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A review on evolution of emerging SARS-CoV-2 variants based on spike glycoprotein

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ABSTRACT
Since the inception of SARS-CoV-2 in December 2019, many variants have emerged over time. Some of these variants have resulted in transmissibility changes of the virus and may also have impact on diagnosis, therapeutics and even vaccines, thereby raising particular concerns in the scientific community. The variants which have mutations in Spike glycoprotein are the primary focus as it is the main target for neutralising antibodies. SARS-CoV-2 is known to infect human through Spike glycoprotein and uses receptor-binding domain (RBD) to bind to the ACE2 receptor in human. Thus, it is of utmost importance to study these variants and their corresponding mutations. Such 12 different important variants identified so far are B.1.1.7 (Alpha), B.1.351 (Beta), B.1.525 (Eta), B.1.427/B.1.429 (Epsilon), B.1.526 (Iota), B.1.617.1 (Kappa), B.1.617.2 (Delta), C.37 (Lambda), P.1 (Gamma), P.2 (Zeta), P.3 (Theta) and the recently discovered B.1.1.529 (Omicron). These variants have 84 unique mutations in Spike glycoprotein. To analyse such mutations, multiple sequence alignment of 77681 SARS-CoV-2 genomes of 98 countries over the period from January 2020 to July 2021 is performed followed by phylogenetic analysis. Also, characteristics of new emerging variants are elaborately discussed. The individual evolution of these mutation points and the respective variants are visualised and their characteristics are also reported. Moreover, to judge the characteristics of the non-synonymous mutation points (substitutions), their biological functions are evaluated by PolyPhen-2 while protein structural stability is evaluated using I-Mutant 2.0.

1. Introduction
The ongoing wave of COVID-19 caused by SARS-CoV-2 virus was first identified in the city of Wuhan, China during December 2019. Since then, the virus has spread very rapidly and has affected millions of people worldwide. SARS-CoV-2 is a positive stranded RNA virus with a length of about 30 kb encompassing non-structural and structural proteins. Spike glycoprotein, a structural protein present on the virus surface plays an important role in binding with ACE2. This RNA virus can make a replica of its own after binding with the host cell, thereby causing several mutations [24]. Whenever the mutation is significant, the structure of the virus changes, resulting in a new variant or lineage of the virus [38]. Motivated by this observation, in this study we have performed a competitive analysis of several variants of SARS-CoV-2. The mutation of SARS-CoV-2 is happening over time, thereby resulting in new variants. Whenever a new variant emerges, it can be called as an “emerging variant” which have some potential consequences viz. increase in transmissibility, morbidity as well as mortality. It is to be noted that the different variants have some unique as well as some common mutations. In this regard, there are 12 important variants as declared by W.H.O and 84 unique mutations that are reported in this work. Some of these variants have been categorised as either variants of concern, variants of interest or variants under monitoring based on their transmissibility, immunity and infection severity. As of now, the variants of...
Sharing All Influenza Data (GISAID) of 98 countries over the period from January 2020 to July 2021 using global SARS-CoV-2 genomes are collected from Global Initiative on per- formed multiple sequence alignment of 77681 SARS-CoV-2 genomes subunit binds to the ACE2 host cell receptors, then the S2 subunits to the cell membrane.

2.1. Data preparation

2.2. Pipeline of the work

This study is carried out according to the pipeline as given in Fig. 1 (a). Initially, 77681 global SARS-CoV-2 genomes are considered for multiple sequence alignment using MAFFT followed by their phyloge- netic analysis using Nextstrain. Once the aforementioned analysis is over, the different known mutations in the Spike glycoprotein pertaining to the important SARS-CoV-2 variants are identified as shown in Fig. 1 (b) while the different domains are shown in Fig. 1(c). The entropy of the genomic coordinates of these mutation points are also calculated to show the evolution of the different variants. The entropy is calculated as follows:

\[
\lambda = \ln 5 + \sum \eta \left[ \ln (\eta_i) \right]
\]

where \( \eta_i \) represents the frequency of each residue occurring at position \( i \) and 5 represents the four possible residues as nucleotides plus gap. Furthermore, maximum entropy per position is taken as 0.2 with no gaps. All these values are taken after following the literature. Thereafter, analysis of the functional characteristics for the mutations in the Spike glycoprotein for the different variants are carried out. Finally, these mutations for each of the variants are visualised in the Spike glycoprotein structure as well.

3. Results

SARS-CoV-2 infects the human cell and after attaching itself to the receptor cell ACE2, it makes the replica of their RNA. Whenever the virus replicates, sometimes the change or mutation is trivial, but whenever the virus changes one or more times it is referred to as a new variant of the original virus. There are several variants that have been reported for SARS-CoV-2. To study these variants in this work, initially multiple sequence alignment of 77681 global SARS-CoV-2 genomic se- quences collected from January 2020 to July 2021 is carried out using MAFFT followed by their phylogenetic analysis using Nextstrain. The statistics of the number of sequences considered from each country is reported in Table 1. The phylogenetic analysis of the sequences are given in Fig. 2. After the analysis is completed, in this study, we have reported the 12 important variants or lineages and the corresponding mutations of such variants are reported in Table 2. For example, Alpha first identi- fied in the United Kingdom is characterised by a surprising number of mutations such as H69-, V70-, Y144-L452R, E484K, S494P, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H and K1191N. When compared to the parental strain or the reference sequence, there is a possibility that this variant is associated with a higher viral load and prolonged viral persistence [4] as well as an increased risk of death [3]. Also, epidemiological investigations suggested that Alpha is more transmissible (43–82% higher) than the existing lineages [12]. Beta variant discovered in South Africa [39] has D80A, D215G, L241-, L242-, A243-, P384L, K417N, E484K, N501Y, E516Q, D614G and A701V mu- tations. This variant has four mutation points K417N, E484K, N501Y and E516Q present in the RBD region of the Spike glycoprotein, thus making it easier for the virus to attach itself to ACE2. Also this variant has been known to significantly reduce neutralisation in antibodies [34]. It also possibly has increased the fatality rate. Preliminary study by Centre of Mathematical Modelling of Infectious Diseases (CMMID COVID-19 working group, London School of Hygiene and Tropical Medicine) has shown that Beta is more transmissible and less susceptible to cross-protection from previous exposure⁸. Epsilon variant was first

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⁷ https://www.gisaid.org/
⁶ https://www.ncbi.nlm.nih.gov/nuccore/1798174254/
⁵ https://zhanglab.ccmbr.med.umich.edu/COVID-19/
⁸ https://cmmid.github.io/topics/covid19/sa-novel-variant.html.
found in USA with the mutation points S13I, W152C, L452R and D614G. In-vitro and epidemiological studies have suggested that this lineage is related to high transmissibility and infectivity. It is also known to escape neutralisation convalescent plasma and antibodies induced by vaccine [12]. Eta variant found in Nigeria has the mutation points A67V, H69-, V70-, Y144-, E484K, D614G, Q677H and F888L. Iota variant found in USA has mutations such as L5F, D80G, T95I, Y142D, E154K, L452R, S477N, E484Q, D614G, P681R and Q1071H. On the other hand, mutations like T19R, V70F, T95I, G142D, Y145D, N211I, L212I, G339D, R346K, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, Q496S, Q498R, N501Y, V505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K and L981F. All the mutation details for the different variants along with the entropy values are reported in Table 3. Please note that Omicron shares some mutations (A67V, T95I, G142D, K417N, S477N, T478K, N501Y, D614G and P681H) with other variants like Alpha, Beta, Epsilon, Eta, Iota, Kappa, Delta, Gamma and Theta. Thus, these mutations would have the same entropy as mentioned in Table 3. The rest of the unique mutations pertaining to Omicron should be available for the sequences from November onward and thus their entropies are not very conclusive at the moment. Therefore, they are not included in the analysis hereafter.

The entropy for 77681 SARS-CoV-2 genomes are shown in Fig. 2(c) while the average entropy for each month is visualised in Fig. 3. As can be seen from Fig. 3, the month of March 2020 shows high entropy which even coincides with the 1st wave that swept through the world. Then there was a dip from April to October 2020. During June 2021, again the entropy has a steep rise which marked the 2nd wave. The month wise virus evolution in terms of entropy for the different mutations are visualised in Fig. 4 while the month wise evolution of the mutations pertaining to the different variants like Alpha, Beta, Epsilon, Eta, Iota, Kappa, Delta, Lambda, Gamma, Zeta and Theta are shown in Fig. 5 respectively.

The percentage and frequency of change of nucleotide and amino
Table 1
Statistics of SARS-CoV-2 genomes in different countries.

| Name of the Country | Number of Sequences | Name of the Country | Number of Sequences | Name of the Country | Number of Sequences | Name of the Country | Number of Sequences |
|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| USA                 | 13387               | Northern Ireland    | 535                 | Turkey              | 93                  | Pakistan            | 19                  |
| England             | 12126               | Luxembourg          | 530                 | Peru                | 90                  | Hungary             | 17                  |
| India               | 10007               | Canada              | 496                 | Slovenia            | 90                  | Serbia              | 16                  |
| Scotland            | 3910                | Austria             | 470                 | Ghana               | 82                  | Belarus             | 15                  |
| Australia           | 3428                | Russia              | 404                 | Slovakia            | 79                  | Suriname            | 14                  |
| Denmark             | 2584                | Israel              | 359                 | Malaysia            | 79                  | Georgia             | 12                  |
| Wales               | 2544                | Indonesia           | 333                 | Thailand            | 69                  | Mali                | 11                  |
| Iceland             | 1886                | Mexico              | 310                 | Romania             | 67                  | Morocco             | 11                  |
| Belgium             | 1799                | Bangladesh          | 302                 | Lithuania           | 66                  | Kenya               | 10                  |
| Germany             | 1690                | Norway              | 267                 | Croatia             | 62                  | Malta               | 10                  |
| Switzerland         | 1592                | Jordan              | 253                 | Saudi Arabia        | 61                  | Bosnia and Herzegovina | 4                  |
| Spain               | 1451                | Ecuador             | 221                 | Oman                | 59                  | Lebanon             | 4                   |
| Netherlands         | 1432                | New Zealand         | 210                 | Colombia            | 53                  | Bulgaria            | 4                   |
| Italy               | 1398                | Poland              | 208                 | North Macedonia     | 50                  | Cyprus              | 4                   |
| South Korea         | 1373                | United Arab Emirates| 185                | Kuwait              | 45                  | Guatemala           | 3                   |
| Brazil              | 1310                | Aruba               | 180                 | Sri Lanka           | 44                  | Kosovo              | 3                   |
| France              | 1230                | Cambodia            | 169                 | Argentina           | 41                  | Iran                | 3                   |
| Singapore           | 1127                | Greece              | 151                 | Curacao             | 36                  | Jamaica             | 3                   |
| Japan               | 976                 | Latvia              | 149                 | Senegal             | 35                  | Sierra Leone        | 3                   |
| South Africa        | 803                 | Estonia             | 147                 | Vietnam             | 35                  | Rwanda              | 2                   |
| Sweden              | 768                 | Czech Republic      | 141                 | Tunisia             | 31                  | Brunei              | 2                   |
| China               | 698                 | Uganda              | 130                 | Costa Rica          | 30                  | Panama              | 1                   |
| Finland             | 669                 | Egypt               | 123                 | Kazakhstan          | 29                  | Nepal               | 1                   |
| Portugal            | 662                 | Chile               | 123                 | Montenegro          | 25                  |                     |                     |
| Ireland             | 585                 | Nigeria             | 94                  | Bahrain             | 23                  |                     |                     |

Fig. 2. Phylogenetic analysis of 77681 Global SARS-CoV-2 genomes.
Table 2
Variants of SARS-CoV-2 along with their mutations in Spike Glycoprotein.

| Variant (Lineage) | Alpha (B.1.1.7) | Beta (B.1.351) | Epsilon (B.1.427/1.429) | Iota (B.1.525) | Kappa (B.1.617.1) | Delta (B.1.617.2) | Lambda (C.37) | Gamma (P.1) | Zeta (P.2) | Theta (P.3) | Omicron (B.1.1.529) |
|-----------------|----------------|----------------|--------------------------|----------------|--------------------|-------------------|----------------|-----------|-----------|-----------|---------------------|
| Country of Detection | United Kingdom | South Africa | USA | Nigeria | USA | India | India | Peru | Brazil | Brazil | The Philippines | South Africa |
| Mutations in Spike Glycoprotein | L5F | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S13I | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L18F | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| T19R | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| T20N | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| P26S | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| A67V | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| H69- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| V70- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| V70G | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| D80A | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| D80G | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| T99I | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| G142D | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Y144- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Y145D | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| W152C | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E154K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E156- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| F157- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| F157S | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| R190S | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| N211I | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L212I | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| D215G | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| A222V | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L241- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L242- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| A243- | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| D253G | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| W258L | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| G339D | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| R346K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S371L | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S373P | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S375F | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| P384L | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| K417T | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| K417N | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| N446K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| G446S | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L452R | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| L452Q | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S477N | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Y478K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E484A | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E484K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E484Q | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| F490S | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Q493R | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| S494P | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Q496S | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Q498R | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| N501Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Y505H | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| E515Q | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| T577K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| A570D | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| D614G | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| H655Y | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Q677H | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| N679K | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| P681H | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| P681R | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| A701V | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

(continued on next page)
Table 2 (continued)

| Variant (Lineage) | Alpha (B.1.1.7) | Beta (B.1.351) | Epsilon (B.1.427/B.1.429) | Iota (B.1.526) | Kappa (B.1.617.1) | Delta (B.1.617.2) | Lambda (C.37) | Gamma (P.1) | Zeta (P.2) | Theta (P.3) | Omicron (B.1.529) |
|-------------------|-----------------|-----------------|-----------------------------|-----------------|-------------------|-------------------|---------------|--------------|-------------|-------------|-----------------|
| Country of Detection | United Kingdom | South Africa | USA | Nigeria | USA | India | India | Peru | Brazil | Brazil | The Philippines | South Africa |
| Mutations in Spike Glycoprotein | | | | | | | | | | | | |
| T716I | ✓ | | | | | | | | | | | |
| N764K | | ✓ | | | | | | | | | | |
| D796Y | | | ✓ | | | | | | | | | |
| N856K | | | | ✓ | | | | | | | | |
| V859N | | | | | ✓ | | | | | | | |
| R888L | | ✓ | | | | | | | | | | |
| D905N | | | ✓ | | | | | | | | | |
| D950H | | | ✓ | | | | | | | | | |
| Q957R | | ✓ | | | | | | | | | | |
| Q954H | | | ✓ | | | | | | | | | |
| N969K | | | | ✓ | | | | | | | | |
| L981F | | | | | ✓ | | | | | | | |
| T1027 | | | ✓ | | | | | | | | | |
| Q1071H | | ✓ | | | | | | | | | | |
| K1191N | | ✓ | | | | | | | | | | |

Table 3
All mutations in Spike Glycoprotein with relevant details after analysing 77681 Global SARS-CoV-2 genomes.

| Mutations in Spike Glycoprotein | Genomic Coordinate | Nucleotide change | Entropy | Mutation in Spike Glycoprotein | Genomic Coordinate | Nucleotide change | Entropy |
|-------------------------------|-------------------|-----------------|--------|-------------------------------|-------------------|-----------------|--------|
| L5F                           | 21575             | C->T            | 0.1051 | L242-                         | 22286             | C-->            | 0.0292 |
| L18F                          | 21614             | C->T            | 0.1917 | L242-                         | 22287             | T-->            | 0.0303 |
| S13H                          | 21600             | G>T             | 0.0255 | L242-                         | 22288             | T-->            | 0.0279 |
| T19R                          | 21618             | C>G             | 0.2303 | A243-                         | 22289             | G-->            | 0.0360 |
| T20N                          | 21621             | C>A             | 0.0976 | A243-                         | 22290             | C-->            | 0.0098 |
| P26S                          | 21638             | C>T             | 0.0941 | A243-                         | 22291             | T-->            | 0.0102 |
| A67V                          | 21762             | C>T             | 0.0288 | D253G                         | 22320             | A>G             | 0.0377 |
| H69                           | 21767             | C-->            | 0.4524 | W258L                         | 22335             | G>T             | 0.0225 |
| H69                           | 21768             | A-->            | 0.4497 | P384L                         | 22713             | C>T             | 0.0115 |
| T716I                         | 21769             | T-->            | 0.4490 | K147T                         | 22812             | A>C             | 0.0841 |
| V70F/-                        | 21770             | G>T/-           | 0.4611 | K147N                         | 22813             | G>T             | 0.0286 |
| V70                           | 21771             | T-->            | 0.0401 | L452R/Q                       | 22917             | T>G/A           | 0.2774 |
| V70                           | 21772             | C-->            | 0.0166 | S477N                         | 22992             | G>A             | 0.1758 |
| D80A/G                        | 21801             | A>C/G           | 0.0370 | T478K                         | 22995             | C>A             | 0.2395 |
| T95I                          | 21846             | C>T             | 0.2267 | E484K/Q                       | 23012             | G>A/C           | 0.2041 |
| D138Y                         | 21974             | G>T             | 0.1320 | F490S                         | 23031             | T>C             | 0.0180 |
| G142D                         | 21987             | G>A             | 0.3117 | S494P                         | 23042             | T>C             | 0.0140 |
| Y144                          | 21992             | T-->            | 0.4425 | N501Y                         | 23063             | A>T             | 0.4805 |
| Y144                          | 21993             | A-->            | 0.4853 | E516Q                         | 23108             | G>C             | 0.0084 |
| Y144                          | 21994             | T-->            | 0.0713 | A570D                         | 23271             | C>A             | 0.4401 |
| W152C                         | 22018             | G>T             | 0.0261 | D614G                         | 23403             | A>Q             | 0.1576 |
| E154K                         | 22022             | G>A             | 0.0480 | H655Y                         | 23525             | C>T             | 0.0905 |
| E156                          | 22028             | G-->            | 0.0687 | Q677H                         | 23593             | G>T             | 0.0659 |
| E156                          | 22029             | A-->            | 0.2265 | P681H/R                       | 23604             | C>A/G           | 0.6381 |
| E156                          | 22030             | G-->            | 0.2169 | A701V                         | 23664             | C>T             | 0.0484 |
| F157                          | 22031             | T-->            | 0.2167 | T161I                         | 23709             | C>T             | 0.4387 |
| F157S/-                       | 22032             | T>C/-           | 0.2410 | T859N                         | 24138             | C>A             | 0.0260 |
| F157                          | 22033             | C-->            | 0.2586 | F888L                         | 24224             | T>C             | 0.0089 |
| R158G                         | 22034             | A>G             | 0.2712 | D950H/N                       | 24410             | G>C/A           | 0.2490 |
| R190S                         | 22132             | G>T             | 0.0850 | Q957R                         | 24432             | A>G             | 0.0238 |
| D215G                         | 22206             | A>G             | 0.0264 | S982A                         | 24506             | T>G             | 0.4380 |
| A222V                         | 22227             | C>T             | 0.3203 | T1027I                        | 24642             | C>T             | 0.1019 |
| L241                          | 22283             | T-->            | 0.0261 | Q1071H                        | 24775             | A>T             | 0.0475 |
| L241                          | 22284             | T-->            | 0.0260 | D1118H                        | 24914             | G>C             | 0.4439 |
| L241                          | 22285             | A-->            | 0.0262 | K1191N                        | 25135             | T>G             | 0.0307 |
Fig. 3. Average entropy for each month for 77681 Global SARS-CoV-2 genomes.

Structural changes in amino acid residues may sometimes lead to functional instability in proteins due to change in protein translations. These changes are demonstrated through sequence and structural homology-based prediction for the mutations of the different variants in Table 4. Please note that Omicron is not included in this table for the same reason as mentioned before. The tools used for the predictions in Table 4 are PolyPhen-2 (Polymorphism Phenotyping) [1] and I-Mutant 2.0 [5]. Polyphen-2 works with sequence, structural and phylogenetic information of mutations while I-Mutant 2.0 uses support vector machine (SVM) for the automatic prediction of protein stability changes upon mutations. Polyphen-2 is used to find the damaging mutations and I-Mutant 2.0 determines the corresponding protein stability. To determine if a mutation is damaging using Polyphen-2, its score which lies between 0 and 1 is considered. If the score is close to 1, then a mutation is considered to be damaging. It can be concluded from Table 4 that out of the 53 unique amino acid changes for the 11 variants (apart from Omicron), 22 are damaging. Another important parameter to judge the functional and structural activity of a protein is protein stability which dictates the conformational structure of a protein. Any change in protein stability may cause misfolding, degradation or aberrant conglomeration of proteins. I-Mutant 2.0 uses free energy change values (DDG) to predict the changes in the protein stability wherein a negative value of DDG indicates that the protein has a decreasing stability. The results from I-mutant 2.0 show that out of the 22 unique damaging changes, 18 changes decrease the stability of the protein structures.

4. Discussion

In this section, discussion on the mutation points and the effects of vaccine and therapeutics on the different variants of SARS-CoV-2.

4.1. Characteristics of notable mutation points

There are a total of 84 unique mutation points in the reported 12 SARS-CoV-2 variants. The characteristics of some of the mutations are reported in Table 5.

S13I and W152C are parts of Epsilon variant and help SARS-CoV-2 to escape from therapeutic monoclonal antibodies (mAb). L18F which belongs to Gamma variant helps immune escape from neutralising antibodies (NAbs) against N-terminus. H69- and V70- belonging to Alpha and Eta variants lead to increase in infectivity and reduced sera neutralisation. Y144- present in Alpha, Eta and Iota variants reduce affinity of antibody binding. D253G belonging to Iota variant may aid SARS-CoV-2 to resist NAbs. K417T in Gamma variant is known for resistance to neutralisation by antibodies. The same characteristics is exhibited by K417N which is a part of the Beta and Delta variants. The mutation L452R is part of the Alpha, Epsilon, Iota, Kappa and Delta variants and is largely involved in the significant surge of COVID-19 in India. L452R can increase the binding ability of the ACE2 receptor and can also reduce the attaching capability of vaccine-simulated antibodies with Spike glycoprotein. L452Q belonging to Lambda variant increases viral infectivity. The mutation S477N in Iota and Omicron variants

acid are depicted in Fig. 6 respectively. For example, in Fig. 6(a), the occurrence of T>G in 77681 global SARS-CoV-2 genomes is 18% while Fig. 6(b) shows that the number of times it occurs among 70 nucleotide changes is 2 as is also evident from Table 3. It can also be seen from Fig. 6(b) that 11 out of 70 mutations in Spike glycoprotein are from C to T thereby representing abundant transition. This transition increases the frequency of codons for hydrophobic amino acids and provides evidence of potential anti-viral editing mechanisms driven by host [41]. Also, more C to T transition means less CpG abundance indicating rapid adaptation of virus in host. This CpG deficiency which leads to evasion of host anti-viral defence mechanisms is exhibited the most in SARS-CoV-2 virus [40]. In Fig. 6(c), the occurrence for A>D change in amino acid is 19% while as can be seen from Fig. 6(d), its frequency is 1. All the unique 76 mutations as substitutions corresponding to each of the 12 variant are shown in Fig. 7 along with the structure of Spike glycoprotein.

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9 http://genetics.bwh.harvard.edu/pph2/.
10 https://folding.biofold.org/i-mutant/i-mutant2.0.html.
present in the RBD region of SARS-CoV-2 results in escape from mAbs. The mutation E484K which is a part of Alpha, Beta, Eta, Iota, Gamma, Zeta and Theta variants is responsible for improving the ability of the virus to escape the host’s immune system [17]. Akin to L452R, mutation E484Q also belongs to Kappa variant and is associated with reduced sera neutralisation. F490S in the Lambda variant is associated with reduced susceptibility to antibody neutralisation. The mutation N501Y associated with Alpha, Beta, Gamma, Theta and Omicron variants is present in the receptor binding domain of Spike glycoprotein and has the highest binding affinity with ACE2. N501Y is also known to be associated with immune escape [6]. D614G present in all the 12 reported variants is a significant mutation whose frequency has increased rapidly during the pandemic and is a common mutation in all the lineages or variants. The prevalence of loss of smell has been attributed particularly to this mutation. According to [22], D614G is associated with higher infectivity as well as higher viral load and s1 shedding in Spike glycoprotein. H655Y belonging to Gamma and Omicron variants may affect transmissibility of the virus. Q6777H belonging to Eta variant is also known to affect the

Fig. 4. Month wise evolution of all mutations in Spike Glycoprotein based on entropy after analysing 77681 global SARS-CoV-2 genomes.
transmissibility of SARS-CoV-2. P681H which is a part of Alpha, Gamma and Theta variants and P681R belonging to Kappa and Delta variants have similar functionality as H655Y and Q677R. In January 2021, scientists reported that similar to D614G, P681H is showing a significant circulation as well and may affect the transmissibility of the virus. Most of the mutations in Omicron like S371L, S373P, S375F, Q493R, and Q498R have high binding affinity with ACE2 receptor. Furthermore, S371L, N440K, G446S and Q493R are also responsible for antibody resistance. It is to be noted that mutations like S371L, S373P, S375F, T478K, Q493R, Q498R and N501Y can induce higher stability in Spike glycoprotein, thereby having high binding affinity with ACE2. This high binding can be attributed to hydrophobic contact at the interfaces of the RBD part of Spike glycoprotein and ACE2 protein [36] and is established by docking studies [23,35] as well.
It is to be noted that apart from ACE2, recent research [14] has identified cellular proteins like asialoglycoprotein receptor-1 (ASGR1) and Kringle Containing Transmembrane Protein 1 (KREMEN1) as SARS-CoV-2 receptors in Spike glycoprotein. The authors in [14] have shown that both RBD and N-terminal domain bind of Spike glycoprotein bind to ASGR1 and KREMEN1. These two proteins are also believed to affect the viral target cell range as well as antibody-mediated neutralization [16].

4.2. Effects of vaccine and therapeutics on different variants

Vaccines are the most advanced weapon that the human race has devised to fight against this deadly virus. There are several vaccines like Oxford-AstraZeneca, Pfizer-BioNTech, Moderna, Novavax, Covaxin, Sputnik V and Johnson & Johnson which have been developed till now by the scientists around the world. However, some emerging variants like Omicron [26] may be somewhat resistant to the antibody response evoked by these vaccines, thereby making the modifications to these vaccines an absolute necessity. Trials have indicated that many of these vaccines have shown lower efficacy against some of the variants but are effective against the common circulating strains. Table 6 reports the efficacy of the most widely used vaccines for symptomatic as well as severely affected patients. The efficacy of Pfizer-BioNTech and Moderna produced vaccines have an efficacy of 82–100% and 96.3% against the original strain for symptomatic patients while against Delta the efficacy reduces to 42–79% for Pfizer-BioNTech and around 80% for Moderna. For severe patients, efficacy against Delta variant are around 85% and 90% respectively. Gamma variant has been found to partially escape vaccination with Pfizer-BioNTech. Oxford-AstraZeneca vaccine shows an efficacy of 79% against Alpha as opposed to less than 60% against other variants for symptomatic patients. The efficacy of Oxford-AstraZeneca vaccine against Beta was put into question in February 2021 when it was reported that the vaccine is not very effective against this strain. As can be seen from Table 6, the efficacy is indeed very low at 10%. In January 2021, Johnson & Johnson reported that their vaccine was 72% effective against moderate to severe COVID-19 infection in US while such efficiency is 57% in South Africa. According to latest data, Johnson & Johnson vaccine has shown 72% and 86% efficacy in preventing symptomatic COVID-19 and severe COVID-19 respectively for the original strain while for other variants the results vary from 40% to around 75% for both symptomatic and severe patients. Covaxin has also shown promising results for Alpha, Beta, Gamma and Delta variants for symptomatic patients. It is to be noted that Covaxin, Covishield (Indian made Oxford-AstraZeneca vaccine) and Sputnik V have shown effectiveness in neutralising Alpha variant [37]. In March 2021, Novavax vaccine was reported to have a preliminary efficiency of 51% for mild, moderate and severe COVID-19 for HIV-negative patients. According to [11,7], K417N/T, E484K and N501Y are also resistant to neutralisation by vaccines. Despite this, [7] has also reported that sera from infected and Moderna-vaccinated individuals having polyclonal antibodies to the Spike glycoprotein can neutralise the Beta variant. This suggests that protective humoral immunity may be retained against Beta. Research regarding effectiveness of the existing vaccines against the latest
Monoclonal antibody therapies like LY-CoV555 (Bamlanivimab) has been shown to work against Alpha but Beta, Gamma and Epsilon are resistant against it while Alpha, Beta and Gamma variants are resistant against Etesevimab but there is no data for Epsilon variant. Though, Alpha is susceptible to both REGN10933 (Casirivimab) and REGN10987 (Imdevimab), Beta and Gamma are both partially resistant to Casirivimab but Imdevimab is effective against them. As of 22nd December circulating Omicron variant is ongoing.
Table 4
Biological functionality and protein structural stability of the mutations for different variants.

| Nucleotide | Amino Acid | PolyPhen-2 | I-Mutant 2.0 | Change in | Change in | PolyPhen-2 | I-Mutant 2.0 |
|------------|------------|------------|--------------|-----------|-----------|------------|--------------|
| C21575T    | L5F        | Not Generated | Not Generated | Decrease  | -0.10     |            |              |
| G21600T    | S13I       | Not Generated | Not Generated | Increase   | 0.39      |            |              |
| C21614T    | L18F       | Possibly     | Damaging     | Decrease   | -0.39     |            |              |
| G21618G    | T19R       | Benign       | 0.004        | Decrease   | -0.12     |            |              |
| C21621A    | T20N       | Benign       | 0.000        | Decrease   | -0.78     |            |              |
| C21638T    | P26S       | Benign       | 0.009        | Decrease   | -2.19     |            |              |
| C21762T    | A07V       | Benign       | 0.054        | Decrease   | -0.02     |            |              |
| G21770T    | V70F       | Benign       | 0.111        | Decrease   | -2.72     |            |              |
| A21801C    | D80A       | Possibly     | Damaging     | Decrease   | -1.91     |            |              |
| A21801G    | D80G       | Benign       | 0.016        | Decrease   | -1.81     |            |              |
| C21846T    | T95I       | Damage       | 0.999        | Decrease   | -1.80     |            |              |
| G21974T    | D138Y      | Probably     | Damaging     | Increase   | 1.47      |            |              |
| G21987A    | G142D      | Benign       | 0.051        | Decrease   | -1.17     |            |              |
| G22018T    | W152C      | Probably     | Damaging     | Decrease   | -1.66     |            |              |
| G22022A    | E154K      | Not Generated | Not Decrease  | -1.40     |            |            |              |
| T22032C    | F157S      | Not Generated | Not Generated | Decrease   | -2.57     |            |              |
| A22034G    | R158G      | Not Generated | Not Generated | Decrease   | -2.63     |            |              |
| G22132T    | R190S      | Probably     | Damaging     | Decrease   | -2.09     |            |              |
| A2206G     | D215G      | Benign       | 0.002        | Decrease   | -1.06     |            |              |
| C22227T    | A222V      | Benign       | 0.001        | Increase   | 0.48      |            |              |
| A23202G    | D253G      | Not Generated | Not Decrease  | -2.43     |            |            |              |
| G22335T    | W258L      | Benign       | 0.055        | Decrease   | -0.61     |            |              |
| C22713T    | P384L      | Probably     | Damaging     | Decrease   | -1.74     |            |              |
| A22812C    | K417T      | Benign       | 0.012        | Decrease   | -0.88     |            |              |
| G22813T    | K417N      | Benign       | 0.341        | Decrease   | -0.33     |            |              |
| T22917G    | L452R      | Benign       | 0.040        | Decrease   | -1.40     |            |              |
| T22917A    | L452Q      | Benign       | 0.077        | Decrease   | -1.52     |            |              |
| G22992A    | S477N      | Benign       | 0.007        | Increase   | 0.01      |            |              |
| C22995A    | T478K      | Benign       | 0.000        | Decrease   | -0.09     |            |              |
| G23012A    | E484K      | Benign       | 0.427        | Decrease   | -0.85     |            |              |
| G23012C    | E484Q      | Possibly     | Damaging     | Decrease   | -0.48     |            |              |
| T23031C    | F490S      | Benign       | 0.012        | Decrease   | -2.99     |            |              |
| T23042C    | S494P      | Benign       | 0.889        | Decrease   | -0.66     |            |              |
| A23063T    | N501Y      | Benign       | 0.145        | Decrease   | -0.34     |            |              |
| G23108C    | E516Q      | Probably     | Damaging     | Decrease   | -0.93     |            |              |
| C23271A    | A570D      | Benign       | 0.031        | Decrease   | -1.32     |            |              |
| G23403G    | D614G      | Benign       | 0.002        | Decrease   | -1.94     |            |              |
| C23525T    | H655Y      | Benign       | 0.002        | Decrease   | 0.43      |            |              |
| G23593T    | Q677H      | Benign       | 0.157        | Decrease   | 0.10      |            |              |
| C23604A    | P681H      | Not Generated | Not Decrease  | -0.92     |            |            |              |
| C23604G    | P681R      | Not Generated | Not Generated | Decrease   | -0.79     |            |              |
| C23664T    | A701V      | Possibly     | Damaging     | Increase   | 0.05      |            |              |
| C23709T    | T716I      | Possible     | Damaging     | Decrease   | -0.95     |            |              |
| C24138A    | T859N      | Probably     | Damaging     | Decrease   | -0.82     |            |              |
| T24224C    | F88L       | Probably     | Damaging     | Increase   | 0.13      |            |              |
| G24410A    | D950N      | Possibly     | Damaging     | Increase   | 0.15      |            |              |
| G24410C    | D950H      | Possibly     | Damaging     | Decrease   | -0.10     |            |              |

Table 4 (continued)

| Nucleotide | Amino Acid | PolyPhen-2 | I-Mutant 2.0 | Change in | Change in | PolyPhen-2 | I-Mutant 2.0 |
|------------|------------|------------|--------------|-----------|-----------|------------|--------------|
| A24432G    | Q957R      | Possibly   | Damaging     | 0.679     | Decrease   | -0.93     |              |
| T24506G    | S982A      | Possibly   | Damaging     | 0.996     | Decrease   | -1.36     |              |
| C24642T    | T1027I     | Possibly   | Damaging     | 1.000     | Decrease   | -0.22     |              |
| A24775T    | Q1071H     | Possibly   | Damaging     | 0.998     | Decrease   | -1.19     |              |
| G24914C    | D1118H     | Possibly   | Damaging     | 0.998     | Decrease   | -0.10     |              |
| G25135T    | K1191N     | Possibly   | Damaging     | 0.996     | Decrease   | -1.40     |              |

Table 5
Characteristics of mutations in Spike Glycoprotein.

| Mutations | Characteristics |
|-----------|-----------------|
| S13I      | Highest binding affinity with ACE2 and resistant to antibody resistance [26] |
| L18F      | Helps SARS-CoV-2 to escape from mAbs [30] |
| G446S     | Responsible for antibody resistance [26] |
| Q493R     | High binding affinity with ACE2 [23] and responsible for antibody resistance [26] |
| N501Y     | Highest binding affinity with ACE2 and resistant to neutralisation [28] |
| H655Y     | Near furin cleavage site, may affect transmissibility of the virus [10] |
| Q498R     | Responsible for improving the ability of the virus to escape the host's immune system [18] |

2021, FDA has authorised Pfizer’s Paxlovid for the treatment of mild-to-moderate COVID-19 disease in adults and pediatric patients.

5. Conclusion
In this work, we have provided a comprehensive study of the different important variants of SARS-CoV-2 and their corresponding unique mutation points in Spike glycoprotein. This is especially important to understand the effect of the mutations on the vaccines. In this regard, there are 12 important variants of SARS-CoV-2 which are identified; they being Alpha, Beta, Eta, Epsilon, Iota, Kappa, Delta, Lambda, Gamma, Zeta, Theta and lately, Omicron and they have 84 unique mutations in the Spike glycoprotein. These 84 include such mutations like S371L, N440K, G446S, Q493R, N501Y etc. which are

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html.
known to resist antibodies. With the current surge of Omicron variant throughout the world and it being highly resistant to neutralisation by the existing vaccines, booster shots are being recommended worldwide and new phases of partial lockdowns are also coming into effect. In this current scenario, the existing vaccines are getting modified and new vaccines are also being manufactured. We hope that this work provides the readers a comprehensive review of the emerging variants and the characteristics of the corresponding mutation points along with the effects of vaccine and therapeutics on the variants.

Ethics approval and consent to participate

The ethical approval or individual consent was not applicable.

Availability of data and materials

The aligned 77681 SARS-CoV-2 genomes with reference sequence are available at “http://www.nitttkol.ac.in/indrajit/projects/Covid-SpikeVariantsReview-77K”.

Consent for publication

Not applicable.

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Author contributions

Nimisha Ghosh: Conceptualization; Data curation; Formal analysis; Validation; Visualization; Writing - original draft; Suman Nandi: Conceptualization; Formal analysis; Software; Validation; Visualization; Writing - review and editing; Indrajit Saha: Conceptualization; Data curation; Supervision; Formal analysis; Investigation; Project administration; Resources; Validation; Writing - review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] I.A. Adzhubei, S. Schmidt, L. Peshkin, et al., A method and server for predicting damaging missense mutations, Nat. Methods 7 (2010) 248–249, https://doi.org/10.1038/nmeth0410-248.
[2] E. Boehm, I. Kronig, R.A. Neher, et al., Novel SARS-CoV-2 variants: the pandemics within the pandemic, Clin. Microbiol. Infect. 27 (8) (2021) 1109–1117, https://doi.org/10.1016/j.cmi.2021.05.022.
[3] T. Burki, Understanding variants of sars-cov-2, The Lancet 397 (2021) 462, https://doi.org/10.1016/S0140-6736(21)00298-1.
[4] P. Cattini, L. Amato, I. Puglia, et al., Infection sustained by lineage B.1.1.7 of SARS-CoV-2 is characterised by longer persistence and higher viral RNA loads in nasopharyngeal swabs, Int. J. Infect. Dis. 105 (2021) 753–755, https://doi.org/10.1016/j.ijid.2021.03.005.
[5] E. Caprioni, P. Farielli, R. Casado, I-mutant2.0: Predicting stability changes upon mutation from the protein sequence or structure, Nucleic Acids Res. 33 (2005) 306–310, https://doi.org/10.1093/nar/gki375.
[6] P. Colson, A. Levasseur, J. Delerce, et al., Spreading of a new SARS-CoV-2 N501Y spike variant in a new lineage, Clin. Microbiol. Infect. (2021), https://doi.org/10.1016/j.cmi.2021.05.006.
[7] V.V. Edara, C. Norwood, K. Floyd, et al., Infection- and vaccine-induced antibody binding and neutralization of the B.1.351 SARS-CoV-2 variant, Cell Host Microbe 29 (4) (2021) 516–521.e3, https://doi.org/10.1016/j.chom.2021.03.009.
[8] R. Ella, S. Reddy, W. Blackwelder, et al., Efficacy, safety, and lot-to-lot immunogenicity of an inactivated SARS-CoV-2 vaccine (BBV152): interim results of a randomised, double-blind, controlled, phase 3 trial, The Lancet 398 (2021) 2172–2184, https://doi.org/10.1016/S0140-6736(21)00200-6.
[9] T. Fiolet, Y. Kherabi, C.J. MacDonald, et al., Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review, Clin. Microbiol. Infect. (2021), https://doi.org/10.1016/j.cmi.2021.05.005.
[10] W.F. Garcia-Beltran, E.C. Lam, K.S. Denis, et al., Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity, Cell 184 (9) (2021) 2372–2383.e9, https://doi.org/10.1016/j.cell.2021.03.013.
[11] W.F. Garcia-Beltran, E.C. Lam, K. St. Denis, et al., Multiple SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity, Cell 184 (9) (2021) 2372–2383.e9, https://doi.org/10.1016/j.cell.2021.03.013.
[12] F. González-Candelas, M.A. Shaw, T. Phan, et al., One year into the pandemic: Short-term evolution of SARS-CoV-2 and emergence of new lineages, Infect. Genet. Evol. 92 (2021) 104869, https://doi.org/10.1016/j.meegid.2021.104869.

[13] A. Greaney, T. Starr, P. Gilchuk, et al., Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition, Cell Host Microbe 29 (1) (2021) 44–57.e9, https://doi.org/10.1016/j.chom.2020.11.007.

[14] Y. Gu, J. Cao, X. Zhang, et al., Receptome profiling identifies KREMEN1 and ASGR1 as alternative functional receptors of SARS-CoV-2, Cell Res. 32 (2021) 24–37, https://doi.org/10.1038/s41422-021-00595-6.

[15] L. Guruprasad, Human SARS-CoV-2 spike protein mutations, Proteins: Struct., Funct., Bioinf. 89 (2021) 569–576, https://doi.org/10.1002/prot.26042.

[16] M. Hoffmann, S. Pohlmann, Novel SARS-CoV-2 receptors: ASGR1 and KREMEN1, Cell Res. 32 (2021) 1–2, https://doi.org/10.1038/s41422-021-00595-6.

[17] S. Jangra, C. Ye, R. Rathnasinghe, et al., SARS-CoV-2 spike E484K mutation reduces antibody neutralisation, Lancet Microbe (2021), https://doi.org/10.1016/j.s2666-5247(21)00068-9.

[18] S. Jangra, C. Ye, R. Rathnasinghe, et al., SARS-CoV-2 spike E484K mutation reduces antibody neutralisation, The Lancet (2) (2021) E283–E284, https://doi.org/10.1016/j.s2666-5247(21)00068-9.

[19] K. Katoh, K. Misawa, K. i Kuma, et al., MAFFT: a novel method for rapid multiple sequence alignment based on fast Fourier transform, Nucleic Acids Res. 30 (14) (2002) 3059–3066, https://doi.org/10.1093/nar/gkf436.

[20] S.A. Kemp, B. Meng, L.A. Ferreirra, et al., Recurrent emergence and transmission of a sars-cov-2 spike deletion h69/v70. BioRxiv, 2021.

[21] I. Kimura, Y. Kosugi, J. Wu, et al., The SARS-CoV-2 Lambda variant exhibits enhanced infectivity and immune resistance, Cell Reports 32 (2021) 110218, https://doi.org/10.1016/j.celrep.2021.110218.

[22] B. Korber, W.M. Fischer, S. Gnanakaran, et al., Tracking changes in SARS-CoV-2: A comparative computational study of spike protein, J. Med. Virol. (2021), https://doi.org/10.1002/jmv.27526.

[23] S. Kumar, T.S. Thambiraja, K. Karuppanan, et al., Omicron and Delta variant of SARS-CoV-2 spike E484K mutation enhances infectivity and immune resistance, Cell Reports 38 (2) (2022) 110218, https://doi.org/10.1016/j.celrep.2021.110218.

[24] S.D. Lam, N. Bordin, V.P. Waman, et al., SARS-CoV-2 spike protein predicted to form complexes with host receptor protein orthologues from a broad range of mammals, Sci. Rep. 10 (2020) 1–14, https://doi.org/10.1038/s41598-020-71936-5.

[25] E. Lasek-Nesselquist, P. Lapierre, E. Schneider et al., The localized rise of a B. 1.526 variant containing an E484K mutation in New York State. medRxiv, 2021.

[26] L. Liu, S. Iketani, Y. Guo, et al., Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2, Nature (2021), https://doi.org/10.1038/s41586-021-03402-9.

[27] Z. Liu, L.A. VanBliargan, L.M. Boyet, et al., Identification of SARS-CoV-2 spike mutations that attenuate monoclonal and serum antibody neutralization, Cell Host Microbe 29 (3) (2021) 477–488.e4, https://doi.org/10.1016/j.chom.2021.01.014.