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Variability in Severe Acute Respiratory Syndrome Coronavirus 2 IgG Antibody Affinity to Omicron and Delta Variants in Convalescent and Community mRNA-Vaccinated Individuals

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ABSTRACT

The emergence of the omicron and delta variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has begun a number of discussions regarding breakthrough infection, waning immunity, need and timing for vaccine boosters, and whether existing mRNA vaccines for the original SARS-CoV-2 strain are adequate. Our work leverages a biosensor-based technique to evaluate the binding efficacy of SARS-CoV-2 S1-specific salivary Abs to the omicron and delta variants using a cohort of mRNA-vaccinated (n = 109) and convalescent (n = 19) subjects. We discovered a wide range of binding efficacies to the variant strains, with a mean reduction of 60.5, 26.7, and 14.7% in measurable signal to the omicron strain and 13.4, 2.4, and −6.4% mean reduction to the delta variant for convalescent, Pfizer-, and Moderna-vaccinated groups, respectively. This assay may be an important tool in determining susceptibility to infection or need for booster immunization as the pandemic evolves. ImmunoHorizons, 2022, 6: 307–311.

INTRODUCTION

As the coronavirus disease 2019 (COVID-19) epidemic continues into its third year, two major variants (first the delta and subsequently the omicron) have become the predominant circulating strains in infected individuals. The two US Food and Drug Administration–approved mRNA vaccines are based on wild-type sequences of the Spike protein. With the emergence of the omicron variant, some fully vaccinated individuals (those who have had the two initial doses of the mRNA vaccines, but also including those who have had a third booster injection) were still susceptible to COVID infection. The susceptibility to infection could be the result of waning immunity, a reduction of vaccine-induced Abs to the omicron S1 protein, or a combination of the two. Although emerging research appears to suggest that there is efficacy in omicron being neutralized by additional doses of the current mRNA vaccines being in active use, the dynamics of the pandemic still require active investigation (1). Questions regarding susceptibility to infection and long-term immunity are being actively investigated (2), as well as speculation regarding the relationship between natural immunity and vaccine-induced Ab production (3).

Our laboratory has previously developed a noninvasive saliva-based quantitative biosensor assay for anti-S1 IgG Ab levels to the wild-type SARS-CoV-2 using a proprietary platform called Amperial. We demonstrated that this assay is highly specific to COVID-19 infection (4) and can be used to serially monitor the saliva of vaccinated patients for waning Ab levels (5). As the COVID-19 pandemic continues with a number of variants being monitored to determine their potential harm and differences in transmission rate, a major point of interest is whether existing mRNA vaccines based on the wild-type S1 sequence would remain efficacious with successive new variants.

The Amperial platform allows rapid development of quantitative assays for Abs to SARS-CoV-2 variants. As soon
as a variant S1 Ag becomes available commercially, it can be immobilized in the conducting gel and used to quantify IgG levels in saliva. In this study, we developed quantitative Amperial assays to both delta and omicron S1 Ags. We then simultaneously measured IgG levels to the wild-type and variant S1 Ags in a cohort of >100 Pfizer- or Moderna-vaccinated individuals and 19 convalescent patients who contracted COVID-19 before the emergence of either the delta or omicron variants. We found a significant reduction in Abs detected for the delta and omicron variants in all three cohorts, with Abs to omicron more reduced than to delta. We also found that Pfizer-vaccinated individuals have lower measured Ab levels to the omicron variant than salivary IgG from Moderna-vaccinated individuals. Our work also indicates that Abs derived from natural immunity have reduced reactivity to the omicron variant relative to the wild-type or delta variant.

MATERIALS AND METHODS

SARS-CoV-2 salivary quantitative Ab assay

As previously described, the Amperial platform uses an integrated electrode and electrochemical reader system (EZLife Bio, Los Angeles, CA) to read the oxidation-reduction by-product of the Ab capture process. The detailed description of the Amperial COVID-19 Ab assay and the assay performance and validation have been described previously (4). We reported the utility of this assay in monitoring the kinetics of Ab response (5) using immobilized Ab subunit to the wild-type virus immobilized in a conducting gel on the surface of the gold electrode.

We selected the S1 Ag as the capture Ab because both the Pfizer and Moderna vaccines use mRNA coding for the S1 Ag. In our work we evaluated the difference between the original nonvariant, omicron, and delta SARS-CoV-2 through the immobilization of the identical concentrations of delta and omicron S1 Ag and electrochemically measuring the captured SARS-CoV-2 S1-specific Abs present in saliva. The nonvariant assay was a recombinant SARS-CoV-2 S1 Ag (40591-V08H; SinoBiological, Wayne, PA) as previously described and characterized (4, 5). For the delta variant, we used SARS-CoV-2 variant S1 Ag B.1.6.617.2 (40591-V08H23; SinoBiological, Wayne, PA), a recombinant Ag that included T194, G142D, E156G, 157-158 deletion, and the L452R, T478K, D614G, 681R mutations. For the omicron variant, we used SARS-CoV-2 variant S1 Ag B.1.1.529 (40591-V08H41), a recombinant Ag with the stated mutations of *A67V, HV69-70 deletion, T95I, G142D, VYY143-145 deletion, N211 deletion, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H* (6).

Equal concentrations of the original, omicron, or delta SARS-CoV-2 S1 Ag were immobilized in separate gold electrodes (0.3 µg/well) on a 96-well electrochemical plate via an electropolymerized polypyrrole. After coating of the SARS-CoV-2 Ag on the surface with the conducting polymer, salivary samples were diluted 1:10 in Casein/PBS and incubated on the plate for 10 min. After a PBS-T wash, biotinylated anti-human IgG Fc was incubated on the plate as a secondary Ab, washed off with PBS-T, and then an HRP enzyme chain was incubated and washed off. The final measurement is performed by adding a H2O2/tetramethylbenzidine solution and performing chronoamperometric measurement at −200 mV at 60 s to measure the final electrochemical current generated by the completed assay complex. For the evaluation of SARS-CoV-2 efficacy, each experimental run consisted of wells where each sample was pipetted on a surface coated with nonvariant Ag, variant Ag (omicron or delta Ag), and a polymer-only well that was used to normalize for background effects.

RESULTS

Measured Abs to delta and omicron variants

Available samples were tested using the AMPERIAL assay, with each plate containing a wild-type in comparison with a variant Ag (omicron or delta) for each sample. After completion of each experiment, comparisons were calculated between the measured current of the nonvariant Ag on each plate and the variant Ag on each plate. For the omicron Ag, 55 Moderna, 54 Pfizer, and 19 convalescent samples were tested. For the delta Ag, 53 Moderna, 55 Pfizer, and 19 convalescent samples were tested. We then calculated a percent reduction using the Ab
level to the nonvariant strain minus the Ab level to the variant divided by the Ab level to the wild-type Ag. This calculation yields the percentage of reduction in Abs that are able to bind to the variant (Fig. 1).

Analysis of the different groups showed that for the omicron variant there were reductions of 60.5, 26.7, and 14.7% in mean signal compared with nonvariant SARS-CoV-2 for the convalescent, Pfizer, and Moderna samples, respectively. For the delta variant, a 13.4, 2.4, and −6.4% mean reduction to the delta variant was observed for convalescent, Pfizer, and Moderna samples, respectively. There was a wide variation in affinities among individuals. Many individuals had little reduction or even increased Ab levels to the variants, whereas others had a significant reduction of ≥50%.

We performed paired sample paired $t$ tests for each individual sample run with both the wild-type and the variant assays (Fig. 2). Within the omicron variant group, statistical significance was found between the Pfizer and Moderna vaccines ($p = 0.0042$), the Pfizer and Convalescent group ($p = 2.7e−6$), and the Moderna and Convalescent group ($p = 1.7e−8$). Within the delta variant group, statistical significance was found between the Pfizer and Moderna vaccines ($p = 0.017$) and the Moderna and Convalescent groups ($p = 0.0049$), whereas no significance was found between the Pfizer and Convalescent groups ($p = 0.18$).

For comparisons within the same category of Abs (Fig. 3), within the convalescent group, statistical significance was found between the omicron and delta variants ($p = 2e−7$). Within the Moderna group, significance was found between omicron and delta variants ($p = 5.4e−6$). Within the Pfizer group, significance was found between the omicron and delta variants ($p = 8e−7$).

To summarize, statistical significance was found in all cases of comparisons within variant groups and within Ab groups excluding the case between Pfizer and Convalescent Abs for the delta variant.

Table II is summary of the percentage of individuals in each group who experience a >50% reduction in Ab affinity to the variant. Of note is that in the convalescent group, 3 individuals (15%) had a >50% reduction in affinity to the delta variant, and 13 of 19 individuals (79%) had a >50% reduction in Ab affinity to the omicron variant. In the vaccinated cohorts, 22% of Pfizer-vaccinated individuals experienced a >50% reduction in Ab affinity to the omicron variant, and 11% of Moderna-vaccinated individuals had similar decreases.

**DISCUSSION**

The data presented demonstrate the omicron variant provides a greater risk and susceptibility compared with nonvariant or delta variant of SARS-CoV-2. As the experimental results show, there is a significant decrease in binding affinity (14.7–26.7%) for the omicron variant relative to the nonvariant, and there are significant differences between all groups of delta and omicron variants, suggesting a greater risk for susceptibility to the omicron variant than the delta variant. The reduction in Ab affinity is highly variable among individuals. More than 50% show little or no reduction in affinity to the omicron variant, while in some groups >20% experience a >50% reduction in affinity. This may explain the somewhat haphazard susceptibility to COVID-19 among vaccinated individuals. Our data also demonstrate that individuals vaccinated with the Moderna vaccine have lower incidences of affinity reduction to the omicron variant. There is no guarantee that the next variant will show the same differences. Perhaps a “mix and match” scenario where individuals receive boosters of a brand different from their original vaccine may be a possible strategy for inducing a broad range of protection.

In this study, we specifically evaluated the affinity of only IgG Abs to the S1 subunit of the spike protein of SARS-CoV-2, and consequently it serves only as an evaluation of a subset of the Abs related to immunogenicity. Nevertheless, inasmuch as the S1 subunit is the component coded for by the existing mRNA vaccines, the results herein presented still offer a large
degree of insight into the reduced efficacy of Abs in light of the various mutations present in the variant strains.

There was a wide variety of Ab affinity to the omicron variant among individuals, with some having equivalent binding while others had close to a 70% reduction in binding efficacy. Although currently there is no proven method to predict susceptibility to COVID-19 infection using Ab measurement, it is likely that a combination of decreasing Ab levels with decreased affinity of Abs to the omicron variant is contributing to the current spike in COVID-19 infections among vaccinated individuals.

Our data suggest that as more variants emerge, a modification to the existing mRNA vaccines may be required to prevent infection and transmission. By serially measuring both Ab levels...
and Ab affinity, we may be able to determine appropriate timing of booster vaccinations. Although managing a global pandemic typically involves a large variety of assessments beyond functional Abs, this study adds to the mounting evidence that salivary Ab assessment is a noninvasive, scalable, and viable method of evaluating for the dynamics of immunity during a pandemic. In particular, our work builds on other studies wherein SARS-CoV-2 Ab evaluation was explored in convalescent and vaccinated populations (7–9), with these publication results suggesting that IgG-based monitoring is the most appropriate for longer-term evaluation of Abs for SARS-CoV-2. Our results herein demonstrated add to the body of evidence of salivary COVID-19 Ab assessment as a rapid and scaleable methodology for immunity. Because saliva measurement can be done without the involvement of health care professionals, this platform can allow broad-based testing of entire populations to inform decision making.

DISCLOSURES

D.T.W.W. is a consultant to Colgate-Palmolive, Mars Wrigley, and GSK. D.T.W.W. also has equity in Liquid Diagnostics and RNAmeTRIX. D.T.W.W., C.M.S., and M.K.T. are shareholders in Liquid Diagnostics LLC. M.K.T. is a shareholder of EZLife Bio. M.K.T. is a paid consultant of Liquid Diagnostics LLC.

REFERENCES


ACKNOWLEDGMENTS

We thank our volunteers who participated in the study.

TABLE II. Percentage of individuals experiencing a >50% decline in affinity to SARS-CoV-2 variants

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<th>Moderna Individuals</th>
<th>Pfizer Individuals</th>
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<td>Delta</td>
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<td>0/53 (0%)</td>
<td>1/55 (2%)</td>
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<td>Omicron</td>
<td>13/19 (68%)</td>
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