

## REVIEW

# Development of antibody resistance in emerging mutant strains of SARS CoV-2: Impediment for COVID-19 vaccines

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## Abstract

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a highly infectious agent associated with unprecedented morbidity and mortality. A failure to stop growth of COVID-19-linked morbidity rates is caused by SARS-CoV-2 mutations and the emergence of new highly virulent SARS-CoV-2 strains. Several acquired SARS-CoV-2 mutations reflect viral adaptations to host immune defence. Mutations in the virus Spike-protein were associated with the lowered effectiveness of current preventive therapies, including vaccines. Recent in vitro studies detected diminished neutralisation capacity of vaccine-induced antibodies, which are targeted to bind Spike receptor-binding and N-terminal domains in the emerging strains. Lower than expected inhibitory activity of antibodies was reported against viruses with E484K Spike mutation, including B.1.1.7 (UK), P.1 (Brazil), B.1.351 (South African), and new Omicron variant (B.1.1.529) with E484A mutation. The vaccine effectiveness is yet to be examined against new mutant strains of SARS-CoV-2 originating in Europe, Nigeria, Brazil, South Africa, and India. To prevent the loss of anti-viral protection in vivo, often defined as antibody resistance, it is required to target highly conserved viral sequences (including Spike protein) and enhance the potency of antibody cocktails. In this review, we assess the reported mutation-acquiring potential of coronaviruses and compare efficacies of current COVID-19 vaccines against 'parent' and 'mutant' strains of SARS-CoV-2 (Kappa (B.1.617.1), Delta (B.1.617.2), and Omicron (B.1.1.529)).

## KEYWORDS

antibody resistance, COVID-19, mutant variants of concerns, SARS-CoV-2 strains, vaccine

**Abbreviations:** ExoN, exoribonuclease; NTD, N-terminal domain; ORF, open reading frame; RBD, receptor binding domain; TMPRSS2, Transmembrane protease serine 2 precursor; VOCs, variants of concerns.

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## 1 | INTRODUCTION

The causative agent of 21st century pandemic (2019–2021 ongoing), severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), belongs to *Coronaviridae* family in *Nidovirales* order of enveloped viruses [mad1]. There are four genera of coronaviruses in the family (sub-family of *Orthocoronavirinae*):(a) alpha-coronavirus (alpha-CoV or Alpha) (alternative names:201/501Y.V1, VOC-202012/01), (b) beta-coronavirus (also known as Sarbecovirus,<sup>1</sup> 20H/501Y.V2, VOC-202012/02)(beta-CoV or Beta), (c) gamma-coronavirus (gamma-CoV or Gamma) (alternative names: 20J/501Y.V3, VOC-202101/02), and (d) delta-coronavirus (delta-CoV or Delta) (alternative names: VOC-21APR-03, G/452R.V3, 21A/S:478K).<sup>2</sup> Alpha- and beta-CoVs can infect bats, pigs, cats, mice, and humans,<sup>3–9</sup> whereas the gamma- and delta-CoVs were shown to infect birds and mammals<sup>10–13</sup> (Table 1). Recently classified coronaviruses (the family *Coronaviridae*) are represented by 45 species (the latest confirmed count, 4 August 2021<sup>15</sup>) that are grouped in 25 subgenera and 4 genera.<sup>16</sup> The significant changes in CoV taxonomy happened during 2021 years and 39 species (27 subgenera and five genera) were reported in 2020.<sup>15</sup> The list of species is most likely will be extended and adjusted, considering that during 15-year period (2003–2018) 339 SARS-CoV genomes were identified, including 274 CoV genomes from humans.<sup>1</sup> The most recent addition is Omicron variant<sup>17</sup> which is required to be classified by International Committee on Taxonomy of Viruses. For some CoVs discovered in metagenomics studies, host and virus pathogenicity remains unknown,<sup>18</sup> while the genome sequence is the only known characteristic.<sup>15</sup> Currently, 58 complete genome sequences have been reported for *Orthocoronavirinae* subfamily including 24 genomes for alpha-CoVs, 18 for beta-CoVs, 10 for delta-CoVs, 5 for gamma-CoVs, and yet-to-be-identified number of subfamilies for Omicron (Table 1).<sup>19–22</sup> Increasing population immunity, a product of natural infections and immunizations, is predicted to amplify the selection pressure on the mutating virus and increase the evolution of mutants towards emergence of antibody resistant strains.

Human coronavirus NL63 (HCoV-NL63) and 229E (HCoV-229E) were identified as alpha-CoVs.<sup>23,24</sup> Human coronavirus HKU1 (HCoV-HKU1), OC43 (HCoV-OC43, SARS-CoV, MERS-CoV), and SARS-CoV-2 (the causative agent of coronavirus disease 2019 (COVID-19)) were grouped as beta-CoVs.<sup>25–32</sup> The phylogenetic analysis of CoVs revealed that SARS-CoV-2 is more closely related to bat-SL-CoV ZXC21 and bat-SL-CoV ZC45, and more distantly related to SARS-CoV.<sup>33</sup> Beta- (HCoV-OC43 and HCoV-HKU1) and alpha-CoVs (HCoV-229E and HCoVNL63) were shown to infect the upper respiratory tract and cause mild respiratory diseases in humans and animals.<sup>13,15–23</sup> Similar infection-related symptoms were recorded for the most recent variant (Omicron).<sup>17</sup> The lower respiratory tract infection with SARS-CoV, SARS-CoV-2, and MERS-CoV provoked various degrees of respiratory syndromes and extra-respiratory complications in humans.<sup>21,34</sup>

According to the World Health Organization (WHO) statistical report,<sup>35</sup> nearly 350 million COVID-19 infection cases have been

reported on 24 January 2022. The number of SARS-CoV-2-infected patients and related death is constantly growing.<sup>36</sup> The pandemic resulted in nearly 6 million deaths worldwide.<sup>35</sup> COVID-19 infection rate increased globally due to the emergence of mutant SARS-CoV-2 strains and lack of efficient anti-viral agents. In this review, we discuss the integrated genome and emergence of mutant variants of SARS-CoV-2. The efficacy of existing SARS-CoV-2 vaccines is assessed to accentuate the urgent need for the vaccine amendment and design of complex approaches in vaccination schemes. The study also evaluates the progress of SARS-CoV-2 mutations towards development of antibody resistance in mutant strains of this virus. As predicted, emergence of variants of concern (VOCs), including highly infectious delta and omicron strains, indicates direction of viral mutations towards less severe, but more spreadable VOCs. Higher transmissibility was reported for the most recent VOC Omicron (B.1.1.529).<sup>37–39</sup>

## 2 | CORONAVIRUSES (CoVs): STRUCTURAL CHARACTERIZATION

Human-infecting coronaviruses (CoVs) are single positive-stranded RNA viruses (+ssRNA). The presence of 5' cap structure and 3' poly-A tail was detected in CoVs along with 27–32 kbp length of the CoV genome.<sup>40,41</sup> Approximately 2/3rd of SARS-CoV-2 genome is considered as conserved sequence, starting with the replication/transcription-related genes encoded by two large overlapping open reading frames (ORF), such as ORF1a and ORF1b, at 5' terminus (**Graphical abstract**). ORFs are translated into nonstructural proteins by ribosomal frame shifting.<sup>42</sup> The other 1/3<sup>rd</sup> of SARS-CoV-2 genome (at 3' terminus) encodes four important structural components, including spike (S), envelop (E), membrane (M), and nucleocapsid (N) proteins (Figure 1).<sup>43–51</sup> The virus ORF1a and ORF1b codes contain information about polyprotein 1a and 1b that can be consequently cleaved into 16 non-structural proteins (NSP) by specific proteases (chymotrypsin like protease (3CLpro), main protease, and papain like protease.<sup>33,52,53</sup> Genes coding for accessory proteins were also reported in 3' region.<sup>33</sup> HCoV-OC43 and HCoV-HKU1 were shown to encode haemagglutinin esterase (HE) gene.<sup>54–56</sup> CoVs from different viral groups express various numbers of accessory proteins that are not necessary for virus replication, but impact SARS pathogenicity. Notably, six additional ORFs (ORF3a, ORF6, ORF7a, ORF7b, ORF8, and ORF10) that are located between structural genes, may code more accessory proteins.<sup>57</sup> SARS-CoV genome contains codes for eight accessory proteins (3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b).<sup>58,59</sup> Genome of MERS-CoV(≈30 kb) encodes ORF1a (NSP1–11), ORF1b (NSP12–16), four structural proteins (S, E, M, and N), and five accessory proteins (3, 4a, 4b, 5, and 8b).<sup>60</sup> SARS-CoV and MERS-CoV genomes are packed in a capsid structure by N protein, while the other proteins (S, M, and E) form the envelope around the capsid.<sup>61</sup> Debates about the number of accessory proteins in SARS-CoV-2 still continue. For instance, one study reported successful identification of eight predicted accessory protein ORFs (3a, 6, 7a, 7b, 8, 9b, 9c, 10),<sup>62</sup>

TABLE 1 Taxonomic classification of pathogenic coronaviruses and their specific host system

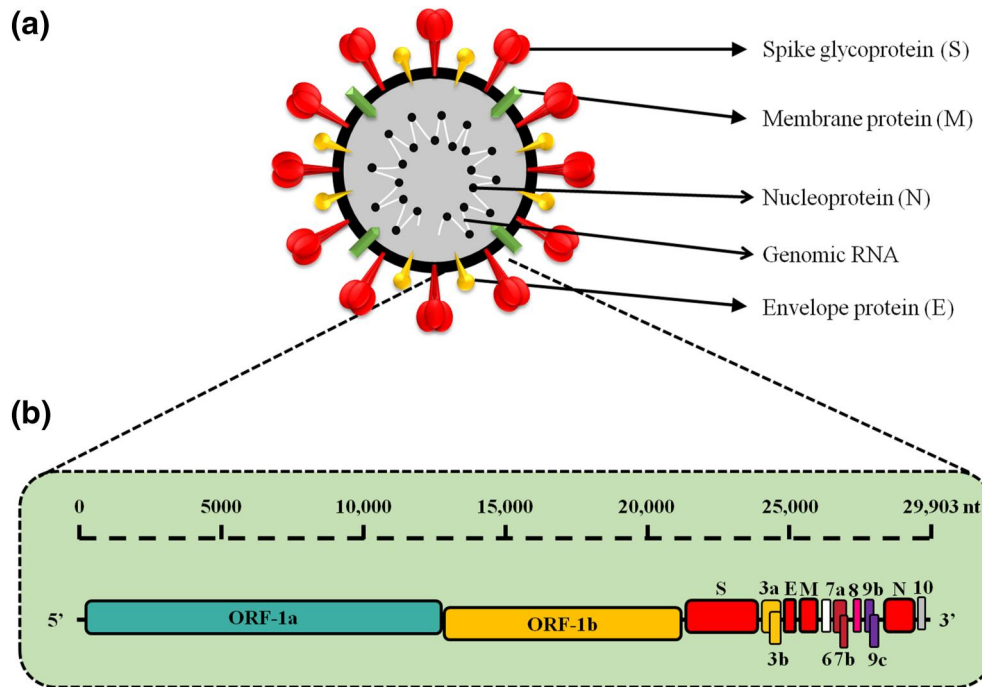
Genera*	Genome	Accession #	Source information	Genome length	Host	
Alpha-coronavirus	Alpha-CoV Bat-CoV/P.kuhlil/Italy/3398-19/2015	NC_046964	strain:Bat-CoV/P.kuhlil/Italy/3398-19/2015	28128 nt	vertebrates	
	Bat CoV 1A	NC_010437	strain:AFCD62	28326 nt	vertebrates	
	Bat CoV CDPHE15/USA/2006	NC_022103	strain:bat/USA/CDPHE15/2006	28035 nt	vertebrates	
	BtMr-AlphaCoV/SAX2011	NC_028811	isolate:BtMr-SAX2011	27935 nt	vertebrates	
	BtNv-AlphaCoV/SC2013	NC_028833	isolate:BtNv-SC2013	27783 nt	vertebrates	
	BtRf-AlphaCoV/HuB2013	NC_028814	isolate:BtRf-HuB2013	27608 nt	vertebrates	
	BtRf-AlphaCoV/YN2012	NC_028824	isolate:BtRf-YN2012	26975 nt	vertebrates	
	<b>Human coronavirus 229E</b>					
	Camel alpha-CoV	NC_028752	isolate:camel/Riyadh/Ry141/2015	27395 nt	human, vertebrates	
	HumanCoV 229E	NC_002645	strain:229E	27317 nt	human, vertebrates	
	Coronavirus AcCoV-JC34	NC_034972	isolate:AcCoV-JC34	27682 nt	vertebrates	
	<b>Alpha-CoV 1</b>					
	Feline infectious peritonitis virus	NC_002306	serotype:2; isolate:79-1146	29355 nt	vertebrates	
	Swine enteric CoV	NC_028806	strain:Italy/213306/2009	28111 nt	vertebrates	
	Transmissible gastroenteritis virus	NC_038861	strain:Purdue; isolate:PUR46-MAD	28586 nt	vertebrates	
Ferret CoV	NC_030292	isolate:FRCoV-NL-2010	28434 nt	vertebrates		
Beta-coronavirus	Human CoV NL63	NC_005831	strain:Amsterdam I	27553 nt	human;	
	Lucheng Rn rat CoV	NC_032730	isolate:Lucheng-19	28763 nt	vertebrates	
	Miniopterus bat CoV HKU8	NC_010438	strain:AFCD77	28773 nt	vertebrates	
	Mink CoVstrain WD1127	NC_023760	strain:WD1127	28941 nt	vertebrates	
	NL63-related bat CoV	-	strain:BtKYNL63-9a	57042 nt	Vertebrates	
	NL63-related batCoV	NC_032107		28363 nt		
	NL63-related batCoV	NC_048216		28679 nt		
	Porcine epidemic diarrhea virus	NC_003436	strain:CV777	28033 nt	vertebrates	
	Rhinolophus batCoV HKU2	NC_009988	strain:HKU2/GD/430/2006	27165 nt	vertebrates	
	Rousettus batCoV HKU10	NC_018871	isolate:183A	28494 nt	vertebrates	
	ScotophilusbatCoV 512	NC_009657	strain:BtCoV/512/2005	28203 nt	vertebrates	
	<b>WenchengSm shrew CoV</b>			isolate:Xingguo-74	51979 nt	Vertebrates
	WenchengSm shrew CoV	NC_048211		25984 nt		
	WenchengSm shrewCoV	NC_035191		25995 nt		
	Bat Hp-beta-CoV/Zhejiang2013	NC_025217	isolate:Zhejiang2013	31491 nt	vertebrates	
BatCoV BM48-31/BGR/2008	NC_014470	strain:BtCoV/BM48-31/BGR/2008	29276 nt	vertebrates		
<b>Middle East respiratory syndrome-(MERS) related coronavirus</b>						
Beta-CoV England 1	NC_038294	strain:England 1; isolate:H123990006	30111 nt	human, vertebrates		
MERS-related CoV	NC_019843	strain:HCoV-EMC; isolate:HCoV-EMC/2012	30119 nt	human, vertebrates		
Beta-CoV	NC_039207	isolate:ErinaceusCoV/2012-	30148 nt	vertebrates		

	Erinaceus/VMC/DEU/2012		174/GER/2012		
	Beta-CoV HKU24	NC_026011	strain:HKU24-R05005I	31249 nt	vertebrates
	<b>Beta-CoV 1</b>				
	BovineCoV	NC_003045	isolate:BCoV-ENT	31028 nt	human, vertebrates
	HumanCoV OC43	NC_006213	strain:ATCC VR-759; serotype:OC43	30741 nt	human, vertebrates
	HumanCoV HKU1	NC_006577	isolate:HKU1	29926 nt	human
	<b>MurineCoV</b>				
	Murine hepatitis virus	-	strain:MHV-A59	62692 nt	Vertebrates
	Murine hepatitis virus	NC_001846		31357 nt	
	Murine hepatitis virus	NC_048217		31335 nt	
	RatCoV Parker	NC_012936	strain:Parker	31250 nt	vertebrates
	Pipistrellus batCoV HKU5	NC_009020	strain:HKU5-1 LMH03f	30482 nt	vertebrates
	RabbitCoV HKU14	NC_017083	strain:HKU14-1	31100 nt	vertebrates
	Rousettus batCoV	NC_030886	isolate:GCCDC1 356	30161 nt	vertebrates
	Rousettus batCoV HKU9	NC_009021	strain:HKU9-1 BF_005I	29114 nt	vertebrates
	<b>Severe acute respiratory syndrome-related coronavirus (SARS-CoV)</b>				
	SARS-CoV Tor2	NC_004718	isolate:Tor2	29751 nt	human, vertebrates
	SARS-CoV-2	NC_045512	isolate:Wuhan-Hu-1	29903 nt	human, vertebrates
	Tylonycteris bat CoV HKU4	NC_009019	strain:HKU4-1 B04f	30286 nt	vertebrates
Delta-coronavirus	BulbulCoV HKU11-934	NC_011547	-	26487 nt	vertebrates
	Common moorhen CoV HKU21	NC_016996	strain:HKU21-8295	26223 nt	vertebrates
	Magpie-robincov HKU18	NC_016993	strain:HKU18-chu3	26689 nt	vertebrates
	MuniaCoV HKU13-3514	NC_011550	-	26552 nt	vertebrates

	Night heronCoV HKU19	NC_016994	strain:HKU19-6918	26077 nt	vertebrates	
	PorcineCoV HKU15	NC_039208	strain:HKU15-155	25425 nt	vertebrates	
	Sparrow CoV HKU17	NC_016992	strain:HKU17-6124	26083 nt	vertebrates	
	Thrush CoV HKU12-600	NC_011549	-	26396 nt	vertebrates	
	White-eye CoV HKU16	NC_016991	strain:HKU16-6847	26041 nt	vertebrates	
	Wigeon CoV HKU20	NC_016995	strain:HKU20-9243	26227 nt	vertebrates	
Gamma-coronavirus	Beluga whaleCoV SW1	NC_010646	isolate:SW1	31686 nt	vertebrates	
	Canada gooseCoV	NC_046965	strain:Cambridge_Bay_2017	28539 nt	vertebrates	
	<b>Avian CoV</b>					
	Duck CoV	NC_048214	isolate:DK/GD/27/2014	27754 nt	human, vertebrates	
	Infectious bronchitis virus	-	strain:Beaudette	55072 nt	human, vertebrates	
	Infectious bronchitis virus	NC_001451		27608 nt		
	Infectious bronchitis virus	NC_048213		27464 nt		
Turkey CoV	NC_010800	isolate:MG10	27657 nt	human, vertebrates		
Unclassified	Shrew CoV	NC_046955	isolate:Shrew-CoV/Tibet2014	27102 nt	vertebrates	
Epsilon-coronavirus	B.1.427/B.1.429	Not classified. 20C/S:452R	Lineages emerged from California, although this remains to be confirmed [Yang et al., 2021]	Not reported	Human	
Omicron-coronavirus	hCov-19/Botswana/R40B59_BHP_33210012_48/2021	Not classified EPI_ISL_6640916	South Africa	29684 nt	Human	

Note: The table was adjusted according to the current classification reported at <https://talk.ictvonline.org/taxonomy/>.

<sup>a</sup>Genera of *Orthocoronavirinae*(taxid 10239). The table reflects the total number of currently identified *Orthocoronavirinae* species. **Order:** *Nidovirales*; **Sub-order:** *Cornidovirineae*; **Family:** *Coronaviridae*; **Subfamily:** *Orthocoronavirinae*.<sup>14</sup>



**FIGURE 1** Characteristic structure of SARS-CoV-2 and its genomic organization. (a) SARS-CoV-2 is composed of single-stranded RNA, spike (S)-glycoprotein, and structural N, M, and E proteins. (b) Schematic organization of SARS-CoV-2 genome

while the other indicated expression of only five canonical accessory ORFs (3a, 6, 7a, 7b, 8).<sup>63</sup>

The trimeric, cell-surface glycoprotein spike (S-protein) was identified as a potential SARS-CoV-2 therapeutic target responsible for the binding and penetration of the virus to the host cells. However, S-proteins are required to be primed (cleaved) by the host serine protease TMPRSS2.<sup>64</sup> The S-protein priming allows successful virus binding the angiotensin-converting enzyme 2 (ACE2), a receptor for the entry of both SARS-CoV and SARS-CoV-2 viruses. Cell entrance of MERS-CoV is mediated by a different receptor, dipeptidyl peptidase 4 (DPP4).<sup>65</sup> Variations (mutations) in the S-protein are associated with the host tissue tropism and severity response range to CoVs.<sup>65</sup> Genomic sequencing analysis of S-protein structure in SARS-CoV and SARS-CoV-2 delineated 76% sequence homology. Both SARS-CoV and SARS-CoV-2 share eight conserved binding positions and six semi-conserved positions in S-protein domains.<sup>66,67</sup> Aside from ACE2, SARS-CoV-2 S-protein was shown to interact with neuropilin 1 (NRP1)<sup>68</sup> and Basigin2/EMMPRIN/CD147 (CD147).<sup>69</sup> The involvement of CD147 in pathogenesis of other widely spread and highly harmful viruses was demonstrated.<sup>70</sup>

### 3 | CORONAVIRUSES AND INFLAMMATION

Several biological functions of SARS-CoV-2 accessory proteins have been described. For instance, 3a and 3b proteins were shown to activate apoptosis and stimulate release of proinflammatory cytokines.<sup>71</sup> Alternatively, protein 6 blocked pro-inflammatory interferon (INF) signalling, but stimulated DNA synthesis. Activation of nuclear

factor kappa B (NF- $\kappa$ B) by ORF3a, M, ORF7a, and N proteins was reported.<sup>72</sup> Accordingly, ORF7a was indicated as a promising anti-inflammatory therapeutic target in COVID-19 patients.<sup>72</sup> Previously, SARS-CoV protein 7a was also shown to trigger NF- $\kappa$ B and mitogen-activated protein kinase p38 (MAPK) signalling pathways.<sup>73,74</sup> Alternatively, it was reported that SARS-CoV structural M protein can block NF- $\kappa$ B activity in cell models in vitro,<sup>75</sup> suggesting complex involvement of viral proteins in the regulation of pro-inflammatory pathways. The functional role of protein 7b remains unclear. ORF3b, ORF6, ORF7a and ORF8 may interfere with IFN type I pathway and damage host immunity.<sup>76</sup> Moreover, protein 8 (ORF8a and ORF8b) induces endoplasmic reticulum (ER) stress and triggers the activating transcription factor 6 (ATF6), responsible for the regulation of unfolded protein responses.<sup>77</sup> Interestingly, it seems that signalling roles of protein 8a and 8b are different. Protein 8a was detected to activate caspase-dependent apoptosis, whereas protein 8b may impact host DNA synthesis. Intracellular roles and structure of SARS-CoV-2 accessory proteins was recently reviewed.<sup>76</sup>

### 4 | MUTATIONS IN SARS-CoV-2 VARIANTS

Since the beginning of COVID-19 outbreak in Wuhan (China), over 12,000 mutations have been observed in the reference SARS-CoV-2 sequence (hCoV-19/Wuhan/WIV04/2019).<sup>78</sup> According to phylogenetic, variant, and microsatellite analysis, coronaviruses acquire genomic mutations during the course of transmission and replication in the host cells, with approximately one nucleotide substitution

every  $\approx 11$  days.<sup>79</sup> Consequently, over 1.4 million SARS-CoV-2 sequences, including 3913 major representative variants genomes, have been detected worldwide and stored in the global SARS-CoV-2 sequence database (Global Initiative on Sharing Avian Influenza Data (GISAID)).<sup>80</sup> Notably, functional changes in major SARS proteins associated with virus infectivity were preceded by limited numbers of genetic mutations that will be discussed in this review.

Specific mutations in SARS-CoV-2 trigger divergent phenotypic alterations that may enhance virus adaptation to the host environment. Mutational study of codon bias revealed host-virus interactions and linked specific mutational changes to the severity of SARS-CoV-2 pathogenesis.<sup>81</sup> Mutational hotspots inflicted in SARS-CoV-2 NSPs were shown to promote virulence of the pathogen.<sup>82</sup> NSP2 and NSP3, S-protein, and NSP12 RNA-dependent RNA polymerase (RdRp/NSP12) are major SARS components associated with enhanced infectivity. Accordingly, specific mutations in NSP2, NSP3, and S-proteins were linked to the increased virulence of SARS-CoV-2.<sup>83</sup> The genomic analysis demonstrated that mutations in SARS-CoV-2 can accumulate at a slower rate than mutation rates observed in other RNA viruses, including flu virus, and HIV.<sup>84</sup> S-protein located mutations were identified in SARS-CoV-2 VOCs with higher virus infectivity and disease severity, including Delta (B.1.617.1 and B.1.617.2)<sup>85</sup> and Omicron (BA.1/B.1.1.529)<sup>39</sup> variants that caused global health crisis.<sup>86</sup> Presence of mutations facilitated development of resistance to vaccine-generated immunity. While vaccinated (2 doses of BNT162b2 or ChAdOx1 nCoV-19) patients infected with Alpha variant indicated good level of immune protection,<sup>85</sup> patients infected with mutated S-protein variants were less protected and indicated lower level of anti-viral antibodies.<sup>85</sup> Mutations in other regions, including modifications within SARS ORF1a genome, a key region for NSP mutations, have largely unclear consequences for human health<sup>86</sup> and require thorough investigation.

The main function of S-protein of SARS-CoV-2 is associated with the targeted binding to ACE2 receptors and receptor-facilitated intracellular transmission.<sup>66</sup> Gussow et al., assessed the role of S-protein and other components and characteristics of SARS-CoV-2, SARS-CoV, and MERS-CoV.<sup>87</sup> Enhanced virulence of SARS variants was linked to the mutations pertaining to S-protein mutations that allowed a better cell binding and promoted higher fatality rates.<sup>88</sup> Multiple SARS-CoV-2 mutant variants with high virulence were reported.<sup>89</sup> For instance, African and Asian countries were marked by the highest percentages of unique mutations in S-proteins.<sup>90</sup> European and North American S-protein variants were marked by a larger number of diverse haplotype blocks that contained nonsynonymous variants.<sup>84,88</sup> Among all the variants, mutations in S-protein were associated with higher virulence and, therefore, S-protein is considered to be the most significant target for neutralising antibodies and vaccine development.<sup>84,88</sup> However, recently reports delineated the emergence of more virulent double mutant strains of SARS-CoV-2<sup>64</sup> which suggests that several targets (including, but not limited to S-protein) should be considered during the development of more effective vaccines.

Mutations in NSP1 of ORF1a/ORF1b were directly associated with abnormal levels of virulence and transmissibility. Accordingly, antibodies against NSP1 were shown to regulate and antagonise viral replication.<sup>91,92</sup> Mutations in ORF allow the generation viral proteins which can induce MHC-I expression in the infected hosts and promote viral escape from immune surveillance.<sup>93,94</sup> It has been shown that Alpha variant contains ORF with a premature stop codon at 27<sup>th</sup> position.<sup>95</sup> Interestingly, partial deletions of NSP1 and ORF8 ( $\Delta 382$  variant in Singapore) were observed in VOCs detected in Sichuan, China (NSP1:  $\Delta 500-532$  variant).<sup>92-94</sup> A side from NSP1, non-RBD regions mutation D614G is one of the most widely occurring mutations reported in 99% of current variants.<sup>96,97</sup> The mutation helps to enhance S-protein density, prevent S2 shedding, and facilitate a higher infection rate.<sup>98,99</sup> Higher rate of deletions was also detected in antibodies-recognising domain (N-terminus region of S1 subunit).<sup>100</sup> For instance, Alpha and Beta variants were shown to contain numerous mutations in S1 subunit, including  $\Delta RDR1$  (recurrent deletion region (RDR)),  $\Delta HV 69-70$ ,  $\Delta RDR2$ ,  $\Delta Y144$ ,  $\Delta RDR4$ , and  $\Delta LAL 242-244$ ; whereas  $\Delta RDR3$  and  $\Delta I210$  were reported in B.1.36 (Indian Delta variant).<sup>100</sup>

#### 4.1 | SARS-CoV-2 mutations in Indian isolates

Growing number of SARS cases and deaths in India was associated with the emergence of a novel variant, B.1.617 (defined as Delta variant). This variant gained eight mutations in RBD of the S-protein. Among those, the mutations such as L452R and E484Q were shown to facilitate binding of the RBD to ACE2.<sup>101</sup> The introduced mutation-linked changes were suggested to modulate antibody-mediated neutralisation. Supporting this, B.1.617 was predominantly reported to be resistant to the treatment with bamlanivimab and escaped the antibody-dependent eradication, activated by infection or vaccination.<sup>64</sup>

Comparative whole genome sequencing analysis of SARS isolates in the Indian population delineated the occurrence of different mutations, including nonsynonymous, synonymous, and nonsense mutations in SARS-CoV-2. Nonsynonymous mutations that alter the protein sequences were 3.07 times more prevalent than synonymous mutations in Indian isolates.<sup>81</sup> The isolates were segregated into 22 groups according to the phylogenetic clade analysis which depicted various sub-clades categorisation of the variants with unique-coexisting mutations. The mutant variant dominance in the Indian subcontinent was distributed as follows: 73.34% of A2a clade, 23.29% of A3 clade, and 5.36% of B clade variants. Furthermore, 33 mutations were reported in 9 different protein coding genes (NSP3 (7 mutations), NSP12 (5 mutations), NSP2 (4 mutations), N (3 mutations), NSP4 (2 mutations), NSP6 (1 mutation), ORF3a (1 mutation), ORF8 (1 mutation)), and one mutation in 5'-UTR region of the isolated SARS-CoV-2 genome. C241T, C3037T, A23403G and C14408T mutations were observed at a higher frequency (<50%) in Indian isolates.<sup>102</sup> Alternatively, G25563T (in ORF3a), C26735T (in NSP14),

and C18877T (in M protein) mutations were observed less frequently (15%) in the Indian genome.<sup>102</sup>

Further analysis demonstrated the presence of 4 silent mutations (in D294D/S, F106F/NSP3, S76S/NSP4 and Y789Y/S) without an apparent effect in the protein structure modulation. However, it was suggested that these mutations may influence the codon usage and modulate the translation process.<sup>103</sup> Mutation observed in the 5'-UTR region could impact protein folding and transcription of SARS-CoV-2 genome.<sup>103</sup> Specific mutations in S-protein (L54F, K77M, R78M, D294D, E583D, Q677H),<sup>103,104</sup> NSP3 (G716I, T749I, A994D, D1121G, S1197R), RdRp/NSP12 (A97V, L329I, G571S, V880I), NSP2 (S301F, G339S), and N-protein (S194L) coding genes were unique to Indian isolates.<sup>27,28</sup> L54F, K77M, and R88M mutations were identified in the N-terminal domain (NTD) domain of S1 subunit. NTD mutations were suggested to impact the virus binding ability in host cells.<sup>105</sup> Mutations of E583D and Q677H in the linker domain located in between S1 and S2 subunits could also influence the virus entry via modulating the serine proteases.<sup>105</sup> Q57H (in ORF3a), T265I (NSP3, T85I) and L3606F (NSP6, L37F)(in ORF1ab), L84S (ORF8), and N203 (204del-insKR) mutations were also reported in Indian isolates.<sup>105</sup>

SARS-CoV-2 genomic integrity predominantly depends on the functional efficacy of RdRp/NSP12. The functional alterations in this region, including A97V and L329I (NiRaN domain), V880I (thumb domain), and G571S (finger domain) mutations, were suggested to change the viral susceptibility to the anti-viral drugs remdesivir, ribavirin, and favipiravir.<sup>106</sup> S194L mutation in the central region of N-protein was associated with alterations in oligomerisation during viral assembly and replication.<sup>107,108</sup> Dominant presence of four specific mutations (C241T/5'-UTR, D614G/S, F106F/NSP3 and P323L/RdRp) has been observed in the isolates from several geographic regions of the Indian subcontinent. A side from these 4 mutations, a group of 5 co-dominant mutations (L37F/NSP6, T1198K/NSP3, A97V/RdRp, Y789Y/S, and P13L/N) was detected in South India and North India.<sup>109</sup> D614G, NSP12 (P323L) and NSP12 (A97V) dominant mutations were found in the isolates collected in Maharashtra, Tamil Nadu, and New Delhi. D614G (75% dominant) mutation had high prevalence in Maharashtra, although other mutations (NSP12 (P323L), G204R, R203K) in NSPs indicated prevalent rates. The variant strains with NSP12 (A97V), N (S202N), and NSP2 (G339S) mutations were reported highly prevalent in West Bengal<sup>110</sup>.

A computational study by Das et al. (2021)<sup>81</sup> delineated the characteristic mutations in the Indian SARS-CoV-2 genome. The study reported a total of 536 position-specific mutations in SARS-CoV-2 protein coding regions. Most susceptible six protein codes (ORF1ab, S- and N-proteins, ORF3a, ORF7a, and ORF8) were found mutated in Indian isolates. ORF3a exhibited  $\approx$ 4% of its total length mutated. Substantial % of mutation rate was also observed in ORF1ab and S-protein.<sup>81</sup> Deleterious substitutions in the SARS genome were suggested to facilitate decline in the stability of second codon and other putative functional domains. A substantial quantity of single point mutation was reported, including G > T (at first and third positions of codon) and C > T (at second codon) substitutions.

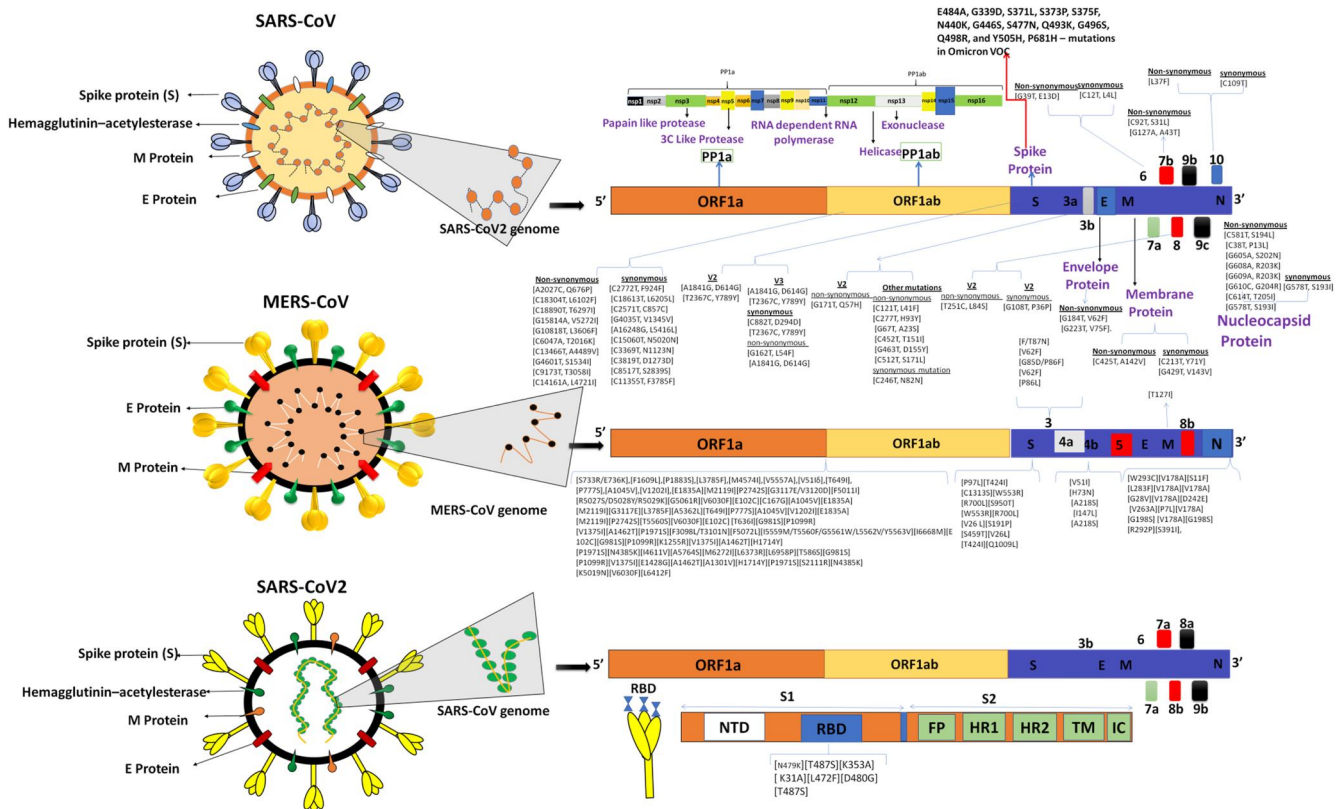
Mutations (57 deleterious amino acid substitutions) in these codons were suggested to impact virus protein functions, disease pathogenesis, and vaccine efficacy against mutant strains.<sup>81</sup>

## 4.2 | Emerging and spreading of SARS COV-2 variants

Whole genome sequencing technique was used to analyse thousands of SARS-CoV-2 isolates around the world. SARS-CoV-2 genome sequences were organised into haplotype groups<sup>111-113</sup> that were later extended and adjusted using data from 56 countries/territories. The large collection of data is stored at the GISAID database and contains information about 66 common haplotypes.<sup>114</sup> Information about SARS-CoV-2 genome mutations (global data from 48 countries) was also collected and stored in the Children's Hospital of Los Angeles (CHLA) COVID-19 Analysis Research Database (CARD). The largest SARS-CoV-2 haplotypes in Europe and USA are presented in Figure 2.<sup>114</sup> The haplotypes were grouped in 13 major clusters (often defined as clades or lineages) (H1-H13). Groups H1-H3 contain the largest collection of variants.<sup>114</sup> Further analysis of 74,992 sequences (collected during the period from 1 June 2020 to 15 November 2020) led to the discovery of new sub-haplotypes (H1a, H1b, H1r), the currently dominating haplotypes at GISAID.<sup>114,115</sup> Many countries attempt to record new rapidly mutating variants using different abbreviations. Consequently, the existing haplotype naming requires unification. For instance, haplotypes H1, H1a, H1b, and H1r are identified in GISAID as clades G, GR, GH, and GV, and in Next strain classification - as 20A, 20B, 20C, and 20E.<sup>114,116</sup>

The co-evolving mutations were registered in the clades G (H1), GH (H1a), and GR (H1b) from isolates collected in developing countries. The commonly mutated variant D614G (in S-protein) was also found in EU and USA patients. The variant was also reported in India as described above, indicating a global spread and high virulence of this variant. Other commonly observed mutations include C241T/5UTR (in ORF1ab), C3037T (in ORF1ab), and mutations in NPS12/RdRp.<sup>117</sup> A novel variant of SARS-CoV-2, named VOC 202012/01 (or B.1.1.7, Alpha variant), was originally observed in UK and later identified in several other nations.<sup>118</sup> This variant exhibited 17 mutations mostly in S-protein.<sup>119</sup> Aside from D614G substitution, S-protein code of this variant contains additional 8 mutations. Two deletions ( $\Delta$ H69/ $\Delta$ V70 and  $\Delta$ Y144) were detected in the NTD. B.1.1.7 S-protein RBD contains one substitution (N501Y) and one substitution (P681H) is near its Furin cleavage site. According to the UK COVID-19 genomics consortium, B.1.1.7 variants exhibit 70% more transmissible efficacy compared to the reference strain.<sup>120</sup>

Mutations in S-protein coding genes were observed in the majority of VOCs. Compared with the Wuhan reference sequence, 10 mutations were found in B.1.351 ( $\beta$  variant, South Africa) and 12 in P.1 ( $\gamma$  variant, Brazil) with three RBD-located changes.<sup>78</sup> B.1.351 (also named N501Y.V2) has some minor mutational similarities to the UK variant B.1.1.7.<sup>118</sup> Notably, B.1.1.7 and B.1.351 demonstrated



**FIGURE 2** Phylogenetic and mutational analyses of lethal (or associated with the disease severity) coronavirus mutations in the reference genome. Upper panel – *SARS-CoV-2*: Approximately 4000 mutations were observed in S-protein of *SARS-CoV-2*. Majority of these mutations do not influence COVID-19 disease severity. Synonymous & nonsynonymous *SARS-CoV-2* mutations in ORF1ab, S-protein (v2, v3), E/M/N proteins, and amino acid substitutions (E484K) can enhance virus transmissibility via more effective S-protein and ACE2 receptor binding.<sup>81</sup> **Middle panel: *MERS CoV***: The Saudi Arabian human isolates contained a number of unique amino acid substitutions in ORF1ab (41 mutations), N-protein (10 mutations), S-protein (9), and ORF4b (5 mutations) which could enhance virulence of this strain in human body. **Lower panel: *SARS-CoV***: Naturally selected mutations were observed in RBD region (7 mutations). These mutations can modulate RBD/hACE2 interactions of evolving *SARS-CoV* variants

resistance to the monoclonal antibodies that target NTD.<sup>64</sup> B.1.351 variant contains 9 mutations in the S-protein gene, including a cluster of mutations in the NTD, substitutions (K417N, E484K and N501Y) in the RBD and near the Furin cleavage site. The substitution at position 484 (E484K; RBD of the S-protein) was found in both B.1.351 and P.1 lineages. However, B.1.351 is resistant to major antibodies that target the RBD.

RBD locus of S-protein mediates *SARS-CoV-2* binding to ACE2<sup>22,64,121</sup> and consequent viral transport into intracellular space. Notably, S-protein's RBD is the target for many potent neutralising antibodies.<sup>122</sup> The S-targeting antibodies were suggested to block RBD-ACE2 interaction and provide natural and vaccine-induced protection from *SARS-CoV-2* infection. Recently discovered ε variant B.1.427/429 (reported in the USA along another new variant B.1.526<sup>123,124</sup> and B.1.617.1 (κ variant, reported in India also contain mutations in the RBD of the S-protein, including L452R. The mutations can enhance virus binding efficacy to ACE2 and protect those variants from anti-viral immunity associated with human leucocyte antigen (HLA)-A24 defence mechanisms.<sup>125</sup> It has been reported that L452R mutation could promote replication-promoting change which

consequently increases s-protein stability, viral infectivity (fusogenicity), and promotes viral replication.<sup>125</sup> Enhanced transmissibility was observed for the B.1.351 (N501Y.V2) variant which substantially increased the binding capacity to the host cells.<sup>118</sup> Thus, similar to the other RNA viruses, *SARS-CoV-2* has been evolving with divergent mutations and novel variants are expected.<sup>118</sup>

WHO registered the emergence of Lambda variant (also named as the C.37 lineage, designated on 14 June 2021) in many South American countries ("Tracking *SARS-CoV-2* variants"<sup>126</sup>). Despite being a very recent addition to the VOC list, presence of Lambda variant has been observed in 26 countries<sup>127</sup> (GISAID database; <https://www.gisaid.org>). The variant contains three notable mutations (G75V, T76I, and RSYLTPGD246-253N) in the NTD. Two other important mutations, L452Q and F490S, were detected in the RBD region. However, the S-protein NTD-located unique mutation (RSYLTPGD246-253N) in the Lambda variant was suggested responsible for the virulence of this strain.<sup>128</sup> There is a possibility that RSYLTPGD246-253N, L452Q and F490S mutations may facilitate strong resistance of this strain to the 'natural and vaccine-related immune defence mechanisms'.<sup>129</sup> Recent study reported



detection of antibodies to S-protein NTD and to the Nucleocapsid (N) protein.<sup>130</sup>

Omicron variant (BA.1/B.1.1.529) genome contains unprecedented number of mutations (over 18,261) with majority of them (97%) detected in the coding region, and only 3% located in the extragenic region.<sup>131</sup> Omicron genetic signature was reported by GISAID and demonstrated 11 mutations (6 deletions and one insertion) in NTD, with unique N211 and in s214EPE mutations.<sup>131</sup> Several mutations (N501Y, D614G, K417N, T478K) were suggested to amplify the reinfection risk and facilitate vaccine resistance.<sup>132</sup> Omicron and Delta contain two similar RBD mutations that lead to S-protein modifications, increased ACE2 binding affinity, and ability to evade immune surveillance.<sup>133,134</sup> Notably, S-protein is the target of T-cell neutralising antibodies during clearance of the viral infection. Comparing the variant infection rate, it was found that omicron is four times more infectious than the wild type and twice more than the Delta variant.<sup>36</sup> However, it was recently demonstrated that additional (booster) mRNA vaccine doses may help to improve antiviral antibody responses against new SARS-CoV-2 variants.<sup>135</sup>

It was also noted that Omicron is rapidly spreading,<sup>133,136</sup> escaping from the convalescent sera.<sup>131,137,138</sup> Two-dose course with existing vaccine indicated escape of omicron from immune cross-neutralisation.<sup>37</sup> Minimal neutralisation efficacy observed against Omicron variants with the convalescent sera (from vaccinated individuals) could be associated with presence of more than 30 amino acid mutations across S-protein in RBD.<sup>38</sup> Other RBD-located mutation (G339D, S371L, S373P, S375F, N440K, G446S, S477N, Q493K, G496S, Q498R, and Y505H) may also contribute fast spreading of Omicron variant,<sup>37</sup> although further investigations are required. Recent in vitro study demonstrated that geometric mean neutralisation titres (GMT) against Omicron (used as pseudovirus variant) after two doses of BNT162b2 were 22.8-fold lower compared to the original Wuhan variant.<sup>137</sup> Surprisingly, the booster (third dose) of BNT162b2 provided higher neutralising GMT levels against the Omicron variant (23.4-fold increase) compared to the effect observed after second vaccine dose.<sup>137</sup> Supporting these findings, another recent study indicated significant protective effects of 3<sup>rd</sup> dose ( $\geq 6$  months after second injection) of mRNA vaccine (BNT162b2 or mRNA-1273) against Omicron and Delta variants. The adjusted odds ratio (OR) for Omicron cases (with third mRNA vaccine dose) versus unvaccinated controls was 0.33 (95% CI, 0.31–0.35). The adjusted OR among Delta cases versus unvaccinated was 0.065 (95% CI, 0.059–0.071), indicating a better protection against Delta.<sup>138</sup> The data may be called preliminary as the study included only 244 Omicron and 679 Delta cases injected with third dose of vaccine.<sup>138</sup> Notably, extended intervals (>42 days) between second and 3<sup>rd</sup> vaccine doses provided better immunogenicity.<sup>38,39,139</sup> A significant gain in the neutralisation activity against Omicron has been observed in the individuals who received vaccination of third dose (booster) of mRNA vaccine (6 months after second dose).<sup>140–142</sup> BNT162b2 third dose was also more effective against Beta and Delta variants.<sup>143,144</sup> Future studies should evaluate Omicron variant resistance to the other vaccine-generated responses.

Despite mutations across the S-protein's RBD region could support a strain resistance against host immunity,<sup>74–76</sup> NTD-located mutations may provide an additional pathway for the viral escape from antibody-based neutralisation.<sup>145–147</sup> Antibody-linked sensitivity and infection spread were recently associated with the natural mutations in NTD.<sup>148</sup> Polyclonal antibodies generated by the human immune system were shown to bind to the several RBD sites that are undergoing intense evolutionary changes.<sup>149</sup> Therefore, current RBD-targeting antibodies alone may not provide an efficient protection from the virus.<sup>150</sup> It was suggested to search for the non-RBD-targeting antibodies and design antibody cocktails. This suggestion requires experimental confirmation.

#### 4.2.1 | RBD mutations and SARS-CoV-2 virulence

Evolutionary selection pushes SARS viruses to adapt towards better penetration into host cells via receptor (ACE2) binding and higher resistance to the host anti-viral immunity. Both adaptations can facilitate the increased virulence of COVID-19 strains. Mutations in the RBD region were observed in recently identified variants, including mutations K417N/E484K (in Beta-variant), E484A and N501Y (in Omicron), which enhanced the mutant virulence. Moreover, the increased mortality was also linked to the N501Y in the B.1.1.7 variant.<sup>151</sup> Two mutations, N479K and T487S located on S-protein can modulate the RBD/ACE2 binding affinity.<sup>152,153</sup> Furthermore, N479K fosters the formation of energetically unfavourable positive charge at RBD/ACE2 interface, while T487S can eliminate an energetically favourable hydrophobic interaction when RBD interact with Lys-353 in human ACE2 (hACE2).<sup>121,154</sup> Similar effect was observed in the strains with D480G mutation which can foster Tyr-436 interactions and enhance binding efficacy of RBD with chimeric ACE2 (Figure 2). Asp-480 and Gly-480 can also confer viral adaptation in order to bind A to CE2.<sup>155</sup> Another mutation L472F can reinforce RBD/hACE2 interactions. However, L472P can weaken the interactions of RBD with ACE2 due to steric clash of Phe-472 with Thr-82 in chimeric ACE2.<sup>155</sup> Exact molecular and structural mechanisms underlying the mutant-host interactions are not completely clarified and require further investigation. It is also necessary to elucidate the mechanism of natural selection of RBD-located mutation.

## 5 | MUTATIONS AND MERS-CoV VIRULENCE

Similarly, the enhancement in virulence was observed in the mutated strains of MERS-CoV. Unique amino acid substitutions of eight MERS-CoV isolates were observed in *ORF1ab* (41 mutations), N-protein (10 mutations), S-protein (9 mutations), and *ORF4b* (5 mutations).<sup>156,157</sup> Distinct to SARS, a low mutation rate was observed in MERS-CoV strains isolated from the humans. It was attributed to the decline in immunological pressure against MERS-CoV strains in humans.<sup>158</sup> Furthermore, random mutations were

also observed in nsp1-nsp3, nsp12, nsp13, and nsp16 (*ORF1ab* replicase) (Figure 2).<sup>156</sup> S1 and S2 subunits of S-protein in MERS-CoV were shown to gain substitutions (such as T424I, S459T, W553R) in RBD.<sup>159</sup> The S2 subunit-located substitutions S950T, Q1009L, and C1313S were also observed in the fusion peptide, heptad repeat region-1, and transmembrane region, respectively.<sup>156</sup> In addition, MERS-CoV key-components for regulation of viral genomic RNA were also shown to contain substitutions, including V178A (in NTD), A300 (in C-terminal domain (CTD)) G198S, D242E, S11F, P7L, and G28V (in N-arm).<sup>83</sup> Several substitutions (L293F, V263A, R292P, and W293C) were detected at the MERS-CoV CTD region.<sup>156</sup> Similar to other Beta-coronaviruses, the MERS-CoV encodes 5 accessory proteins (*ORF3*, *ORF4a/4b*, *ORF5*, and *ORF8b*).<sup>159</sup> Mutations were detected in *ORF3* (G85D/P86F, V62F, and T87N), *ORF4a* (E102Q), *ORF4b* (H73N, A218S, V51I, I147L, H243Q), *ORF5* (198M), and of M-protein (T127I). The indicated mutations were suggested to enhance MERS-CoV virulence (Figure 2).

## 6 | SARS MUTATIONS AND MICROSATELLITE ANALYSIS

The adapted phylogenetic strategies including WGS, analysis of mutational variations in nucleotide sequences, and microsatellite analysis were used to understand, compare, and predict evolutionary development of coronaviruses.<sup>160</sup> For instance, it has been shown that the average MERS-CoV and BAT-CoV genomes may differ at 134.21 and 136.72 sites, respectively. Microsatellite comparative analysis of viral strains also indicated differences between MERS-CoV and SARS-CoV-2 (106.8 and 107 sites, respectively). The microsatellite difference was higher than the difference between SARS-CoV and BAT-CoV (95.8 and 98.5, respectively). However, SARS-CoV genome is significantly less distinct from SARS-CoV-2 reference genome (only 26.64 site differences). Interestingly, novel SARS-CoV-2 strains may be related to BAT-CoV (88% genome identity), while MERS-CoV is more distinct from SARS-CoV-2 reference genome.<sup>160</sup> The comparison helped to identify a unique PRPA peptide in the mutated SARS-CoV-2 genomes.

The ratio of non-synonymous to synonymous mutations was found to be different in all strains. It was the lowest (0.29) in BAT-CoV. Other strains had higher ratios as follows: 0.31 for SARS-CoV, 1.46 for MERS-CoV, and 1.57 for SARS-CoV-2 genomes. MERS-CoV and SARS-CoV-2 were shown to acquire mutations across missense regions.<sup>160</sup> MERS-CoV, SARS-CoV-2, BAT-CoV, and SARS-CoV were screened for highly recurrent (dominant) mutations. SARS-CoV-2 exhibited changes at four major mutation sites (nucleotide positions) as follows: 241 (C/T, upstream), 3037 (C/T), 14408 (C/T), and 23403 (A/G) (Figure 2). BAT-CoV, SARS-CoV, and MERS-CoV exhibited 1690, 2178, and 4390 mutations, respectively.<sup>160</sup> Potentially, SARS-CoV-2 genome exhibited the largest occurrence of microsatellites compared to the other strains. This information about highly mutated regions in new strains is valuable for the design of novel vaccines.

## 7 | CURRENTLY EFFECTIVE COVID-19 VACCINES

During the development of COVID-19 vaccines, the key-role of S-protein in the interaction of the virus with human ACE2 receptors was considered as the leading factor for the onset of infection. Therefore, current vaccines and available antibodies were designed to target the S-protein of the virus. The S-protein RBD and NTD are the current targets of most vaccine-generated neutralising antibodies. Notably, anti-RBD antibodies are 10- to 100-fold more powerful than anti-NTD antibodies.<sup>161</sup> Anti-RBD antibody pool in convalescent patients represents 90% of the serum-circulating neutralising activity,<sup>162</sup> thus confirming the importance of this region. Variations in RBD mutations are limited as virus has to maintain its ACE2-binding capacity. Alternatively, NTD encoding sequence is more open for mutational variability.<sup>163</sup> However, the receptor binding motif of S-protein has operational plasticity and excessive mutations in RBD, which may abrogate the antibody efficacy after vaccination.<sup>164</sup> The currently available anti-COVID-19 vaccines and their targets are discussed below.

**Comirnaty** (also known as **Tozinameran** or **BNT162b2**) vaccine has been developed by Pfizer-BioNTech and approved in 85 countries. It is mRNA-based vaccine with a high level of safety<sup>165</sup> and act against the full-length Spike gene. Vaccination with this agent resulted in the formation of persistent germinal centres and B cell-based responses associated with the generation of strong humoral immunity.<sup>166</sup> As a promising sign of long lasting immunity, the presence of plasmablast responses was also reported.<sup>167</sup> It has been previously shown that antigen-specific germinal B cells may remain functional for a year.<sup>168,169</sup> However, the vaccine induced production of fewer antibodies targeting NTD of the S-protein,<sup>166</sup> indicating a need to introduce a wide range of vaccine-related targets. Recently, 18 clinical trials of this vaccine were reported in 12 countries. Total of 43, 548 individuals (aged  $\geq 16$  years) participated in one of the clinical trials and the vaccine showed 95% efficacy (30  $\mu\text{g}$  per dose, two doses) and exhibited an efficient level of protection against the symptomatic COVID-19.<sup>170</sup> BNT162b2 can also neutralise SARS-CoV-2 variants and deliver combined adaptive humoral & cellular immune responses through the activation of antigen-specific CD8+ and Th1-type CD4+ T-cell (anti-Spike) responses.<sup>171</sup>

**mRNA-1273** vaccine (developed by Moderna and often named as **Spikevax**) trials were approved in 46 countries and 16 clinical trials have been initiated in 3 countries.<sup>156,172</sup> Approximately 30,420 individuals ( $\geq 18$  years old) participated in one of the clinical trials.<sup>173,174</sup> The vaccine showed 90% efficacy (100  $\mu\text{g}$  per dose, two doses). The vaccine targets mRNA-1273 which encodes the S-2P antigen and induces CD4+ T-cell responses and activation of Th1 cytokine production.<sup>173,174</sup> **Spikevax** is often offered as booster dose after two previous doses of other mRNA vaccines, including BNT162b2. However, it remains to determine the efficacy of **Spikevax** against Omicron variant.

Both BNT162b2 and mRNA-1273 vaccines were shown to generate IgM/IgG responses and provide good humoral anti-viral

immunity.<sup>171,173-177</sup> However, these vaccines were only partially protective against VOCs with RBD mutations.<sup>171,173,174,177</sup> Vaccine-induced neutralisation efficacy of 14 out of 17 detected antibody types declined against variants with K417N, or E484K, or N501Y mutations.<sup>178-182</sup> VOCs with E484K and Q493R mutations exhibited resistance to class 2 antibodies; whereas variants with R346S, N439K, and N440K mutations resisted class 3 antibodies.<sup>178-182</sup>

**EpiVacCorona** (developed by the Vektor State Research Centre of Virology and Biotechnology in Russia) has just been approved in 3 countries. It is a multi-epitope vaccine which targets several regions, including the RBD region in the S2 protein, M, and N proteins.<sup>174,183</sup>

**Sputnik V** (also known as **Gam-Covid-Vac**) vaccine is an adenovirus viral vector-based vaccine which was developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia. It is approved in 65 countries. Currently, 19 clinical trials of this vaccine are reported to be ongoing in 6 countries. Among these, 6 trials are in phase 3 and ongoing in Venezuela (Bolivarian Republic) (NCT04642339), United Arab Emirates (NCT04656613), Russian Federation (NCT04741061; NCT04530396), Belarus (NCT04564716), and India (NCT04640233 – Phase 2 & 3). Total 21,977 adult participants were tested in the trial and indicated promising results with 91.6% efficacy. The vaccination provided robust humoral and cellular immunity that was marked by the presence of activating RBD-specific IgG, virus neutralising antibodies, and IFN- $\gamma$  responses.<sup>184</sup>

**Convidecia** or **Ad5-nCoV** vaccine (developed by CanSino Biologics Inc. ("CanSinoBIO") (SHSE: 688185, HKEX: 06185) in China) is one of the most recently approved COVID-19 vaccines. A single dose administration of this vaccine contains  $5 \times 10^{10}$  viral particles (vp) and was shown to be safe in healthy adults. The vaccine induces efficient immune responses in healthy adults, although the older people exhibited significantly lower anti-viral immune responses. Suggestively, the older people may require additional doses of this vaccine.<sup>185</sup>

**Vaxzevria** (also known as **AZD1222**, **Covishield**, or Oxford-AstraZeneca COVID-19 vaccine) was developed by AstraZeneca. The vaccine has been approved in 40 countries. Currently, clinical trials of Vaxzevria are in Phase 2/3 in India, UK, Brazil, and South Africa with a total of 20,000 participants.<sup>186</sup> The significant problem associated with this vaccine is unexpected, although very rare prothrombotic side effects.<sup>187</sup> **Covishield** (Indian-made version of AstraZeneca's Vaxzevria) is administered in two doses. Each dose contains  $5 \times 10^{10}$  vp in 0.5 ml. The agent is a recombinant, replication-deficient chimpanzee adenovirus vector encoding S-glycoprotein. This vaccine was found to be effective in generating neutralising antibodies against the S-protein in adults from all age groups. The vaccination with this agent resulted in development of immunocompetency on 14<sup>th</sup> day after booster 2<sup>nd</sup> dose.<sup>188,189</sup>

**Ad26.COV2.S** (also known as **JNJ-78436735** or **Ad26.COV2.S**) was developed by Johnson & Johnson. Vaccine is a recombinant S-protein attached to replication-incompetent human adenovirus type 26 vector. The vaccine was approved in 41 countries. The administration of this vaccine can lower viral titre substantially within 14 days. A

single dose of Ad26.COV2.S vaccine exerted effective protective humoral and cellular immune responses.<sup>190,191</sup>

**NVX-CoV2373** (Novavax), recombinant S-protein/nanoparticle (Matrix-M) adjuvant vaccine, was found highly immunogenic.<sup>192,193</sup> The efficacy of this vaccine against new variants was not reported.

**Covaxin** (also known as **BBV152 A, B, C**) was developed by Bharat Biotech in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV) in India. The vaccine has been approved in 9 countries. The vaccine was 78% efficient against mild, moderate, and severe COVID-19. Initial Phase 1 clinical study has shown that the vaccine provokes a prolonged humoral and cell-mediated immunity after second vaccine dose within 3 months.<sup>194</sup>

**CoronaVac** (also known as **Sinovac**) was developed by the Chinese company Sinovac Biotech (Sinovac Life Sciences, Beijing, China). This vaccine was approved in 2 countries. The vaccinated subjects indicated the presence of vaccine-induced antibodies against the S-protein, although the effectiveness was not very high.<sup>195</sup> The vaccine contains the inactivated SARS-CoV-2 particles.<sup>196,197</sup>

**BBIBP-CorV** (also known as the **Sinopharm** or **BIBP**) is one of two inactivated virus COVID-19 vaccines developed by Sinopharm's Beijing Institute of Biological Products. The vaccine contains inactivated SARS-CoV-2 particles and was approved in 40 countries. The vaccine provoked humoral responses generating neutralising antibodies after the second dose of the vaccination<sup>198</sup> (Table 2).

## 8 | DEVELOPMENT OF ANTIBODY-RESISTANCE: COMPARATIVE VACCINE EFFICACY FOR REFERENCE AND MUTANT VARIANTS

The successful generation of anti-COVID-19 immunity by the current vaccines is determined by the virological diversity and epidemiological spreading of variants. The large variety of emerging SARS-CoV-2 strains undermined vaccine efficiency and long-term protection against the virus. Pandemic spread of SARS-CoV-2 is marked by emergence of new mutated strains. Some of those mutations were shown to assist viral escape from antibody-dependent therapies. Approximately, one to two single nucleotide mutations may accumulate in SARS-CoV-2 genome within 30 days ( $\frac{1}{2}$  the rate of influenza and  $\frac{1}{4}$  the rate of HIV). The slower mutating ability of SARS-CoV2 is associated with expression of a novel exoribonuclease (ExoN), the correcting enzyme for coding errors generated during viral replication. Accordingly, the genetic inactivation of ExoN in SARS-CoV and murine CoV enhanced the mutation rate by 15 to 20 folds.<sup>199</sup>

S-protein is composed of 1273 amino acids and most of the successful vaccines were developed to target Spike (S) gene sequence. The reported S gene mutations and conformational changes in S-protein were associated with severity of viral pathogenesis. If these mutation-induced 'RBD of S-protein' with conformational changes are not recognized by the initial antibody response, the virus can escape clearance by immune mechanisms in these

**TABLE 2** Comparative clinical efficacy of mRNA vaccine, viral-vector vaccine, inactivated pathogen vaccine, protein subunit vaccine, virus-like particle vaccine among several participants, and their individual efficacy rate by the assessment of Nab (neutralizing antibody) responses, and Immune response rates

VACCINE CANDIDATES AGAINST PARENTAL SARS-CoV-2 VIRUS													
TYPES OF VACCINE	mRNA VACCINE		REPLICATION DEFECTIVE VIRAL VECTOR VACCINE				INACTIVATED PATHOGEN VACCINE				PROTEIN VACCINE	SUBUNIT	VIRUS LIKE PARTICLE
NAME OF VACCINE	mRNA-1273	BNT162b2 OR Comirnaty	Ad5-nCoV	AZD1222	Gam-COVID-Vac OR Sputnik-V	Ad26.COV2.S OR JNJ-78436735	Corona Vaccine	Sinopharm	BBIBP-CorV	BBV 152 OR Covaxin	NVX-CoV2373	ZF2001	CoVLP
VACCINE PRODUCER	Moderna	Pfizer/BioNTech/ Fosun Pharma	Cansino biological/ Beijing Institute of biotechnology/ Academy of military medical sciences.	AstraZeneca/ Oxford university.	Gamaleya research institute/ Health ministry of the Russian federation/ Acellera contract drug research and development.	Jhonson & Jhonson /Beth Israel Deaconess Medical Center	Sinovac research and development co.,Ltd	Wuhan institute of biological products/Sinopharm	Beijing Institute of biotechnology/Sinopharm	Bharath biotech	Novavax	Longson /Chinese academy of medicine	Glaxo Kine/Medicago Smith
NUMBER OF DOSES	02 (100µg)	02 (30µg)	01 (5×10 <sup>11</sup> VP)	02 (5 × 10 <sup>11</sup> VP)	02(0.5ml/dose)	01 (5 × 10 <sup>11</sup> VP)	02 (3µg)	02	02 (4µg)	02 (3µg)	02 (5µg SARS-CoV-2 rS + 50µg matrix-M1 adjuvant)	02-03 doses (25µg/ dose)	02 3.75µg of CoVLP + 0.5ml of ASO3 adjuvant per dose
IMMUNITY RESPONSE RATE OF NEUTRALISING ANTIBODIES IN PARTICIPANTS	NAbs developed in all individuals (Phase 1)	NAbs developed in all individuals (Phase 1)	NAbs developed in 97% of individuals (Phase 2)	NAbs developed in all individuals (Phase 1/2)	NAbs developed in all individuals (Phase 1/2)	NAbs developed in 92% of individuals. (Phase 2)	NAbs developed in 92.4% and 97.4%(in participants with 2 and 4 weeks of gap in immunization regimen)	NAbs developed in high titers in all individuals (Phase 1/2)	NAbs developed in high titers in all individuals (Phase 1/2)	NAbs developed in 93.4% of individuals. (Phase 2)	NAbs developed in high titers in all individuals (Phase 1/2)	NR	NR
IMMUNITY RESPONSE RATE OF T-CELLS	CD4+T cell responses observed	CD4 and virus specific Th1+ T cell responses observed	T cell responses observed in 88% individuals	T cell responses observed in all individuals.	CD4+CD8+T cell observed in all individuals.	CD4+T cell responses observed in 80% individuals.	NR	NR	NR	Virus specific CD4+CD8+T cell responses observed	CD4+T cell responses observed in all individuals.	NR	NR
EFFICACY REPORTED	94.1%	95% (94%(>65 years old)	NR	62.1%(after 1 <sup>st</sup> dose) 90%(after 2 <sup>nd</sup> dose in 18 to 55 years old) 70.4%(after 2 weeks of 2 <sup>nd</sup> dose)	91.4%	NR	NR	NR	79.34%	NR	NR	NR	NR

Abbreviations: NAbs, Neutralizing Antibodies; NR, Not Reported.

circumstances. Consequently, the vaccines that were designed to target the reference SARS-CoV-2 or similar variants may be inefficient against later SARS mutants.<sup>200</sup>

Newly identified SARS-CoV-2 variants in the UK exhibited higher evolutionary advantages in transmission and virulence. To investigate the mutation-associated changes, three mutant strains of SARS-CoV-2 were engineered and included (a) N501Y (found in UK and SA), (b) 69/70-deletion + N501Y + D614G (found in UK); and (c) E484K + N501Y + D614G (found in South Africa). All these mutants were neutralised using the sera of 20 BTN162b2-vaccinated recipients.<sup>200</sup> The neutralisation geometric mean titres (GMTs) of the collected human sera against the engineered viruses was not much different from parental GMTs (0.81–1.46-fold). This finding indicates that presence of mutation did not influence the neutralisation process by the sera from BTN162b2-vaccinated subjects, compared to the vaccine effect against the parental strains. However, it does not eliminate a possibility that other mutants will be neutralised effectively. Clinical characteristics of some variants were shown to foster biological advantages of the virus in host systems, indicating a higher virulence, lower efficacy of vaccines and targeted therapies.<sup>201</sup>

Epidemiological reports indicated that SARS variants with the emerging D614G amino acid (AC) mutation in S-protein RBD demonstrated a higher virulence and more severely affected the exposed population, compared to the reference strain.<sup>202</sup> The

presence of G614 form was also associated with the substantial rise in viral load and infectivity as the conformation delivers a greater capability for binding to the human ACE2 receptor.<sup>202</sup> The G614 variant exhibited a greater replication rate than the ancestral D614 strain in both cell lines and primary airway human epithelial cells. G614 variants were more resistant to the vaccine administration.<sup>202,203</sup>

Majority of vaccines have been designed to target S-protein to block its binding to ACE2 receptors. However, the vaccine-induced antibodies may not effectively recognise mutant variants of SARS-CoV-2 for neutralisation.<sup>204</sup> The current vaccines can trigger specific antibody responses to specific immunogenic regions of the virus. However, these antibodies may not neutralise mutant S-protein strains. This suggestion was unfortunately supported by the study of vaccine efficacy against the South African 1.351 mutant variant, which has mutations in the immunogenic region of S-protein. This variant managed to escape vaccine-induced antibody attack generated by previous vaccination.<sup>205</sup> Another clinical study reported the low efficacy of Moderna (mRNA1273-based) and Pfizer-BioNTech (BNT162b2) vaccines against mutant variants in 20 patients.<sup>109</sup>

Significantly higher levels of anti-SARS-CoV-2 IgM and IgG antibodies were detected 8 weeks after second dose vaccination with mRNA vaccines (BNT162b2 or mRNA-1273).<sup>171,173,174,177</sup> However,



## B

MUTANT STRAIN	ORIGIN	WHO LABELLED AS	DATE OF DECLARATION AS VARIANT OF CONCERN	SPREAD	MUTATIONS	TRANSMISSIBILITY IN COMPARISON WITH PARENT STRAIN	VIRULENCE IN COMPARISON WITH PARENT STRAIN	ANTIGENECITY WHEN COMPARED TO PARENT STRAIN	LETHALITY OR HAZARD OF DEATH
(B.1.1.7)	United Kingdom	Alpha	Dec 2020	Global	N501Y, 69–70del, P681H	43 to 90% more	61% (42–82%)	Unchanged [Ref: European Centre for Disease Prevention and Control. Feb-2021].	61% (42–82%)
(B.1.351)	South Africa	Beta	Dec 2020	Global	N501Y, K417N, E484K	50% more (20–113%) [Ref: European Centre for Disease Prevention and Control. Feb-2021].	NR	Mitigated the levels of host antibodies for neutralisation when compared to parent strains <sup>8</sup> .	NR
(P.1)	Brazil	Gamma	Jan 2021	Global	N501Y, E484K, K417T <sup>1</sup>	161% (145–176%) more <sup>9</sup>	≈50% <sup>10</sup>	Mitigated the levels of host antibodies for neutralisation when compared to parent strains <sup>8</sup> .	10–80% <sup>10</sup>
Delta (B.1.617.2), Kappa (B.1.617.1)	India	Delta Kappa	Apr 2021	Global	E484Q, L452R, P681R	≈160% more [Ref: SAGE 89 minutes: Coronavirus (COVID-19) response, 13 May 2021 (Report). gov.uk. Retrieved 22 May 2021]	NR	Mitigated the levels of host antibodies for neutralisation when compared to parent strains <sup>11</sup> .	NR
(B.1.525)	United Kingdom Nigeria	Eta	-	Global	E484K, F888L	NR	NR	Mitigated the levels of host antibodies for neutralisation when compared to parent strains [Ref: Centres for Disease Control and Prevention, USA]	NR
(B.1.429), (B.1.351)	United States	Epsilon	Mar 2021	Global	B.1.429 (S131, W152C, and L452R) B.1.351(L18F, D80A, D215G, Δ242–244, R246I, K417N, E484K, N501Y, and A701V)	≈20% (18.6%–24.2%) <sup>12</sup>	NR	Mitigated the levels of host antibodies moderately for neutralisation when compared to parent strains <sup>13</sup> .	NR

Abbreviation: NR, Not Reported.

compared to the parental strain titres.<sup>164,222,223</sup> Positive charge at E484 and shortened side chain at the residue 417 were suggested to prevent the interaction of virus with antibodies and associated defects in immune responses.<sup>209</sup> The resistance to vaccine-generated antibodies was also associated with NTD-located deletions (Y144del and 242-244del).<sup>223</sup>

BNT162b2 (Pfizer-BioNTech) first dose has not generated the neutralising antibodies against B.1.351 for 2–3 weeks period, although only a small cohort of 15 people was tested.<sup>163</sup> The second dose generated low titres of neutralising antibodies in 60% (1 week after the vaccination) to 77% (3 weeks after the vaccination) of the tested subjects. Presence of E484K mutation could be considered as the main cause for the mitigation in overall vaccine potency.<sup>163</sup>

B.1.351 (N501Y.V2) variant contains 23 mutations and 15 AC substitutions.<sup>224</sup> The strain is marked by the presence of N501Y mutation (asparagine (N) replaced by tyrosine (Y) at 501 position in RBD) in S-protein.<sup>210</sup> B.1.351 strain also contains deletions in the NTD that prevents proper binding of neutralising antibodies.<sup>209</sup> The variant escaped elimination by host immune mechanisms in 48% of convalescent serum samples.<sup>225</sup> Aside from the neutralisation escape,<sup>226</sup> the strain has comparatively a higher viral transmissibility and reinfection capacity than the parental strain. Accordingly, it could induce severe COVID-19 outcomes than parental strains.<sup>210</sup> It seems that current vaccines cannot guarantee reliable protection against 501Y.V2 strain (Table 3).<sup>209</sup>

Low clinical efficacy against B.1.351 mutant was also observed after administration of two doses of ChAdOx1 nCoV-19 vaccine [AZD1222].<sup>227</sup> It has been concluded that the neutralising-antibody

responses failed to protect from B.1.351 strain and the vaccine-primed T-cell responses cannot confer protection from severe COVID-19. Another vaccine trial indicated that 2 doses of NVX-CoV2373 vaccine administration resulted in 49.4% protection against B.1.351 variant.<sup>228</sup> Ad26.COVS.2 vaccine exhibited a better protection against B.1.351 in South African subjects.<sup>190,229</sup> However, Ad26.COVS.2 vaccination also induced thrombotic thrombocytopenia.<sup>230</sup> This vaccine is composed of human Ad26-based vector and encodes S-protein which does not shed S1 subunit due to the knockout of furin cleavage site.<sup>230</sup> The promising data were observed with NVX-CoV2373 and JNJ-78436735 vaccines that demonstrated a high level of protection against the B.1.351 variant and prevented the development of severe disease symptoms.<sup>231</sup>

P.2 variants were also shown to escape neutralisation due to the presence of E484K mutation in the RBD domain. Similarly, P.1 strain (with 3 RBD-located mutations),<sup>224</sup> B.1.1.298, and B.1.429 also exhibited a significant potential to avoid neutralisation by vaccine-induced antibodies.<sup>222</sup> This data indicates an urgent need for the development of complex vaccines capable of generating a wide range of neutralising polyclonal antibodies. The more efficient vaccines should be designed to neutralise multiple antigenic epitopes.

Recent studies indicated a significant drop in the vaccine efficiency in neutralisation of several emerging variants, including B.1.351. For instance, Novavax (NVX-CoV2373) efficiency was decreased from 96% to 48%<sup>231</sup> and Oxford–AstraZeneca (ChAdOx1) neutralisation effect collapsed from 62% to 10%.<sup>233</sup> Significant fall in efficiency was demonstrated with JNJ-78436735 (Johnson & Johnson).<sup>233</sup> However, the neutralisation titre was not changed for the

B.1.1.7 strain.<sup>208</sup> Targeted clinical trials are currently underway to test the efficacy of newly developed vaccines and (vaccine-generated antibodies) against emerging variants. Considering the mutations impact on the vaccine efficiency, continuous monitoring of the viral change and vaccine adjustment are required.

## 9 | CONCLUSIONS

Emergence of SARS-CoV-2 mutants indicates that COVID-19 pandemic is transforming into an ongoing wave-like SARS epidemic. Various SARS strains are detected nearly every day all over the world. It is predictable that new highly virulent strains will appear in the near future in different parts of the world.<sup>20,51</sup> Unfortunately, there is currently no guarantee that existing vaccines can provide required protection against the emerging strains.<sup>209</sup> However, vaccines that target S-protein domains demonstrated encouraging data and lead to the generation of broadly neutralising antibodies. Promising results were also demonstrated after introduction of mRNA vaccine boosts that lead to 1000-fold increase in neutralising titres.<sup>234-236</sup> The data indicated that first-generation vaccines can prime the immune system and, after introduction of a booster, it is possible to provide protection against emerging strains. Another possibility is to use antibody cocktails and generate immunity to a large set of SARS variants. Application of antibody-based therapy should be used cautiously, aiming to avoid the emergence of antibody-resistance mutations.<sup>209</sup> Comparison of S-protein and other virulence-related mutations in common variants (Beta, Delta, and Omicron) of SARS CoV-2 with global transmissibility may deliver essential information for the development of global anti-COVID preventive therapies. Monitoring and reporting of susceptibility to new variants, disease-related complications associated with new mutations, and the rate of re-infection in previously infected and/or vaccinated individuals is required as a global effort to reduce the number of COVID-19 hospitalisation and death. Effects of booster doses look promising at this stage, although development of new vaccines is also warranted. Current data indicates that not all antibodies from the vaccinated individuals were able to neutralise the new strains completely, although there is an indication that booster vaccination will decrease COVID-19 severity.

Frequency of recurrent vaccination and type of booster dose vaccination may be adjusted to enhance protection against the evolving mutant strains. Moderna (USA) manufacturers reported booster dose availability and efficiency against mutant strains of SARS-CoV-2. Following this, it is required to confirm the efficacy of other approved vaccines against strains with the mutated S-protein sites. Meanwhile, it is important to initiate viral genomic surveillance, timely vaccine adjustment, and expedite development of next-generation antibody-based therapies. Using available prediction technologies, it is possible to design second and third generation vaccines against emerging variant viruses. It is also necessary to develop immunogens for several viral genome domains, including more conservative domains that are less likely to be changed.

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## CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

## ETHICS STATEMENT

Not applicable.

## AUTHOR CONTRIBUTIONS

All authors were involved in the design, conceptualisation, and writing of this review. NMB, OS, JL, EL, and RF wrote different subsections of the manuscript. NMB, JL, RF, and OS proofread and edited the final manuscript version. All authors reviewed and approved the final version of the manuscript.

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