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Neutralizing Antibody Responses in Patients Hospitalized with SARS-CoV-2 Delta or Omicron Infection

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Humoral and cellular immune responses contribute to overall protective immunity against SARS-CoV-2 with neutralizing antibody playing a key role in preventing viral infection. This is evident from the large number of Omicron infections in vaccinated and convalescent patients since antibodies induced after vaccination or infection by the ancestral WA1 strain do not neutralize Omicron variants efficiently (1, 2). This has led to the FDA recommendation for inclusion of the Omicron variant in bivalent COVID-19 vaccines. However, issues have been raised about the value of adding Omicron to the vaccine based on data showing only modest differences between antibody responses after booster immunization with Omicron versus WA1 (3, 4). Also, a recent study has shown that booster responses to Omicron infection are impacted by previous SARS-CoV-2 infections (5). Thus, having additional information on the types of neutralizing antibody responses induced after infection with different SARS-CoV-2 variants will be helpful in addressing this important issue.

Here we report live virus neutralization titers against WA1, Delta, BA.1, BA.2 and BA.5 variants in serum samples collected from hospitalized patients infected with SARS-COV-2 Delta or Omicron strains. Blood samples were collected from 187 patients hospitalized with acute COVID-19 between July 2021 – March 2022 at 8 U.S. hospitals (Supplemental Methods). 26% of these patients were immunocompromised, the details of which are given in Supplemental Table 1. The majority (69%) of these patients were sequence confirmed for Delta or Omicron infection and the remaining were classified according to calendar period of circulation. Patients were either unvaccinated (n=80) or vaccinated with COVID-19 mRNA vaccine (n=100) or adenovirus vector vaccine (n=7) before infection.

Unvaccinated Delta infected patients made a highly biased neutralizing antibody response towards the infecting Delta strain with lower titers against WA1 (6-fold) and strikingly lower titers against BA.1 (60-fold) and BA.2 (22-fold) (Figure 1A). In vaccinated Delta patients the neutralization titers were similar between Delta and WA1 but were again much lower against BA.1 (17-fold) and BA.2 (9-fold) (Figure 1B). Thus, both unvaccinated and vaccinated Delta infected patients made significantly lower neutralizing antibody responses to Omicron (as determined by Wilcoxon rank sums test). A strikingly different pattern was seen in Omicron infected patients irrespective of their vaccination history with a more favorable neutralizing antibody response to BA.1 and BA.2. While BA.1 and BA.2 neutralizing titers were modestly lower in vaccinated compared to unvaccinated Omicron patients, there was a clear trend for a broader and more balanced antibody response with similar neutralization titers to Delta, BA.1, and BA.2 (Figures 1C, 1D). Importantly, the ratio of BA.1 to WA1 neutralizing titers was significantly higher in Omicron patients compared to Delta patients in both unvaccinated (19-fold) and vaccinated (11-fold) patients (Figure 1E, 1F). This analysis of the ratio between neutralizing antibody to
Omicron versus WA1 within a given individual nicely documents that Omicron infection favors Omicron specific antibody responses. These Omicron neutralizing antibodies could have emerged from either de novo naïve B cells or from cross-reactive memory B cells.

Given the importance of the currently dominant BA.5 strain we then tested neutralization against BA.5. Note that our samples were collected prior to dominance of BA.5 and most of our patients were infected with BA.1 (Supplemental Table 1). In the subset of Omicron patient samples that we analyzed, there was detectable neutralization of BA.5 but it was lower than for BA.1. and BA.2 in both vaccinated and unvaccinated patients (Figure 1G, 1H, Supplemental Figure 1). This reduced neutralization activity against BA.5 in patients infected with BA.1 suggests that it is better to have BA.5 than BA.1 in the vaccine.

In summary, our results show that Omicron infection of unvaccinated or vaccinated patients induces a more proportional and balanced neutralizing antibody response to Omicron variants supporting the recent decision to include Omicron in the bivalent SARS-CoV-2 vaccine. However, it remains to be seen how these findings from infection will translate to vaccination. Our results are from hospitalized patients with high levels of infected cells and antigen that would have efficiently induced a primary response to Omicron in addition to selectively recruiting Omicron reactive memory B cells. It is possible that a single immunization with the Omicron bivalent vaccine may not be sufficient and that two doses may be needed to give the desired antibody response (6). Future studies should address this issue, and it will also be interesting to see how the bivalent vaccine works in people who have already been infected with an Omicron strain.

Figure 1: Live virus neutralizing antibody titers in hospitalized patients infected with SARS-CoV-2 Delta or Omicron variants. In vitro neutralization titers against live WA1, Delta, BA.1, or BA.2 variant in unvaccinated (A,C) and vaccinated (B,D) hospitalized patients infected with a Delta (A,B) or Omicron (C,D) strain. Solid lines: sequence confirmed infections; Dashed lines: not sequence confirmed, Red: immunocompromised patients. The ratio of BA.1 to WA1 neutralizing titers in unvaccinated (E) or vaccinated (F) patients. Geometric mean and 95% CI are indicated. For a subset of Omicron patients who were unvaccinated (G) or vaccinated (H), BA5 neutralization was also assessed. P values were calculated by Wilcoxon rank sum test.