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BRIEF REPORT

TRANSFUSION

Vaccination of COVID-19 convalescent plasma donors increases binding and neutralizing antibodies against SARS-CoV-2 variants

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Abstract

Background: COVID-19 convalescent plasma (CCP) was widely used as passive immunotherapy during the first waves of SARS-CoV-2 infection in the US. However, based on observational studies and randomized controlled trials, the beneficial effects of CCP were limited, and its use was virtually discontinued early in 2021, in concurrence with increased vaccination rates and availability of monoclonal antibody (mAb) therapeutics. Yet, as new variants of the SARS-CoV-2 spread, interest in CCP derived from vaccine-boosted CCP donors is resurging. The effect of vaccination of previously infected CCP donors on antibodies against rapidly spreading variants is still under investigation.

Study design/methods: In this study, paired-samples from 11 CCP donors collected before and after vaccination was tested to measure binding antibody levels and neutralization activity against the ancestral Wuhan-Hu-1 and SARS-CoV-2 variants (Wuhan-Hu-1 with D614G, alpha, beta, gamma, delta, epsilon) on the Ortho Vitros Spike Total Ig and IgG assays, the MSD V-PLEX SARS-CoV-2 arrays for IgG binding and ACE2 inhibition, and variant-specific Spike Reporter Viral Particle Neutralization (RVPN) assays.

Results/findings: Binding and neutralizing antibodies were significantly boosted by vaccination, with several logs higher neutralization for all the variants tested post-vaccination compared to the pre-vaccination samples, with no difference found among the individual variants.

Discussion: Vaccination of previously infected individuals boosts antibodies including neutralizing activity against all SARS-CoV-2 variants.

1 | INTRODUCTION

During the first waves of COVID-19 effective therapies were lacking, so the medical community resorted to the use of COVID-19 convalescent plasma (CCP) from recovered patients as passive immunotherapy in hospitalized patients.[1,2] The widespread collection and transfusion of CCP in the United States (US) was facilitated by an Expanded Access Program approved by FDA and supported by BARDA in mid-2020, followed by the FDA granting Emergency Use Authorization (EUA) status to

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high titer CCP in the fall of 2020. However, based on further findings from observational studies, the beneficial effects of CCP were limited to units with high titers of binding (bAbs) and neutralizing antibodies (nAbs) administered early after infection, and efficacy was not confirmed by recent large randomized controlled trials,[3] including the Clinical Trial of COVID-19 Convalescent Plasma in Outpatients (C3PO) study,[4] and the CONCOR-1 study in hospitalized patients[5] (both halted early for futility).

Consequently, CCP use was virtually discontinued in the US during the spring of 2021, coinciding with increased vaccination rates and the availability of effective but costly monoclonal antibody (mAb) therapeutics. However, there is a renewed interest in CCP as new variants of SARS-CoV-2 emerged and spread, especially the delta and omicron variants that are the main variants responsible for hospitalizations and deaths in non-vaccinated patients as well as breakthrough infections in vaccinated people[6] and are resistant to some mAbs.[7] In fact, despite the WHO issuing a recent report discouraging the use of CCP derived from previously infected (but not vaccine boosted) donors following resolution of first COVID-19 infections in non-immunosuppressed hospitalized COVID-19 patients,[8] the FDA recently modified their EUA supporting the use of high titer CCP derived from previously infected and vaccinated or vaccine breakthrough cases, specifically recommending use in immunocompromised patients with poor humoral immunity in both outpatients and inpatient setting,[9] although additional controlled studies in immunosuppressed or other populations lacking antibody or early in infection are needed to establish efficacy. Based on multiple studies reporting the positive impact of vaccination (including single doses of mRNA vaccines) on boosting bAbs and nAbs in previously infected patients,[10] we hypothesized that such boosting could provide a protective effect against SARS-CoV-2 variants. Thus, the aim of the current study is to assess whether vaccination of previously infected CCP donors can provide units with enhanced bAbs and nAbs against the rapidly spreading variants.

2 | MATERIALS AND METHODS

2.1 | Sample collection and coding

Eleven paired pre- and post-vaccination samples were provided by Dr. Thomas Gniadek, at NorthShore University HealthSystem, Evanston, IL. The samples had been collected in serum separator tubes between January and March 2021 from previously infected CCP donors. The average time from the positive PCR result to the resolution of symptoms was 16.7 days, while the first dose of the vaccine was administered on average 142.4 days after symptoms resolution. The collection time after the first dose of the vaccine ranged from 8 to 58 days. Five post-vaccination samples were collected after the first dose and six after the second dose. Five donors had received mRNA-1273 (Moderna) while six had received BNT162b2 (Pfizer) vaccines. The interval between doses was 21 days for Pfizer and 28 for Moderna. All testing was performed on coded, anonymized samples.

2.2 | Antibody characterization

Samples were tested at Vitalant Research Institute to measure the levels of total Ig and IgG antibodies against the S1 domain of the SARS-CoV-2 spike antigen, in vitro binding and ACE2 inhibition against S1, N (nucleocapsid) and RBD (receptor binding domain), and neutralization titers. Additional tests were conducted to assess binding and neutralization activity against different SARS-CoV-2 S1 variants (B.1.1.7 - alpha, B.1.351 -beta, P.1-gamma, D614G, B.1.617-delta, B.1.427-epsilon).

Samples were first screened on the Ortho Vitros instrument (Ortho-Clinical Diagnostics, Inc., Rochester, NY) using SARS-CoV2 Total Ig (COV2T) and IgG (COV2G) assays against the S1 antigen, as previously described.[11] Since all the post-vaccination samples reached the upper limit of signal-to-cutoff (S/CO) values reported for these assays, they were further tested following dilutions (10- and 100-fold), with the derivation of S/CO ratios based on reactivity levels multiplied by the dilution factors.

To assess binding and ACE2 blocking activity against ancestral SARS-CoV-2 and variants, samples were also tested on the MSD platform (MESO QuickPlex SQ 120, MesoScale Discovery, Rockville, MD) V-PLEX SARS-CoV-2 Kit using IgG binding and ACE2 inhibition protocols following the manufacturer instruction.

This panel includes SARS-CoV-2 N, S1 RBD, and SARS-CoV-2 Spikes from the ancestral Wuhan-Hu-1, Wuhan-Hu-1 with D614G, and the alpha, beta, and gamma variants. Briefly, plates were first incubated for 30 min with a blocking solution, then diluted samples were added, along with controls and calibrators, and incubated for 2 h. After washing, the Detection Antibody Solution was added and incubated for 1 h, after which the plates were washed again, followed by the addition of Read Buffer, and analyzed on the MESO QuickPlex SQ 120. For direct binding serology, samples were diluted 1:25,000, whereas for ACE2 inhibition the dilution was 1:500. Results were calculated as Arbitrary Units (AU)/ml based on a reference standard used to establish a calibration curve for the serology assay and as %

inhibition compared to the negative control for the ACE2 inhibition assay.

In-vitro SARS-CoV-2 reporter viral particle neutralization (RVPN) was performed using lentivirus-based vectors (Integral Molecular, Philadelphia, PA) as previously described.[11] Briefly, Renilla luciferase RVPs bearing Spike from the ancestral strain Wuhan-Hu-1, alpha, alpha+E484K, beta, gamma, delta, and epsilon were first titrated on 293 T/ACE2/TMPRSS2 cells. Virus concentration was then normalized, and the virus was incubated with equal volumes of four-fold serial dilutions of heat-inactivated serum. After 1-h incubation at 37°C, 2×10^4 293T/ACE2/TMPRSS2 cells were added to each well and incubated for 3 days at 37°C. Plates were then analyzed for luciferase activity as per manufacturer's instructions (Renilla-GLO, Promega, Madison, WI). Results were calculated as percent neutralization relative to no serum controls, and dose-response curves produced in Prism 9 (GraphPad) were generated to calculate 50% neutralization titers (NT_{50}).

2.3 | Statistical analysis

Ortho Vitros IgG and Ig Total dilutions data were compared using matched, non-parametric Friedman test ANOVA. MSD and RVPN pre- and post-vaccination data for each of the variants were analyzed using the Kruskal-Wallis test ANOVA, followed by Dunn's multiple comparisons test. All tests were performed on GraphPad Prism 9.0.0.

3 | RESULTS

3.1 | Ortho vitros IgG and Ig total binding

Antibody levels measured on the Ortho Vitros IgG assay were significantly lower before vaccination (mean S/CO 9.09, 95% CI 5.63–12.6) than after vaccination (mean S/CO 25.2, 95% CI 24.4–25.9) (Figure 1). Similarly, the Ortho Vitros Ig Total levels were lower before the vaccination (mean S/CO 396, 95% CI 175–616) compared to post-vaccination (mean S/CO 1197, 95% CI 1093–1301). Both assays reached the upper limit of detection after vaccination when tested according to the EUA instructions for use, prompting additional dilutional testing. After 1:10 and 1:100 dilution, the S/CO for the Ig Total post-vaccination showed an average S/CO of 12,670 (95% CI 10,917-14,423) at 1:10 and S/CO of 67,524 (95% CI 39,837-95,211) at 1:100 after multiplying the S/CO values by the dilution factor. For the IgG assay, the post-vaccination average S/CO was 193 (95% CI 169–217) at 1:10 and S/CO 545 (95% CI 275–816) at 1:100, after adjusting S/CO results for the dilution factors.

3.2 | MSD IgG binding and ACE2 inhibition

The MSD serology assay showed that the post-vaccination samples had an increased average AU/ml for the anti-spike and anti-RBD binding antibodies, but not

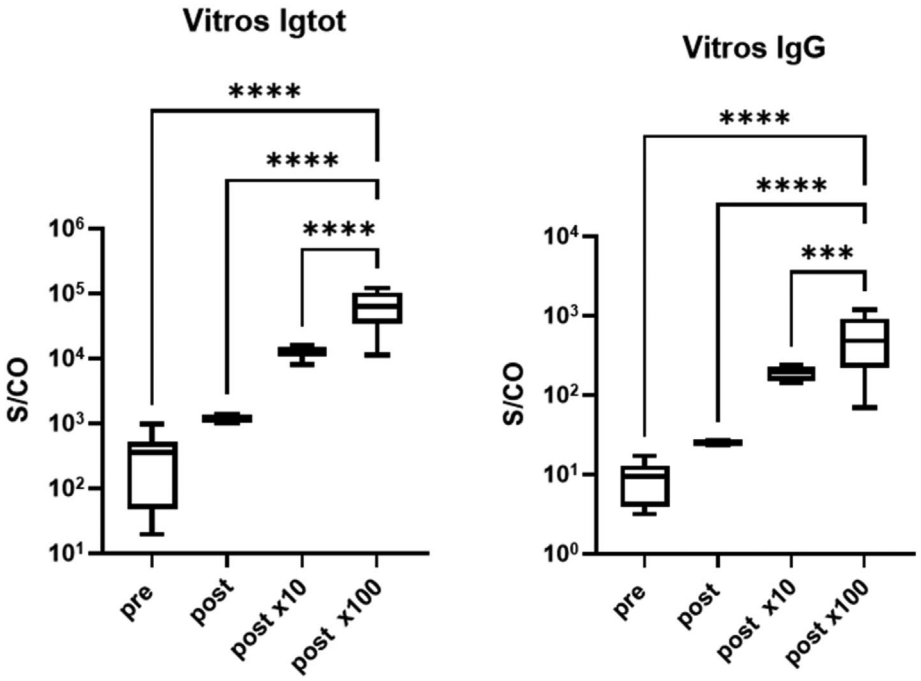

FIGURE 1 Binding antibodies levels measured on the Ortho Vitros IgG and total Ig. The total Ig S/CO (signal/cut-off) increases after vaccination, reaching the limit of detection of the assay (~1000–1500 S/CO). After 10-fold and 100-fold dilutions, the values increase 10^2–10^3. (*** = 0.0005, **** = <0.0001) n = 11

for the anti-nucleocapsid, which, indeed, decreased slightly (ratio post-vaccination/pre-vaccination = 0.887) (Figure 2). RBD binding antibodies increased the most, with a ratio of post-vaccination/pre-vaccination values of 196.3. For the SARS-CoV-2 variants, the post-vaccination levels of binding antibodies on the MSD platform increased significantly ($p < .001$) across all the variants tested compared to the pre-vaccination samples, with a ratio of post-vaccination/pre-vaccination mean AU/ml between 134.1 (gamma) and 78.9 (Wuhan-Hu-1 with D614G). The increased levels were not significantly different among variants.

The ACE-2 inhibition assay showed similar trajectories following vaccination (Figure 2). All samples showed low inhibitory activity against each of the variants following natural infection, with no difference among variants before vaccination (mean = 12.2%, ±2.29). After vaccination levels rose 4- to 7-fold, and similarly among all variants. The ACE2 inhibitory activity of the antibodies following vaccination of the CCP donors against all variants was on average 67.9% ± 10.7.

3.3 | Variant-specific RVPN

RVPN assays were used on pre- and post-vaccination samples to measure the ability of CCP donor antibodies to inhibit virus entry. All the pre-vaccination samples showed neutralizing activity due to natural infection, especially for the Wuhan-Hu-1 strain, with a mean NT_{50} of 547, which was significantly higher than the NT_{50} for alpha+ E484K, beta, and delta variants (Figure 3). After vaccination, the neutralizing activity increased significantly ($p < .001$) against the ancestral virus and all the

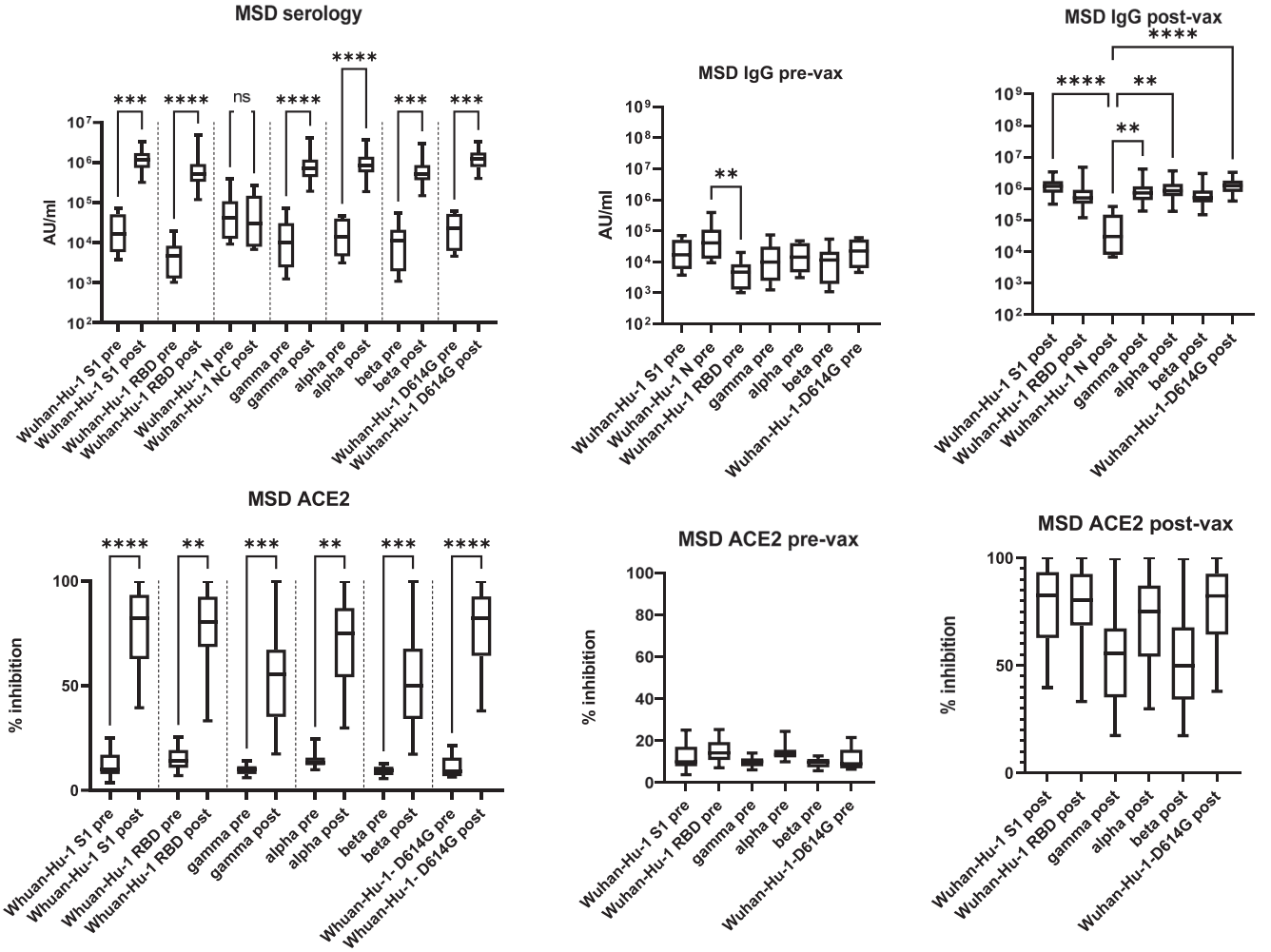

FIGURE 2 Binding IgG and ACE2 inhibition measured on the MSD V-Plex. The AU/ml IgG increases for all the post-vaccination samples, for both S1 and RBD of the Wuhan-Hu-1, but not for NC. Antibodies against all the variants increase similarly after vaccination. The percentage of ACE2 inhibition increases for all the post-vaccination samples, for Wuhan-Hu-1 S1 and RBS, and all the variants tested. There is no significance difference among all the variants, neither before, nor after vaccination. (** = 0.001, *** = 0.0005, **** = <0.0001). n = 11

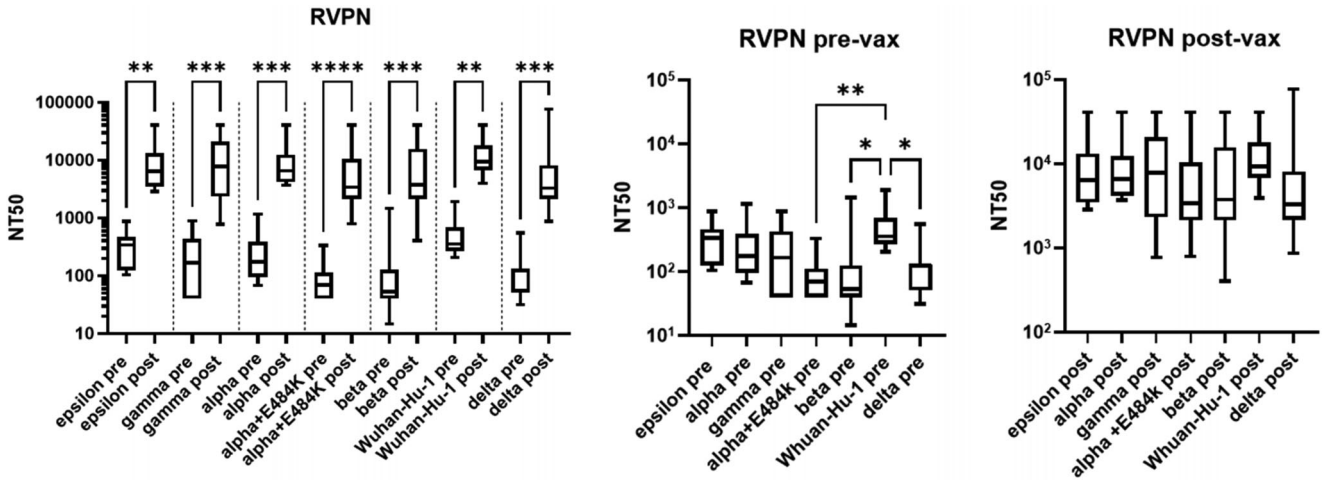

FIGURE 3 Pseudovirus neutralization measured by RVPN. The NT50 was higher against the Wuhan-Hu-1 pseudovirus before vaccination, compared to the other variants alpha+ E484K, beta and delta. After vaccination, the NT50 were significantly higher and comparable across variants. (* = 0.05, ** = 0.001, *** = 0.0005). N = 11

virus variants, with no significant differences in the levels of boosting between the variants. The average NT_{50} following vaccination was 10,831 ± 2000. Spearman correlation analysis between the RVPN and MSD ACE2 inhibition for the variants showed that the results of the two assays were strongly correlated, with r = 0.8587 (95% CI 0.78–0.91).

4 | DISCUSSION

Despite the emergence of variants with decreased susceptibility to vaccine-induced immune responses,[7,12] vaccination still offers significant levels of protection from hospitalization and severe disease.[13] However, following the emergence of delta and omicron, there has been a dramatic surge in hospitalizations and deaths among non-vaccinated persons and reduced level of protection from infection in vaccinated individuals,[13,14] causing so-called vaccine breakthrough infections. Several studies have reported that vaccination of previously infected individuals significantly boosts anti-SARS-CoV-2 antibody titers, and that one dose of the normal two-dose Pfizer or Moderna regimens is sufficient to boost immunity.[15–17] We, therefore, assessed the ability of vaccination to boost anti-SARS-CoV-2 antibody levels in previously infected CCP donors, and importantly determined whether the titers of neutralizing antibody against variants may indicate a potential value in CCP specifically collected from vaccinated, previously infected donors for neutralization of SARS-CoV-2 variants in future recipients of vaccine-boosted CCP.

Paired pre-vaccination and post-vaccination samples from 11 CCP donors were tested on five different assays to assess antibody levels and neutralizing activity against ancestral and variant SARS-CoV-2. As expected, both Ortho Vitros S1 IgG and total Ig S/CO levels approached or exceeded the upper limit of detection with samples from previously infected, vaccinated subjects, making it difficult to clearly assess the levels of antibodies.

Diluting the samples expanded the dynamic range of the assays and allowed us to calculate the levels of SARS-CoV-2 antibodies in the vaccine-boosted samples, which were beyond the EUA upper limits derived from testing neat samples. The data demonstrated that the 1:10 dilution was still too concentrated to get accurate readings, which was obtained at 1:100 dilutions. The first WHO international standards used to calibrate COVID-19 serologic assays were originally based on naturally infected individuals, while based on our dilutional studies it is clear that vaccination after natural infection synergically boosts the antibodies levels resulting in extremely high levels of so-called "hybrid immunity".[10,18,19]

Neutralizing antibodies have been proposed as a humoral correlate of immunity for SARS-CoV-2[20,21] and neutralization titers measured using lentiviral-based RVPNs correlate with vaccine-induced protection.[22] Thus, the finding that nAbs elicited by previous infection and vaccination are able to neutralize different variants in vitro is reassuring.

Based on the Chicago Department of Public Health report,[23] during the timeframe of sample collection for this study (January–March 2021) the majority of the infections were not from variants. This is supported by the fact that pre-vaccination CCP donor samples were able to neutralize the ancestral Wuhan-Hu-1 more than any other variants, but after vaccination, all variants were neutralized similarly, as others have reported[18] including neutralization of cross-clade pan-sarbecoviruses.[24]

This study has some limitations, including the small sample size and that data are limited to outcomes in recipients of mRNA vaccine-boosted CCP (testing was not performed on samples from CCP donors who received inactivated-virus or vector-based vaccines). These data confirm that while natural infections induce nAb and provide a basic level of protection, one or two doses of vaccine are highly efficacious at boosting binding antibody reactivity and nAb titers, which have been demonstrated to increase protection against reinfection and vaccine breakthrough infections, especially from new variants.[18,25] It appears that vaccination following prior infection elicits higher levels of circulating neutralizing Ab, while natural infection stimulates more robust and durable B cell maturation that eventually responds with more potent and broader nAb following a subsequent infection or vaccination.[26] Our findings support the need for future controlled studies using vaccine boosted CCP, particularly in immunosuppressed patients.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. T. G. is a consultant for Fresenius Kabi.

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