Journal of Microbiology and Modern Techniques
Volume 8 | Issue 1
ISSN: 2575-5498

Review Article Open Access

Omicron SARS-CoV-2: The Newest Variant

Ahmed M Elsayed[1], Najeba Alsalem[2], Ghalas Sabah[2], Reem Almutairi[2], Amal Z Barakat[3], Afaf Eladl[4], Abdel-Nasser A El-Shorbagi[2], Mohamed I Husseiny[4, 5, *], Sameh S M Soliman[2, 6]

[1]Department of Society and Genetics, College of Letters and Science, University of California, Los Angeles, California, United States of America

[2]Department of Medicinal Chemistry, College of pharmacy, University of Sharjah P.O.Box 27272, Sharjah, United Arab Emirates

[3]Department of Molecular Biology, Biotechnology Research Institute, National Research Center, Cairo, Egypt

[4]Department of Microbiology and Immunology, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt

[5]Department of Translational Research & Cellular Therapeutics, Arthur Riggs Diabetes & Metabolism Research Institute, Beckman Research Institute, City of Hope National Medical Center, Duarte, CA, United States of America

[6]Research Institute for Medical and Health Sciences (RIMHS), University of Sharjah P.O.Box 27272, Sharjah, United Arab Emirates

[*]**Corresponding Author:** Mohamed I Husseiny, Department of Translational Research & Cellular Therapeutics, Arthur Riggs Diabetes & Metabolism Research Institute, Beckman Research Institute, City of Hope National Medical Center, Duarte, CA, United States of America, Tel.: +13107551530, E-mail: melsayed@coh.org

Citation: Ahmed M Elsayed, Najeba Alsalem, Ghalas Sabah, Reem Almutairi, Amal Z Barakat et al. (2024) Omicron SARS-CoV-2: The Newest Variant, J Microbiol Modern Tech 8(1): 101

Received Date: March 23, 2024 **Accepted Date:** April 23, 2024 **Published Date:** April 27, 2024

Abstract

SARS-CoV-2 evolution has undergone several mutations since its initial emergence in late 2019. Successive mutations are a common characteristic of RNA viruses like coronavirus. The emergence of new variants is a result of mutations that differ in their characteristics such as their infectiousness and mortality. Several variants of concern have been identified since the start of the pandemic, including Alpha, Beta, Gamma, Delta, and Omicron. Each of these variants showed unique mutations that raised concerns about their transmission rate, disease severity, and vaccine efficacy. The omicron variant (XBB 1.6), also known as B.1.1.529, attracted significant attention due to its high number of mutations, particularly in the spike protein. These mutations have raised concerns about potential impacts on vaccine efficacy and their ability to evade immunity. The effectiveness of existing vaccines against omicron and other variants may vary. Public health authorities and researchers worldwide are working to adapt strategies and develop new tools to combat the pandemic effectively. Booster doses have been recommended to enhance immunity, especially in the face of emerging variants. Rapid genome sequencing and analysis of the new variants are essential for monitoring their spread and understanding their characteristics. This helps in adapting public health measures and vaccine strategies accordingly. Developing a multivalent vaccine that can generate a broad immune response, capable of addressing multiple variants, is an important consideration in vaccine research and development.

Keywords: SARS-CoV-2; COVID-19; Omicron; New variant; XBB 1.6

Introduction

COVID-19 has grown over recent years with a significant impact on the world's healthcare strategies. The emergence of several mutations had led the virus to become more sophisticated with the Omicron XBB.1.5 subvariant rapidly overtaking the other variants. Since its initial discovery in October 2022, XBB.1.5 had emerged as the most common variant in the United States (U.S). According to the Centers for Disease Control and Prevention's (CDC) genomic surveillance data, XBB.1.5 was thought to be the cause of 89.5% of all infections at that time (https://www.contagionlive.com/view/omicron-xbb-1-5-heightened-transmissibility-infectivity-and-immune-resistance). The fast increase in occurrence of this subvariant may be explained by its immunological escape from vaccinations, spike protein mutations, and higher affinity for the angiotensin converting enzyme-2 (ACE-2) receptor [1]. It varies by location in the US; during the same week, the prevalence of XBB.1.5 infections in the Midwest including Iowa, Kansas, Missouri, and Nebraska reached ~53% (Figure 1 and 2). XBB.1.5 was the most common variant in the nation, accounting for 75% of infections as of mid-February 2022, up from less than 2% in December 2022 (https://www.worldometers.info/coronavirus/country/us/).

In January 2023, a rapidly spreading new subvariant of the novel coronavirus that causes COVID-19 known as Arcturus was in 31 countries. Currently, the Arcturus coronavirus, XBB.1.6 and EG.5 (with the nickname "Eris") are the most prominent variants in the U.S. Several other omicron subvariants, BA.2.86 and XBB.2.3, are also increasing across the country.

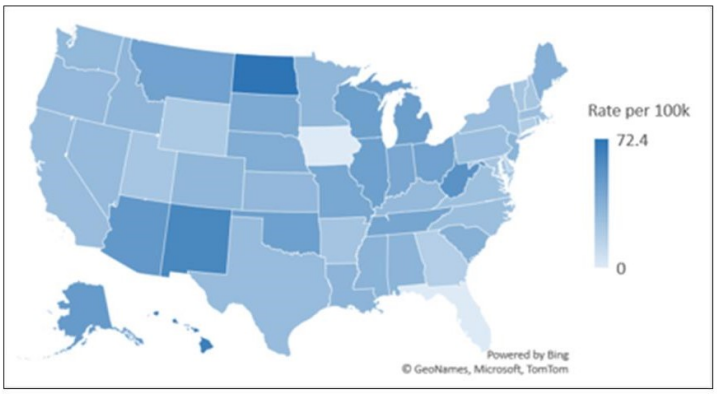

Figure 1: The number of COVID-19 cases per 100,000 people in different areas of US in the week of 19th April 2023. The global heatmap was performed by Microsoft excel, and the information was obtained from (https://www.worldometers.info/coronavirus/country/us/).

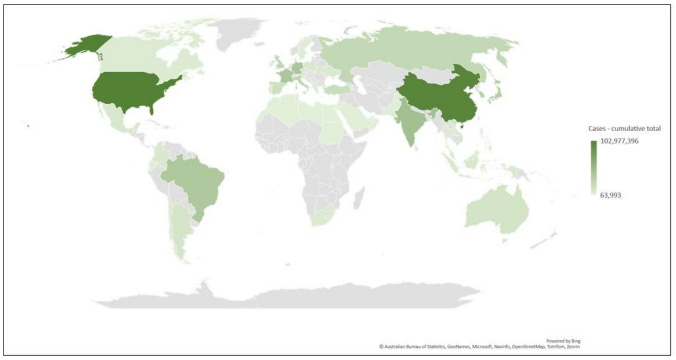

Figure 2: Global cumulative cases. On 19, April 2023, there have been 763,740,140 confirmed cases of COVID-19, including 6,908,554 deaths, reported to WHO. The global heatmap was performed by Microsoft excel, and the information was obtained from (https://data.who.int/dashboards/covid19/cases?n=c).

SARS-CoV-2 Variants

The CDC and World Health Organization (WHO) has divided SARS-CoV-2 variants into two main groups (i) variant of concern (VOC), and (ii) variant of interest (VOI) [2]. VOC poses the traditional hazards to human life by modifying various clinical presentations of the disease, making them more virulent and transmissible compared to earlier forms of the virus. VOI contains mutation causing amino acid substitutions that affect various viral properties [2].

The WHO has currently discovered five VOC, namely Alpha, Beta, Gamma, Delta, and Omicron. VOCs are more contagious than the original SARS-CoV-2 strains, which may be due to higher disease severity and lower neutralization by antibodies, resulting in subsequent pandemic waves. After being discovered toward the end of September 2020, variant B.1.1.7 (Alpha) quickly established itself as the predominant strain in the United Kingdom (UK) [3]. In the second wave in South Africa, the B.1.351 (Beta) variant, which was discovered in October 2020, emerged as the dominant strain [4]. In a similar vein, variation P.1 (Gamma) was discovered in Brazilians traveling to Japan in January 2021 [5], resulting in the reemergence of infections in Manaus, despite the country's high rates of previous infections [6]. A significant increase in cases was caused by the variant B.1.617.2 (Delta), which was discovered in December 2020. This variant was the cause of a second wave of cases in India [7] and an outbreak of infections in various places in the US [8]. SARS-CoV-2 spike protein mutations altered the efficiency of protein binding and immune responses, yielding more invasive, adaptable, and transmittable infections of the Alpha and Delta variants [9]. The Omicron variant swiftly took over and competed with other VOCs (Table 1).

The spike protein of the Alpha variant contains 9 mutations (Table 1). It has been reported that N501Y mutation is crucial in increasing its affinity to ACE-2 receptors, as well as viral adherence and capacity to penetrate the host cells. Beta variants also have 9 mutations (Table 1). The mutations; K417N, E484K, and N501Y are in the receptor binding domain (RBD) increasing the binding to ACE-2 receptors and transition [10]. Twelve key spike protein mutations (were identified in the Gamma lineage (Table 1). The Gamma variant shares three mutations with the Beta lineage but it is more transmissible [10]. The D614G mutation is found in all five lineages of interest, whereas all Alpha, Beta, Gamma, and Omicron variants contain the N501Y mutation in the RBD, which has been shown to enhance the risk of transmission by 40-70% [11].

The Delta's transmissibility was observed to have a rise by 97% and viral load compared with the wild type [12]. T19R, L452R, G142D, T478K, D614G, P681R, D950N, and del157/158 were the most noticeable spike protein alterations in the Delta variant (Table 1). The spike with the D614G, L452R, P681R, and T478K mutations confers enhanced transmissibility and pathogenicity [13]. Computational study revealed that major alterations in the RBD region of the Omicron may contribute to high binding specificity with ACE-2, leading to a higher rate of transmission and a significant impact on pathogenicity compared with Delta variant [14].

Omicron Variants and Subvariants

Omicron variant (B.1.1.529 or BA.1) has more than 30 mutations in the spike protein compared to other VOCs (Table 1) [13]. Higher binding affinity of Omicron to ACE-2 has been imparted by Q493R, N501Y, S371L, S373P, S375F, Q498R, and T478K mutations in RBD. Moreover, it has three amino acid substitutions; N679K, H655Y, and P681H near the cleavage site of furin, which increases the viral fusion with the host cells [15]. Following the BA.1 original variant of Omicron, various Omicron sub-lineages have arisen, including BA.1.1 (B.1.1.529.1.1), BA.2 (B.1.1.529.2), BA.3 (B.1.1.529.3), BA.4 (B.1.1.529.4), and BA.5 (B.1.1.529.5) (Table 1). BA.1, BA.1.1, BA.2, and BA.3 variants were discovered in South Africa in late 2021, which contained 21 common mutations.

The mutations in the RBD of those variants (Y505H, N786K, T95I, N211I, N856K, and V213R) significantly increased the pathogenicity [16]. Moreover, the N501Y and Q498R mutations are expected to improve ACE-2 receptor binding, and the H655Y, N679K, and P681H mutations are thought to improve spike breakup and virus transmission [17]. The BA.2 subvariant was discov-

ered in European countries in June 2022. BA.2 was then subdivided into various subvariants including BA.2.74, BA.2.75, BA.2.76, etc. It has been suggested that the prevalence of BA.2.75 may soon increase. When compared to BA.2, BA.2.75 has 9 additional mutations K147E, W152R, F157L, I210V, G257S, G339H, G446S, N460K, and R493Q (Table 1) that could be associated with immunological evasion and tolerance to antibody treatments [18].

It has been reported that the Omicron variants have distinct interaction patterns that are like those of the Alpha (N501Y) and Delta (L452R and T478K) variants. The RBD force is larger than the viral original strain due to the N501Y, Q493K/R, and T478K mutations in Omicron, leading to enhanced infectivity [19]. In early 2022, BA.4 and BA.5 were discovered in South Africa. Spike proteins of BA.4 and BA.5 are most like BA.2. BA.4 and BA.5 sublineages (referred to as BA.4/5), that demonstrated more immune evasion and subsequent dominance. The development of various other subvariants, including BA.4.6, BF.7, BQ.1, and BQ.1.1 created from BA.4/5, as well as BA.2.75.2 derived from BA.2.75 (BA.2.75.3.1.1.1) has led to a greater diversity in the spreading of SARS--CoV-2 [9]. BA.2.75.2 is spreading very quickly in India, Chile, England, Singapore, Spain and Germany [20].

BA.4 subvariant BA.4.6, BA.5 sublineages BF.7 and BQ.1.1, BA.2 sublineage BA.2.75.2, and BA.2 lineage recombinant XBB.1 are all recent Omicron variants. In a short period of time, BQ.1.1 and XBB.1 superseded BA.5 as the most prevalent variations globally [21]. Both BA.4.6 and BQ.1 have mutations that are R346T/N658S and K444T/N460K, respectively. In comparison to BA.2.75, the BA.2.75.2 subvariant showed R346T, F486S, and D1199N mutations. Concerns regarding potential immune escape have grown because of these mutations [22].

Omicron's BA.5 subvariant BQ.1 and its sub lineages BQ.1 have recently become common in worldwide infections. BQ.1 carries spike mutations such as K444T and N460K in critical antigenic sites [9]. BQ.1 also contains a double mutation (C28311U, C28312U) from the BA.1 [23]. A recombination between two BA.2 lineages, BJ.1 (BA.2.10.1.1) and BA.2.75 produced XBB and XBB.1 that contain the G252V mutation. XBB derived further to XBB.1.5, which has F486P and G252V key mutations. Greater transmission rate is conferred by the F486P mutation; however immune evasion is not boosted [24]. BF.7 and BA.5.2 have been spread in China. China's recent easing of its zero COVID policy is contributing to the current rise in outbreaks. The outbreaks are being driven by the new BF.7 SARS-CoV-2 strain, which has become a major strain in Beijing.

R346T substitution, a particular mutation in Omicron BF.7, is linked to the virus' capacity to resist neutralizing antibodies generated by vaccinations, especially those made in China [25]. Additional strains of SARS-CoV-2 continue to emerge on a regular basis. A subvariant of the highly contagious Omicron variant, XBB 1.16, was initially detected in January 2023. It has spread most widely in India but has been found in another 31 countries (https://www.ecdc.europa.eu/en/covid-19/variants-concern). By mid of August 2023, the latest strain, called BA.2.86 nicknamed "Pirola" was identified in the U.S. The strain is of particular concern because of its 36 spike amino acid mutations relative to the variant XBB.1.5 (the dominant strain earlier this year) and 38 such changes compared with variant EG.5 (the current most prevalent strain). This means it may behave very differently than the previous dominant variant of the virus. The CDC shows that COVID-related hospitalizations have increased to 14.3% and deaths increasing by 8.3%. They also predict hospitalizations due to the virus will continue through mid-September 2023 (https://www.ecdc.europa.eu/en/covid-19/variants-concern).

Distribution of Omicron Variants and Subvariants

With a prevalence of 76.6% as of September 4, 2022, BA.5 descendant lineages had the largest global incidence, followed by BA.4 with a prevalence of 7.5% [26]. There are several Omicron variants spreading in the US, each of them was responsible for < 6% of illnesses as of mid-December 2022. Among them are BF.7, XBB, BN.1, BF.11, and many others [27]. By the end of 2022, BQ.1.1 accounts for 34% of all cases in the US, followed by XBB.1.5, which accounts for 28% of all cases. However, XBB.1.5 remains under 5% in the UK [28]. The Omicron variant included. BQ.1.1, XBB.1.5, BQ.1, XBB.1.5 and BA.2.86 are the Omicron subvariants that have been spread (https://www.ecdc.europa.eu/en/covid-19/variants-concern). The collective data from Denmark, France, Germany, and UK indicate that the XBB.1.5 is becoming more prevalent.

In China, more than 2000 genomes were collected and sequenced as of December 2022, for locally acquired infections. Omicron lineages BA.5.2 and BF.7 dominated local infections (97.5%), according to the China CDC analysis. BF.7 was the main cause for the rise in instances in this nation and the infectivity frequency for this variant is high. Omicron BA.1 and BA.2 were the most common in the Netherlands, followed by BA.5. BQ.1 (including BQ.1.1) has been predominantly responsible for most infections. According to the data estimations, BQ.1 continues to be the dominant variant in the Netherlands for some time. Furthermore, the percentages of BA.2.75 and XBB, as well as XBB.1.5, are increasing. Currently, the EG.5 variant is estimated to be the dominant strain in the U.S. as it makes up the largest share of new cases of COVID-19 compared to other variants (https://vov-world.vn/en-US/news/who-declares-eris-covid-strain-a-variant-of-interest-as-cases-rise-globally-1223094.vov). On August 18, 2023, the CDC estimated EG.5 contributed to 20.6% of new infections and XBB.1.16, was responsible for more than 17% of new COVID-19 infections (https://www.usnews.com/news/health-news/articles/2023-07-07/new-covid-19-variants-giving-xbb-1-16-or-arcturus-a-run-for-its-money). Lately, XBB.1.5 and XBB.2.3 were responsible for 16%, and 13% of the new infections, respectively.

Effect of Vaccines and Antibodies against Omicron Variants of SARS-CoV-2

The most efficient method for preventing SARS-CoV-2 infection is vaccination. Companies have been accelerating the manufacture of vaccines in response to COVID's global spread and rapid emergence. A variety of vaccines have been developed by different companies, which led people to question the efficacy and safety of vaccines. Despite the vaccine's approval by the FDA, high rates of rejection were observed because of unknown complications and side effects [29]. COVID-19 vaccine has become mandatory in a number of countries [30]. Although this resulted in a higher vaccination rate [31], most of the population are partially vaccinated, which may contribute to the major reason behind emergence of new variants.

SARS-CoV-2's future infection is uncertain. Worldwide, vaccines are being developed and distributed, which can help prevent severe illnesses and hospitalizations. However, the virus continues to spread throughout the world, and new variants continue to appear [32]. Vaccines have been developed for a wide range of viruses for decades, and the COVID-19 pandemic has fueled even more research into vaccines [33]. New technologies, such as mRNA vaccines, have shown significant promise in providing protection against viruses. It is possible that vaccines will be developed in the future that protect against multiple strains of the same virus or even multiple viruses at the same time. As viruses can mutate and change over time, vaccine development will remain an ongoing process. Despite the 3rd and 4th boosters, vaccine protection against Omicron infection appears weak and transient. There is no doubt that boosters are useful, but the most important priority is to provide initial vaccines to those who have not been vaccinated.

The Moderna mRNA-1273 vaccine, the Pfizer-BioNtech BNT162b2 vaccine, the CoronaVacTM and Sinopharm COVID-19 vaccines, Russia's Sputnik V and EpiVacCorona vaccines, and AstraZeneca's ChAdOx1 vaccine are the COVID-19 vaccines that have been approved for vaccination of priority populations under an Emergency Use Authorization (EUA) [33]. Spike protein mutations have been paid to the changed antigen's potential for immune escape and antibody resistance, which is also the primary goal of vaccine development [34]. In comparison to other VOCs like Alpha and Beta, the Delta variant is more transmissible and resistant to the vaccine [35].

Vaccines are thought to decrease ongoing transmission by lowering virus loads. BNT162b2 and ChAdOx1 nCoV-19 vaccines showed lower risk of SARS-CoV-2 transmission or viral load in the infected vaccinated patients. Injections with the later vaccines were also associated with a lesser reduction in transmission of the Delta variant when compared to the Alpha variant [36].

The N501Y mutation, which is shared by Alpha, Beta, Gamma, and Omicron VOCs, has been linked to increased transmission and infection, decreased vaccine effectiveness, and decreased SARS-CoV-2's -ability to infect new species such as wild-type mice. Another significant mutation is the P681R, which changes the furin cleavage site and has been connected to the Delta variant's increased infections, transmission, and worldwide effects [37]. The spike protein domain, L452R, T478K, D614G, and P681R muta-

tions in VOCs/VOIs especially the Delta variant decreases the antibodies binding [38]. Over 30 nonsynonymous mutations in the spike protein of Omicron may decrease the effectiveness of antibody treatments and inhibit vaccine-induced immunity. Numerous antibodies such as Etesevimab, Bamlanivimab, Imdevimab, and Casivirimab were discovered not to be able to neutralize BA.2.75 [20]. It has been reported that N460K, R346T and K444T mutations in BQ.1 and BQ.1.1 variants and F486S mutation in the BA.2.75.2 up regulate the neutralization resistance [9].

From July to November 2022, BA.5 subvariant predominated, and it significantly outperformed earlier variations in terms of neutralization escape. The BQ.1.1 and XBB.1 variants were more resistant to the neutralization by antibody (BNT162b2) compared to BA.5 due to R346T mutation (Table 1) [21]. EG.5 has shown an increased prevalence, growth advantage, and immune escape properties, due to mutation over the old Omicron known as F456L (Table 1). Mutation supports their spread more than other virus siblings (https://www.who.int/emergencies/overview/tracking-SARS-CoV-2-variants). The CDC risk assessment stated that BA.2.86 may be more capable of causing infection in people who have previously been infected by SARS-CoV-2 or who have received COVID-19 vaccines (https://www.medicalnewstoday.com/articles/what-to-know-about-the-new-covid-19-strain-known-as-arcturus).

Restrictions in Relation to New Variants Emergence

To limit the spread of the virus regardless of variants, many countries implemented various restrictions and protective measures to slow the spread of the virus. These included mask-wearing, physical distancing, quarantine and isolation protocols, PCR testing, cancellation of public events and gatherings, and travel restrictions remain crucial in controlling the spread of the virus and mitigating the impact of variants [39]. These measures were indeed effective in reducing the spread of the virus and mitigating the impact of the first wave. The WHO and various governments lifted some restrictions in response to improving conditions.

Continued monitoring of infections, transparency in reporting cases, hospital admissions, and deaths, and robust surveillance of new variants are crucial to responding effectively to the evolving situation. Widespread vaccination remains one of the most effective tools in controlling the pandemic. Encouraging vaccination and ensuring equitable access to vaccines are critical steps in achieving herd immunity and reducing the severity of the disease. Information sharing, vaccine distribution, and collaborative efforts in research and development are vital to address the ongoing challenges posed by COVID-19 and potential future pandemics.

Table 1: Features of the new variant of concern (VOC) (Omicron: BA.1) and its sub-lineages (BA.1.1, BA.2, BA.32, A.4 and BA. 5)

Lineage	Name	Origin	Date	Spike mutations	Mutation and pathogenicity	Vaccine efficiency
B.1.1.7	Alpha	UK	Late 2020 [3]	7 Mutations: N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.2 Deletions: H69-V70del, Y144del.	N501Y, D614G, and P681H negatively influence viral transmission and N501Y.P681H reduce vaccine neutralization [37].	Neutralization by Moderna and Novavax but their efficiencies slightly decrease than common variant [40]. Reducing vaccine efficacy by N501Y mutations [37]
B.1.617.2	Delta	India	October 2020	7 Mutations: T19R, G142D, L452R, T478K, **D614G**, P681R, and D950N2 Delations: del157/158 [13].	Increasing transmissibility due to mutations as D614G, L452R, P681R, and T478K in the S-protein [13].	Reduction of vaccine efficiency against BNT162b2 (Pfizer-bioNTech) and ChAdOx-1 (AstraZeneca) vaccines comparing with Wuhan-1 wild type and B.1.1.7 [37].
B.1.351	Beta	South Africa	October 2020	9 Mutations: L18F, D80A, D215G, R246I, K417N, E484K, **N501Y**, **D614G**, A701V.1 Deletion: LAL 242-244 del [10].	K417N, E484K, and N501Y increase the receptor binding and transmission [10].	Containing 501Y.V2 in spike protein escapes from neutralization by BioNTech and Moderna [41].

P.1	Gamma	Japan/ Brazil	January 2021 [5]	12 Mutations: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F [10].	Sharing three mutations (K417N, E484K, and N501Y) with Beta variant [10].	Having N501Y like Alpha and Beta variants [37].
B.1.1.529 (or BA.1) (including all BA lineages.	Omicron	South Africa	Nov. 2021	30 Mutations: A67V, T95I, Y145D, L212I, 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, and L981F.3 Deletions: H69/V70, G142/V143/Y144 and N211 [13].	N440K, T478K, and N501Y cause higher transmission [19].	Mutations in RBD: K417N, E484A, and Y505H have negative effect on the antibody interaction [19].
BA.1.1	Omicron	South Africa,	Dec. 2021	Identical spike mutations in the five lineages (G142D, G339D, S373P, S375F, K417N, N440K, S477N, T478K, E484A, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, D796Y, Q954H, N969K) [16].	Mutations in BA1, BA1.1 Y505H, N786K, T95I, N211I, N856K, V213R, N501Y and Q498R [16, 17] and R346K in the spike protein increase pathogenicity [16].	L452Q, L452R and F486V spike mutations in BA.1 escape antibody neutralization.
BA.2Including(BA.2.75,BA.2.3.20, XBB)	Omicron	BA.2: South Africa,	BA.2: Dec. 2021.	BA.2:S371F, D405N, T376A, D405N, R408S, V213G G142D, PPA25-27De T19I [42].		G142D mutation escaping binding with mAbs [42].
BA.2.75	BA 2 sub-var. Omicron	BA.2.75: India	BA.2.75: January 2022 [18]	9 Mutations BA.2.75: K147E, W152R, F157L, I210V, G257S, G339H, G446S, N460K, and R493Q [18].		BA.2.75 contains K147E, W152R, F157L, I210V, G257S, G339H, G446S, N460K, and R493Q arising immune escape [18].BA.2.75.2 sub-var. with F486S mutation resisting neutralization by class I and II antibodies. R346T and K444T mutations escape from the neutralization by class III antibody [9]. It also contains R346T that enhances its immune escape [22]. BA.2.75.2: escaping immune recognition by R346T, F486S, and D1199N mutations [22].
BA.2.12.1	BA 2 sub-var. Omicron	BA.2.12.1: USA,	Dec. 2021	Key mutations are L452Q and S704L		L452Q and S704L facilitate escape from antibodies.
XBB	BA 2 sub-var. Omicron	XBB: USA	Late 2022,XBB.1.6 Jan 2023	Recombinant of BA.2.10.1 and BA.2.75 sublineages, i.e. BJ.1 and BM.1.1.1XBB.1 + S:E180V, S:K478R and S:F486P	XBB1.5: F486P and G225V mutations greatly enhance receptor binding and infection [24].XBB1.6: E180V, T478R, F486P	XBB1.5: F486P causes reduction in immune escaping [43].
BA.3	Omicron	BA 3: South Africa	Nov. 2021	BA.3: shares BA1 mutations including (A67V, H69del, V70del, T95I, V143del, Y144del, Y145del, N211I, L212del, and G446S; two (S371F and D405N) mutations from BA.2	BA3: G496S increases the binding to ACE-2 [17],	
BA.4(BA.4.6)	Omicron	BA 4: South Africa	BA 4: January 2022			BA.4 contains D405N and F486V mutations showing narrow neutralization breadths [44].
BA.5Including (BQ.1, BQ1.1, BF7, BF14)	Omicron	BA 5: South Africa	BA 5: Feb. 2022			BA.5 contains D405N and F486V mutations showing narrow neutralization breadths [44].

BQ 1	BA 5 sub-var. Omicron	BQ.1; Nigeria	BQ.1: July 2022			BQ.1: Key mutations are K444T and N460K, which reduce neutralization sensitivity by Moderna and Pfizer [9].
BF 7	BA 5 sub-var. Omicron	BF7: China	BF7: late 2022			BF7: R346T spike protein mutation enhances antibody evasion [44].
EG.5EG5.1	XBB.1.9.2Sub-var.Omicron"Eris"		EG5.1:July 2023	XBB.1.9.2 + S: F456LIncludes EG.5.1: EG.5 + S: Q52H(https://www.ecdc.europa.eu/en/covid-19/variants-concern).	F456L, N460K, S486P, F490S.	F456L mutation helps them spread more than other virus siblings.
BA.2.86	BA.2. Sub-var. Omicron "Pirola"		August 2023	36 Spike protein mutations, relative to putative ancestor BA.2.(https://www.ecdc.europa.eu/en/covid-19/variants-concern).	Mutations:I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, and F486P.	

Future Expectations

With the continuous evolution of the virus variants, expectations of variants occurrence, development of treatments, and vaccinations strategies will continue. Here are some future expectations based on the trends and knowledge available at the time:

On the Level of Vaccination Strategies: It is expected that efforts to vaccinate populations worldwide will continue and expand. Vaccines still provide strong protection against severe diseases and hospitalization, making it crucial for countries to continue increasing vaccine coverage in order to reach a point of herd immunity that reduces the spread of the virus [33]. Some variants have led to concerns about vaccine efficacy; the Delta variant led to breakthrough infections in vaccinated individuals. Vaccine manufacturers have been working on adapting vaccines to addressing the evolving variants. Booster shots and modified vaccine formulations may be developed to enhance protection against new variants [45]. We also expected that new variants would continue to appear since viruses can mutate easily and change over time, and hence increased transmission throughout the world. Therefore, research for vaccine development is ongoing, and additional boosters might be recommended when necessary. Scientists are still developing new COVID-19 vaccines, including those that offer improved efficacy, be more accessible, multivalent, or target emerging variants. Addressing vaccine hesitancy and increasing vaccine acceptance remains a significant challenge. Public health campaigns and educational efforts are expected to continue.

On the Level of Treatments: Research and development efforts are ongoing to create effective antiviral medications specifically designed to treat COVID-19 [46]. These treatments might help reduce the severity and duration of the illness. Monoclonal antibody therapies were authorized for emergency use in some countries to treat COVID-19, and their availability and effectiveness were expected to improve with further research and development [47]. Some treatments that were developed involved combinations of antiviral drugs, monoclonal antibodies, and other medications to target the virus [48]. Due to the emergence of new variants, the antiviral drugs may not be effective, leading to new wave of virus infection. Therefore, new antiviral agents may be needed or combination of antiviral drugs with monoclonal antibodies. As more was learned about the long-term effects of COVID-19, there was an expectation that healthcare providers would develop better strategies for managing and treating "long COVID" symptoms.

Long-COVID-19: While many people with COVID-19 recover within few weeks, some individuals, including those with mild or asymptomatic cases, continue to experience a variety of symptoms that can significantly impact their quality of life [49]. Long COVID-19 symptoms are characterized by a wide range of symptoms including fatigue, shortness of breath, chest pain, brain fog, difficulty concentrating, joint pain, headaches, loss of taste or smell, and heart palpitations [49]. These symptoms affect various systems in the body, including the respiratory, cardiovascular, neurological, and gastrointestinal systems. Long COVID-19 can affect individuals of all ages and can occur even in people who had mild or asymptomatic COVID-19 [49]. However, it appears to be

more common in individuals who had a more severe acute phase of the disease. There is no specific test for Long COVID-19, and it is largely a clinical diagnosis. Managing Long COVID-19 can be challenging, as there is no specific treatment, but may focus on relieving specific symptoms and improving the patient's quality of life. This may include medications, physical therapy, and mental health support [50]. Vaccination against COVID-19 is strongly recommended as it significantly reduces the risk of infection and its potential long-term consequences [50]. Vaccination has been shown to be effective at preventing severe illness and hospitalization.

Finally, ongoing research and clinical trials are crucial to identify new treatments and refine existing ones based on real-world data and patient outcomes. It's essential to note that the availability and effectiveness of treatments and vaccines may vary by region and be subject to regulatory approvals and changes in public health guidance. The situation with COVID-19 continues to evolve, and the best source for up-to-date information on treatments and vaccinations is health authorities like the WHO and the U.S. CDC.

Conclusion

It is crucial that countries worldwide take steps to prevent the spread of SARS-CoV-2. This mainly includes vaccination, which has proven effective in the prevention of transmission. It's important to investigate and understand the origin, pathogenesis, and treatment of the virus. Several key challenges remain, including vaccine hesitancy, and mutations of the virus. Addressing vaccine hesitancy through education, transparency, and community engagement is essential. SARS-CoV-2 vaccines were developed relatively late in the pandemic, but they remain valuable tools for controlling subsequent waves and preparing for future outbreaks. This pandemic and implemented prevention strategies provide a foundation for dealing with seasonal variations or potential future pandemics and encourage the global health organizations to implement effective response for future health crises.

References

1. Parums DV (2023) Editorial: The XBB.1.5 ('Kraken') Subvariant of Omicron SARS-CoV-2 and its Rapid Global Spread. Med Sci Monit. 29: e939580.

2. Campbell F, Archer B, Laurenson-Schafer H, Jinnai Y, Konings F, Batra N, et al. (2021) Increased transmissibility and global spread of SARS-CoV-2 variants of concern as at June 2021. Euro Surveill. 26.

3. Wise J (2021) Covid-19: New coronavirus variant is identified in UK. BMJ. 371: m4857.

4. Tegally H, Wilkinson E, Giovanetti M, Iranzadeh A, Fonseca V, Giandhari J, et al.(2021) Detection of a SARS-CoV-2 variant of concern in South Africa. Nature, 592: 438-43.

5. Fujino T, Nomoto H, Kutsuna S, Ujiie M, Suzuki T, Sato R, et al. (2021) Novel SARS-CoV-2 Variant in Travelers from Brazil to Japan. Emerg Infect Dis. 27: 1243-5.

6. Faria NR, Mellan TA, Whittaker C, Claro IM, Candido DDS, Mishra S, et al. (2021) Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil. Science. 372: 815-21.

7. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, Das M, et al. (2021) SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India. Microorganisms, 9.

8. Brown CM, Vostok J, Johnson H, Burns M, Gharpure R, Sami S, et al. (2021) Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings - Barnstable County, Massachusetts, July

2021. MMWR Morb Mortal Wkly Rep, 70: 1059-62.

9. Qu P, Evans JP, Faraone J, Zheng YM, Carlin C, Anghelina M, et al. (2022) Distinct Neutralizing Antibody Escape of SARS-CoV--2 Omicron Subvariants BQ.1, BQ.1.1, BA.4.6, BF.7 and BA.2.75.2. bioRxiv. 2022.

10. Zhou Z, Zhu Y, Chu M (2022) Role of COVID-19 Vaccines in SARS-CoV-2 Variants. Front Immunol, 13: 898192.

11. Wang Z, An J, Liu K, Yu P, Fang X, Li J, et al. (2022) A potent, broadly protective vaccine against SARS-CoV-2 variants of concern. NPJ Vaccines, 7:144.

12. Wang Y, Chen R, Hu F, Lan Y, Yang Z, Zhan C, et al. (2021) Transmission, viral kinetics and clinical characteristics of the emergent SARS-CoV-2 Delta VOC in Guangzhou, China. EClinicalMedicine, 40: 101129.

13. Dhawan M, Sharma A, Priyanka, Thakur N, Rajkhowa TK, Choudhary OP. Delta variant (B.1.617.2) of SARS-CoV-2: Mutations, impact, challenges and possible solutions. Hum Vaccin Immunother, 18: 2068883.

14. Kumar S, Thambiraja TS, Karuppanan K, Subramaniam G (2022) Omicron and Delta variant of SARS-CoV-2: A comparative computational study of spike protein. J Med Virol, 94: 1641-9.

15. Shrestha LB, Foster C, Rawlinson W, Tedla N, Bull RA (2022) Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission. Rev Med Virol. 32: e2381.

16. Kumar S, Karuppanan K, Subramaniam G (2022) Omicron (BA.1) and sub-variants (BA.1.1, BA.2, and BA.3) of SARS-CoV-2 spike infectivity and pathogenicity: A comparative sequence and structural-based computational assessment. J Med Virol, 94: 4780-91.

17. Desingu PA, Nagarajan K, Dhama K (2022) Emergence of Omicron third lineage BA.3 and its importance. J Med Virol, 94: 1808-10.

18. Hirotsu Y, Omata M (2023) Detection of the Omicron BA.2.75 subvariant in Japan. J Infect. 86: e5-e7.

19. Kim S, Liu Y, Ziarnik M, Cao Y, Zhang XF, Im W (2022) Binding of Human ACE2 and RBD of Omicron Enhanced by Unique Interaction Patterns Among SARS-CoV-2 Variants of Concern, Journal of Computational Chemistry, 44: 594-601.

20. Chakraborty C, Bhattacharya M, Dhama K (2022) Cases of BA.2.75 and recent BA.2.75.2 subvariant of Omicron are increasing in India: Is it alarming at the global level? Ann Med Surg (Lond), 84: 104963.

21. Miller J, Hachmann NP, Collier AY, Lasrado N, Mazurek CR, Patio RC, et al. (2023) Substantial Neutralization Escape by SARS-CoV-2 Omicron Variants BQ.1.1 and XBB.1. N Engl J Med. 388: 662-4.

22. Qu P, Evans JP, Faraone JN, Zheng YM, Carlin C, Anghelina M, et al.(2023) Enhanced neutralization resistance of SARS-CoV--2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2. Cell Host Microbe, 31: 9-17.e3.

23. Ren G, Langhorst BW, Patton GC (2023) The Omicron variant BQ.1* with mutations at positions 28,311 and 28,312 in the SARS-CoV-2 N gene have minimal impact on CDC N1 target detection. bioRxiv. 2023: 2023.01.26.525759.

24. Lasrado N, Collier AY, Miller J, Hachmann NP, Liu J, Sciacca M, et al. (2023) Waning Immunity Against XBB.1.5 Following Bivalent mRNA Boosters.

25. Velavan TP, Ntoumi F, Kremsner PG, Lee SS, Meyer CG (2023) Emergence and geographic dominance of Omicron sub-variants XBB/XBB.1.5 and BF.7 - the public health challenges. Int J Infect Dis, 128: 307-9.

26. Kumar V, Dhanjal JK, Bhargava P, Kaul A, Wang J, Zhang H, et al. (2020) Withanone and Withaferin-A are predicted to interact with transmembrane protease serine 2 (TMPRSS2) and block entry of SARS-CoV-2 into cells. J Biomol Struct Dyn, 2020: 1-13.

27. Gyebi GA, Ogunro OB, Adegunloye AP, Ogunyemi OM, Afolabi SO (2021) Potential inhibitors of coronavirus 3-chymotrypsin-like protease (3CL(pro)): an in silico screening of alkaloids and terpenoids from African medicinal plants. J Biomol Struct Dyn, 39: 3396-408.

28. El-Aziz Abd NM, Mohamed GS, Awad OME, El-Sohaimy SA (2020) Inhibition of COVID-19 RNA-Dependent RNA Polymerase by natural bioactive compounds: molecular docking analysis. Egyptian Journal of Chemistry, 64: 1989-2001.

29. Kashte S, Gulbake A, El-Amin Iii SF, Gupta A. COVID-19 vaccines: rapid development, implications, challenges and future prospects. Hum Cell. 34: 711-33.

30. Savulescu J (2021) Good reasons to vaccinate: mandatory or payment for risk? Journal of Medical Ethics, 47:78-85.

31. Christensen PA, Olsen RJ, Long SW, Snehal R, Davis JJ, Ojeda Saavedra M, et al. (2022)Signals of Significantly Increased Vaccine Breakthrough, Decreased Hospitalization Rates, and Less Severe Disease in Patients with Coronavirus Disease 2019 Caused by the Omicron Variant of Severe Acute Respiratory Syndrome Coronavirus 2 in Houston, Texas. Am J Pathol, 192: 642-52.

32. Haque A, Pant AB (2022) Mitigating Covid-19 in the face of emerging virus variants, breakthrough infections and vaccine hesitancy. J Autoimmun, 127: 102792.

33. Rauf Bhat SSMS, Magdy M. El-Sayed Ahmed, Mohamed I. Husseiny (2021) COVID-19 pandemic: outbreak, potential vaccines and medications. Russian Open Medical Journal, 10: 1-10.

34. Ou J, Lan W, Wu X, Zhao T, Duan B, Yang P, et al. (2022) Tracking SARS-CoV-2 Omicron diverse spike gene mutations identifies multiple inter-variant recombination events. Signal Transduct Target Ther, 7: 138.

35. Mistry P, Barmania F, Mellet J, Peta K, Strydom A, Viljoen IM, et al. (2021) SARS-CoV-2 Variants, Vaccines, and Host Immunity. Front Immunol, 2: 809244.

36. Eyre DW, Taylor D, Purver M, Chapman D, Fowler T, Pouwels KB, et al. (2022) Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. N Engl J Med, 386: 744-56.

37. Rathnasinghe R, Jangra S, Cupic A, Martínez-Romero C, Mulder LCF, Kehrer T, et al. (2021) The N501Y mutation in SARS--CoV-2 spike leads to morbidity in obese and aged mice and is neutralized by convalescent and post-vaccination human sera, Nature Communications, 13: 1-14.

38. Bian L, Gao Q, Gao F, Wang Q, He Q, Wu X, et al. (2021) Impact of the Delta variant on vaccine efficacy and response strategies. Expert Rev Vaccines, 20: 1201-9.

39. Han E, Tan MMJ, Turk E, Sridhar D, Leung GM, Shibuya K, et al. (2020) Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe. The Lancet, 396: 1525-34.

40. Shen X, Tang H, McDanal C, Wagh K, Fischer W, Theiler J, et al. (2021) SARS-CoV-2 variant B.1.1.7 is susceptible to neutraliz-

ing antibodies elicited by ancestral Spike vaccines, Cell Host & Microbe, 29: 529-39.

41. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature, 579: 270-3.

42. Kannan SR, Spratt AN, Sharma K, Goyal R, Sönnerborg A, Apparsundaram S, et al. (2022) Complex Mutation Pattern of Omicron BA.2: Evading Antibodies without Losing Receptor Interactions. Int J Mol Sci, 23: 5534.

43. Qu P, Faraone JN, Evans JP, Zheng YM, Carlin C, Anghelina M, et al. (2023) Extraordinary Evasion of Neutralizing Antibody Response by Omicron XBB.1.5, CH.1.1 and CA.3.1 Variants. bioRxiv. 2023

44. Cao Y, Yisimayi A, Jian F, Song W, Xiao T, Wang L, et al. (2022) BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. Nature, 608: 593-602.

45. Khoury DS, Docken SS, Subbarao K, Kent SJ, Davenport MP et al. (2023) Predicting the efficacy of variant-modified COVID-19 vaccine boosters. Nat Med, 29: 574-8.

46. Petty LA, Malani PN (2022) Oral Antiviral Medications for COVID-19. JAMA, 327: 2464.

47. Chi WY, Li YD, Huang HC, Chan TEH, Chow SY, Su JH, et al. (2022) COVID-19 vaccine update: vaccine effectiveness, SARS--CoV-2 variants, boosters, adverse effects, and immune correlates of protection. J Biomed Sci, 29.

48. Mikulska M, Sepulcri C, Dentone C, Magne F, Balletto E, Baldi F, et al. (2023) Triple Combination Therapy With 2 Antivirals and Monoclonal Antibodies for Persistent or Relapsed Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Immunocompromised Patients. Clin Infect Dis, 7: 280–6.

49. Davis HE, McCorkell L, Vogel JM, Topol EJ (2023) Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol, 21: 133-46.

50. Bramante CT, Buse JB, Liebovitz DM, Nicklas JM, Puskarich MA, Cohen K, et al. (2023) Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. Lancet Infect Dis, 23: 1119-29.