How do genetic variants of SARS-CoV-2 impact the effectiveness of available vaccines and medical therapies?

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Glossary

Adjuvant - an ingredient (used in some vaccines) that helps create a stronger immune response.

Amino acid substitution - change in a specific amino acid of a spike protein.

Antigenicity - capacity of a virus to bind to specific antibody molecules.

Cytokine - proteins produced by cells to regulate the body's response to disease and infection.

Cytokine storm - elevated levels of circulating cytokines triggering pulmonary inflammation.

Efficacy - the capacity of a designed vaccine or medical therapy to positively influence the course or duration of a disease in the patient population at the dose tested

Epitope - specific parts of an antigen recognised by the immune system: B cells, T cells or antibodies.

Glycoprotein - a protein molecule that has a carbohydrate group (or sugar) attached to amino acid side chains

Haplotype - or haploid genotype, is a group of alleles inherited from a single parent of an organism.

Homoplasy - repeated occurrence in unrelated branches of evolutionary history (phylogeny) of a virus.

Immunogen - an antigen or any substance eliciting an immune response.

Mutation - change in genetic sequence as a natural by-product of viral replication.

Pathogen – disease-causing microorganisms such as virus and bacteria

Pathogenicity - capacity of a microbe (virus or bacteria) to cause disease.

Pathogenesis - the onset and progression of a disease.

Phenotype - observable characteristics of an organism.

Strain - a variant with a demonstrably different phenotype.

Thrombo-inflammatory - coordinated thrombotic (blood clotting) and inflammatory (cytokine release) processes leading to enhanced tissue injury.

Variant - genomes differing in sequence.

Viral load - the amount of measurable virus particles in a standard volume of fluid (blood or plasma). It is commonly used to define how a patient responds to antiviral drugs.

How do genetic variants of SARS-CoV-2 impact the effectiveness of available vaccines and medical therapies?

1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative pathogen of coronavirus disease 2019 (COVID-19), spread across the globe within a relatively short time, posing unprecedented challenges to global health and economy. On 11th March 2020, the World Health Organization (WHO)(Ghebreyesus, 2020) officially declared the outbreak a pandemic due to an alarming increase in the number of reported cases and affected countries, with the potential for the situation to worsen. Confirmed cases of COVID-19 in the UK (as of 13th June 2021) were 4,600,627[1]. The virus was first isolated in Wuhan, China in December 2019, when several patients presented with respiratory distress secondary to an unknown pneumonia (Koyama, Platt and Parida, 2020). Although the specific origin of this virus is still unknown, comparative genomic analysis has shown close homology of SARS-CoV-2 to the bat coronavirus isolate (Bat-Cov-RaTG13 - approximately 96% sequence identity) and an isolate of Malayan pangolins (Pangolin-CoV - approximately 91.02% identity) (Poterico and Mestanza, 2020; Xiao et al., 2020). This is indicative of its likely zoonotic origin and spillover from a natural reservoir to the human environment.

Since its emergence, significant variants of SARS-CoV-2, with improved adaptation to survival, have emerged and have become dominant strains in disparate geographic locations. The rapid evolution can be attributed to the poor accuracy of RNA genome replication and the Darwinian selection of cumulative mutations. The resultant concerning variations in genomic regions have impacted virulence and natural and vaccine-induced immune escape (Burioni and Topol, 2021). Thus, understanding novel mutations in the viral genome is crucial to gaining insight into the pathogenesis of SARS-CoV-2 and effective vaccine design, therapeutics, and diagnostic approaches (Pachetti *et al.*, 2020).

This research essay examines the novel genetic variants of SARS-CoV-2 and their impact on vaccine and medical therapy design and development. The essay intends to analyse how vaccines and treatments presently authorised for use in the UK will work against novel variants.

2. Background

SARS-CoV-2, a member of the Coronaviridae family is one of seven human coronaviruses (HCoVs) causing disease in humans (Dagotto, Yu and Barouch, 2020). Four among these are inconsequential pathogens causing only mild respiratory disease like a common cold. The remaining three, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV - identified in 2002), Middle East Respiratory Syndrome Coronavirus (MERS-CoV - identified in 2012), and the now prevalent SARS-CoV-2, sharing genetic similarities, have emerged as causative agents of highly pathogenic respiratory diseases (Thoms *et al.*, 2020). SARS-CoV, identified in Guangdong Province (China) in 2002, demonstrated the potential of animal CoVs to jump the species barrier, often termed *spillover* (Quammen, 2012).

[1] https://covid19.who.int/region/euro/country/gb

SARS-CoV-2 enters the body through the respiratory tract and infects the lungs, heart, pancreas and blood vessels, amongst other organ systems. The inflammatory response due to infection can cause high temperature, cough, chest pain, shortness of breath, myalgia, arthralgia, altered taste and confusion (Burrage, Koushesh and Sofat, 2020). Mortality from the disease has been higher in individuals older than 65 or with underlying comorbidities, such as severe heart conditions, high blood pressure, diabetes, obesity, and chronic lung disease (Koyama, Platt and Parida, 2020).

2.1 The genetics and structure of SARS-CoV-2

SARS-CoV-2 (Figure 1) is a single-stranded, positive-sense ribonucleic acid (RNA) virus of the β-Coronavirus (CoV) family. It encodes 16 non-structural proteins (NSP's 1–16), 8 accessory proteins (ORF3a, 6, 7a, 7b, 8, 9b, 9c and 10) and 4 structural proteins, including nucleocapsid protein (N) with associated membrane protein (M), envelope protein (E), and surface spike (S)-glycoprotein (Kowarz *et al.*, 2021). The genetic sequence of the virus is encoded in an RNA molecule.

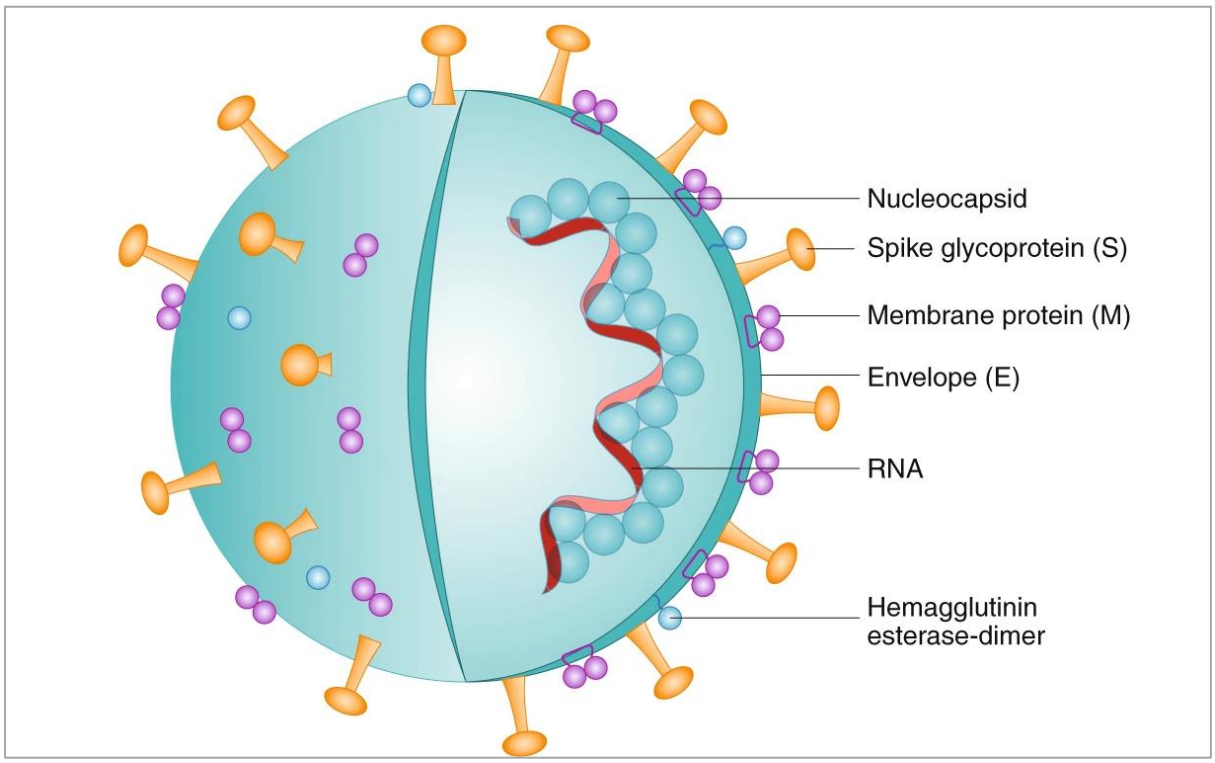


Fig. 1 SARS-CoV-2 structure (Florindo *et al.*, 2020)

The spike (S) protein (Figures 2 and 3) initiates infection by mediating host cell binding and entry using its two subunits, S1 (head) and S2 (stem). The receptor-binding domain (RBD) in S1 binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface. Following this, host cellular serine protease (enzymes that break down proteins) cleave and activate the virus spike for fusion. The active enzymes are proprotein convertase furin, which cleaves the spike protein in the S1/S2 site, and transmembrane protease serine 2 (TMPRSS2), which cleaves the S2' site. Once activated, the fusion peptide (FP) in S2 mediates viral and target cell membrane fusion via two heptad repeat domains (HR1 and HR2) and subsequent release of the viral genome into the host cell. Mutations of crucial amino acid residues in S1 play a vital role in enhancing the interaction with ACE2 (Dagotto, Yu and Barouch, 2020; Huang *et al.*, 2020). Understanding these viral and host cellular interactions are crucial in gaining an insight into the potential vaccine and therapeutic targets for the prevention and treatment of COVID-19.

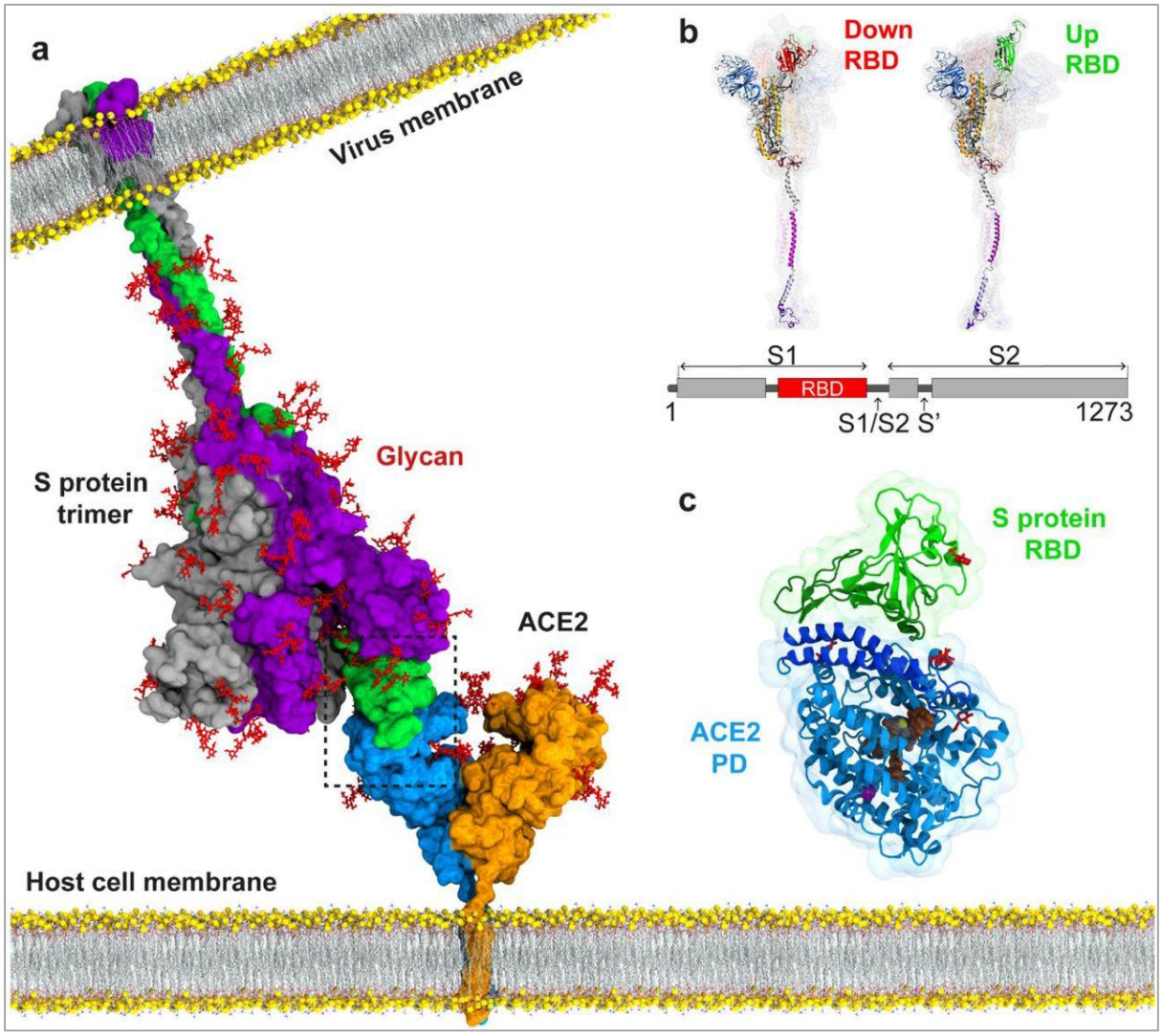
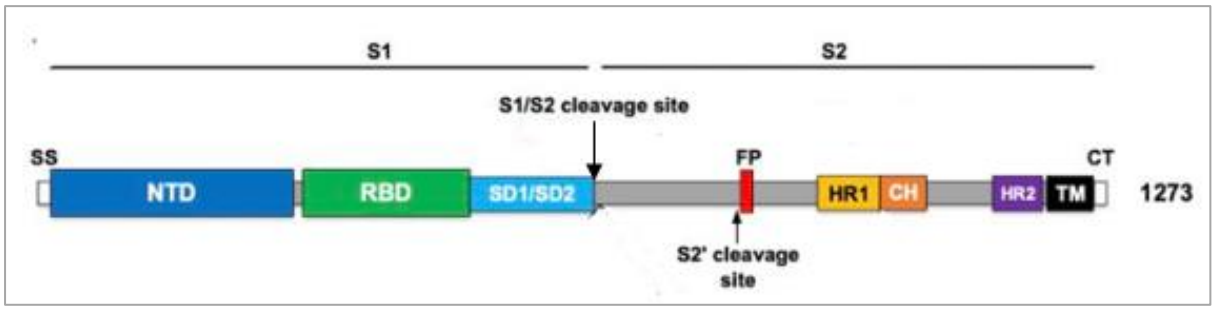


Fig. 2 Atomic model for binding of the S protein to the ACE2 receptor on the host cell membrane (Taka *et al.*, 2021)



SS – signal sequence	FP -fusion peptide
NTD – N-terminal domain	HR1 – heptad repeat 1
RBD – receptor-binding domain	CH – central helix
SD1 – subdomain 1	HR2 – heptad repeat 2
SD2 – subdomain 2	TM – transmembrane domain
S1/S2 & S2' – protease cleavage sites	CT – cytoplasmic tail

Fig. 3 SARS-CoV-2 S protein sequence elements (showing S1 and S2 ectodomain) (Bangaru et al., 2020)

Mutation, or minor change in the genetic sequence, drives the virus' survival, evolution, and genome variability. Community transmission and antiviral treatments can engender novel mutations that result in more virulent strains that can escape host immunity and develop treatment resistance. This highlights the need for systematic tracking of demographic and clinical patient information to identify genetic diversity and phylogenetic analysis of the global sampling of SARS-CoV-2 to identify emerging variants (Korber *et al.*, 2020; Koyama, Platt and Parida, 2020). The following two sections discuss these:

2.2 Viral and host factors affecting SARS-CoV-2 transmission

Understanding the transmission of SARS-CoV-2 is essential to reducing its spread. The basic reproductive number (R_0) describes the average number of secondary cases generated from an incidence or index case in a susceptible population in infectious disease transmission dynamics. The number of secondary transmissions per index case demonstrates levels of transmission heterogeneity (Meyerowitz et al., 2021). A simple formula for the reproduction number is:

$$R_0 = r \,.\, \bar{c} \,.\, d$$

Fig. 3 Formula for the reproduction number (R_0) (Jones, 2007)

In the above equation (Figure 3), τ is the transmissibility, $\bar{c}$ is the average rate of contact between the infected individual and potential secondary case, and *d* is the duration of infectivity.

SARS-CoV-2 has a higher reproductive number compared to SARS-CoV, indicating more efficient transmission. One of the characteristics contributing to this is the structural differences in the surface protein that enables stronger binding of SARS-CoV-2 to ACE2 receptor and efficiency in invading host cells. A second factor is greater affinity and ease of infection of the upper respiratory tract (Cevik *et al.*, 2020), which is the initial site of viral replication and where viral load is the highest early in the disease. In addition to the host factor, viral factors also play a role in transmissibility. For instance, a specific mutation may provide a selective advantage to the virus to infect human cells more efficiently. This may result in higher in vivo viral loads for the variant (Meyerowitz *et al.*, 2021).

2.3 Genomic Pathogenic Surveillance (SARS-CoV-2 Clades and Lineages)

Multiple nomenclature systems have been devised to aid genomic epidemiology surveillance of the naturally expanding genetic diversity of SARS-CoV-2. The Global Initiative on Sharing Avian Influenza Data (GISAID[2] - 8 high-level phylogenetic groupings: S, L, V, G, GH, GR, GV AND GRY) and Nextstrain[3] (Year-Letter nomenclature - 19A, 19B, 20A, 20B and 20C) systems classify the variants into 'clade' trends. A clade is a specific group on a pathogen phylogenetic tree, and this classification helps to capture the evolutionary history of the virus (Rambaut, Holmes, *et al.*, 2020). SARS-CoV-2 is itself a clade within the family *Coronaviridae*, genus *β-coronavirus*, subgenus *Sarbecovirus*, species *Severe acute respiratory syndrome*. In contrast, a 'lineage' represents a single, linear chain of descent and is typically considered subsets of a phylogenetic tree (berkeley.edu, n.d.). The Phylogenetic Assignment of Named Global Outbreak LINeages (PANGOLIN[4]) system is designed on variant 'lineage' with a significant association with geographic origin. The main lineages are A for the original strain and B for the second major haplotype (O'Toole *et al.*, 2021), showing allelic variation among genome sequences

[2] https://www.gisaid.org/hcov19-variants/
[3] https://nextstrain.org/ncov/global
[4] https://cov-lineages.org/lineage_description_list.html

based on amino acid substitutions. What emerges is that in specific geographic regions certain SARS-CoV-2 genotypes are more pathogenic in comparison with others, and these genome polymorphisms may impact case severity, provided other factors are controlled (Goyal *et al.*, 2021). Currently, lineage B.1 with over 70 sublineages (Rambaut *et al.*, 2020) is the predominantly known global lineage, and informs the naming of some of the identified variants of the virus. These databases aid sequence-based genomic pathogenic surveillance and bioinformatic analysis to detect emerging variants based on varying sequences and inform the design of vaccines and therapies.

3. Vaccines and Medical Therapies

Although a cure for SARS-CoV-2 is still not available, the literature documents significant international effort to develop potential vaccines and pharmacotherapies to treat the virus (Burrage, Koushesh and Sofat, 2020). The structural and functional changes associated with spike protein mutations are a target of studies during vaccine and therapy design (Koyama, Platt and Parida, 2020).

3.1 Vaccine candidates

A vaccine is a substance (biological or synthetic) used to safely induce an efficient immune response and protection against a disease-causing pathogen (Pollard and Bijker, 2021). The core issues relevant to vaccine development are antigen selection and engineering, pre-clinical studies, and measurable correlates of immunity (Dagotto, Yu and Barouch, 2020).

Structural and non-structural proteins of a pathogen can serve as immunogens for a vaccine. In case of SARS-CoV-2, the spike protein is the preferred target for vaccines and therapeutics as it plays a pivotal role in viral entry into host cells (Song *et al.*, 2019). Among the technologies used for protective vaccine design, the vaccines that have received UK Medicines and Healthcare products Regulatory Agency (MHRA) emergency use authorisation (EUA) use viral vector- and mRNA-based platforms, both encoding the SARS-CoV-2 spike glycoprotein. In both these approaches, the carrier is processed in human cells to make copies of the antigen. This primes the immune system for specific cellular and antibody-mediated humoral immune responses to an actual pathogen on future exposure (Janssen, 2020). Some of the other vaccine platforms include inactivated virus, live-attenuated virus (whole microbe technology), protein subunit (requiring an adjuvant to stimulate the host immune response) and DNA (nucleic acid) vaccines (Song *et al.*, 2019; WHO, 2021a).

3.1.1 Viral vector vaccine

Viral vector vaccines use genetically engineered unrelated viral genome (such as adenovirus – e.g., Ad5, Ad26 and chimp Ad) encoded with the genetic sequence for the SARS-CoV-2 spike protein as the antigen. Among the four emergency use vaccines in the UK, two use non-replicating adenoviral vectors (common cold adenoviruses) as the vaccine platform. These are Oxford-AstraZeneca (codenamed AZD1222) and a recently authorised single-dose Janssen-Johnson&Johnson (J&J) (codenamed JNJ-78436735). The Janssen-J&J vaccine uses recombinant human adenovirus type 26 (Ad26) as the vector (Sadoff *et al.*, 2021; WHO, 2021a). A limitation of this vaccine is that it may not work in adults having pre-existing immunity to Ad26 (Ryan Cross, 2020). The Oxford (Jenner Institute) vaccine avoids this problem by using a chimpanzee adenovirus vector (ChAdOx1-S) (University of Oxford, 2020a) to generate a vaccine candidate.

3.1.2 Nucleic acid (mRNA) vaccine

mRNA is a new technology that had not been used in human trials before COVID-19. It uses genetically engineered messenger ribonucleic acid (mRNA) as a template for expressing proteins selected as a vaccine candidate (Samrat *et al.*, 2020). In contrast to the use of a viral vector, mRNA vaccines are enveloped in a lipid nanoparticle that delivers the genetic sequence for SARS-CoV-2 full-length spike protein (Public Health England, 2021a). The advantages of this technology are a short production cycle, low manufacturing cost and high potency (Samrat et al., 2020). Two other emergency use vaccines in the UK, Pfizer-BioNTech (codenamed BNT162b2) and Moderna/National Institute of Allergy and Infectious Diseases (NIAID) (codenamed mRNA-1273), use this technology.

Appendix A (Table 1) summarises the four vaccines authorised for use (by MHRA) in the UK, including the vaccine candidates, current trial phase and some of the identified side effects.

3.2 Medical therapies (treatment for SARS-CoV-2 infection)

The SARS-CoV-2 infection has two primary clinical phases: i) viral infection and replication, and ii) an inflammatory phase, the latter requiring hospital admission in most cases to avoid deterioration in respiratory symptoms (Burrage, Koushesh and Sofat, 2020). Candidate treatments include repurposed antiviral drugs, anti-inflammatory medicine and antibody treatments for COVID-19.

3.2.1 Viral replication inhibitors

Antiviral agents are needed to prevent viral entry and replication in host cells (Burrage, Koushesh and Sofat, 2020). Figure 3 shows the lifecycle of the virus and potential therapeutics targeted at various phases.

3.2.1.1 Protease inhibitors

Protease inhibitors can bind to a viral enzyme (called a protease) and prevent the virus from replicating in the cell (Pfizer Inc., 2021). Drugs with the potential for inhibiting the main protease (MPro – plays a role in viral replication and transcription activities) of SARS-CoV-2 include anti-human immunodeficiency virus (HIV) Lopinavir and Darunavir, which are expected to reduce the viral load (Frediansyah *et al.*, 2021). However, a study (Riva et al., 2020) raised concerns over the effectiveness of Lopinavir drug as HIV patients already under treatment with it were reported with SARS-CoV-2 infection. Protease inhibitors that have been proposed for blocking TMPRSS2-induced SARS-CoV-2 spike protein activation are Nafamostat mesylate and inferior Camostat mesylate; the latter is already in a clinical trial for COVID-19 (Yamamoto et al., 2020). Also, Pfizer (Pfizer Inc., 2021) has initiated a Phase 1 study of a novel oral antiviral clinical candidate, PF-07321332, as a SARS-CoV-2 3CL protease inhibitor.

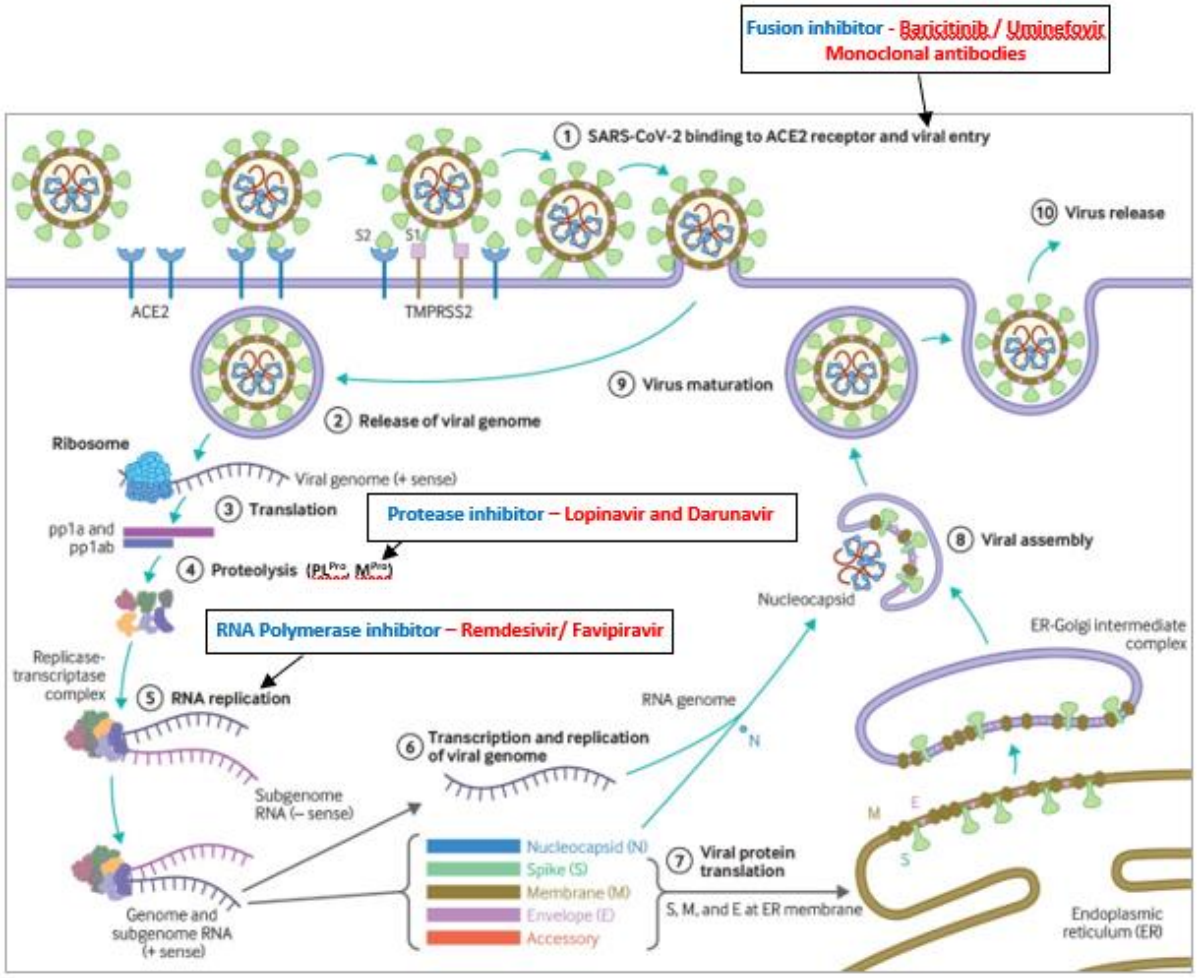


Fig. 3 The lifecycle of SARS-CoV-2 and possible targets of medical therapies (Cevik et al., 2020)

3.2.1.2 RNA polymerase (reverse transcription) inhibitors

The SARS-CoV-2 RNA-dependent RNA polymerase (RdRp, also known as nsp12) is a key enzyme that assists in replication/transcription step of its lifecycle, and is therefore the primary target for antiviral drugs. Among relevant existing RdRp inhibitor drugs, Remdesivir and Favipiravir, have been considered to restrict this single-stranded RNA coronavirus replication. Remdesivir is a broad-spectrum, intravenously administered antiviral drug that reduces disease progression and viral loads in the affected part. It was effective against MERS-CoV (Frediansyah et al., 2021) and used to treat COVID-19 cases in the European Union, US and UK. However, in late 2020, the WHO Solidarity trial (Dyer, 2020) concluded that it has a negligible impact on survival among inpatients. Favipiravir, a drug initially developed for influenza, has been repurposed for COVID-19 due to its broad-spectrum antiviral properties. It arrests the synthesis of viral RNA (Frediansyah *et al.*, 2021). However, naturally occurring mutations in critical amino acid residues (e.g., N501 and E484) of the spike protein can impact the binding affinity of these inhibitors to the RdRp (Pachetti *et al.*, 2020).

3.2.2 Host immune response

The pathology of SARS-CoV-2 infection can range from asymptomatic to acute respiratory distress involving high levels of inflammation (University of Oxford, 2020b). Among the immunomodulatory

agents proposed to target the inflammatory reaction induced in the lungs and the cytokine storm syndrome in affected patients in severe cases are:

3.2.2.1 Corticosteroids

Corticosteroids can suppress inflammation and are effective in the early stages of cytokine storm (Burrage, Koushesh and Sofat, 2020). A significant intervention is the Dexamethasone corticosteroid, a type of anti-inflammatory drug recommended for treating severe COVID-19 symptoms in hospitalised patients on ventilators or needing supplemental oxygen. Studies conducted by the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial (Baraniuk, 2021) in the UK and the WHO Rapid Evidence Appraisal for Covid-19 Therapies (REACT) Working Group found the drug to be effective in reducing deaths. The REACT trial suggested another corticosteroid, Hydrocortisone, as an effective alternative to Dexamethasone. These steroids are only recommended by the UK National Health Service (NHS) for patients with severe and critical disease (Baraniuk, 2021). However, the Data Monitoring Committee (DMC) associated with the RECOVERY clinical trial (Horby *et al.*, 2021) has found Colchicine, the anti-inflammatory drug used to treat gout, to be ineffective on clinical outcomes of hospitalised patients.

Among non-intravenous treatments, inhaled Budesonide, an inexpensive corticosteroid used in inhalers to treat asthma and obstructive pulmonary disease, is effective for non-hospitalised patients and during early stages of infection. The Oxford University's Platform Randomised Trial of Interventions against COVID-19 in Older People (PRINCIPLE) (University of Oxford, 2021a) considers this inexpensive drug as a significant milestone for the pandemic as it shortens recovery times in COVID-19 patients in the community, although this is not recommended as a standard of care in the UK (Mahase, 2021).

3.2.2.2 Immunomodulator therapy

In cases of complicated COVID-19, there is a rapid release of pro-inflammatory cytokines such as interleukin-6 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) to contain the pathogen by activating adaptive immune responses. An overabundance of cytokines may result in clinically significant risks, including multi-organ failure and death. Intravenously administered Tocilizumab, a monoclonal antibody (mAb) traditionally used to treat rheumatoid arthritis, is used as an IL-6 cytokine inhibitor in the acute phase response. This targets and blocks the IL-6 receptor and reduce cytokine storm (Burrage, Koushesh and Sofat, 2020; Poduri, Joshi and Jagadeesh, 2020). mAbs are essentially recombinant proteins derived from the B cells (lymphocytes) of convalescent patients and mimic natural antibodies produced to fight off infections (Chander and Burger, 2021). Preliminary data from the RECOVERY Trial (2021) showed the effectiveness of Tocilizumab in reducing mortality in hospitalised patients. However, phase 3 of the randomised controlled COVACTA trial suggested that IL-6 blockade using it may not be beneficial in the improvement of clinical status in all COVID-19 patients (Garbers and Rose-John, 2021). The Randomised, Embedded, Multifactorial Adaptive Platform trial for Community-Acquired Pneumonia (REMAP-CAP) trial (Gordon et al., 2021) found another monoclonal antibody, Sarilumab, to improve outcomes, including survival and reliance on a mechanical ventilator. Two other anti-SARS-CoV-2 monoclonal antibody treatments authorised by the FDA for emergency use in the US are combinations of Bamlavinimab with Etesevimab and Casirivimab with Imdevimab (MHRA, 2021a). However, the limitations of mAbs are difficulty in administration and their potential to reduce the efficacy of mRNA vaccines by suppressing the immune response. Also, a mAb treatment only contains multiple copies of one type of antibody and could therefore be less effective against new mutations (Cohen, 2021).

Another immune-based treatment is Plasma therapy. Convalescent plasma with high levels of antibodies has been used to treat hospitalised patients early in their illness or those with high viral

loads (Rambaut *et al.*, 2020). However, despite considerable international interest in its use as a possible treatment, the RECOVERY trial (University of Oxford, 2021b) did not find any evidence of the effectiveness of convalescent plasma on clinical outcomes in hospitalised patients.

4. Variant lineages (significant mutations) of SARS-CoV-2 and impact on pharmaceuticals

Mutations of SARS-CoV-2 have altered various aspects of its biology, including pathogenicity, transmissibility infectivity, and antigenicity (Harvey *et al.*, 2021). The genetic sequence (viral genome) of the wild-type SARS-CoV-2 remained stable after detection of the first cases in Wuhan, China in December 2019, with the only exception being D614G (Aspartic acid to Glycine) amino acid change in the viral S protein. This became dominant early in the pandemic and is common to most variant lineages identified so far. This mutation has been associated with moderate infectivity, transmissibility, and the ability to circumvent immunity conferred by natural infection (convalescent sera) or vaccination (Harvey *et al.*, 2021). This was followed by the G614 mutation associated with lower RT-PCR cycle thresholds (Cts) suggesting higher respiratory tract viral loads in patients, although not with increased disease severity (Korber et al., 2020). However, as a natural process that all viruses undergo, SARS-CoV-2 has accumulated several other mutations as it spread across the globe (Koyama, Platt and Parida, 2020). The resultant emerging variant lineages with demonstrably different phenotypes (strains) are manifested in traits such as differing antigenicity, infectivity and transmissibility (Lauring and Hodcroft, 2021). Mutations and deletions in the S protein of these variants are of concern since they may compromise immune control and is a significant target of immunological interventions (Hoffmann *et al.*, 2021; MHRA, 2021b).

The four major variant lineages (SARS-CoV-2 genomes) with several characteristic spike protein mutations currently present in the UK are B.1.1.7, B.1.351, P.1 and B.1.617. The WHO has identified these lineages, labelled Alpha, Beta, Gamma and Delta respectively, as Variants of Concern (VoCs) with possible attributes of significant impact on transmissibility, clinical severity of infection, or decrease in the effectiveness of available vaccines and therapeutics (NCIRD, 2021a; WHO, 2021c). Identification of the variants of concern requires an understanding of the evolution and the genomic epidemiology of SARS-CoV-2 (Lauring and Hodcroft, 2021). The following examines the major variant lineages accumulating functionally significant mutations:

a) **B.1.1.7** (VOC 202012/01 or 501Y.V1 – Alpha variant) – first detected in sequence from Kent, United Kingdom and was associated with a surge in reported cases. The variant shows 9 characteristic spike mutations - 6 located in S1 surface unit and 3 found in S2 transmembrane unit (Hoffmann *et al.*, 2021). This includes N501Y and P681H mutations shared with other identified variants (WHO, 2021b).

The B.1.1.7 variant harbours a significant N501Y change. The mutation (N → Y) represents an Asparagine to Tyrosine substitution at amino acid position 501 in the spike RBD within the S1 domain. This affected its binding affinity to human(h)-ACE2 receptor, thereby increasing human-to-human transmissibility and disease severity (Hoffmann *et al.*, 2021; NCIRD, 2021a). The variant also exhibited increased viral loads and higher mortality rates (R&D Systems, 2021). The mutation has shown homoplasy, with 'convergent evolution' (Weigand, 2021) such as 501Y.V2 (in B.1.351 – Beta variant) and 501Y.V3 (in P.1 – Gamma variant) showing distinct infectivity profile. Despite the concerning N501Y mutation, the lineage shows minimal impact on neutralisation by vaccines (NCIRD, 2021).

b) **B.1.351** (VOC 202012/02 – Beta variant) – first detected in Eastern Cape province of South Africa in May 2020 and became the most dominant strain in the second COVID-19 wave in the country. The variant has 8 characteristic spike mutations (WHO, 2021b), including E484K, K417N and N501Y in the RBD.

An E484**K '**escape mutation' (**Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies**) of concern was first identified in this variant. This has also been found in the P.1 (Brazil) variant, and is similar to the E484**Q** mutation in the sublineages B.1.617.1 and B.1.617.3 of the Delta (B.1.617) strain (WHO, 2021b). The mutation has enabled resistance to neutralising antibodies - e.g., a combination of Bamlanivimab and Etesevimab - although other emergency use monoclonal antibody treatments may be effective (NCIRD, 2021). Also, it showed reduced neutralisation by post-vaccination sera (NCIRD, 2021) and is considered to be a potential threat to the efficacy of mRNA-based vaccines (Collier *et al.*, 2021). A recent study (McGill *et al.*, 2021) demonstrated that convalescent plasma containing polyclonal antibodies was ineffective in neutralising this variant, raising concern for reinfection.

c) **P.1** *alias for* B.1.1.28.1 (VOC 202101/02 – Gamma variant) – first detected in Manaus, Brazil in November 2020. The variant shows 12 characteristic spike protein mutations (WHO, 2021b), including mutations of interest such as E484K and K417T (similar to K417N substitution found in B.1.351) and N501Y in the RBD.

The combination of these three virologically important mutations is associated with increased binding to the ACE2 receptor, leading to enhanced transmissibility and more severe disease. This is in addition to the ability to evade convalescent immunity acquired from infection with earlier variants (Scheuber and van Elsland, 2021). Also, as with B.1.351 (Beta strain), the E484K is a crucial mutation in this lineage that enables resistance to antibody-mediated neutralisation (Nonaka *et al.*, 2021).

The critical mutations detected in the B.1.1.7, B.1.351, and P.1 variants enabled improved host cell interactions and entry and reduced susceptibility to entry inhibitors (Hoffmann *et al.*, 2021). Monoclonal antibodies currently authorised for treatment have proved unsuccessful in inhibiting host cell entry mediated by the B.1.351 and P.1 variants. However, potential solutions proposed are membrane fusion inhibitors and protease inhibitors active against TMPRSS2, such as soluble ACE2 (sACE2). In addition, owing to the E484K mutation, the B.1.351 and P.1 variants were less efficiently inhibited by convalescent plasma and post-vaccination sera from mRNA vaccines (especially Pfizer-BioNTech - BNT162b2) (Hoffmann *et al.*, 2021).

d) **B.1.617** (Delta variant) – first identified in India in late 2020, and currently (as of 21th June 2021) the dominant strain in the UK. The original variant shows 9 characteristic spike protein mutations, including P681R (similar to P681H found in B.1.1.7), E484Q (similar to E484K mutation in Beta and Gamma variants) and L452R. Its three sublineages (B.1.617.1, B.1.617.2 and B.1.617.3) that differ in mutations and phenotypic characteristics have been identified in the UK, with B.1.617.2 designated as a national Variant of Concern (VoC) by both the WHO and Public Health England (2021b). This variant is significantly more transmissible than the Alpha variant.

L452R and E484Q (not present in B.1.617.2) are key mutations in this lineage that have impacted its transmissibility (WHO, 2021b) and reduction in susceptibility to monoclonal antibodies - marked reduction in case of Bamlanivimab and reduced sensitivity in the case of Etesevimab and Casirivimab (MHRA, 2021a). The L452R substitution is possibly a result of viral adaptation in response to increasing immunity in the population (Harvey *et al.*, 2021). The P681R mutation has enabled improved host cell entry (Kmaneck, 2021). Also, a laboratory study at the Pasteur Institute (Planas *et al.*, 2021) reported

diminished efficacy by Pfizer-BioNTech vaccine and low levels of antibodies induction by Oxford-AstraZeneca vaccine against sublineage B.1.617.2.

Appendix B (Table 2) presents a comparative analysis of the lineage-defining mutations of the 4 VoCs, along with convergent mutations shared with the other strain.

In addition to these four variants, Public Health England (2021b) has designated a 5th lineage, (B.1.1.7 with E484K) as a national VoC. Among the other variants detected in the UK, B.1.525 (previously designated UK1188) has been identified by the WHO as a Variant of Interest (VoI – label: Eta) due to enhanced community transmission (WHO, 2021c).

5. Discussion

This essay presents an analysis of the emergent variants of SARS-CoV-2 resulting from mutations of its spike protein and their impact on approved vaccines and medical therapies. The trajectory of the SARS-CoV-2 outbreak is difficult to predict in this rapidly evolving landscape. However, the importance of prompt and effective response in terms of classic public health strategies such as effective countermeasures and sustained preparedness (Paules, Marston and Fauci, 2020) is indisputable. Non-pharmaceutical interventions, including proactive approaches such as travel restrictions and border control, is vital for containing the virus and preventing geographic spread (Head, 2021). The evidence so far suggests that, although medical therapies marginally reduced the risk of death from COVID-19, it was, in fact, vaccines that protected from severe disease in terms of hospitalisation or death.

In severe SARS-CoV-2, the medical therapy of monoclonal antibody (mAbs) is essential as it induces an effective immune response against one particular virus variant. However, single mAb treatments of some variants such as B.1.351, P.1 (Hoffmann *et al.*, 2021) and B.1.617 (Karthikeyan, 2021) have shown reduced effectiveness. This is primarily because such treatments exert selective pressure that increases the possibility of mutational escape of the target antigen. A potential solution is using cocktails of two or more mAbs such as Regeneron/Eli Lilly REGN- COV2 (included in the RECOVERY trial) and AstraZeneca AZD7742 that target non-overlapping epitopes (Harvey *et al.*, 2021). However, the result from a recent late-stage trial (Chander and Burger, 2021) showed AZD7742 failing to meet the primary endpoint of protecting people exposed to an infected person. Among other therapeutics, repurposed corticosteroids and antiviral drugs remain effective in reducing disease burden, especially in poorer countries. As COVID-19 is a thrombo-inflammatory process that affects several organs (lungs, heart, pancreas), a combination of drugs with multiple targets is likely to prove to be beneficial. While the drug industry continues in their pursuit of finding more targeted alternatives to COVID-19 vaccination, appropriate doses and evidence of clinical efficacy and safety of these drugs should be considered (Poduri, Joshi and Jagadeesh, 2020).

Although two doses of the current vaccines have been able to retain their efficacy against the majority of the SARS-CoV-2 variants, emerging evidence suggests that some variants such as B.1.351 (Beta), P.1 (Gamma) and B.1.617 (Delta) had a considerable impact on vaccine effectiveness (Head, 2021; Hoffmann *et al.*, 2021)**.** This is primarily due to the E484K mutation and its combination with other mutations of concern, such as K417N (present in B.1.351) and L452R (present in B.1.617). However, they still protect against hospitalisation and death. Also, the Oxford–AstraZeneca vaccine showed less effectiveness than the Pfizer–BioNTech vaccine in preventing SARS-CoV-2 infection from the Delta (B.1.617) variant (Sheikh *et al.*, 2021).

Research and clinical trials are ongoing to understand the mechanisms and correlates of protection (natural infection or vaccination) and evaluate how vaccine effectiveness is impacted (Bingham, 2021; ClinicalTrials.gov, 2021). An essential aspect of an effective response is preparing updated vaccine sequences targeted at emerging antigenic variants that are adequately cross-reactive against all circulating variants with novel mutations of concern. This is currently the focus of vaccine developers. An mRNA vaccine is particularly suitable due to its short production cycle and low manufacturing cost. Also, there is a need for new targeted therapeutic approaches to address any emergent vaccine-resistant variants. Mutations of the spike RBD that affect antigenic profiles are of particular importance for its role in developing vaccine immunogens and medical therapies. However, the biological significance of the other spike regions, especially NTD and S2 subunits, may need to be investigated to understand their role in antigenicity (Harvey *et al.*, 2021).

An annual or biannual revaccination booster program similar to that for influenza may be introduced to maintain durable protection (Bingham, 2021; McGill *et al.*, 2021), especially since COVID-19 vaccines have had very short trial periods and rapid development to meet global supply demands. Some of the current vaccines have been linked to side effects such as bleeding disorders (in the case of Oxford-AstraZeneca vaccine) (Craig, 2021) and heart inflammation in young people (in the case of Pfizer and Moderna's vaccines (Sharp, 2021). Therefore, besides efficacy, it is crucial to ensure that vaccines and medical therapies are safe and do not produce unwanted immune responses or side effects.

As antigenically different variants continue to emerge, a crucial requirement is systematic surveillance of genetic and antigenic changes in the virus to detect mutation frequencies in global sequence datasets for timely response to emerging variants, including targeted control measures and recommendations on vaccine composition (Harvey *et al.*, 2021). Escape variants able to evade antiviral- or vaccination-induced immune response in the host and able to retain transmission fitness and infectivity should be efficiently identified through genomic surveillance and careful clinical observation of the disease. PCR-based assays targeted at new variants is needed for efficient real-time tracking of their spread (Burioni and Topol, 2021). Global sequencing enabled by GISAID and Pangolin datasets can help keep pace with the antigenic evolution of SARS-CoV-2 and automated detection of emerging potential variants of concern before they spread widely.

6. Conclusion

Based on the results and analyses of the trials conducted so far involving multiple mutations of the binding site, it is unlikely that the efficacy of the developed vaccines will be impacted. This is because the detected mutations in the spike protein are only minor variations in the viral RNA, which should not affect the current vaccines. If modifications are required, it could potentially take only 30-40 days to do so. However, this conclusion is primarily based on predictions that can change as further evidence from scientific studies becomes available. Phenotypic impacts of specific mutations in emerging variants need to be carefully monitored to understand the pathogenesis for SARS-CoV-2 for vaccine and therapy design to remain responsive. To address the lack of effective treatments for SARS-CoV-2, more targeted therapeutics, including monoclonal antibodies, need to be identified through clinical trials.

Finally, it is particularly challenging to predict outcomes due to the varying virus, different global responses, different vaccines, and availability. In the context of easy global travel, dependence upon foreign goods and services, and continuous intensive farming and interaction with wildlife, there may be an ongoing need for spillover surveillance, the development of new vaccines, and global regulation.

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Appendix A

Table 1 – Vaccines authorised for use in the UK (WHO, 2021a)

Vaccine platform	**Key attributes**	**Type of candidate vaccine**	**Developer**	**Number of doses**	**Trial phase**	**Side effects** (EMA, 2021; NCIRD, 2021b)
Viral vector (non-replicating)	use of Chimp Ad adenovirus	ChAdOx1-S - (AZD1222)	University of Oxford + AstraZeneca	2	4	very rare risk of blood clotting disorders (thromboembolic events), in addition to commonly reported side effects such as breathlessness, severe headache, etc. Also, not recommended for persons with a history of severe allergic reaction to any of the vaccine's component or under 18 years of age)
Viral vector (non-replicating)	use of recombinant human Ad26 adenovirus	Ad26.COV2.S (JNJ-78436735)	Janssen Pharmaceutical	1-2	3	rare risk of blood clots (especially in women younger than 50 years old) after vaccination, in addition to possible side effects such as muscle aches, fever, nausea. Also, not recommended for individuals with severe (anaphylaxis) or immediate (non-severe) allergic reaction to any ingredient (such as polysorbate).
RNA based	use of lipid nanoparticle (LNP)	mRNA-1273	Moderna + NIAID	2	4	remote chance of severe allergic reaction, with reported non-severe side effects such as hives, chills, swollen lymph nodes (lymphadenopathy) and diarrhoea. Also, not advised for anyone under 12 years of age.
RNA based	use of lipid nanoparticle (LNP)	BNT162b2 (3 LNP-mRNAs), also known as "Comirnaty"	Pfizer-BioNTech + Fosun Pharma	2	4	common side effects include local reactions (pain, swelling) and systemic reactions (tiredness, chills)

Appendix B

Table 2 – Lineage-defining mutations in the viral genome detected in Variants of Concern

PANGO lineage GISAID clade Nextstrain clade WHO label[5]	**First detected in**	**RBD (S protein) Mutations and attributes of concern**					**Increased case severity**	**Neutralisation by antibody therapies** (Scobie, 2021)	**Efficacy of vaccines** (Harvey *et al.*, 2021)
		D614G	**N501Y**	**E484K**	**K417N**	**L452R**			
Spike amino acid substitution (SignalChem Biotech Inc., 2021)		D → G representing Aspartic acid-to-Glycine change (at amino acid position 614 in spike RBD)	Asparagine-to-Tyrosine	Glutamic acid-to-Lysine	Lysine-to-Asparagine	Leucine-to-Arginine			
		- increased transmissibility (National Center for Immunisation and Respiratory Diseases (NCIRD, 2021) - increased case severity (Goyal *et al.*, 2021) - reduced vaccine effectiveness (Koyama, Platt and Parida, 2020)	- increased transmissibility (National Center for Immunisation and Respiratory Diseases (NCIRD, 2021) - potential increased viral load (Harvey *et al.*, 2021) and disease severity (hospitalisation and death) (National Center for	- reduced antibody binding (Harvey *et al.*, 2021) and efficacy of some monoclonal antibody treatments (Roberts, 2021) - reduced neutralisation by polyclonal antibody (convalescent plasma)	- significant decrease in antibody binding to S1 RBD (fully abolish the antibody effect in a combination with N501Y) (Fratev, 2020)	- reduced neutralisation by monoclonal antibodies and convalescent plasma (Harvey *et al.*, 2021) - reduced neutralisation by vaccine sera (Scobie, 2021)			

[5] https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/

			Immunisation and Respiratory Diseases (NCIRD, 2021) - minimal impact on effectiveness of vaccines (National Center for Immunisation and Respiratory Diseases (NCIRD, 2021)	(Harvey *et al.*, 2021) - reduced efficacy of vaccine-induced immunity (threat to the efficacy of viral vector- (Harvey *et al.*, 2021) and mRNA-based vaccines (Collier *et al.*, 2021; NCIRD, 2021)					
B.1.1.7 GR/501Y.V1 20I/501Y.V1 Alpha	United Kingdom	✓	✓				Yes	Minimal	Mild
B.1.351 GH/501Y.V2 20H/501Y.V2 Beta	South Africa	✓	✓	✓	✓		Yes	Reduced	Moderate
P.1 (*alias of* B.1.1.28.1) GR/501Y.V3 20J/501Y.V3 Gamma	Brazil	✓	✓	✓	K417**T**		Yes	Reduced	Moderate
B.1.617.2 G/452R.V3 21A Delta	India			E484**Q**		✓	Yes	Reduced	Moderate