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# A Comprehensive Review on Covid-19 Variants

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**Abstract:** SARS-Cov-2, the new coronavirus which caused COVID-19 was first detected in Wuhan, China in december 2019. The first case of COVID-19 infection in India was reported in Kerala on Jan 27, 2020. Later on this contagious disease had quickly spread around the world.

*This review article aims at providing an exhaustive knowledge about the COVID-19 outbreak, mutant strains of coronavirus, mutation in spike protein of the virus, efficiency of vaccines on variants of concerns. It's important to study the epidemiology of each variants/strains [alpha (B.1.1.7), beta (B.1.351), delta(B.1.617.2), omicron(B.11.529)] in order to develop vaccines and to cure this malady. How symptoms of different variants/strain and the reaction of these variants to different types of vaccines is also discussed.*

**Keywords:** Variants of concern, Variants of interest, Mutation, SARS-CoV-2 vaccine efficacy, Treatment.

## I. INTRODUCTION

COVID-19 was caused by SARS-CoV-2 virus. Coronaviruses are the family of viruses that will cause severe respiratory illness in humans. They named it "Corona" because of crown-like spikes on the surface of the virus. The new strain of coronavirus- SARS-CoV-2- was first reported in Wuhan, China in December 2019. Since it has spread to every country around the world (Wang et al. 2020). Common cold, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) are the best examples of coronaviruses that cause illness in humans (Fan et al, 2019). They are often found in bats, cats and camels. They live in but don't infect the animals. Sometimes these Viruses can spread to different animal species. These viruses can transfer from animal species and begin to infect humans. These viruses may change (mutate) as when they transfer to other species (Guo et al, 2020). COVID-19 can cause mild to severe respiratory illness and even cause death. The most effective preventive measures include wearing a mask during times of high transmission, staying 6 feet apart, washing hands often and avoiding contact with sick people, and getting vaccinated (CDC). As of now, Coronavirus can spread through droplets and virus particles released into the air by the infected person through the breaths, talks, laughs, coughs or sneezes (Wang et al, 2021). The large droplets may fall to the ground in a few seconds, but tiny infectious particles can linger in the air and accumulate in indoor places which have poor ventilation. When the air droplets enter the body through the mouth, nose or eyes. Then it transfers to the back of nasal passages and the mucous membrane in the back of the throat. There it attaches to cells there, begins to multiply and moves into the lung tissue. From there, The virus spread to other bodies. (Bourouiba, 2021) It may take several days to develop symptoms- but during this time the person is contagious. A person is not contagious 10 days after the symptoms began. The best way to avoid spreading COVID-19 to others is to: Maintain a safe distance from others (at least 1 meter) even if they don't appear to be sick. Wear a mask in public, especially indoors or when physical distancing is not possible. Choose open, well-ventilated spaces over closed ones. Open a window indoors (REALLY CORRECT). Clean your hands often. Use soap and water, or an alcohol-based hand rub. Get vaccinated when it's your turn. Follow local guidance about vaccination. Cover your nose and mouth with your bent (CDC) Persons at greatest risk of contracting COVID-19 include those who: Live in or have recently traveled to any area with ongoing active spread. Having close contact with the infected person. It is defined as being within 6 feet with an infected person for a cumulative total of 15 minutes or more than a 24- hour period. Over the age of 60 with pre-existing medical conditions or weakened immune system (BMJ Best Practice).

## II. STRUCTURE OF SARS-COV-2

Coronavirus belongs to the family of Coronaviridae. The genome of CoVs is a +ssRNA and it is about 27-32 kb in length (MD et al.) It is larger than the other RNA viruses.

The nucleocapsid protein(N) forms the capsid outside the genome and it is packed by an envelope and it is associated with 3 structural proteins namely Membrane protein(M), Spike protein(S) and Envelope protein(E) (Baric). The surface spike(S) glycoprotein resembles a crown and it is located at the outer surface of the virion. The spike [protein undergoes cleavage and an amino(N)- terminal S1 subunit and a Carboxyl(C)- terminal S2 subunit (Baric).

S1 subunit enables the incorporation of the virus into the host cell. S2 subunit contains a fusion peptide, a transmembrane area and a cytoplasmic area and it is liable for virus cell membrane. The S1 subunit is divided into a receptor-binding domain (RBD) and N-terminal domain (NTD). RBD and NTD enable viral access into the host cell (Li, 2005). The membrane protein (M) is important for viral assembly. It contains a short N-terminal domain. It projects onto the envelope.

The Envelope protein (E) along with N and M proteins helps in viral assembly and release.

SARS-COV-2 contains 4 structural proteins and 16 Non-structural proteins (NSP1-16) and 5-8 accessory proteins (Li et al, 2020).

All 16 NSP perform different roles in the life cycle of SARS-COV-2.

Functions of NSP are given below (Turub naqvi et al, 2022)

Proteins	Functions
NSP-1	Mediates RNA processing and replication
NSP-2	Modulates survival signaling pathway of host cell
NSP-3	Separates the translated proteins
NSP-4	Contains the transmembrane domain 2 (TM2)
NSP-5	Helps in the process of polyprotein during replication
NSP-6	Presumptive transmembrane domain
NSP-7&8	Increases the combination of NSP12 and template-primer RNA
NSP-9	Functions as an ssRNA-binding protein
NSP-10	Critical for cap methylation of viral mRNAs
NSP-11	No known function
NSP-12	Contains the RNA-dependant RNA polymerase which helps in replication/transcription
NSP-13	Binds with ATP and helps in replication and transcription
NSP-14	It is a proofreading exoribonuclease domain
NSP-15	It has Mn <sup>2+</sup> -dependent endoribonuclease activity
NSP-16	It is a 2'-O-ribose methyltransferase.

(Uhal, 2020).

### III. LIFE CYCLE

For the replication of the virus to begin, the spike protein binds to the host cell surface receptors that are present in the host cell membrane and this step is known as host cell recognition.

The receptor in the human body for SARS-COV-2 is the ACE2 receptor (Angiotensin-converting enzyme 2).

1) ACE2 is the cellular protein used by the virus for the virus to gain entry into the cell. After the receptor and spike protein binds, the virus enters into the cell by two processes.

Membrane fusion- Viral and cellular membranes fuse and the RNA genome of the virus enters into the cytosol.

Endocytosis- Receptor-bound virus is enveloped by cell membrane and it enters into the cytosol without a vesicle. (R and Denison, 2004)

- a) After entering by any one of the ways, the viral RNA is released into the genome.
- b) It is followed by uncoating of the RNA.
- c) After entering into the host cytoplasm, the Replicase gene on the RNA strand is translated into two replicase polyproteins.
- d) A polyprotein is formed after translation and it can be cleaved into smaller proteins. The polyproteins are processed by viral proteinases and it yields individual replicase proteins. (Fehr et al, 2015)
- e) The replicases mediate the production of negative strand RNA. This RNA strand serves as a template for positive strand virus genomic RNA.
- f) The negative strand RNA is transcribed to produce shorter mRNAs
- g) These shorter mRNAs code for the structural proteins, non-structural proteins, accessory proteins and viral proteinases.
- h) The positive strand RNA and proteins are translocated and assembled at the transitional zone between the golgi apparatus and the endoplasmic reticulum(ER).
- i) Both the organelles are involved in protein synthesis, post-translational modification of the proteins and protein transport.
- j) The virions assemble, start maturing and shed off from the Golgi membranes as vesicles.
- k) These vesicles are translocated to the host cell membrane where they fuse with the host cell membrane and these are released into the extracellular space.
- l) The releasing process will not rupture the host cell and it is known as nonlytic exocytosis. (Zhong et al, 2012)

WHO has divided variants into three groups to prioritize monitoring and research: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs).

#### IV. VARIANTS OF CONCERN

The transmissivity rate of VOCs is high when compared to the original virus, and thus increases the disease severity. In addition, VOCs exhibit decreased susceptibility to vaccine-induced and infection-induced immune responses, and have the ability to reinfect previously infected and recovered individuals (Choi et al, 2021).

The following are different types of variants of concern:

##### A. Alpha Variant(B.1.1.7)

It is also known as VOC202012/01 was first detected in the UK.This variant has 23 mutations when compared to parental virus.Eight of these mutations are found in spike protein. The notable mutations are N501Y, 69/70 deletion and P681H (Ali et al, 2022)

##### B. Beta Variant(B.1.1351)

It was first reported on Dec 18 2020,in South Africa.Beta variant is also known as 501Y.V2.This variant includes nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) in the spike protein, of which three mutations (K417N, E484K, and N501Y) are located in the RBD. (Choi et al, 2021)

##### C. Delta Variant(B.1.617.2)

It was first detected in Maharashtra, India in late 2020.The first sublineage to be detected was B.1.617.1 , followed by B.1.617.2, both bearing the L452R spike receptor-binding motif (RBM) substitution also observed in B.1.427/B.1.429 . This mutation contributed to increasing the infectivity rate and a modest loss of susceptibility to neutralizing antibodies (Mlcochova et al, 2021.)

##### D. Omicron Variant(B.1.1.529)

It was first detected in South Africa, on Nov 24,2021.Omicron variant has a total of 60 mutations when compared to the original virus found in Wuhan.The mutations includes 50 non synonymous, 8 synonymous and 2 non coding mutations (khan et al, 2022).



## V. VARIANTS OF INTEREST

### A. Epsilon Variant

Epsilon variant, also known as CAL.20C and referring to two PANGO lineages B.1.427 and B.1.429, is one of the variants of SARS-CoV-2, the virus that causes COVID-19. It was first detected in California, USA in July 2020. As of March 2022, Epsilon is previously considered as a circulating variant of interest in the WHO. It is considered a variant being monitored by the CDC. (Cedars Sinai)

### B. Eta Variant

The Eta variant is a variant of SARS-CoV-2, the virus that causes COVID-19. The Eta variant or lineage B.1.525, also called VUI-21 FEB-03 (previously VUI-202102/03) by Public Health England (PHE) and formerly known as UK1188, 21D or 20A/S:484K, does not carry the same N501Y mutation found in Alpha, Beta and Gamma, but carries the same E484K-mutation as found in the Gamma, Zeta, and Beta variants, and also carries the same  $\Delta$ H69/ $\Delta$ V70 deletion (a deletion of the amino acids histidine and valine in positions 69 and 70) as found in Alpha, N439K variant (B.1.141 and B.1.258) and Y453F variant (Cluster 5). (“Variant-PCR-testen (tidl. Delta-PCR-testen)”)

### C. Iota Variant

The Iota variant, also known as lineage B.1.526, is one of the variants of SARS-CoV-2, the virus that causes COVID-19. It was first detected in New York City in November 2020 (CDC).

The variant has appeared with two notable mutations: the E484K spike mutation, which may help the virus evade antibodies, and the S477N mutation, which may help the virus bind more tightly to human cells. By February 2021, it had spread rapidly in the New York region and accounted for about one in four viral sequences. By 11 April 2021, the variant had been detected in at least 48 U.S. states and 18 countries (Stieb and Rosa, 2021).

Under the simplified naming scheme proposed by the World Health Organization, B.1.526 has been labeled Iota variant, and is considered a variant of interest (VOI), but not yet a variant of concern (CDC).

### D. Kappa Variant

Kappa variant is a variant of SARS-CoV-2, the virus that causes COVID-19. It is one of the three sub lineages of Pango lineage B.1.617. The SARS-CoV-2 Kappa variant is also known as lineage B.1.617.1 and was first detected in India in December 2020 (Le Page, 2021). By the end of March 2021, the Kappa sub-variant accounted for more than half of the sequences being submitted from India. On 1 April 2021, it was designated a Variant Under Investigation (VUI-21 APR-01) by Public Health England (CDC) (“SARS-CoV-2 variants of concern and variants under investigation in England Technical briefing 10”).

### E. Mu Variant

The Mu variant, also known as lineage B.1.621 or VUI-21 JUL-1, is one of the variants of SARS-CoV-2, the virus that causes COVID-19. It was first detected in Colombia in January 2021 and was designated by the WHO as a variant of interest on August 30, 2021 (CDC). The WHO said the variant has mutations that indicate a risk of resistance to the current vaccines, and stressed that further studies were needed to better understand it. Outbreaks of the Mu variant were reported in South America and Europe (Scher). The B.1.621 lineages has a sublineage, labeled B.1.621.1 under the PANGO nomenclature, which has already been detected in more than 20 countries worldwide. Under the simplified naming scheme proposed by the World Health Organization, B.1.621 was labeled “Mu variant”, and was considered a variant of interest (VOI), but not a variant of concern (FRANCE24).

### F. Zeta Variant

Zeta variant, also known as lineage P.2, is a variant of SARS-CoV-2, the virus that causes COVID-19. It was first detected in the state of Rio de Janeiro; it harbors the E484K mutation, but not the N501Y and K417T mutations (Scher). It evolved independently in Rio de Janeiro without being directly related to the Gamma variant from Manaus. Under the simplified naming scheme submitted by the World Health Organization, P.2 was labeled “Zeta variant”, and was considered a variant of interest (VOI), but not a variant of concern. A second wave was preceded in November 2020 by an increase in the prevalence of the Zeta variant among genetic sequences from São Paulo state, deposited into the GISAID database. As of July 2021, Zeta is no longer considered a variant of interest in the WHO (CDC).

### G. Theta Variant

Theta variant, also known as lineage P.3, is one of the variants of SARS-CoV-2, the virus that causes COVID-19. The variant was first identified in the Philippines on February 18, 2021, when two mutations of concern were detected in Central Visayas (CNN Philippines staff).

It was detected in Japan on March 12, 2021, when a traveler from the Philippines arrived at Narita International Airport in Tokyo. It is distinct from those first discovered in the United Kingdom, South Africa, and Brazil, and is thought to pose a similar threat ("New coronavirus variant found in traveler from Philippines: Japan").

The variant is more resistant to neutralizing antibodies, including those gained through vaccination, like how the South African and Brazilian variants appear to be. Under the simplified naming scheme proposed by the World Health Organization, P.3 has been labeled Theta variant, and is considered a variant of interest (VOI), but not yet a variant of concern (CDC).

As of July 2021, Theta is no longer considered as a variant of interest in the WHO.

### H. Lambda Variant

Lambda variant, also known as lineage C.37, is a variant of SARS-CoV-2, the virus that causes COVID-19 (CDC). It was first detected in Peru in August 2020. On 14 June 2021, the World Health Organization (WHO) named it Lambda variant ] and designated it as a variant of interest.

It has spread to at least 30 countries around the world and is known to be more resistant to neutralizing antibodies compared to other strains (Van Homrigh).

There is evidence that suggests the Lambda variant is both more infectious and resistant to vaccines than the Alpha and Gamma variant ("Infectivity and immune escape of the new SARS-CoV-2 variant of interest Lambda").

## VI. ALPHA B.1.1.7 VARIANT

The B.1.1.7 strain, referred to as the Alpha variant, was first detected in England on 20 September 2020. The number of people infected with this strain increased exponentially, and by February 2021, the Alpha variant accounted for nearly 95% of SARS-CoV-2 transmission in England. Regarding the demographic effect on SARS-CoV-2, B.1.1.7 affects mainly healthier and younger patients. (Thye et al, 2021)

### A. Structure and Gene Mutation

The B.1.1.7 lineage contains many genetic changes. The spike protein amino acid substitution N501Y which enhances binding to the ACE2 receptor and it increases the transmissivity. (Ty et al, 2022)

The protein-coding mutations found within the spike proteins of the virus include;

del 69-70 HV, del144Y, N501Y, A570D, D614G, P619H, T761I, S982A, D1118H (Socher et al, 2021).

The N501Y mutation is located in the RBD. It interacts with ACE2 and the deletions present on the N-terminal domain of S-protein. (Mohammad et al, 2021)

Increased flexibility around the fusion peptide induced by the D614G mutation and reduced binding affinity between RBD and ACE2 due to conformational reorganization of the RBD-ACE2 interface mediated by N501Y. Upon proteolytic processing at the S20 Cleavage site (Arg815/Ser816), a conformational switch alters partial salt bridge formation between arginine 815 and negatively charged aspartate and glutamate residues in the vicinity to keep the new C-terminus in place via noncovalent interactions. (Socher et al, 2021)

The mutations at A570D, D614G and S982A reduced contact between individual chains of the trimeric spike protomer, which enhances cleavage into S1 and S2 subunits, dynamic structural rearrangement and host cell fusion mechanisms. The mutations unique to variant B.1.1.7 enable high affinity binding to ACE2 and enhanced replication properties. The D614G mutation, associated with increased virus transmissibility, opens a potentially druggable structural pocket at the interface between spike glycoprotein subunits S1 and S2. (Ostrov, 2021)

The proline to histidine mutation at position 681 (P681H) immediately upstream of the polybasic furin cleavage site may affect furin processing of the S protein which plays a role in viral transfer (Yang et al, 2021)

Gene	Nucleotide	Amino acid
ORF1ab	C3267T	T10011
	C5388A	A1708D
	T6954C	12230T
	11288-11296 deletion	SGF3675-3677 deletion
Spike	21765-21770 deletion	HV69-70 deletion
	21991-21993 deletion	Y144 deletion
	A23063T	N501Y
	C23271A	A570D
	C23604A	P681D
	C23709T	T7161
	T24506G	S982A
	G24914C	D1118H
ORF8	C27972T	Q27stop
	G28048T	R521
	A28111G	Y73C
	282820 GAT-CTA	D3L
N	C28977T	S2357

### B. Life cycle

The transmission rate of alpha B.1.1.7 variant was estimated to be 43–90%, which is higher than the pre-existing variant . Although the impact of the virulence is not clear, it is estimated that pathogenicity is higher among patients under 70 years old . This variant is characterized by 17 no synonymous mutations and 3 deletions, including N501Y mutation associated with higher transmissibility, P681H mutation related to the enhancement of virus entry into cells and 69–70 deletion in protein S. (Garcia et al.)

Alpha B.1.1.7 variant has higher viral load, longer duration of infection,, higher hospitalization rate], and higher mortality rate when compared to other variants. The B.1.1.7 has been reported to have a higher reproduction rate of 40-90%

### C. Symptoms

A set of 26 clinically relevant symptoms are potentially related to COVID-19 and these includes;

- 1) Loss or change of sense of smell and loss or change of sense of taste
- 2) Coryzal symptoms- runny nose, sneezing, blocked nose, sore eyes, sore throat, and hoarse voice
- 3) Gastrointestinal symptoms like appetite loss, nausea/vomiting, diarrhea, and abdominal pain/belly ache
- 4) Fatigue-related symptoms that includes- tiredness, severe fatigue, heavy arms/legs, and difficulty sleeping
- 5) Respiratory and cardiac symptoms -new persistent cough, shortness of breath, chest pain, and tight chest
- 6) Other flu-like and miscellaneous symptoms-fever, muscle aches, chills, headache, dizziness, and numbness/tingling.

The same symptoms were selected as jointly predictive of B.1.1.7 infection . When B.1.1.7 is compared with wild type, new persistent cough and sore throat were more shown in B.1.1.7 variant while loss or change of sense of smell was more shown in the wild type (Elliott et al, 2021)

## VII. BETA VARIANT

Beta variant was first reported in South Africa in May 2020, the beta variant was linked with an increase in hospitalizations and deaths during the country's second wave.

Vaccines are also less effective in preventing COVID-19 from the beta variant.

In one study researchers found that two doses of the Pfizer vaccine was 75% effective against any infection from the beta variant.

However, vaccine effectiveness against the severe disease from beta variants is very high at 97.4% (Duong, 2021).

Evans says that "Everybody was worried about the beta because of the vaccine escape issue". Novavax clinical trials showed 89% efficacy in the UK compared to just 60% in South Africa, where the beta strain was common.

Meanwhile, South Africa stopped plans to roll out the AstraZeneca vaccine because clinical trials did not show any protection against mild or moderate illness caused by the beta variant. It seems to be no more transmissible than early strains of the virus.

To date, Canada has documented more than 1900 cases (Duong, 2021).

These viruses include types of virus found in the bats which has the great similarity in amino acid structure when compared with the SARS coronavirus. The origin of beta-coronavirus is now thought to be from bats. These viruses have caused MERS, SARS and COVID-19 in humans. (Osborn)

It is more dangerous because Beta contains the spike protein-the part which gains the virus entry into human cells.

Beta carries a mutation, called N501Y, which appears to make it more dangerous or easy to spread. Another mutation, called E484K, could help the virus dodge a person's immune system, and may affect how well the vaccines work.

It is also the bit that vaccines are designed around which is why experts are concerned about these particular mutations.

Beta virus is unique because Beta-coronaviruses all have a special kind of protein called hemagglutinin esterase and it has an ORF1ab replicase polyprotein present, which is not found in any other types of coronavirus.

### A. Mutation

There are three mutations of particular interest in the spike region of the lineage B.1.351 genome (Hancock)

K417N

E484K

N501Y

and a further five spike mutations which have so far generated less concern:

L18F

D80A

D215G

R246I

A701V

Away from the spike region, it also carries K1655N, SGF 3675-3677 deletion, P71L and T205I (Zimmer, 2022). Scientists noted that variant was able to attach more easily to human cells because of their three mutations in the receptor-binding domain (RBD) in the spike glycoprotein of the virus. N501Y is a change from Asparagine (N) to Tyrosine (Y) in the amino-acid position of 501 (Malingo). K417N, and E484K these two mutants, E484K and N501Y are within the receptor-binding motif (RBM) of the receptor-binding domain (RBD) (Tegally, 2020). The N501Y mutation was detected in the UK. Beta has the 69-70del mutation found in the other variant.



Gene	Nucleotide	Amino acid
ORF1ab	C1059T	T265I
	G5230T	K1655N
	C8660T	H2799Y
	C8964T	S2900L
	A10323G	K3353R
	G13843T	D4527Y
	C14408T	P4715L
	C17999T	T5912I
	C21614T	L18F
	A21801C	D80A
	A22206G	D215G
	G22299T	R246I
Spike	G22813T	K417N
	G23012A	E484K
	A23063T	N501Y
	A23403G	D614G
	G23664T	A701V
ORF3a	G25563T	Q57H
	C25904T	S171L
E	C26456T	P71L
N	C28887T	T205I

(Tegally and Wilkinson)

### B. Symptoms

There are no significant symptoms that would help in differentiating this variant from the rest of the variants (Gulland et al, 2021). The beta variant didn't give rise to a large number of cases in other countries that is why this variant was not given much importance or in depth study. In comparison to the Wuhan strain this variant is considered to be more transmissible. As compared to the Alpha strain people developed 25% more severe symptoms and required 50% more cases.

New symptoms associated with the variant are yet to be confirmed by health experts. Some common symptoms of the variants could be runny nose, persistent cough, throat pain, body ache, loss of smell and a taste, fever, muscle cramps, diarrhea, pneumonia and affecting the multiple organs of the body. In several cases patients undergo multiple organ failure and die (Radcliffe et al, 2021)

## VIII. DELTA VARIANT

The Delta variant (B.1.617.2) is a variant of SARS-CoV-2 (WHO). It causes COVID-19. Delta variant was 1st detected in India in late 2020. The name 'Delta variant' was given on 31 May 2021. The World Health Organization (WHO) indicated in June 2021 that the Delta variant was changing into the dominant strain globally (Lovelace, 2021).

The Delta variant has mutations within the gene of SARS-CoV-2 spike protein (Shang et al, 2020), inflicting the substitutions D614G, T478K, P681R and L452R (Harvey et al, 2021). It's identified as the 21A, 21I, and 21J clades under the Nextstrain phylogenetic arrangement.

### A. Nomenclature

The virus has conjointly been said by the term "Indian Variant" because it was originally detected in India (Schraer, 2021).

There are 3 sub lineages of lineage B.1.617 classified up to now.

B.1.617.1 which is known as kappa variant was selected as a Variant in April 2021 by Public Health England. In April 2021, 2 different variants B.1.617.2 and B.1.617.3 were selected as Variants underneath Investigation. B.1.617.3 contains the L452R and E484Q mutations and this mutation is found in B.1.617.1 (CDC).

B.1.617.2 lacks the E484Q mutation. B.1.617.2 has the T478K mutation and it is not found in B.1.617.1 and B.1.617.3

### B. Structure

Delta virus, which is a variant of SARS-CoV-2, shares the same biological characteristics as SARS-CoV-2. It consists of enveloped positive-sense single stranded RNA virus, which belongs to the beta coronavirus ( $\beta$ -CoV). The genome of SARS-CoV-2 contains 14 open reading frames (ORFs), which encodes 16 non-structural proteins (NSP), 9 accessory proteins and 4 structural proteins (Wang et al, 2020). NSPs participate within the formation of replicase complexes and remaining components are involved in viral entry, assembly and release (Kovski et al, 2020). Spike supermolecule (S) is essential for infection, and is a vital target for combating SARS-CoV-2. S supermolecule has a receptor-binding domain (RBD), associate S1/S2 polybasic cleavage site and 3 O-linked glycans (Cai et al, 2020). All specific practical structures are the merchandise of natural evolution.

### C. Mutation

The Biological Characteristics of Key organic compound (Amino acid) Mutations within the Spike protein of the SARS-CoV-2 Delta Variant

SARS-CoV-2 enters into the host cells by binding the spike protein to angiotensin-converting enzyme-2 (ACE2) (Hoffman et al, 2020).

The spike protein is cleaved by furin and forms S1 unit and S2 unit.

The S1 unit consists of N-terminal domain (NTD) and a receptor-binding domain (RBD). NTD and RBD help in binding to the host-cell ACE2 receptor (Lan et al, 2020).

The S2 unit includes the trimeric core of the macromolecule and it is present for membrane fusion (Perlman and Fehr). Mutations within the S macromolecule have an effect on the transmissibility, pathogenicity, and immune escape of SARS-CoV-2 variants.

The mutations that are responsible for the delta variant to spread more rapidly are present in the spike proteins.

The spike sequence mutations within this B.1.617.2 variant are, L452R, T478K, T19R, P681R, D614G and d960N, with deletions at positions 157 and 158 (Harvey et al, 2021).

Mostly L452R and P681R spike protein mutations are seen.

This mutation results in substitution of Arginine with leucine at the position number 452. According to a study, this mutation will allow the spike protein to bind to the ACE2.

### 1) L452R

It is present in the receptor-binding motif (RBM) region within the RBD region (Deng et al, 2021). The RBD region contains residues that will bind to the ACE2 receptor. According to an analysis L452R residue doesn't directly come in contact with ACE2 receptors. Instead, L452, alongside F490 and L492, will form a hydrophobic patch on the surface of the spike RBD(Mohandas et al, 2021). This mutation will cause structural changes and this will result in the stabilization of the interaction between the spike protein and ACE2 receptor. This will result in increasing infectivity.

### 2) T478K

Delta (B.1.617.2) doesn't have the E484Q mutation when compared to other 2 B.1.617 lineages (B.1.617.1 and B.1.617.3) but it has a different T478K mutation (Harvey et al, 2021) As a result of this mutation, threonine substitutes with lysine and this will alter the electricity surface of the macromolecule and increase steric hindrance of the spike macromolecule. This enhances the binding affinity of RBD to ACE2 and helps the virus to invade the host cell (Giacomo et al, 2021)

### 3) P681R

The P681R mutation is found in the S protein of the B.1.617 lineage. It is found at the furin cleavage site, and it is the key to host cell entry. Many analyses have found that the P681R mutation affects microorganism replication dynamics and probably determines the B.1.617 variants (Johnson et al, 2021). P681R mutation facilitates furin-mediated cleavage of the SARS-CoV-2 S macromolecule, accelerates microorganism fusion, and promotes cell-cell infection (Saito et al.)

These are the key mutations of the SARS-CoV-2 Delta variant.

Gene	Amino acid
Spike	T19R, del 157/158, L452R, T478K, D614G, P681R, D950N
ORF1a	A1306S, P2046L, P2287S, V2930L, T3255I, T3646A
ORF1b	P314L, G662S, P1000L, A1918V
ORF3a	S26L
M	I82T
ORF7a	V82A, T120I
ORF7b	T40I
ORF8	del 119/120
N	D63G, R203M, D2

CDC

### D. Life Cycle

The virus needs to enter and exit the cell for the infection to begin. It first starts with the binding of the spike protein of the delta virus to the ACE2 receptor on the host cell. Then the spike protein is cleaved and this happens with the help of transmembrane serine protease 2 (TMPRSS2) (Lan et al, 2020). Cleavage takes place to expose the parts that are necessary for the fusion of the virus and host cell membranes.

After cleavage, the virus inserts its RNA genome into the host cell and then viral RNA and proteins are synthesized (He et al, 2021) The molecules that are made after the synthesis of viral RNA and proteins and processed and stored in Golgi apparatus. The spike protein is cleaved by a host enzyme known as furin and it prepares the virus to strike the other cell.

A higher rate of snipped spike protein in the virus can result in higher infectivity (Korber et al, 2020)

### E. Symptoms

Infection with Delta virus causes flu-like symptoms.

Fever, weakness, dry cough, coughing with sputum, headache, short breath and body ache are considered as common symptoms (Tellez et al.)

Few patients had hypoesthesia or loss of smell and taste (Jiang et al.).

Some patients with severe infection often have dyspnea or hypoxemia, Some develop into acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction and multiple organ failure (Li and Ma).

Very few have the manifestations of central nervous system involvement and ischemic necrosis.

Possible reasons for rapid spread of Delta variant.

The Delta variant seems to be more transmissible than the Alpha variant.

A study says that the ratio is 40-60%.

Some factors responsible for the rapid spread are;

More mutations and closer synergy (Motozono et al, 2021)—

P681R- This mutation changes the furin cleavage site of the virus which will accelerate cell-cell fusion.

L452R- This mutation increases the ability to invade the cells.

Immune escape- Recently a study was conducted and it shows that L452R variant (Deng et al, 2021)

## IX. OMICRON

The WHO identified an entirely unique variant called Omicron (B.1.1.529) because of the fifth Variant of concern on 26 November 2021 by South Africa, causing widespread worry. The origins of the Omicron are yet to be found. The examination of Severe acute respiratory syndrome-covid-2 variant sequences demonstrates that Omicron is well-defined from the opposite SARS-CoV-2 types, which identifying its closest neighbor is problematic (Kupferschmidt, 2021). As demanded by the findings of phylogenetic analyses, the Omicron variant had disunited early from the other severe acute respiratory syndrome-covid-2 types instead of developing from previous VOCs (Kupferschmidt, 2021). There is a very high chance that the Omicron variant was bred in immunocompromised individuals. The Human immune virus (HIV) patients are coinfecting with SARS-CoV-2 over an extended period; otherwise, if it developed in a very nonhuman species and was lately reintroduced into humans (Kumar et al, 2022).

The WHO declared it a VOC (a variant of concern) on 26 November 2021 and described it as Omicron and denoted it as the fifteenth character within the alphabet (Wong et al, 2022). Therefore, for this reason, the Variant was quickly labeled as a variant of concern. The Omicron variant features exceptionally multiple unique mutations (Torjesen, 2021), many of which impaired the spike protein aimed by most COVID-19 immunizations at discovery. The concerns about its spread, immune system by-pass, and vaccination defiance have arisen because of this level of heterogeneity. However, as of 14 January 2022, Omicron had spread to over 139 countries. As of 20 January 2022, the Omicron variant had been identified in 171 nations throughout the globe (NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES).

### A. Classification

On 26 November, the World Health Organization's Technical Advisory Group on SARS-CoV-2 Virus Origin assigned Phylogenetic Assignment of Named Global Outbreak lineage B.1.1.529 as VOC and given the Greek letter Omicron (Wong et al, 2022) (Parekh et al, 2021).

### B. Nomenclature

The lineage and component mutations of SARS-CoV-2 variants are classified (Tao et al, 2021). Many institutions, including governments and several news organizations, mentioned relevant variants in colloquial terms by the country where they were initially discovered (Baca et al, 2021). The World Health Organization stated that Nu is readily confused with "new" and that Xi is the familiar rearmost name. Finally, the World Health Organization adopts the entire Greek alphabet, and future variations may be named after constellations (SKY news).

### C. Mutations

There are numerous variations present in the Variant, some of which have scientists concerned (Hurst et al, 2021). Compared with the original Wuhan variety, the Omicron variant comprises 60 mutations: 50 non-synonymous mutations, eight synonymous mutations, and two non-coding mutants (Haseltine). In the spike protein, the principal antigenic aim of antibodies produced by



infections and are more commonly used in vaccinations, and has 30 mutations. Most of those modifications have not been observed before in any other species (Financial times, 2021). In collation with the earlier virus, the spike protein has 30 amino acid modifications, 15 from the receptor-binding domain (Kumar et al, 2022). Additional genomic areas have many deletions and alterations, and three alterations at the furin break site in this Variant. The furin braking area enlarges SARS-CoV-2 infections (Zhang et al, 2021).

#### D. Stealth variant

Omicron (BA.1) has more mutations than any previous SARS-CoV-2 variant with 50 mutations and approximately 32 of these pertain to the spike protein which most vaccines target to neutralize the virus. Many of the mutations are novel and are not found in previous variants of the virus. The variant is characterized by 30 amino acid changes, three small deletions, and one small insertion in the spike protein compared with the original virus, of which 15 are located in the receptor-binding domain (residues 319–541) It also carries a number of changes and deletions in other genomic regions. Additionally, the variant has three mutations at the furin cleavage site, which facilitate transmission of the virus.

Omicron has 2 types. As per researcher, the 'standard' one is now known as BA.1 /B.1.1.529.1, whereas BA.2 /B.1.1.529.2 is Omicron's second Variant. BA.2 is characterized as 'Camouflage Omicron' because it excludes the 'S' Gene Target Failure (SGTF)- causing deletion seen within the 'standard' form. (69–70) that allowed several PCR tests to identify it as an Alpha or Omicron variant (Sample and Walker, 2021).

#### E. Characteristics of omicron variant

Within 100 days of the outbreak, the proportion of infections connected with the Beta variant grew to 50% of whole day-to-day infections, according to epidemiological data. However, during the same time frame, the Delta variant's infection rate increased to 80%, which indicates the Delta version is highly transmissible among people as matched to the Beta variant.

Early doubling times were calculated to be 1.7, 1.5, and 1.2 days (Karim et al, 2021). From a population-based epidemiological data retrospective study, it is also worth noting that a recent retrospective study found a link between Omicron and serious sars-cov-2 re-infection (Pulliam et al, 2021).

The Omicron variant's genomic sequences found the highest non-synonymous mutations, with some in a spike linked to the disease severity, immune evasion, and transmission. To the greatest extent, higher than 60 substitutions, removals, and additions were found in the Omicron variant (hadfield, 2021), creating the Variant with the most mutation places of all the SARS-CoV-2 variations studied thus far.

The variant has two additions within ORF1b (P314L and I1566V). The envelope (E) protein has one substitution (T9I), the membrane (M) protein has three additions (D3G, Q19E, and A63T), and the nucleocapsid (N) protein has three additions and a three-residue removal. While the changes mentioned above appear across the viral genome, the other mutations are aggregated in the spike, and the bulk of all Omicron mutations have been discovered.

Three deletions of H69/V70, G142/V143/Y144, and N211, and one addition of three amino acids (EPE) at place 214 (from rough statements, the fluctuations are narrated as the V143/Y144/Y145 removal in union with G142D and the L212 removal in union with N211I).

D614G was linked to more tremendous viral heaps in the higher respiratory region and affected younger people (Korber et al, 2022) (Plante et al, 2021) (Volz et al, 2021), This alteration is considered to boost the spike's attachment to angiotensin-converting enzyme 2 (ACE2) and its communication (Yang et al.). The communication may be extended even higher when added with the H69/V70 removal.

Besides, near the furin braking site, Omicron has changed N679K and P681H. Essential amino acids on the furin breaking site may help the spike cleave into S1 and S2, leading to better amalgamation and virus contamination (Leung et al, 2020).

The Omicron variant's RBD contains 15 mutations, whereas the RBD of the contemporary major Delta variant only has the L452R and T478K alterations. It's worth mentioning that neutralizing antibodies most commonly target the spike RBD, and Omicron has 15 RBD mutations (Yuan et al, 2021).

All 15 mutations discovered in Omicron spike RBD may be linked back to further of these antigenic locations, implying that Omicron is resistant to monoclonal antibodies directed at these sites.

The previous study has discovered that immune evasion is connected to mutations at the spike's 484 and 417 positions (Zimerman et al, 2022) and that both Gamma and Beta variants can avoid nullification by LY-CoV016 (due to K417N/T) and LY- CoV555 (due to E484K) (Starr et al, 2021).

These changes have been linked to enhanced ACE2 binding affinity, increased transmissibility and pathogenic, decreased ability to neutralize monoclonal antibodies, and immunological by-pass. However, the effects of other mutations and whether combinations of mutations occur are unknown, creating a great deal of mystery regarding how viral behavior and susceptibility may evolve (He et al, 2021).

The spike protein of the Receptor binding domain is currently under the most extraordinary investigations. According to a recent investigation of the Omicron variant, it appears to have higher sialic acid-binding energy than prior versions, leading to more extraordinary transmission (Datt 2021). While many Omicron genomes have been posted to foreign sites, some may not contain the complete set of identifying mutations and have their unique mutations. A suggestion has been made to broaden the scope of the B.1.1.529 (Omicron) lineage to incorporate variations related to Omicron (BA.1.).

Gene	Amino acid
ORF1ab	NSP3: K38R, V1069I, $\Delta$ 1265, L1266I, A1892T
	NSP4: T492I
	NSP5: P132H
	NSP6: $\Delta$ 105-107, A189V
	NSP12: P323L
	NSP14: I42V
Spike	A67V, $\Delta$ 69-70, T95I, G142D, $\Delta$ 143-145, $\Delta$ 211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F
E	T91I
M	D3G, Q19E, A63T
N	P13L, $\Delta$ 31-33, R203K, G204R

(UK health security agency, 2021)

#### F. Furin cleavage site in Omicron

Around the furin breaking site, Omicron has N679K and P681H changes. Therefore the essential amino acids on the furin breaking site may help the spike cleave into S1 and S2, which leads to better amalgamation and virus contamination. The Alpha-version also has a P681H mutation. This mutation is thought to increase SARS-CoV-2 infectivity (Zuckerman et al, 2021).

A recent study published on the bioRxiv preprint service by Bailey Lubinski et al. It tested the host cell furin-mediated cleavability of the spike (S) protein of the Omicron (B.1.529) variant. In conclusion, when they compared the contribution of the two S gene alterations, P681H and N679K, to the furin cleavage site activity in Omicron S to other SARS-CoV-2 variants and other coronaviruses and found Furin has a higher affinity for cleaving Omicron S than the Wuhan- Hu-1, Alpha, and Delta strains. In the end, this increased furin-mediated cleavage was caused by the N679K mutation in Omicron S, which was located outside the furin binding pocket (Lubinski et al, 2022).

*G. Symptoms of Omicron variant*

- 1) Fever
- 2) Cough
- 3) A runny nose, and bodily pains are some of the most significant symptoms.
- 4) Deprivation of sensation (smell and taste).
- 5) Breathing difficulties are common signs.
- 6) Severe body cramps, cold, confusion, and a mild temperature (Abdullah, 2021)

## X. VACCINES

Covid 19 pandemic led to the rapid international search for effective and safe vaccines against the SARS-CoV-2 virus (Amanat et al, 2020).

According to a study, as of 24 January 2022, 33 vaccines were approved and were used in 197 countries. Among 33 vaccines, 10 vaccines are approved for emergency use by WHO (Covid 19 Vaccine tracker).

*A. Pfizer-BioNTech(BNT162b2)*

- 1) This vaccine was developed by Pfizer(New York) and BioNTech(Mainz, Germany).
- 2) The BNT162b2 vaccine is a lipid nanoparticle formulated with a nucleoside modified mRNA vaccine and this encodes a modified SARS-COV-2 S protein (Polack et al, 2020).
- 3) WHO listed the vaccine for emergency use on 31 December 2020 (WHO).

*B. Oxford-AstraZeneca(ChAdOx1 nCoV-19)*

- 1) The vaccine was developed through collaboration between the University of Oxford and AstraZeneca (Cambridge, UK).
- 2) The ChAdOx1 nCoV-19 vaccine is a non-replicating vector of the chimpanzee adenovirus ChAdOx1 which is modified to encode the SARS-CoV-2 S protein (Sharma et al, 2020)..
- 3) WHO listed this vaccine for emergency use on 16 February 2021 (WHO).

*C. Johnson & Johnson (Ad26.COV.2.S)*

- 1) The vaccine was developed by the Janssen pharmaceutical company Johnson & Johnson (New Brunswick, NJ, USA).
- 2) The Ad26.COV.2.S vaccine is a non-replicating vector which was developed from the recombinant human adenovirus type 26 and it is modified to contain the SARS-COV-2 S protein in a pre-fusion stabilized conformation (Sadoff et al, 2021)
- 3) WHO listed this vaccine for emergency use on 12 March 2021 (WHO).

*D. Moderna (mRNA-1273)*

- 1) The vaccine was developed by Moderna (MA, USA)
- 2) The mRNA vaccine is a lipid-nanoparticle encapsulated mRNA vaccine which expresses the SARS-COV-2 S protein that has been pre-fusion stabilized (Baden et al, 2021).
- 3) WHO listed this vaccine for emergency use on 30 April 2021 (WHO).

*E. Sinovac (corona vac)*

- 1) The vaccine was developed by Sinovac.
- 2) It is an aluminum-hydroxide-adjuvanted, inactivated whole virus vaccine which is based on the SARS-CoV-2 CZ02 strain.
- 3) WHO listed this vaccine for emergency use on 1 June 2021 (WHO).

*F. Bharat biotech(Covaxin)*

- 1) Covaxin was developed by Bharat Biotech.
- 2) It is a virion inactivated virus vaccine (WHO).
- 3) WHO listed this vaccine for emergency use on 03 November 2021 (WHO).

Vaccine	Vaccine type	Developed by	Listed for emergency use	Recommended use
BNT162b2	mRNA	Pfizer(NY) and BioNtech(Germany )	31 December 2020	2 doses
ChAdOx1	Non-replication vector of the chimpanzee adenovirus ChAdOx1	University of oxford and Astrazeneca(UK)	16 February 2021	2 doses
ad26.cov2.s	Non-replication adenovirus vector	Janssen pharmaceutical company (Johnson and Johnson)	12 March 2021	1 dose
mRNA-1273	mRNA vaccine	Modern(MA,USA)	24 January 2022	2 doses
Corona Vac	Aluminum-hydroxide-adjuvanted, inactivated whole virus vaccine	Sinovac	1 June 2021	2 doses
Covaxin	Virion inactivated virus vaccine	Bharat biotech	03 November 2021	2 doses

## XI. EVALUATION OF COVID-19

A detailed clinical history regarding the onset and duration of symptoms, travel history, exposure to people with COVID-19 infection, underlying pre-existing medical conditions, and drug history should be elicited by treating providers.

- 1) *Molecular Testing*: SARS-CoV-2 antigen tests are less sensitive but have a faster turnaround time compared to molecular PCR testing (Gandhi et al, 2020) Comprehensive testing for other respiratory viral pathogens should be considered for appropriate patients as well
- 2) *Serology Testing* :Despite the numerous antibody tests designed to date, serologic testing has limitations in specificity and sensitivity, and results from different tests vary. An antibody test with a specificity higher than 99% and a sensitivity of 96% has been developed by the CDC, which can identify past SARS-CoV-2 infection.
- 3) *Other Laboratory Assessment*: Complete blood count (CBC), a comprehensive metabolic panel (CMP) that includes testing for renal and liver function, and a coagulation panel should be performed in all hospitalized patients.Additional tests such as testing for ESR, C-reactive protein(CRP),ferritin,lactate dehydrogenase, D-dimer, and procalcitonin can be considered.
- 4) *Chest X-ray*: Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes; it can be completely normal in the initial stages of the disease.
- 5) *Chest Computed Tomography (CT)*: Chest computed tomography (CT), particularly high-resolution CT (HRCT), is the diagnostic method of choice in evaluating COVID-19 pneumonia, particularly when associated with disease progression.Several non-specific findings and radiologic patterns can be found on Chest CT.
- 6) *Lung Ultrasound*: Considering its noninvasive nature and zero risks of radiation, it is a useful diagnostic modality for patient follow-up and assists in determining the setting of mechanical ventilation and prone positioning (Samad).



## XII. PHARMACOLOGIC THERAPIES IN THE MANAGEMENT OF ADULTS WITH COVID-19

Currently, a variety of therapeutic options are available that include antiviral drugs, anti-SARS-CoV-2 monoclonal antibodies, anti-inflammatory drugs, immunomodulators agents are available under FDA issued Emergency Use Authorization (EUA) or being evaluated in the management of COVID-19

The clinical utility of these treatments is specific and is based on the severity of illness or certain risk factors. The clinical course of the COVID-19 illness occurs in 2 phases, an early phase when SARS-CoV-2 replication is greatest before or soon after the onset of symptoms. Antiviral medications and antibody-based treatments are likely to be more effective during this stage of viral replication. (Gandhi et al, 2020)

### A. Antiviral Therapies

- 1) *Balapiravir* ( Named after the Norse god Thor's Mjolnir)
- 2) *Remdesivir*
- 3) *Hydroxychloroquine and Chloroquine*
- 4) *Lopinavir/ ritonavir*
- 5) *Ivermectin*

### B. Anti-SARS-CoV-2 Neutralizing Antibody Products

Individuals recovering from COVID-19 develop neutralizing antibodies against SARS-CoV-2, and the duration of how long this immunity lasts is unclear. Nevertheless, their role as therapeutic agents in the management of COVID-19 is extensively being pursued in ongoing clinical trials.

The FDA approved convalescent plasma therapy under a EUA for patients with severe life-threatening COVID-19. One retrospective study based on a U.S national registry reported that among patients hospitalized with COVID-19, not on mechanical ventilation , there was a lower risk of death in patients who received a transfusion of convalescent plasma with higher anti-SARS-CoV-2 IgG antibody than patients who received a transfusion of convalescent plasma with low antibody levels (Joyner et al, 2020).

- 1) *Regn-Cov-2* ( Casirivimab and Imdevimab)
- 2) *Bamlanivimab*
- 3) *Sotrovimab* ( VIR-7831)
- 4) *Regn -Cov2*

### C. Immunomodulatory Agents

Some of the immunomodulatory agents are listed below ;

- 1) *Corticosteroids*
- 2) *Interferon- Beta- 1a* ( IFN- beta-1a)
- 3) *Interleukin ( IL)-1 Antagonists*
- 4) *Tocilizumab*
- 5) *Sarilumab and siltuximab*
- 6) *Janus kinase ( JAK) inhibitors*
- 7) *Ruxolitinib*
- 8) *Tofacitnib*
- 9) *Brustion's tyrosine kinase inhibitors.*

### D. Oxygenation and and ventilation management in covid -19

(Ni et al, 2019)

Conventional oxygen therapy

COVID-19 patients with associated respiratory insufficiency should be monitored closely with continuous pulse oximetry.

Supplemental oxygen supplementation via nasal cannula or venturi mask must be administered to maintain oxygen saturation (SpO2) between 92 to 96% (<88-90% if COPD). If there is no clinical and oxygen saturation, supplemental oxygen should be continued with periodic reassessment.

Management of acute hypoxemic respiratory failure in COVID-19

Acute hypoxemic respiratory failure is the most common complication in adult patients with COVID-19, and conventional oxygen therapy is not helpful to address the oxygen demand in these patients. These patients should be managed with enhanced respiratory support modalities such as high-flow nasal cannula (HFNC), noninvasive positive pressure ventilation (NIPPV), endotracheal intubation, and invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO).

#### *E. Asymptomatic or Pre Symptomatic Infection*

##### *1) Mild illness*

- a) Based on the NH guidelines, individuals with mild illness are manageable in the ambulatory setting with supportive care and isolation.
- b) Laboratory and radiographic evaluations are routinely not indicated.
- c) Elderly patients and those with pre-existing conditions should be monitored closely until clinical recovery is achieved.
- d) The National Institutes of Health (NIH) COVID-19 treatment guidelines panel recommends against dexamethasone in mild illness.

##### *2) Moderate illness*

- a) Patients with moderate COVID-19 illness should be hospitalized for close monitoring.
- b) Clinicians and healthcare staff should don appropriate personal protective equipment (PPE) while interacting or taking care of the patient.
- c) All hospitalized patients should receive supportive care with isotonic fluid resuscitation if volume-depleted, and supplemental oxygen therapy must be initiated if SpO<sub>2</sub> and be maintained no higher than 96%.
- d) Remdesivir and dexamethasone can be considered for patients who are hospitalized and require supplemental oxygen. (Alhazzani et al, 2020)

##### *3) Severe / critical illness*

- a) Patients with severe/critical COVID-19 illness require hospitalization.
- b) All the patients should be maintained on prophylactic anticoagulation, considering COVID-19 is associated with a prothrombotic state.
- c) Renal replacement therapy should be considered in renal failure when indicated.
- d) HFNC Or NIPPV can be considered in patients who do not require intubation.
- e) Having awake patients self-prone while receiving HFNC can improve oxygenation if endotracheal intubation is not indicated.
- f) Vasopressors should be started to maintain mean arterial pressure (MAP) between 60mmHg and 65mmHg.
- g) Norepinephrine is the preferred initial vasopressor.
- h) ECMO should be considered in patients with refractory respiratory failure as previously described.
- i) Empiric antibacterial therapy should be considered if there is a concern for a secondary bacterial infection (Cook et al, 2020).

### **XIII. CONCLUSION**

The SARS-CoV-2 (parent virus) underwent many mutations and gave rise to various strains of coronavirus. They are again classified into VOCs (variants of concern) and VOIs (variants of interest). These variants are different from each other with one or more mutations. These variants are also called lineages, as they have evolved from a common ancestor. These variants have different transmissibility rates, and symptoms when compared to previous strains. Because of these mutated variants, the coronavirus pandemic continued to date. To prevent this pandemic, many vaccines are being manufactured by different companies across the world. These VOCs can impact the effectiveness of vaccines, but are still effective in preventing the disease. The effect of coronavirus has been reduced but not eradicated.

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