Prior COVID-19 Infection and Antibody Response to Single Versus Double Dose mRNA SARS-CoV-2 Vaccination

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ABSTRACT

The double dose regimen for mRNA vaccines against SARS-CoV-2 presents both a hope and a

challenge for global efforts to curb the COVID-19 pandemic. With supply chain logistics

impacting the rollout of population-scale vaccination programs, increasing attention has turned

to the potential efficacy of single versus double dose vaccine administration for select

individuals. To this end, we examined response to Pfizer-BioNTech mRNA vaccine in a large

cohort of healthcare workers including those with versus without prior COVID-19 infection. For

all participants, we quantified circulating levels of SARS-CoV-2 anti-spike (S) protein IgG at

baseline prior to vaccine, after vaccine dose 1, and after vaccine dose 2. We observed that the

anti-S IgG antibody response following a single vaccine dose in persons who had recovered

from confirmed prior COVID-19 infection was similar to the antibody response following two

doses of vaccine in persons without prior infection (P≥0.58). Patterns were similar for the post-

vaccine symptoms experienced by infection recovered persons following their first dose

compared to the symptoms experienced by infection naïve persons following their second dose

(P=0.66). These results support the premise that a single dose of mRNA vaccine could provoke

in COVID-19 recovered individuals a level of immunity that is comparable to that seen in

infection naïve persons following a double dose regimen. Additional studies are needed to

validate our findings, which could allow for public health programs to expand the reach of

population wide vaccination efforts.

INTRODUCTION

Rapid development of vaccines against SARS-CoV-2, the causative agent of Coronavirus

Disease 2019 (COVID-19), offers great promise for curbing spread of infection and accelerating

the timeline towards a potential level of herd immunity.[1-3] Amidst ongoing efforts to rapidly

deploy vaccinations, challenges to the supply chain have prompted queries around whether

single rather than double dose administration may suffice for certain individuals – including

those recovered from prior COVID-19 infection.[4] Emerging data from small studies suggest that

individuals who have recovered from either a recent or remote COVID-19 infection may have a

sustained immunity that could be assessed via measurable antibody response to a single

vaccine dose administration.[5,6] To this end, we evaluated the SARS-CoV-2 antibody response

following first and second doses of mRNA vaccination administered in a large and diverse

cohort of healthcare workers while specifically focusing on the response in persons with

confirmed prior COVID-19 compared to those without prior infection.

METHODS

In a cohort of healthcare workers who received Pfizer-BioNTech vaccination at our medical

center in Southern California,[7] we used the Abbott Architect immunoassays (Abbott Park, IL) to

quantify circulating levels of SARS-CoV-2 anti-nucleocapsid (N) protein IgG and anti-spike (S)

protein IgG at 3 time points: before or up to 3 days after dose 1, within 7 to 21 days after dose 1,

and within 7 to 21 days after dose 2. The Abbott anti-S IgG assay is CE marked with anticipated

near-future emergency use authorization. Given that a conservative high titer plaque reduction

neutralization (PRNT) assay of 1:250 has been correlated to the anti-S IgG cutoff of 4160

AU/mL, we additionally examined the proportion of vaccine recipients who achieved this

threshold following administration of one dose or two.

All participants provided survey data on prior COVID-19 infection and symptoms experienced after each vaccine dose. We determined prior infection status and timing in relation to first vaccine date, based on concordance of data documented in health records, presence of anti-N IgG antibodies at baseline pre-vaccination testing, and the self-reported survey information collected. All cases of data discrepancy regarding prior COVID-19 infection status underwent manual physician adjudication.

We compared antibody level and symptom responses between those with and without a prior COVID-19 diagnosis. We analyzed data at both matched and shifted time points, including examining measures for those with a prior COVID-19 diagnosis (at baseline and following dose 1) compared to those without a prior COVID-19 diagnosis (following dose 1 and dose 2). We log-transformed non-normally distributed values. For comparing between-group continuous values, we used the non-parametric Wilcoxon Rank Sum test. For comparing between-group proportions of values above a give threshold, we used two-sided Chi-square tests. We performed sensitivity analyses for those participants with immunoassays at all 3 time points. We conducted all statistical analyses using R (v3.6.1) and considered statistical significance as a two-tailed P value <0.05. All participants provided written informed consent; all protocols were approved by the Cedars-Sinai institutional review board.

RESULTS

A total of N=1089 vaccine recipients provided at least one blood sample for antibody testing, with an average age of 41.8±12.1 years, 60.8% female and 53.4% non-white (**Table 1**). Of this total sample, N=980 (78 with prior COVID-19 infection) provided baseline (pre-vaccine) samples, N=525 (35 with prior infection) provided samples after dose 1, and 238 (11 with prior

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infection) provided samples after dose 2. A total of 216 individuals (10 with prior infection) provided blood samples at all 3 time points.

For both anti-N IgG (representing response to prior infection) and anti-S IgG (representing response to either prior infection or vaccine), COVID-19 recovered persons had expectedly higher antibody levels at all time points (P≤0.001) (**Tables S1-S2** and **Figures S1-S2**). Notably, anti-S IgG levels were only slightly lower in COVID-19 recovered persons at baseline, when compared to infection naïve persons who had received a single vaccine dose (log median AU/mL [IQR], 6.0 [4.6, 6.9] vs 7.0 [6.3, 7.6], P<0.001). Moreover, anti-S IgG levels were not significantly different between COVID-19 recovered persons following a single dose and infection naïve persons who had received 2 doses (10.0 [9.2, 10.4] vs 9.9 [9.4, 10.3], P=0.91) (**Figure 1**). In parallel with analyses of antibody response, we also observed that overall frequency and severity of post-vaccine symptoms were more prominent for COVID-19 recovered after dose 1 compared to infection naïve persons after dose 2 (**Figure S3**).

Similar results were found in a sensitivity analysis including only individuals who had antibody immunoassays performed at all 3 time points (**Tables S3-S4**). Specifically, those with prior COVID-19 infection had higher anti-S IgG than those without prior infection at all time points. No difference in anti-S IgG level was detected between those with a prior COVID-19 infection after one dose of vaccine compared with those without prior infection following two doses (10.2 [8.4, 10.5] vs 9.9 [9.4, 10.3], P=0.58). In sensitivity analyses, frequency and severity of post-vaccine symptoms were also similar to those seen in the main analyses.

In the total sample, proportions of anti-S IgG levels at or above the 4160 AU/mL threshold were similar in COVID-19 recovered persons at baseline compared to infection naïve persons after a single dose (P=0.94). Notably, these proportions were lower in COVID recovered after a single

dose compared to infection naïve persons after 2 doses (P<0.001), and then no different when
both groups were compared after 2 doses (**Table S5** and **Figure S4**).

DISCUSSION

We found that COVID-19 recovered individuals develop a level of provoked antibody response,
following a single dose of mRNA vaccine, that is comparable to the provoked antibody response
seen after a two-dose vaccination course administered to infection naïve persons. Extending
from similar results seen in smaller studies,[5,6] our findings in a large and diverse cohort of
healthcare workers highlight the potential of a strategy for maximizing vaccine supply that
warrants further investigation.

Recent work has demonstrated that COVID-19 specific antibodies are efficiently generated and
detectable in the circulation following a single dose of vaccines that were originally intended for
complete administration to include an additional booster dose.[5] These findings have prompted
some organizations to favor prioritizing at least a first vaccine dose to majority segments of the
population while considering variable timing for the second dose. In the absence of clinical
outcomes data to support any variations from pre-specified vaccination protocols,[8-10] there are
immuno-biological data suggesting possible alternate strategies for COVID-19 recovered
individuals. In fact, detectable presence of naturally acquired anti-SARS-CoV-2 antibodies and
measures of discernible T-cell mediated immunity, especially in persons who have successfully
recovered from recent versus remote infection, have prompted some experts to suggest
delaying any vaccination for these individuals.[11-13] However, acknowledging the unclear duration
of naturally acquired immunity and the unknown extent to which immunity to one strain of
SARS-CoV-2 confers protection from variants, there is general agreement that vaccination
strategies for COVID-19 recovered persons warrants careful consideration.

Our data suggest the potential benefit of at least one vaccine dose, given that we observed pre-vaccine levels of anti-S IgG in COVID-19 recovered persons to be somewhat lower than levels detected among infection naïve persons following a single vaccine dose. In the absence of directly measured neutralizing antibody levels, we secondarily examined the proportion of anti-S IgG values known to correspond with high titers of the PRNT assay and found a comparable albeit slightly lower frequency in COVID-19 recovered persons after a single vaccine dose compared to infection naïve persons after two doses. Notwithstanding the need for further studies with additional serologic phenotyping, this finding may be related to heterogeneity within the COVID-19 recovered persons including variations in timing and severity of prior illness. Although circulating antibody levels alone are not definitive measures of immune status, serial measures of the serological response to either natural or inoculated exposures are known to correlate well with effective immunity[14] and our results indicate their potential utility in guiding vaccine deployment strategies for both infection recovered and naïve persons.

Several limitations of our study merit consideration. We examined antibody response within 7 to 21 days following each vaccine dose, and longer-term follow up is likely to provide additionally informative data – particular regarding the putative duration of immunity acquired from receiving a single versus double dose of vaccine administration. Direct measures of neutralizing antibody levels are a part of our ongoing work. Notwithstanding the size of our study cohort, yet larger-sized samples are needed for sufficient statistical power to examine differences across demographic and clinical subgroups that are known to exhibit variation in antibody response following vaccination.[15-17]

In summary, we found in diverse cohort of mRNA vaccine recipients that anti-S IgG levels are similar between those with and without prior COVID-19 infection after receiving their first and

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second doses, respectively. These results offer preliminary evidence in support of a middle

ground between public health motivated and immunologically supported vaccine strategies. If

validated, an approach that involves providing a single dose of vaccine to persons with a

confirmed history of COVID-19 infection along with an on-time complete vaccine schedule for

infection naïve persons could assist with maximizing the benefit of a limited vaccine supply.

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DATA AVAILABILITY

The data supporting the findings of this study are available from Cedars-Sinai Medical Center,
upon reasonable request and via institutional data sharing policies. The data are not publicly
available due to the contents containing information that could compromise participant privacy.

CODE AVAILABILITY

The code used for all analyses is available upon reasonable request.

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Table 1. Characteristics of the Study Sample.

	Total	Pre-Vaccine	Post-Vaccine Dose 1	Post-Vaccine Dose 2
N	1089	980	525	238
Age in years, mean (SD)	41.77 (12.06)	41.47 (11.92)	43.56 (12.72)	44.02 (12.60)
Race, n (%)				
White	508 (46.6)	452 (46.1)	263 (50.1	130 (54.6)
Black or African American	36 (3.3)	33 (3.4)	22 (4.2)	9 (3.8)
Asian	302 (27.7)	266 (27.1)	155 (29.5)	67 (28.2)
Native Hawaiian/Pacific Islander	29 (2.7)	27 (2.8)	14 (2.7)	2 (0.8)
American Indian/Alaska Native	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)
Multiple/Other	139 (12.8)	130 (13.2)	58 (11.1)	27 (11.4)
Prefer not to answer	73 (6.7)	70 (7.1)	13 (2.4)	3 (1.3)
Ethnicity, n (%)				
Hispanic/Latinx	138 (12.7)	125 (12.8)	55 (10.5)	20 (8.4)
Non-Hispanic/Latinx	883 (81.1)	789 (80.5)	461 (87.8)	215 (90.3)
Prefer not to answer	68 (6.2)	66 (6.7)	9 (1.7)	3 (1.3)
Sex, n (%)				
Male	363 (33.3)	332 (33.9)	159 (30.3)	65 (27.3)
Female	662 (60.8)	586 (59.8)	354 (67.4)	167 (70.2)
Other	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.4)
Prefer not to answer	63 (5.8)	61 (6.2)	11 (2.1)	5 (2.1)
Prior COVID-19 Infection, n (%)	86 (7.9)	78 (8.0)	35 (6.7)	11 (4.6)
Antibody Levels, mean (%)				
Architect IgG Index (S/C)	0.30 (0.86)	0.25 (0.84)	0.36 (0.90)	0.34 (0.83)
Architect IgM Index (S/C)	0.99 (2.41)	0.26 (1.24)	2.11 (4.11)	3.38 (5.97)
Architect Quant IgG II (AU/mL)	2798.65 (6161.33)	104.00 (694.24)	3183.38 (7299.73)	24115.75 (16394.77)

Figure 1. Anti-Spike IgG Antibody Response to mRNA SARS-CoV-2 Vaccination in Persons With and Without Prior COVID-19 Infection. Box plots display the median values with the interquartile range (lower and upper hinge) and ±1.5-fold the interquartile range from the first and third quartile (lower and upper whiskers).