Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals after mRNA vaccination

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mRNA vaccines for SARS-CoV-2 have been authorized for emergency use. Despite their efficacy in clinical trials, data on mRNA vaccine–induced immune responses are mostly limited to serological analyses. Here, we interrogated antibody and antigen-specific memory B cells over time in 33 SARS-CoV-2 naïve and 11 SARS-CoV-2 recovered subjects. SARS-CoV-2 naïve individuals required both vaccine doses for optimal increases in antibodies, particularly for neutralizing titers against the B.1.351 variant. Memory B cells specific for full-length spike protein and the spike receptor binding domain (RBD) were also efficiently primed by mRNA vaccination and detectable in all SARS-CoV-2 naïve subjects after the second vaccine dose, although the memory B cell response declined slightly with age. In SARS-CoV-2 recovered individuals, antibody and memory B cell responses were significantly boosted after the first vaccine dose; however, there was no increase in circulating antibodies, neutralizing titers, or antigen-specific memory B cells after the second dose. This robust boosting after the first vaccine dose strongly correlated with levels of preexisting memory B cells in recovered individuals, identifying a key role for memory B cells in mounting recall responses to SARS-CoV-2 antigens. Together, our data demonstrated robust serological and cellular priming by mRNA vaccines and revealed distinct responses based on prior SARS-CoV-2 exposure, whereby COVID-19 recovered subjects may only require a single vaccine dose to achieve peak antibody and memory B cell responses. These findings also highlight the utility of defining cellular responses in addition to serologies and may inform SARS-CoV-2 vaccine distribution in a resource-limited setting.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in hundreds of millions of infections and millions of deaths worldwide (1). Novel vaccines have recently been issued emergency use authorization by the U.S. Food and Drug Administration and are being widely administered (2, 3). Early data from clinical trials suggest that these vaccines are safe and effective (4, 5); however, there is still a paucity of information on how these novel mRNA vaccines elicit immune responses at the cellular and molecular level.

The humoral immune response to infection or vaccination results in two major outcomes: the production of antibodies by antibody-secreting cells (ASCs) that can provide rapid serological immunity and the generation of long-lived memory B cells capable of mounting recall responses (6, 7). If circulating antibodies fail to confer protection to a future exposure, memory B cells drive the recall response by producing new antibodies through forming new ASCs or reentering germinal centers for additional rounds of somatic hypermutation (SHM) (8, 9). In the context of acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, immunological memory in the form of antibodies and memory B cells are durable for over 8 months after symptom onset (10–14). However, studies on vaccinated individuals have largely focused on measuring binding and/or neutralizing antibodies as primary endpoints (15–17), and the induction of memory B cells by mRNA vaccines remains poorly understood. Although antibodies are a central component of vaccine efficacy, memory B cells may be important for long-term protection, responses to subsequent infection, and the ability to respond to emerging variant strains (18). Furthermore, it is unclear how memory B cell responses relate to serological responses for novel SARS-CoV-2 mRNA vaccines, and how memory B cell responses differ after vaccination in subjects who previously experienced SARS-CoV-2 infection compared with those who are SARS-CoV-2 naïve.

A related question is whether individuals who experienced prior SARS-CoV-2 infection require a second dose of mRNA vaccine. As these individuals have already generated a primary immune response to SARS-CoV-2 during their natural infection, it is possible that a single dose of vaccine could be sufficient to boost antibody and memory B cell responses. This question is particularly relevant in
settings of limited vaccine supply and challenging vaccine deployment (19). Several recent studies have indicated that antibody responses can be robustly induced in SARS-CoV-2 experienced individuals, consistent with an anamnestic response (20–23). Although one study suggests that memory B cells might also be boosted after a single vaccine dose (24), it remains unclear how memory B cell responses are affected by the second dose of mRNA vaccine in SARS-CoV-2 naïve versus recovered individuals. These key gaps in our understanding require longitudinal analysis of antibodies together with memory B cell responses after the first and second dose of mRNA vaccine in SARS-CoV-2 naïve and experienced subjects.

Here, we established a longitudinal cohort of SARS-CoV-2 naïve and SARS-CoV-2 recovered individuals who received SARS-CoV-2 mRNA vaccines. From these longitudinal samples, we assessed both circulating antibodies and antigen-specific memory B cells over the course of first and second immunization. We also compared vaccine responses with demographic and clinical metadata, including age and side effects. These data offer new insights into the B cell response to SARS-CoV-2 mRNA vaccines.

RESULTS
For this study, we recruited 44 healthy individuals (i.e., no self-reported chronic health conditions) who received SARS-CoV-2 mRNA vaccines (Pfizer BNT162b2 or Moderna mRNA-1273) at the University of Pennsylvania Health System. Full cohort information is described in fig. S1. Of this cohort, 11 individuals had a prior SARS-CoV-2 infection, ranging from 65 to 275 days before vaccination. Peripheral blood samples were collected for immunological analysis at four key time points (Fig. 1A): prevaccine baseline (time point 1), 2 weeks after the first dose (time point 2), the day of second dose (time point 3), and 1 week after the second dose (time point 4). This study design allowed us to investigate the kinetics of immune responses after both primary and secondary immunizations.

Antibody responses to SARS-CoV-2 mRNA vaccination
We first measured circulating antibody responses in longitudinal serum samples by enzyme-linked immunosorbent assay (ELISA). At baseline, SARS-CoV-2 naïve individuals had undetectable levels of immunoglobulin G (IgG) antibodies specific for either full-length spike protein or the spike receptor binding domain (RBD) (Fig. 1B). Primary vaccination induced a significant increase in SARS-CoV-2–specific antibodies, which was further enhanced by the booster dose (Fig. 1B). In contrast, all SARS-CoV-2 recovered individuals had detectable levels of anti-spike and anti-RBD IgG at baseline, and these antibody responses were significantly increased after the first dose of vaccine (Fig. 1B). However, in SARS-CoV-2 recovered subjects, there was no additional increase in antibody levels after the second vaccine dose (Fig. 1B). Notably, the levels of anti-RBD IgG were similar in the SARS-CoV-2 naïve and SARS-CoV-2 recovered individuals at 1 week after boost (time point 4) (Fig. 1B).

In addition to total spike- and RBD-binding antibody, we further assessed antibody function using a pseudovirus neutralization assay. Specifically, we tested the ability of vaccine-induced sera to neutralize pseudotyped virus expressing either the D614G (the initial dominant strain at the time of the study) spike protein or the B.1.351 variant (originally referred to as the South African variant; now called Beta) spike protein. SARS-CoV-2 naïve individuals had a moderate response to primary immunization, with ~50% of participants developing detectable levels of neutralizing antibodies against D614G 2 weeks after primary (Fig. 1, C and D). In contrast, primary immunization was largely ineffective to induce functional antibodies against the B.1.351 variant with only 4 of 25 individuals developing neutralizing titers above limit of detection (LOD) over the same time frame (Fig. 1, C and D). Neutralizing titers were significantly increased after the second dose in SARS-CoV-2 naïve individuals, with all participants achieving neutralization against D614G and 26 of 27 achieving detectable neutralization against B.1.351 at 7 days after boost (Fig. 1, C and D). Consistent with anti-spike and anti-RBD antibody levels, SARS-CoV-2 experienced individuals had a robust increase in neutralizing antibodies after primary immunization, with no further increase in neutralization titers against D614G and B.1.351 after the second dose (Fig. 1C). The first dose of vaccine also appeared to resolve baseline differences in neutralization between D614G and B.1.351 in this group (Fig. 1D).

On the basis of these data, we quantified the relationship between total antibody levels and neutralization ability in SARS-CoV-2 naïve individuals to assess the relative quality of antibodies induced by the first and second dose of mRNA vaccine. Before the second dose, anti-spike antibodies were only moderately correlated with neutralizing titers against D614G, with further drop-off for the B.1.351 variant (Fig. 1E). Preboost anti-RBD antibodies were more predictive of neutralization titers against D614G and B.1.351 (Fig. 1E) than anti-spike antibodies. Both anti-spike and anti-RBD antibodies correlated more strongly with neutralizing titers against D614G and B.1.351 after the second dose (Fig. 1E), indicating a marked improvement in the quality of the antibody response. Together, these data supported the importance of a two-dose regimen for effective antibody responses, especially against the B.1.351 variant, in SARS-CoV-2 naïve individuals. Conversely, a single dose of vaccine was able to achieve highly effective antibody responses in SARS-CoV-2 recovered individuals with no further improvement postboost.

Memory B cell responses to SARS-CoV-2 mRNA vaccination
We next asked how mRNA vaccination affected the responses of memory B cells specific for SARS-CoV-2. To address this question, we developed a flow cytometric assay using a combination of fluorescently labeled antigens as probes to track the induction of virus-specific memory B cells in longitudinal peripheral blood mononuclear cell (PBMC) samples (fig. S2A) (11, 13, 25). Analysis of bulk B cell populations revealed no change in the frequency of naïve, non-naïve, or memory B cells across the time course of vaccination, or between SARS-CoV-2 naïve and recovered individuals (fig. S2B), highlighting the stability of the overall B cell compartment.

Despite a stable frequency of total memory B cells, there were marked changes in SARS-CoV-2 antigen–specific B cell populations in response to vaccination. Consistent with the antibody data, SARS-CoV-2 naïve individuals had minimal spike-specific memory B cells at baseline, whereas SARS-CoV-2 recovered individuals had a significant population of spike-specific memory B cells ranging from ~0.15 to 0.8% of total memory B cells (Fig. 2, A and B). Memory B cells targeting the spike RBD followed a similar trend and the frequency of these antigen–specific memory B cells was comparable to a separate cohort of nonvaccinated SARS-CoV-2 recovered donors (Fig. 2, A and B). After primary immunization, SARS-CoV-2 naïve individuals had a significant increase in spike-specific and RBD-specific memory B cells over baseline (Fig. 2B). These memory B cells were also significantly boosted after administration of the second vaccine.
Fig. 1. Antibody responses after mRNA vaccination in SARS-CoV-2 naïve and recovered individuals. (A) University of Pennsylvania Immune Health COVID vaccine study design. (B) Concentration of anti-spike and anti-RBD IgG antibodies in vaccinated individuals over time. (C) FRNT50 of vaccine-induced sera against pseudotyped virus expressing SARS-CoV-2 D614G (wild-type) or B.1.351 (South African) variant spike protein. (D) Paired analysis of neutralization titers against D614G and B.1.351 in vaccine-induced sera at baseline (time point 1), preboost (time point 2), and postboost (time point 4). (E) Bivariate analysis of total anti-spike and anti-RBD binding antibodies with pseudovirus neutralization titers against D614G and B.1.351. Associations between total antibody levels and neutralizing ability were calculated using Spearman's rank correlation and are shown with linear trend lines. Dotted lines indicate the LOD for the assay. Statistics were calculated using unpaired Wilcoxon test (comparisons between time points and comparisons between naïve and recovered) or paired Wilcoxon test (comparisons between naïve and recovered groups). Black values indicate statistical comparisons between naïve and recovered groups.

dose, approaching the levels of memory B cells observed in nonvaccinated SARS-CoV-2 recovered donors (Fig. 2B). In contrast, SARS-CoV-2 recovered individuals had a robust expansion of spike- and RBD-specific memory B cells after primary immunization but had no additional boosting after the second vaccine dose (Fig. 2B). As a control, we also examined the frequency of influenza hemagglutinin (HA)–specific memory B cells in both SARS-CoV-2 naïve and recovered individuals after SARS-CoV-2 vaccination. The frequency of these antigen–unrelated memory B cells remained stable throughout the mRNA vaccination time course (Fig. 2B), confirming the specificity of this memory B cell assay. Together, these results demonstrated robust induction of SARS-CoV-2–specific memory B cells by two doses of mRNA vaccine in SARS-CoV-2 naïve subjects. In contrast, a single dose of mRNA vaccine amplified
Fig. 2. Antigen-specific memory B cell responses after mRNA vaccination in SARS-CoV-2 naïve and recovered individuals. (A) Gating strategy and representative plots for flow cytometric analysis of SARS-CoV-2–specific B cells. (B) Frequency of spike⁺, spike⁺/RBD⁺, and HA⁺ memory B cells over time in vaccinated individuals. Data are represented as frequency of antigen-specific cells in the total memory B cell compartment. (C) Frequency of IgG and IgM isotypes over time in the antigen-specific memory B cell compartments. (D) Frequency of RBD⁺ memory B cells over time in vaccinated individuals, as a percentage of spike⁺ memory B cells. (E) SHM status of spike⁺ memory B cell clones over time in SARS-CoV-2 naïve or recovered individuals. Data are represented as percent of VH gene nucleotides that are mutated. (F) SHM of productive spike-binding clones sampled at time point 1, which were also found in at least one other time point. Clones with fewer than 10 copies in each patient were excluded. (G) Clonal evolution of spike-binding memory B cell lineages that were present before vaccination in a recovered individual. For representative lineages, numbers refer to mutations compared with the preceding vertical node. Colors indicate time point, black dots indicate inferred nodes, and size is proportional to sequence copy number; GL, germline sequence. All panels: Dotted lines indicate the mean at baseline. RD, nonvaccinated, SARS-CoV-2 recovered donors. Statistics were calculated using unpaired Wilcoxon test (comparisons between time points and comparisons between naïve and recovered) with Holm correction for multiple comparisons. Blue and red values indicate statistical comparisons within naïve or recovered groups. Black values indicate statistical comparisons between naïve or recovered groups.
preexisting antigen-specific memory B cells in SARS-CoV-2 recovered subjects, with no additional quantitative benefit after the second vaccine dose.

We further analyzed the phenotype of SARS-CoV-2–specific memory B cells. On day 15 after primary immunization, ~25 to 30% of spike-specific memory B cells were IgG+ and ~40 to 50% were IgM+ in SARS-CoV-2 naïve individuals (Fig. 2C). The frequency of IgG+ memory B cells increased to >50% after the second dose of vaccine in these subjects (Fig. 2C), consistent with a qualitative improvement in memory B cells after the boost. Conversely, in SARS-CoV-2 recovered individuals, ~60 to 70% of spike-specific memory B cells detected before vaccination were IgG+ (Fig. 2C). Although the frequency of IgG+ memory B cells increased slightly to ~75% after the first dose of vaccine, further increases were not observed after the second immunization (Fig. 2, C and D). A similar pattern of IgG frequency was observed for RBD-specific memory B cells (Fig. 2C).

In addition, the fraction of spike-specific memory B cells that recognized RBD remained stable over time in SARS-CoV-2 recovered individuals. In SARS-CoV-2 naïve subjects, the fraction of the overall spike-specific memory B cell response that was focused on RBD increased over time, becoming equivalent to that observed in SARS-CoV-2 recovered individuals after the second vaccine dose (Fig. 2D). Overall, these data indicated a qualitative benefit to the virus-specific memory B cell response after both doses of vaccine in SARS-CoV-2 naïve individuals and qualitative improvement after the first but not the second vaccine dose in SARS-CoV-2 recovered subjects.

Last, we sorted spike+ memory B cells from five recovered donors at baseline (time point 1), postprimary (time point 2), and postboost (time point 4) for B cell receptor (BCR) sequencing to further evaluate potential changes in the memory B cell response induced by vaccination. SHM is a process of DNA point hypermutation that occurs in immunoglobulin variable gene sequences and usually accompanies T cell–dependent B cell responses within germinal centers (26). Accordingly, SHM is a frequently used marker for the evaluation of immune memory (27). Here, SHM was calculated as the average percentage of mutated VH gene nucleotides in each clone, counting each clone only once. Full sequencing information, including the number of clones identified for each sample, is listed in table S3. Mutational analysis of total spike-binding memory clones revealed a modest shift toward higher SHM at the postprimary and second immunization (Fig. 2, C and D). A similar pattern of IgG frequency was observed for RBD-specific memory B cells (Fig. 2C).

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Demographic and clinical factors associate with B cell responses to SARS-CoV-2 mRNA vaccination

In addition to prior SARS-CoV-2 exposure, we also investigated associations between other demographic and clinical metadata with vaccine-induced B cell responses. Several previous studies have reported a negative association between age and vaccine-induced antibody titers after a single dose of mRNA vaccines (28, 29). We therefore investigated potential relationships between sex or age and B cell responses after one or two doses of vaccine. In our cohort of SARS-CoV-2 naïve vaccinees, there were no associations between sex and antibody or memory B cell responses (Fig. 3, A and B). While there was no association between age and anti-spike IgG after the first immunization (i.e., preboost), there was a trend toward a negative relationship between age and preboost RBD-specific IgG (Fig. 3C). Antibody for both spike and RBD had a similarly negative, but statistically insignificant, correlation with age after the second vaccine dose (Fig. 3C). However, there was a clear negative correlation between the postboost frequency of antigen–specific memory B cells and age (Fig. 3D). Although this relationship represented weaker induction of memory B cells with older age, all age groups still displayed an increase in the frequency of SARS-CoV-2–specific memory B cells compared with prevaccine baseline (Fig. 3, C and D). There was also no change in the frequency of total memory B cells by sex or age, indicating the antigen-specific nature of this effect (fig. S4). Although our cohort is not extensively enriched in those over 50 years old and does not directly address elderly vaccinees, these data pointed to potentially relevant age-related changes in immune response to vaccination.

An additional question is whether vaccine-induced side effects have any relationship to immune responses (20). We addressed this question by comparing vaccine-induced antibody and memory B cell responses in subjects with or without self-reported systemic side effects (i.e., fever, chills, headache, fatigue, and myalgia; fig. S1C). In SARS-CoV-2 naïve vaccinees with systemic side effects after the second dose, there was a trend toward an increase in antibody responses at the postboost time point (Fig. 3E). Such a trend was not observed for the memory B cell response (Fig. 3E). We further investigated the potential association between reactogenicity and increased antibody response using a multivariate regression to control for the effects of sex and age. This multivariate analysis similarly revealed a positive association of systemic side effects with anti-spike and anti-RBD antibody levels 7 days after the booster immunization (Fig. 3F). Although these data only represent a statistical trend ($P = 0.051$), they do provoke questions about potential relationships between early vaccine-induced inflammation and the induction of antibody responses that should be addressed in future studies.

Relationships between antibody and memory B cell responses to SARS-CoV-2 mRNA vaccination

Last, we investigated the potential relationships between antibody and memory B cell responses. To address this question, we first performed hierarchical clustering of vaccine-induced B cell responses in SARS-CoV-2 naïve subjects. As expected, postboost (time point 4) samples clustered away from the earlier time points, with some subgrouping of patients based on the relative magnitude of antibody and memory B cell responses (Fig. 4A). Hierarchical clustering of the different readouts of antigen-specific humoral immunity also revealed that antibodies and memory B cells clustered separately
Fig. 3. Association of age and side effects with B cell responses after mRNA vaccination. (A) and (C) Concentration of anti–spike and anti–RBD IgG antibodies over time compared with sex (A) and age (C) in SARS-CoV-2 naive individuals. Dotted lines indicate the LOD for the assay. (B and D) Frequency of spike+ and spike+/RBD+ memory B cells over time compared with sex (B) and age (D) in SARS-CoV-2 naive individuals. Dotted lines indicate the mean frequency of cells at baseline. Preboost indicates samples collected at time point 2 (~15 days after primary vaccination). Postboost indicates samples collected at time point 4 (~7 days after secondary vaccination). Statistics for sex were calculated using Wilcoxon test. Associations with age were calculated using Spearman rank correlation and are shown with linear trend lines. 

(Fig. 4A). We next performed a principal components analysis (PCA) of postboost B cell responses. Antibody and memory B cell measurements had distinct contributions to the first two principal components, with total binding antibodies and neutralizing titers primarily contributing to dimension 1 (Dim1) and memory cells primarily contributing to Dim2 (Fig. 4B). On the basis of these data, we further examined the relationship between circulating antibody responses and corresponding memory B cell responses after two doses of vaccine in a bivariate analysis. Despite strong induction of both spike- and RBD-specific antibody and memory B cells in these subjects, there was no association between the levels of postboost antibodies and B cell memory (Fig. 4C), indicating that short-term serological responses and memory B cell responses may be distinct immunological features of response to mRNA vaccination. Similarly,
Overall, we tracked antibody and antigen-specific memory B cells over time after SARS-CoV-2 mRNA vaccination and documented robust priming of antibody and memory B cell responses (Fig. 5A). Our analysis revealed key differences in vaccine-induced immune response between SARS-CoV-2 naïve and recovered subjects after the first versus second dose of vaccine. (Fig. 5B). SARS-CoV-2 naïve individuals required two doses of vaccine to achieve optimal priming of antibodies, including neutralizing antibodies to the B.1.351 strain and memory B cells. In contrast, SARS-CoV-2 recovered subjects may only require a single vaccine dose to achieve peak antibody and memory B cell responses. We also revealed age-related differences in vaccine-induction of immune responses (Fig. 5C) and highlighted the importance of memory B cells in mounting recall antibodies in SARS-CoV-2 recovered subjects (Fig. 5D).

### DISCUSSION

Here, we demonstrated that mRNA vaccines to SARS-CoV-2 induced robust antibody and memory B cell responses to full-length spike and the RBD. These results are encouraging for both short- and long-term vaccine efficacy and add to our understanding of SARS-CoV-2 mRNA vaccine–induced immune responses in several ways. First, our serological data are consistent with several other recent studies (20, 21, 23, 24, 28, 29), indicating robust boosting of antibody responses in SARS-CoV-2 recovered subjects after the first vaccine dose but little benefit to antibody levels after the second vaccine dose. This finding was also reflected in the observation that neutralizing titers against both D614G and the B.1.351 South African variant reached a peak after the first dose in recovered subjects. Moreover, we found a similar effect for virus-specific memory B cells, identifying a quantitative and qualitative plateau in vaccine-induced memory B cells in COVID-19 recovered subjects after the first dose of vaccine with little additional change to the memory B cell response after booster vaccination. These data suggest that only a single vaccine dose in individuals confirmed to have previously been infected with SARS-CoV-2 may be enough to induce antibody and memory B cell responses.

The data presented document key differences in immune responses associated with vaccine efficacy in SARS-CoV-2 naïve versus SARS-CoV-2 recovered individuals. However, with a study of this size designed for deep immunological analysis, it was not possible to directly address protection or true vaccine efficacy. Accordingly, larger-scale clinical studies would be necessary to fully examine the question of a one- or two-dose regimen in SARS-CoV-2 recovered individuals.
individuals. Our cohort also consisted of individuals who were not hospitalized during their SARS-CoV-2 infections, and it may be necessary to address this question of one versus two doses of vaccine in individuals who experienced more severe COVID-19. Moreover, there may be practical challenges to identifying SARS-CoV-2 recovered individuals based on self-reported infection or laboratory confirmed tests such as reverse transcription polymerase chain reaction (PCR) or serology. Despite these limitations, the robust boosting of both antibody and memory B cells in these subjects after one dose may have implications for vaccine distribution in settings where supply is limited.

An additional question is whether the second vaccine dose in recovered individuals has other immunological effects not reflected in overall antibody titers or memory B cell frequency and phenotype. Given the relatively short time frame of this study, future studies will be necessary to evaluate durability of immune responses in these subjects and investigate potential differences in long-term immunological memory. Our data indicate that preformed spike-binding memory B cell clones that were resampled at multiple time points did not have obvious increases in SHM, suggesting that the B cell clones boosted by mRNA vaccination in SARS-CoV-2 recovered individuals have stable SHM profiles. However, these analyses were only performed on a small number of individuals, and samples were limited to only the first few weeks after vaccination. Thus, it will be important to determine whether these clones evolve and undergo further SHM over time as occurs after natural SARS-CoV-2 infection (9, 30, 31). Even small changes in SHM may be biologically relevant, as somatically mutated clones can exhibit higher degrees of cross-protection against different mutant strains of the virus (30). It is also possible that other postgerminal center clones emerge later in the memory phase. Last, it is possible that booster vaccination has some beneficial effects on virus-specific T cell responses in SARS-CoV-2 recovered individuals. Given the capacity of mRNA vaccines to induce CD4\(^+\) T cell responses (32), this topic merits further investigation.

In contrast to SARS-CoV-2 recovered subjects, SARS-CoV-2 naïve individuals demonstrated considerable benefit to antibody and memory B cell responses from the second dose of mRNA vaccine. It is possible that some of this benefit would occur over time in the absence of a second vaccine dose; however, the spike- and RBD-specific antibody levels appeared to plateau between the first and second doses of vaccine before increasing again after the second dose. In addition, only half of SARS-CoV-2 naïve individuals had neutralizing antibodies to wild-type virus, and only 2 of 25 had neutralizing antibodies to the B.1.351 variant after the first dose of vaccine, whereas nearly all subjects achieved neutralizing antibodies after dose two.

Moreover, the frequency of memory B cells that were IgG\(^+\) and the fraction that was focused on RBD both increased after the second vaccine dose, indicating an improvement in the quality of the memory B cell response. Together, these data are consistent with the need for a two-dose mRNA vaccine schedule in SARS-CoV-2 naïve individuals to achieve optimal levels of humoral immunity, including neutralizing antibodies against the B.1.351 variant.

We also observed a negative association of age with induction of B cell memory. Others have reported a negative association between age and serum antibody titers after a single mRNA vaccine dose (28, 29). We found a similar trend for antibodies after two doses of mRNA vaccination, but this did not reach statistical significance for our cohort. However, the magnitude of the memory B cell response after the second dose was lower with increased age, confirming age as a key variable in mRNA vaccine–induced immunity. It remains unclear whether the age-associated effect on memory B cell induction represents a true difference in the magnitude of response or a difference in kinetics that will resolve at later time points. It is also challenging to define an exact threshold for how much immunological memory is sufficient to provide long-term protection. Although all subjects, regardless of age, had significant humoral and memory B cell responses to vaccination, these data highlight a need to further understand the age-related changes in responses to mRNA vaccination (33). In examining correlates of vaccine-induced immune responses, we also uncovered a trend suggesting that vaccine-induced side effects may be related to postvaccination serum antibodies, but not...
memory B cells. Although more data are needed, it is possible that systemic inflammation early after vaccination could contribute to an initial induction of antibody with less of an impact on the development of memory B cells. Larger cohorts and more quantitative measures of vaccine-induced side effects may further clarify these relationships.

Last, these analyses highlight the importance of interrogating vaccine-induced memory B cell responses alongside serological analyses. Specifically, we found no relationship between postvaccination serum antibody levels and memory B cells in SARS-CoV-2 naïve subjects, indicating that antibody and memory B cell induction may be independent features of the immune response to mRNA vaccination. Previous work has found that antibodies and memory B cells correlate for some vaccines or antigens but do not correlate for many others (34). Current research on SARS-CoV-2 vaccines has largely focused on measuring circulating antibodies without measuring memory B cells, which are important for durability of immune memory and potential recall responses to infection or future booster. Preexisting memory B cells in SARS-CoV-2 recovered subjects correlated strongly with postvaccination antibody levels in our cohort, underscoring the immunological connection between memory B cells and antibody recall responses (35). Together, our findings highlight the importance of evaluating memory B cells in addition to serologies to more completely characterize humoral immunity. Although high circulating titers of neutralizing antibodies are common surrogates of protective immunity, there are many scenarios where circulating antibodies may not achieve sterilizing immunity and additional immune responses from memory cells will be necessary (36). For example, high-dose viral inoculums may require rapid generation of additional antibody from memory B cells. Moreover, if circulating antibodies wane over time, our data suggest that durable memory B cells are likely to provide a rapid source of protective antibody upon SARS-CoV-2 reexposure. Last, infection with variant strains that partially escape neutralization by existing circulating antibodies (37–39) might require strong memory B cell populations that can reseed germinal centers and diversify to respond to novel spike antigens (40).

In summary, our analysis of antibodies and cellular memory reveals distinct responses to SARS-CoV-2 mRNA vaccines based on prior history of infection. The addition of memory B cells in this analysis, both in terms of frequency and phenotype, provides complementary data that strengthen current serology-based evidence (20, 21, 23, 24, 28, 29) for a single-dose vaccine schedule in COVID-19 recovered individuals. We also find associations of vaccine-induced immune responses with age and side effects, which may have relevance for future booster vaccines and public health campaigns. Thus, our study provides insight into the underlying immunobiology of mRNA vaccines in humans and may have implications for vaccination strategies in the future.

[**MATERIALS AND METHODS**](#)

**Study design**
The objective of this study was to define antigen-specific measures of humoral immunity in peripheral blood of healthy adults after SARS-CoV-2 mRNA vaccination. A secondary objective of this study was to compare antigen-specific responses with mRNA vaccination in SARS-CoV-2 naïve and recovered individuals. This study began in December 2020 and is continuing to enroll participants.

**Recruitment and clinical sample collection**
Forty-four individuals (33 SARS-CoV-2 naïve and 11 SARS-CoV-2 recovered) were consented and enrolled in the study with approval from the University of Pennsylvania Institutional Review Board (IRB# 844642). All participants were otherwise healthy and, based on self-reported health screening, did not report any history of chronic health conditions. Subjects were stratified on the basis of self-reported and laboratory evidence of a prior SARS-CoV-2 infection. Of the self-reported naïve subjects, one individual was found to have positive SARS-CoV-2–specific antibodies and memory B cells at baseline and was retroactively classified as SARS-CoV-2 recovered. All subjects received either Pfizer (BNT162b2) or Moderna (mRNA-1273) mRNA vaccines. Samples were collected at four time points: baseline, 2 weeks after primary immunization, day 1 of booster immunization, and 1 week after booster immunization. Time points were chosen a priori to capture the peak antigen-specific response for primary (41) and secondary responses (42, 43) in SARS-CoV-2 naïve individuals. Eighty to 100 ml of peripheral blood samples and clinical questionnaire data were collected at each study visit. Full cohort and demographic information is provided in fig. S1. Nonvaccinated recovered COVID-19 donors (RD) were adults with a prior positive COVID-19 PCR test by self-report who met the definition of recovery by the Centers for Disease Control (44).

**Sample processing**
Venous blood was collected into sodium heparin and EDTA tubes by standard phlebotomy. Blood tubes were centrifuged at 3000 rpm for 15 min to separate plasma. Heparin and EDTA plasma were stored at −80°C for downstream antibody analysis. Remaining whole blood was diluted 1:1 with RPMI + 1% fetal bovine serum (FBS) + 2 mM l-glutamine + 100 U of penicillin/streptomycin and layered onto SEPMATE tubes (STEMCELL Technologies) containing lymphoprep gradient (STEMCELL Technologies). SEPMATE tubes were centrifuged at 1200g for 10 min and the PBMC fraction was collected into new tubes. PBMCs were then washed with RPMI + 1% FBS + 2 mM l-glutamine + 100 U of penicillin/streptomycin and treated with ammonium-chloride-potassium (ACK) lysis buffer (Thermo Fisher Scientific) for 5 min. Samples were washed again with RPMI + 1% FBS + 2 mM l-glutamine + 100 U of penicillin/streptomycin, filtered with a 70-μm filter, and counted using a Countess automated cell counter (Thermo Fisher Scientific). Aliquots containing 5 × 10⁶ PBMCs were cryopreserved in fresh 90% FBS and 10% dimethyl sulfoxide.

**Detection of SARS-CoV-2–specific antibodies**
Plasma samples were tested for SARS-CoV-2–specific antibody by ELISA as previously described (45). The estimated sensitivity of the test is 100% [95% confidence interval (CI), 89.1 to 100.0%], and the specificity is 98.9% (95% CI, 98.0 to 99.5%) (45). Plasmids encoding the recombinant full-length spike protein and the RBD were provided by F. Krammer (Mt. Sinai) and purified by nickel–nitrilotriacetic acid resin (Qiagen). ELISA plates (Immulon 4 HBX, Thermo Fisher Scientific) were coated with phosphate-buffered saline (PBS) or recombinant protein (2 μg/ml) and stored overnight at 4°C. The next day, plates were washed with PBS containing 0.1% Tween 20 (PBS-T) and blocked for 1 hour with PBS-T supplemented with 3% nonfat milk powder. Samples were heat inactivated for 1 hour at 56°C and diluted in PBS-T supplemented with 1% nonfat milk powder.
After washing the plates with PBS-T, 50 µl of diluted sample was added to each well. Plates were incubated for 2 hours and washed with PBS-T. Next, 50 µl of diluted goat anti-human IgG–horseradish peroxidase (HRP) (1:5000; Jackson ImmunoResearch Laboratories) or diluted goat anti-human IgM–HRP (1:1000; SouthernBiotech) was added to each well, and plates were incubated for 1 hour. Plates were washed with PBS-T before 50 µl of SureBlue 3,3',5,5'-tetramethylbenzidine substrate (KPL) was added to each well. After 5-min incubation, 25 µl of 250 mM hydrochloric acid was added to each well to stop the reaction. Plates were read with the SpectraMax 190 microplate reader (Molecular Devices) at an optical density (OD) of 450 nm. monoclonal antibody CR3022 was included on each plate to convert OD values into relative antibody concentrations. Plasmids to express CR3022 were provided by I. Wilson (Scripps).

SARS-CoV-2 neutralization assay

Production of vesicular stomatitis virus (VSV) pseudotypes with SARS-CoV-2 spike

293T cells plated 24 hours previously at 5 × 10^6 cells per 10-cm dish were transfected using calcium phosphate with 35 µg of pCG1 SARS-CoV-2 S D614G delta 18 or pCG1 SARS-CoV-2 S B.1.351 delta 18 expression plasmid encoding a codon-optimized SARS-CoV-2 S gene with an 18-residue truncation in the cytoplasmic tail (provided by S. Pohlmann). Twelve hours after transfection, the cells were fed with fresh media containing 1 mM sodium butyrate to increase expression of the transfected DNA. Twenty-four hours after transfection, the SARS-CoV-2 spike–expressing cells were infected for 2 hours with VSV–G pseudotyped VSVAG–RFP (red fluorescent protein) at a multiplicity of infection of ~1. Virus-containing media was removed and the cells were refed with media without serum. Media containing the VSVAG–RFP SARS-CoV-2 pseudotypes were harvested 28 to 30 hours after infection and clarified by centrifugation twice at 6000g then aliquoted and stored at −80°C until being used for antibody neutralization analysis.

Antibody neutralization assay using VSVΔG-RFP SARS-CoV-2

All sera were heat inactivated for 30 min at 55°C before use in neutralization assay. Vero E6 cells stably expressing TMPRSS2 were seeded in 100 µl at 2.5 × 10^4 cells per well in a 96-well collagen-coated plate. The next day, twofold serially diluted serum samples were mixed with VSVAG–RFP SARS-CoV-2 S pseudotype virus (100 to 300 focus-forming units per well) and incubated for 1 hour at 37°C. Also included in this mixture to neutralize any potential VSV–G carryover virus was 1E9F9, a mouse anti-VSV Indiana G, at a concentration of 600 ng/ml (Absolute Antibody, Ab01402-2.0). The serum–virus mixture was then used to replace the media on VeroE6 TMPRSS2 cells. Twenty-two hours after infection, the cells were washed and fixed with 4% paraformaldehyde before visualization on an S6 FluoroSpot Analyzer (CTL, Shaker Heights OH). Individual infected foci were enumerated, and the values compared with control wells without antibody. The focus reduction neutralization titer 50% (FRNT50) was measured as the greatest serum dilution at which focus count was reduced by at least 50% relative to control cells that were infected with pseudotype virus in the absence of human serum. FRNT50 titers for each sample were measured in at least two technical replicates and were reported for each sample as the geometric mean of the technical replicates.

Detection of SARS-CoV-2–specific memory B cells

Antigen–specific B cells were detected using biotinylated proteins in combination with different streptavidin (SA)–fluorophore conjugates. Biotinylated proteins were multimerized with fluorescently labeled SA for 1 hour at 4°C. Full-length spike protein (R&D Systems) was mixed with SA-BV421 (BioLegend) at a 10:1 mass ratio (e.g., 200 ng of spike with 20 ng of SA: ~4:1 molar ratio). Spike RBD (R&D Systems) was mixed with SA-APC (BioLegend) at a 2:1 mass ratio (e.g., 25 ng of RBD with 12.5 ng of SA: ~4:1 molar ratio). Biotinylated influenza HA pools were mixed with SA-PE (BioLegend) at a 6.25:1 mass ratio (e.g., 100 ng of HA pool with 16 ng of SA: ~6:1 molar ratio). Individual influenza HA antigens corresponding with the 2019 trivalent vaccine (A/Brisbane/02/2018/H1N1 and B/Colorado/06/2017; Immune Technology) were biotinylated using the EZ-Link Micro NHS–PEG4 Biotinylation Kit (Thermo Fisher Scientific) according to the manufacturer’s instructions. Excess biotin was subsequently removed using Zebra Spin Desalting Columns 7K MWCO (Thermo Fisher Scientific), and protein was quantified with a Pierce BCA Assay (Thermo Fisher Scientific). SA-BV711 (BD Bioscience) was used as a decay probe without biotinylated protein to gate out cells that nonspecifically bind SA. All experimental steps were performed in a 50/50 mixture of PBS + 2% FBS and Brilliant Buffer (BD Bioscience). Antigen probes for spike, RBD, and HA were prepared individually and mixed together after multimerization with 5 µM free d-biotin (Avidity LLC) to minimize potential cross-reactivity between probes. For staining, 5 × 10^6 cryopreserved PBMC samples were prepared in a 96-well U-bottom plate. Cells were first stained with Fc block (BioLegend, 1:200) and Ghost 510 Viability Dye (Tonbo Biosciences, 1:600) for 15 min at 4°C. Cells were then washed and stained with 50 µl of antigen probe master mix containing 200 ng of spike-BV421, 25 ng of RBD-APC, 100 ng of HA-PE, and 20 ng of SA-BV711 for 1 hour at 4°C. After incubation with antigen probe, cells were washed again and stained with anti-CD3 (BD Bioscience, 1:200), anti-CD19 (BioLegend, 1:100), anti-CD20 (BD Bioscience, 1:500), anti-CD27 (BD Bioscience, 1:200), anti-CD38 (BD Bioscience, 1:200), anti-CD71 (BD Bioscience, 1:50), anti-IgD (BD Bioscience, 1:50), anti-IgM (BioLegend, 1:200), and anti-IgG (BioLegend, 1:400). After surface stain, cells were washed and fixed in 1% paraformaldehyde overnight at 4°C. For sorting, cells were stained with spike and HA probes followed by Fc block and Ghost 510 Viability Dye as described above. Cells were then stained for surface markers with anti-CD4 (Invitrogen, 1:333.3), anti-CD8 (BioLegend, 1:667), anti-CD14 (BioLegend, 1:200), anti-CD19 (BD Bioscience, 1:100), anti-CD27 (BioLegend, 1:667), and anti-CD38 (1:200). After surface stain, cells were washed and resuspended in PBS + 2% FBS for acquisition. All antibodies and recombinant proteins are listed in tables S1 and S2.

Flow cytometry and cell sorting

Samples were acquired on a BD Symphony A5 instrument. Standardized SPHERO rainbow beads (Spherotech) were used to track and adjust photomultiplier tubes over time. UltraComp eBeads (Thermo Fisher Scientific) were used for compensation. Up to 5 × 10^6 cells were acquired per sample. Data were analyzed using FlowJo v10 (BD Bioscience). Antigen–specific gates were set on the basis of healthy donors stained without antigen probes [similar to an fluorescence minus one (FMO) control] and were kept the same for all experimental runs. All time points for individual subjects were run in the same experiment to minimize batch effects. The full gating strategy is shown in fig. S2. Cell sorting was performed on a BD FACSAria II instrument in low-pressure mode, using a 70-µm nozzle. SARS-CoV-2–specific memory B cells were similarly identified.
as live, CD14^+, CD19^+, CD27^+ CD38int/low, and HA^- spike^+. Cells were sorted into 1.5 DNA LoBind Eppendorf tubes containing 300 µl of cell lysis buffer (Qiagen) and stored at room temperature until nucleic acid extraction.  

**BCR sequencing**

DNA was extracted from sorted cells using a Gentra Puregene Cell kit (Qiagen, catalog no. 158767). Immunoglobulin heavy-chain family–specific PCRs were performed on genomic DNA samples using primers in FR1 and JH as described previously (46, 47). Two biological replicates were run on all samples. Sequencing was performed in the Human Immunology Core Facility at the University of Pennsylvania using an Illumina 2× 300-bp paired-end kit (Illumina MiSeq Reagent Kit v3, 600-cycle, Illumina MS-102-3003).

**BCR sequence analysis**

Raw reads from the Illumina MiSeq were quality controlled with preRESTO v0.6.0 (48) as described in (49). Sequences passing the quality control procedure were imported into IgBLAST v1.17.0 (50) for gene identification and alignment. The primer binding region (IMGT nucleotide positions 1 to 80) was replaced with Ns and sequences beginning after IMGT position 90 were removed to avoid incorrect V gene calls and skewed SHM analysis. The remaining sequences were imported into ImmuneDB v0.29.10 (51) for clonal inference, lineage construction, and downstream analyses. Sequences sharing the same VH gene, JH gene, CDR3 length, and 85% amino acid homology in the CDR3 were aggregated into clones. After sequences were collapsed into clones, nonproductive sequences and clones with one copy number sequences were excluded from all downstream analysis.

Lineages were constructed within ImmuneDB as described in (51). Within each lineage, sequences with fewer than 10 copies across all samples in a donor were excluded to reduce the effect of sequencing error and improve fidelity. The resulting lineage structures were visualized with ete3 (52). Each node represents a unique sequence and the size of each node is proportional to the total copy number of the sequence. Nodes are depicted as pie charts where each wedge indicates the proportion of copies at each time point and inferred nodes are shown in black. The number next to each node represents the number of nucleotide mutations as compared with the preceding vertical node.

**Data visualization and statistics**

All antibody and memory B cell data were analyzed using custom scripts in R Studio. BCR sequencing data were analyzed as discussed above. Data were visualized using ggplot2 in R Studio. Boxplots represent median with interquartile range. Line plots represent means with a 95% CI. For heatmaps, data were scaled by variable (z score normalization) and cells with z > 3.5 were assigned a maximum value of 3.5. For PCA, data were also scaled by variable (z score normalization). Statistical tests are indicated in the corresponding figure legends. All tests were performed two sided with a nominal significance threshold of P < 0.05. In all cases of multiple comparisons, adjustment was performed using Holm correction. For comparisons between time points, unpaired tests were used due to missing data/samples for some participants. *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001. ns indicates no significant difference. Blue and red values indicate statistical comparisons within naïve or recovered groups. Black values indicate statistical comparisons between naïve or recovered groups. Source code is available upon request from the authors. All raw data are provided in table S4.

**SUPPLEMENTAL MATERIALS**

immunology.sciencemag.org/cgi/content/full/6/58/eabj6950/DC1

Figs. S1 to S5
Tables S1 to S4

View/request a protocol for this paper from Bio-protocol.
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Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals after mRNA vaccination

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B cell memory after SARS-CoV-2 mRNA vaccination

Clinical trials of mRNA-based vaccines for SARS-CoV-2 have confirmed their ability to provide robust protection against COVID-19. Many studies demonstrate antibody responses to these vaccines, but the timing of B cell memory formation after vaccination is unclear. Goel et al. studied the antibody and B cell memory responses to SARS-CoV-2 mRNA vaccines using a cohort of SARS-CoV-2 naïve and convalescent patients that received the Pfizer or Moderna vaccines. Two shots of the mRNA vaccines were needed to induce peak antibody and memory B cell responses against SARS-CoV-2 in naïve patients, whereas only one shot induced peak responses in convalescent patients. These antibodies could neutralize the more infectious B.1.351 variant. These data provide further evidence of robust, protective immune responses to SARS-CoV-2 after mRNA vaccination.