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:20I/S01Y.V1, VOC-202012/01), (b) beta-coronavirus (also known as Sarbecovirus,5 20H/S01Y.V2, VOC-202012/02)(beta-CoV or Beta), (c) gamma-coronavirus (gamma-CoV or Gamma) (alternative names: 20J/S01Y.V3, VOC-202101/02), and (d) delta-coronavirus (delta-CoV or Delta) (alternative names: VOC-21APR-03, G/452R.V3, 21A/S/478K).2 Alpha- and beta-CoVs can infect bats, pigs, cats, mice, and humans,3,9 whereas the gamma- and delta-CoVs were shown to infect birds and mammals10–13 (Table 1). Recently classified coronaviruses (the family Coronaviridae) are represented by 45 species (the latest confirmed count, 4 August 202115) that are grouped in 25 subgenera and four genera.14 The significant changes in CoV taxonomy happened during 2021 years and 39 species (27 subgenera and five genera) were reported in 2020.15 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.5 The most recent addition is Omicron variant17 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,18 while the genome sequence is the only known characteristic.15 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).19–22 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.23,24 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-CoVs25–32 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.33 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.15,15–23 Similar infection-related symptoms were recorded for the most recent variant (Omicron).17 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.21,34

According to the World Health Organization (WHO) statistical report,35 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.36 The pandemic resulted in nearly 6 million deaths worldwide.35 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).37–39

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.40,41 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.42 The other 1/3’d 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).43–51 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).33,35,52,53 Genes coding for accessory proteins were also reported in 3’ region.33 HCoV-OC43 and HCoV-HKU1 were shown to encode haemagglutinin esterase (HE) gene.54,55 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.57 SARS-CoV genome contains codes for eight accessory proteins (3a, 3b, 6, 7a, 7b, 8a, 8b, and 9b).38,59 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).60 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.61 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).62
| Genera* | Genome | Accession # | Source information | Genome length | Host |
|---------|--------|-------------|-------------------|--------------|------|
| Alpha-coronavirus | Alpha-CoV Bat-CoV/P.kuhlii/Italy/3398-19/2015 | NC_046964 | strain:Bat-CoV/P.kuhlii/Italy/3398-19/2015 | 28128 nt | vertebrates |
|         | Bat CoV CDPHE15/USA/2006 | NC_021103 | strain:bat/USA/CDPHE15/2006 | 28035 nt | vertebrates |
|         | BtMr-AlphaCoV/SAX2011 | NC_028811 | isolate:BtMr-SAX2011 | 27935 nt | vertebrates |
|         | BtNv-AlpacaCoV/SC2013 | NC_028833 | isolate:BtNv-SC2013 | 27783 nt | vertebrates |
|         | BtRF-AlpacaCoV/HuB2013 | NC_028814 | isolate:BtRF-HuB2013 | 27608 nt | vertebrates |
|         | BtRF-AlpacaCoV/YN2012 | NC_028824 | isolate:BtRF-YN2012 | 26975 nt | vertebrates |
| Human coronavirus 229E | 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-IC34 | NC_034972 | isolate:AcCoV-IC34 | 27682 nt | vertebrates |
| Alpha-CoV 1 | 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 |
|         | 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 CoV strain WD1127 | NC_023760 | strain:WD1127 | 28941 nt | vertebrates |
|         | NL63-related bat CoV | - | strain:BIKYNL63-9a | 57042 nt | Vertebrates |
|         | NL63-related batCoV | NC_032107 | | 28363 nt | Vertebrates |
|         | NL63-related batCoV | NC_048216 | | 28679 nt | Vertebrates |
|         | Porcine epidemic diarrhea virus | NC_003436 | strain:CV777 | 28033 nt | vertebrates |
|         | Rhinolophus batCoV HKU2 | NC_009988 | strain:HKU2/G12430/2006 | 27165 nt | vertebrates |
|         | Roussetus batCoV HKU10 | NC_018871 | isolate:183A | 28494 nt | vertebrates |
|         | ScotophilusbatCoV 512 | NC_009657 | strain:BiCoV/512/2005 | 28203 nt | vertebrates |
|         | WenchengSm shrew CoV | - | isolate:Xingguo-74 | 51979 nt | Vertebrates |
|         | WenchengSm shrew CoV | NC_048211 | | 25984 nt | Vertebrates |
|         | WenchengSm shrew CoV | NC_035191 | | 25995 nt | Vertebrates |
| Middle East respiratory syndrome-(MERS) related coronavirus | Bat Hp-beta-CoV/Zhejiang2013 | NC_025217 | isolate:Zhejiang2013 | 31491 nt | vertebrates |
|         | BatCoV BM48-31/BGR/2008 | NC_014470 | strain:BatCoV/BM48-31/BGR/2008 | 29276 nt | vertebrates |
| Beta-coronavirus | Beta-CoV England 1 | NC_038294 | strain:England | 1 | 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 |
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.  

| Species/Strain | Accession | Isolate/Strain | Classification |
|----------------|-----------|----------------|----------------|
| Erinaceus/VMC/DEU/2012 | NC_026011 | strain:HKU24-R05005i | vertebrates |
| Beta-CoV HKU24 | NC_026011 | strain:174/GER/2012 | 31249 nt |
| Betacoronavirus | NC_003045 | isolate:BCoV-ENT | 31028 nt |
| HumanCoV OCA43 | NC_006213 | strain:ATCC serotype:OC43 VR-759 | 30741 nt |
| HumanCoV HKU1 | NC_006577 | isolate:HKU1 | 29926 nt |
| MurineCoV | - | strain:MHV-A59 | 62692 nt |
| Murine hepatitis virus | - | strain:MHV-A59 | 62692 nt |
| Murine hepatitis virus | NC_001846 | - | 31357 nt |
| Murine hepatitis virus | NC_048217 | - | 31335 nt |
| RatCoV Parker | NC_012936 | strain:Parker | 31250 nt |
| Pipistrellus batCoV H505 | NC_009020 | strain:HKU5-1 LSMH03f | 30482 nt |
| RabbitCoV HKU14 | NC_017083 | strain:HKU14-1 | 31100 nt |
| Rousettus batCoV | NC_030866 | isolate:GCDC1 356 | 30161 nt |
| Rousettus batCoV HKU9 | NC_009021 | strain:HKU9-1 BF_0051 | 29114 nt |
| Severe acute respiratory syndrome-related coronavirus (SARS-CoV) | - | - | 29751 nt |
| SARS-CoV-2 | NC_045512 | isolate:Wuhan-Hu-1 | 29903 nt |
| Tylokynteris bat CoV HKU4 | NC_009019 | strain:HKU4-1 B04f | 30286 nt |
| Common moomoong CoV HKU21 | NC_016996 | strain:HKU21-8295 | 26223 nt |
| Magpie-robin CoV HKU18 | NC_016993 | strain:HKU18-chu3 | 26689 nt |
| MuniaCoV HKU13-3514 | NC_011550 | - | 26552 nt |

**Delta-coronavirus**

| Species/Strain | Accession | Isolate/Strain | Classification |
|----------------|-----------|----------------|----------------|
| Night heron CoV HKU19 | NC_016994 | strain:HKU19-6918 | 26077 nt |
| PorcineCoV HKU15 | NC_039208 | strain:HKU15-155 | 25425 nt |
| Sparrow CoV HKU17 | NC_016992 | strain:HKU17-6124 | 26083 nt |
| Thrush CoV HKU12-600 | NC_011549 | - | 26396 nt |
| White-eye CoV HKU16 | NC_016991 | strain:HKU16-6847 | 26041 nt |
| Wigeon CoV HKU20 | NC_016995 | strain:HKU20-9243 | 26227 nt |
| Beluga whale CoV SW1 | NC_010646 | isolate:SW1 | 31686 nt |
| Canada goose CoV | NC_046965 | strain:Cambridge_Bay_2017 | 28539 nt |

**Avian CoV**

| Species/Strain | Accession | Isolate/Strain | Classification |
|----------------|-----------|----------------|----------------|
| Duck CoV | NC_048214 | isolate:DK/GD/27/2014 | 27754 nt |
| Infectious bronchitis virus | - | strain:Beaudette | 55072 nt |
| Infectious bronchitis virus | NC_001451 | - | 27608 nt |
| Infectious bronchitis virus | NC_048213 | - | 27464 nt |
| Turkey CoV | NC_010800 | isolate:MG10 | 27657 nt |

**Unclassified**

| Species/Strain | Accession | Isolate/Strain | Classification |
|----------------|-----------|----------------|----------------|
| Shrew CoV | NC_046955 | isolate:Shrew-CoV/Tibet2014 | 27102 nt |

**Epsilon-coronavirus**

| Species/Strain | Accession | Isolate/Strain | Classification |
|----------------|-----------|----------------|----------------|
| B.1.427/B.1.429 | Notclassified. 20C/S:452R | - | Human |

**Omicron-coronavirus**

| Species/Strain | Accession | Isolate/Strain | Classification |
|----------------|-----------|----------------|----------------|
| hCoV-19/Botswana/48/2021 | Not classified | - | Human |

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

*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.*
while the other indicated expression of only five canonical accessory ORFs (3a, 6, 7a, 7b, 8). 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. 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). Variations (mutations) in the S-protein are associated with the host tissue tropism and severity response range to CoVs. 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. Aside from ACE2, SARS-CoV-2 S-protein was shown to interact with neuropilin 1 (NRP1) and Basigin2/EMMPRIN/CD147 (CD147). The involvement of CD147 in pathogenesis of other widely spread and highly harmful viruses was demonstrated.

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. Alternatively, protein 6 blocked pro-inflammatory interferon (INF) signalling, but stimulated DNA synthesis. Activation of nuclear factor kappa B (NF-κB) by ORF3a, M, ORF7a, and N proteins was reported. Accordingly, ORF7a was indicated as a promising anti-inflammatory therapeutic target in COVID-19 patients. Previously, SARS-CoV protein 7a was also shown to trigger NF-κB and mitogen-activated protein kinase p38 (MAPK) signalling pathways. Alternatively, it was reported that SARS-CoV structural M protein can block NF-κB activity in cell models in vitro, 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. 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. 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 were recently reviewed.

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). 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 ≈11 days.79 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)).80 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.81 Mutational hotspots inflicted in SARS-CoV-2 NSPs were shown to promote virulence of the pathogen.82 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-2.83 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.84 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)85 and Omicron (BA.1/B.1.1.529)86 variants that caused global health crisis.86 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,87 patients infected with mutated S-protein variants were less protected and indicated lower level of anti-viral antibodies.85 Mutations in other regions, including modifications within SARS ORF1a genome, a key region for NSP mutations, have largely unclear consequences for human health86 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.66 Gussow et al., assessed the role of S-protein and other components and characteristics of SARS-CoV-2, SARS-CoV, and MERS-CoV.87 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.88 Multiple SARS-CoV-2 mutant variants with high virulence were reported.88 For instance, African and Asian countries were marked by the highest percentages of unique mutations in S-proteins.90 European and North American S-protein variants were marked by a larger number of diverse haplotype blocks that contained nonsynonymous variants.8488 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.8488 However, recently reports delineate the emergence of more virulent double mutant strains of SARS-CoV-2 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.9192 Mutations in ORF allow the generation viral proteins which can induce MHC-1 expression in the infected hosts and promote viral escape from immune surveillance.9394 It has been shown that Alpha variant contains ORF with a premature stop codon at 27th position.95 Interestingly, partial deletions of NSP1 and ORF8 (Δ382 variant in Singapore) were observed in VOCs detected in Sichuan, China (NSP1: Δ500-532 variant).9294 A side from NSP1, non-RBD regions mutation D614G is one of the most widely occurring mutations reported in 99% of current variants.9697 The mutation helps to enhance S-protein density, prevent S2 shedding, and facilitate a higher infection rate.9899 Higher rate of deletions was also detected in antibodies-recognising domain (N-terminus region of S1 subunit).100 For instance, Alpha and Beta variants were shown to contain numerous mutations in S1 subunit, including ΔRDR1 (recurrent deletion region (RDR)), ΔHV 69–70, ΔRDR2, ΔY144, ΔRDR4, and ΔAL 242–244; whereas ΔRDR3 and ΔI210 were reported in B.1.36 (Indian Delta variant).100

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 receptors. Supporting this, B.1.617 was predominantly reported to be resistant to the treatment with bamlanivimab 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.54

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.81 The isolates were segregated into 22 groups according to the phylogenetic clade analysis which depicted various sub-clades categorisation of the variants with unique co-existing 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.102 Alternatively, G25563T (in ORF3a), C26735T (in NSP14),
and C18877T (in M protein) mutations were observed less frequently (15%) in the Indian genome.

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. Observation mutation in the 5’-UTR region could impact protein folding and transcription of SARS-CoV-2 genome. Specific mutations in S-protein (L54F, K77M, R78M, D294D, E583D, Q677H),

NSP3 (G716L, T749I, A994D, D1112G, S1119J), RdRp/NSP12 (A97V, L329I, G571S, V880I), NSP2 (S301F, G339S), and N-protein (S194L) coding genes were unique to Indian isolates. 

The variant strains with mutations were also reported in Indian isolates.

Ribavirin, and favipiravir.

SARS-CoV-2 proteases.

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 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.

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. 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. 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. 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.

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/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/NSP2) was detected in South India and North India. 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.

A computational study by Das et al. (2021) 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 codons (ORF1ab, S- and N-proteins, ORF3a, ORF7a, and ORF8) were found mutated in Indian isolates. ORF3a exhibited 4% of its total length mutated. Substantial % of mutation rate was also observed in ORF1ab and S-protein. 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.
resistance to the monoclonal antibodies that target NTD. 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 and consequent viral transport into intracellular space. Notably, S-protein’s RBD is the target for many potent neutralising antibodies. 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) 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. 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. Enhanced transmissibility was observed for the B.1.351 (N501Y.V2) variant which substantially increased the binding capacity to the host cells. Thus, similar to the other RNA viruses, SARS-CoV-2 has been evolving with divergent mutations and novel variants are expected.

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’). Despite being a very recent addition to the VOC list, presence of Lambda variant has been observed in 26 countries (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. 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. Recent study reported

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**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. 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 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.
variants. BNT162b2 third dose was also more effective against Beta and Delta escaping from the convalescent sera. Several mutations (N501Y, D614G, K417N, T478K) were suggested to amplify the reinfection risk and facilitate vaccine resistance. Omicron and Delta contain two similar RBD mutations that lead to S-protein modifications, increased ACE2 binding affinity, and ability to evade immune surveillance. 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. However, it was recently demonstrated that additional (booster) mRNA vaccine doses may help to improve antiviral antibody responses against new SARS-CoV-2 variants.

It was also noted that Omicron is rapidly spreading, escaping from the convalescent sera. Two-dose course with existing vaccine indicated escape of omicron from immune cross-neutralisation. 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. Other RBD-located mutation (G339D, S371L, S373P, S375F, N440K, G446S, S477N, Q493K, Q496S, Q498R, and Y505H) may also contribute fast spreading of Omicron variant, 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. 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. Supporting these findings, another recent study indicated significant protective effects of 3rd dose (>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. The data may be called preliminary as the study included only 244 Omicron and 679 Delta cases injected with third dose of vaccine. Notably, extended intervals (>42 days) between second and 3rd vaccine doses provided better immunogenicity. 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). BNT162b2 third dose was also more effective against Beta and Delta variants. 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. NTD-located mutations may provide an additional pathway for the viral escape from antibody-based neutralisation. Antibody-linked sensitivity and infection spread were recently associated with the natural mutations in NTD. Polyclonal antibodies generated by the human immune system were shown to bind to the several RBD sites that are undergoing intense evolutionary changes. Therefore, current RBD-targeting antibodies alone may not provide an efficient protection from the virus. 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. Two mutations, N479K and T487S located on S-protein can modulate the RBD/ACE2 binding affinity. 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. 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. 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. 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). 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. Furthermore, random mutations were...
also observed in nsp1-nsp3, nsp12, nsp13, and nsp16 (ORF1ab replicase) (Figure 2).\textsuperscript{156} S1 and S2 subunits of S-protein in MERS-CoV were shown to gain substitutions (such as T424I, S459T, W553R) in RBD.\textsuperscript{159} The S2 subunit-located substitutions S950T, Q1009L, and C1313S were also observed in the fusion peptide, heptad repeat region-1, and transmembrane region, respectively.\textsuperscript{156} 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).\textsuperscript{83} Several substitutions (L293F, V263A, R292P, and W293C) were detected at the MERS-CoV CTD region.\textsuperscript{156} Similar to other Beta-coronaviruses, the MERS-CoV encodes 5 accessory proteins (ORF3, ORF4a/4b, ORF5, and ORF8b).\textsuperscript{159} 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.\textsuperscript{160} 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.\textsuperscript{160} 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.\textsuperscript{160} 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.\textsuperscript{160} 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.\textsuperscript{161} Anti-RBD antibody pool in convalescent patients represents 90% of the serum-circulating neutralising activity,\textsuperscript{162} 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.\textsuperscript{163} However, the receptor binding motif of S-protein has operational plasticity and excessive mutations in RBD, which may abrogate the antibody efficacy after vaccination.\textsuperscript{164} 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\textsuperscript{165} 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.\textsuperscript{166} As a promising sign of long lasting immunity, the presence of plasmablast responses was also reported.\textsuperscript{167} It has been previously shown that antigen-specific germinal B cells may remain functional for a year.\textsuperscript{168,169} However, the vaccine induced production of fewer antibodies targeting NTD of the S-protein,\textsuperscript{166} 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 ≥16 years) participated in one of the clinical trials and the vaccine showed 95% efficacy (30 μg per dose, two doses) and exhibited an efficient level of protection against the symptomatic COVID-19.\textsuperscript{170} 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.\textsuperscript{171}

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.\textsuperscript{156,172} Approximately 30,420 individuals (≥18 years old) participated in one of the clinical trials.\textsuperscript{173,174} The vaccine showed 90% efficacy (100 μg 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.\textsuperscript{173,174} 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.\textsuperscript{171,173-177} However, these vaccines were only partially protective against VOCs with RBD mutations.\textsuperscript{171,173,174,177} Vaccine-induced neutralisation efficacy of 14 out of 17 detected antibody types declined against variants with K417N, or E484K, or N501Y mutations.\textsuperscript{178-182} VOCs with E484K and Q493R mutations exhibited resistance to class 2 antibodies; whereas variants with R346S, N439K, and N440K mutations resisted class 3 antibodies.\textsuperscript{178-182}

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.\textsuperscript{174,183}

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 (NCT0471061; 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-γ responses.\textsuperscript{184}

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.\textsuperscript{185}

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.\textsuperscript{186} The significant problem associated with this vaccine is unexpected, although very rare prothrombotic side effects.\textsuperscript{187} 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 protective against VOCs with RBD mutations.

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.\textsuperscript{186} The significant problem associated with this vaccine is unexpected, although very rare prothrombotic side effects.\textsuperscript{187} 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 protective against VOCs with RBD mutations.

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 (½ the rate of influenza and ¼ 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.\textsuperscript{179}

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

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.  

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.

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. 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. 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.

As a result, 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. 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. Another clinical study reported the low efficacy of Moderna (mRNA1273-based) and Pfizer-BioNTech (BNT162b2) vaccines against mutant variants in 20 patients.  

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). However,
14 extracted antibodies (out of the detected 17) were inefficient in the neutralisation of mutant variants with K417N, or E484K, and N501Y mutations. Effects of neutralising antibodies were also moderately decreased against UK B.1.1.7 mutant strain. Notably, a single dose of BNT162b2 was sufficient to generate some neutralising antibody responses against UK B.1.17 which contains 23 mutations (17 amino acid (AC) substitutions with 8 of them in S-protein). A significant decrease was observed for antibodies that targeted NTD and receptor-binding motifs, but not the RBD part that is responsible for ACE2 interaction in B.1.1.7. Furthermore, recognition of NTD by antibodies can also be influenced by presence of deletion, substitutions, and insertions in mutated variants, although some antibodies are still able to bind RBD and neutralise the virus. The vaccine sera was shown to contain a wide range of neutralising titres of <1:4 and predominantly mitigated the mutant UK B.1.117 viral titres by 3.85-fold. Further decline in the neutralisation was observed after introduction of E484K substitution (observed in VOC 202102/02), suggesting an inefficiency of BNT162b2 against this mutant. Current and future studies should delineate the comparative efficacy of vaccines against co-evolving mutant variants B.1.17 (Tables 2 and 3).

BNT162b2 and other mRNA-based vaccines are delivered using lipid nanoparticles. The vaccines demonstrated a very high neutralisation efficiency (>94%) and disease prevention in clinical studies. However, the emergence of SARS mutant variants raised several concerns about the future efficacy of current vaccines. Other inactivated protein vaccines, including AZD1222, JNJ-78436735, NVX-CoV2373, and CoronaVac, indicated good clinical efficacy. However, the emerging data from South Africa and Brazil where pandemics were widely dominated by novel variant strains, suggests that the neutralisation-resistant variants may have contributed to the decline in vaccine efficacy. Another study which tested the cross-neutralisation of B.1.1.7 mutant variants by convalescent and vaccine sera indicated a minimal efficacy of BNT162b2 or mRNA-1273 vaccinations. It was concluded that P.1 (35 mutations, 17 AC substitutions) and B.1.351 variants (N501Y.V2), both with K417N/T, E484K, and N501Y RBD-located mutations, exhibit the minimal neutralisation titres with of BNT162b2/mRNA-1273

### Table 3

Comparative clinical efficacy of mRNA vaccine, viral-vector vaccine, inactivated pathogen vaccine, protein subunit vaccine, virus-like particle vaccines against various mutant variants of SARS CoV-2 in UK, USA, South Africa, Brazil, India, and Nigeria compared to their efficacy against parental strain and their individual Neutralization antibody responses, and Immune response rates

| MUTANT STRAIN | mRNA-1273 | BNT162b2 or Comirnaty | Ad5-nCoV | AZD1222 | Gam-COVID-Vac or Sputnik-V | AZD1222.COV OR JNJ-78436735 | Corona Vaccine | Sinopharm | BBEFP. CorV | BBV 152 OR Covaxin | NVX-CoV2373 | ZZF2001 | CoVLP |
|---------------|-----------|-----------------------|---------|---------|-----------------------------|-------------------------------|----------------------------|-------------|------------|----------------|----------------|-------------|
| **United Kingdom (B.1.1.7)** | Neutralization: Decrease by 1.8×**<sup>1</sup>** | Effect: Decrease by 1.8× | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR |
| | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: Similar | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR |
| **South Africa (three variants of the B.1.35I lineage)** | Neutralization: Decrease by 58.6×**<sup>1</sup>** | Effect: Decrease by 58.6× | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR |
| | Efficiency: 94.1% | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: 69% | Efficiency: NR | Efficiency: NR |
| **United States (B.1.429, B.1.427)** | Neutralization: Effective against B.1.429, magnitude of resistance seen with the B.1.35I variant is of greater concern | Effect: Effective against B.1.429, magnitude of resistance seen with the B.1.35I variant is of greater concern | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR |
| | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR |
| **Brazil (P.1)** | Neutralization: Decrease by 4.5× | Effect: Decrease by 4.5× | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR | Neutralization: NR |
| | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR | Efficiency: NR |
compared to the parental strain titres.\textsuperscript{164,222,223} 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.\textsuperscript{209} The resistance to vaccine-generated antibodies was also associated with NTD-located deletions (Y144del and 242-244del).\textsuperscript{223}

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.\textsuperscript{163} 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.\textsuperscript{163}

B.1.351 (N501Y.V2) variant contains 23 mutations and 15 AC substitutions.\textsuperscript{224} The strain is marked by the presence of N501Y mutation (asparagine (N) replaced by tyrosine (Y) at 501 position in RBD) in S-protein.\textsuperscript{210} B.1.351 strain also contains deletions in the NTD that prevents proper binding of neutralising antibodies.\textsuperscript{209} The variant escaped elimination by host immune mechanisms in 48% of convalescent serum samples.\textsuperscript{225} Aside from the neutralisation escape,\textsuperscript{226} the strain has comparatively a higher viral transmissibility and reinfec tion capacity than the parental strain. Accordingly, it could induce severe COVID-19 outcomes than parental strains.\textsuperscript{210} It seems that current vaccines cannot guarantee reliable protection against S01Y.V2 strain (Table 3).\textsuperscript{209}

Low clinical efficacy against B.1.351 mutant was also observed after administration of two doses of ChAdOx1 nCoV-19 vaccine [AZD1222].\textsuperscript{227} 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.\textsuperscript{228} Ad26.COV2.S vaccine exhibited a better protection against B.1.351 in South African subjects.\textsuperscript{190,229} However, Ad26.COV2.S vaccination also induced thrombotic thrombocytopenia.\textsuperscript{230} 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.\textsuperscript{230} 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.\textsuperscript{231}

Delta 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), B.1.1.298, and B.1.429 also exhibited a significant potential to avoid neutralisation by vaccine-induced antibodies.\textsuperscript{222} 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%\textsuperscript{233} and Oxford–AstraZeneca (ChAdOx1) neutralisation effect collapsed from 62% to 10%.\textsuperscript{223} Significant fall in efficiency was demonstrated with JNJ-78436735 (Johnson & Johnson).\textsuperscript{233} However, the neutralisation titre was not changed for the
B.1.1.7 strain. 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. Unfortunately, there is currently no guarantee that existing vaccines can provide required protection against the emerging strains. 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. 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. 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 genome 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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