African Journal of Biology and Medical Research
ISSN: 2689-534X
Volume 6, Issue 3, 2023 (pp. 81-98)
www.abjournals.org

NOTABLE VARIANTS OF SARS COV 2 VIRUS - A MINI-REVIEW

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Cite this article:

Lawani-Luwaji E., Alade T., John B.U. (2023), Notable variants of SARS COV 2 Virus - A Mini-Review. African Journal of Biology and Medical Research 6(3), 81-98. DOI: 10.52589/AJBMR-EO2RWPKP

Manuscript History

Received: 13 Sept 2023

Accepted: 1 Nov 2023

Published: 29 Nov 2023

ABSTRACT: *Viruses undergo mutations over time, and sometimes these changes do not have any significant impact on the virus's properties. However, certain mutations can alter the way the virus interacts with the host's major components, leading to modifications in the host's machinery within the cell. These modifications can affect the virus's properties, such as its transmissibility, severity of the disease, effectiveness of therapeutic medications, vaccines, and other social and public measures related to health. This review paper aims to discuss the different variants of SARS-CoV-2 that have emerged since the first documented case of the virus. We searched for keywords such as severe acute respiratory syndrome coronavirus 2 and variants on websites like the World Health Organization and databases like PubMed, Medline, and blogs. We examined these sources to find relevant materials published on the topic. The variants are classified based on ancestry and segment mutations, and they are grouped into distinct categories based on their potential for causing severe disease. The identification of five notable variants since December 2020, namely the Alpha, Beta, Gamma, Delta, and Omicron variants, has blown up the virus lineages. These variants have added complexity to COVID-19 research and have required extra epidemiological, laboratory, and clinical research avenues.*

KEYWORDS: SARS-CoV-2, Evolution, Mutations, Variants.

Article DOI: 10.52589/AJBMR-EO2RWPKP
DOI URL: https://doi.org/10.52589/AJBMR-EO2RWPKP

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ISSN: 2689-534X
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INTRODUCTION

In December 2019, the first instance of COVID-19 was reported in Wuhan, China. This epidemic later spread globally and became a pandemic a century after the Spanish flu in 1918. The early cases of the disease were connected to a seafood marketplace that sold wild animals like bats and reptiles. The virus was believed to have been transmitted from animals to humans [Li et al., 2020].

The viral genome sequencing revealed a significant similarity between it and a bat virus called Bat-CoV-RaTG13. Additionally, some experts believe that pangolins, which are natural carriers of coronaviruses, might have played a role in the transmission of the virus [Zhang et al., 2020; Hu et al., 2021].

SARS-CoV-2 is a virus that belongs to the Coronaviridae family. It has a single-stranded, positive-sense RNA and crown-like spikes on its surface, typical of coronaviruses. Its genome encodes 29 proteins involved in virion assembly, infection, and replication. The virus enters human cells through endocytosis, aided by the spike proteins on its surface. These spike proteins contain a receptor-binding domain that binds to human angiotensin-converting enzyme 2. This promotes membrane fusion and uptake of the virus. In January 2020, the World Health Organisation visited Wuhan, the disease's epicentre, and found convincing evidence of human-to-human transmission. (Schoeman & Fielding, 2019). Since the first reported and documented cases, mutations of the novel virus have led to different variants, which is the aim of this review paper.

Methodology Design

We created the review process according to the framework designed by Arksey and O'Malley (2005). We searched online literature articles in Cochrane, Google Scholar, EBSCO, PubMed and databases. We used the search words COVID-19, SARS-COV-2 virus, and variants of SARS-COV-2. We included all the relevant scientific articles involving human subjects written in English in the review.

Main Text

SARS-CoV-2 genes

All β-coronaviruses genomes are positive-sense single-stranded non-segmented enveloped RNA viruses. Whole-genome analyses show that the genome of β-CoVs to which SARS-CoV-2 belongs encodes many non-structural and four structural proteins (NSP). Fig 1 shows a representation of the different proteins as well as the membrane (M), envelope (E), nucleocapsid (N) and spikes (S) (Frey & Himmel, 2021). A third of all coronaviruses' genomes comprise open-reading frames (ORFs) and are grouped into ORF1a and ORF1b [Ramesh et al., 2021].

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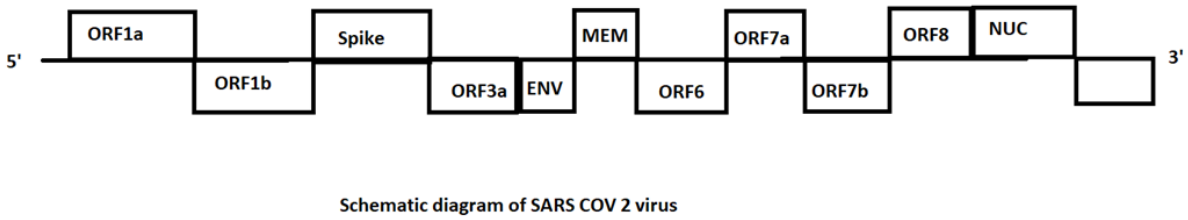

Figure 1: A schematic diagram showing SARS COV 2 genes

A schematic diagram showing SARS COV 2 genes, open-reading frames (ORFs), Membrane protein (MEM.) Nucleocapsid (NUC) and Envelope (ENV).

ORF1ab refers to six accessory proteins: ORF3a, ORF6, ORF7a, ORF7b, ORF8a, and ORF8b present in the genome. The S protein plays a significant role in entry into the host cells by binding to the human ACE2 receptor. In contrast, the E protein, a minor structural protein, is involved in pathogenesis, virus assembly and release. In association with the M protein, the S protein also mediates host immune responses [Schoeman & Fielding, 2019].

Variants Determining Factors

Between 2019 and the present day, the progression of SARS-CoV-2 has led to several genetic variants. Viruses continuously change, and such mutations lead to the advent of a new form of the virus [Otto et al., 2021; CDC, 2021]. Some modifications could affect the virus' properties, such as its transmissibility, disease severity, therapeutic medications, vaccines, or other social and public health measures. It could also be less transmissible and virulent [WHO, 2021].

Variants usually arise during replication; a significant selection factor for success is the number of infected individuals. Usually, variants may have an advantage or disadvantage over the ancestor and sometimes might become dominant [Cantón et al., 2021].

The SARS-CoV-2 variants, like other coronaviruses, have a high mutation rate, but with this virus, an enzyme that amends errors throughout the replication process limits the mutation rate [Lauring et al., 2021]. However, mistakes still arise, accumulating mutations that may affect the RNA sequence but not the protein produced. Other mutations result in amino acid changes that affect viral proteins with implications for infection and transmissibility. Over the years, multiple selection parameters might have led SARS-CoV-2 to evolve in humans. Such selection changes the intrinsic characteristic of the virus with a resultant altered replication and transmission process [Plante et al., 2021].

Mutations that can alter interactions with major host components, such as substitutions in critical viral proteins, might change the control of the host machinery, sway epigenetic regulation in the host cell and interrupt membrane/vesicle trafficking [Gordon et al., 2020]. Spike protein mutations affect viral replication and spread, so changes on the spike surface are more likely to affect binding and entry mechanisms. Some of these mutations are seen to

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improve replication and transmission processes. [Hou et al., 2020; Cottam et al., 2014; Narayanan et al., 2008].

Mutations affecting viral non-structural proteins (NSP) change the host defence system dynamics and subdue the innate immune functions [Narayanan et al., 2008]. NSP6 decreases autophagosome expansion (Korbere et al., 2020), and accessory protein ORF6 disrupts nucleocytoplasmic trafficking to advance viral replication [Miyamoto et al., 2021].

Mutations in the receptor-binding domain are essential, as most neutralising antibodies and vaccines target the domain. Mutations in the N-terminal domain (NTD) could damage the ability of the neutralising antibodies [Ju et al., 2020; Mccallum, 2021].

Researchers identified the ancestry of the SARS-CoV-2 virus from samples collected from Wuhan compared with earlier genomes obtained from pangolins and bats. The ancestral genome was categorised as "S", and the subsequent dominant type "L". Later, as the pandemic progressed, other researchers in the west characterised the ancestral type "A" and the mutant type "B" [Tang et al., 2021; Rambaut et al., 2020].

There was a further mutation of the B-type into other types, including B.1, the predecessor of the leading global variants of public health concern. The World Health Organization has named these Alpha, Beta, Delta, and Omicron variants [WHO, 2022].

Vital mutations associated with the SARS-CoV-2 variant are shown in Table 1 [(Nelson et al., 2021; Starr et al., 2021; Greaney et al., 2021; Garcia-Beltran et al., 2021; McCarthy et al., 2021; Shah et al., 2020; Gaebler et al., 2021).

Table 1: Principal Mutations Associated with SARS-CoV-2 Variants

Mutation	**Some effects of mutation**
N501Y	Ability to escape some neutralising antibodies Increases the interaction with ACE2 receptor Increases binding affinity
K417N and K417T	Ability to escape some neutralising antibodies Ability to escape some neutralising antibodies Increases interaction with ACE2 receptor K417N attenuates affinity for ACE2 but is compensated by N501Y mutation,
E484K, E484Q, and E484P	Loss of monoclonal antibody efficacy Reduced sera neutralisation Immune escape
L452R	Immune escape Increased transmissibility Loss of monoclonal antibody efficacy Reduced sera neutralisation

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S477G, S44N, S477R	Escape from some monoclonal antibodies Increased affinity for ACE2 receptor Conformational alteration in the S protein
R2461I/M	It may be involved in neutralising antibody resistance
69Del, 70 Del	Reduced sera neutralisation Increased infectivity There is S gene target failure during Multiplex RT PCR
S13I. W152C	Escape from monoclonal antibodies designed against the N-terminus
L18F	Escapes from neutralising antibodies targeting the N-terminus
141-143DEL	Escapes monoclonal antibodies
144Del	Resistant to monoclonal antibodies
D614G	Increased ACE2 binding Increased infectivity
H655Y	Monoclonal antibody escape
P681H/R	Has the possibility of increasing transmission and infectivity

Taxonomy of SARS-CoV-2 Variants

The grouping of SARS-CoV-2 variants is based on ancestry, and segment mutations (Tao et al., 2021), and the World Health Organization declared the use of Greek names for the significant variants [WHO, 2021]. Researchers, scientists, and global public health authorities use the Phylogenetic Assignment of Named Global Outbreak Lineage (Pango) nomenclature to track the spread and transmission of SARS-CoV-2 [Rambaut et al., 2020].

The PANGO lineage comprises the two main ancestries: A and B, and descendants from either lineage have numerical designations to differentiate them. It is labelled as lineage A.1 or B.2 and can progress to sublevels such as A.1.1. and A.1.1.1. Specific criteria for determining a new lineage include phylogenetic evidence and nucleotide difference from the ancestral lineage [Ramesh et al., 2021].

Variants are placed into distinct categories based on the potential for causing severe disease: variants of interest (VOI), variants of concern (VOC), variants under monitoring (VUM) and variants of high Consequence (VOHC). A variant is classified as VOI when it affects the virus' characteristics, such as transmissibility, disease severity, immune escape, and diagnostic or therapeutic escape. VOC variant has increased transmissibility, virulence, and reduced efficiency of vaccines and therapeutics. A SARS-CoV-2 variant is called VUM when genetic changes affect virus characteristics and pose an imminent risk but with an unclear epidemiological impact (26). The CDC used a VOHC when there was unmistakable evidence that the intervention measures for a particular variant were decreased [CDC, 2020; Wyllie et al., 2020; Lauring et al., 2021].

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SARS-CoV-2 Alpha Variant (B.1.1.7)

The Alpha variant (Kent variant) was identified in October 2020 in the United Kingdom and is more easily transmitted than the wild-type virus [British Broadcasting Corporation, 2021]. Scientists estimated the transmission rate to be 40-80% more because of the virus's spread and surge between October and December. The virus's prevalence doubled every 6.5 days, and the generational interval correlated with a significant increase in the disease rate in the United Kingdom [Volz et al., 2021].

The upsurge of the disease was assumed to be partly because of mutations in the spike protein, which had more mutations than was usually seen. It was named the alpha variant after being detected in about one hundred and twenty countries [WHO, 2022].

After investigating over a million persons with the alpha variant in the United Kingdom, the Imperial College London discovered an array of further symptoms linked to COVID-19. Besides cough, fever and loss of smell and taste, typical disease symptoms, loss of appetite, muscle aches, headache, and chills, were most common in infected persons with the alpha variant [Justine, 2022].

An essential change in lineage B.1.1.7 is the change in amino acid position 501 from asparagine (N) to tyrosine (Y), which causes the virus to become more infectious. The N501Y mutation alone or combined with a deletion at position 69/70 in the N-terminal domain (NTD) enhances transmissibility [Wise, 2020; Chand, 2020]. The alpha variant also attained a P681H change, which confers resistance to interferon-β (IFNβ) functions in lung epithelial cells [Lista et al., 2022]. Other mutations associated with the alpha variant are shown in Table 2 [Wise, 2020; Chand, 2020; Lista et al., 2022].

Table 2: Mutations Associated with the Alpha Variant

WHO nomenclature	PANGO lineage	First discovered	Mutations		Prominent mutations
			Gene	Amino acid	
Alpha	B.1.1.7	United Kingdom	ORF1a	T1001I	69–70del, N501Y, P681H
			ORF1a	A1708D	
			ORF1a	I2230T	
			ORF1a	del3675/3677	
			ORF1b	P314L	
			S	N501Y	
			S	del144/144	
			S	del69/70	
			S	A570D	
			S	D614G	
			S	D614G	
			S	P681H	
			S	T716I	
			S	S982A	
			S	D1118H	
			ORF8	Q27*	
			ORF8	R52I	
			ORF8	Y73C	
			ORF8	S84L	

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SARS-CoV-2 Beta Variant B.1.351

The country's health department detected and reported the Beta variant in South Africa. Scientists and researchers discovered the variant was more prevalent among young people when compared with other variants. It caused severe illness even in people with no underlying health conditions and was more transmissible than the earlier variants. The mutation on the spike glycoprotein allowed for stronger attachment to human cells. Notable mutations in the Beta variant were N501Y, K417N, and E484K; these mutations found on the receptor-binding domain in the spike glycoprotein of the virus are responsible for viral attachment [WHO, 2022; CDC, 2022; Choi et al., 2021].

The Beta variant was 50% more transmissible than the earlier lineages and contained the three prominent mutations K417N, E484K and N501Y (Table 1). These mutations made the virus attach more readily to human cells (WHO,2022). Other mutations associated with the beta variants are shown in Table 3 [Ramesh et al., 2021, WHO,2022].

Table 3: Mutations Associated with the Beta Variant

WHO nomenclature	PANGO lineage	First discovered	Mutations		Prominent mutations
			Gene	Amino acid	
Beta	B.1.351	South Africa	ORF1a	T265I	N501Y
			ORF1a	K1655N	K417N
			ORF1a	OK3353R	E484K
			ORF1a	del3675/3677	
			ORF1b	P314L	
			S	D80A	
			S	D215G	
			S	del241/243	
			S	K417N	
			S	E484K	
			S	N501Y	
			S	D614G	
			S	A701V	
			ORF3a	Q57H	
			ORF3a	S171L	
			E	P71L	
			ORF8	S84L	
			N	T205I	

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SARS-CoV-2 Gamma variant P.1 (B.1.1.28.1)

On 6 January 2021, the Japanese National Institute of Infectious Diseases (NIID) detected the Gamma variant of the SARS-CoV-2. This variant was initially detected in four people who had been to Brazil for a visit. After considering it a variant of concern, the WHO labelled it the Gamma variant [Faria et al., 2021].

The Brazilian variant belongs to the P.1 lineage and has seventeen mutations with amino acid substitutions on the spike proteins. This variant contains two different sub-variants: 28-AM-1 and 28-AM-2, and both still carry the K417T, E484K, and N501Y mutations (Toovey et al., 2021). This variant caused widespread infection in Manaus, and by 2021 there was already a high seroprevalence of SARS-CoV-2 antibodies. It is more transmissible (1.4–2.2 times) than the predecessor [Buss et al., 2021].

This variant can avoid between 25-75% immunity from previous coronavirus diseases, leading to reinfection after recovery from an earlier COVID-19 infection. The fatality rate after infections by the Gamma variant is 10–80% more deadly than the predecessor. [Faria et al., 2021]. Other important mutations associated with the gamma variant are listed in Table 4 [Ramesh et al., 2021; Faria et al., 2021; Toovey et al., 2021].

Table 4: Important variants associated with the gamma variant

WHO nomenclature	PANGO lineage	First discovered	Mutations		Prominent mutations
			Gene	Amino acid	
Gamma	**B.1.1.28.1**	**Brazil**	ORF1a	S1188L	K417T,
			ORF1a	K1795Q	E484K
			ORF1a	del3675/3677	N501Y
			ORF1b	P314L	
			ORF1b	E1264D	
			S	L18F	
			S	T20N	
			S	P26S	
			S	D138Y	
			S	R190S	
			S	K417T	
			S	E484K	
			S	N501Y	
			S	D614G	
			S	H655Y	
			S	T1027I	
			S	V1176F	
			ORF3a	S253P	
			ORF8	S84L	
			ORF8	E92K	
			N	P80R	
			N	R203K	
			N	G204R	

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SARS-CoV-2 Delta variant B.1.617.2

The Delta variant, detected in late 2020, was named a variant of concern by May 2021, and it gradually became the dominant variant globally by June 2021 [Lovelace, 2021; BBC, 2022]. This variant caused the second COVID-19 wave in India, which spread, causing the third wave in Fiji, South Africa (The Guardian, 4 July 2021) and the United Kingdom [Mishra et al., 2021]. By July 2021, it had a similar effect in both Europe and Africa, and in late July, the United States [BBC, 2022; Kathy, 202], New Zealand [Dyer, 2021], and Australia [Nunes-Vaz, 2021]. There are substitution mutations on the original SARS-CoV-2 gene that encodes for the spike proteins at P681R, T478K and L452R. These changes affected the transmission and neutralisation of the virus [Starr et al., 2021].

Evidence obtained during the pandemic showed that the gamma variant was highly contagious, caused severe disease, avoided immunity more than previous variants, and was more resistant to public health preventive measures, therapeutics, and vaccines. B.1.617.3 was the first sub-lineage in India, followed by two other sub-lineages, B.1.617.1 and B.1.617.2, identified in the United Kingdom. B.1.617.2, detected in December 2020, was finally designated a variant of concern by the WHO and CDC [WHO, 2022].

Significant mutations observed in this variant are L452R and P681R (table 1). These mutations increased the transmission and pathogenicity of the virus by enhancing its binding affinity to the ACE2 receptor [Tchesnokova et al., 2021].

A Delta-plus variant with the mutation K417N was detected in Europe in March 2021, and this variant could resist monoclonal antibodies and evade immunity gained by an earlier infection [BBC,2022]. The Delta-plus variant was not listed as a concern because of insufficient data. [Public Health England, 2022]. Prominent mutations associated with the gamma variant are listed in Table 5 [Starr et al., 2021; Tchesnokova et al., 2021].

Table 5: Prominent Mutations Associated with the Gamma Variant

WHO nomenclature	PANGO lineage	First discovered	Mutations		Prominent mutations
			Gene	Amino acid	
Delta	**B.1.617.2**	**India**	ORF1a	A1306	L452R
			ORF1a	P2046L	P681R
			ORF1a	P2287S	
			ORF1a	V2930L	
			ORF1a	T3255I	
			ORF1a	T3646A	
			ORF1b	P314L	
			ORF1b	G662S	
			ORF1b	P1000L	
			ORF1b	A1918V	
			S	T19R	
			S	E156G	
			S	del157/158	
			S	L452R	
			S	T478K	
			S	D614G	

Article DOI: 10.52589/AJBMR-EO2RWPKP
DOI URL: https://doi.org/10.52589/AJBMR-EO2RWPKP

			S	P681R	
			S	D950N	
			ORF3a	S26L	
			M	I82T	
			ORF7a	V82A	
			ORF7a	T120I	
			ORF7b	T40I	
			ORF8	S84L	
			ORF8	del119/120	
			N	D63G	
			N	R203M	
			N	G215C	
			N	D377Y	

Omicron B.1.1.529

This variant was first detected in South Africa in late November 2021 with distinct hypotheses. One such theory believes that the modifications in the Omicron variant were acquired from HCoV-229E, another coronavirus responsible for the common cold (Alkhatib et al., 2022). Another school of thought suggests a connection with HIV might be accountable for the substantial number of mutations detected in the Omicron genome sequence [Tarcsai et al., 2022]. Another school of thought felt the omicron variant did not advance from any other va**r**iant but deviated on a distinct track around mid-2020 [Saxena et al., 2022].

The South African sub-lineage referred to as B.1.1.529.1 or BA.1 has two sub-lineages: B.1.1.529.2 (BA.2) and B.1.1.529.3 (BA.3) [Arora et al., 2022]. New variants BA.4 and BA.5 were detected in some countries with similar mutations [Mohapatra et al., 2024]. BA.1 mutated into two, the original BA.1 and BA.1.1, with a critical difference where BA.1 has an R346K mutation. Subvariants BA.1 and BA.2 share 32 mutations with the original Omicron strain but have 28 distinct modifications [Vauhkonen et al., 2022].

Approximately 50 mutations have been detected in the Omicron variant, with the spike protein having 32 amino acid changes (66). Other SARS-CoV-2 variants share several crucial mutations in the S protein of RBD and the S1 subunit of the Omicron variant. These mutations affected the virulence and infectivity features of the Omicron variant, which might either surpass the Alpha, Beta and Delta variants or be in a transitional phase between the variants [Mohapatra et al., 2022; Ramesh et al., 2021; WHO,2022].

Mutation at residue K417N is mutual between Omicron and Beta variants. E484K mutation is found in both Beta and Gamma variants, but glutamic acid is replaced with alanine instead of lysine in the Omicron variant. The mutation at position 501 from asparagine to tyrosine (N501Y) present in the Omicron variant was also identified earlier in previous variants [Kannan et al., 2022]. Omicron has a higher mutation rate of 5.5 to 11 times. Apart from the critical mutations (E484A, T478K, N501Y and Q493R), other substitutions exist at five distinct positions: P499, Q493, and F486, respectively A475 and L455, which increase the binding

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affinity [Tian et al., 2022]. Additional mutations are listed in Table 5 [Vauhkonen et al., 2022; Tian et al., 2022].

Table 5: Prominent Mutations Associated with the Gamma Variant

WHO nomenclature	PANGO lineage	First discovered	Mutations		Prominent mutations
			Gene	Amino acid	
Omicron			ORF1a	T3255I	E484A, T478K, N501Y and Q493R
			ORF1a	P3395H	
			ORF1b	P314L	
			ORF1b	I1566V	
			S	G142D	
			S	G339D	
			S	S373P	
			S	S375F	
			S	K417N	
			S	N440K	
			S	S477N	
			S	T478K	
			S	E484A	
			S	Q493R	
			S	Q498R	
			S	N501Y	
			S	Y505H	
			S	D614G	
			S	H655Y	
			S	N679K	
			S	P681H	
			S	N764K	
			S	D796Y	
			S	Q954H	
			S	N969K	
			E	T9I	
			M	Q19E	
			M	A63T	
			ORF8	S84L	
			N	P13L	
			N	del31/33	
			N	R203K	
			N	G204R	

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DISCUSSION

Presently, the dominant variant is BA.5, though sub-variants BA.4, BA.5 and BA.2.12.1 are circulating, and the novel omicron variant has been replaced with the variants. Three years after the pandemic, the number of daily cases globally had decreased to its lowest levels for months.

According to the statistics released by the WHO, the global weekly cases of COVID-19 are on the rise again after a decreasing trend since March 2022. As of June 26, 2022, around 541 million confirmed cases and over 6.3 million deaths have been reported worldwide. The virus has continued to evolve since the emergence of Omicron. As of April 30, 2023, approximately 2.8 million new COVID-19 cases and about 17,000 deaths were reported globally. However, there has been a decrease in the reported cases from different regions compared to the statistics obtained between March 6 and April 2, 2023. Currently, over 500 sub-lineages of this variant are in circulation, but none have been classified as a new variant of concern.

CONCLUSION

The transition from epidemic to endemic presented a global healthcare challenge. New variants will continue to emerge with mutations. It is crucial to prioritise controlling the spread of COVID-19, especially now that many places no longer mandate wearing masks. Although there are still many unanswered questions regarding the pandemic's future, it is evident that SARS-CoV-2 will not be entirely eradicated. Therefore, we need to adapt to living with it and implement measures to mitigate its spread in our communities in the coming months. Continuous focus on improving and encouraging vaccination might continue to be the basis of COVID-19 prevention and alleviation globally.

LIST OF ABBREVIATIONS

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
Bat-CoV-RaTG13	SARS-like betacoronavirus
B-CoVs	β-coronaviruses
N.S.P.	Non-structural proteins
ORF	Open-reading frames
ACE2	Angiotensin-converting enzyme 2
IFNβ	Interferon-β
MEM	Membrane
S	Spike
NUC	Nucleocapsid
CDC	Centre for Disease Control and Prevention

Article DOI: 10.52589/AJBMR-EO2RWPKP
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WHO	World Health Organization
RNA	Ribonucleic acid
RBD	Receptor Binding domain
VOI	Variants of Interest
VOC	Variants of concern
VUM	Variants under monitoring
VOHC	Variant of high Consequence

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

The authors give their permission for publication

Availability of Data and Material

Not applicable

Consent for Publication

Not applicable

Competing Interests

The authors declare that they have no competing interests.

Funding

No funding available

Authors' Contributions

ELL conceptualised the study, conducted the searches and wrote the manuscript. TB and BUJ contributed to the manuscript revision.

All authors read and approved the manuscript.

Acknowledgements

Not applicable

Article DOI: 10.52589/AJBMR-EO2RWPKP
DOI URL: https://doi.org/10.52589/AJBMR-EO2RWPKP

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