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A comparative review of the current SARS-CoV-2 strains and the updated COVID management

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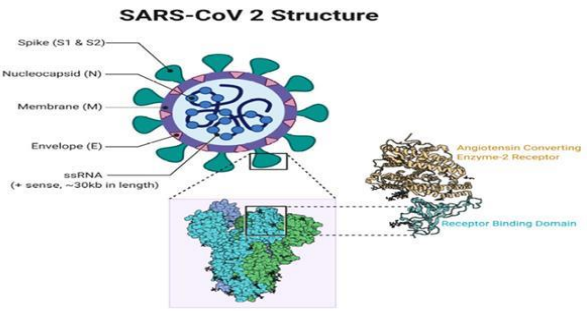
SARS-CoV-2, like other RNA viruses, is susceptible to genetic evolution, with mutations forming over time, resulting in mutant strains with differing characteristics from the original strains. With so many variants discovered the CDC and WHO created its own classification system for SARS-CoV-2 variants, dividing them into variants of concern (VOCs) and variants of interest (VOIs). Convalescent plasma, antiviral medicines, dexamethasone, monoclonal antibodies, and immuno modulators, which are currently available to treat SARS-CoV-2 infection, could help manage SARS-CoV-2 infection, although their effectiveness is limited. COVID-19 vaccines have been created in a variety of techniques, all of which are briefly discussed in this article. The development of affordable and effective oral anti-COVID-19 drugs along with increased vaccination uptake, will go a long way toward not just reducing COVID-19's progression but also bringing hope for the end of this devastating pandemic caused by Covid 19. The rationale of this study is to give a comparison of the many Covid strains that exist around the world.

Keywords: Covid strains, Structure, Clinical presentation, Virulence, Vaccines, and Oral drugs

INTRODUCTION

Corona viruses [CoVs] belong to the subfamily of the Orthocoronavirinae of the Coronaviridae family, Order Nidovirales. Alpha corona virus [-CoV], Beta corona virus [-CoV], Gamma corona virus [-CoV], and Delta coronavirus [-CoV] are the four genera that make up the Ortho Coronaviridae subfamily. [Banerjee et al. 2019 and Yang D et al. 2015]. The CoV genome is a single-stranded, enveloped, positive-sense RNA with a size ranging from 26 to 32 kb, making it the biggest genome of any known RNA viruses.

Structure of the SARS – CoV-2 genome:



SARS-CoV-2 has changed the world's idea of normalcy, with some severe ramifications for humanity (Tabish S.A 2020). Flu-like symptoms, muscle aches, runny nose, sore throat, gastrointestinal problems, anosmia and ageusia are all reported in most of the cases and it is detected by reverse transcriptase-polymerase chain reaction [RT-PCR] procedures (Lai c.c et al. 2020). However, 20% of individuals experience serious symptoms such as pneumonia and respiratory problems. Coagulation disorders, septic shock, multi organ failure, and consequences from a systemic inflammatory response are also linked to increased mortality among patients. Recent evidence had shown that many of the symptoms may remain after acute SARS-CoV-2 infection.

SARS-CoV-2, unlike DNA viruses, is susceptible to genomic alterations over the time leading to the formulation of new mutagenic variant with distinct features than the original strain. Several SARS-CoV-2 variations have been identified during the pandemic [COVID Facts/strains http://umms.org].However only a few are classified as variants of concern [VOCs] by the WHO due to their worldwide public health implications. Since the start of the pandemic, four SARS-CoV-2 VOCs have been detected, according to a recent WHO epidemiological update, as of June 22, 2021:

Alpha [B.1.1.7]: First Described in United Kingdom during early November of 2020

Beta [B.1.351]: First detected in Nelson Mandela Bay ,South Africa in Mid December 2020

Gamma [P.1]: It was seen to be first reported in Brazil in early January 2021

Delta [B.1.617.2]: First reported in India during late

December 2020

By late 2021, the two most significant variants are Delta and Omicron.

Delta [B.1.617.2] – This variant was initially identified in India in late 2020. This variant was the most highly transmissible of the variants identified at that point. It caused more severe implications than all the other variants. Since August 2021, Delta has been the dominant variant causing illnesses in the United States.

Omicron [B.1.1.529] - First identified in Botswana and South Africa, the Omicron variant is likely to spread more easily than the original virus.

Epsilon, Theta, and Zeta were at one point listed as variants of interest and were downgraded by the WHO. They are still being monitored. (Ramaiah et al. 2020)

Overall Goal:

To provide a comparative review regarding the different COVID strains present worldwide and to study their structure and virulence, clinical presentations of the diseases and the vaccines and latest oral drugs for the effective management of COVID-19.

MATERIALS AND METHODS

The literature review for this work was conducted after conducting thorough research using the following keywords: Covid strains, Structure, Clinical presentation, Virulence, Vaccines, and Oral drugs, in prominent databases such as Science Direct, PubMed, Cochrane, and Google Scholar.

Inclusion criteria: The publication date till September 2021 was chosen as the inclusion criterion. During data collection, only the resources which were published in English language were used. Case reports and research articles from reputable sources were considered for this study, with their trustworthiness determined by their respective publishers and the citation count.

Exclusion criteria: Any research that was written in non-English language has not been examined and hence excluded. Alongside, any research papers that were not published in peer-reviewed journals were also excluded. Articles that did not clearly address the topic at hand were again omitted from the study, and only relevant articles that matched the inclusion criteria were utilised as references. Finally, in the context of different types of Covid strains available at present, the key goal was to gather high-quality, authentic, and non-subjective knowledge so as to include in this comprehensive review.

Structural characteristics of SARS CoV-2

The SARS-CoV-2 genome encodes a large, non-structural polyproteins that is further proteolytically cleaved to generate 15/16 proteins, structural proteins and 5 accessory proteins (Chan JF 2020, Wu a et al, Wrapp D 2020). The four structural proteins consist of the surface spike glycoprotein, membrane, envelope and the nucleocapsid protein respectively, which are essential for its assembly and infection.

The spike surface glycoprotein is essential for host cell attachment, and it can be split by host proteases into two terminal components. Binding of the S1 subunit to a host receptor can destabilise the prefusion trimer, causing the S1 subunit to shed and transition the S2 subunit into a more stable post-fusion conformation. The S1 subunit's receptor-binding domain undergoes hinge-like conformational changes in order to engage a host receptor, which transiently conceal or expose the determinants of receptor binding (Li F 2016, Aleem A et al. 2021).(Figure 1)

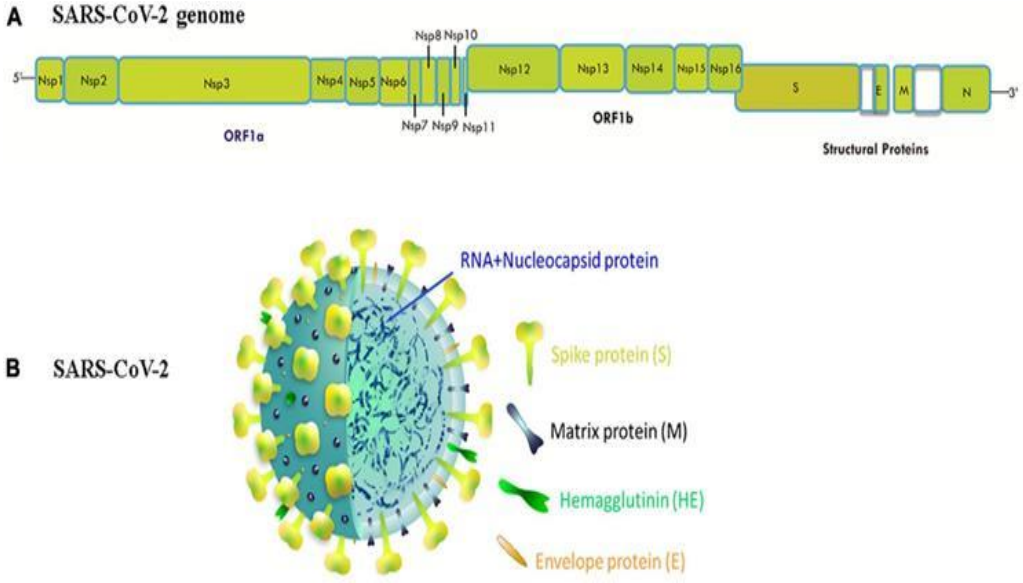


Figure 1: structural characteristic of SARS CoV-2

SARS-CoV-2 Variants of Concern [VOCs]

With the discovery of many variants, the CDC and WHO have developed their own classification system for categorizing SARS-CoV-2 variants into variants of concern (VOCs) and variants of interest (VOIs). (Wrapp D 2020)

RNA viruses are known for their ability to rapidly mutate and change in order to adapt to and survive in changing surroundings. The constellation of more than 50 mutations in the OMICRON variant, of which roughly 30 mutations are in the spike protein, is the most worrying feature. The 15 mutated sites in the receptor-binding domain (RBD) that interacts with human cells before cell entrance, potentially increasing transmissibility are the most worrying. These modifications in its spike's receptor-binding domain (RBD) suggest that they may either reduce or evade individuals' immune responses triggered by immunisation and/or previous infection (Table 1 and Table 3 and Figure 1). Immune evasion has the potential to have major effects, such as higher infection rates, reinfection, and/or improved viral fitness during evolution (online library.wiley.com).

Table 1: Delta and Kappa are derived from the lineage B.1.617;

Variant of concern		Alpha B.1.1.7	Beta B.1.351	Gamma P.1	Delta and Kappa* B1.617.2,B1.617.1
Epidemiology	First identified	September 2020, UK	October 2020, South Africa	December 2021, Japan and Brazil	December 2020, India
	Global frequency	48%	7%	7%	14%
	Major geographic distribution	Worldwide	South Africa	South America	Asia
Predominant mutations	Spike RBD mutations	N501Y	K417N,E484K,N501Y	K417N,E484K,N501Y	L452R,E484Q,T478K(Delta)
	Spike non-RBD mutations	D614G,P681H	D614G	D614G	D614G,P681R
Clinical considerations***	Transmissibility	↑ ****	↑ ?	↑ ?	↑ ?
	Virulence	↑ ?	↑ ?	↑ ?	↑ ?
	Host immune response	↓	↓	↓ ?	↓ ?
	Diagnostic tools	↔	↔	↔	↔
Therapeutic considerations***	**Vaccination effectivity**				
	mRNA-based	↔	↓	↔	?
	Adenovirus -based	↓	↓	↓	?
	Recombinant protein-based vaccines	↓	↓↓	?	?
	Inactivated virus-based	↔	↓	↔	?
	Potential therapeutic strategies				
	S1 RBD targeted therapeutics Soluble human recombinant ACE2, anti-RBD nanobodies Endosomal formation interruption TMPRSS2 inhibitors (e.g., Camostat), ADAM17 inhibitors, Viral replication-oriented therapies: RdRp inhibitors(e.g., Remdesivir,GS-441524), Cas13d-based PAC-MAN				

***All data is suggestive according to in vitro experiments unless mentioned otherwise; ****Based on clinical studies suggesting higher transmissibility rate of 35–45% especially in younger group ages and children.

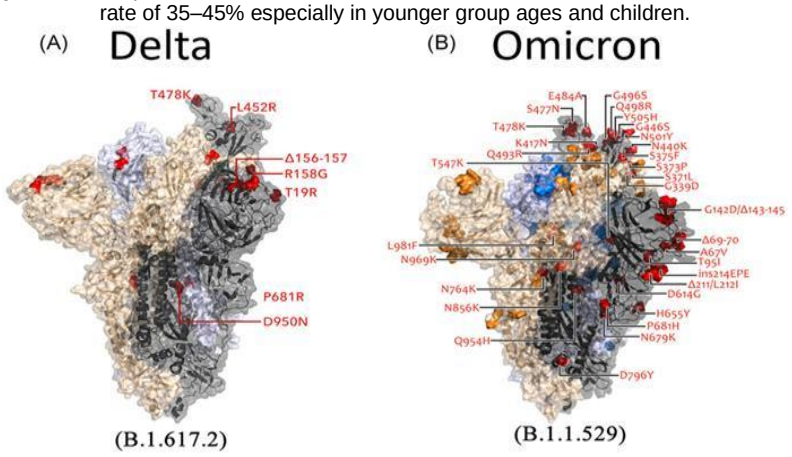


Figure 2: A comparison of (A) Delta and (B) Omicron variant spike mutation (Image source: Modified from COVID-19 Genomics UK Consortium). [17]

Table 2: Comparison of the frequency of Symptoms of Omicron and Delta Variants

SYMPTOM	OMICRON	DELTA
RUNNY NOSE	Common	Common
HEADACHE	Common	Common
FATIGUE	Common	Common
SNEEZING	Common	Sometimes
SORE THROAT	Common	Common
PERSISTANT COUGH	Sometimes	Common
CHILLS OR SHIVERS	Sometimes	Sometimes
FEVER	Sometimes	Sometimes
LOSS OF TASTE ANS SMELL	Rare	Common

Table 3: Spike protein mutation in Delta and Omicron variant compared to wild-type (Wuhan-Hu-1) [16]

Variant	Sequence ID	Mutation
Wuhan-Hu-1(wild type)	NCBI ID: P0DTC2	-
Delta variant (B1.617.2)	NCBI: QQWK65230.1	T19R, G142D, D156-157, R158G, D213-214, L452R, T478K, D614G, P681R, D950N
Omicron (B1.1.529)	GSAID ID: R40B60_BHP_3321001247/2021	A67V, D69-70, T951, G142D, D143-145, N2111, L212V, ins213-214RE, VIP215P, R216E, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N7664K, D796Y, N856K, Q954H, N969K, L981F

WHO has mentioned seven variants as the variants of Interest (Table 4) based on the following mechanism

-"if, compared to a reference isolate, its genome has mutations with established or suspected phenotypic implications, and either:

• has been identified to cause community transmission/multiple COVID-19 cases/clusters, or has been detected in multiple countries; OR

• is otherwise assessed to be a VOI by WHO in consultation with the WHO SARS-CoV-2 Virus Evolution Working Group"

Clinical Presentation

SARSCoV2 is mostly transmitted by respiratory droplets, although it can also be spread through contact with contaminated fomites or by aerosols in some conditions.

Symptomatic COVID19 infection usually manifests as a respiratory illness, with fever and cough being the frequently observed symptoms (Wu Z 2020).

Fever has been reported in up to 99 percent of individuals at some point during their illness, although in one cohort, it was observed in only 44 percent of patients at the time of hospital presentation, and in 89 %patients during hospitalisation. Cough, dyspnoea, tiredness, anorexia, anosmia, myalgia, and disorientation are all prevalent symptoms. Diarrhoea can affect as many as 10% of people. Sore throat, rhinorrhoea, headache, chest discomfort, dizziness, abdominal pain, and nausea are few of the symptoms reported less commonly (5% of cases) (Merck et al. 2021)

Around 80% of COVID19 infections manifest as a moderate respiratory illness in ambulatory patients and can usually be treated outside of the hospital. Approximately 15% of people require hospitalisation [generally for medical reasons] and another 5 % of people have critical issues that require more intensive treatments. (Merck et al. 2021)

The Delta variant causes more infections and spreads faster than the original SARS-CoV-2 strain of the virus that cause COVID-19. Loss of sense of smell and taste which was common in the delta variant is not a characteristic of Omicron variant.(Table 2) Of the first 43 Omicron cases identified in the USA in early December, only three people reported losing smell or taste, according to the Canters for Disease Control and Prevention(CDCP). But about 48 percent of people infected with the original COVID-19 strain experienced loss of smell or taste, based on a review of 27 medical studies (Jansen L et al.2021).

Vaccines

COVID-19 vaccines have been developed in a number of ways. Messenger RNA [mRNA] vaccines are the first vaccines accessible in the United States [by Pfizer-BioNTech [Comirnaty] and Moderna]. In Europe, there is another mRNA vaccination called CureVac. Human and primate adenovirus vectors are used in the development of other vaccines [by Janssen-Johnson & Johnson, Astra-Zeneca, Sputnik-V, and CanSino]. An inactivated whole-virus SARS-CoV-2 vaccine [by Bharat Biotech, Sinopharm, and Sinovac] is a third form of vaccine accessible outside of the United States. None of the vaccines are live, and none of them are likely to be excreted in breast milk or absorbed by the newborn

Latest Oral Drugs

To treat coronavirus disease-2019 (COVID-19) and prevent transmission of severe acute respiratory syndrome coronavirus 2, oral antivirals that may be easily distributed are urgently needed (SARS-CoV-2).

The Food and Drug Administration (FDA) permitted the use of two novel oral antiviral medicines in this patient namely ritonavir-boosted nirmatrelvir (Paxlovid) and molnupiravir .

Table 4: SARS-CoV-2 Variants of Interest [VOIs]

Pango lineage*	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
AV.1	GR	-	United Kingdom, Mar-2021	VUM: 26-May-2021 Reclassified: 21-Jul-2021
AT.1	GR	-	Russian Federation, Jan-2021	VUM: 09-Jun-2021 Reclassified: 21-Jul-2021
P.2§	GR/484K.V2	20B/S.484K	Brazil, Apr-2020	VOI: 17-Mar-2021 VUM: 6-Jul-2021 Reclassified: 17-Aug-2021
P.3§	GR/1092K.V1	21E	Philippines, Jan-2021	VOI: 24 Mar 2021 VUM: 6 Jul 2021 Reclassified: 17-Aug-2021
R.1	GR	-	Multiple countries, Jan-2021	VUM: 07-Apr-2021 Reclassified: 9-Nov-2021
B.1.466.2	GH	-	Indonesia, Nov-2020	VUM: 28-Apr-2021 Reclassified: 9-Nov-2021
B.1.1.519	GR	20B/S.732A	Multiple countries, Nov-2020	VUM: 02-Jun-2021 Reclassified: 9-Nov-2021
C.36.3	GR	-	Multiple countries, Jan-2021	VUM: 16-Jun-2021 Reclassified: 9-Nov-2021
B.1.214.2	G	-	Multiple countries, Nov-2020	VUM: 30-Jun-2021 Reclassified: 9-Nov-2021
B.1.427 B.1.429§	GH/452R.V1	21C	United States of America, Mar-2020	VOI: 5-Mar-2021 VUM: 6-Jul-2021 Reclassified: 9-Nov-2021
B.1.1.523	GR	-	Multiple countries, May-2020	VUM:14-July-2021 Reclassified: 9-Nov-2021
B.1.619	G	20A/S.126A	Multiple countries, May-2020	VUM:14-July-2021 Reclassified: 9-Nov-2021
B.1.620	G	-	Multiple countries, Nov-2020	VUM:14-July-2021 Reclassified: 9-Nov-2021
B.1.526§	GH/253G.V1	21F	United States of America, Nov-2020	VOI: 24-Mar-2021 VUM: 20-Sep-2021 Reclassified: 22-Dec-2021
B.1.525§	G/484K.V3	21D	Multiple countries, Dec-2020	VOI:17-Mar-2021 VUM: 20-Sep-2021 Reclassified: 22-Dec-2021
B.1.617.1§	G/452R.V3	21B	India, Oct-2020	VOI: 4-Apr-2021 VUM: 20-Sep-2021 Reclassified: 29-Dec-2021
B.1.630	GH	-	Dominican Republic, Mar-2021	VUM: 12-Oct-2021 Reclassified: 29-Dec-2021

VUM : Variant under monitoring ;VOI – Variant of Interest
§ Former VOIs: Epsilon: B.1.427/B.1.429 ; Zeta: P.2; Theta: P.3 ; Iota: B.1.526; Eta: B.1.525 ; Kappa : B.1.617.1

Currently designated variants of Interest (updated on 01/02/22)

O label	Pango lineage*	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
Lambda	C.37	GR/452Q.V1	21G	Peru, Dec-2020	14-Jun-2021
Mu	B.1.621	GH	21H	Colombia, Jan-2021	30-Aug-2021

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Nirmatrelvir (PF-07321332) is an orally available protease inhibitor that inhibits M^{PRO}, a viral protease that cleaves the two viral polyproteins required for viral replication. It has shown antiviral activity against all known coronaviruses that infect people. Nirmatrelvir is combined with ritonavir (Paxlovid), a potent cytochrome P450 3A4 inhibitor and pharmacokinetic enhancer. Nirmatrelvir concentrations must be increased to therapeutic levels using ritonavir (Owen DR et al. 2021).

Molnupiravir

Molnupiravir (MK-4482/EIDD-2801) is an orally administered experimental version of a powerful ribonucleoside analogue that inhibits the replication of SARS-CoV-2, the COVID-19 causative agent. Molnupiravir has been proven to be effective in a variety of

preclinical SARS-CoV-2 models, including prophylaxis, therapy, and prevention of transmission. Molnupiravir has also been proven to be effective against the most frequent SARS-CoV-2 mutations in preclinical and clinical studies.

The clinical study's eligibility requirements required that all 775 participants have mild-to-moderate COVID-19, with symptoms appearing within 5 days of study randomization. At the time of enrolment, all patients had to have at least one risk factor linked to a poor illness outcome. Molnupiravir decreased the probability of hospitalisation and/or death in all important subgroups; efficacy was unaffected by symptom onset time or underlying risk factors.Additionally, based on the participants with available viral sequencing data (approximately 40% of participants), molnupiravir demonstrated consistent efficacy across viral variants Gamma, Delta, and Mu (Malone B 2021).

Molnupiravir also showed consistent efficacy across viral variants Gamma, Delta, and Mu, based on the participants with accessible viral sequencing data (about 40% of participants) (Malone B 2021).

PF-07321332 (developed by Pfizer [New York, NY, USA]) and s217622 (developed by Shionogi [Osaka, Japan]), the RdRp inhibitor AT-527 (developed jointly by Roche [Basel, Switzerland] and Atea [Boston, MA, USA]), and the SARS-CoV-2 ACE2 and TMPRSS2 antagonist proxalutamide (developed by Roche [Basel, Switzerland (initiated by Kintor Pharma [Suzhou, China]).

While COVID-19 is widespread, the use of immunomodulatory or anti-inflammatory medications, antivirals, and host-factor antagonists in combination may be the most effective treatment.

The development of affordable and effective oral anti-COVID-19 medications, as well as increasing vaccination uptake, will contribute greatly towards not only limiting the progression of COVID-19 but also in providing hope for the end of this disastrous pandemic caused due to Covid 19.

CONCLUSION

With this comprehensive review coming to an end, we hope that the reader is well equipped with the latest knowledge available at the moment regarding the different strains of Covid. There is still a wide ocean of mysteries that are yet to unravel when it comes to Covid and scientists and researchers are burning their midnight oil to unleash them. With their continuous efforts, soon the understanding of the healthcare force regarding this virus will improve, leading to defeating these deadly strains and their repercussions.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

IR Rangraze and SS Khan contributed equally to the composition, review, and collection of references, as well as proofreading the final document. The final version was read and approved by both authors.

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