

Review

# Variants of SARS CoV-2: mutations, transmissibility, virulence, drug resistance, and antibody/vaccine sensitivity

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Academic Editor: Graham Pawelec

Submitted: 18 December 2021 Revised: 15 January 2022 Accepted: 20 January 2022 Published: 14 February 2022

## Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) is the causative agent of coronavirus disease-19 (Covid-19) which has been designated a worldwide pandemic by the World Health Organization on March 11, 2020. Since that time, the virus has mutated and an assortment of variants have been successful at establishing themselves in the human population. This review article describes the SARS CoV-2 genome, hot spot mutations, variants, and then focuses on the Delta variant, finishing up with an update on the Omicron variant. The genome encompasses 11 open reading frames, one of which encodes the spike or S protein that has been the target for vaccines and some of the drugs because of its role in attachment to the human host cell, as well as antibodies. Mutations in the S protein that are common among several of the variants include D614G that increases transmissibility and viral load and is often associated with P323L on the RNA dependent RNA polymerase. N501Y is a mutation in the receptor binding domain of the S protein that increases binding to the ACE-2 receptor on the human host cells by 10 fold. The discussed variants carry combinations of these and other mutations and are classified by the World Health Organization as variants of concern, variants of interest, and variants under monitoring. All variants are characterized by increased transmissibility (relative to the original SARS CoV-2), which is the reason for their ability to establish themselves. Several but not all variants are more resistant to antiviral drugs and less susceptible to antibodies/vaccines. The Delta variant that dominated the world until November 2021 causes an increased risk for hospitalization and death, but is still very susceptible to the current vaccines. The most recent variant, Omicron, is characterized by increased transmissibility and decreased antibody susceptibility.

**Keywords:** SARS CoV-2; Covid-19; variants; mutations; transmissibility; virulence; drug resistance; antibody sensitivity

## 1. Introduction

SARS CoV-2 and the associated disease Covid-19 were first detected in China in December of 2019 [1] and spread across the world at an alarming speed. On March 11, the World Health Organization (WHO; [www.who.int](http://www.who.int)) declared Covid-19 a world-wide pandemic. SARS CoV-2 belongs to the family of Coronaviridae or coronaviruses that also encompass SARS CoV [2] and MERS [3]. Coronaviruses are single stranded positive sense RNA viruses of approximately 30 kb.

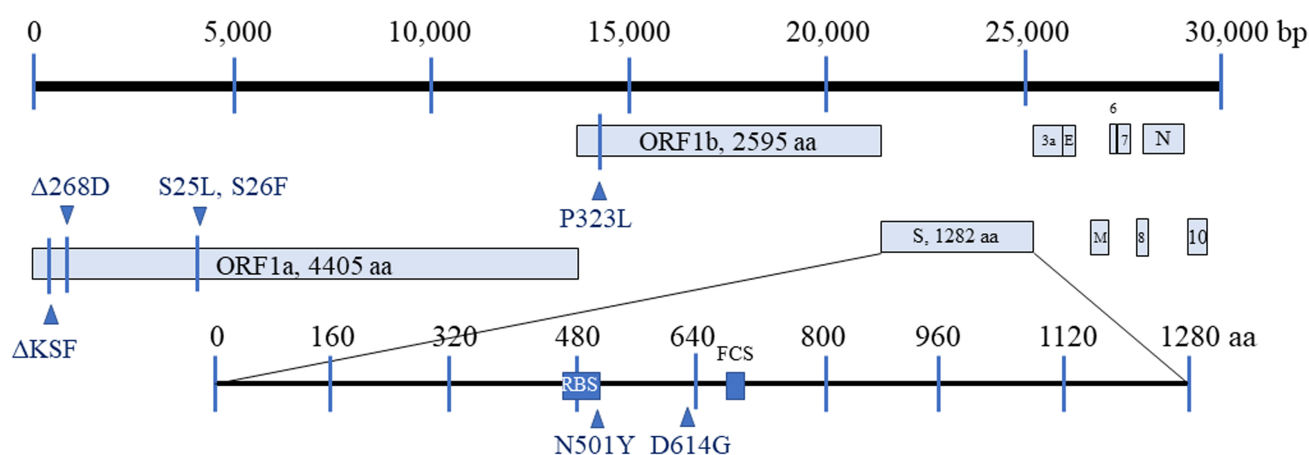
On December 13, 2021 the WHO listed a total of 318,648,834 confirmed cases, 5,518,343 deaths, and the administration of 9,222,5036,080 vaccine doses. Since the first detection of SARS CoV-2, the original virus has mutated, yielding an impressive array of variants, of which a moderate number have been able to establish themselves in the population. This review article focuses on those of the variants that the WHO lists as variant of concern, interest, or under monitoring. The article is structured into five chapters; (i) the SARS CoV-2 genome, (ii) hotspot mutations, (iii) variants of concern, interest, or under monitoring, (iv) the Delta variant, and (v) updates on the Omicron variant. Chapter I outlines the 30 kb genome sequence, the open reading frames, the encoded proteins and shows the locations of some of the hotspot mutations. Chapter II dis-

cusses the dominant mutations that are carried by several of the variants and that impact viral phenotypes, such as transmissibility or susceptibility to antibodies. Chapter III lists the variants of concern, interest, or under monitoring and describes important S protein mutations, as well as the resulting impact on transmissibility, viral load, resistance to drugs, and sensitivity to antibodies/vaccines. Chapter IV focuses on mutations, transmissibility, antibody sensitivity, and spread of the currently dominant Delta variant. The final Chapter V provides an update on the most recent variant, Omicron.

## 2. The SARS CoV-2 genome

The SARS CoV-2 virus has a genome of about 30,000 bp and is organized in 11 open reading frames (ORF) [4], as summarized in Fig. 1 (Ref. [5]). The ORFs are flanked by 5'- and 3'-untranslated regions (UTR) [6] that are not included in Fig. 1. Together, ORF1a and ORF1b at the 5'-end of the genome sequence encompass approximately two thirds to three quarters of the genome; the two ORFs are translated into the pp1a and pp1ab polypeptides, yielding 16 non-structural proteins (NSP1-16) after proteolytic cleavage [7]. The remaining one third of the genome towards the 3'-end encodes four structural proteins; the S or spike protein, the E or envelope protein, the M or membrane





**Fig. 1. Genome organization of SARS CoV-2 with an enlargement of the S protein.** The sizes of the 11 ORFs discussed in Chapter I were taken from [5]. Hot spot mutations that are discussed in Chapter II are indicated, references for these are indicated in the text. ORF1a, polyprotein; ORF1b, polyprotein; S, Spike protein; ORF3a, virion structural protein; E, envelope protein; M, membrane glycoprotein; ORF6, interferon antagonist; ORF7a, virion structural protein; ORF8, ORF8 protein; N, nucleocapsid phosphoprotein; ORF10, protein.

glycoprotein, and the N protein or nucleocapsid phosphoprotein (reviewed by [8]). Also encoded by this region are five accessory proteins.

Of the structural proteins, the S protein is probably the most heavily researched as it facilitates the first two steps of the replication cycle, attachment to the angiotensin converting enzyme 2 (ACE-2) receptor on the human host cells by the means of the S1 subunit and membrane fusion by the S2 subunit [9]. The S protein has been the primary target for the development of vaccines and some of the drugs, both reviewed by this author previously [10,11]. It also served as initial evidence that SARS CoV-2 belongs to the family of the Coronaviridae [12]. As can be seen later in this manuscript, the S protein carries many of the mutations that make some of the variants so successful and dominant.

The very small E protein (76 to 109 aa) is an integral membrane protein, whose structural components are very similar to those of the SARS CoV protein [13]. Among the differences between the E protein of SARS CoV and that of SARS CoV-2 are a substitution of arginine in position 69 by either alanine, glutamine, or aspartate and the presence of threonine and valine in positions 55 and 56 [14]. The E protein is responsible for virus production, assembly, and release from the host cell. It enables the production of virus particles by interacting with NSP2 and NSP3 to generate a conformation of the endoplasmic reticulum (ER) that enables the production of spherical particles [15]. It aids the assembly and release of assembled viruses from the host cell by forming viroporins, small hydrophobic channels within in the host cell membrane [16].

The M and N proteins both suppress the human host response through  $\text{NF}\kappa\text{B}$  and  $\text{IFN}\beta$ , respectively. The M protein is a membrane protein of 220 to 260 aa length and belongs to a group of N-linked glycosylated proteins [17]. It exists in a long and a compact form that act as homod-

imers. The M protein aids the translation of viral proteins on the ER and then interacts with the E protein on the Golgi complex to generate virions [18]. The M protein inhibits  $\text{NF}\kappa\text{B}$ , and has consequently been proposed as a drug target [8]. The N protein is a very abundant protein that binds to the viral RNA and facilitates host cell entry [19]. It binds to and inhibits  $\text{IFN}\beta$  [20].

A second group of proteins whose ORFs (ORF3a, ORF6, ORF7a, ORF8, ORF10) are located in the one third of the SARS CoV-2 genome towards the 3'-end (Fig. 1) and encode five accessory proteins. The ORF3a gene product blocks fusion of autophagosomes with lysosomes and consequently blocks autophagy, a mechanism by which SARS CoV-2 evades lysosomal destruction [21]. The ORF6 and ORF8 gene products aid the N protein in inhibiting the type I interferon pathway by binding to and inhibiting the  $\text{IFN}\beta$  and  $\text{NF}\kappa\text{B}$  promoters [22]. The ORF7a gene product, too, is involved in regulating the type I interferon signaling pathway; the virus is capable of using the host cell ubiquitin system to polyubiquitinate the ORF7a gene product, which enhances the ability of the protein to inhibit interferon signaling [23]. ORF10 is apparently an open reading frame that encodes a 38 aa protein of no sequence similarity to known proteins. It cannot be associated to a protein function and appears to be non-essential [24].

The ORF1a and ORF1b open reading frames at the 5'-end of the genome sequence, these contain the genome replicase genes. ORF1a and ORF1b encode for two polypeptides, designated pp1a and pp1ab that are produced by a -1 frameshift between ORF1a and ORF1b. Proteolytic cleavage includes a virus main protease and other minor proteases into 16 NSPs [25]. A recent review summarizes the functions of the NSPs [26]. NSP1 is the N-terminal product of the replicase with a length of 180 aa and acts as a host translation inhibitor and mRNA degrader [27]. NSP2

is located at 181 to 808 aa on ORF1a and binds to prohibitin 1 and 2 [28]. NSP3 is at 819 to 263 aa and a papain-like protease that releases NSP1-3 from the N-terminal region of pp1a and pp1ab [29]. NSP4 is transmembrane protein that is part of the viral replication and transcription complexes [30]. It is located at aa 2764–3263 on ORF1a. NSP5 is the main protease that cleaves pp1a and pp1ab to yield mature NSPs. NSP6 is another transmembrane protein that is located at aa 3570–3859 and induces the formation of ER-derived autophagosomes and membrane vesicles [31]. NSP7 and NSP8 encoded by ORF1a form a complex with NSP12 encoded by ORF1b, yielding RNA dependent RNA polymerase (RdRp) enzyme [32,33]. NSP9 is an RNA-binding protein that may bind to helicase and NSP10 is of unknown function, but possesses two zinc binding motifs. NSP11 is the last protein on pp1ab and consists of 13 amino acids only. Its function is unknown.

A recent review summarizes the functions of the proteins encoded by ORF1b [34], namely Nsp12 through Nsp16. As mentioned above, NSP12 forms the RdRp, together with NSP7 and NSP8. NSP13 is the helicase core; it has an ATP binding domain and a zinc-domain to aid replication and transcription [35]. Nsp14 is the ExoN 3' to 5' exonuclease. This is a mismatch repair system that reduces the mutation rate of the coronaviruses. Nsp15 is an endonuclease, consisting of an Mn<sup>2+</sup>-dependent endonuclease activity and a methyltransferase [36]. Nsp16 the 2'-O-MTase, 2'-O-methyltransferase [36].

### 3. Hot spot mutations

In general, the mutational rate for RNA viruses is high [37], more so if the genome is as large as that of the coronaviruses. However, SARS CoV-2 and other coronaviruses have the exonuclease activity of NSP14. In fact, mutations in NSP14 were associated with an increased genome-wide mutation load [38]. At this point, the mutation rate of SARS CoV-2 has been low [5]. However, at a population of approximately 8 billions of humans, all of which were initially susceptible to the new virus, SARS CoV-2 has ample of opportunity to mutate. This chapter summarizes hot spot mutations that occur in many of the variants. Additional mutations occurring in the variants of concern, interest, or under monitoring will be discussed in the respective chapter.

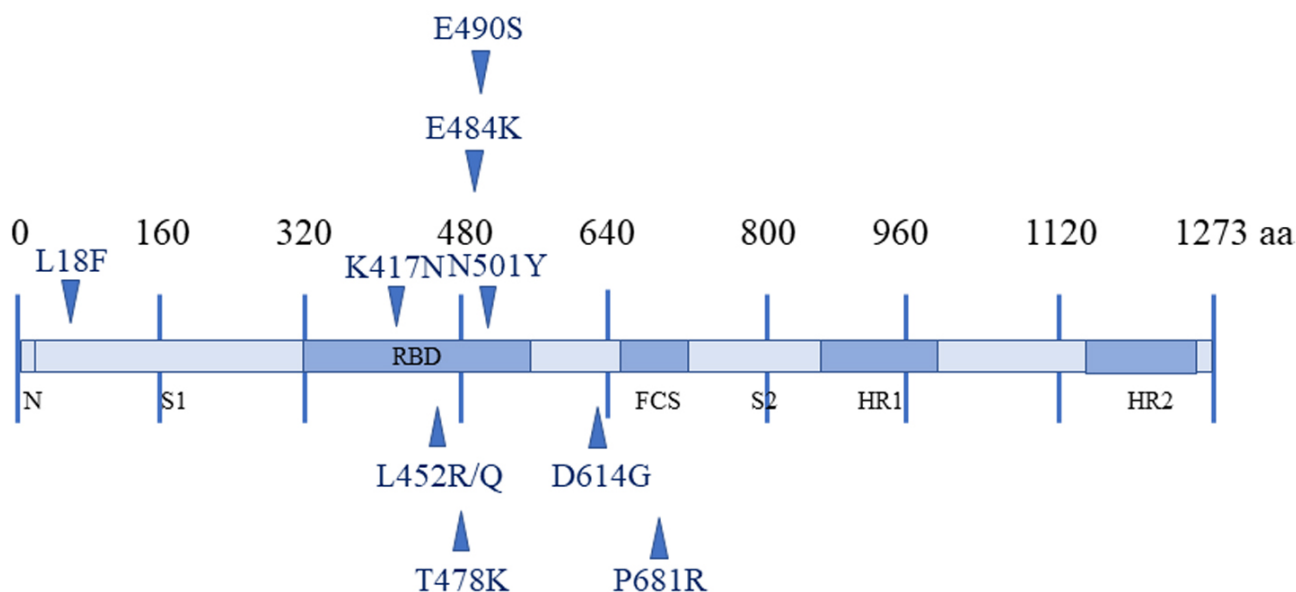
An early mutation that became widespread quickly is the D614G mutation in the S protein that was simultaneously reported by multiple research groups, starting in April 2020 [39]. This mutation co-occurred with a point mutation in location 14,408 on the SARS CoV-2 genome (Fig. 1), which translates into a P323L point mutation in RdRp or NSP14 [39,40].

When infecting hamsters with the D614G modified S protein containing SARS CoV-2, viral replication and the resulting viral load were increased in the upper respiratory tract and not in the lungs [41]. This might explain the increase in transmission due to this mutation, as an increase

in virus replication in the upper respiratory tract was associated with increased pharyngeal virus shedding in a human patient study [42]. Analyzing 25,000 whole genome sequences, it was determined that human patients infected with the 614G variant of the S protein did indeed exhibit a higher viral load [43]. The molecular mechanism which underlies the increased viral load is not fully understood, but the D614G mutation does not appear to modulate the binding affinity for the ACE-2 receptor on the human host cells [44]. Among the discussed hypotheses [45], the promotion of a conformation of the S protein that allows for RBD/ACE-2 interaction ranks high. Other hypotheses include a modulation of cleavage efficiency of S protein and the integration of more S protein incorporation into the virion.

The hypotheses which have been discussed in the literature may be distilled into several central ideas (Fig. 2): the D614G mutation (a) modulates cleavage efficiency of S protein, (b) promotes a conformation favorable for RBD-ACE2 interaction (“openness” hypothesis), (c) facilitates more efficient S protein incorporation into the virion (“density” hypothesis), and (d) stabilizes the association of pre-fusion spike trimers (“stability” hypothesis). It is noteworthy that the D614G mutation does not modulate the S protein binding affinity for ACE2; independent studies have found that monomers of S(D614) and S(G614) have similar affinity for ACE2 as measured by surface plasmon resonance [35] or bio-layer interferometry [39]. While others reported affinity changes [44,46], caution should be taken to interpret the data, depending on the nature of the S protein used in the study. If soluble spike trimers are used, ACE2 binding is determined not only by affinity but also by S1 shedding. On the other hand, if soluble spike trimers containing a furin-null mutation is used, although this mutation addresses the S1-shedding problem, the difference between D614 and G614 may no longer be observed.

Since neutralizing by antibodies is important in assessing vaccine efficacy against variants, sera from spike-immunized humans, non-human primates, and mice were evaluated for neutralization of SARS CoV-2, either containing the D614 or the G614 variant of the S protein [47]. It turned out that the mutated form of the S protein, G614, was more susceptible to neutralization, meaning that this mutation does not currently constitute a problem for our vaccine efforts. Other studies confirmed the increase in transmissibility of the D614G variant, accompanied by unchanged antibody neutralization properties [48,49]. In contrast, a recent review summarizing clinical trials on convalescent plasma therapy described the D614G mutation as one that renders most convalescent plasma and monoclonal antibody therapies less effective [46]. In general, convalescent plasma therapy is considered safe and effective, if special care is taken that the antibody titer of the donor has been determined enough [46].



**Fig. 2. Organization of the S protein.** Mutations that are discussed in Chapters III and IV are indicated. Organizational data are taken from [60]. N light blue, N-terminal domain aa1-13; S1 light blue interrupted by RBD, S1 subunit aa 14–685; S2 light blue interrupted by HR1 and HR2, S2 subunit aa 686–1273; RBD dark blue, RBD domain within S1 aa 319–541; FCS dark blue at beginning of S2, furin cleavage site; HR1, dark blue within S2, heptarepeat 1 of fusion site; HR2 dark blue within S2, heptarepeat 2 of fusion site.

Whether the D614G variant of SARS CoV-2 is associated with an increase in the severity of Covid-19 and/or mortality has been discussed widely and the early reports were contradictory. A publication from July 2020 discusses whether the variants may be the reason behind the differences in mortality around the world [50]. The study by Volz and coworkers that was published in January of 2021 did not see any differences in mortality between SARS CoV-2 and its D614G variant, however, disease prevalence was increased in younger aged cohorts [43]. A January 2021 study from Europe associated variants with the D614G mutation with higher infectivity rate [51].

The above mentioned hamster study was published in April 2021 and tested the effect of changes in the 614 residue (614D vs 614G) as the sole difference between the S-proteins in the viruses that the hamsters were infected with [41]. However, the D614G mutations is typically associated with multiple other mutations. One such mutation is the P323L mutation on the RdRp (Fig. 1) and increased disease severity of Covid-19 was observed for variants containing both, the D614G mutation on the S protein and the P323L mutation on RdRp [52]. It is possible that the success of the Delta variant is dependent on both, the mutation in position 614 on the S protein and the mutation in position 323 on the RdRp. Interestingly, the P323L mutated RdRp appears exhibit an increased ability to bind to remdesivir which is used as an antiviral drug against Covid-19 [53], meaning this mutation does not render remdesivir less effective. Since RdRp forms a complex with NSP7 and NSP8, mutants in the latter two proteins were investigated as well [54]. Mutations in NSP7

at positions 25 and 26 (S25L; S26F; Fig. 1) occurred frequently together with the P323L mutation in RdRp. The S25L mutation in NSP7 increased surface complementary in the RdRp/NSP7/NSP8 complex, from which was concluded that this mutation might be beneficial for the formation of the complex.

Another hot spot mutation in the S protein is position 501 (Fig. 1) at the end of the receptor binding domain (RBD). The N501Y mutation was originally seen in the United Kingdom (UK) in a variant of the lineage lineage B.1.1.7, which is been referred to as Alpha variant [55]. The mutated S protein has a ~10 fold increased binding affinity towards ACE-2 [56], leading to the variant being 70 to 80% more transmissible than the original SARS CoV-2 virus. Since the same RBD on the S protein is targeted by the current vaccines, the question is raised whether the vaccines are effective against variants carrying the N501Y mutation. It was shown that sera from 20 patients that had received two doses of the BioNTech/Pfizer vaccine in the phase I/phase II trial [57] showed no reduction in virus neutralizing activity between the N501Y variant and the original SARS CoV-2 [58]. Also, the mutated spike protein was still able to bind the therapeutic antibody, Bamlanivimab [56].

Unrelated to the D614G, P323L, and N501Y mutations in the S protein and RdRp, mutations have been described in many different parts of the SARS CoV-2 genome. As one example, sequence analysis with 17,928 SARS CoV-2 genome sequences pointed towards a deletion in aa position 241–243 ( $\Delta$ KSF) on NSP1 [4] (Fig. 1). This mutation impacted the structure of the C-terminus of NSP1,



which exerted a negative effect on gene expression in the host cells. In particular, the expression of IFN $\alpha$  was reduced. As a second example, a deletion of aa 268 on NSP2 (Fig. 1) was described in France that had temporarily spread across Europe [59]. Additional mutations will be described in Chapter III.

#### 4. Variants of concern, interest, and under monitoring

The WHO defines a Variant of Interest (VOI) as a variant that has genetic changes impacting transmissibility and disease severity, as well as community transmission in multiple countries. A Variant of Concern (VOC) has the characteristics of a VOI, as well as increases in virulence and decreases in the effectiveness of public health measures. The five variants designated VOC as of November 24, 2021 are listed in Table 1. Also listed in Table 1 are two VOI and six Variants under Monitoring (VUM), of which the first three are former VOIs. The Centers for Disease Control and Prevention in the US (CDC; [www.cdc.gov](http://www.cdc.gov)) also define a Variant of High Consequence (VOHC), but don't currently list any variants in this classification. Note that the status of variants can change. Also note that only VOC and VOI are designated using letters of the Greek Alphabet. The designations in parentheses are Pango lineages. Fig. 2 (Ref. [60]) includes the positions of the mutations on the S protein in the variants (Chapters III and IV).

The Alpha variant (Table 1) has been discussed briefly in this article when the N501Y mutation in the S protein was introduced. This variant was first reported in the UK in December of 2020 [61], spread across Europe between January and April 2021 [62], and within Japan between January and May 2021 [63]. It was seen in the US in December 2020 [64]. The WHO classified the Alpha variant as a VOC on December 18, 2020. The variant carries the N501Y mutation, which was associated with increased affinity of the mutated S protein to ACE-2 on the human host cells [55]. It is considered 43% to 82% more transmissible [65]. While early studies did not see a significant difference in disease severity and mortality when comparing patients infected with the Alpha variant with patients infected with the original SARS CoV-2, it was later reported in the UK that patients infected with the Alpha variant had a 3.8 fold higher risk of severe disease and death [62]. A study in Israel determined that the double dose of the BNT162b2 vaccine by BioNTech/Pfizer was 95% as effective against the Alpha variant as against the original SARS CoV-2 [60]. One dose of the Moderna vaccine mRNA-1273 had an efficacy of 88.1% against the Alpha variant, the second dose increased efficacy (at two weeks after the second dose) to 100% [66]. A systematic review yielded revealed that the full course of vaccine had 84% efficacy against the Alpha variant in 13 out of 15 studies [67]. The study included the BNT162b2 vaccine by BioNTech/Pfizer, the mRNA-1273 vaccine by Moderna, the ChAdOx1 nCoV-19 vaccine by

Oxford/Astra Zeneca, and the NVX-CoV2373 vaccine by Novavax, administered in the recommended double dose.

The Beta variant (Table 1) was first reported from South Africa [68], where it had caused the second wave of Covid-19 infections and later in Brazil [69]. It was also seen in Hong Kong [70]. The Beta variant was classified as a VOC by the WHO on December 18, 2020. This variant also carries the N501Y mutation on the S protein that increases transmissibility. The neutralization ability of antibodies in the Beta variant is decreased, which renders monoclonal antibodies, such as Bamlanivimab and Etesivimab less effective [71]. Bamlanivimab was developed by AbCellera Biologics and Eli Lilly to treat Covid-19. It initially received emergency use authorization (EUA) by the FDA, but due to ineffectiveness against several of the variants, the EUA was later revoked. A EUA for the combination of Bamlanivimab with Etesivimab, is still in effect. The Moderna vaccine was tested against the Beta variant in multiple studies with non-human primates. One study showed that vaccination with two doses of 100  $\mu$ g of the vaccine resulted in an antibody titer that was significantly lower against the Beta variant than the original SARS CoV-2, however, the immunity was still considered effective. In a second study, the Moderna vaccine was tested on non-human primates at 100  $\mu$ g and vaccinations, with a booster at week 29 [72]. It was determined that primates boosted with the Moderna vaccine had a 20 fold increase in the immune response (e.g., neutralizing antibody titer) and were considered protected against the Beta variant and Covid-19. A study in Israel tested the effectiveness of the BioNTech/Pfizer vaccine against the Alpha variant and determined that the vaccine provided solid immunity against the Beta variant [73]. In contrast, the Astra Zeneca vaccine offered little protection against the Beta variant [71]. The Systematic Review that was mentioned in the paragraph on the Alpha variant reported varying results for the Beta variant; four out of seven studies reported efficacies between 22 and 60%, while the remaining studies reported efficacies between 75 and 100% [67]. The includes the Pfizer, Moderna, Astra Zeneca, and Novavax vaccines.

The Gamma variant (Table 1) was first seen in Brazil in December 2020 [74] and has since spread across 45 countries. The WHO classified this variant as a VOC on January 11, 2021. The variant also carries the N501Y mutation on the S protein, as well as several others [74]. It shares three mutations (L18F, K417N/T, and E484K) with the Beta variant, two of these mutations are located in the RBD of the S protein (Fig. 2). This may explain the fact that transmissibility is increased between 1.7 and 2.6 times relative to the original SARS CoV-2 [71]. Also, the mortality risk is increased between 1.2 and 1.9 fold in adults, in children the mortality risk is increased by 5 to 8 fold [71]. Additionally, the 484 location is involved in the interaction of the RDB with Bamlanivimab and the E484K mutation abolishes this interaction, rendering the drug ineffective in the Gamma

**Table 1. SARS CoV-2 variants of concern, interest, and under monitoring.**

Variant	S protein mutations	Origin	Effects	Spread
Variants of Concern				
Alpha (B.1.1.7)	Δ69-70, Δ144, N501Y, A570D, P681H, T716I, S982A, D1118H	UK, December 2020	-Increased affinity of S protein to ACE-2 -Increased transmissibility -Sensitive to BioNTech/Pfizer, Moderna, Oxford/Astra Zeneca, and Novavax vaccines	UK, Europe, Japan, South Africa, US
Beta (B.1.351)	L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V	South Africa, December 2020	-Increased transmissibility -Resistant to Bamlanivimab/Etesivimab -Sensitive to BioNTech/Pfizer and Moderna vaccines after booster shot -Oxford/Astra Zeneca vaccine less effective	Brazil, Hong Kong, USA
Gamma (P.1)	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, H655Y, T1027I, V1176	Brazil, January 2021	-Increased transmissibility -Resistant to Bamlanivimab -Reduced neutralization by antibody therapy and convalescent sera -Moderate protection by Coronavac and BioNTech/Pfizer vaccine and good protection by Oxford/Astra Zeneca vaccine	45 countries
Delta (B.1.617.2)	T19R, Δ157-158, L452R, T478K, D614G, P681R, D950N	India, December 2020	-Increased transmissibility, viral load, and infection rate -Increased risk of hospitalization -Slight to moderate reduction in sensitivity to vaccines	Worldwide
Omicron (B.1.1.529)	15 mutations on RBD: S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, N501Y, Y505H	South Africa, November 24, 2021	-Increased transmissibility -Decreased sensitivity to all tested antibodies (e.g. vaccines, re-convalescent sera, monoclonal antibodies)	Multiple countries
Variants of Interest				
Lambda (C.37)	G75V, T76I, Δ246 to 252, D253N, L452Q, F490S, D614G, T859N	Peru, December 2020	-Increased transmissibility, viral load, and infection rate -Resistant to Bamlanivimab -Reduced antibody binding -Best chance at breaking through vaccines	South America

**Table 1. SARS CoV-2 variants of concern, interest, and under monitoring.**

Variant	S protein mutations	Origin	Effects	Spread
Mu (B.1.621)	T95I, Y144S, Y145N, R346K, E484K, N501Y, D614G, P681H, D950N	Colombia, January 2021	-Decreased viral transduction relative to delta variant -Moderate cell to cell fusion -Probably less transmissible than delta variant -Antibody and vaccine resistant	51 countries
Variants under Monitoring				
Eta (B.1.525)	A67V, Δ69, Δ70, Δ144, E484K, D614G, Q677H, F888L	New York, November 2020	-Reduced neutralization by antibody	Italy
Iota (B.1.526)	L5F, T95I, D253G, S477N, E484K, D614G, A701V	New York, November 2020	-Reduced neutralization by antibody	USA, other countries
Kappa (B.1.617.1)	T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	India, October 2020	-Reduced neutralization by antibody	Morocco
(AZ.5) Formerly (B.1.1.318)	D614G, D796H, E484K, P681H, T95I, ΔY144	Gabon, Central Africa	-Increased transmissibility -Decreased vaccine efficacy	Multiple countries, January 2021
(C.1.2)		South Africa, May 2021	-Possibly increased transmissibility	Africa, Europe, Asia, Oceania
(B.1.630)		Dominican Republic, December 2020		

The information is taken from the WHO website (<https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/>), supplemented with references that are provided in the text.

variant [75]. Interestingly, the Gamma variant may have reduced neutralization by antibody therapy and convalescent sera [76]. The effectiveness of the Chinese vaccine CoronaVac by Sinovac Biotech was determined against the Gamma variant in Brazil [77]. Vaccine effectiveness after the second dose was 55% against hospitalization and 61.2% against death. Vaccine effectiveness was low until completion of the two dose vaccination. Likewise, effectiveness of the Oxford/Astra Zeneca vaccine increased after the second dose to 87.6% against hospitalization and 93.6% against death [78]. The Systematic Review [67] yielded an efficacy of 36.8% for the CoronaVac vaccine and 60% for the BNT162b2 vaccine with insufficient data for the ChAdOx1 and NVX-CoV2373 vaccines.

The Delta variant (Table 1) was initially seen in India in December 2020. The Delta variant was classified as VOI on April 4, 2021 and a VOC on May 11. It was comprehensively reviewed in October 2021 [79]. Delta has a total of 23 mutations, of which seven are in the S protein. Interestingly, the Delta variant is lacking the N501Y mutation that is carried by the Alpha, Beta, and Gamma variants. It does, however, carry the D614G mutation. It is considered 40 to 60% more transmissible than the Alpha variant, increases the risks for hospitalization when compared to the Alpha variant, and is more common in younger populations [80,81]. The Delta variant can break through immunity that was generated by vaccines targeting the original SARS CoV-2 [82], however, the virus gets cleared more quickly in vaccinated humans [83]. The Delta variant has been the dominant variant across the world for almost a year and more information will be provided in the Delta Variant chapter.

The Omicron variant (Table 1) is the most recent of the variants. It was first reported from South Africa on November 24, 2021 from a specimen collected on November 9, 2021. Omicron was classified as VOC by the WHO on November 26, 2021. It was reported from multiple countries within days of the first report. The variant is heavily mutated with >30 changes on the S protein, of which ten are located within the RBD [84]. In comparison, the Delta variant has two mutations on the RBD, the beta variant has three mutations in this region. The mutations suggest changes in transmissibility and antibody sensitivity, possibly also impacting the response to T cells. Since the Omicron variant is by now the dominant variant in the world, it will be discussed in detail in a separate chapter.

The Lambda variant (Table 1) is the first of the variants that are currently classified as VOI. It was originally reported from Peru and spread rapidly across South America. The WHO classified the variant as VOI on June 14, 2021. Like the Delta variant, this variant does not carry the N501Y mutation in the S protein. However, it does have two mutations in the RBD, L452Q and F490S. It also carries the D614G mutation which was associated with an increased viral load and transmissibility. The Lambda variant quickly

became dominant in South America, where it was responsible for the infection of vaccinated people [85]. The Lambda variant completely lost its binding ability to Bamlanivimab and drastically reduced binding antibodies from sera of individuals that were vaccinated with Pfizer-BioNTech vaccine [86]. Before the evolution of Omicron, the Lambda variant was probably the variant that had the best chance of escaping the protection by the vaccines. Note that the use of Bamlanivimab as an antibody treatment against Covid-19 has been discontinued in some countries because its ineffectiveness against numerous of the variants.

The Mu variant is the only other variant that was classified as VOI at the time of writing this manuscript. It was first reported from Colombia and designated as a VOI on August 30, 2021. The Global Influenza Surveillance and Response System (GISAIID; <https://www.gisaid.org>) lists 51 countries through which the Mu variant has spread. The variant carries nine mutations on the S protein, of which many are in common with previous variants. In particular, it carries the D614G and N501Y mutations that were associated with increased transmissibility and the E484K mutation that is responsible for reduced antibody sensitivity. Experimentally, the Mu variant was characterized by a reduction in viral transduction, when compared to the Delta variant. In addition, cell to cell fusion was moderate and the variant exhibited prominent resistance to vaccine-elicited antibodies [87].

Three variants have previously been classified as VOI [64] and are now classified as VUM; Eta, Iota, and Kappa. Eta and Iota were first reported from New York in November 2020, Kappa from India in December 2020. The three variants carry some of the key S protein mutations, such as E484K(Q). The Eta variant was also reported from Italy [88], the Iota variant was seen in all 50 of the United States and other countries [89]. The Kappa variant was found in Morocco [90]. In addition to the mutations in the S protein, the Kappa variant has mutations in ORF1ab, ORF3a, the M protein, ORF7a, and the N protein. The Eta, Iota, and Kappa variants have a reduced neutralization ability by antibodies, which led to the original classification as VOI.

The variant AZ.5 was formerly known under the designation B.1.1.318. It has been identified in Gabon, South Africa [91]. The mutations on the S protein include the D614G mutation that is associated with increased transmissibility, and the E484K mutation that causes decreased vaccine efficacy. The variant C.1.2 is different from the Lambda variant, but from the same lineage. It was first identified in South Africa in May 2021 and has since spread to Africa, Europe, Asia, and Oceania [92]. It shares many mutations with other variants, including Alpha, Beta, Gamma, Delta, and Lambda. This author was unable to find any peer-reviewed research on the variant B.1.630, the final one of the VUM. Altogether, there are different variants of VOC, VOI or VUM status (Table 1), the majority of which were first reported in winter of 2020/2021, that share multi-



ple key mutations on the S protein and are characterized by increased transmissibility (D614G, N501Y) and sometimes a reduced ability to bind to antibodies (E484K) that were either produced by previous infection, vaccine, or given as convalescent sera or monoclonal antibody treatment.

## 5. The Delta variant

When looking through the dates at which the VOC, VOI, and VUM were first detected (Table 1), most dates range from October 2020 to January 2021. Exceptions include variant C.1.2 from May 2021 and Omicron from November 2021. Additionally, three variants were originally classified as VOI, but later classified as VUM because they were unable to establish themselves in the SARS CoV-2 population. This author believes that this is due to the strong prevalence and dominance of the Delta variant that quickly conquered the world, which is facilitated at least in large part by the much increased viral load in the infected patients [93]. It is also interesting that it took almost a year from the emergence of Delta for Omicron to evolve. While we do not know yet how big a problem Omicron is going to be, Delta is certainly a very successful variant of SARS CoV-2.

A key region on the S protein is the RBD, which has accumulated mutations in all the VOC, VOI, and VUM (L452R, E484K, E484Q, N501Y, K417N) (Table 1, Fig. 2). A mutation adjacent to the RBD is the D614G mutation which was discussed in this article earlier. Within the RBD, Delta only has two mutations, L452R and T478K. It does have the D614G mutation, but is lacking the N501Y mutation from the Alpha, Beta, and Gamma variants. Both, L452R and T478K are in the receptor binding interface between aa 438 and 508, which is also used for the binding of antibodies. Structural analysis of the original SARS CoV-2 S protein and that of the Delta variant showed similar hydrogen bond interaction patterns [94]. However, a small difference in the orientation of aa G496 due to the L452R mutation in Delta increases the strength of the hydrogen between the two  $\beta$ -sheets that form a key portion of the RBD [94]. Investigation of the  $\beta$ -loop- $\beta$  motif showed a reduced flexibility in the loop structure of the Delta variant S protein due to the T478K mutation that lies within this loop [94]. Between the difference in the  $\beta$ -sheet region and the  $\beta$ -loop- $\beta$  motif, the key regions 2 and 3 within the RBD are further apart in the Delta variant than in the original SARS CoV-2. This change does not appear to impact binding ACE-2. With respect to antibody binding, the change impacts binding of antibodies that bind at A-F, but does not impact antibodies that bind to different sites [94]. A variant of Delta, designated Delta Plus harbors an additional mutation that in the RBD, K417N. This mutation has also been seen in the Beta variant and increases the virus' ability for immune evasion [95]. It does however also decrease binding to ACE-2 by about 6.4 fold [96], which comes as a trade off to the decreased antibody sensitivity.

The P681R mutation of the Delta variant is located within the furin cleavage site (FCS, Fig. 2) that contains an arginine rich region of Arg-Arg-Ala-Arg as the actual target of cleavage. Replacing proline with arginine adjacent to this site increases the basicity of the RRAR motif and increases the rate of membrane fusions (reviewed by [97]). Together with the increase in ACE-2 binding facilitated by L452R and T478K, increasing membrane fusion by P681R leads to the impressive transmissibility that permitted the Delta variant to spread across the world, which has been quantified by the Centers of Disease Control and Prevention (CDC; [www.cdc.gov](http://www.cdc.gov)) in the US as twice as fast as the original SARS CoV-2. In further quantification of the Delta spread, the WHO Covid dashboard ([covid19.who.int](https://covid19.who.int)) indicates that the wave that started in February 2021 already contained more Delta variants than original SARS CoV-2 viruses. Airborne transmission was estimated as increased in the Delta variant (64% vs 29% in the original SARS CoV-2) in a study that performed a Monte Carlo simulation on a contact network and exponential dose-response model [98].

In addition to increased transmissibility relative to the original SARS CoV-2, the Delta variant is also characterized by an increase in virulence. Using Thermo Fisher's TaqPath RT-PCR that tests for three target genes, a cohort analysis was performed with 19,543 confirmed Covid-19 cases and showed that the S gene-positive cases were associated with an increased risk for hospitalization with a hazard ratio of 1.85 [80]. Additionally, the Delta variant was found in younger and more affluent test groups [80]. A retrospective study with 212,326 Covid-positive patients by the University of Toronto in Canada investigated virulence of Delta and other VOCs in comparison with the original SARS CoV-2 [99]. The Delta variant was characterized by 108% risk for hospitalization, 235% for ICU admission and 133% for death.

Since binding to ACE-2 and antibodies are both associated with a very similar region within the RBD and the Delta variant has critical mutations in this region, the question was asked whether the vaccines that were targeted against the original SARS CoV-2 would still be effective against this variant. As of the BioNTech/Pfizer vaccine BNT162b2, effectiveness of a single dose of vaccine was lower in patients with the Delta variant (37%) than in those with the Alpha variant (48%) [100]. After two doses of the vaccine, effectiveness was 88% for patients with the Delta variant and 93.7% for those with the Alpha variant. A study with nursing home residents showed a larger reduction in effectiveness of both the BioNTech/Pfizer vaccine BNT162b2 and the Moderna vaccine mRNA-1273 during the time period when the Delta variant was dominant in the US (53.1%), when compared to the pre-Delta time period (74.7%) [101]. Similarly, vaccination with two doses of the Oxford/Astra Zeneca vaccine ChAdOx1 was effective at 67% for patients with the Delta variant and 74.5% for those with the Alpha variant [100]. Vaccination with one dose of

the Janssen/Johnson&Johnson vaccine Ad26.COV2.S led to incidence rate ratios of 0.26 when comparing vaccinated vs unvaccinated cohorts (60 of 8889 vaccinated participants vs 2236 of 88,898 unvaccinated participants) [102]. While this study did not distinguish between the Delta variant and the original SARS CoV-2, it was performed at a time where the Delta variant was predominant (February to July 2021) and yielded results that were similar to an earlier phase III trial from the pre-Delta time [103]. A prospective, longitudinal, cohort study from the UK saw a reduced risk of delta variant infection in vaccinated people than in unvaccinated ones [104]. Interestingly, the viral load was similar between vaccinated and unvaccinated people. Altogether, the Delta variant is more transmissible, more virulent and slightly to moderately less susceptible to vaccines.

## 6. Updates on the Omicron variant

Since the first report of Omicron in November 2021, it has become obvious that the pandemic most likely won't be ended, but that Covid-19 will (or already has) become endemic. This is in part because of the continuous emergence of new variants [105], but also because of the short lived nature of the infection or vaccine induced antibodies [106], which contributes to breakthrough infections in both recovered Covid-19 patients and vaccinated individuals [107]. This is not to talk about lack of access to the current vaccines in large parts of the world, as well as vaccine hesitancy among large parts of populations in countries that do have ample vaccine access.

Based upon 32 mutations on the S protein among other mutations on NSP3, NSP4, NSP5, NSP6, NSP12, NSP14, E protein, M protein, and N protein, the question was raised which of the Omicron mutations might impact binding to ACE-2 and antibodies. An early study on Omicron used an artificial intelligence (AI) model to study the effect of 15 mutations (S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, N501Y, and Y505H) within the RBD [108]. This approach had been successful at predicting weakening antibody binding based on S protein mutations earlier [109]. A first prediction was that due to the combination of mutations N440K, T478K, and N501Y, the Omicron mutant might be twice as infective as the Delta variant.

Empirical evidence is consistent with this first prediction. The WHO reported that Omicron had overtaken Delta in South Africa by early December 2021. A report by CNN [110] indicated that infections in Britain by the Omicron variant doubled every two to three days. The CDC reported at least one case of the Omicron variant in 31 states by December 13, 2021. By January 1, 2022, it had been determined that the Omicron variant replicates and infects about 70 times faster than previous variants in the bronchial tract, but infection of the lungs is lower [111]. A most recent paper in Journal of Autoimmunity [112] discusses host immunity in the context of Covid-19 and vaccine breakthroughs. The immune response to SARS CoV-2 is heavily based on

T cells in addition to antibody producing B cells. In particular, T follicular helper (Tfh) cells help the development of a stable and persistent B cell memory [113]. Since the expansion of T cells gets stimulated by certain peptides of the S protein, such as the ones used for the vaccines, booster shots of the vaccines can increase the number of SARS CoV-2 specific T cells [114]. However, breakthrough infections can still happen in dependence on the amount of virus the person got exposed to, the current antibody levels of the infected person, and the susceptibility of the respective variant to the vaccine the person got vaccinated with [107]. Intriguingly, a 50% protection against symptomatic infection can be accomplished if the antibody level of the infected person is around 20% of the post-infection level from the previous infection, but a 50% protection against severe disease is still accomplished at 3% of post-infection level antibodies [115].

In further agreement with the prediction from the AI study [108], the mutation N501Y was determined experimentally to impact hydrogen bond formation between the RBD and ACE-2 [116]. Altogether, the study identified five stable hydrogen bonds between the RBD on SARS CoV-2 and ACE-2 on the human host cell. Two hydrogen bonds were reduced in the Omicron variant. This was accomplished by the mutation K417N which caused loss of hydrogen bonding with ACE-2 residue D30 and Y505H which reduced bonding to ACE-2 residue E37 [116]. In contrast, hydrogen bonds of Q493 (on the virus) with E35 (on ACE-2), Q498-K353, and Y505-E37) were enhanced by the respective mutations in the Omicron variant. Altogether, binding between the RBD of the Omicron variant S protein to the ACE-2 receptor was slightly stronger than for the original SARS CoV-2 [116]. The authors consider this the molecular basis for the increase in transmissibility. A second structural study modeled the co-operativity between the R493, S496, Y501, and R498 residues on the RPB of Omicron variant S protein to be a key factor in the increased binding of the RBD to ACE-2 [117].

As a second prediction from the AI study [108], it was calculated that the combination of mutations K417N, E484A, and Y505H might give Omicron a stronger vaccine resistance than Delta. This too has been partially confirmed by other groups by now. Complexes of neutralizing antibodies with the Omicron S protein RBD suffered a loss of interfacial interaction by mutations, such as K417N [117]. Representatives from all four Barnes classes of antibodies were modeled for their interaction with the Omicron S protein RBD. A distinction was made between class ½ and class ¾ antibodies, where binding to class ½ antibodies would be considerably altered, which class ¾ antibodies might still be moderately functionable [117]. Likewise the AI study [108] had also predicted that the Regeneron monoclonal antibody cocktail (Barnes class 3) should still be moderately functional. This antibody, however, has since been proven ineffective [118] against Omicron.

Vaccine susceptibility of the Omicron variant has by now been tested for several of the vaccines in numerous studies. The BNT162b2 vaccine by BioNTech/Pfizer and the Coronavac vaccine by the Chinese company Sinovac showed little effectiveness against two different Omicron variants, when administered in the originally recommended two doses [119]. BNT162b2 recipients had neutralizing antibodies above the detection limit in just about 20% of the vaccine recipients, while the Coronavac vaccine did not give any of the participants neutralizing antibodies against the two Omicron variants. The BNT162b2 results from this study are consistent with an early press release by BioNTech and Pfizer, where two doses of the vaccine did little to prevent infection with Omicron, but may still be effective against severe disease as recognition by CD8<sup>+</sup> T cells was not affected by the mutations [120]. Three doses of BNT162b2 neutralized the Omicron variant to an extent that was similar to that for the original SARS CoV-2 S protein [120]. A study with the South African Omicron variant determined Omicron escaped antibody neutralization by the two doses of the BNT162b2 vaccine by a factor of 22 fold [121]. For both mRNA vaccines, BNT162b and mRNA-1273, as well as the Ad26.COV2.S vaccine by Janssen/Johnson & Johnson, neutralization of the Omicron variant was below the detection limit, when the vaccines were administered at the originally recommended one (J&J) or two doses (Pfizer/Moderna) [122]. However, the booster shot for the mRNA vaccines neutralized the Omicron variant to a level that was only 4 to 6 fold lower than for the original SARS CoV-2, which still yields some moderate protection [122]. An Omicron variant from Belgium was barely inhibited by sera from the BioNTech/Pfizer vaccine or the Oxford/Astra Zeneca vaccine [123]. Still, the Pfizer booster led to an antibody response that was between 6 and 23 fold lower for Omicron than for Delta, but detectable [123]. Altogether, the Omicron variant escapes most antibodies, whether acquired by previous infection or vaccine, of administered as convalescent sera or as monoclonal antibodies. Booster shots of the mRNA vaccines are still partially effective.

## 7. Conclusions

Altogether, the SARS CoV-2 variants have impressive abilities to transmit to new hosts and varying abilities to evade antibodies. In particular, the Omicron variant has changed the way we see the pandemic and our vaccination efforts. Covid-19 may be here to stay and our current vaccines are only partially effective. However, the booster shots in particular for the mRNA vaccines still provide a good protection from severe disease and a moderate protection from infection. Therefore, it is imperative that our vaccination efforts be maintained and increased. In addition, current vaccines may have to be revised using the sequence of the variant S protein or another region of the chromosome that may not change quite as rapidly as the RBD.

## Abbreviations

ACE, angiotensin converting enzyme; AI, artificial intelligence; CDC, Centers for Disease Control and Prevention; FCS, furin cleavage site; ORF, open reading frame; RBD, receptor binding domain; VOC, variant of concern; VOI, variant of interest; VUM, variant under monitoring; WHO, World Health Organization.

## Author contributions

BMP designed the project and wrote the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of interest

The author declares no conflict of interest.

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