SARS-CoV-2 Variants and Their Clinical Significance: An Update as of May 2022

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SARS-CoV-2 has demonstrated a remarkable ability to mutate and evade the human immune system.[1] In this issue of the *Rhode Island Medical Journal* (RIMJ), Dr. Rami Kantor and his group provide an especially important update on COVID-19 variants in RI.[2] Dr. Kantor's group examines variants of concern (VOCs) in our area, and helps us understand the dynamics of the pandemic while forming some important projections. The report highlights the dramatic increase in cases that coincided with the Omicron wave that spread quickly throughout the globe in December 2021 and January 2022, followed by a secondary wave in April 2022 that coincided with Omicron subvariants.

Omicron variants and lineages are antigenically distinct compared to early SARS-CoV-2 variants (614G, Alpha, Beta, Gamma, Zeta, Delta and Mu).[3] Months-long COVID-19 infections probably facilitate new variants[4] and the mutations and viral lineages have significant biological effect because they allow the virus to evade antibody responses, either from the vaccine or previous infection. The genetic, antigenic, fitness and clinical variability is now continuing with the Omicron subvariants as the BA.4 and BA.5 sub-lineages are spreading.

In Portugal and other countries, BA.5 is quickly becoming the dominant SARS-CoV-2 variant resulting in a surge in COVID-19 cases. The growth advantage reported for BA.4 and BA.5 suggests that these variants will become dominant, resulting in an increase in COVID-19 cases in the coming weeks.[5] Notably, there are significant differences between different Omicron lineages. For example, the Omicron BA.2 spike protein differs from that of BA.1 and the fusion peptide in BA.2 spike protein is less accessible to antibodies than in BA.1.[6]

Mutations such as L452R and F486V play a key role in the ability of BA.4 and BA.5 to escape immune response and these subvariants resist neutralization by triple-dosed vaccine serum more than BA.1 and BA2.[7] As a result, vaccine efficacy or effectiveness against the Delta variant is 82.8% (95% prediction interval: 68.7–96.0) using the mRNA vaccine platform. Among the sub-lineages of Omicron, the predicted vaccine efficacy or effectiveness against infection seems to be only up to 33.3%.[8] Also, the rapid evolution of the virus has resulted in declining efficacy of monoclonal antibodies against SARS-CoV-2. Natural immunity, and even passive immunotherapy through monoclonal antibodies seems to have not been able to keep up with the rapidly evolving virus.[9]

This is particularly concerning since effective antiviral therapy options are extremely limited, and for advanced disease in hospitalized individuals an effective antiviral remains only a goal. For example, nirmatrelvir is only effective during early stages of the disease among outpatients and recrudescence after nirmatrelvir/ritonavir has been reported.[10] As we move forward, it is likely that we need to expand monitoring for mutations substitutions, such as L50F, E166A and L167F in SARS-CoV-2 that have been linked to resistance to nirmatrelvir.[11,12]

Importantly, the Omicron subvariants have shown substantial resistance to vaccine-induced and infection-induced serum neutralizing activity and the new BA.2.12.1, BA.2.13, BA.4, and BA.5 subvariants that contain Leu452 substitutions show more infectious potential.[13] As a result of this increased ability of the virus to evade immune responses, along with the decrease in public health measures such as masking, and a decrease in booster adoption and waning of immunity, the potential for ongoing waves over the coming winter months is increasing. These changes even alter the Omicron entry process towards a TMPRSS2-independent fusion.[14]

Vaccines provide significant protection from severe infection, hospitalization, and death. In this regard, we are expecting the need for additional booster vaccinations and the use of the upcoming Omicron-based vaccine. However, even BA.1-derived vaccine boosters may not achieve broad-spectrum protection against new Omicron variants[15] and future surveillance needs to monitor if Omicron (or other emerging variants) evolve further to evade the humoral immunity.

This environment is particularly concerning for those who are immunosuppressed, individuals of older age, and those with comorbid conditions. For example, immunological changes after infection in aged individuals, along with the inability to mount a proper anti-viral response, can exacerbate disease severity in older patients.[16] Surveillance is also needed in order to monitor for any increase in cases in the population, especially with the decrease in adherence to infection prevention policies, the increase in travel, and the waning immunity to initial vaccinations.

Surveillance data need to be correlated with clinical metrics on admissions and disease severity. Even though Omicron variant infections are associated with substantially

reduced risk of progression to severe clinical outcomes relative to time-matched Delta (B.1.617.2) variant infections[17], the concerning possibility is that future variants with large antigenic distance from currently circulating and vaccine strains will not necessarily display the lower intrinsic severity seen during Omicron infection.[18] Also, reinfections need to be monitored as previous infection seems to alter the immune response to newer variants. For example, infection with the earlier B.1.1.7 (Alpha) variant may have resulted in less durable binding antibody against Omicron.[19] The impact in post-acute ("long") COVID-19 should also be monitored. Even though risk of long-COVID-19 appears to be lower with Omicron,[20] the high number of cases could have extensive clinical and social ramifications.

Specific surveillance should monitor COVID-19 case rates among the more vulnerable groups, as well as severity indicators and the interconnection between different viral waves. Studies in animals suggest that co-infection with SARS-CoV-2 and the influenza virus is associated with altered disease severity and tissue tropism, as well as hematological changes, compared to infection with either virus alone.[21]

As we continue to work on new antiviral agents, immunomodulatory treatments, and pan-β-coronavirus and intranasal vaccines, for the immediate and midterm future we should prepare for ongoing evolution of the virus with upcoming waves for the forthcoming winter months. The public, as well as those working in health care, are exhausted and our lives have been disrupted. However, the end of the pandemic and the return to normalcy is not a decision we can make.

The summer should help control case numbers, but the fall and winter months are likely to bring another wave of cases. Complex decisions will need to consider the health of the community and the most vulnerable populations, the economy, and the long-term ramifications from post-acute ("long") COVID-19. Improving COVID-19 vaccine uptake (including appropriate boosters) remains a priority. It is expected that additional booster doses will be needed at least for those at higher risk of severe disease. Ongoing adherence to vaccination protocols and early diagnosis and infection prevention measures provide what we need in order to fight the COVID-19 pandemic over the next few months.

Monitoring for SARS-CoV-2 lineages and sub-lineages is going to provide actionable and valuable information so that we can project waves, prepare our health care facilities, and inform those who are more vulnerable from COVID-19. In this regard, for our state the monitoring is based on the collaboration between the Rhode Island Department of Health, hospitals, health centers, laboratories, and academic groups such as Dr. Kantor's, and this collaboration provides important, actionable information that should continue to inform our decisions and protect our community. The extent of the increase in future cases will depend on vaccination coverage, previous SARS-CoV-2 pandemic waves, and our ability to leverage surveillance to actionable information and sensible infection-prevention policies.

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