COMMENTARY

SARS-CoV-2 Variants and Vaccination

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused global destruction since its emergence in late 2019. Over the past 2 years, the virus has continually evolved in human hosts, thus leading to the emergence of variants with altered viral transmission, disease severity, and evasion of immunity. Although vaccines for coronavirus disease 2019 (COVID-19) have been developed at an unprecedented pace, the emergence of variants has posed a constant threat to the effectiveness of the approved vaccines. In this Commentary, we review the key variants and discuss their implications in viral replication, transmission, and immune evasion.

Key words: SARS-CoV-2 variants, spike mutations, neutralization, vaccine, COVID-19

DOMINANT SARS-COV-2 VARIANTS

Among all SARS-CoV-2 strains, some notable variants have fitness advantages and have outcompeted other variants during viral evolution. The first dominant spike (S) protein D614G substitution increases viral replication in the human upper respiratory tract; this mutant rapidly replaced nearly all prior SARS-CoV-2 strains from June 2020 onward [4]. Subsequently, the Alpha variant (B.1.1.7 lineage) first reported in the United Kingdom and quickly spread to many parts of the world, owing to its increased binding affinity for human ACE2 receptor [5-7]. Next, the Delta variant (B.1.617.2 lineage) first reported in India in October 2020, spread rapidly, and displaced the Alpha variants worldwide [8-10]. Recently, the heavily mutated Omicron variant, first detected in South Africa in November 2021, has explosively spread to many countries and led to global Omicron surges [11-13].

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observations, the Omicron variant is transmitted much more rapidly than the Delta variant, with a case doubling time as short as 1.5–3 days. In addition, Omicron can escape many monoclonal antibodies and evade vaccine-elicited neutralization [14–16]. Furthermore, infection with previous non-Omicron variants does not appear to elicit robust neutralization against Omicron [17]. However, booster vaccination (e.g., a third dose of the Pfizer/BioNTech vaccine or a booster dose of the Moderna vaccine) elicits good neutralization against Omicron [18], thus supporting a booster vaccination strategy. The durability of the protective immunity of booster vaccination against Omicron remains to be determined. Omicron’s high transmissibility and immune evasion have enabled it to become the new dominant SARS-CoV-2 variant. More than 1 million cases in a single day have been recorded in the United States (Fig 1).

NOTABLE MUTATIONS IN THE S PROTEIN

The trimeric S glycoprotein of coronaviruses is the major surface protein present on the viral envelope [19]. Mature S protein, formed through cleavage by furin and transmembrane serine protease 2 (TMPRSS2), mediates viral binding to the ACE2 receptor, entry, and immune escape. Thus, S protein is considered the key determinant of viral infectivity and transmissibility [20]. The D614G substitution is the first dominant mutation that occurred in the S protein. Elevated quantities of D614G virus have been detected in the respiratory tracts in both patients and animal models, thus indicating this mutant’s higher infectivity and transmissibility [21,22]. Another mutation, N501Y, located at the receptor-binding domain in the S protein, has been demonstrated to be the most important amino acid substitution in the Alpha variant. The N501Y substitution markedly increases the binding affinity to the human ACE2 receptor, thus leading to rapid infection in the upper respiratory tract and higher viral transmission [7,23]. The Delta variant has the spike mutation P681R, which is located at a furin-cleavage site in the S protein. Experimental results in human primary airway epithelial culture and animal models have demonstrated that the P681R substitution enhances viral replication and infection, possibly through increasing the furin cleavage of the full-length S protein into S1 and S2 subunits [10,24]. Many other amino acid changes in the S protein, including S13I, L18F, 69–70 deletion, W152C, K417N/T, N439K, N440K, L452R, Y453F, S477G/N/R, E484K/Q/P, S494P, and H655Y, have been reported to decrease vaccinated serum neutralization and monoclonal-antibody inhibition, and/or increase viral infection and transmission (Table 1). The Omicron variant contains more than 30 mutations in the S protein, several of which are present in other variants of concern, including Alpha, Beta, Gamma, and Delta [39]. Some of these mutations, including 69–70 deletion, K417N, N440K, S477N, E484A, N501Y, D614G, H655Y, and P681H, have been well studied and are known to enhance viral infectivity, transmissibility, and immune escape, thus leading to high concern regarding the pandemic’s potential severity resulting from ongoing Omicron surges.

NEUTRALIZATION OF SARS-COV-2 VARIANTS AND VACCINE STRATEGIES

Several COVID-19 vaccines have been approved and used for immunization globally to develop herd immunity against COVID-19 [40]. The Pfizer/BioNTech BNT162b2 nucleoside-modified mRNA vaccine is one of the most common vaccines, which has been widely used in North America and Europe [41]. Because of the high mutation frequency of SARS-CoV-2 S protein, some newly emerged variants have diminished susceptibility to neutralization by antibodies generated by vaccination or natural infection. Several approaches have been used to measure the neutralization sensitivity of variants to human sera, including pseudotype virus for expression of SARS-CoV-2 S protein, clinical viral
isolates, and chimeric SARS-CoV-2 bearing the S protein from different variants [13,14,42]. Among these approaches, the use of chimeric SARS-CoV-2 bearing variant S has two major advantages. First, this approach does not require waiting for the isolation of clinical viral strains; as soon as the S sequence is available, the variant S sequence can be synthesized and engineered into the original SARS-CoV-2 backbone [43]. Second, in this approach, in contrast to the pseudovirus approach, the chimeric virus is an authentic SARS-CoV-2. The 50% plaque-reduction neutralization titer against various recombinant viruses can be easily tested and accurately compared among all variants. The Alpha variants have higher infection and transmission efficiency, but the neutralization titers are approximately equivalent to those of the WT strain [42]. The D614G and representative Delta variants exhibit modestly lower neutralization titers than the WT virus [44,45]. Unfortunately, two doses of the Pfizer vaccine are insufficient to induce robust antibody neutralization against the Omicron variant [46]. The above studies were all performed on the same set of human sera collected 2 or 4 weeks after the administration of two doses of the Pfizer vaccine (Fig 2). Many other studies have also demonstrated that the neutralization titers of infected and vaccinated people are significantly lower against Omicron than the WT virus [17,18]. However, as described above, a third dose of the Pfizer vaccine increases the magnitude and breadth of neutralization, thus leading to robust neutralization against the Omicron variant [18,46,47]. To date, the

### TABLE 1 | Notable mutations increasing SARS-CoV-2 infectivity, transmissibility, and immune escape.

<table>
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<tr>
<th>Mutations</th>
<th>Locations</th>
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<td>del69–70</td>
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<tr>
<td>W152C</td>
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</tr>
<tr>
<td>K417N/T</td>
<td>Receptor-binding domain</td>
<td>Beta, Gamma, Omicron</td>
<td>Attenuated binding affinity to ACE2/immune escape</td>
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</tr>
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<td>N439K</td>
<td>Receptor-binding domain</td>
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<td>Y453F</td>
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<tr>
<td>S477G/N/R</td>
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<tr>
<td>E484K/Q/P</td>
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<td>Alpha</td>
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<tr>
<td>N501Y</td>
<td>Receptor-binding domain</td>
<td>Alpha, Beta, Gamma, Mu, Omicron</td>
<td>Increased infection and transmissibility</td>
<td>[7,28]</td>
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<tr>
<td>D614G</td>
<td>The C-terminal of S1 domain</td>
<td>All lineages</td>
<td>Increased infectivity</td>
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<td>H655Y</td>
<td>Near S1/S2 cleavage site</td>
<td>Gamma, Omicron</td>
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<tr>
<td>P681H/R</td>
<td>Near S1/S2 cleavage site</td>
<td>Alpha, Kappa, Mu, Omicron</td>
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<td>[10]</td>
</tr>
</tbody>
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*Omicron is underlined to indicate multiple mutations and deletions with respect to other variants.

![FIGURE 2 | Serum neutralization titers of different lineages of SARS-CoV-2.](image-url)

The D614G mutation or genes encoding S protein from different lineages of SARS-CoV-2 were engineered into the USA-WA1/2020 backbone. The 50% plaque-reduction neutralization testing (PRNT<sub>50</sub>) for 20 samples obtained from 15 trial participants after administration of the second dose of the BNT162b2 vaccine is shown. Each data point represents the geometric mean PRNT<sub>50</sub> obtained with a serum sample against the indicated virus. The heights of bars and the numbers over the bars indicate geometric mean titers. The error bars indicate 95% confidence intervals.
neutralization level has been found to remain robust as long as 4 months after the third dose of the Pfizer vaccine; however, the durability of neutralization beyond 4 months after the third dose remains to be determined [46]. These results support a two-pronged vaccine strategy against Omicron and other newly emerged variants, involving (i) booster vaccination with the currently approved safe vaccines and (ii) modification of the vaccine S sequences to match those of Omicron and new variants. The mRNA vaccine technology allows for rapid modification of the S sequence. Real-world vaccine effectiveness data and laboratory studies are needed to guide the implementation of this two-pronged vaccine strategy.

Two years have elapsed since the onset of the COVID-19 pandemic, and various SARS-CoV-2 variants, in turns, have dominated viral transmission and surged. The current Omicron surge may not be the last. Although some variants have become able to escape immune protection from vaccination and/or natural infection [43–45,48], compelling evidence demonstrates that vaccination minimizes the risk of severe disease, and lowers the rates of hospitalization and death [49,50]. Thus, mass immunization and administration of booster shots with highly effective and safe vaccines, together with mask wearing and social distancing, will continue to be the most effective strategies to finally end the COVID-19 pandemic.

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COMPETING INTERESTS

P.-Y.S. has filed a patent on the reverse genetic system of SARS-CoV-2. The laboratory of P.-Y.S. has received funding support in the third dose remains to be determined [46]. These results support a two-pronged vaccine strategy against Omicron and other newly emerged variants, involving (i) booster vaccination with the currently approved safe vaccines and (ii) modification of the vaccine S sequences to match those of Omicron and new variants. The mRNA vaccine technology allows for rapid modification of the S sequence. Real-world vaccine effectiveness data and laboratory studies are needed to guide the implementation of this two-pronged vaccine strategy.

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