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LETTER

Emerging SARS-CoV-2 variants: impact on vaccine efficacy and neutralizing antibodies

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ABSTRACT

The genetic variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been emerging and circulating in different parts of the world from the beginning of the coronavirus disease (COVID-19) pandemic. Variants are divided into three classes: variant of interest, variant of concern, and variant of high consequence depending on its impact on the transmission, disease severity, diagnostics, vaccines, and therapeutics. The variants of concern include the United Kingdom variant (B.1.1.7), South Africa variant (B.1.351), two related California variants (B.1.427 and B.1.429), and Brazil variant (P.1). These SARS-CoV-2 variants have a direct impact on the available COVID-19 vaccines and immunotherapeutics as they can alter the neutralizing activity of vaccine-elicited antibodies and monoclonal antibodies resulting in mild-to-substantial loss of efficacy. There is a need to establish surveillance systems that can monitor the emergence of novel SARS-CoV-2 variants worldwide.

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Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has already affected 131.3 millions[1] people, resulting in the death of 2.8 million[1] individuals globally as of April 4, 2021. SARS-CoV-2 has spread rapidly worldwide over the past 1 year, causing clusters of cases that can be linked to the importation of cases across international borders, mainly via air travel.[1] Although RNA viruses are reported to accumulate mutations rapidly because they replicate inside their hosts, SARS-CoV-2 mutates much slower than other RNA viruses. The nucleotide substitution rate of SARS-CoV-2 roughly estimates to 1×10^{-3} substitutions per year, almost similar to that of the Ebola virus (1.42×10^{-3}).[2] Coronaviruses, including SARS-CoV-2, can generate novel variants by accumulating point mutations, recombination, insertions, and deletions within the genome. Such changes might a have direct impact on the pathogenesis, transmission potential, and disease severity. Furthermore, mutations in the spike protein can alter the interaction with human cell-surface angiotensin-converting enzyme 2 receptors.[2]

Since the beginning of this pandemic, genetic variants of SARS-CoV-2 have been emerging and circulating in different parts of the world. However, toward the end of 2020, several novel variants with superior transmission potential and infectivity have been reported, which were associated with a severe form of the disease.[3] These variants had one or more mutations/spike protein substitutions that helped to differentiate them from other variants in circulation. For ease of understanding, these variants were divided into three classes: variant of interest, variant of concern (VOC), and variant of high consequence (Table 1).[3] The inclusion of a novel variant into one of these classes depends on its impact on transmission, disease severity, diagnostics, vaccines, and therapeutics. Therefore, the status of a variant might escalate or de-escalate depending on the most recent scientific evidence.

As of March 27, 2021, VOC includes the United Kingdom variant (B.1.1.7), South Africa variant (B.1.351), two related California variants (B.1.427 and B.1.429), and Brazil variant (P.1).[3] Compared to the SARS-CoV-2 Wuhan reference sequence, all current VOCs have the D614G substitution (Table 1). SARS-CoV-2 containing the D614G substitution in the spike protein is the predominant circulating variant. Experimental studies have confirmed that the SARS-CoV-2 variant containing D614G substitution has enhanced ACE2-binding ability, with increased replication in human ACE2 knock-in mouse model and *in vitro* cultures (nasal airway epithelial and primary human bronchial cultures).[4] D614G substitution was also found to enhance the replication and transmissibility of SARS-CoV-2 in hamster and ferret models.[4] In addition to the human-to-human transmission, the rapid transmission of SARS-CoV-2 in non-human hosts such as farmed minks can result in the emergence of novel variants that can later transmit back to humans.[5] The mink-associated variant identified in both minks and humans was later referred to as "Cluster 5." However, only 12 human cases have been reported in Denmark.[6] Owing to efficient preventive measures, such as the implementation of lockdown and mass testing, Cluster 5

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Table 1. Major SARS-CoV-2 variants and their characteristic features.

Name (Pango lineage)	Name (Nextstrain)[a]	First detected	Spike protein substitutions[b]	Characteristics	Vaccine efficacy	Neutralizing antibody efficacy
Variants of Concern (B.1.1.7, B.1.351, B.1.427, B.1.429, and P.1)						
B.1.1.7	20I/501Y.V1	United Kingdom	Δ69/70 Δ144Y N501Y A570D D614G P681H E484K* S494P*	The variant is associated with ~50% increased transmission.[7] The variant has higher reproduction number than that of preexisting variants.[7] The variant binds with ACE2 with two-fold greater affinity than the original receptor binding domain.[8] The risk of mortality is increased compared with that associated with previously circulating variants.[9]	The presence of E484K mutation in B.1.1.7 variant led to a substantial loss of neutralizing activity by vaccine-elicited antibodies (BNT162b2).[10] This variant remained sensitive (but at moderately reduced levels) to neutralization by serum samples from recipients of mRNA-1273 (Moderna) and NVX-CoV2373 (Novavax) vaccine.[11] The AZD1222 vaccine (Oxford-AstraZeneca) efficacy against COVID-19 due to the B.1.1.7 variant was reported to be 74.6% (non-B1.1.7, 84%).[12] The inactivated COVID-19 vaccine BBV152 (Bharat Biotech)-elicited antibodies retained neutralizing activity against B 1.1.7 variant.[13]	This variant showed decreased neutralization with monoclonal antibodies targeting the N-terminal domain.[10] A subset of monoclonal antibodies targeting receptor-binding domain of spike protein are less effective against the variant.[11]
B.1.351	20H/501.V2	South Africa	K417N E484K N501Y D614G	The variant binds with ACE2 with five-fold greater affinity than the original receptor-binding domain.[8] This variant is associated with ~50% increased transmission.[14]	Reduction in the neutralization capacity of sera from mRNA-1273 vaccinated individuals was observed.[15] The neutralizing activity of the sera was found to be significantly lowered in mRNA-1273 (12.4 fold) and BNT162b2 (10.3 fold) vaccinated individuals.[16] A 9.5-fold reduction in the virus neutralizing antibody titer was observed in AZD1222 vaccinated (Oxford-AstraZeneca) hamster sera against B.1.351 compared with B.1.1.7.[17] The AZD1222 vaccine efficacy against mild-to-moderate COVID-19 due to the B.1.351 variant was reported to be only 10.4%.[18]	The variant is refractory to neutralization by most monoclonal antibodies targeting N-terminal domain and receptor-binding motif on RBD due to the E484K mutation.[16]
B.1.427	20C/S:452R	United States (California)	L452R D614G	B.1.427/B.1.429 exhibited an 18.6–24% increase in transmissibility compared with wild-type strains.[19] A 2-fold increase in the B.1.427/B.1.429 viral shedding was also observed *in vivo*.[19]	Antibody neutralization assays showed 2.0-fold decrease in the neutralizing titers from vaccine recipients (mRNA-1273 and BNT162b2).[19]	Antibody neutralization assays showed 4.0–6.7-fold decrease in the neutralizing titers from convalescent patients.[19]
B.1.429	20C/S:452R	United States (California)	S13I W152C L452R D614G			
P.1	20J/501Y.V3	Japan/Brazil	K417N/T E484K N501Y D614G	The emergence of P.1 lineage was linked to a rapid increase in COVID-19 cases and associated hospitalization.[20]	The variant exhibited more resistance to neutralization by vaccine sera from mRNA-1273 (2.8 fold) and BNT162b2 (2.2 fold) vaccinated individuals.[21]	The variant is refractory to multiple neutralizing monoclonal antibodies. It is also resistant (6.5 fold) to neutralization by convalescent plasma.[21] The neutralizing activities of REGN10933 (casirivimab), CB6 (etesevimab), and LY-CoV555 (bamlanivimab) were markedly or completely abolished.[21]
Variants of Interest (B.1.525, B.1.526, and P.2)						
B.1.525	20C	United States (New York)	A67V Δ69/70 Δ144 E484K D614G Q677H F888L	It is now designated as variant under investigation and will undergo risk assessment studies. It may be re-designated as Variant of Concern (VOC).	Potential for reducing the neutralization by convalescent and post-vaccination sera.[3]	Potential for reducing the neutralization by monoclonal antibody treatments.[3]

(*Continued*)

Table 1. (Continued).

Name (Pango lineage)	Name (Nextstrain)[a]	First detected	Spike protein substitutions[b]	Characteristics	Vaccine efficacy	Neutralizing antibody efficacy
B.1.526	20C	United States (New York)	T95I D253G D614G A701V* S477N* E484K* L5F*	This variant has multiple mutations that might facilitate SARS-CoV-2 infection and spread.[22]	Recent findings indicate that current vaccines will remain protective against the B.1.526 variant.[23]	Recent findings indicate that current therapeutic monoclonal antibodies will remain protective against the B.1.526 variants.[23]
P.2	20J	Brazil	E484K D614G V1176F	No data	Potential for reducing the neutralization by convalescent and post-vaccination sera.[3]	Potential for reducing the neutralization by monoclonal antibody treatments.[3]

Variant of High Consequence (Currently, there are no SARS-CoV-2 variants that has the potential to attain the level of high consequence)

*Detected in some sequence.
[a]https://nextstrain.org/
[b]https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

is not in circulation in the human population and is therefore considered extinct.

SARS-CoV-2 variants, especially VOCs, pose a threat to the ongoing efforts to control the COVID-19 pandemic. Some of the variants may even possess superior transmission potential, altered pathogenesis and disease severity and can be linked to the rapid increase in COVID-19 cases and associated hospitalization. The VOCs have a direct impact on the available COVID-19 vaccines and immunotherapeutics by altering the neutralizing activity of vaccine-elicited antibodies and monoclonal antibodies resulting in mild-to-substantial loss of efficacy. Currently, there are no SARS-CoV-2 variants having the potential to attain the level of high consequence to be classified under "variant of high consequence." However, the possibility of the emergence of such a variant cannot be excluded in the future. Therefore, it is necessary to establish surveillance systems that can monitor the emergence of novel SARS-CoV-2 variants worldwide. This will ensure that even if novel variants of high consequence emerge, they can be prevented from spreading globally by implementing prevention and control measures at an early stage.

Note

1. https://www.worldometers.info/coronavirus/.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Author contributions

KS and KD conceptualized the manuscript; KS wrote the first draft with input from KD. RT, TBE, AAR and AAM reviewed and updated the manuscript. All authors contributed to revisions and approved the final manuscript.

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