Immunity Escape of SARS-CoV-2 Variants: Omicron leads the way

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Abstract

With the emergence of COVID-19 pandemic in 2019, the world saw a humungous loss of human life and economic resources globally but also the rapid appearance of SARS-CoV-2 variants which have exhibited a higher transmissibility and/or virulence and which also evade immune system to such an extent that it raises a big question mark on the efficacy of current diagnostics, vaccines and convalescent plasma and mAb therapies. This has been attributed to the emergence of huge spectrum of mutations, especially in the virus's spike (S) protein, occurring in regions harboring high concentration of B cell epitopes thus allowing neutralizing antibody escape. The mutations resulting in ACE 2 receptor recognition failure (T19R), unfavorable electrostatic interactions (E484K), structural change (Δ69-70), disruption of hydrogen bonds, salt bridges or hydrophobic interactions (K417N, N501Y, ΔY145) and change in orientation (N501Y) cause strong immune evasion by these variants. Further, the recent emergence of Omicron with more than 30 mutations in the S protein VOC allows it to escape and fail diagnosis as well as immune system and the protection generated by different vaccination regimes. Yet Omicron may not be the end of the story. This review presents an insight of the immunity escape and its mechanisms followed by different SARS-CoV-2 variant of concerns.

Keywords: SARS-CoV-2, Mutations, Omicron, Delta, Variants of Concern, Variants of Interest, Immunity Escape, Mechanisms.

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1. Introduction

The year 2019 saw the onset of a horrendous global pandemic, COVID-19 (Coronavirus disease 2019) which was caused by a novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) (WHO 2020). The alarming spread of virus posed a massive threat to mankind making this upsurge a Public Health Emergency of International Concern on 30 January 2020 and later a global pandemic on March 11, 2020 by the World Health Organization (WHO 2020) (Li et al., 2020a). But soon after this onset, various new variants of SARS-CoV-2 emerged that brought about newer waves of infection worldwide because of the never-ending mutations acquired by the virus. Good evidence of this is the newly emerged variant- Omicron (B.1.529) exhibiting more than 60 mutations than the original Wuhan strain. As of 24 March, 2022, accounting for more than 474 million cases and 6.1 million deaths, this pandemic is one of the deadliest in the history of mankind (WHO 2022).

HCoVs (Human Coronaviruses) are enveloped viruses which contain non-segmented 30 kb ssRNA (+ve sense) genome and belong to subfamily *Coronavirinae* of family *Coronaviridae*. They primarily host the vertebrates. The International Committee for Taxonomy of Viruses has classified HCoVs into four major genera; alpha, beta, gamma, and delta on the genotypic and serological basis out of which beta CoV is known to cause severe infection (Wu et al., 2020). SARS-CoV2 is a novel beta CoV following formerly discovered SARS-CoV and MERS-CoV that caused outbreaks characterized by respiratory failure and potentially fatal tracheal infection (Kirtipal et al., 2020)

Symptomatology of COVID-19 varies from asymptomatic to severe life-threatening complications. Major symptoms include, persistent cough, fever or chills, difficulty in breathing, loss of smell or taste. Age and underlying medical conditions are the pre-disposing factors for severe illness. Nonetheless, SARS-CoV-2 is airborne and spread via air contaminated with virus particle (Rocklov et al., 2020). To exterminate the pandemic arised due to COVID-19 pandemic, globally scientists made tremendous efforts to develop diagnostic methods, drugs and anti-SARS-COV-2 vaccines (Hossain et al., 2021; Sharma et al., 2021) but as all viruses, SARS-CoV-2 also evolved over time. This is not totally surprising since RNA viruses, insert mutations quite rapidly because enzymes copying RNA are prone to errors (Callaway., 2020). For DNA viruses, mutation rate ranges from 10^{-8} to10^{-6} s/n/c (substitutions per nucleotide per cell infection) while it is 10^{-6} to 10^{-4} s/n/c for RNA viruses. However, SARS- CoV-2's replication machinery, RNA-dependent RNA polymerase (RDRP), has exonuclease activity with a proofreading mechanism, which results in a decreased incidence of new mutations. (Denison et al,

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2011). Silent mutations in SARS-CoV-2's RDRP (or proteins interacting with it) and various antiviral restriction aspects have been offered as a possible explanation for the virus's increased mutation rate (Pachetti et al., 2020). When through various cycles of viral replication, a mutation is selected, it results in the emergence of a viral variant. The same was observed in case of SARS-COV-2 when the first variant D614G was identified in March 2020 and spread all over the World. Typically, mutations in these variants are associated with S protein, specifically the N-Terminal Domain (NTD) and the Receptor Binding Domain (RBD), thereby enhancing virulence of virus by increasing its transmissibility, infectivity, severity and allowing it to escape immune response of the body. The SARS-COV-2 mutant B.1.1.7 (UK), B.1.1.298 (Denmark), B.1.1. 351 (South Africa), B.1.429 (US), P.1 (Brazil) and B.1.617 (India) triggered huge concern. These variants led to multiple waves of COVID-19 all over the world making this pandemic more critical and out of control. The problem became more alarming when the vaccines demonstrated a reduction in overall efficacy in neutralizing these emerging variants (Beltran et al., 2021). This is because the main target of the neutralizing antibodies (Abs) is the viral spike protein which has undergone continuous change. Hence these mutations occur within the major target of numerous neutralizing and monoclonal Abs (mAbs) responsible for natural and vaccine-induced protection. This enhances the ability of mutant viruses to infect new hosts and to by-pass pre-existing humoral response providing them a potential survival advantage. This means that those with previous history of SARS-CoV-2 infection are still susceptible to reinfection and also there is a decreased efficiency of the vaccine against some of these new variants (Kumar., 2021a). Nonetheless, there are increased chances of appearance of new mutations as more people are vaccinated. This is because the virus will face an increased pressure to escape immune system resulting in subsequent generation of new SARS-CoV-2 mutants such as the recent emergence of Omicron and IHU (Mahase., 2021b).

This review collates the reports concerning the important characteristics (occurrence, mutations and their effect) of the SARS-CoV-2 Variants of Concern (VOC) (a variant that shows confirmatory evidence for higher transmissibility and fatality and a significant decrease in neutralization by vaccines, therapy and other health measures), Variants of Interests (VOI) (A variant with a predicted enhanced transmissibility or severity that exhibits a decrement in neutralization by vaccines, treatments and Abs generated as a result of prior infection) (WHO 2021a) and Former VOI and their escape from infection and vaccine mediated immunity with the mechanisms known so far.

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2. SARS-CoV2 Variants- What makes them different?

The emergence of D614G variant in March 2020 raised concerning alarm worldwide. The mutation was found to enhance viral replication and was associated with increased infectivity. Soon it was found in SARS-CoV-2 samples all over the world. Then, different parts of world saw independent outburst of new mutants of SARS-CoV-2. All recently identified variants have acquired mutations especially in the ACE2 interacting surface of the RBD (Figure 1): N501Y in B.1.1.7 (UK); K417N, E484K and N501Y in B.1.351 (South Africa); K417T, E484K, and N501Y in P.1 (Brazil) and in the NTD of S protein: Δ 69-70 and Δ 144 in B.1.17; D253G in B.1.526, Δ 242-244 in B.1.351 (Table 1). These mutations may lead to enhanced transmission, as observed in alpha and delta. Another important clinical outcome includes the ability to escape natural and vaccine derived immunity, as shown by B.1.351 and P1 variants possessing E484K mutation in S protein. The mutants have quickly spread over the world, becoming the domineering strains in the areas where they were first discovered.

3. How do variants escape immunity?

The structural architect of SARS-CoV-2 constitute 4 types of major proteins- spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and also several accessory proteins (Jiang et al., 2020). The interaction between RBD of trimeric S protein and SARS-CoV-2 cellular receptor- ACE2 lead to membrane fusion of host and virion leading to release of viral genome into cell which initiate infection cycle (Hoffmann et al., 2020). The immune system of the body recognizes and act against this foreign pathogen (Figure 2).

Hence, mutations in RBD are of greatest concern. Notably, the ACE2 interacting surface of RBD , which binds to potent neutralizing Abs is located at the tip (a segment of 25 amino acid residues) (Cerutti et al., 2021). Obstructing this RBD-ACE2 interaction is the major mechanism in case of both active and vaccine-elicited immunity from SARS-CoV-2 infection. But as it is so small, even small changes in it can result in escape from neutralizing antibodies. This hence reduces the ability of the immune system to fight off the infection. Whether the present known variants evade the immune response and if yes, how do they do so, is reviewed below.

3.1 Variants of concern (VOC): (Table 2)

3.1.1 Alpha variant (B.1.1.7)

On December 14, 2020, cases of a new variant of SARS-CoV-2 were reported in the UK. The VOC was designated as B.1.1.7, also referred to as VOC 202012/01 or 20I/501Y.V1. It was first identified in September 2020 and was found to have 23 mutations including 17 amino acid substations in S protein. The variant quickly became the dominant one in England and has spread over 122 countries. This is because B.1.1.7 is more effectively transmitted

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as compared to the original SARS-CoV-2 strain. Recently a new variant of B.1.1.7 having E484K mutation was detected in UK and named, 'B.1.1.7 with E484K' or 'Bristol variant'. Multiple lines of evidence indicate that N501Y mutation increases the S protein's affinity for ACE2 receptor (Supasa et al., 2021) and compromises neutralization by various Abs having public V-region IGHV3-53 as various SARS-CoV-2 RBD/ Fab immune complexes are directed for immunoglobins that exhibit public Ig heavy chain variable (IGHV) region IGHV3-53. These public Ig define CDR1 (Complementarity determining region 1) and CDR2 which cause the antibody to align such that the light-chain CDR1 region lies above RBD residue 501. Hence a mutation at 501 position is likely to affect binding of majority of these Abs since as unlike ACE2, the occurrence of asparagine is more favored. This results in reduced neutralization by some important class of public immunoglobulins through light-chain interaction at 501 (Supasa et al., 2021). Mutation P618H increased the susceptibility of cleavage site to transmembrane protease thereby increasing the viral load and hence the viral transmission. The variant exhibited rapid spread in early 2021 in the US, becoming the dominant variant in March.

Substitution in receptor recognition site of S protein, further confer immune escape potential. The 69-70 amino acid deletion changed the structure of S1 and S2 because of which many Abs produced against the original SARS-CoV2 are unable to bind to this variant allowing it to evade the immune response of neutralizing Abs (Meng et al., 2021). Moreover, the failure of RT-PCR that targets S protein gene was also caused by this deletion (Galloway et al., 2021). Additional mutations in B.1.1.7, most notably the deletion 144 in the NTD, may have an impact on neutralization. However those NTD binding antibodies which do not obstruct interaction with ACE2, are capable of neutralizing SARS-CoV-2 (Supasa et al., 2021). ΔY144 deletion abolishes neutralization by a range of Abs as it alters the anatomy of the N3 NTD loop (positions 140–156) (McCallum et al., 2021b).

B.1.1.7 variant exhibited a moderate decrease in neutralization by natural immunity (Karim and Oliveira., 2021). Decrease in B.1.1.7 neutralization was also noted with mAbs, more with one's targeting NTD than the receptor binding antibodies, but was not seen in neutralizing mAbs binding outside the Receptor Binding Motif (RBM) (Collier et al., 2021). Thus, sera from convalescent individuals and vaccinees cross-neutralize B.1.1.7 variants with a little reduction in potency. The production of Abs against the epitopes that are not part of ACE2 interacting surface are expected to form remarkable components in therapeutic mix as they would not be affected by mutations in the ACE2 interacting sites.

This shows that protection can be attained against the future infection with this variant following vaccination or prior infection with wild-type SARS-CoV-2. B.1.1.7 can evade neutralization by most NTD targeting mAbs but to a few mAbs against RBM. It is not much resistant to plasma from convalescent patients or sera from individuals

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(Wang et al., 2021a). This means that variant B.1.1.7 is unlikely to represent a major source of concern for current vaccinations or a danger of reinfection (Shen et al., 2021; Supasa et al., 2021). In addition, protective immunity through the production of memory T cells against symptomatic and severe COVID-19 may be conferred by natural exposure and vaccination (Altmann et al., 2020).

3.1.2 Beta variant (B.1.351)

B.1.351 (501Y.V2) variant (Oct. 2020, South Africa) and has 10 mutations in spike that can aid in immune evasion (E484K) (Wise., 2021) and increase the viral transmission (N501Y and K417). The variant caused an alarming concern when it was found to escape both natural and vaccine generated immune response more than the earlier found UK variant. In a case study, the beta variant has entirely escaped the neutralization by Abs in 48% of convalescent serum samples from patients who were earlier infected with COVID-19 (Wibmer et al., 2021). Furthermore, the entry of B.1.351 and P.1 variant mediated by S protein was found to be completely resistant to monoclonal antibodies: REGN10989 and Bamlanivimab- that received EUA (Emergency Use Authorization) for COVID-19 therapy (Hoffmann et al., 2021). The mutations K417N, E484K and N501Y in S protein caused widespread escape from mAbs. In addition, NTD deletion mutations in B.1.351 escape neutralization by a potent neutralizing human mAb.

Amino acid replacements in RBD i.e N501Y, E484K and K417N are nominally present in different epitopes (Zhou et al., 2021). But as they have an overlapping nature, they are so close that the binding of any one antibody is affected (Dejnirattisai et al., 2021a). As already stated, Fab/SARS-CoV-2 RBD complexes have public IGHV region IGHV3-53. The IGHV3-53 immunoglobulin family binds to the same epitope in back of RBD neck as IGHV3-66 Fabs, with identical orientations. The major point here is that most of these Abs make direct contact with N501 and K417, but not with E484. Heavy chain CDR3s of these Fabs are generally placed exactly above K417, which make salt bridges or H bonds and hydrophobic interactions, whereas N501 binds with light chain CDR1 loop (Dejnirattisai et al., 2021a). Therefore, it is imperative to note that interaction of IGHV3-53 and IGHV3-66 class mAbs is adversely affected with N501Y and K417N mutations. Further, E484K mutation within the RBD, as already described, makes the virus able to escape immune system recognition, suggesting a reduction in neutralization by sera from convalescent plasma and vaccinated individuals (Greaey et al., 2021) (Table 3). The findings indicate that highly efficient ACE2 blocking mAbs are present at two sites, residues E484–F486 bridge. Hence, the mutation at these sites affects the binding of a large number of mAbs (Supasa et al., 2021). E484–F486 is also involved in making double-sided anti-parallel beta sheet with residues A92–A94 of L3 and makes stacking bonding from F486 to Y32 of L1, suggesting that a mutation at these sites leads to large escape from Abs.

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Furthermore, at the rear of the left shoulder, Fab 88 interacts with RBD. G104 and K108 of heavy chain CDR3 engage with E484, while LC CDR2 interacts with Y51 via hydrophobic interactions and H bonding, as well as forming a salt bridge from D53 to K417. As a result of substitution mutation at 484, the change of negative to positive charge and contraction of residue 417 side chain is expected to abolish all these contacts owing to the unfavorable electrostatic interactions caused by the mutation, resulting in hundred-time loss in K_D (Wang et al., 2021d). R246I and L18F which occur in the NTD supersite can also affect antibody binding while NTD deletion, Δ243–244 terminates interaction with antibody 4A8 (MacCallum et al., 2020; MacCarthy et al., 2020; Yuan et al., 2020)

Thus B.1.351 variant is of more concern because of its ability to evade Immune response. However, not much escape from T cell – mediated immunity produced against original S protein was seen with both B.1.351 and B.1.1.7 as no major change in T cell activation was observed (Geers, 2021). Reduced neutralization by polyclonal Abs is observed primarily because of the co-existence of K417N, E484K and the substitutions in NTD. When compared to original Wuhan strain, B.1.351 had a higher resistance to neutralization by convalescent plasma (9.4-fold) and sera from vaccinated patients (10.3–12.4-fold) (Wang et al., 2021c). Hence B.1.351 and emerging variants with parallel mutations threaten mAb therapies and protective efficacy of current vaccines. B.1.351 variant currently spans more than 85 nations globally with 3 sub lineages- Botswana (B.1.351.1), Mayotte (B.1.351.2), B.1.351.3 (Singapore and Bangladesh) (Chadha et al., 2021; Zhou et al., 2021).

3.1.3 Gamma variant (P1)

The Brazilian variant- P1 or B.1.1.28.1, which first appeared in December 2020, evolved from B.1.1.28 lineage, first reported in 4 travelers coming from Brazil to Japan (January 2021) and was found to have E484K, K417N, and N501Y mutations. Similar to UK and African variant, the Brazilian variant has also shown an increase in transmission, immune evasion and global spread (Oliveira et al., 2021; Voloch et al., 2021). P1 contains about 35 mutations including L18F, T20N, P26S, D138Y, and R190S in the NTD; K417T, E484K, N501Y and D614G in RBD and H655Y near FCS. Unlike its ancestral strain B.1.1.28, the P1 variant exhibits a higher number of mutations in S protein, including E484K and N501Y, indicating its biological similarity with B.1.351 strain and shows reduced neutralization by current mAb therapies and vaccines. Moreover, P1 infects young adults. Between the ages of 20 and 39, the mortality toll from variants has been increased by 2.7 times (Freitas et al., 2021). As compared to the non-P1 lineages, the variant can escape 25–61% of the protecting immunity produced from prior viral infection.

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P1 is not only resistance to neutralization by convalescent plasma and vaccine sera but is also resistant to multiple neutralizing mAbs as the variant harbors the potential immune escape mutation (E484K). The extent of resistance is higher for mAb than vaccinee sera. This is apparent from the cryoelectronic microscopy construction of a soluble prefusion-stabilized spike which discloses 'Up' position of one of the RBD of P1 trimer. This conformation is adopted exclusively by the P1 trimer which facilitate binding to cellular receptor ACE2. (Wang et al., 2021b)

P1 variant shows high similarity to the D614G structure in terms of complete conformation and hence the functional effect of the P1 mutation arises principally from variations in structure rather than global conformational alterations. Except H655Y and T1027I, all other mutations in P1 are present within NTD or RBD. The pattern of resistant is noticeably different between P1 and B.1.351 for the NTD-directed mAbs, which is attributed to their separate mutations in NTD. P26S and T20N substitutions also befall in or close to NTD supersite at sites having a high antibody accessibility. Furthermore, T20N causes an essential glycosylation site, which may cause glycan shielding of a portion of supersite (McCallum et al., 2021b). Though, there is a significant reduction in neutralization activity for P1 with both convalescent plasma and vaccinee sera against P.1, however the extent of decrease is lesser than that of B.1.351(Garcia-Beltran et al., 2021b). This indicates that NTD mutations have an imperative impact neutralization of virus as RBD mutation are almost same for these variants. One of the major concerns related to P1 variant is its ability to threaten current antibody therapies and reduce the efficacy of present-day protective vaccines (Wang et al., 2021b). Neutralization with mAbs like REGN10933 (casirivimab), CB6 (etesevimab) and LY-CoV555 (bamlanivimab) were significantly or completely eliminated against the variant. REGN10987 (mdevimab) remained effective (Wang et al., 2021b).

Thus, P1 variant showed threats of increased re-infection, decreased vaccine protection and escapes potential mAbs.

3.1.4 Delta variant (B.1.617.2)

A new lineage of SARS-CoV-2 called B.1.617 became leading variant circulating in many parts of India and has spread to other countries. (Novelli et al., 2021) The lineage consists of three key subtypes (B1.617.1, B.1.617.2 and B.1.617.3). A highly contagious subtype, B.1.617.2 has been the primary root of 2nd COVID-19 wave in India. It was first reported in Maharashtra (India) in October 2020 (CDC 2021c) and was designated as a VOC on 11th May 2021owing to its high infectivity, a reduction in effectiveness of mAbs and therapeutic drugs and recurrent cluster outbursts in many countries (WHO 2021a). Sub-lineage B.1.617.1 was designated as Kappa variant (Former VOI). The Delta variant harbors 13 distinct mutations, with 8 of them occurring in S protein, with 2 in

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the RBD (L452R and T478K), 4 in the NTD (T19R, G142D, Δ156–157 and R158G), 1 near FCS (P681R) and 1 in S2 region (D950N). The E484Q and L425R mutations are parallel. The variant is 50% more contagious than alpha and able to evade some neutralizing Abs. Notably, the anti-NTD mAbs are comparatively less effective than anti-RBD mAb.

Other variants, such as B.1.429, have previously been reported to have L452R in the RBD. P681R, which is sited in FCS, may increase the S protein's fusogenic activity (Kannan et al., 2021). The E484Q substitution—considered to be functionally comparable to Ab-escape mutation- E484K prevalent in Beta and Gamma variants- was found in ancestral sequence (B.1.617) and is present in Kappa (B.1.617.1) and B.1.617.3 subtypes. In the Delta sub lineage, however, it is expected to have reverted. The Alpha and Beta variant's 144 and 241–243 deletions, respectively, plot to the same surface as Δ 156–157 and G158R mutation in the delta variant. The T19R mutation is located on a surface patch containing many mutations in the Alpha variant. These altered residues occur in NTD 'supersite' which is the target of many anti-NTD neutralizing Abs. RBD mutations occurring in VOCs are present on the periphery of ACE2-binding surface, which results in to escape from recognition by Abs while keeping bound to ACE2. A unique Delta mutation- T478K falls within epitope region of class 1 neutralizing mAbs. This mutation is analogous to E484K that enables antibody escape. Further, the hydrophobic side chain of L452 is buried in a pocket on the outside of HLA-A*24:02. Disruption of hydrophobic interaction and weakening of the binding has been observed when this leucine is replaced by +vely charged arginine as in the B.1.617.2 variant which can lead to disruption of binding with HLA-A*24:02. (Zhang et al., 2021a).

Delta variant showed six- and four-fold decrease in neutralization titers in comparison to D614G and Alpha, respectively, with convalescent sera. On the other hand, sera from vaccinated individuals exhibited a noticeable rise in neutralizing Ab titers for Alpha, Beta and Delta variants than unvaccinated convalescent participants. Fully vaccinated people have the potential to spread the virus but for a short period of time (CDC 2021c). This suggests that one dose of vaccine elevates cross-neutralizing Ab response to Delta variant (Planas et al., 2021). Because of impaired binding to S protein, Delta variant is found to be resilient to some anti-RBD and anti-NTD mAbs, including bamlanivimab. A recently engineered mAb- bsAb15 has shown a higher neutralization than the parental antibodies (B38 and H4), with maximum activity against the Delta variant (Li et al., 2022).

These findings suggest that Delta variant is one of the most concerning variants of SARS-CoV2 with at least a 40–60% increase in transmissibility and decreased neutralization with convalescent sera and sera from vaccinated than the original Wuhan strain as well as B.1.1.7 variant (Table 3). However, vaccines have continued to remain operative at preventing hospitalizations, severe illness and death.

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3.1.5 Omicron variant (B.1.1.529)

Recently, a severely mutated variant was reported in South Africa, called Omicron (B.1.1.529) and was designated as a new VOC (B.1,1.529 By Luke Hurst & AFP • Updated: 25/11/2021). The variant has been split further into three lineages; BA.1, BA.2, BA.3. Lineage BA.1 is the globally distributed original lineage that gives S-Gene Target Failure (SGTF) because of deletion mutations in NTD and cannot be detected through existing RT-PCR test, and BA.2- the new outlier with around 24 mutations that does not give SGTF (Majumdar et al., 2021). Except BA.2, both BA.1 and BA.3 have the 69-70 deletion in S protein.

The initial known case of omicron was reported on Nov 9, 2021, despite the fact that there may have been unidentified cases in numerous nations around the world prior to that (Gao et al., 2021). The phylogenetic analysis indicated that this variant did not evolve from other VOCs, but evolved discretely through convergent evolution. The variant has spread to more than 150 countries with maximum cases reported in UK as of March 1 (WHO 2021b) (Figure 3). The variant is found to contain extremely high number of mutations, more than 60 as compared to original SARS-CoV-2, 37 of them being in the spike, which poses an alarming question on the effect of these mutation in its spread and in evading vaccines. The origin of a variant with such a high number of mutations is speculated to be because of reverse zoonosis when a rat infection that might have occurred in June or July resulted in the evolution of Omicron. The theory is supported by the fact that Omicron exhibits five mouse-adapted mutations (Sun et al., 2021). Some of the mutations in Omicron have already been reported in Alpha, Beta, Gamma and Lambda variants with proven change in transmissibility, immune escape and virulence. Omicron exhibits an insertion mutation (ins214EPE), detected for the first time in any observed SARS-CoV-2 lineage (Venkatakrishnan et al., 2021). Four new mutations Q339D, S371L, S737P and S375F may create additional obstacles. The variant has shown three additional deletions at position L105 and S106 and also G107 in NSP6 (non-spike protein) which are thought to enhance immune evasion (Martin et al, 2021). The deletion of Y145, the amino acid that exhibited hydrophobic bonding with antibody residues V98 and A97, results in loss of this interaction resulting in reduction in binding affinity of antibodies. Mutations for instance G446S, Q493R and G496S may also result in steric hinderance for Abs interacting with S-RBD while mutations E484A and Y505H may cause a total loss of binding with Ab (Kannan et al., 2022). H655Y may be linked to enhanced S cleavage and resistance to human mAb. Because the Omicron variant exhibits a higher amount of hydrophobic amino acids like leucine and phenylalanine in S protein, it exhibits a greater attraction for human ACE2 (Figure 4). Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K mutations also cause an increased binding affinity with human ACE2 (Kumar et al., 2021b; Jung et al., 2022). Hence it can infect people at a lower dose than other variants

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because of its more efficient entry into human cells. However, the effect of other mutations when reported in combination or standalone needs more study. Overall, mutations in Omicron impact 550 B cell epitopes (IEDB) which is substantially higher than other variants which allows it to widely escape neutralizing antibodies.

The variant has been found to be 10 and 2.8 times more infectious than the original Wuhan strain and Delta variant respectively. The cause of such a high infectivity is attributed to RBD mutations N440K, T478K, and N501Y (Chen et al., 2021a). The fast spread of Omicron from person to person is also attributed to the reason that the variant multiplies 70 times faster in human bronchial tissue than the Delta variant but 10 times slower in lung tissue relative to Wuhan strain. It is also reported to be better at infiltrating and infecting human embryonic kidney cells as compared to other variants (Garcia-Beltran et al., 2021a). Thus, the variant has shown evidences of increased transmission but chances of a high disease severity and wide escape from immunity esp. T- cell mediated immunity are less.

Neutralization with sera from people who have received the vaccine is found to be much less effective for this variant than any other variant analysed (Roessler et al., 2021). Unlike Beta and Delta variants, evidences suggests that Omicron has considerable ability to avoid immunity that has been generated from prior infection at population level (Pulliam et al., 2021). The variant has shown a greater tendency to escape the interaction with 185 Abs because Y505H, E484A and K417N in the RBD. This indicates a robust capability of vaccine-breakthrough than any other variant (Chen et al., 2021a). Neutralization Effective Dose (ED50) of sera from patients who have previously been infected with original Wuhan strain, against omicron decreased to 66 as compared to neutralization activity against other VOC and VOI pseudo typed viruses where decrease was only about 1.2-4.5 folds (Schmidt et al., 2021). RBD mutations K417N, E484A, and Q493R result in reduction of efficacy of mAb cocktail (Chen et al., 2021a). Plasma from people vaccinated with two doses of mRNA vaccine was180 -fold less effective compared to Wuhan strain (Schmidt et al., 2021; Zhang et al., 2021b). But, by creating a strong neutralizing capacity, a combination of infection and immunization, as well as possible boosting, could retain reasonable efficiency against Omicron. (Cele et al., 2021). Despite the fact that the omicron exhibits a higher infectivity, it can still bind to a reasonable array of Abs created by many doses of existing vaccinations, preventing severe sickness. (Li et al., 2021). Because severe disease protection necessitates lower neutralization levels and T cell immunity, such protection may be sustained. This is due to the fact that in Omicron, a high proportion of CD4+ and CD8+ T cell epitopes in S protein remain unmodified, and only 14% and 28% of CD4+ and CD8+ T cell epitopes, respectively, have at least a site carrying mutation (impact in 348 Immune Epitope Database (IEDB) T cell epitopes) (Bernasconi et al., 2021) (Figure 5). Deletions in S protein leads to loss of seven $CD8^{+}$ and twelve

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$CD4^+$ epitopes while six $CD8^+$ and four $CD4^+$ epitopes are thought to become non-binders. However, most of the $CD8^+$ and $CD4^+$ epitopes, including the one's harboring mutations, retain HLA binding, which suggests that T cell immunity generated from previous infection or S protein based COVID-19 vaccines could remain effective against Omicron. Further, memory T- cell response (84 % of CD4+ and 85 % of CD8+) were retained in Omicron, except the one's derived from S protein which also indicates an intact T cell immunity against the variant (Ahmed et al., 2021; Flemming., 2022). Moreover, mutations in regions not recognized by MHC allotypes do not affect memory (Pontarotti et al., 2022). Omicron is found to be resistant to mAb like casirivimab and imdevimab (Wilhelm et al., 2021). Recent studies indicate that neutralization of Omicron for most vaccines is undetectable (complete loss for more than 50% recently mRNA-1273 and BNT162b vaccinated individuals). Only mRNA vaccines boosters result in potent neutralization which is also 4 to 6-fold lower than Wuhan strain (Cameroni et al., 2021; Garcia-Beltran et al., 2021a) (Table 3).

While there has been a large increase in COVID-19 cases in South Africa with Omicron responsible for the 90% of them, the death rate is still less (29% than last wave). A rapid surge in SARS-CoV-2 positive cases and hospitalizations was reported among children and adolescents aged 19 years and younger in Tshwane District, South Africa, which is co-related to the increasing dominance of Omicron variant from mid-November, 2021 (Cloete et al., 2022). However, its high immune escape and vaccine escape ability (14 times than that of Delta variant) puts a question mark on the efficacy of present-day vaccines and mAb therapies. Existing vaccines are expected to shield against severe sickness, hospitalizations and mortality because of Omicron infection. However, there is four to five-fold increase in the risk of hospitalization for recently vaccinated, or individuals with waned antibody titers. A third dose of inactivated or recombinant subunit vaccination generated larger NAb titres, with a broader neutralizing capacity against VOCs, including Omicron (Zhao et al., 2022). Hence third/ Booster dose is expected to restore titers and protection (Gardner et al., 2021). This is supported by higher neutralization titers against Omicron elicited by a third dose of Pfizer vaccine (Abdullah et al., 2021). However even vaccinated individuals can spread the infection as there are chances of breakthrough infections even in fully vaccinated people (CDC 2021b). Providing medical care to a large number of patients because of the virus's high transmission rate and ability to escape both immune system and two dose vaccination, is a major challenge. Omicron's emergence underscores the significance of immunization and booster shots.

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3.2 Variants of Interest (VOI) (Table 4)

3.2.1 Mu variant (B.1.621)

The variant arose in January 2021 in Colombia and on August 30, 2021 was designated as VOI. The variant exhibits over-all 21 mutations some of which (E484K, N51Y and P681H) have already been reported in other VOCs (Beta and Gamma) (Uriu et al., 2021) along with addition of several new changes affecting spike protein. This includes amino acid changes R346K, E484K and N501Y in RBD; I95I, Y144T, Y145S and NTD insertion 146 in S1/S2 cleavage site of S protein (Laiton-Donato et al., 2021). In Colombia the variant led to an immense rise in COVID-19 cases in march 2021 outnumbering the earlier dominant gamma variant. The Mu variant showed significant reduction in neutralization which is accounted to its immune escape mutation E484K. The variant exhibited 10.6 times reduction in neutralization than B.1 lineage virus (parental virus) and was 2.0 and 1.5 times tolerant to neutralization by convalescent and vaccine serum, respectively (Uriu et al., 2021). However, sera from patients vaccinated with two doses of Pfizer vaccine effectively neutralized the B.1.621 variant (Messali et al., 2021).

The occurrence of Mu variant is less than 0.1% globally at present, but is higher in Colombia (39%) and Ecuador (13%). Preliminary data specify that the variant may possess immune evasion properties somewhat parallel to the Beta variant. However, additional studies need to elucidate its clinical importance.

3.2.2 Lambda variant (lineage C.37)

The Lambda variant was first reported in August 2020 in Peru and was assigned as VOI on 14 June 2021. The variant contains a novel seven amino acid deletion (Δ246 to 252) in NTD and exhibits 7 nonsynonymous mutations in S gene. L452Q is exclusive to C.37 although L452R is found in VOC Delta and VOI- epsilon and kappa and is responsible for increased binding for the ACE2 receptor (Romero et al., 2021). The variant caused a big surge of cases in Chile in Spring 2021 suggesting that it is more infectious and is proficient in escaping immunity elicited by vaccination. The increased infectivity is associated with T76I and L452Q mutations while L452Q, F490S and the unique amino acid deletion confer resistance to immunity (Kimura et al., 2021; Wang et al., 2022; Weisblum et al., 2020). This is supported by bioinformatics analysis that indicate that a combination of shortening of the immunogenic epitope loops is responsible for the variant's ability to escape immune response (Pascarella et al., 2021). Reports suggests that the variant demonstrated an increased infectivity which was even more than D614G, Alpha and Gamma variants.

Lambda demonstrated 3.3 and 1.5-fold greater infectivity in Calu-3 and LLC-MK2 cells, respectively. The Lambda variant had a 3.05-fold drop in neutralization when compared to Wuhan strain (Acevedo et al., 2021).

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Furthermore, 1.3–2.5-fold reduced neutralizing titres were observed in case of convalescent- and vaccine-immunized sera from Pfizer-BioNTech vaccinee. Monoclonal Ab- Bamlanivimab fully lost binding to Lambda variant (Liu et al., 2021a; Wang et al., 2022). Further findings about this variant still needs to be clarified. In the meantime, the variant continues to be an important VOI with active monitoring and investigation.

3. 3 Former VOI (Table 5)

3.3.1 Epsilon variant (B.1.427 and B.1.429)

On January 20, 2021, a new strain was reported in Southern California called the Epsilon variant. It was declared as a VOC on 16 March. The mutant was introduced as CAL.20C (Zhang et al., 2021c) and has been found in two forms- B.1.427 and B.1.429, both of which shares three mutations in S protein which are not present in B.1.1.7, B.1.351, P.1 or B.1.526. Both B.1.427 and B.1.429 have their own set of mutations, however they are grouped together as a single variant since they share some discrete mutations that impact the S protein. The key mutation represented by epsilon variant is L452R occurring in the RBD and enhances the affinity of RBD with ACE2. (Stanley., 2021). In March 2021, the Colorado Department of Public Health and Environment (CDPHE) had documented 327 COVID-19 B.1.427/B.1.429 instances characterized by more severe illness, more infectiousness and the ability to escape immune system and neutralizing monoclonal Abs such as bamlanivimab (Webb et al., 2021). The Epsilon variant harbors 1 mutation in RBD region(L452R) and different mutations (S13I, W152C and D614G) in regions other than RBD. The variant showed a significant decrease in neutralization by vaccine elicited or infection elicited immune response. The ability to avoid neutralization by RBD- and NTD-specific mAbs has resulted in a considerable reduction in potency.

As per the experimental data (McCallum et al., 2021a), a reduction in neutralization potency was seen when S protein of B.1.427/B.1.429 and wildtype virus was compared and out of 35 RBD-specific mAbs, 14 of them showed a reduced or abolished neutralization against the variant. The rationale for this was the presence of L452R substitution as a potential escape from some RBD-targeting mAbs. Additionally, S13I and W152C mutations are thought to result in eradication of neutralization by all NTD-specific mAbs. The S13I and W152C alterations affect the signal peptide cleavage site, resulting in loss of S glycoprotein's first two amino acid residues (Q14 and C15). As a result, there is disruption of disulfide bond between C15/C136 that connects N-terminus to rest of the NTD galectin-like β-sandwich. This disturbs the integrity of the NTD site. Hence mutation S13I/W152C are accountable for efficient escape from NTD-specific mAbs while the L452R mutation leads to evasion by some RBD specific mAb. Therefore, B.1.427/B.1.429 variant exhibits an indirect and uncommon neutralization-escape strategy. The neutralization titre of plasma from vaccinated or convalescent people against the B.1.427/B.1.429

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variant was 3 to 6 times lower than that of wildtype pseudoviruses. (McCallum et al., 2021a). The variant exhibits a two-fold increase in viral shedding and transmissibility, as well as a two- to seven-fold reduction in anti-SASR-CoV-2 neutralizing ability (Chui et al., 2021; Deng et al., 2021).

Thus, this variant is of significance because of increased disease severity and ability to escape immune system as well as mAbs. Although because of its severity the variant remains an important VOC, the number of cases have decreased substantially from February 2021 in US as it is outcompeted by B.1.17 variant.

3.3.2 Iota variant (B.1.526)

The B.1.526 variant was reported in NewYork in November 2020. This lineage has been divided into two subclades, both of which carry the common D614G mutation as well as several unique mutations (L5F, S477N/G, E484K, A701V, T95I, D253G). Because one of them has E484K and the other has S477N, both of which cause an increase in receptor binding affinity, both variants may display a higher viral infectivity. T951 and D253G are present in the RBD. (Annavajhala et al., 2021). E484K is an important immune escape mutation, as described in Beta and Gamma variants and diminishes *in vitro* neutralization by multiple SARS-CoV-2 antibodies. S477N provides resistance to neutralization by multiple mAb (Liu et al., 2021c). Modest increase in transmission rate (15-25%) and to some degree immune evasion (around 10%). are major characteristics shown by B.1.526. Infection fatality rate (IFR) relative to B.1.526 (those under 45 years) was higher than the previous rate among younger age groups. However, the magnitude was even higher for older ages (>60% higher for those above 65 years) (Yang et al., 2021). Though the emergence of B.1.526 variant was very rapid in NYC, in comparison to other SARS-CoV-2 variations, it did not induce severe disease or an elevated risk of breakthrough infection or reinfection. (Thompson et al., 2021). The spread of this variant slowed afterward with the rise of B.1.1.7 and other variants.

3.3.3 Zeta variant (P2)

P2 (or B.1.1.28.2), was reported on 15th April 2020 in Rio de Janeiro (Brazil), is a descendant of the Brazilian lineage B.1.1.28 and emerged independent of P.1 lineage (VOC) (Sant'Anna et al., 2021). P2 currently manifests in 33 countries with majority of cases from Brazil and the USA. It exhibits 4 mutations in S protein; F565L, D614G, V1176F and previously categorized E484K (CDC 2021a) which is responsible for immune evasion. P2 shows a lowering of neutralizing Ab titer in convalescent plasma or vaccinee sera and reinfections have also been reported (Beltran et al., 2021). A 5.8- and 2.9-fold decrease in the neutralization by postvaccination serum of Pfizer and Moderna vaccine was observed for the P.2 variant respectively (Beltran et al., 2021). Although this

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variant exhibit increased virulence by immune evasion which is due to E484K mutation, but there is still a need to validate the consequences of described mutations on severity of disease and transmissibility.

3.3.4 Theta variant (P3)

P3 (B.1.1.28.3) first appeared in February 2021 in Philippines. P3 variant has same ancestor as P1 and carries mutations N501Y, E484K, Δ141–143, D614G, P681H, E1092K, H1101Y and V1176F variant in the viral S protein (CDC 2021a) that allow it to display enhanced transmissibility, infectivity and immunity escape (Bascos et al., 2021). P3 is also prominent for the presence of N501Y mutation which is also displayed by the 3 VOCs (alpha, beta and gamma). Enhanced ACEII binding affinity, ability to utilize ACEII in rats and mice and reduction in etesevimab efficacy are found to be associated with this mutation (Yao et al., 2021). P3 had a lower sensitivity to sera from mRNA vaccinees or COVID-19 patients infected with non-VOC/VOI strains, implying that P.3 is capable of surviving spontaneous infection or vaccine-associated neutralization (Chen et al., 2021b).

3.3.5 Eta variant (B. 1. 525)

First appeared in Nigeria and UK on 11th December 2020, the Eta variant has spread over 51 countries, with USA being the most affected one. Ita variant contains mutations include A67V, Δ69–70, Δ144, D614G, Q677H, F888L and E484K (CDC 2021a). B.1.525 variant also exhibits E484K mutation and is quite close to VOC B.1.1.7 that exhibits higher transmissibility. The biological properties of this variant are yet unknown. However, convalescent- and post-vaccination sera and EUA mAbs (FDA, 2021a) have proved to exhibit decreased antibody-mediated virus neutralization (Jangra et al., 2021). The clinical manifestation of other mutations on virus transmission and infectivity still needs to be fully explored.

3.3.6 Kappa variant (B.1.617.1)

Kappa variant, first discovered in India in December 2020, is one of Pango lineage B.1.617's three sub lineages. The variant harbors three notable mutations L452R, E484Q, P681R. Several monoclonal Abs are rendered ineffective by mutations in the Kappa and Delta spike glycoproteins, which modify important antigenic sites, one of which, E484Q, is thought to be responsible for immune evasion (McCallum et al., 2021c). The Kappa sub-variant was found to be responsible for more than half of the sequences submitted from India by the end of March 2021. Class 4 mAbs recognized a unique epitope located far from the mutation dominant site of Kappa and Delta variants, suggesting that neutralizing activity may still be retained (Cheng et al., 2021). Covaxin, AZD1222 and BNT162b2 vaccines are effective against Kappa and Delta variants although there are slight reductions in neutralization (Yadav et al., 2021a). Though there is 3.3-3.4-fold reduction in neutralizing titre by Moderna vaccine but it is still effective (Yadav et al., 2021c).

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3.4 Other variants

IHU or B.1.640.2, a new variant detected in Southern Africa contains 46 mutations including N501Y and E484K and 37 deletions. About 12 people have been found positive for the variant with majority of the victims being hospitalized. There are speculations about the variant being more severe and able to escape immunity more than Omicron variant. Further details about the variant still needs to be investigated.

B.1.616 variant that showed poor detection by RT-PCR when using upper respiratory track samples was detected in France in January 2021. RT-PCR was positive for lower respiratory tract samples. Two more prominent mutations are found in RBD (E484K and N501Y) while the other S protein mutation constellation in H66D, G142V, Δ144, D215G, V483A, D614G, H655Y, G669S, Q949R and N1187D (WHO 2021a). B.1.616 exhibited higher transmissibility due to presence of D614G mutation (Korber et al., 2020) and V483A pertains resilient to mAbs (Li et al., 2020b). Mutation H655Y is responsible for evasion from human mAbs (Braun et al., 2021). B.1.616 has been associated with high degree of disease severity and fatality (Fillatre et al., 2021).

A.23.1, a new variant reported in Uganda, differs from the first three VOCs as it lacks D614G but has Q613H mutation instead that may function similarly. The variant emerged from lineage A.23 and has been reported in more than 26 other countries. Three characteristic spike changes of A.23 lineage are- F157L, Q613H and V367F. A.23.1 shows similar mutations in the spike-protein-coding region (eg 613), but it also shows distinct alteration in the immunogenic NTD and FCS. Nsp6, ORF8, and ORF9, which are similarly altered in other VOCs, are among the non-spike proteins that have changed. The variant has been reported to show a higher transmissibility but the other clinical impacts still need to be answered. (Bugembe et al., 2021)

Other Brazil lineages. Till now 59 lineages are announced in Brazil (Franceschi et al., 2021). B.1 lineage is more recent in circulation introduced in Brazil. It is the foremost introduced ancestral lineage and includes B.1.1.33, B.1.1.74, B.1.1.28, B.1.1.143, B.1.1.94, B.1.1.212 and three recently allocated lineages, P.1, P.2, and N.9, evolved from B.1.1.28 and B.1.1.33 (Franceschi et al., 2021). MG variant which was identified in Brazil is a new lineage with N501T and E484Q mutations. The B.1.1.28 derivative virus is lineage P.4. It was first investigated in Itirapina, Brazil despite the fact experts have yet to pinpoint its origin. It has a dangerous mutation in S protein-L452R. The P.4.1 (VUI-NP13L), branch of this lineage, is thought to have originated in Goiás, Brazil, in June–July 2020. In spike protein P.4.1 possess mutations V1176F and D614G. It was discovered all around the world, with incidences in Japan, Netherlands and England.

The Pango lineage naming system has previously classified Delta into sub lineages ranging from AY.1 to AY.95 with AY.4 being the most common worldwide (ECDC 2022) Recently a new subtype of Delta has been identified

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in England, called AY.4.2. It is designated as a "variant under investigation" (VUI) and is discovered to have Y145H and A222V genetic fingerprints present in the S protein. Recently it has also been detected in Indian states -Madhya Pradesh and Maharashtra. The scientists have indicated that this variant may show higher transmissibility and may be more contagious than the delta strain. (Sahoo et al., 2021)

HMN.19B – Henri Mondor 19B was first identified during a nosocomial outbreak in Brittany, France carries the two mutations- L452R and N501Y both of which are associated with increased contagiousness. Clade 19B lacks the common D614G mutation. The occurrence of this lineage has decreased in the late 2020. Information about its clinical impacts and potential risks need to be explored yet (Fourati et al., 2021). The B.1.616 strain has been linked to weaker RT-PCR positives and a reduced detection rate in nasopharyngeal samples. Still variant does not cause severe infection and has shown very few reinfection cases.

4 How do B and T cell epitopes change in variants?

Notably, surface proteins of the virus are chosen as antigens so that Abs produced by a vaccine-trained B-cell can bind to the virus and generate antigenic peptides, which are presented by MHC, stimulating the production of plasma cell that produces antibodies. Besides the generation of antibodies, the CD8+ T cells also play a significant role for eradicating the virus in case of both natural and vaccine induced immunity.

As for antibody responses, the variants have shown a significant decrease on neutralizing antibody titers as many SARS-CoV-2 mutations have been found to affect individual epitopes that are the targets of potent neutralizing Abs (Sette et al., 2021) (Figure 5). D614G mutation, harbored by almost all variants and located in the middle epitope in S protein among residue 601 and 640 is one of the most significant mutations among out of all. This is because the amino acid change involves substitution of a large acidic aspartic acid to a small hydrophobic glycine. Hence, the binding affinity of Abs trained by vaccines produced against the Wuhan strain would be compromised by such a considerable difference in hydrophobicity and size in the center of the epitope (Koyama et al., 2020). Furthermore, RBD is targeted by 90% of plasma or serum neutralizing Abs due to its lack of glycan shielding, which is responsible for RBD immunodominance (Greaney et al., 2021; Piccoli et al., 2020; Watanabe et al., 2020). RBM epitopes that overlap with ACE2 site are immunodominant within the RBD (Piccoli et al., 2020) (Figure 5).

Many potently neutralizing Abs target mutations in three key epitopes in RBD: a surface patch in the core RBD, the receptor-binding point within RBM, and the straddling (443–450) and adjacent sites (494–50) that create a loop in the RBD (Greaney et al., 2021; Hansen et al., 2020; Starr et al., 2021). Mutation at site E484 to K, Q, or P (in B.1.351 and P1 variants) reduces the neutralization potency of human plasmas by >10 folds. E484K escapes

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mAbs C121 and C144 (Weisblum et al., 2020) as well as convalescent plasma (Andreano et al., 2021), and was the only mutation that causes a reduction in the neutralization by mixture of mAbs (REGN10989 and REGN10934) to an immeasurable level (Baum et al., 2020). In addition, mutation at site F456 also reduced binding by neutralizing antibodies. Both these sites are reported to be present in the receptor-binding ridge epitope. Epitomal mutation in the core RBD results in locking of spike into a "closed" conformation as these are bunched around the lipid-binding pocket in the RBD where free fatty acids bind resulting in reduced binding of Abs (Carrique et al., 2020; Toelzer et al., 2020) . Mutation G446V caused ~30-fold decrease in neutralizing titer while G485R and S494P mutations demonstrated somewhat less but still considerable (~3- to 5-fold) decrease in neutralizing titer (Greaney et al., 2021). Class 1 antibody binding is affected by the K417 mutation, but not polyclonal Ab responses to the RBD, which are dominated by class 2 antibody responses (Greaney et al., 2021; Wibmer et al., 2021). In the NTD, most of the immune evasion occurs due to changes in the region centered at conformational epitope that occur at residues 140–156 (N3 loop) and 246–260 (N5 loop), that involves the epitope of the antibody 4A8 (Chi et al., 2020). For example, deletion in NTD - Δ141–144 and Δ146and Δ243–244 abolished binding of 4A8. The Δ140 spike mutant next acquired E484K mutation, leading to drastic evasion (4-fold decrease) of the polyclonal antibody response (Andreno et al., 2020). For the recent variant Omicron, a higher number of mutations occur in B cell epitopes of the Spike (i.e., 67-70, 142-145, 211-214, 477-505, 796) and affect 30.91% (550) IEDB B cell epitopes, which is thought to be responsible for the variant's ability to escape most neutralizing Abs and vaccines while Beta, Gamma and Delta impact 12.9, 15.3 and 11.12% of B-cell epitopes (Bernasconi et al., 2021). CD4+ T cell responses to SARS-CoV-2 are more prominent than CD8+ T cell responses because neutralizing antibody responses are generally T cell dependent (Grifoni et al., 2020; Sekine et al., 2020). Mutations are found in four CD8+ T cell epitopes (KIA_S, GVY_S , YLQ_S and RLQ_S) in the variants B.1.1.7, B.1.351, P.1, and B.1.617.2, three of which occur in S protein and one in nsp2 protein of ORF1a (Pretti et al., 2021). Both KIA_S (e.g., K417N) and GVY_S have mutations in anticipated anchoring sites, required for epitope binding by the human leukocyte antigen (HLA) (Figure 5). The L452R mutation also contributes to escape from HLA-A24-mediated cellular immunity (Zhang et al., 2021a). However, for most variants, sequences of a massive proportion of SARS-CoV-2 T cell epitopes remain unaffected by mutations. This is evident from the analysis that 97.1, 89.6, 90 and 94.3% (av 93%) of the $CD4^+$ T cell epitopes and 97.9, 97.1, 97.3 and 97.3% of the $CD8^+$ T cell epitopes are conserved in the CAL20C, B.1.1.7, B1.351 and P.1 variants respectively (Tarke et al., 2020). Mutations in Beta, Gamma, Delta and Omicron impact 9.8, 12.47, 8.47 27.29% of the total T- cell epitopes, with Omicron affecting the highest number of both B and T cell epitopes. With the exception of B.1.351, mutations

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observed in SARS-CoV-2 variants have no effect on CD4+ and CD8+ T cell responses in convalescent COVID-19 individuals or COVID-19 mRNA vaccinees (Tarke et al., 2021). This shows that almost all anti-SARS-CoV-2 CD8+ T-cell responses should be responsive to other variants, including Omicron (B.1.529), which appears to be immune to neutralizing Abs (Ahmed et al., 2021). As a result, B cell epitopes contain a lot of variation, whereas T cell epitopes have a lot of stability (Ge et al., 2021), implying that T cell vaccine methods have the best lifetime against mutations before they need to be reformulated. (Altmann et al., 2020; Reynolds et al., 2021). Thus, if SARS-CoV-2 T cell responses hold up, it can minimize immune escape and disease severity (Ameratunga et al., 2022; Redd et al., 2022).

5. Conclusion

There has been independent emergence of a number of SARS-CoV2 mutants in different parts of the world and some of them have shown global spread. The most important clinical outcomes of these mutation in the variants include increased transmissibility (B.1.1.7 and B.1.617), severity of disease, ability to avoid detection (B.1.1.7), resistance to treatment as well as evasion of natural or vaccine-induced immunity (B.1.351 and P1). All these outcomes are due to the specific mutations possessed by these variants providing them an extra survival advantage. However, there are other examples of variants that appeared frightening on paper but ultimately failed. At the start of the year, the Beta variety was at the top of people's minds since it was regarded to be the greatest at evading the immune system. But in the end, the planet was conquered by the faster-spreading Delta. The emergence of new variant – Omicron (B.1.1.529) and IHU has again put the vaccine effectiveness under a question mark against new variants. Nonetheless, there are many substantial challenges in ensuring equitable vaccine access around the globe, putting concern on the adequate number of doses of a particular vaccine that must be administered. The newer vaccines like Inovio, AnGes, ReiThera, The Chinese Shifa, Cuba, COVAXX, which are still in the Phase 3 trials are also thought to provide a considerable amount of protection against the wild SARS-CoV2 and its variants. But as quoted, “The great structural flexibility we saw in the SARS-CoV-2 spike protein suggests that omicron is not likely to be the end of the story for this virus”, the world needs to be prepared with better surveillance, diagnosis, treatment and preventive methods. Nonetheless a universal vaccine against the non-mutating epitopes of virus may be an ultimate barricade for all the more severe variants paving their way to create massive global damage.

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Conflict of interest

The authors declare no conflict of interests

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Figure 1: Mutations acquired by variants in different regions of Spike gene.

Figure 2: Immune response against SARS-CoV-2 under mild and severe conditions. APC- Antigen Presenting Cell; IL- Interleukin; TNF- Tumor necrosis Factor; MCP 1- Monocyte Chemoattractant Protein 1; IFNs- Interferons; IRFs – Interferons regulatory Factors; TRIF- TIR-domain-containing adapter-inducing interferon-β.

Figure 3: Map showing prevalence of Omicron variant in different countries: Intensity of the colour is directly proportional to the number of Omicron confirmed cases. UK, Denmark, Germany and US being the most affected countries.

Figure 4: Representative 3D models of Spike protein, containing mutations. a) Wild type b) Delta variant c) Omicron lineages- i) BA.1 ii) BA.2 iii) BA.3.

Figure 5: A step-plot for SARS-CoV-2 linear epitopes as predicted from IEDB. The x-axis contains the coverage of epitopes in the S gene while y-axis represents the Bepipred score (Sequences with score above 0.5 are considered as potential linear B-cell epitopes). The plot counts B cell epitopes and the mutations are marked on the graph in red. The plot highlights mutations occurring in S regions with a high concentration of B cell epitopes in different variants (A – Wild type; B- Delta variant; C- Omicron lineage BA.1; D- Omicron lineage- BA.2; E- Omicron lineage- BA.3).

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Figure 1:

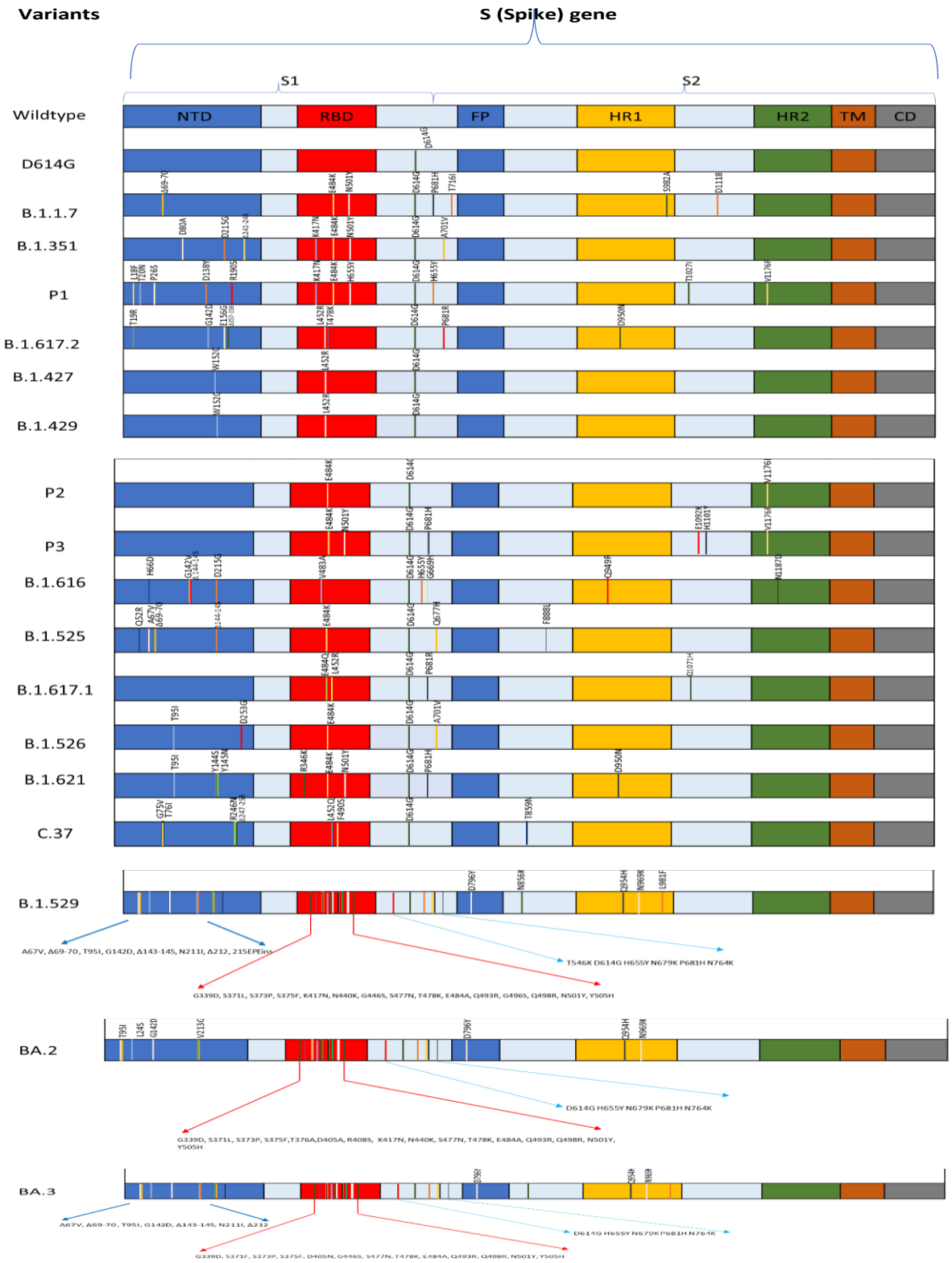

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Figure 2:

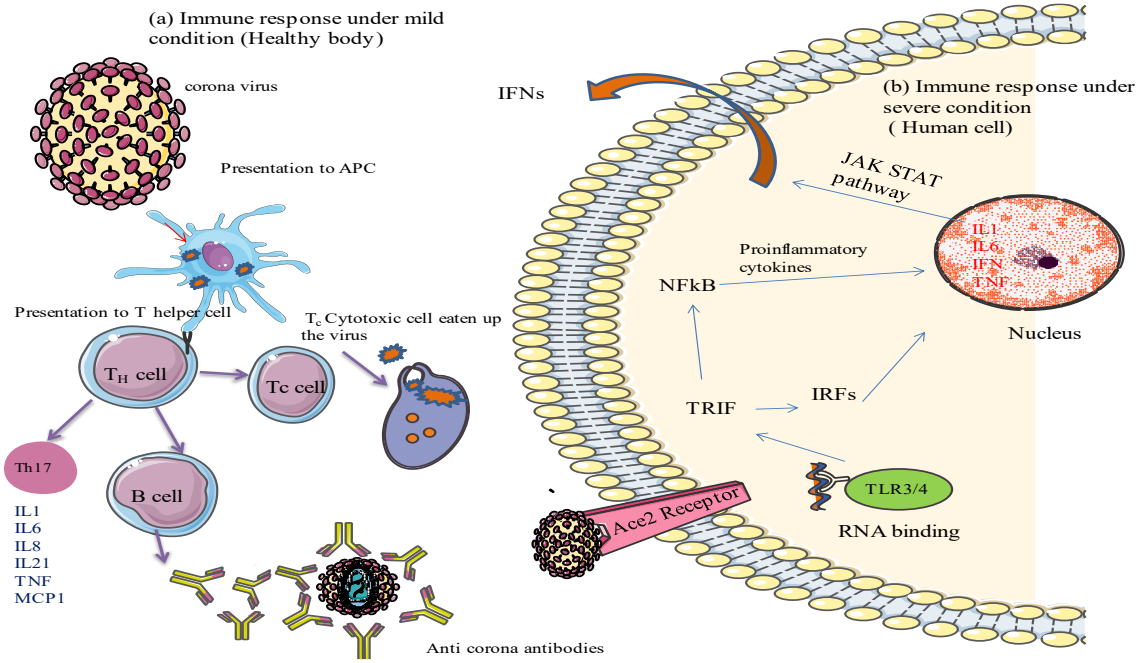

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Figure 3:

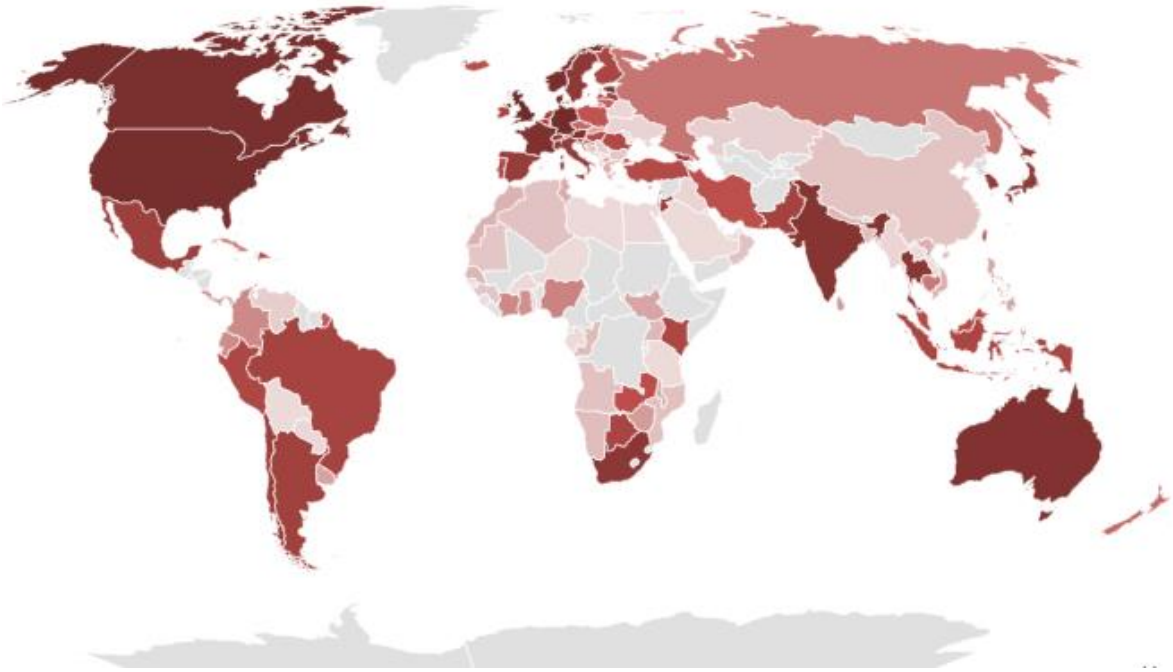

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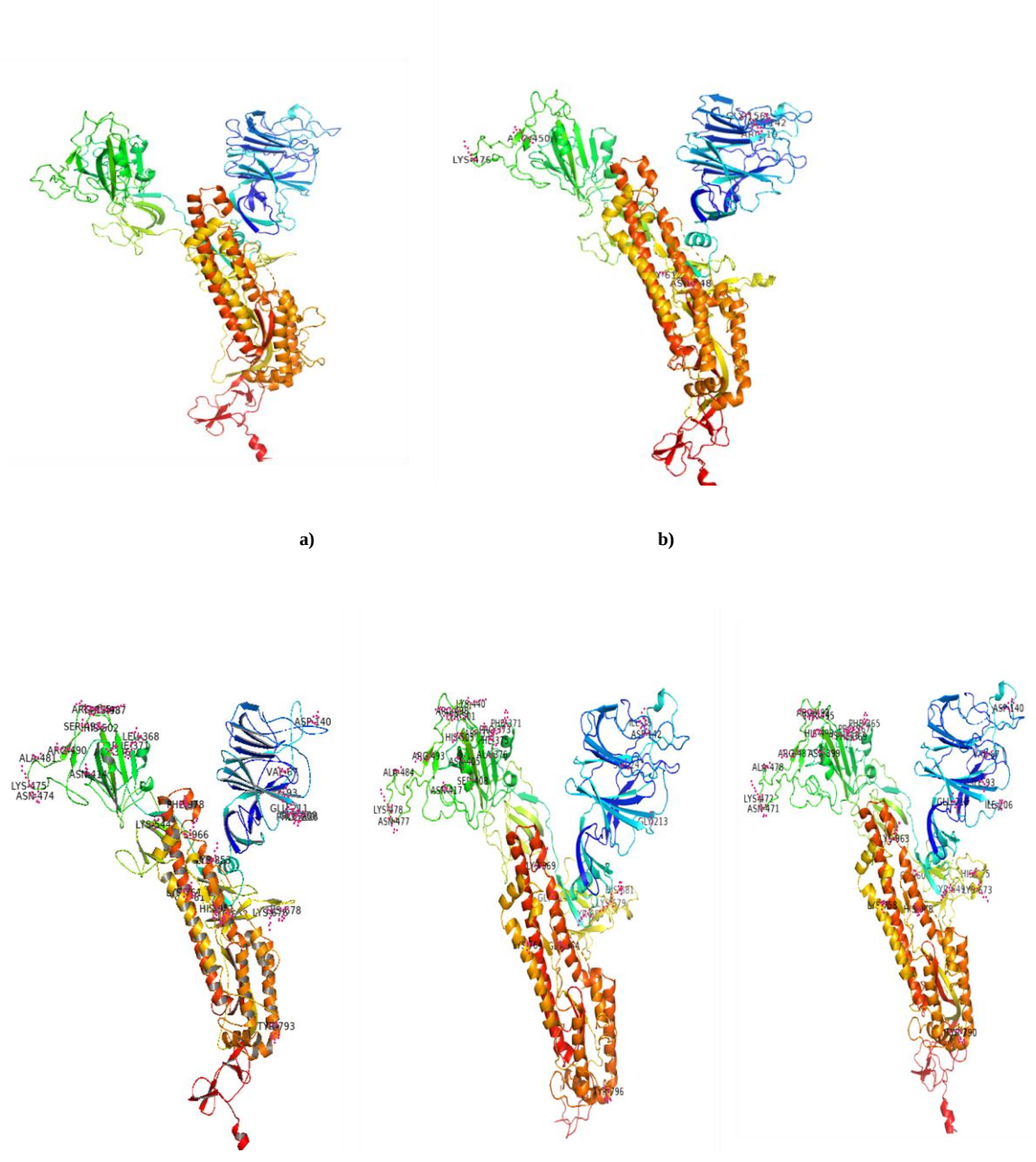
Figure 4:



a) b)

C) i) ii) iii)

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Figure 5:

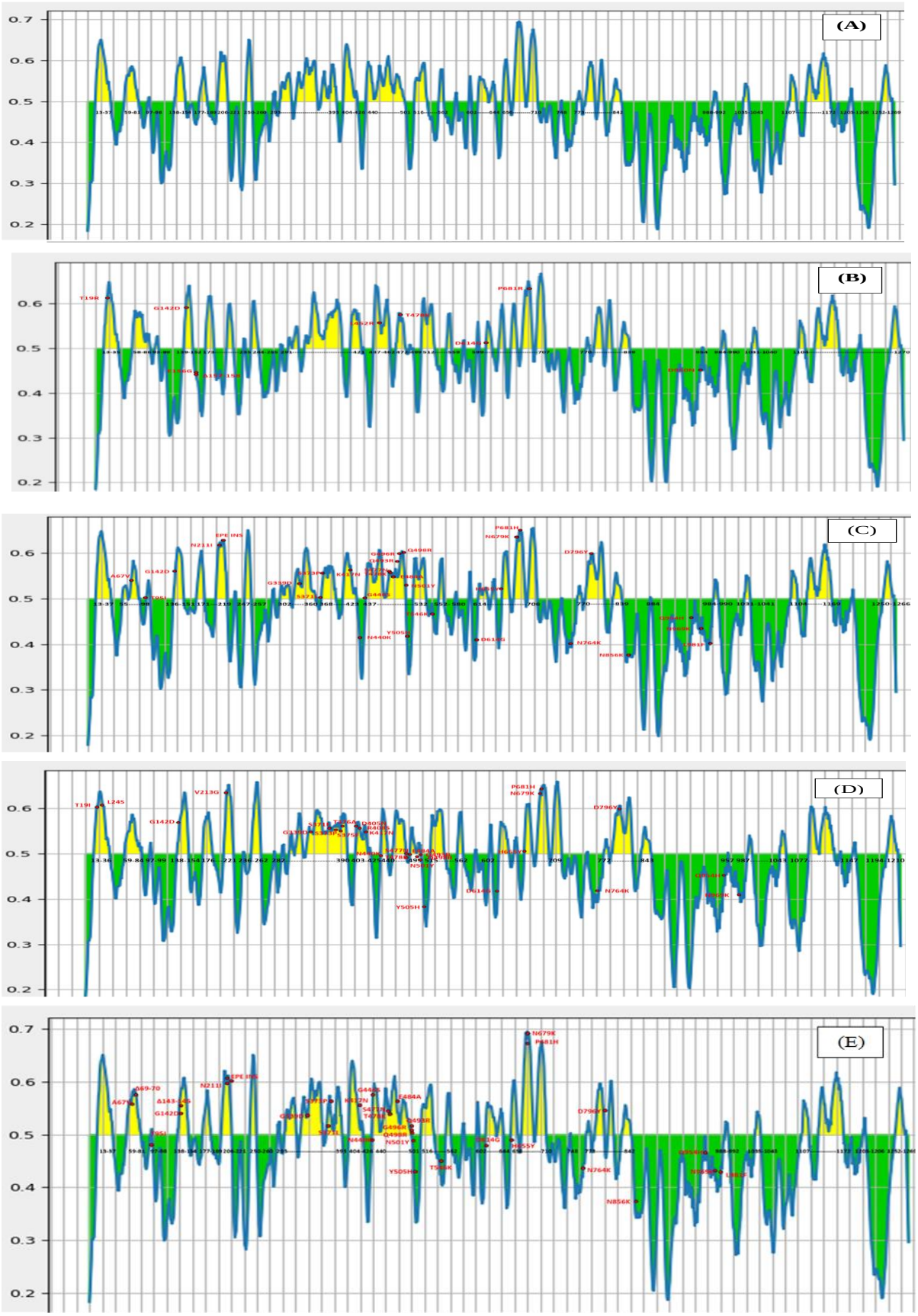

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Table 1: Effect of individual mutation on SARS-CoV-2 transmissibility, pathogenicity and immunity escape.

Mutations	**Effect of mutation**	**Reference**
D614G	Global spread characterized by higher viral loads	Volz et al., 2021a
N501Y	Increased affinity for the ACEII receptor	Luan et al., 2021
E484K	Enhanced binding with ACEII receptor, K and Q reduction in sera neutralization	Nelson et al., 2021; Wise et al., 2021
Δ69, Δ70	Infectivity increase, reduced sera neutralization	Meng et al., 2021
S13I, W152C	Escape from mAbs against the N-terminus	McCallum et al., 2021b
L452R	Higher infectivity and transmission, reduced neutralization by certain therapeutic antibodies	Li et al., 2020b, Starr et al., 2021
L18F	Immune escape from mAbs against N-terminus	McCallum et al., 2021b
Δ 141-143	mAB escape	Kemp et al., 2021
Δ144	Resistance to 4A8 mAb	Kemp et al., 2021
L249S	May aid resistance to neutralizing Abs	Li et al., 2020b
D253G	May aid resistance to neutralizing Abs	Lasek-Nesselquist et al., 2021
K417N/T	Conformational change, escapes some mAbs	Greaney et al., 2021
R203K	Enhanced transmission	Kiryanov et al., 2021

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V367F	Modest infectivity increase, higher ACEII affinity	Li et al., 2020b
V483	Escape from mAbs	Li et al., 2020b
H655Y	mAb escape, linked to feline propagation	Braun et al., 2021
Q677H	Close to furin- cleavage site (FCS), may affect transmissibility	Li et al., 2021
G204R	Enhanced transmissibility	Kiryanov et al., 2021
S477N	Resistant to neutralization by multiple mAbs, increased binding affinity for hACE2	Liu et al., 2021c; Singh et al., 2021

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Table 2: Important VOC of SARS-CoV-2 and their characteristics

VOC/ Origin / First detected	Mutations	Variant characteristics	Immunity escape	References
Alpha (B.1.1.7)/ UK/ September 2020	S protein- N501Y, P681H, E484K, S494P, Δ 69-70, 144del, A570D, D614G, T716I, S982A, D1118H, K1191N Orf1ab- T1001I, A1708D, I2230T, SGF Δ 3675–3677 N-S235F, D3L, Orf8- Y73C, R52I, Q27stop	• Increased Transmission rate. • Responsible for 60% of local cases in UK. • Diagnostic failure by RT PCR. • Increased 61-64%mortality in the UK.	• Moderate decrease in neutralization by natural immunity. • Decreased neutralization with NTD targeting mAb and plasma from convalescent and vaccinated individuals. • Non-spike mutations in increase the production of RNA and protein levels of viral innate immune antagonists (N, Orf6 and Orf9b).	Davies et al., 2021; Krammer et al., 2021; Volz et al., 2021b; Thorne et al., 2021; Wang et al., 2021c.
Beta (B.1.351)/ South Africa / October	S protein- N501Y, K417N, E484K, D80A, D215G, Δ 241-243, D614G, A701V, 2020 L18F, R246I	• 50% increase in transmissibility. • 20% increase in mortality.	• E484K, K417N, and N501Y and NTD deletion cause	Madhi et al., 2021; Volz et al., 2021a; Wang et al.,

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	Orf1ab- T265I, K1655N, H2799Y, S2900L, K3353R, D4527Y, P4715L, T5912I Orf3a- Q57H, S171L E- P71L N- T205I		widespread escape from mAbs. • Resistance to neutralization by convalescent plasma (9.4-fold) and sera from vaccinated individuals (10.3–12.4-fold). • Reduced neutralization by class 1 and 2 RBD-specific Abs and NTD-specific Abs. • Complete evasion of Abs in 48% of convalescent serum samples.	2021c; Zhou et al., 2021
Gamma (P.1 or B.1.1.248)/ Brazil/ December 2020	S protein- N501Y, K417T, E484K, L18F, T20N, P26S, D138Y, R190S, D614G, H655Y, T1027I,	• 40% increase in transmissibility.	• Evades neutralizing Abs after infection and post vaccination.	Beltran et al., 2021; Faria et al.,

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	Orf1ab- synT733C, synC2749T, S1188L, K1795Q, del11288-11296 (3675-3677 SGF), synC12778T, synC13860T, E5665D Orf8- E92K, ins28269-28273 N- P80R	• 3 times increase in mortality in people between 20 -39 years.	• Ability to evade from CD8+ T-cell responses. • Abolished neutralizing activities of mAbs, like REGN10933.	2021; Yang et al., 2021
Omicron (B.1.529) • BA.1 lineage /South Africa/ November 2021	S protein- A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F Orf1ab- K38R, V1069I, Δ1265, L1266I, A1892T, T492I,	• 10 times higher transmissibility and infectivity than original Wuhan strain. • gives SGTF.	• High potential of immune escape. • ED50 decreased to 66. • Reduction in efficacy of mAb. • Breakthrough infection in already vaccinated people. • 14 times vaccine escape ability than Delta variant.	CDC 2021b; Karim and Karim 2021; Syed et al., 2021; WHO 2021b

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	P132H, Δ105-107, A189V, P323L, I42V E- T9I M- D3G, Q19E, A63T N- P13L, Δ31-33, R203K, G204R			
• BA.2 lineage	S protein- G142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K, T19L, LPPA24S, V213G, S371F, T37A, D405N, R408S Orf1ab- T32551, P3395H, SGF3675del, P4715L, I5967V, S135R, T842I, G1307S, L3027F, T3090I, L3201F, F3677L, R5716C, T6564I	• Higher transmission rate. • More pathogenic. • More fusogenic and replicative. • Does not give SGTF.	• Similar immune evasion properties as BA.1, though exhibit different antigenicity.	Majumdar et al., 2021; Syed et al., 2021; Yamasoba et al., 2022

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• BA.3 lineage	Orf3a- T223I Orf6- D61L N- S413R, P13L, ERS31del, RG203KR E- T91I M- Q19E, A63T S protein- A67V, Δ69-70, T95I, G142D, Δ 143-145, N211I, Δ212, G339D, S371F, S373P, S375F, D405N, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K Orf1ab- A3657V, G1307S, P3395H, T3090I, T32551, S135R, Δ3675/3677 Orf1b- P314L, I1566V	• More infectious that Original Wuhan strain.	• Expected to escape immunity as BA.1.	Majumdar et al., 2021

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	M- A63T, Q19E Orf 8- S84L N- R203K, G204R, S413R, P13L, Δ31/33			
Delta (B.1.617.2)/ India/ December 2020	S protein- T19R, T95I, G142D, E156-, F157-, R158G, L452R, T478K, D614G, P681R, D950N Orf1b - P314L, P1000L M- I82T N- D63G, R203M, D377Y Orf3a-S26L Orf7a- V82A, T120I	• Increased transmissibility (faster than B.1.17), • Disease severity- May cause more severe cases than Alpha • Breakthrough infections in vaccinated individuals	• Escapes neutralizing Abs with 4-6-fold decrease in neutralization titers than alpha variant. • Ability to evade T cell immunity.	CDC 2021a; Kannan et al., 2021; Liu et al., 2021a; Twohig et al., 2021; Zhang et al., 2021a
• AY.1 (Delta plus)/ India/ April, 2021	S protein- T19R, V70F, E156G, Δ157-158, W258L, **K417N**, L452R, T478K, D614G, P681R, D950N.	• Increased transmissibility	• Reduced neutralization by sera Abs of COVID recovered and vaccinated individuals	Rahman et al., 2021

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	Orf 1ab- A488S, P1228L, P1469S, V167L, T492I, T77A, P323L, G671S, P77L, A394V Orf 3a- S26L M- I82T Orf 7- V82A, T120I, T40I Orf 8- D119I, Δ120-121 N- D63G, R203M, G215C, D377Y		• Potential reduced susceptibility to some EUA monoclonal antibody treatment.	
• AY.4.2 (Delta sub lineage)/ England/ August 2021	S protein- T19R, V70F, E156G, Δ157-158, A222V, **K417N**, L452R, T478K, D614G, P681R, D950N. Orf 1ab- A328T, P822L, A446V, V149A, T181I, P323L, G671S, P77L, T367I Orf 3a- S26L M- I82T Orf7- V82A, T120I	• Higher transmissibility than Delta strain (10-15%)	• Similar immune evasion as Delta	Angeletti et al., 2021; ECDC 2022

 doi:10.20944/preprints202203.0376.v1

	Orf 8- D119I, Δ120-121 N- D63G, R203M, D377Y			

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Table 3: Efficacy of current COVID-19 vaccines against SARS-CoV-2 variants.

Vaccine	**B1 strain (D614G)**	**Alpha (B.1.1.7)**	**Beta (B.1.351)**	**Gamma (P1)**	**Delta (B.1.617.2)**	**Omicron (B.1.529)**
Astra Zeneca (AZD1222)	66.7% efficacy (Voysey et al., 2021).	70.4% efficacy (Emary et al., 2021).	Extremely low efficacy (10.4%) (Madhi et al., 2021).	9-fold reduction in neutralization (Dejnirattisai et al., 2021b)	>60% effectiveness by single dose.	No effect from 15 weeks after two doses (Andrews et al., 2021)
Pfizer (BNT162b2)	94.6% efficacy (Karim and Oliveira., 2021)	93.4% efficacy (Bernal et al., 2021), 0 to 3.3-fold reduction in neutralization (Collier et al., 2021; Skowronski et al., 2021; Xie et al., 2021)	75% efficacy (Raddad et al., 2021). Reduction in serum neutralizing activity by ~6.5 folds (Karim and Oliveira., 2021; Xie et al., 2021).	Effectively susceptible to vaccine-elicited serum (Liu et al., 2021c). But with reduction in serum neutralizing activity of vaccinees by ~6.7 folds (Karim and Oliveira., 2021).	3-fold reduction in neutralization ability (Far et al., 2021)	32 folds reduction in neutralization, 33% protection with double dose (Wilhelm et al., 2021)
Johnson &Johnson (Ad26.COV2. S)	Not reported	70% efficacy (Sadoff et al., 2021)	64% efficacy (Sadoff et al., 2021).	68% effectiveness, 3.4-fold reduction (Jongeneelen et al.,	47-79% effectiveness (Rosenberg et al., 2021)	Not reported

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				2021; Sadoff et al., 2021)		
Moderna (mRNA-1273)	Not reported	84-99% effectiveness (Tang et al., 2021), Decrease in neutralization by 1.8× (Karim and Oliveira., 2021).	Significant reduction (~5–10 folds) in serum neutralizing activity post-immunization (Wu et al., 2021).	Reduction in serum neutralizing activity of vaccinees by ~4.5 folds (Karim and Oliveira., 2021).	70 (45–85) % efficacy against symptomatic infection, 4-fold reduction in neutralization (Far et al., 2021)	20-fold reduction in neutralization with sera from double dose (Wilhelm et al., 2021), 30.4% and 95.3% efficacy with double and triple dose, respectively (Tseng et al., 2022). Booster dose reduces vaccine escape (Doria-Rose et al., 2021)
Covaxine (BBV152)	Not reported	No reduction in vaccine efficacy (Sapkal et al., 2021)	Effective neutralization potentional though with slight reduction (Yadav et al., 2021a)	Not reported	2-fold reduction in neutralization (Far et al., 2021), 65.2% protective efficacy against Delta variant (Ella et al., 2021) After two doses of	Not reported

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					administration at least 14 days before testing was 50% (Desai et al., 2021)	
Sinopharm (BBIBP-CorV)	79% efficacy (Karim and Oliveira., 2021).	no significant reduction in neutralizing activity (Wu et al., 2021)	Resistance to post-vaccination sera (2.5–3.3 folds) with complete or partial loss in neutralizing activity (Wang et al., 2021c).	Not reported	Not reported	Not reported
Sinovac (Coronavac)	50.7% efficacy (Shapiro et al., 2021)	1.5 to 4.1-fold reduction in neutralization (Chen et al., 2021c; Wang et al., 2021c)	3.3-to-5.3-fold reduction (Chen et al., 2021c)	49.6% vaccine efficacy (Shapiro et al., 2021)	2.5-fold reductionin neutralization (Hu et al., 2021)	two doses provide poor neutralising antibody responses or virus killing. Even a third does not provide much protective antibody (Cheng et al., 2022)
Novavax (NVX-CoV2373)	2.1-fold reduction in neutralization (Shen et al., 2021)	85.6% efficacy, 95.6% efficacy against non-B.1.1.7	60% efficacy in HIV (–) subjects in South Africa (92.7% of	Not reported	60 % efficacy (Altmann et al., 2021)	Not reported

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		(Mahase., 2021a)	sequences were B.1.351), 51% against B.1.351 specifically (Mahase., 2021a)			
Sputnik V (Gam-COVID-Vac)	Not reported	No reduction for Sputnik V (Ikegame et al., 2021)	Not reported	2.8-fold reduction (Ledesma et al., 2021)	2.5-fold reduction in neutralization (Gushchin et al., 2021)	Not reported

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Table 4: Important VOI of SARS-CoV-2 and their characteristics

VOI/ Origin / First detected	Mutations	Variant characteristics	Immunity escape	Reference
Mu (B.1.621)/ Colombia/ January 2021	S protein- T95I, Y144S, Y145N, R346K, E484K, N501Y, D614G, P681H Orf1ab- T237A, T720I, T492I, Q160R, P323L, P419S Orf 3a- Q57H, Δ 257 Orf 8- T11K, P38S, S67F N- T2051	• Higher infectivity. • Significant reduction in neutralization because of immune escape mutation E484K.	• 10.6 times reduction in neutralization than B.1 lineage virus (parental virus). • 2.0 times resistant to neutralization by convalescent serum. • 1.5 times reduction in neutralization by vaccine serum.	Uriu et al., 2021
Lambda (lineage C.37)/ Peru/ August 2020	S protein- G75V, T76I, R246N, Δ247-253, L452Q, F490S, D614G, T859N Orf1ab- T428I, P1469S, F1569V, L438P, T491I, GI5S, K109R, P323L	• Higher transmissibility and infectivity- 3.3 and 1.5-fold enhanced infectivity in Calu-3 and LLC-MK2 cells.	• 3.05-fold decrease in neutralization compared to Wuhan strain. • 1.3–2.5-fold lower neutralizing titres against convalescent- and	Acevedo et al., 2021; Liu et al., 2021a; Wang et al., 2022

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	Orf 9b- P10S N- P13L, R203K, R204G, R214C		vaccine-immunized sera, respectively.	

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Table 5: Former VOI of SARS-CoV-2 and their characteristics.

VOI/ Origin / First detected	Mutations	Variant characteristics	Immunity escape	Reference
Epsilon (B.1.427 and B.1.429)/ California, USA/ November 2020	S protein- L452R, D614G, ± (S13I, W152C) Orf1ab- T85I, I64V, P323L, D260Y N- Q57H	• More virulent.	• Reduced neutralizing activity in a subset of RBD-specific monoclonal Abs.	Carroll et al., 2021
Iota (B.1.526)/ New York, USA/ November 2020	S protein- E484K, S477N/G, L5F, T95I, D253G, D614G, A701V, Orf1ab- Δ106-108	• 15-25% higher transmissibility but do not cause severe disease. • Increased Infection fatality rate (IFR) in older adults: by 46% among 45–64-year-olds, 82% among 65–74-year-olds, and 62% among 75+.	• Escape immunity up to 10% in previously infected persons. • Increased risk of re-infection.	Chadha et al., 2021; Yang et al., 2021

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Zeta (P.2)/ Brazil/ March 2020	S protein- F565L, E484K, D614G, V1176F, Orf1ab- L205V, L71F, P323L N- A119S	• Reports of reinfection. • Increased virulence by immune evasion.	• Decrease in neutralizing antibody titers of convalescent plasma or vaccine sera (5.8 fold decrease for Pfizer and 2.9 fold decrease for Moderna).	Beltran et al., 2021; Sant'Anna et al., 2021
Theta (P.3)/ Philippines / February 2021	S protein- N501Y, E484K, Δ141–143, D614G, P681H, E1092K, H1101Y and V1176F Orf1ab- D736G, L438P, D112P, L71F, P323L, A368V Orf8- K2Q N- R203K, G204R	• Increased ACEII affinity/transmissibility.	• Reduction in susceptibility to sera from mRNA vaccinee or from COVID-19 patients infected with non-VOC/VOI strains.	Chen et al., 2021b; Yao et al., 2021

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			• Decreased effectiveness of mAb like etesevimab. • Reduced sensitivity to mRNA vaccines.	
B.1.616/ France/ January 2021	H66D, G142V, 144del, D215G, D614G, H655Y, G669S, Q949R, N1187D, V483A	• Poor detection by RT-PCR when using samples from upper respiratory track. • 44% increase in lethality • Increased viral transmissibility due to presence of D614G.	• Resistance to mAbs.	Fillatre et al., 2021; Korber et al., 2020; Li et al., 2020a
Ita (B.1.525)/ UK/Nigeria/ December 2020	S Protein- E484K, A67V, 69del, 70del, 144del, D614G, Q677H, F888L Orfab- T1189I, P323F E- L21F	• Increased transmissibility similar to B.1.1.7.	• Evades neutralizing Absin convalescent and	Jangra et al., 2021

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	M- I82T Orf6- del 2 N- del 3, A12G, T205I		vaccine induced sera.	
Kappa (B.1.617.1)	S protein- T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H Orf1ab- T749I, T77A, P323L, M429I, K259R Orf3- S26L Orf7a- V82A N- R203M, 377Y	• Higher transmissibility • Virulence similar to Delta.	• Immune evasion due to presence of E484Q. • 3.3-3.4-fold reduction in neutralization by Moderna vaccine. • Escape from mAbs.	McCallum et al., 2021c; Yadav et al., 2021c