

Cite as: L. Stamatatos *et al.*, *Science*
10.1126/science.abg9175 (2021).

mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection

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Emerging SARS-CoV-2 variants have raised concerns about resistance to neutralizing antibodies elicited by previous infection or vaccination. We examined whether sera from recovered and naïve donors collected prior to, and following immunizations with existing mRNA vaccines, could neutralize the Wuhan-Hu-1 and B.1.351 variants. Pre-vaccination sera from recovered donors neutralized Wuhan-Hu-1 and sporadically neutralized B.1.351, but a single immunization boosted neutralizing titers against all variants and SARS-CoV-1 by up to 1000-fold. Neutralization was due to antibodies targeting the receptor binding domain and was not boosted by a second immunization. Immunization of naïve donors also elicited cross-neutralizing responses, but at lower titers. Our study highlights the importance of vaccinating both uninfected and previously infected persons to elicit cross-variant neutralizing antibodies.

The SARS-CoV-2 betacoronavirus first emerged in the Hubei Province of China in late 2019 and has since infected over 115 million people and caused over 2.5 million deaths in 192 countries (1–3).

Infection is mediated by the viral spike protein (S) which is comprised of an S1 domain that contains a N-terminal domain (NTD), a C-terminal domain (CTD), and a receptor binding domain (RBD) which mediates attachment to the entry receptor angiotensin converting enzyme 2 (ACE2), and an S2 domain that contains the fusion machinery (4–8).

Pre-existing immunity to SARS-CoV-2 is associated with protection against re-infection in humans (9–11) and in non-human primates (12, 13). Although the correlates of protection in humans against repeat infection or following vaccination have not been firmly established, neutralizing antibodies (nAbs) are thought to be an important component of a protective immune response against SARS-CoV-2 (14, 15). In support of this, passive transfer of nAbs limits respiratory tract infection and protects against infection in animal models (16–20) and may contribute to protection against infection in humans (9). SARS-CoV-2 infection rapidly elicits nAbs (16, 21–24) that decline, but remain detectable over several months (25–29).

The majority of serum neutralizing antibody responses elicited during natural infection are directed at the receptor binding domain (RBD) (21, 23, 30, 31). Numerous neutralizing anti-RBD monoclonal antibodies (mAbs) have been

characterized, the most potent of which block the RBD-ACE2 interaction (16, 17, 22–24, 32–37). Neutralizing against other region of the viral spike have also been identified (24, 33, 38–42).

Two mRNA-based vaccines (Pfizer/BioNTech BNT162b2, and Moderna mRNA-1273) have received emergency use authorization in several countries. Both encode a stabilized ectodomain version of the S protein derived from the Wuhan-Hu-1 variant isolated in December 2019 (43), show greater than 94% efficacy at preventing COVID-19 illness (44–47), and elicit nAbs (48, 49).

Due to the high global burden of SARS-CoV-2 transmission, viral evolution is occurring. Recently, viral variants of concern have emerged in the United Kingdom (B.1.1.7), South Africa (B.1.351), and Brazil (P.1) that harbor specific mutations in their S proteins that may be associated with increased transmissibility (50–55).

Of particular concern are mutations found in the B.1.351 lineage, which is defined by the D80A and D215G in the N-terminal domain (NTD), and the K417N, E484K, N501Y mutations in the RBD and the D614G mutation in S2 (52, 56). An A701V mutation in S2 is also observed at high frequencies, while deletions in 242–244 and R246I and L18F mutations in the NTD are present at lower frequencies (52).

The B.1.1.7, B.1.351, and P.1 lineages all harbor a N501Y mutation in the RBD which increases the affinity for the ACE2 receptor (57, 58), and a D614G mutation which

increases virion spike density, infectivity and transmissibility (59, 60). The B.1.351 and P.1 lineages also share the E484K mutations in the RBD and both variants are mutated at 417 (K417T in P.1).

Mutations found in emergent S variants decrease sensitivity to neutralization by mAbs, convalescent plasma, and sera from vaccinated individuals (27, 37, 58, 61–70). As a result, there is concern that these and other emerging variants can evade neutralizing antibody responses generated during infection with variants circulating earlier in the pandemic and also from neutralizing antibody responses elicited by vaccines based on the spike protein of the Wuhan-Hu-1 variant. Indeed, there is concern that these mutations are responsible for reduced efficacy observed in ongoing trials of SARS-CoV-2 vaccines in South Africa (71, 72).

Here, we evaluated the neutralization susceptibility of spike variants harboring lineage-defining and prevalent B.1.351 mutations to sera from 15 donors with previously confirmed SARS-CoV-2 infection (herein referred to as previously infected donors or PIDs), that were collected prior to, and following one or two immunizations with either mRNA vaccine, or from 13 uninfected donors who received two doses of the above vaccines (herein called naïve donors or NDs; tables S1 and S2), as well as anti-spike mAbs isolated from infected but not vaccinated patients.

Antibody neutralization experiments were performed with pseudoviruses expressing either the full-length Wuhan-Hu-1 S, or either of two versions of the B.1.351 lineage S, one herein referred to as B.1.351 containing the lineage-defining S mutations D80A, D215G, K417N, E484K, N501Y and D614G mutations and the A701V mutation that is highly prevalent in this lineage, and a second variant that also includes a Δ 242–243 deletion (B.1.351 Δ 242–243). The viral stocks were appropriately diluted to achieve comparable entry levels during the neutralization experiments (fig. S1).

We first evaluated the neutralizing potency of several mAbs isolated from non-vaccinated patients infected early in the pandemic, which target different epitopes: three against the RBD (CV30, CV3-1 and CV2-75) and one against the NTD (CV1) (fig. S2). CV30 is a member of the VH3-53 class of antibodies that bind to the receptor binding motif (RBM) (22, 32, 73–78). It makes direct contact with the K417 and N501 residues in the RBM that are mutated in the B.1.351 and P.1 lineages, but unlike other known VH3-53 mAbs it does not contact E484 (78). The neutralization potency of this mAb was ~10-fold weaker toward both B.1.351 variants (Fig. 1A). Similarly, the non-VH3-53 mAb CV3-1 was 3–4-fold less potent against the B.1.351 variants (Fig. 1B), while CV2-75 was modestly less effective (Fig. 1C). In contrast, the anti-NTD CV1 mAb was unable to neutralize either B.1.351 variant (Fig. 1D). As expected, the control anti-EBV mAb AMMO1 was non-neutralizing (79) (Fig. 1E). Collectively, these data indicate that

the B.1.351 variants tested here are more resistant to neutralization by mAbs isolated from subjects infected by viral variants from early in the pandemic. We therefore examined whether the B.1.351 variants are resistant to neutralizing antibody responses elicited by the Pfizer/BioNTech or Moderna mRNA vaccines, in PIDs and NDs.

The RBD-specific IgG, IgM and IgA binding responses to the RBD from the Wuhan-Hu1 variant were measured before (average, 202 days post symptom onset; table S1), and 5–29 days (table S1) after the first and second immunizations in the PIDs, and 6–28 days after the second immunization in the NDs. Three PIDs experienced asymptomatic SARS-CoV-2 infection (donors D, L, and M; table S1) two of whom, L and M, did not have detectable anti-RBD IgG antibodies prior to immunization, while the third, D, had low but detectable serum anti-RBD IgG antibody titers (Fig. 2A). In the 13 PIDs with RBD-specific IgG antibodies prior to vaccination, a single dose of either vaccine boosted these titers by ~500-fold (Fig. 2A). Across all PIDs there was a 200-fold increase in median RBD-specific IgA titers post-vaccination (Fig. 2B). Overall, in PIDs, a single vaccine dose elicited 4.5-fold higher IgG, and 7.7-fold higher IgA titers than two vaccinations in NDs. RBD-specific IgM titers were generally lower and were not significantly boosted in response to vaccination in both PIDs and NDs (Fig. 2C). In PIDs, a concomitant increase in RBD- (Fig. 2D) and S-specific IgG⁺ (Fig. 2E) memory B cell frequencies took place after vaccination. The two PIDs that lacked RBD-specific IgG titers prior to immunization (donors L and M) also lacked RBD-specific IgG⁺ memory B cells (Fig. 2D) and had lower frequencies of S-specific IgG⁺ memory B cells after vaccination. Consistent with the serology data, an increase in the frequency of IgA⁺ (Fig. 2F) but not IgM⁺ spike-specific memory B cells was observed (fig. S3). Vaccination also induced S-specific CD4⁺ T-cell responses (Fig. 2G).

Sera from 12 of 15 PIDs sampled before vaccination neutralized the Wuhan-Hu-1 SARS-CoV-2 variant (Fig. 3A and fig. S4). The non-neutralizing sera were from the three asymptomatic PIDs who had low or undetectable anti-RBD IgG titers (Fig. 3A, dashed lines, and fig. S4), while pre-vaccine sera from the NDs were also non-neutralizing (fig. S5). Consistent with the observed increase in binding antibodies following a single immunization in PIDs with pre-existing RBD-specific IgG titers, the median half-maximal neutralizing titers (ID₅₀) were boosted approximately 1000-fold after the first dose, while the second dose had no effect (Fig. 3A). In the two PIDs lacking RBD-specific IgG titers prior to vaccination, the first vaccine dose elicited lower neutralizing titers (ID₅₀ = ~100 in donor L and ~1,100 in donor M; Fig. 3A). In the NDs, two doses of the vaccine elicited ID₅₀ titers that were ~10- and 5-fold lower than those elicited by one or two doses in the PIDs, respectively (Fig. 3A and fig. S6). Collectively, these data indicate that in PIDs who generate adequate immunological

memory to the RBD, a single vaccine dose elicits an anamnestic response resulting in RBD-binding and neutralizing antibody responses that are superior to a two-dose regimen in uninfected donors. A similar boost in binding and/or vaccine-matched neutralizing titers has been observed in PIDs who received a single mRNA vaccine dose in two recent studies (80, 81).

We next evaluated the ability of sera collected before and after immunization in NDs and PIDs to neutralize the more resistant B.1.351 and B.1.351- Δ 242-243 pseudoviruses. These variants are 0.5% and 0.7% divergent from the Wuhan-Hu-1 variant. We also included SARS-CoV-1 pseudoviruses in this analysis, as a representative variant that is even more dissimilar to the vaccine. SARS-CoV-1 and SARS-CoV-2 are 24%, 26% and 50% divergent in the overall S protein, RBD and receptor binding motif, respectively (82). As a consequence, several mAbs that potentially neutralize SARS-CoV-2 fail to bind SARS-CoV-1 (16, 22–24).

Prior to vaccination, 5 of 15 sera from PIDs neutralized B.1.351 and only three had ID₅₀ titers above 100 (Fig. 3, B and E, and fig. S4), 7 of 15 neutralized B.1.351- Δ 242-243, and only one had titers above 100 (Fig. 3, C and E, and fig. S4). Only two pre-vaccine PID sera achieved 80% neutralization of B.1.351, and only one achieved 80% neutralization of B.1.351- Δ 242-243 (fig. S7A). The median ID₅₀ of the pre-vaccine sera against Wuhan Hu-1 was significantly higher than against B.1.351 or B.1.351- Δ 242-243 (Fig. 3E). Consistent with the high level of sequence disparity, sera from only one PID showed very weak neutralizing activity toward SARS-CoV-1 prior to vaccination (Fig. 3, D and E, and fig. S7).

A single immunization boosted the nAb titers against all three SARS-CoV-2 variants and SARS-CoV-1 in 13 of 15 PIDs (Fig. 3, A to D); however, the median ID₅₀ titers were ~3-fold lower against B.1.351, ~10-fold lower against B.1.351- Δ 242-243, and 100-fold lower against SARS-CoV-1 than Wuhan-Hu-1 (Fig. 3E). A single immunization did not elicit nAbs against the B.1.351 variants or SARS-CoV-1 in the two asymptomatic donors who lacked RBD-specific IgG memory (donor L and M; Fig. 3, A to D, and Fig. 3E, open circles). The median ID₈₀ values were also lower for the B.1.351 and B.1.351- Δ 242-243 as compared to Wuhan-Hu-1 (fig. S7A).

The neutralizing titers elicited by a single immunization in PIDs were significantly higher than those elicited by two immunizations in NDs against all pseudoviruses tested; 10-fold higher against Wuhan-Hu-1 (Fig. 3A), 20-fold higher against B.1.351 (Fig. 3B), 30-fold higher against B.1.351- Δ 242-243 (Fig. 3C), and 7-fold higher against SARS-CoV-1 (Fig. 3D). Only 8 of 13 vaccinated NDs were able to achieve 80% neutralization of B.1.351- Δ 242-243, and none could achieve 80% neutralization of SARS-CoV-1 (fig. S7B).

The B.1.351 and B.1.351- Δ 242-243 variants contain three RBD mutations that affect the neutralization potency of anti-

RBD mAbs (Fig. 1). Moreover, pre-existing anti-RBD IgG memory appears to be important for a robust recall response to vaccination. To determine the relative contribution of anti-RBD antibodies to serum neutralization, we depleted RBD-specific antibodies from the sera of ten PIDs following one vaccination and from nine NDs after two vaccinations. This approach efficiently removed RBD-specific (Fig. 4, A and C) but not anti-S2P specific antibodies from sera, as measured by ELISA (Fig. 4, B and D). This depletion abrogated serum neutralization of Wuhan-Hu-1 virus (Fig. 4, C and F), suggesting that the majority of neutralizing antibodies elicited or boosted by vaccination target this subdomain.

The above results indicate that in NDs, two doses of either the Pfizer/BioNTech or Moderna vaccines elicited nAb titers against the vaccine matched Wuhan-Hu-1, lower titers against B.1.351 and even lower titers against B.1.351- Δ 242-243. Reduced sensitivity to vaccine-elicited nAbs has been reported for other B.1.351 variants (66, 83, 84).

Similarly, sera from PIDs who experienced symptomatic SARS-CoV-2 infection and who had detectable anti-RBD IgG titers prior to vaccination displayed generally weak nAb titers against Wuhan-Hu-1 at one to nine months post-infection and lower, or non-existent titers against the B.1.351 variants, in agreement with another report (69). However, provided RBD-specific IgG⁺ memory B cell and antibody responses were generated during infection, a single immunization with either mRNA vaccine elicited a robust recall response that boosted the autologous neutralizing titers by approximately 1000-fold and importantly, these antibody responses cross-neutralized the B.1.351 variants, but at lower titers. In the majority of previously infected vaccinees, the anti-B.1.351- Δ 242-243 neutralizing titers were comparable to those against the vaccine-matched Wuhan-Hu-1 in uninfected vaccinees. This is notable as these titers were associated with 95% protection from COVID-19 in phase 3 trials (44, 46, 48, 49). Moreover, vaccine-elicited antibody responses also neutralized SARS-CoV-1, but with much lower potencies. Collectively, our data suggest that the two mRNA vaccines that are based on the Wuhan-Hu-1 variant can elicit and/or boost neutralizing antibody responses, but that their potency is reduced against divergent variants.

Here, we show that the cross-neutralizing antibody responses generated after immunization in previously infected subjects are due to anti-RBD antibodies. Combined with the observation that the vaccines elicited neutralizing antibody responses that are less potent against the B.1.351 variant with the 242-243 deletion in the NTD suggests that NTD mutations can modulate the sensitivity of emerging variants to anti-RBD neutralizing antibodies. In contrast, the NTD region itself, which appears to tolerate antigenic variation in SARS-CoV-2 and other coronaviruses (50, 52, 55, 85), does not appear to be the target of cross-neutralizing antibodies

elicited by infection or vaccination. We note that there are other less-frequent mutations associated with this lineage, such as L18F, Δ 244, L244H, and R246I that were not examined here which may further increase resistance to vaccine-elicited antibodies. In this study, a pseudovirus assay was used to measure neutralizing antibodies. Several studies have now shown that authentic virus and pseudovirus neutralization correlate quite well (16, 86, 87). Although the absolute sensitivity of the authentic and pseudovirus assays may differ, we anticipate that the relative differences we report here will not vary between the two.

Although the correlates of protection for SARS-CoV-2 vaccines have not been established, studies in non-human primates indicate that even low titers of neutralizing antibodies are sufficient to prevent experimental SARS-CoV-2 infection, particularly if CD8⁺ T-cell responses are mounted (18). Our study suggests that most previously infected subjects will benefit from a single immunization with either the Pfizer/BioNTech or Moderna vaccines as it will lead to significant increases in serum neutralizing antibody responses against vaccine-matched and emerging variants. The observation that a second dose administered three to four weeks following the first in previously infected donors who have clear evidence of RBD-directed immunological memory prior to vaccination did not further boost neutralizing titers, suggests that the second dose of an mRNA vaccine could be delayed in some persons who have previously been infected with SARS-CoV-2. Longitudinal monitoring of the neutralizing antibody titers before and following the first dose should be used to determine the necessity, or optimal timing of the second dose in the context of previous infection.

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ACKNOWLEDGMENTS

We thank the study participants for their dedication to this project, Trevor Bedford for assistance with the selection of spike mutations to include, Laura Richert Spuhler for assistance with figure preparation, Todd Haight and the Seattle Vaccine Unit specimen processing lab and staff for their service. This work was conducted under Fred Hutchinson Cancer Research Center Institutional Review Board IR10440 and IR5567. **Funding:** This work was supported by generous

donations to Fred Hutch COVID-19 Research Fund, and to MJM from the Paul G. Allen Family Foundation, the Joel D. Meyers Endowed Chair, and NIAID UM1 AI068618-14S1, 2UM1 AI069481-15, and UM1A057266-S1, and Sanofi Pasteur to Z.M. **Author contributions:** Conceptualization, M.J.M., A.T.M., and L.S.; Investigation, Y.-H. W., E.S., M.L., V.R., K.W.C., Z.M., M.N., L.J.H., A.J.M., M.J., J.F., G.M., H.G., and A.T.M.; Writing - Original Draft, A.T.M., and L.S.; Writing - Review & Editing, A.T.M., L.S., M.J.M., and E.S.; Funding Acquisition, L.S. and M.J.M.; Resources, M.J.M., J.C., A.F.; Supervision, A.T.M. **Competing interests:** L.S. and A.T.M. have filed a provisional patent application on the CV1, CV30 and CV2-75 SARS-CoV-2 specific monoclonal antibodies. L.S., A.T.M., and A.F. have filed a provisional patent application on the CV3-1 SARS-CoV-2 specific monoclonal antibody. All other authors declare no competing interests. **Data and materials availability:** All data are available in the manuscript or the supplementary materials. The accession numbers for the sequences of the CV3-1 and CV2-75 heavy and light chain variable regions have been deposited in GenBank: MW681558, MW681586, MW681758 and MW68175. The expression plasmids for the mAbs in this study are derived from the pTT3 vector which requires a license from the National Research Council Canada (88). This work is licensed under a Creative Commons Attribution 4.0 International (CC BY 4.0) license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>. This license does not apply to figures/photos/artwork or other content included in the article that is credited to a third party; obtain authorization from the rights holder before using such material.

SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S8

Tables S1 to S4

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MDAR Reproducibility Checklist

4 February 2021; accepted 19 March 2021

Published online 25 March 2021

10.1126/science.abg9175

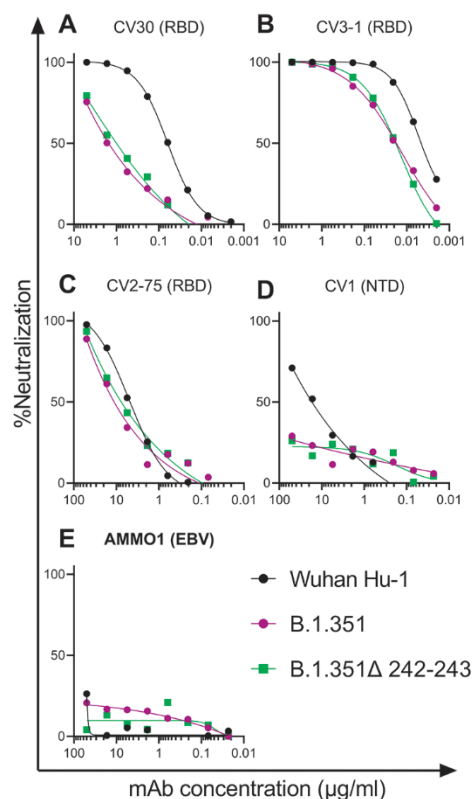


Fig. 1. B.1.351 variants show decreased susceptibility to neutralizing monoclonal antibodies. (A to E) The ability of the indicated monoclonal antibodies (mAbs) to neutralize Wuhan-Hu-1, B.1.351 and B.1.351Δ242-243 pseudovirus infectivity in 293T-hACE2 cells was measured as indicated. The epitope specificity of each mAb is shown in parentheses (RBD: receptor binding domain; NTD: N-terminal domain; EBV: Epstein-Barr virus). Data points represent the mean of two technical replicates. Data are representative of two independent experiments.

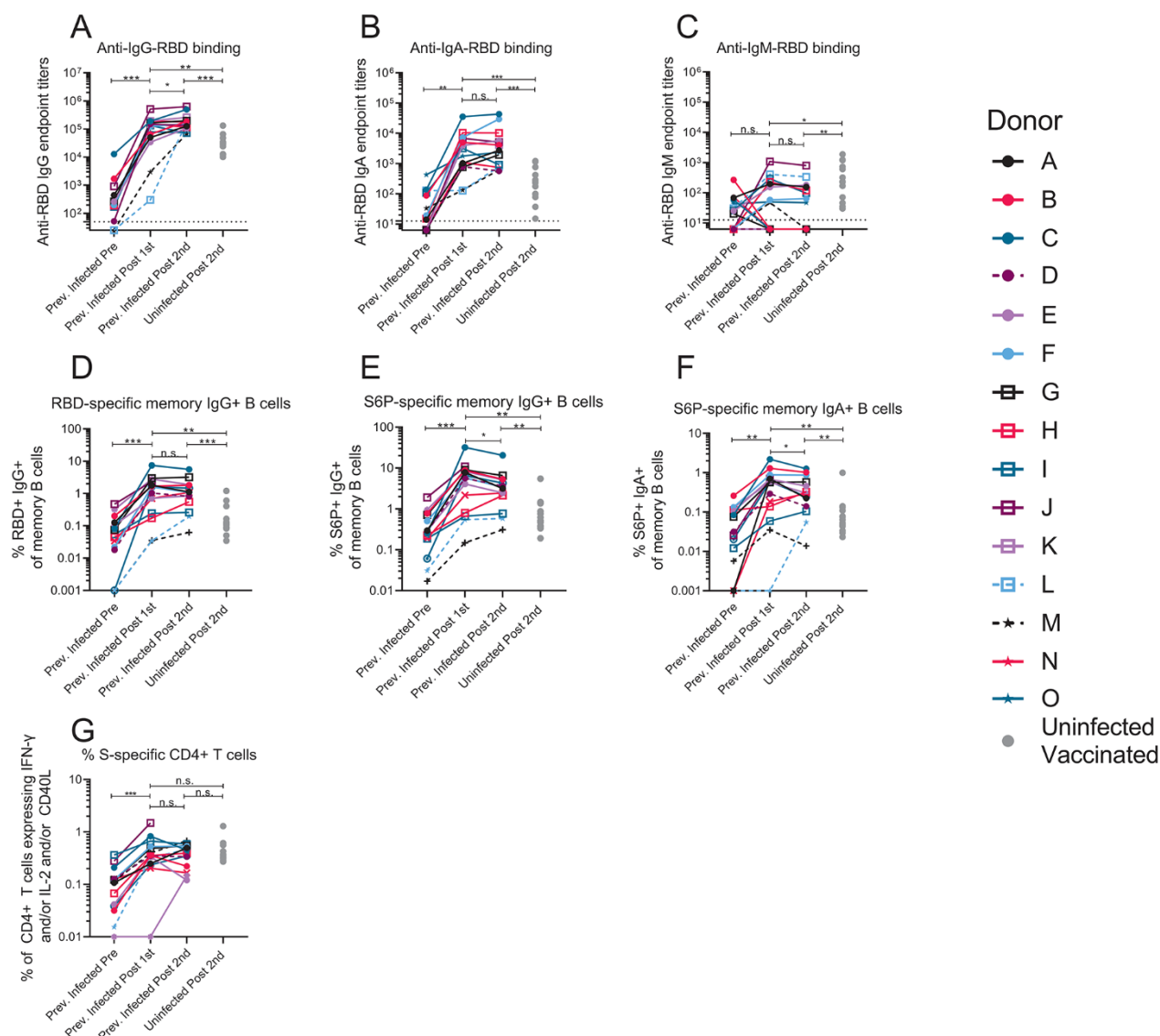


Fig. 2. A single dose of a spike-derived mRNA vaccine elicits a strong recall response. IgG (A), IgA (B) and IgM (C) end-point antibody titers specific to the receptor binding domain of the Wuhan-Hu-1 variant were measured in serum collected from donors previously infected with SARS-CoV-2 before and after one or two immunizations with the Pfizer/BioNTech or Moderna mRNA vaccines by ELISA, as indicated. Endpoint titers measured in sera from uninfected donors following two vaccine doses are shown for comparison (gray dots). (D) Frequency of Wuhan-Hu-1 RBD-specific IgG⁺ memory B cells (live, IgD⁻, CD19⁺, CD20⁺, CD3⁻, CD14⁻, CD56⁻, singlet, lymphocytes) in PBMC from previously infected donors was measured before and after one or two immunizations. The frequency of S6P-specific IgG⁺ (E) and IgA⁺ (F) memory B cells in PBMC previously infected donors were measured before and after one or two immunizations. The frequency of memory B cells from uninfected donors following two vaccine doses are shown for comparison in D-F (gray dots). (G) The frequency of S-specific CD4⁺ T cells expressing IFN- γ and/or IL-2 and/or CD40L in PBMC from previously infected donors was measured before and after one or two immunizations. The frequency of S-specific CD4⁺ T cells in PBMC from uninfected donors following two vaccine doses are shown for comparison (gray dots). Experiments were performed once. Significant differences in infected donors before or after vaccination (A-D) or between pseudoviruses (E) were determined using a Wilcoxon signed rank test (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$). Significant differences between previously infected and uninfected donors (A-D) were determined using a Wilcoxon rank sum test (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$).

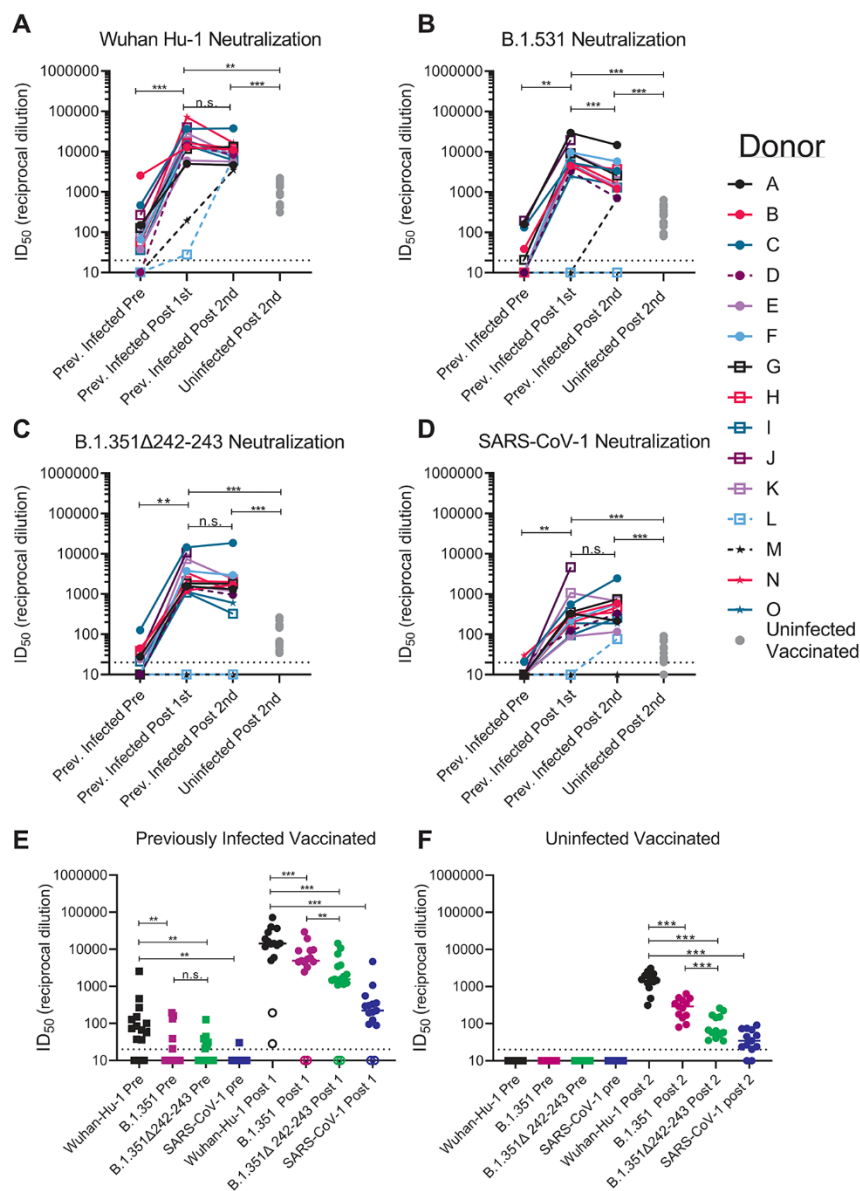


Fig. 3. Pre-existing SARS-CoV-2 neutralizing antibody responses are boosted by a single dose of a spike-derived mRNA vaccine. The serum dilution resulting in 50% neutralization (ID_{50}) of (A) Wuhan-Hu-1, (B) B.1.351, (C) B.1.351Δ242-243, and (D) SARS-CoV-1 pseudoviruses was measured in recovered COVID-19 donors prior to and following a one or two immunizations with the Pfizer/BioNTech or Moderna vaccines, and in uninfected donors following two vaccine doses as indicated. Data points between previously infected donors who were symptomatic and asymptomatic are connected by solid and dashed lines, respectively in A-D. (E) Serum dilution resulting in 50% neutralization (ID_{50}) from recovered donors prior to (squares) and following a single immunization (circles) with the Pfizer/BioNTech or Moderna vaccines against Wuhan-Hu-1, B.1.351, B.1.351Δ242-243 and SARS-CoV-1 pseudoviruses as indicated. Previously infected donors who were asymptomatic, negative for anti-IgG RBD antibodies, and RBD-specific IgG+ memory B cells prior to vaccination are shown as open circles. (F) Neutralizing potency (ID_{50}) of serum from uninfected donors following two immunizations with the Pfizer/BioNTech or Moderna vaccines against the indicated pseudoviruses. Each data point represents a different donor and the horizontal bars represent the medians in E and F. The dashed lines demarcate the lowest serum dilutions tested. Experiments were performed once. Significant differences in infected donors before or after vaccination, or from the same timepoint against different variants (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$) were determined using a Wilcoxon signed rank test. Significant differences between previously infected and uninfected donors (* $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$) were determined using a Wilcoxon rank sum test.

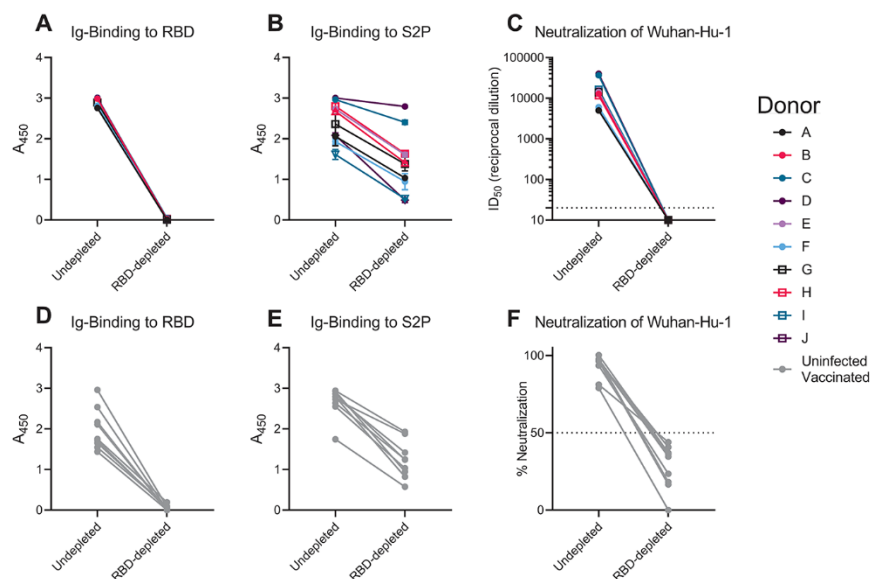


Fig. 4. Vaccine-elicited neutralizing antibodies target the RBD. RBD-binding antibodies were adsorbed from sera from previously infected donors after receiving a single vaccine dose, or from uninfected donors after receiving two vaccine doses using Wuhan-Hu-1 RBD immobilized to magnetic beads. Antibody binding in undepleted or RBD-depleted serum from previously infected donors was measured to RBD at a 1:500 dilution (A), and S2P at a 1:4500 dilution (B) by ELISA as indicated. (C) The serum dilution resulting in 50% neutralization (ID_{50}) of the Wuhan-Hu-1 pseudovirus was measured in undepleted or RBD-depleted of serum from the previously SARS-CoV-2 infected donors in A and B. Antibody binding in undepleted and RBD-depleted and sera from uninfected vaccinated donors was measured to RBD at a 1:500 dilution (D), and S2P at a 1:500 dilution (E) by ELISA. (F) The percent neutralization of a 1:120 dilution of undepleted or RBD-depleted of serum from the donors in D and E was measured against the Wuhan-Hu-1 rixipseudovirus. Experiments were performed once.

mRNA vaccination boosts cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection

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published online March 25, 2021

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