SARS-CoV-2 vaccines and their challenges against the variants

Umid Kumar Shrestha*
Nepal Mediciti Hospital, Bhaisepati, Lalitpur, Nepal

Keywords: COVID-19; SARS-CoV-2; vaccines; variants; mutation

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has lead to the several researches for the development of the new severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) vaccines, namely mRNA vaccine, viral vector vaccine, recombinant protein vaccine and inactivated vaccine, with an objective to achieve the response which include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease. Over a course of time, the SARS-CoV-2 virus has evolved and lead to mutations; the virus with one or more new mutations is referred to as a "variant" of the original virus. All new strains (P.1 from Brazil, B.1.351 from South Africa, B.1.1.7 from the UK and B.1.617 from India) have mutations in the spike protein, resulting in the threat to the effectiveness of the current available first generation vaccines. Hence, there might be the need of the development of the modified next generation of vaccines, which take care of all those variants. Nevertheless, the current first generation vaccines may still provide satisfying immunity against SARS-CoV-2 variants. Most vaccines are expected to provide protection against hospitalizations/deaths from these variants and a booster vaccine against these variants is likely to be effective. Hence, the current vaccination must proceed. As we are aware that the more the virus spreads, the more variants are likely to appear. In order to stop the spread of SARS-CoV-2 variants, it is important to get the vaccines once it is available and not to forget about the need to wash hands frequently, keep at least 1m distance from others and wear a mask. With the development of the effective SARS-CoV-2 vaccines and implementation of public health measures, we can surely defeat SARS-CoV-2 virus in COVID-19 battle and end this pandemic.

The coronavirus disease 2019 (COVID-19) pandemic has lead to the several researches for the development of the new severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) vaccines. During this process, spike (S) protein (particularly in its prefusion [native] conformation) was identified as the immunodominant antigen of the SARS-CoV 2 virus[1]; it was found that the binding and neutralizing antibodies primarily target the receptor-binding domain (RBD) of the S1 subunit.[2] After identifying the vaccine target, several SARS-CoV-2 vaccines were developed with an objective to achieve the response which include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease.

The SARS-CoV-2 vaccines that have been developed to combat COVID-19 are shown in the table 1.[3]

Over a course of time, the SARS-CoV-2 evolve and lead to mutations; the virus with one or more new mutations is referred to as a "variant" of the original virus. The new SARS-CoV-2 variants B.1.427 and B.1.429 (the "California" or "West Coast" variants) share S gene non-synonymous mutations at sites 13, 152, 452, and 614 and were seen during the December 2020 to February 2021 period when California was experiencing a huge peak. A modest increase in transmissibility was noted in those variants.[4] The B.1.1.7 variant (also known as 501Y.V1, having a N501Y mutation in the RBD) emerged in the UK.[5] N501Y signifies that there is a change in their

*Corresponding Author:
Umid Kumar Shrestha, MD, PhD
Nepal Mediciti Hospital, Bhaisepati, Lalitpur, Nepal
E-mail: umidshrestha@gmail.com

501st amino acid from asparagine (an amide-containing amino acid) to tyrosine (a phenol-containing amino acid). This variant has eight spike mutations that include two deletions, one of which is in an antibody supersite epitope (Y144) and the other of which increases infectivity but has little impact on immune escape.[1] The sole RBD mutation is N501Y, which also seems to increase binding to the host cell receptor ACE2. The epidemiological studies showed that B.1.1.7 was more transmissible.[6]

Table 1: SARS-Co-V-2 vaccines

Vaccine name	Developer	Antigens
mRNA vaccine:		
BNT162b1	BioNTech/Pfizer	RBD trimer
BNT162b2	BioNTech/Pfizer	S-full length (pre-fusion)
mRNA-1273	Moderna	S-full length (pre-fusion)
Viral vector vaccine:		
Ad5-nCoV	CanSino	S-full length
Ad26.COV2.S	Janssen/Johnson & Johnson	S-full length (pre-fusion)
AZD-1222 / ChAdOx1-S	Oxford/AstraZeneca (brand name COVISHIELD) is manufactured by Serum Institute of India in collaboration with Oxford/ AstraZeneca)	S-full length
Sputnik-V	Gamaleya	S-full length
Recombinant protein vaccine:		
NVX-CoV2373	Novavax	S-full length (pre-fusion)
Inactivated vaccine:		
Inactivated vaccine (Vero cell)	Wuhan Institute of Biological Products (WIBP)	Inactivated SARS-CoV2 protein
BIBP-CorV (Vero cell)	Beijing Institute of Biological Products (BIBP)	Inactivated SARS-CoV2 protein
CoronaVac (Vero cell)	Sinovac	Inactivated SARS-CoV2 protein
Inactivated vaccine (Vero cell)	Institute of Medical Biology, Chinese Academy of Medical Sciences (IMBCAMS)	Inactivated SARS-CoV2 protein

The two variants, B.1.351 and P.1 variants (also known as 501Y.V2 and 501Y.V3) emerged in South Africa and Brazil having additional mutations in the RBD at positions E484 and K417, respectively. Viral variants with the triple combination of N501Y, E484K and K417N/T have significantly reduced susceptibility to vaccine-induced and convalescent sera.[7] Other variants of concern are P.3 in the Philippines, B.1.526 in the USA and B.1.525 in the UK and west Africa, having mutations of N501Y and E484K. The new variant, called B.1.617, was initially detected in India with two mutations - the E484Q and L452R. In addition to these RBD mutations, a neglected area of SARS-CoV-2 evolution pertains to the amino-terminal domain (NTD) mutations in spike protein, which lead to the reduced sensitivity to neutralizing antibodies.

The AstraZeneca ChAdOx1 vaccine showed only 10% protection against mild-to-moderate disease associated with the B.1.351 variant in a young population with median age of 30 in South Africa.[8] By contrast, in the UK, ChAdOx1 demonstrated 75% protection against B.1.1.7 (including asymptomatic infection). The Novavax vaccine, which consists of purified spike protein, showed approximately 50% protection against infection in South Africa (largely the B.1.351 variant) and 86% protection against infection in the UK (predominantly the B.1.1.7 variant).[9] Johnson & Johnson's human adenovirus-vectored vaccine showed 64% protection against moderate-to-severe disease in South Africa (dominated by the B.1.351 variant) and 66% protection against moderate-to-severe disease in the USA (mainly the Wuhan-1 variant with D614G), as assessed 29 days after vaccination.[10] The Pfizer/BioNTech BNT162b2 mRNA vaccine was reported to be less effective against B.1.351 than against non-B.1.351 variants based on a small analysis of breakthrough infections that were enriched for B.1.351 in Israel.[11] The efficacy of CoronaVac/Sinovac inactivated virus vaccine in Brazil, where 75% of infections were with the P.1 variant, was estimated at around 50% against symptomatic infection.[12]

The SARS-CoV-2 S protein has been the target of most first-generation vaccines, almost exclusively using the D614 sequence, an early variant with an aspartic acid (D) to glycine (G) mutation at position 614, D614G. The recent fast-spreading variants-including the B.1.1.7 (501Y.V1) lineage from the UK, the B.1.351 (501Y.V2) lineage from South Africa, and the B.1.1.28 (484K.V2; P.1) lineage from Brazil all contain the D614G substitution. The enhanced infectivity of the G614 virus largely results from the increased stability of the S trimer, rather than the better-exposed RBDs.[13] As the G614 strain has become dominant, the current first generation vaccines are constrained and may not target the prefusion form of the spike protein. Hence, next-generation vaccines including G614 strain would need to be designed to overcome such variants.

The mutations that would need to be included in a modified next generation of vaccines are E484K, N501Y and L452R mutations in the RBD (L452R being found in the recently reported B.1.617 variant emerging in India and in the B.1.429 variant that has emerged in the USA), and P681H/R mutation in the furin cleavage site (which is found in the B.1.1.7 variant) as well as NTD deletions.[14] Regularly updated consensus document from the World Health Organization should be published about the mutations to be included in the next generation of vaccines.

Despite the challenges imposed by the new variants, the current first generation vaccines may still provide satisfying immunity against SARS-CoV-2 variants. Most vaccines are expected to provide protection against hospitalizations/deaths from these variants and a booster vaccine against these variants is likely to be effective.

Hence, the vaccination must proceed. As we are aware that the more the virus spreads, the more variants are likely to appear. In order to stop the spread of SARS-CoV-2 variants, it is important to get the vaccines once it is available and not to forget about the need to wash hands frequently, keep at least 1m distance from others and wear a mask. With the development of the effective SARS-CoV-2 vaccines and implementation of public health measures, we can surely defeat SARS-CoV-2 in COVID-19 battle and end this pandemic.

May 2, 2021

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