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Methods matter – Tailoring SARS-CoV-2 antibody targets to vaccination status

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ABSTRACT

Individuals who have been vaccinated for COVID19 should have IgG antibody in response to the specific antigen that is the target in the vaccine development. There are several options for targeted COVID19 antigen, but most manufacturers have focused on the spike protein. Using our understanding of the targeted antigen for vaccine development, we can develop testing algorithmic scheme for anti-spike and anti-nucleocapsid antibody assays to aid delineation of infection versus vaccination in our patient population. Clear communication from laboratories specifying the specific SARS-CoV-2 antibodies (i.e., anti-spike, anti-nucleocapsid, or both) in their antibody tests at both the ordering and reporting levels will play crucial role in the development of this approach and is essential to avoid potential provider/patient confusion in the interpretation of serologic testing.

Dear Editors,

The COVID-19 pandemic has brought unparalleled challenges, but it has also catalyzed the implementation of emerging technologies, most notably the widespread use of mRNA vaccines. While using mRNA vaccination has not been entirely novel and has long been a subject of medical research [1], the FDA Emergency Use Authorization of BioNTech-Pfizer and Moderna vaccines has brought mRNA vaccination to the medical forefront.

As progressively more people become vaccinated, we have noticed an increasing number of patients without prior COVID-19 illness being tested for SARS-CoV-2 antibodies as a means of documenting immunity post-vaccination. As of early February 2021, the FDA's website lists approximately 20 IgG-specific antibody tests, with around 70% of those tests targeting anti-spike protein IgG antibodies. The other remaining tests target anti-nucleocapsid IgG antibodies or IgG antibodies against both immunogenic targets [2].

In our clinical practice, we have had concerns from vaccinated patients who had SARS-CoV-2 IgG testing performed at outside facilities who unexpectedly tested negative. Because mRNA vaccines contain genetic information only for the spike protein, we suspected that these patients were tested with antibody assays that targeted exclusively nucleocapsid antibodies. This hypothesis is in accordance with the CDC's statement that vaccinated individuals may test positive for antibodies against the spike protein but not for antibodies against other non-vaccine antigenic proteins [3].

To further investigate these concerns, we tested serum samples from 10 vaccinated individuals, 13 randomly chosen patients with nucleic acid amplification test (PCR or Rapid ID NOW)-confirmed SARS-CoV-2 infection, and two randomly selected patients with no history of vaccination or infection on both our institution's Ortho-Clinical Diagnostics Vitros anti-spike IgG and Abbott Architect anti-nucleocapsid IgG assays. We chose a small sample size for this endeavor in order to expeditiously corroborate for ourselves, our patients, and our clinical providers what has been published by the CDC regarding vaccination and antibody positivity. All 10 vaccinated subjects were negative for anti-nucleocapsid antibodies but positive for anti-spike antibodies. In contrast, for the patients with test-confirmed infection, most (10 out of 13) had detectable anti-nucleocapsid IgG antibodies and all had detectable anti-spike IgG antibodies (Fig. 1). For these patients, antibodies were measured a median of approximately one-and-a-half months after nucleic acid amplification test positivity (range: 1 day before PCR/Rapid ID Nowpositivity to 8 months after PCR/Rapid ID Now positivity). For the 2 patients who had not been infected or vaccinated, their serum samples were negative on both IgG assays and our institution's DXI anti-spike IgM assay. For those vaccinated or infected, IgM detectability was variable in both groups, likely dependent on timing of specimen collection in relation to infection/vaccination, as the IgM antibody response is not as durable [4]. These findings were consistent with our hypothesis and CDC published statements [3].

In summary, if a patient who has been vaccinated has negative IgG antibody results, it may likely be that the chosen assay targeted anti-nucleocapsid IgG antibodies. Therefore, it may be more prudent to use anti-spike IgG antibody assays as the initial antibody test for patients with a history of vaccination. However, anti-spike antibody assays cannot differentiate vaccination from past infection, the latter for which anti-nucleocapsid antibody testing may provide useful diagnostic information. Thus, we advocate for a targeted antibody testing approach dependent on the patient's clinical history. Clear communication from laboratories specifying the specific SARS-CoV-2 antibodies (i.e., anti-spike, anti-nucleocapsid, or both) their antibody tests detect at both the ordering and reporting level will play a crucial role in the development of this approach and is essential to avoid potential provider/patient confusion in the interpretation of serologic testing.

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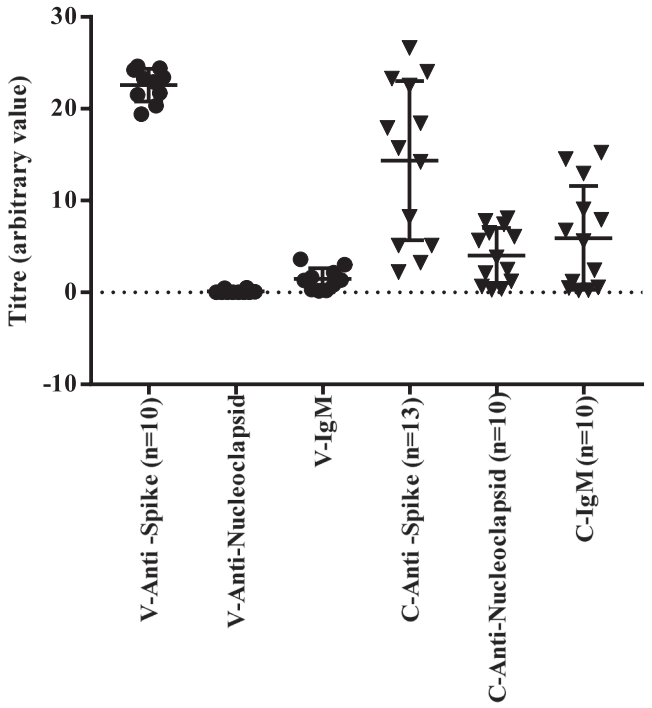

Fig. 1. Comparing anti spike and anti nucleocapsid antibodies in vaccinated (V) and COVID-19 infected (C) subjects.

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