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Commentary

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The COVID-19 Test Most of Us Need Now

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Abstract

More than two years into the COVID-19 pandemic, a correlation of protection (probability of infection) is still unknown. Under certain circumstances, neither natural infection nor vaccination protects against re-infection. Re-infection is dependent on several factors, such as waning immunity and the emergence of variants prone to immune escape. A rapid test that measures levels of neutralizing antibodies could provide a probability of infection that would allow immunocompromised individuals and their healthcare providers to make informed decisions about their healthcare and lifestyle, but only if the test reflects the viral sub-variant(s) in circulation at the time an individual takes the rapid test.

Keywords: *COVID-19; Neutralizing Antibody Rapid Test; Variants of concern*

Introduction

As SARS-CoV-2 becomes endemic, it is not known what percentage of the population has been infected with ancestral or current sub-variants of SARS-CoV-2. However, infection does not equate to protection, as viral infection may not induce protective immunity for two reasons. First, a mild infection may not elicit high levels of neutralizing antibodies (NAbs) [1]. In fact, NAbs were undetectable in over one-third of previously infected individuals [2,3]. Second, as the virus continues to mutate, variants arise that can escape neutralization, causing both symptomatic and asymptomatic infections which allow for continued viral transmission.

Prior to further discussion, it is important to distinguish infection from disease. Fortunately, the mRNA vaccines were ~95% effective at preventing hospitalization and severe disease [4,5]. The vaccines induce both NAbs [6] as well as anti-viral T cells [7,8]. However, as NAbs wane [9,10] -albeit faster for some than others–symptomatic re-infection occurred in many vaccine recipients [11,12] even before Omicron variants existed. Now that Omicron sub-variants are prevalent in the population, is there a test that can predict the probability of infection? The answer, of course, is "it depends".

Discussion

Early in the pandemic when the ancestral strain first detected in Wuhan was prevalent, we developed a rapid test [13] that measures titers of antibodies that block the receptor binding domain (RBD) of spike protein from binding to angiotensin-converting enzyme 2 (ACE2), the host cellular receptor for the virus [13]. These NAbs prevent the virus from infecting susceptible cells. Although there are additional regions on the SARS-CoV-2 spike protein that elicit NAbs [14], RBD is the principal neutralizing domain. NAbs apply selective pressure to the virus so that viral particles which escape neutralization will infect cells, replicate, and release progeny that may no longer be neutralized by vaccine-induced antibodies, leading to the evolution and spread of variants of concern.

As stated above, natural infection occurs on the virus' terms, and may not induce high titer NAbs in at least one-third of infections [2,3,15]. We confirmed this finding using our rapid NAb test on previously infected individuals. As shown in Figure 1 (baseline), the full spectrum of NAb titers was observed in previously infected individuals–from high NAb titers to non-detectable NAb titers, despite the previous infection. Interestingly, after previously infected individuals received their first dose of vaccine, over half showed high NAb titers (>1:640), suggesting immunologic priming during natural infection. Two weeks after a second mRNA vaccine dose, >77% of previously infected individuals had NAb titers at the highest level, 18% had NAb titers <1:320, ≥1:160, and curiously, 4.6% had low NAb titers (<1:80, ≥1:40). These findings suggest that hybrid immunity, even after 2 doses of mRNA vaccine, does not always induce high NAb titers.

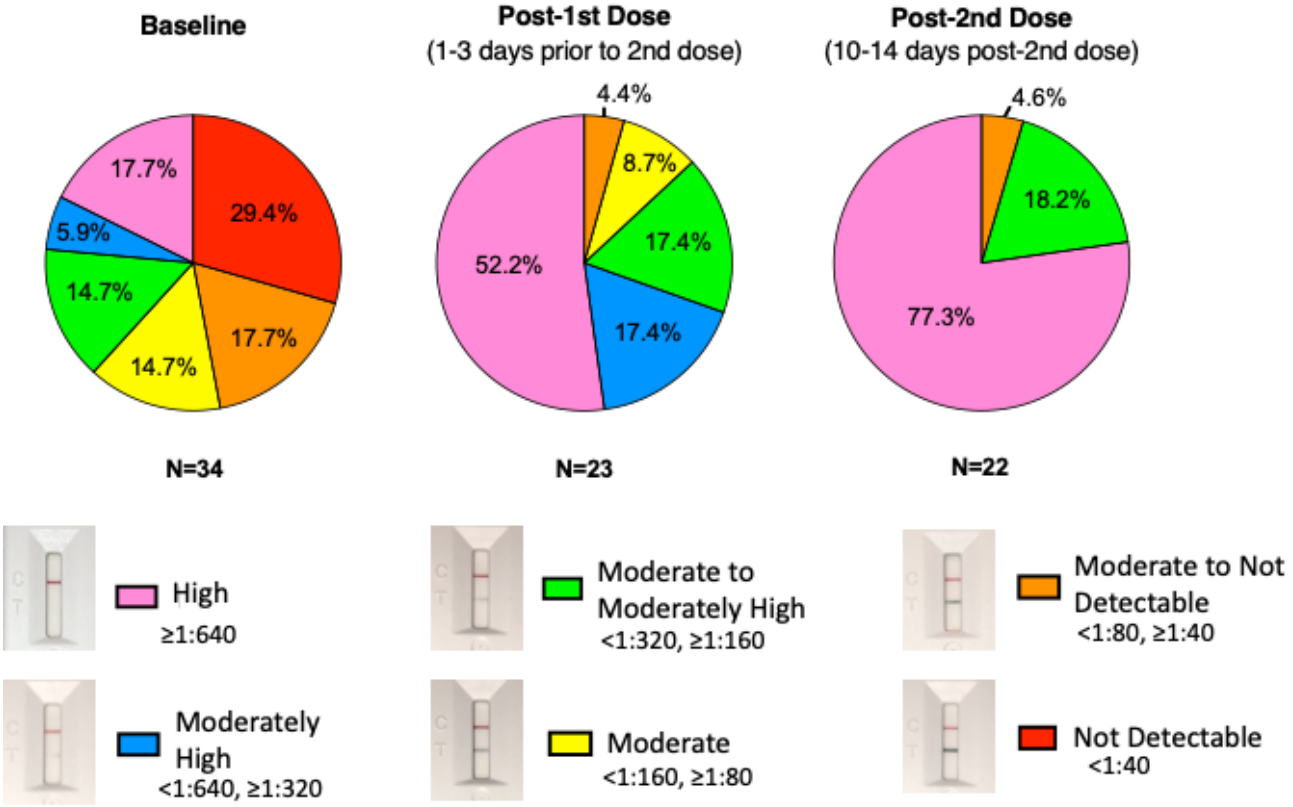

Figure 1: Neutralizing Antibody levels in previously infected individuals pre- and post-vaccination. Timepoints include baseline, post-1st dose, and post-2nd dose. Baseline refers to study participants prior to vaccination who were ≥2 weeks and ≤3 months post-infection. Post- 1st dose (1-3 days prior to 2nd dose) indicates either 21 or 28 days after the 2nd vaccine. All participants received either BNT162b2 or mRNA-1273 vaccines. Six levels of neutralization were calculated using test line density values based on the principle that neutralizing antibodies prevent RBD conjugated to gold beads from binding to ACE2 on a lateral flow strip, as previously described [13]. Percent neutralization was calculated as follows: 1-(Test Line Density/Limit of Detection)*100%. The limit of detection was determined to be a line density of 942,481. Percent neutralization ranges are follows: High (pink)=90-99%; Moderately high (blue)=80-89%; Moderate to Moderately high (green)=61-79%; Moderate (yellow)=36-60%; Moderate to Not Detectable (orange)=15-35%; Not detectable (Red)=≤15% neutralization. Test line densities were quantified using an RDS-2500 lateral flow reader (Detekt Biomedical, Austin TX).

Many people have received 2 or 3 mRNA vaccine doses designed to protect against ancestral SARS-CoV-2. Since the emergence of Omicron in November/December 2021, hundreds of thousands of symptomatic breakthrough infections have occurred [16]. Since results of rapid at-home antigen tests are often not reported it has become difficult–if not impossible–to know what percentage of the population has had a breakthrough infection with an Omicron variant. Although currently available mRNA vaccines provide some cross-protection against severe disease and hospitalization, they do not protect against Omicron variant infection, viral replication and, evidently, transmission [16,17].

Many immunosuppressed individuals or healthcare providers who work with immunocompromised patients do not know when immunity is waning, such that their probability of infection upon exposure is increased. Exposure and infection are particularly problematic for immunosuppressed persons as their cellular immunity is often impaired. Once infected due to inadequate levels of protective NAbs, disease may occur and is more likely to be severe, leading to poor patient outcomes [18].

Conclusion

The COVID-19 pandemic has unfortunately demonstrated that individuals cannot rely on one another to practice protective behaviors such as wearing a mask and getting vaccinated. As a result, we have entered the age of communicable diseases in which individuals must protect themselves. Rapid tests that measure levels of NAbs from a finger-stick drop of blood could be used to monitor immunocompromised individuals for when a booster vaccine might be warranted. However, the rapid test must employ RBD or spike protein from the SARS-CoV-2 variant currently circulating in the population. Otherwise, the test result would measure high titers of NAbs to vaccines based on the ancestral virus, but have limited bearing on protection from infection with the variant that is currently circulating. Similarly to manufacturers of the influenza vaccine, manufacturers of rapid

NAb tests must monitor viral variants in the population, such that the results of their tests predict a probability of infection that reflects the current SARS-CoV-2 variant in circulation.

Authors' Contributions

Conceptualization, writing, reviewing and editing: DFL, AJR

Conflict of Interest

DFL is co-founder of Axim Biotech, a company that manufactures a rapid neutralizing antibody test. AJR has no potential conflict of interest relevant to this article.

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