 1; Supplemental Table 2). No symptoms were rated more severely in participants receiving Pfizer compared with those who received Moderna. Symptoms with low prevalence, including vomiting, gastrointestinal upset, cough, body rash, sweating, lymph node swelling, and unsolicited symptoms ("other") are not displayed in Figure 1.

Participants in both the Moderna and Pfizer groups reported a statistically significant increase in overall side effect severity between dose 1 and dose 2 (Figure 1; Supplemental Table 3). This change in severity from dose 1 to dose 2 was present for overall symptom severity, lethargy, headache, body aches, chills, fever, nausea, and sweating. Lethargy and headache demonstrated significantly increased severity after dose 2 relative to dose 1 for those who received Moderna but did not differ significantly between dose 1 and dose 2 for Pfizer (Figure 1). In general, the increase in symptom severity between doses 1 and 2 was greater for those who received Moderna than those who received Pfizer.

Gender- and Age-Related Difference in Vaccine Response

Overall symptom severity did not differ between women and men (Figure 2, A), but sore arm at injection site, swelling, nausea, gastrointestinal upset, headache, body aches, and lethargy were reported to be more severe by women (Supplemental Table 4).

The severity of symptoms after vaccination was negatively associated with age regardless of vaccine manufacturer or dose (Figure 2, B; Supplemental Table 5). Participants aged 36 to 59 years exhibited reduced symptom severity (dose 1, 55 of 67; 82.1%; dose 2, 59 of 67; 88.1%) compared with those aged 35 years and younger (dose 1, 53 of 57; 93.0%; dose 2, 57 of 57; 100%). Participants aged ≥60 years trended toward lower symptom severity relative to the ≤35 years group. A total of 17 of 24 participants (70.1%) aged ≥60 years reported symptoms after dose 1, whereas 19 of 24 (79.1%) reported symptoms after dose 2. This did not reach

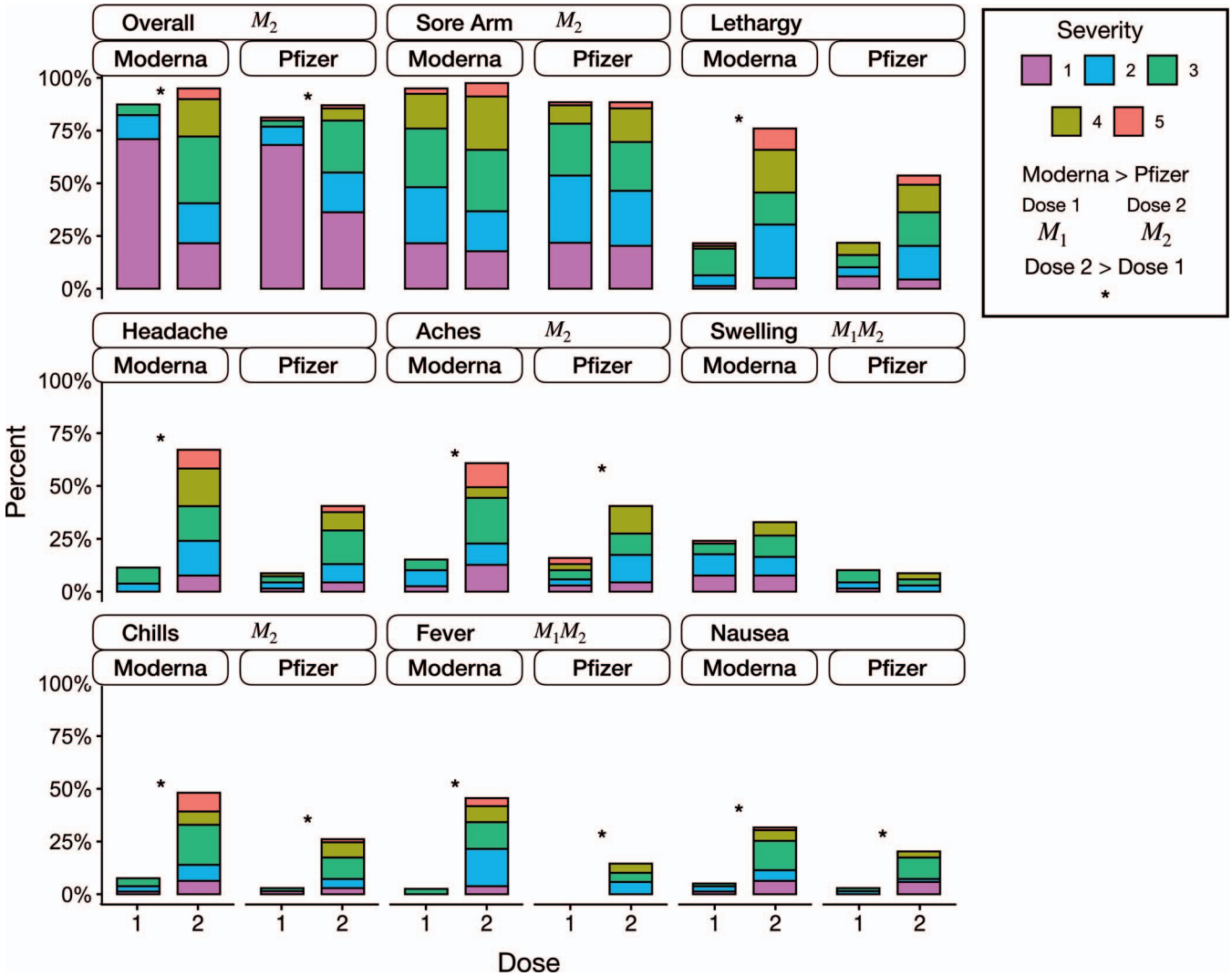

Figure 1. *Summary of symptom severity after vaccination. Stacked bar plots indicating percentages (y-axis) and severity rating (1–5) are shown for participants following doses 1 and 2 (x-axis) of either Pfizer (n = 69) or Moderna (n = 79) vaccination for overall severity, sore arm at injection site, lethargy or fatigue, headache, body aches or joint pain, swelling at injection site, chills, fever, and nausea. Statistical significance is indicated in the subheadings if symptoms experienced in the Moderna group were significantly more severe than Pfizer after dose 1 (M_1) or after dose 2 (M_2). Statistical significance is indicated by an asterisk above the bar plot if dose 2 severity was greater than dose 1 for Moderna or for Pfizer.*

statistical significance, likely because of the lower sample size in the ≥60 years age group.

Antibody Response After Vaccination

Spike antibody responses before and after vaccination, and in serum from convalescent donors, are shown in Figure 3, A. The median antibody response in the Moderna group before dose 2 (27 days after dose 1) was not significantly different from the median response in convalescent donors, whereas the median response in the Pfizer group (20 days after dose 1) was significantly lower (95% CI, 0.117–1.266; Table; Supplemental Table 6). The median antibody response in both groups of vaccinated participants, up to 180 days after dose 2 (208 days Moderna, 201 days Pfizer after dose 1), was significantly higher than the antibody response in convalescent donors.

The median antibody response after vaccination was higher in participants receiving the Moderna vaccine than in those receiving Pfizer at all measured time points (95% CI, 0.781–1.299; Figure 3, A; Supplemental Tables 6 and 7). All immunocompetent participants exhibited a substantial increase in antibody response after the second dose of vaccine, which dropped by 37.1% for Moderna and 31.0% for Pfizer from 14 to 30 days after vaccine dose 2. Percentages were determined based on regression modeling and methods for post hoc comparisons between collection dates in R using the emmeans package (95% CI, 27.5%–46.4% Moderna, and 19.2%–41.9% Pfizer; Supplemental Table 9). Antibody response continued to decline throughout the study. Participants receiving the Moderna vaccine series saw an 84% drop in antibody levels at 180 days relative to 14 days after dose 2 (95% CI, 81.7%–86.7%). Pfizer recipients saw a similar reduction in antibody response of 79% during the same time interval (95% CI, 74.7%–82.3%; Supplemental Table 9).

Prior to dose 2, antibody response was negatively correlated with age in recipients of both vaccines (Figure 3, B; Supplemental Figure 2; Supplemental Tables 6 and 10). Participants aged 60 years or older had a significantly lower antibody response than participants aged ≤35 years (95%

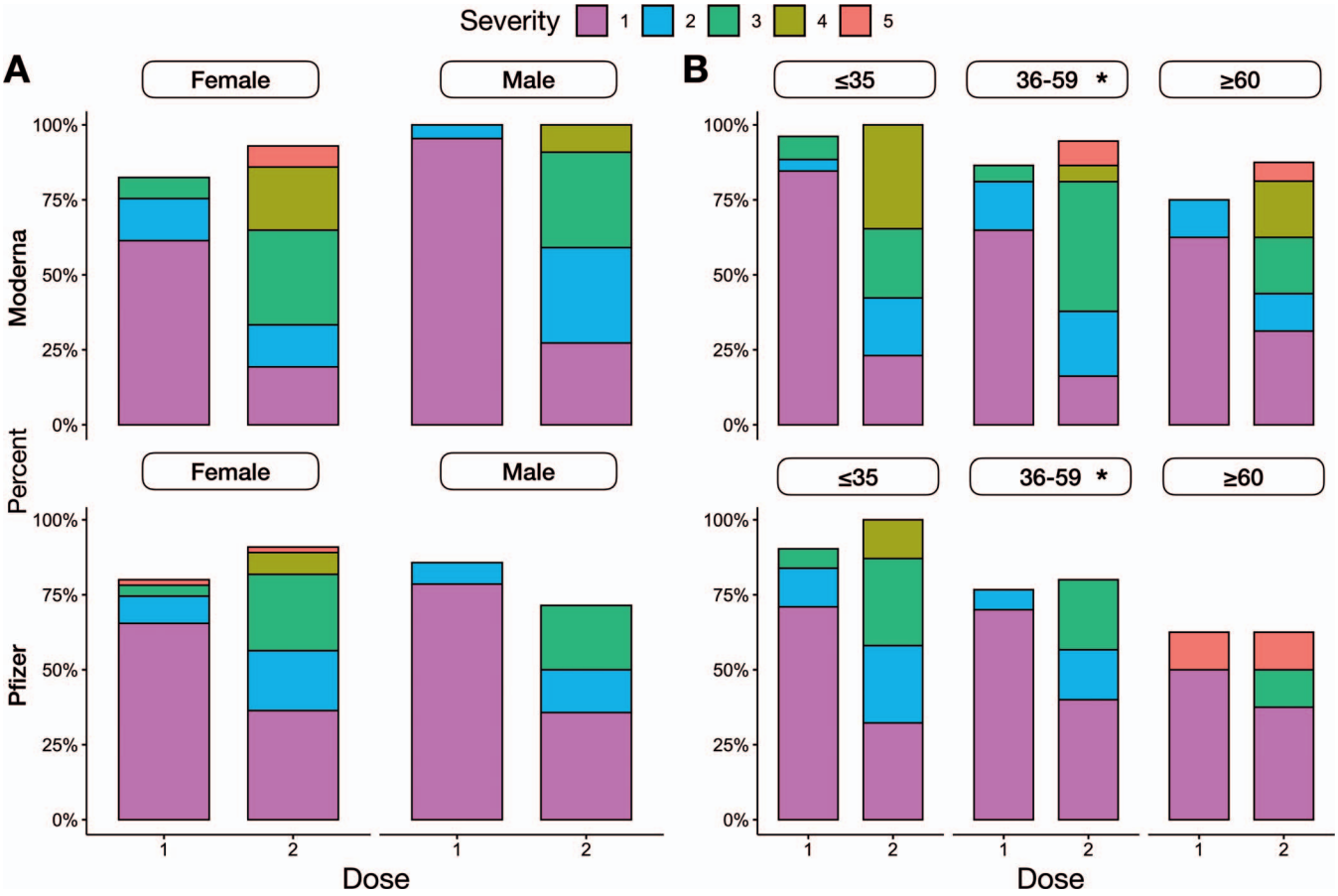

Figure 2. *Comparison of overall symptom severity after vaccination by gender and age. Stacked bar plots indicating percentages (y-axis) and overall severity ratings (1–5) are shown for participants following doses 1 and 2 (x-axis) after either Moderna (top) or Pfizer (bottom) vaccination for (A) females and males and (B) participants aged ≤35, 36 to 59, and ≥60 years. A statistically significant reduction in overall symptom severity compared with participants aged ≤35 years is indicated by an asterisk.*

CI, 0.426–1.182). This negative correlation was seen for Pfizer recipients throughout the study (Figure 3, C through F). However, following dose 2 of the Moderna vaccine, there was no correlation between age and antibody response at any of the time points measured (Figure 3, C through F). Antibody response did not significantly differ between men and women (Supplemental Figure 3, Supplemental Table 6).

Overall Symptom Severity Versus Antibody Response

Participants receiving the Moderna vaccine reported greater severity of side effects after vaccination and had consistently higher antibody responses after each vaccine dose. However, no correlation existed between symptom severity and antibody response that was not accounted for by other confounding factors following dose 1 or dose 2 of the vaccine (Figure 4; Supplemental Table 7).

Reference Intervals

Reference intervals for expected antibody response at each time point after vaccination were determined using non-parametric bootstrapped 95% credible intervals (Table). Because of the significantly higher antibody response in those who received Moderna compared with those who received Pfizer, separate reference intervals were reported. Prior to dose 2, the reference interval for antibody response was 15 to 1068 U/mL for Moderna and 3 to 783 U/mL for Pfizer. Fourteen days after vaccine dose 2, the reference interval for Moderna was 1931 to 37 987 U/mL, whereas Pfizer was 679 to 9420 U/mL. By 180 days, the expected responses dropped to 144 to 5792 U/mL and 78 to 1882 U/mL for Moderna and Pfizer recipients, respectively.

DISCUSSION

This study was the first to compare both self-reported side effects and antibody response during the course of 6 months after vaccination with either Moderna (mRNA-1272) or Pfizer (BNT126b2) in a single population independent of manufacturer oversight. We found that although participants who received Moderna had a higher antibody response, they also experienced an increased severity of side effects, particularly after the second dose. Consistent with previous publications, participants in this study reported increased side effect severity in both Moderna and Pfizer groups following dose 2 relative to dose 1, including lethargy, headache, body aches, chills, fever, nausea, and sweating.[5–7,13,22] When comparing side effects after vaccination with either Moderna or Pfizer, the reactions were more severe for those who received Moderna, with the difference between manufacturers particularly evident after dose 2. This is consistent with prior studies that compared COVID mRNA vaccine reactogenicity.[9,11,13]

Participants who received Moderna had a higher antibody response than those who received Pfizer at every time point

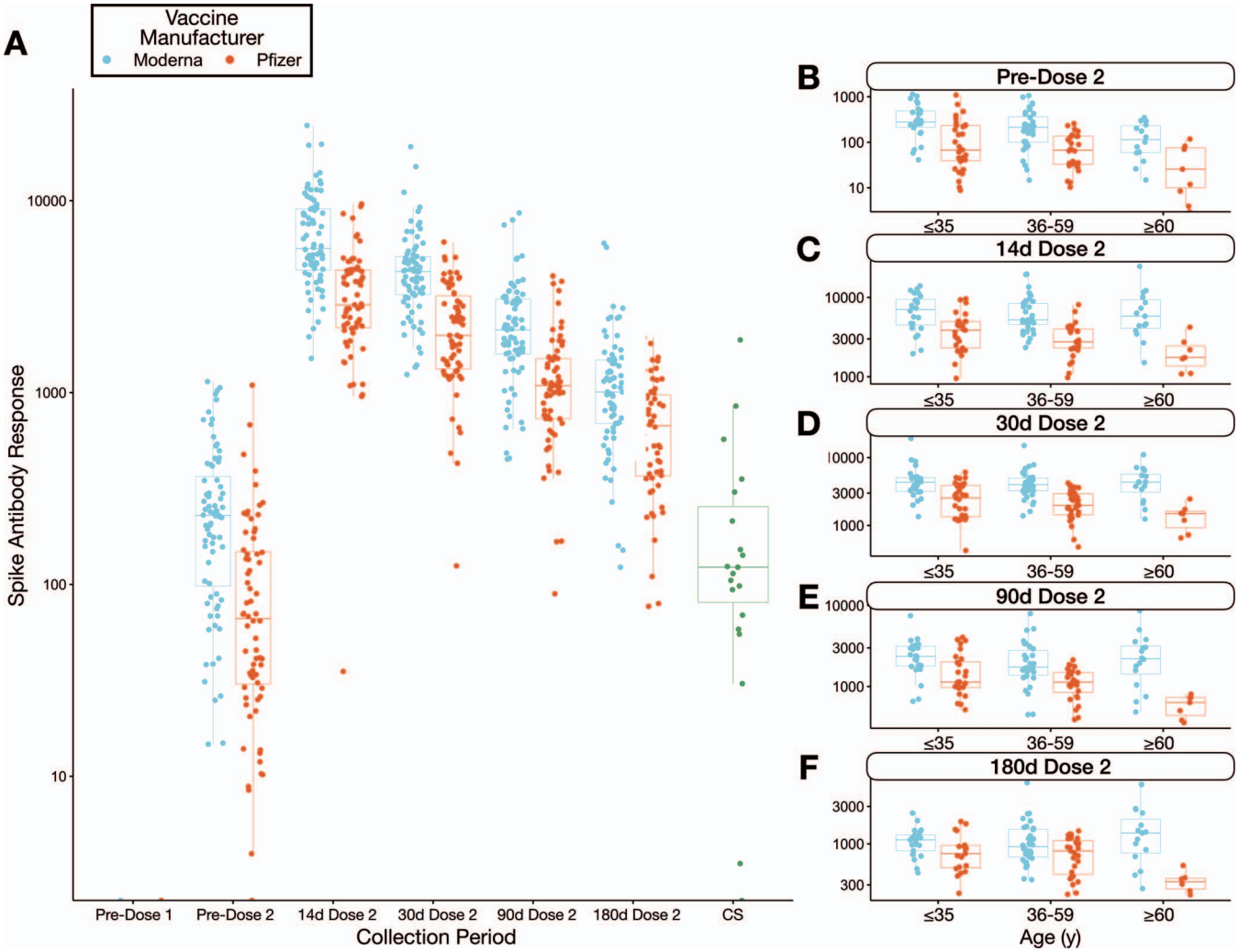

Figure 3. *Spike antibody response after vaccination. A, Grouped box and scatter plots representing the median of log-transformed spike antibody response (y-axis) at specified time intervals (x-axis) are shown before and after vaccination with Moderna (blue), Pfizer (red), or in convalescent donors 32 to 54 days after polymerase chain reaction–confirmed SARS-CoV-2 infection (green). Grouped box and scatter plots representing the median of log-transformed spike antibody response (y-axis) are displayed for participants aged ≤35, 36 to 59, and ≥60 years (B) prior to vaccine dose 2, (C) 14 days after dose 2, (D) 30 days after dose 2, (E) 90 days after dose 2, and (F) 180 days after dose 2 after administration of either the Moderna (blue) or Pfizer (red) vaccine. Statistical significance can be found in Supplemental Table 6.*

examined during the 6 months following vaccination. Each dose of the Moderna vaccine contains 100 μg of mRNA[6,7] and is given 28 days apart, whereas the Pfizer vaccine contains 30 μg of mRNA[5] and is given 21 days apart. The Moderna and Pfizer vaccines use different RNA sequences and the absolute number of mRNA copies may not be comparable, but previous studies have shown that immunogenicity to both mRNA-1272 and BNT126b2 vaccines were dose-dependent, with higher doses eliciting a stronger antibody response.[5,7,23,24] The CDC also released information showing that vaccination with Moderna offers greater protection against severe infection.[18] Participants receiving Moderna have an additional week to seroconvert after dose 1, and spike antibody titers rise rapidly over time shortly after vaccination.[22] Therefore, differences in antibody response were likely due to a combination of dosing and

Median Antibody Response and Reference Intervals (RIs) After Vaccination

	Moderna, U/mL		Pfizer, U/mL		
Time of Collection	Median	RI	Median	RI	Convalescent Median, U/mL
Before dose 2	229	15–1068	65	3–783	—
14 d after dose 2	5705	1931–37 987	2865	679–9420	—
30 d after dose 2	4146	1343–15 562	1985	322–5434	119
90 d after dose 2	2122	453–8053	1082	140–3886	—
180 d after dose 2	1008	144–5792	631	78–1882	—

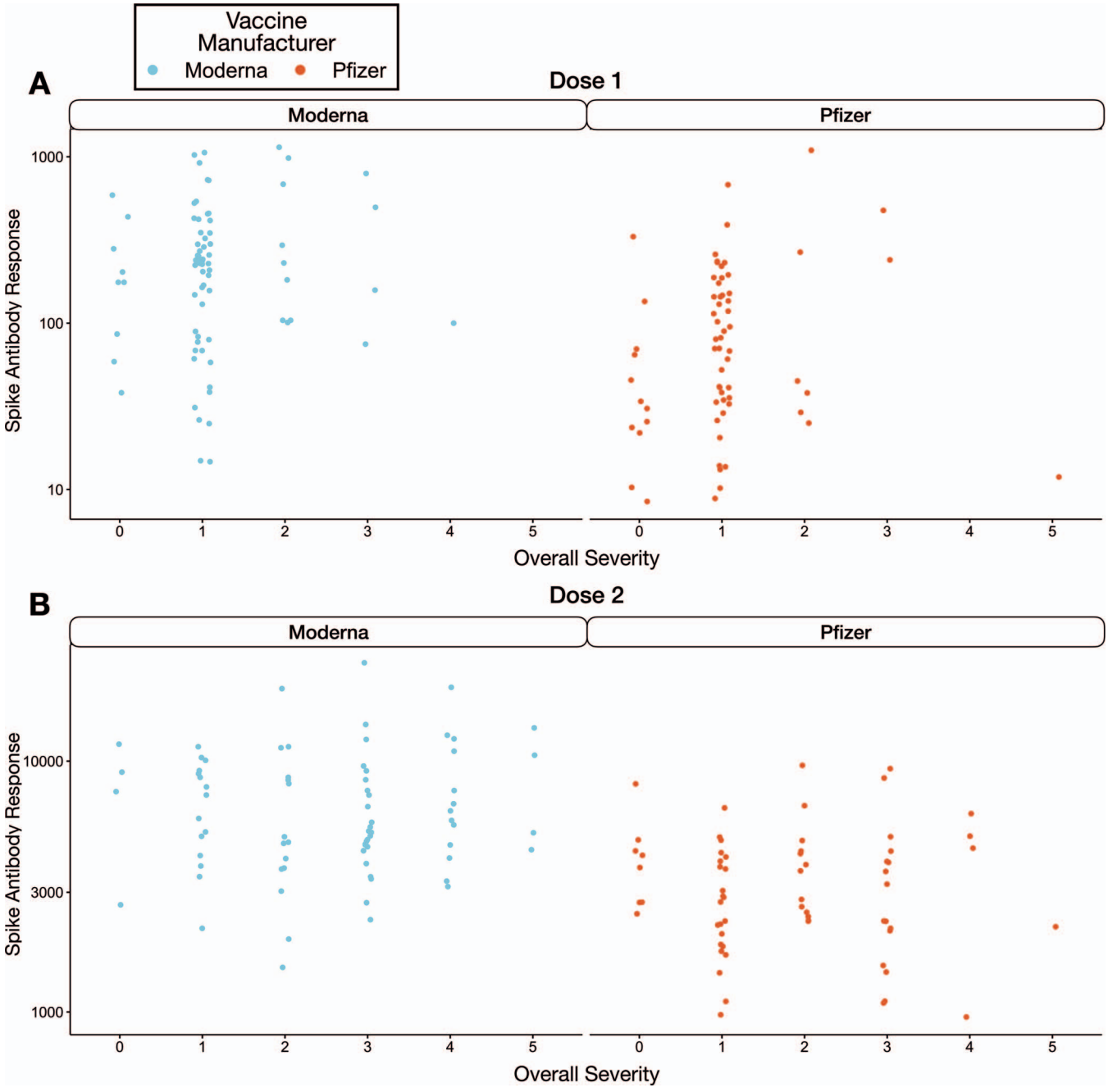

Figure 4. *Lack of correlation between overall symptom severity and spike antibody response after vaccination. Scatter plot of log-transformed spike antibody response (y-axis) is plotted against overall symptom severity score (x-axis) after administration of the Moderna (blue) or Pfizer (red) vaccine. The pre–dose 2 antibody response is plotted against the overall severity after dose 1 (A), and the 14-day post–dose 2 antibody response is plotted against the overall severity after dose 2 (B).*

timeline differences between the Moderna and Pfizer vaccines.

We observed that older participants exhibited a lower prevalence of side effects than younger participants and antibody response declined with age, consistent with phase 1 clinical trials.[5,6] In Pfizer recipients, the lower antibody response was observed throughout the 6-month study, consistent with recent publications.[25–27] Because of immunosenescence, older individuals tend to exhibit a suboptimal immune response to vaccination compared with younger individuals, which may contribute to the reduced symptom burden after vaccination.[28] However, we, like others,[26] did not observe this negative correlation in Moderna recipients following dose 2. It is possible that the increased mRNA dosage in the Moderna vaccine is sufficient to counteract age-dependent differences in immune response. Although the exact relationship between spike protein antibodies and protection against SARS-CoV-2 remains to be established, the lower immune response observed in older individuals may be a contributing factor to the higher death rates and disease burden seen after SARS-CoV-2 infection in that population.[29]

We predicted that increased symptom severity after vaccination with Moderna would correlate with the higher antibody signal, but no such relationship was found. Instead, overall symptom severity ratings were independent of antibody response, which agrees with a recent report looking at IgG response to the Pfizer vaccine.[30] However, key differences in antibody response after vaccination have been observed in specific populations. A recent meta-analysis demonstrated that in patients being treated for multiple sclerosis, serum antibody concentrations were approximately 3.25-fold higher in those who received the Moderna vaccine relative to those receiving Pfizer.[31] Another study found that in patients being treated by dialysis, a greater percentage of Pfizer recipients had a diminished antibody response relative to those patients who received the Moderna vaccine.[32] Taken together, our findings and recently published literature could help selectively target each vaccine to a specific patient demographic, with Moderna preferred in individuals in need of greater immune stimulation (elderly, immunocompromised, etc) and Pfizer preferred in those who are primarily concerned about vaccine reactions.

Antibody response after full vaccination (14 days after dose 2) with either Moderna or Pfizer was higher than in convalescent donors 32 to 54 days after confirmed infection. In phase 1 clinical trials of the Pfizer BNT162b2 vaccine, average IgG antibody response to the S-1 binding domain after full vaccination was reported to be higher (8147 U/mL) than antibody titers seen in convalescent donors (631 U/mL).[5] In our study, the median total antibody response after full vaccination with Pfizer was 2880 U/mL, whereas the response in convalescent donors was 119 U/mL. Although the absolute antibody signals differed, likely due to analytic differences between platforms, we both observed substantially higher antibody signal in previously seronegative, vaccinated individuals relative to convalescent donors at a similar time point. Future studies should monitor long-term antibody and adaptive immune response in both populations to determine if vaccination offers longer-term protection than immunity arising from natural infection.

Previous studies have demonstrated that antibody response can vary significantly between different analytic platforms.[14,33–35] Assays can differ by epitope target, immunoassay design, antibody class detected (IgG-specific versus total antibody), detector antibody label, and buffer composition. We reported an expected antibody response for both the Moderna and Pfizer cohorts at each of the measured time points for the Roche Anti–SARS-CoV-2 S assay. It has now been shown that the antibody signal measured by the Roche assay does have a slight correlation ($R^2 = 0.39$) with the production of neutralizing antibodies.[14] At present, it is unknown what level of antibody response is considered protective. Should measurement of spike antibody response be used to assess immune status in the future, assay-specific reference intervals or standardized assay results will be required in addition to vaccine-specific reference intervals. As the World Health Organization has recently released an accepted international standard, efforts to standardize spike antibody assays and develop established reference intervals should start to increase. Our results can contribute to the large amount of data necessary to establish these values.

We observed a significant increase in antibody response from the pre–dose 2 time point to the 14-day post–dose 2 time point, followed by a continued decrease in antibody signal out to the 180-day collection. Another group reported a similar median decrease in antibody response of 29.4% for Pfizer recipients between samples drawn at 3 and 6 months following vaccination when measured using the Roche assay.[36] It is possible that at least a portion of this drop in antibody response is due to the disappearance of the IgM and IgA antibodies over time. The Roche Anti–SARS-CoV-2 S assay is a total antibody assay, and although it predominantly detects IgG antibodies, it can also detect IgM and IgA antibodies. However, 1 study of 41 Pfizer recipients, where antibodies were measured out to 6 months, saw both IgM and IgG antibodies decrease by 80.9% and 88.6%, respectively.[37] Additional studies using IgG-specific platforms also demonstrated a similar drop in antibody signal, suggesting that a global decline in antibodies is responsible for the decrease.[5,7] Although antibody signal drops, it is still unknown what values correspond to protection. Studies have shown there is a slight correlation with neutralizing antibody production.[14,38–40] Unfortunately, there is still no consensus on the cutoff for protection. One research study estimates that the neutralization level for 50% protection from severe infection is only 3% of the mean convalescent level.[8] Although the exact correlation of spike antibody response to neutralizing antibodies is unknown, it is promising that the median antibody response 180 days after vaccination is approximately 5- or 10-fold higher than convalescent samples for Pfizer or Moderna recipients, respectively.

There are several limitations to our study. The postvaccination symptom survey was given to participants at either 14 or 30 days after dose 2, meaning that some participants completed the survey 2 weeks later than others, potentially introducing recall bias. However, there was no difference in overall symptom severity between those who answered at 14 days and those who answered at 30 days. Although we did not see a trend with symptom severity and antibody response, others have reported a correlation between antibody response and the presence of systemic reactions to the vaccine.[25,27] It might be pertinent to look at whether antibody responses were different in recipients who reported specific symptoms versus those who did not. More women than men volunteered for this study, resulting in an uneven gender distribution. Our sample size for participants aged $\geq$60 years was limited, which diminished our ability to establish statistically significant effects for this group. The age distribution was slightly skewed to younger participants assigned to the Pfizer group, but this difference between the Moderna and Pfizer groups was not statistically significant ($P = .06$). Additionally, the multivariable regression models removed any potential impact of these confounders when assessing key relationships. Because each vaccine group contained fewer than 120 participants at each time point, reference intervals defined here should be considered preliminary. The number of participants in our study with a previous or concurrent SARS-CoV-2 infection was too low to identify differences in vaccine response between previously infected and uninfected participants. Medical history and race/ethnicity for participants were not recorded in our study because of institutional review board constraints. Finally, although participants were seemingly healthy, it is possible that antibody response was affected by underlying medical conditions that were not disclosed.

The use of commercial SARS-CoV-2 antibody assays against the spike protein is not currently approved for assessing the immune status of an individual. However, the

symptom profiles and expected antibody responses determined in our study may help personalize vaccine selection, with Moderna preferred in individuals with a suboptimal vaccine response (eg, older patients) and Pfizer for those who are concerned about side effects after vaccination. Future studies will continue to address long-term immunity after vaccination.

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