Review Article

Emerging Omicron Subvariants EG.5 and BA.2.86: Implications for COVID-19 Immunity and Surveillance

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The SARS-CoV-2 virus, responsible for the COVID-19 pandemic, has continuously evolved since its emergence. Among its variants, the Omicron lineage has become globally dominant, displaying a diverse range of sublineages. Two significant sublineages within Omicron are EG.5 and BA.2.8, which have gained attention due to their unique characteristics and potential implications. EG.5 is characterized by a constellation of mutations, including N501Y, L452R, and D614G. Similarly, BA.2.8 carries the L452Q and P681R mutations, which enhance its ability to evade antibodies elicited by prior infection or vaccination. Similar to those in EG.5, the clinical severity and impact of BA.2.8 on public health measures are still being assessed. These sublineages, with their unique genetic profiles and transmissibility characteristics, pose challenges to virulence response efforts. Continued surveillance, genomic sequencing, and research are essential to understand their behavior, assess their impact, and inform public health strategies accordingly. By a comprehensive synthesis of the literature, genomic data, and epidemiological insights, this study provides an analysis of Omicron mutations' transmission dynamics and clinical implications associated with these variants. The significance of variant surveillance in informing public health responses to the COVID-19 pandemic is underscored, highlighting the critical role of genomic sequencing in tracking viral evolution and guiding interventions. This manuscript aims to elucidate the mechanisms underlying variant emergence, assess vaccine effectiveness against emerging strains, and explore the broader implications for global public health. This study provides insights into vaccine-induced immunity and the potential impact of variants on vaccine efficacy. Overall, this communication aims to inform public health practitioners,

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policymakers, and researchers engaged in the battle against COVID-19, offering actionable insights to mitigate the spread of the virus and improve pandemic response strategies.

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I. Introduction

Background on the COVID-19 Pandemic

Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. SARS-CoV-2 belongs to the coronavirus family, which has a strong ability to infect humans[2]. Coronaviruses are enveloped, round-shaped viruses with club-shaped spike projections. They can sometimes be pleomorphic, with a diameter of 80 to 120 nm[3]. Their genome is composed of 29.8 to 29.9 kilobases of single-stranded positive-sense RNA, which encodes sixteen nonstructural proteins responsible for viral replication and transcription, such as RNA-dependent RNA polymerase, and several structural proteins, such as spike surface glycoproteins, nucleocapsid proteins, and envelope and matrix proteins[4].

Coronavirus is a zoonotic virus that can spread from animals to humans, with bats being its reservoir. COVID-19 utilizes angiotensin-converting enzyme II (ACE2) receptors for binding to the host cell surface. Coronavirus infections in humans have severe impacts on the upper respiratory and gastrointestinal tracts and are often associated with common colds or more severe bronchitis and acute pneumonia. It causes acute immune injury characterized by a high count of Th17 cells, a lower count, and high cytotoxicity of CD8+ T cells[5].

The emergence of COVID-19 was associated with a seafood wholesale market in Wuhan Province, which was involved in selling different types of wild animals. Several cases (> 50 people) of acute pneumonia due to COVID-19 were reported in China[6]. Soon after, the number of infected individuals increased to ten million, causing the COVID-19 pandemic. The spread of the virus occurs mostly through exposure to cough, sneezing, respiratory droplets, or aerosols, which mediate human-to-human transmission of SARS-CoV-2[7].

The widespread transmission of the disease has caused public health departments and government bodies to develop strategies for the cessation of viral spread, such as restrictions on travel, large-scale

curfews, isolation, and quarantine of infected individuals. The guidelines for a global pandemic were devised by the World Health Organization and consist of two steps: risk assessment and risk management.

Research and studies on the formulation of vaccines have started at different research institutes, universities, and medical facilities. Companies such as Pfizer, BioNTech, and Moderna have synthesized mRNA vaccines. Sinopharm and Sinovac synthesized the inactivated vaccines. These vaccines have helped build antibodies against COVID-19 and have stopped the spread of the virus[8].

Methodology

An extensive search was conducted using reputable scientific databases, including PubMed, ScienceDirect, and Google Scholar, to identify relevant studies published up to date. The search included MeSH terms: "SARS-CoV-2," "Omicron," "EG.5," "BA.2.86," "genomics," "epidemiology," "immunity," and "surveillance." The search results were screened by title and abstract to identify studies that focused on the genomic and epidemiological characteristics of the Omicron subvariants EG.5 and BA.2.86. Studies that did not meet the inclusion criteria or were not available in English were excluded.

Full-text articles of the selected studies were retrieved, and relevant data were extracted, including study design, sample size, genomic characteristics, epidemiological findings, and implications for COVID-19 immunity and surveillance.

The extracted data were synthesized to provide a comprehensive overview of the genomic and epidemiological characteristics of the Omicron subvariants EG.5 and BA.2.86. The findings were organized into themes and subthemes to facilitate analysis and interpretation.

Moreover, an analysis of genomic sequences of EG.5 and BA.2.86 obtained from databases like GISAID (Global Initiative on Sharing All Influenza Data) was conducted to identify specific mutations characterizing these subvariants and to understand their potential impact on transmissibility, immune evasion, and virulence. Furthermore, epidemiological data from sources such as the World Health Organization (WHO) were evaluated to track the prevalence, spread, and clinical manifestations of EG.5 and BA.2.86 infections globally. This incorporates insights from ongoing surveillance efforts, genomic sequencing initiatives, and laboratory studies to assess the effectiveness of existing vaccines and therapeutic interventions against these emerging subvariants.

The Dynamics of SARS-CoV-2 Variants

Coronavirus variants (CoVs) are members of the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae[9]. The World Health Organization (WHO) has classified SARS-CoV-2 variants into three main categories: variants of concern (VOCs), variants of interest (VOIs), and variants under monitoring (VUMs). The alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2), and micron (B.1.1.529) variants are the five reported VOCs[10].

The alpha variant (B.1.1.7) consists of eight mutations in the S protein that affect the conformation of the receptor-binding domain. Due to these mutations, faster syncytium formation occurs, which is involved in viral replication and the pathogenesis of severe COVID-19, leading to rapid viral kinetics and infectivity. This variant has been found to have enhanced binding to the ACE2 receptor and to suppress the innate immune response. Its first variant was reported in September 2020 and spread quickly, accounting for 95% of cases in England in 2021, with a death hazard of 55%. With the increase in other variants, the alpha variant vanished after September 2021[11].

The beta variant (B.1.351) mutations in the spike protein have been identified in the receptor-binding domain, N-terminal domain, and loop 2, creating a more open spike trimer[12][13]. These mutations resulted in enhanced binding to the ACE2 receptor and increased resistance to receptor-binding motif monoclonal antibodies. The B.1.351 variant was first reported in South Africa, as it became the most common variant infecting the population, with a 28.8% fatality rate. Single doses of vaccines, such as the mRNA-1273 vaccine, are highly effective against alpha- and beta-variant infections[14].

The gamma variant (P.1) has 17 mutations, three of which affect the S protein[15]. These mutations are involved in enhanced binding to the human ACE2 receptor, increased transmission, and increased viral load. It was first reported in November 2020 in Manaus, Brazil, and it has spread quickly to more than 36 countries. The gamma variant became a major variant in Brazil in approximately 96% of cases until it was replaced by the highly transmissible delta variant[16].

The B.1.617.2 variant had approximately 656 unique mutations, while the B.1.617.2.1 variant had 269 mutations. It has a mutation in the Furin cleavage site (FCS), which causes enhancement of fusion and severity of infection with uncommon symptoms. These mutations increase SARS-CoV-2 fitness and stability, leading to increased infectivity and transmission. This variant has high viral loads, increased resistance against neutralizing antibodies, and viral evasion against monoclonal and polyclonal antibodies prompted by a vaccine. It was first reported in October 2020 in Maharashtra, India[17].

The Omicron variant has approximately 60 mutations, half of which are present in the S protein. There were three to four times more Omicron S protein mutations than in previous VOCs. These mutations influence host immunity, viral entry, the infectivity rate, and viral transmission[18].

Omicron Variants

The Omicron variant had sublineages BA.1, BA.1.1, BA.2, BA.4, BA.5, BQ.1, BQ.1.1, XBB.1.5, XBB.1.16, EG.5, BA.2.86, and JN1. BA.1 has more than 50 mutations dispersed throughout the genome, which are present in the RBD and NTD regions of the spike protein[19][20]. All of these mutations impact antibody binding and immune escape. BA.1.1 is a sublineage of BA.1 with a genetic makeup similar to that of BA.1. It has 40 mutations that cause enhanced ACE2 receptor binding, increasing its infectivity. BA.1 and BA.1.1 displayed significant immune escape, making them potentially as dangerous as previous variants[21].

The BA.2 sublineage has 51 mutations dispersed throughout its genome, linking it with a higher secondary attack rate, high infectivity, and increased susceptibility to infection. BA.2 lineages have the potential to differentially affect antibody binding and antibody binding evasion and can modulate neutralization due to their location at the edge of the ACE2 binding footprint[22].

The BA.4 and BA.5 sublineages are more similar to BA.2, even though both BA.4 and BA.5 carry unique mutations. The BA.4 and BA.5 subvariants could spike globally because they could spread faster than other circulating variants. Both BA.4 and BA.5 could evade host immune responses and were not significantly affected by previous vaccines[23].

The BQ.1 and BQ.1.1 sublineages have mutations in the spike protein that cause antibody evasion[24].

The XBB.1.5 sublineage has a spike RBD mutation that causes enhanced binding to the host cell ACE2 receptor, resulting in increased transmission and infection rates.

The XBB.1.16 sublineage has two substitutions in the spike protein, one in the N-terminal domain and one in the receptor-binding domain. XBB.1.16 has enhanced ACE2 receptor binding, a greater growth advantage, greater infectivity, and a high ability to escape from humoral immunity[25].

The emergence of Omicron EG.5 and BA.2.86 in 2023

Omicron EG.5 (Eris) has been labeled a “variant of interest” by the World Health Organization (WHO), and the first report of this variant was made to the WHO in February. This variant has spread globally in the summer by doubling its reported sequence from approximately 8% on June 25 to approximately 17% on

July 23[26]. Approximately 88% of these samples belonged to a subvariant called EG.5.1, which carries an extra spike mutation[27]. Spike mutations of the EG.5 variant have improved its immune escape ability and increased its prevalence and growth advantage[28]. EG.5 is a rapidly growing variant in several areas of the world, causing an increase in hospital admissions in Japan, New Zealand, South Korea, the UK, and the US. The EG.5 lineage has been reported in 51 countries, and EG.5.1 is replacing the XBB.1.5 and XBB.1.16 lineages[29].

Omicron BA.2.86 (Pirola) is a derivative of Omicron BA.2. BA.2.86, nicknamed Pirola, is a highly mutated new Omicron sublineage of SARS-CoV-2 that was first detected in Denmark in July 2023. According to the CDC[30], this variant has been reported in 11 countries, including Israel, Denmark, the UK, the US, South Africa, Switzerland, Thailand, Australia, Japan, and South Korea. The World Health Organization is currently classifying BA.2.86 as a variant under monitoring due to 30 mutations in its genome[31].

Significance of Omicron EG.5 and BA.2.86

The Omicron EG.5 sublineage has mutations that are responsible for enhanced binding to cell receptors, neutralizing antibody evasion, and innate immune system evasion. The EG.5 variant descends from and resembles the still circulating XBB.1.9.2 subvariant, but with the addition of one FLip mutation, F456L, which switches the positions of the two amino acids on the spike protein labeled F and L. These mutations have adverse outcomes and are signaling that there is more to come with SARS-CoV-2[32].

BA.2.86 is a derivative of BA.2 and has 33 distinct spike mutations. Among the new mutations that BA.2.86 carries, 14 reside within an area of the spike protein called the receptor-binding domain, which binds to the receptors on host cells. Mutations in BA.2.86 have a direct effect on antibody evasion, disease severity, and infection capacity. Many of these new mutations also help viruses evade neutralizing antibodies (nAbs) induced by prior infection and vaccination[33][34].

The purpose of this study was to analyze the genomic and epidemiological characteristics and vaccine efficacy of the new Omicron variants EG.5 and BA.2.86. This study also highlights public health measures, global responses, and preventative strategies for these variants.

II. Epidemiological analysis

We have entered a new phase of the pandemic, and most nations have returned to regular life after the World Health Organization (WHO) formally proclaimed an end to COVID-19 as a worldwide public health

emergency on May 5, 2023. This announcement was caused by the pandemic's 12-month downward trend, increasing protection from highly effective vaccines, declining death rates, and reduced stress on overburdened health care systems. Although all of these findings are true, the Omicron variants are still mutating, and COVID-19 is still a threat to world health. The disease is still prevalent and causes a significant number of deaths per year.[35] A case–control or cohort study is usually performed in an epidemiologic investigation, which may also be experimental. In addition, descriptive studies group data by time, place, and person, while a structured method of problem-solving is used in epidemiology by confirming the existence of an epidemic and confirming the diagnosis, creating a case definition and compiling data on cases, analyzing data by time, place, and person, developing a hypothesis, conducting additional studies, if necessary, developing and implementing control and prevention measures, preparing and disseminating a public report, and evaluating control and prevention measures. The study of health and disease in certain populations' causes, manifestations, and distributions is known as epidemiology.

For instance, the WHO final report estimates that between July 31st and August 27, 2023, there were 1.4 million new COVID-19 cases worldwide, 55,728 hospitalizations, up to 38% and 40%, respectively—from the previous month to 1800 COVID-19-related fatalities. Similarly, according to recent research, a new wave of COVID-19, likely driven by EG.5, has begun globally. Omicron, which first appeared in November 2021, has a shorter incubation period than Delta and is considerably more effective at directly evading neutralizing antibody responses. Even people with very strong neutralizing antibody titers against the ancestral strain may not have much neutralizing action against Omicron. In response, scientists have created new booster vaccines that were approved in the autumn of 2022. Bivalent booster vaccines that include both the ancestral spike and the spike of the BA.5 Omicron subvariants have become the norm. These bivalent booster vaccines are more effective at providing protection against Omicron. Bivalent vaccines.

Spread and Prevalence

To date, the Global Initiative on Sharing All Influenza Data (GISAID) database contains 40,099 genome sequences that belong to EG.5 and its sublineages, which have been reported in 77 different countries as of September 26, 2023. According to the Centers for Disease Control and Prevention (CDC), EG.5 is now the predominant strain in the United States, accounting for 24.5% of SARS-CoV-2 cases, while EG.5.1 has been the predominant strain in China for the last three months. Additionally, a troubling lineage, BA.2.86,

which has been found in 22 nations and includes a number of mutations in its spike (S) protein linked to BA.2 or XBB.1.5 and is evocative of the emergence of the Omicron variant in late 2021, has generated serious worries.

The propagation and evolution of SARS-CoV-2 are ongoing. The Omicron EG.5 lineage, which differs from its ancestor XBB.1.9.2 in carrying an additional F456L mutation in the spike (S) protein, as well as its subvariant EG.5.1, which includes an additional Q52H mutation, has recently sparked controversy due to its increasing prevalence and prolonged immune escape capabilities. In addition, a variant known as BA.2.86 has drawn attention from scientists worldwide because, compared to BA.2, it has more than 30 amino acid mutations in its S protein, including more than 10 modifications in the receptor-binding domain (RBD), which is representative of the Omicron variant's debut in late 2021.

Transmission Dynamics

A mutation known as F456L is present in both EG.5 and FL.1.5.1, two XBB variant progenies that appear to aid in their propagation more than other viral siblings. Authorities have also been monitoring a brand-new, severely altered variant of the virus, known as BA.2.86. The prevalence of BA.2.86 is now combined with its distant ancestor BA.2.86 since it is still too rare to appear in the CDC estimates. The disease is thought to be spread particularly well by Omicron's subvariants. Compared with that of Delta, the original strain of Omicron was more contagious. One explanation is that Omicron has more than 30 mutations, many of which are thought to increase the risk of infection, on the spike protein of the virus, which connects to human cells.

Researchers are still investigating whether the most recent Omicron strains are more virulent than the ones that came before them. According to the data, the CDC believes that the original Omicron strain was generally less harmful than earlier variations. However, it has also been noted that spikes in cases may result in appreciable increases in hospitalizations and fatalities, as they did during the variant's spread at the beginning of 2022, when the estimated death rates rose to the same level as or even higher than they had been at the time of the Delta variant surge the previous autumn.

III. Genomic characteristics

The SARS-CoV-2 subvariant EG.5 (Eris) is derived from the XBB Omicron strain of SARS-CoV-2 and has a clinical presentation similar to that of other Omicron subvariants[36]. EG.5 (Eris) is one of the fastest-growing subvariants worldwide, possibly due to a mutation in the spike protein that increases its

transmission compared to that of other variants and subvariants (Table 1). Notably, compared with XBB.1.9.2, EG.5.1 carries two additional mutations, S:F456L and S:Q52H. F456L is a T22928C mutation characterized by a substitution at amino acid position 456 of the spike protein. The EG.5 variant descends from and resembles the still circulating XBB.1.9.2 subvariant, but with the addition of one FLip mutation, F456L. Its subvariant EG.5.1 carries a further spike mutation called Q52H. The role of Q52H is still unclear, but it appears to boost potency, as this subvariant has already overtaken its progenitor[29]. The EG.5.1 subvariant, which accounts for 88% of available EG.5 sequences, contains an additional spike protein mutation, Q52H[32].

BA.2.86, nicknamed “Pirola,” is another subvariant of the Omicron variant, which descends from the BA.2 strain that led to widespread COVID-19 cases at the start of 2022. The new strain has 34 more mutations than BA.2 and 36 more than XBB.1.5, according to an early analysis by Jesse Bloom, a computational virologist at the Fred Hutchinson Cancer Research Institute in Seattle, USA[37]. The emergence of Omicron BA.2.86 is concerning because many of these new mutations allow for the escape of neutralizing antibodies (nAbs) induced by prior infection and vaccination.

IV. Clinical manifestations and severity

In July 2023, the WHO labeled EG.5 as a Variant under Monitoring (VUM), which progressed to a Variant of Interest (VOI) by August 2023. Its incidence increased to 17.4% of COVID-19 cases by August 9, 2023[26][38]. The EG.5 lineage has been detected in 51 countries. In China, during the third week of June, EG.5 and its subvariants constituted 24.7% of COVID infections, a figure that increased to 45% within a month. In the UK, at the start of August, EG.5 and its subvariants were responsible for 14.6% of infections. The clinical data paint a vivid picture of EG.5′s rapid increase, which is driven by its heightened transmissibility attributed to a spike protein mutation. While current data suggest a low public health risk, its association with increased hospitalizations and mortality in the United States challenges previous assumptions regarding seasonality and endemism. The substantial growth advantage and reproductive (R) number suggest continued predominance of EG.5 and its sublineages in the coming months. Despite robust vaccination efforts, these variants pose considerable challenges to public health[32][39][40].

The most recent data, as of August 19, 2023, revealed an increase in COVID-19 cases, with a total cumulative hospitalization count of 6,244,216, indicating a recent increase of +14.3%. The cumulative death toll from COVID-19 reached 1,137,742, showing an increase of +8.3%. By August 19, 2023, a total of

1,525,084,650 bivalent SARS-CoV-2 vaccine doses had been administered in the United States. Notably, the most common causes of COVID-19 at that time were new SARS-CoV-2 Omicron variants, with EG.5 accounting for 20.6% of cases, FL.1.5.1 accounting for 13.3% of cases, and XBB.1.16 accounting for 10.7% of cases[26]. To date, there have been no reports that EG.5 leads to more severe cases of COVID-19, resulting in the WHO categorizing its potential risk for causing severe disease as minimal. The surge in COVID-19 cases and, consequently, hospitalizations is likely associated with EG.5 due to its increased transmissibility rather than its severity[32].

By September 5, 2023, 33 cases of infection with the SARS-CoV-2 variant BA.2.86 had been reported globally from nine countries[41]. Among 8,756 individuals tested in Denmark between July and August 2023, 876 had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. Notably, 10 (2.4%) of these cases were attributed to the new BA.2.86 variant, with other variants such as EG.5.1 and XBB.1.16 being more prevalent. The individuals affected, primarily women (7 out of 10), had a median age of 49 years, with 50% having preexisting comorbidities. The majority resided in the Greater Copenhagen region and had received at least three COVID-19 vaccinations, with some even receiving the BA.1 updated vaccine as their fourth dose. A few patients had a prior history of PCR-confirmed SARS-CoV-2 infection. Importantly, none of the BA.2.86 patients experienced severe illness. Conversely, the BA.2.86 variant's clinical data indicate a milder impact, as none of the patients in Denmark suffered severe illness. However, it is important to note that the overall clinical severity of the BA.2.86 variant has yet to be fully resolved, and its global trajectory remains uncertain.

V. Vaccine efficacy and immune responses to Omicron BA.2.86 and EG.5

The emergence of new variants of SARS-CoV-2, such as Omicron BA.2.86 and EG.5, has raised concerns about the effectiveness of COVID-19 vaccines against these strains. Since all currently available COVID-19 vaccines were created based on ancestral SARS-CoV-2 strains, it is crucial to determine whether they are protective against Omicron subvariants.

The ongoing development of the SARS-CoV-2 virus could result in evasion of both natural and vaccine-induced immunity. By comparing BA.2.86 to other Omicron variants that are currently in circulation, it is unknown whether BA.2.86 is capable of preventing NAbs[42]. According to Lasrado et al.[43], NAb responses to BA.2.86 were inferior to those to BA.2 but equivalent to or slightly superior to those of

recombinant versions that are currently in circulation, including XBB.1.5, XBB.1.16, EG.5, EG.5.1, and FL.1.5.1. The Omicron variant has 60 amino acid alterations, 37 of which have been identified in the S protein RBD, which interacts with the ACE2 receptor, and any of these modifications in the S protein RBD will modify binding epitopes to many existing antibodies[44].

When Walls et al.[45] combined the atomic structures of the Omicron spike protein with three antibody classes that were effective against all five variations of concern, the binding and neutralizing determinants were revealed. Furthermore, these structures identified a major antibody escape site, G446S. This modification increases resistance to antibodies binding to the receptor-binding domain, causing a local conformational shift at the binding interface[46]. According to a study by Gupta[47], the effects of Omicron variants on disease severity may be significantly influenced by structural deviation of the spike protein. [48] investigated whether structural modifications in Omicron spikes may help improve immune escape ability. These structural alterations may include the E484A, G446S, G339D, G496S, K440N, Q498R, S477N, S371L, and Y505H mutations. The N679K mutation adds amino acids to the cleavage site near furin, and a split in the spike protein enhances viral fusion and infection[18].

The EG.5 variant is better equipped to bind to the corresponding receptors on human cells and escape antibodies[29]. Compared with the parent subvariants, EG.5 has an additional F456L amino acid mutation in the spike protein. This mutation has been shown to prevent or decrease the neutralization of most XBB.1.5-neutralizing antibodies. The subvariant EG.5.1 has another spike mutation, Q52H[26]. The confidence in the ability of antibodies to escape is low because the immune escape results are based on work from one laboratory that used pseudotyped viruses. Additional laboratory studies are needed to further assess the risk of antibody escape[49].

BA.2.86 is less immune evasive than other XBB variants, which is consistent with the antigenic distances. Importantly, distinct from XBB variants, mAb S309 was unable to neutralize BA.2.86, likely due to a D339H mutation based on modeling. BA.2.86 had relatively high fusogenicity and infectivity in CaLu-3 cells but low fusion and infectivity in 293T-ACE2 cells compared to some XBB variants, suggesting potential differences in the conformational stability of the BA.2.86 spike protein[50]. Overall, this study underscores the importance of SARS-CoV-2 variant surveillance and the need for updated COVID-19 vaccines.

Although COVID-19 immunizations have remained effective against serious health conditions and deaths, as well as those caused by the widespread Delta variant, fading immunity and enormous

breakthrough infections due to viral diversity indicate that a third vaccine dosage or the development of new vaccines is needed[51]. At the FDA, the third dose appears to be critical since preliminary data show that three doses of the Pfizer-BioNTech mRNA vaccine counteract the Omicron form with a 40-fold decrease in virus amplitude, yet two doses are less potent[52].

VI. Public health measures and policies

Challenges, Response Strategies, and Adaptations

In August 2023, people were slightly excruciating as COVID-19 increased, after which the number of infected individuals peaked, with another variant known as BA.2.86. This particular variant was considered a 'variant under monitoring', and this variant had to be identified because it carries a number of different mutations. This difference in the mutations calls for further investigations. Among the mutations, the major difference 'variant of interest' is that it evolved from an Omicron strain that was previously detected, named B.A.2, a particular strain that dominated in 2022. The WHO (World Health Organization) has paid great attention to the variant, designating the particular BA.2.86 as a 'variant of interest', leading it to be a 'variant of concern' like EG.5. The number of hospitalizations might increase in these areas because of coinfection by the two variants, which is difficult to confirm because the systems that have been operating previously for surveillance are largely downsized or no longer operating. Many countries might also have detected different cases infected with these variants, which would have been unconfirmed and infected[53]. Recent studies have shown that subvariants such as EG.5 and BA.2.86, among which SARS-CoV-2 variants are present, continue to circulate among hosts, consciously shifting our perspective of the Covid-19 pandemic[29]. SARS-CoV-2 variants have significant characteristics, such as transmissibility, severity of disease, and immune cell ingestion, causing new infection surges. A number of strains, such as Alpha, Beta, Gamma, Delta, Omicron, and its subvariants, have also been diagnosed, showing that although the disease severity has not increased gradually, the transmissibility is peaking, which has led the virus to infect as many individuals, evolving with a successful strategy. The process underlying the evolution of the current virus, the evolution that has occurred throughout the pandemic, and the currently emerged SARS-CoV-2 variants that interact with the human immune system must be further studied.

To date, a number of vaccines against SARS-CoV-2 have been suggested to prevent severe disease and death. The prevalence of EG.5 and BA.2.86 has been increasing rapidly. To prevent this increase, certain

measures must be implemented, for example, wearing masks, at least in indoor settings, along with other restrictions. Assuming that the COVID-19 pandemic has not ended but has merely diminished, this has not been the case as the WHO has declared it a public health emergency, and the global community should be ready for any further infection surges in the near future, which may occur due to the rapidly increasing number of variants, calling for an emergency response to maintain their health.

In most cases, where the virus is present and the infection is self-limited, the diagnosis of coronavirus is unnecessary because the disease will naturally progress through its course. However, identifying an etiological agent may be important in certain clinical and veterinary settings or in epidemiological studies[54]. Diagnosis is important for locations where severe CoV outbreaks have occurred, such as in the Middle East, where MERS-CoV continues to circulate. This identification will guide the development of public health measures to control outbreaks. Another important factor for the diagnosis of patients with severe veterinary CoV-induced diseases, such as PEDV and IBV, is controlling the pathogen and protecting different food supplies. The method that has been adapted is RT–PCR, which has generally become the method of choice for the diagnosis of human CoV, as multiplex real-time RT–PCR assays have been developed that are able to detect all four respiratory HCoVs and could be further adapted to novel CoVs[55]. Serologic assays are important for epidemiological studies in cases where RNA is difficult to isolate or is no longer present.

Therapies against SARS-CoV-2, including other pathogenic coronaviruses, except for certain remdesivir, have not yet been approved. This particular therapy was approved in July 2020 by the European Medicine Agency (EMA)[56]. Although the provided therapies have not yet been approved, preventing the spread of SARS-CoV-2 infection is necessary. Several steps can be taken, including vaccines, therapies based on interferons, drugs, call therapy, repurposing of drugs that have been approved, monoclonal antibody therapies, and combinations of convalescent plasma and nonpharmacologic interventions[57][58][59]. BA.2.86 and EG-5 place a great financial burden on healthcare systems, and their outbreaks may be controlled by COVID-19 vaccination[60]. The main concern for researchers at these times is the ability to treat cases of COVID-19 irrespective of the variant type that it carries. A number of studies have also been conducted on these variants, considering that the specific Omicron strain is less infective but comparatively more contagious and may not be treatable with a low dosage and light medicine; for example, a single booster shot might not work in treating this strain, or even two consecutive doses of the vaccination might fail to prevent this variant; however, considering the severity of the disease, this might work out with these vaccinations, and they have the ability to lessen fatalities. People are

vulnerable to this variant even when they are not immunized, are elderly individuals with low immunity, or have parallel underlying conditions. The vaccines developed for the Omicron variant appear to be ineffective, while the panarbovirus vaccines are more convenient and promising[61][62].

Different vaccines have been developed for individuals infected with the coronavirus and its variants, and these vaccines work to protect people from illnesses by inducing humoral and cellular immune responses. Studies have shown that antibody neutralization may completely erase the T-cell-mediated response, as this is a complete protective measure. The Omicron variant is probably very highly resistant, and it also neutralizes the antibodies that were induced by the existing vaccines for coronaviruses; these properties may limit the efficacy of the available vaccines and therapies. Many booster shots are thought to be a barrier to the spread of the Omicron variant, but further studies are required to determine their durability[63][64]. The virus has evolved successfully, and the development of new vaccination systems, which may include mutation resistance, variant certainty, and universal vaccines, is needed to monitor the ongoing surge of coronavirus patients[65].

Many different therapies have been discovered, and two distinct drugs that have synergistic effects and antagonistic effects have been identified[66]. This therapy is called combination therapy and has multiple additive effects, aided by multiple targeting pathways in the replication process. However, despite synergistic effects, combination therapy cannot provide certain results, but it can eventually lead to a good quality of life and prolonged drug resistance due to the increased efficacy of therapeutics. Scientists have multiple experiences while treating viral diseases, and they have also shown good results; recent results show a reduction in SARS-CoV-2 load[66][67][68]. Combination therapy has become an effective way to treat different viruses because it targets specific viral processes, such as the polymerase (RdRp) and protease (Mpro) processes of the SARS-CoV-2 strain[69]. Combination therapy with monotherapies has been very popular among scientists, and there are many ongoing studies on this topic, but only some of them have been of use. The pandemic has been increasing daily and needs to be gradually reduced; furthermore, this can be achieved by antiviral drugs that have been approved by the FDA for efficacy while working against SARS-CoV-2. A high-risk group may be approached for accessing COVID-19 patients to develop more appropriate and significant combination therapies.

Previously, when the Omicron variant was not detected, another virus known as the delta variant, SARS-CoV-2, was known to be the most infectious, with a 40-60% greater percentage than that of the alpha variant. However, there is another strain that is more dangerous and infectious than the initial strain known as the Wuhan strain. This strain is twofold more infectious, and the airways of patients have more

viral particles from this strain. There are currently several studies on this topic, including a Chinese study in which the virus concentration was more (1000-fold greater) than that of other strains[67][68]. The WHO has reported that different variants are the fittest versions for current strains affecting people; however, it has declared the delta variant to be the fittest version of SARS-CoV-2[70]. A study recently identified Omicron as a more transmissible strain than Delta because of decreased vaccine effectiveness and increased infectivity due to mutations in the RBD and S protein[71]. The fight against COVID-19 variants demands an adaptive approach to public health. This must include the rapid development and deployment of vaccines, strategic use of NPIs, effective strategies, and surveillance systems with robust testing. However, due to the ever-changing nature of the virus, there is a great challenge to public compliance, and there is a need for global cooperation to address a global health crisis. Increasing vaccination coverage is likely the most reliable method for controlling the spread of Delta and Omicron strains. Different organizations have worked on issuing guidelines for developments that focus on variants. These organizations include the FDA, UK, and WHO. Research on developing vaccines against particular strains that have distinct patterns is urgently needed.

VII. Preventative strategies and recommendations.

The rapid mutation of omic variants underscores the urgent need for preventive measures and public health strategies to avoid other pandemics. Recent studies have shown that the Omicron variant is 10 times more contagious and could pose a public health concern[72]. This concern is further strengthened by recent research by Shrestha, L., Foster, C., Rawlinson, W., Tedla, N., & Bull, R.[73], which showed that our preventive measures for original SARS-CoV-2 variants have been compromised. This study revealed a nearly 127-fold reduction in the efficacy of the Omicron vaccine. However, booster vaccines compensate for this decrease, with 35-fold lower efficacy against the Omicron variant[73]. Additionally, neutralizing antibodies can also be used against the antigenic shift of SARS-CoV-2 Omicron[74]. Broadly neutralizing antibodies can help overcome the SARS-CoV-2 Omicron antigenic shift[75]. Despite these solutions, current vaccines and monoclonal antibody therapies may not effectively cover all sublineages of the Omicron variant of SARS-CoV-2, threatening vaccine efficacy[76]. Therefore, comprehensive strategies to prevent reinfection with novel strains and accurate, timely detection of reinfection are necessary. Current SARS-CoV-2 vaccines are losing their efficacy against novel Omicron strains, but recently developed COVID-19 vaccines may contribute to disease control by maintaining Omicron variant-specific Fc-mediated effector mechanisms, despite the loss of neutralizing antibodies[77]. Booster mRNA

immunizations also provide a valuable avenue for enhancing vaccine adaptability in the evolving viral landscape. Researchers, practitioners, and policymakers should work cohesively to develop strategies against the transmission and immune escape of evolving SARS-CoV-2 Omicron variants.

The emergence of the Omicron variant's EG5 and BA has made it clear that continuous monitoring of new variants is crucial. This not only diverts our attention to the rapid emergence of new variants but also to how these mutations impact the transmission rate, severity, and vaccine effectiveness. Therefore, thorough multidisciplinary research is needed to investigate the potential health impacts of these new variants beyond acute infection.

The recently identified EG5 variant is predominant in the United States. Despite its rapid transmission rate, insufficient data are available to assess its severity compared to that of other variants. Limited data are available for the recently identified EG5 and BA2.86 variants. Moreover, better diagnostic tests and validation studies for rapid variant differentiation are needed to avoid misdiagnoses, ensure timely diagnosis, and prevent delayed interventions. However, studies are needed to assess how EG5 interacts with acquired immunity and elicits immune reactions. Additionally, BA.2 is dominant over BA.1 and BA1.1. However, compared to those of EG5, initial global surveillance data suggest that BA2.86 is less contagious and capable of immune evasion; however, its transmission dynamics are less explored.

Our knowledge of novel therapeutics for effective targeting of new omic variants is limited; therefore, reliable diagnostic tests that distinguish different omic strains in clinical trials evaluating potential therapeutics and rigorous validation studies that consider variant response and potential side effects are needed. Additionally, a framework for global genomic surveillance with technology and data transfer for novel Omicron strains and longitudinal studies tracking antibody levels and T-cell responses are essential for informed decision-making, especially in low- and middle-income countries.

VIII. Conclusion

The emergence of Omicron EG.5 and BA.2.86 variants in 2023 is a cause for concern, as these variants have a number of mutations that allow them to evade the immune system more effectively than other variants. This implies that they are more likely to cause reinfection in people who have already been infected with COVID-19, and they may also be more likely to cause severe disease.

It is important to continue to monitor these variants and to develop new vaccines and treatments that are effective against rapidly mutating Omicron strains.

As of 18 December 2023, the COVID-19 variants of interest include the XBB.1.5 lineage, classified under Nextstrain clade 23A, and the XBB.1.16 lineage, under clade 23B. Both are recombinants of sublineages BA.2.10.1 and BA.2.75, with XBB.1.5 featuring a notable breakpoint in the S1 region of the spike protein and additional mutations such as S:F486P, which it shares with XBB.1.9.1. The XBB.1.5.70 subvariant has the S:L455F and S:F456L mutations, indicating ongoing evolution. XBB.1.16 carries its own set of mutations, including S:E180V, S:K478R, and S:F486P, suggesting a similar yet distinct mechanism of interaction with the human ACE2 receptor. Documented since late 2022, these variants have undergone multiple risk assessments, reflecting the vigilance of the global health community in monitoring their impact and transmissibility.

Additionally, a record of all variants and their subvariants should be kept with new information about the genomic and epidemiological characteristics of these new variants, as well as their vaccine efficacy. Furthermore, improved surveillance and testing protocols should be implemented to detect and contain these variants as soon as possible. Finally, countries should collaborate and share data to better understand these variants and coordinate control measures. It is crucial to enhance surveillance protocols to effectively combat the spread of virus variants and to prepare for any unknown public health emergency. Improved testing methods should also be implemented to detect and quickly quarantine infected individuals. International collaboration is vital for understanding the nature of these variants, sharing data, and coordinating control measures effectively. This information will help public health officials develop strategies to control the spread of these variants and protect people from severe disease.

Figures

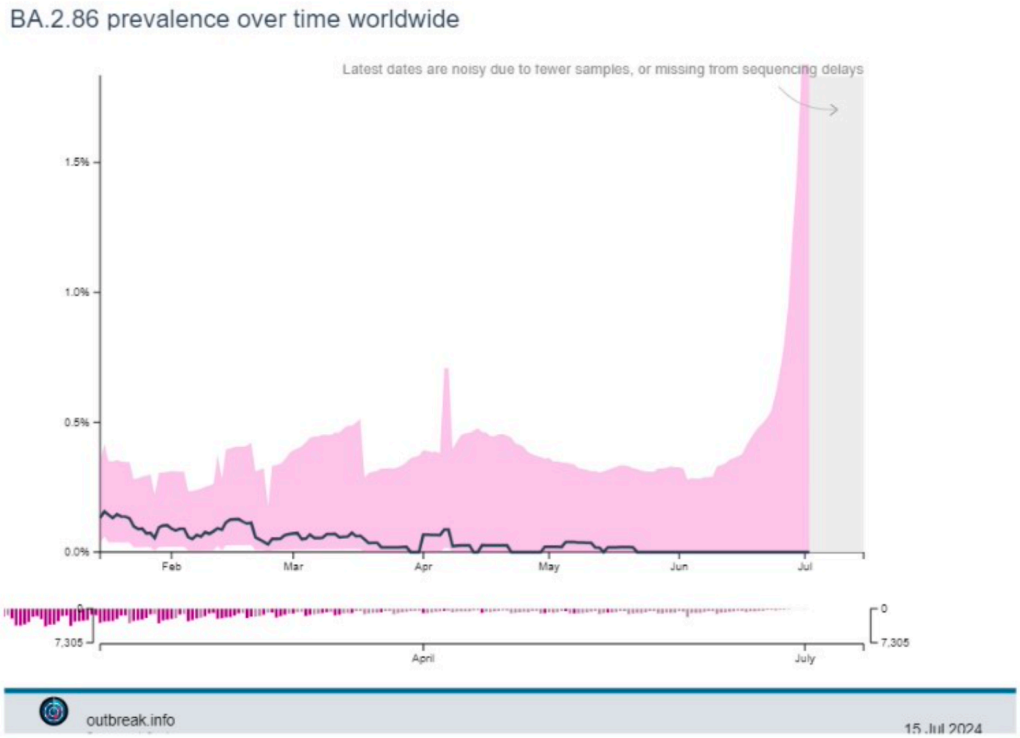

Figure 1.

doi.org/10.32388/8UJC2T.2

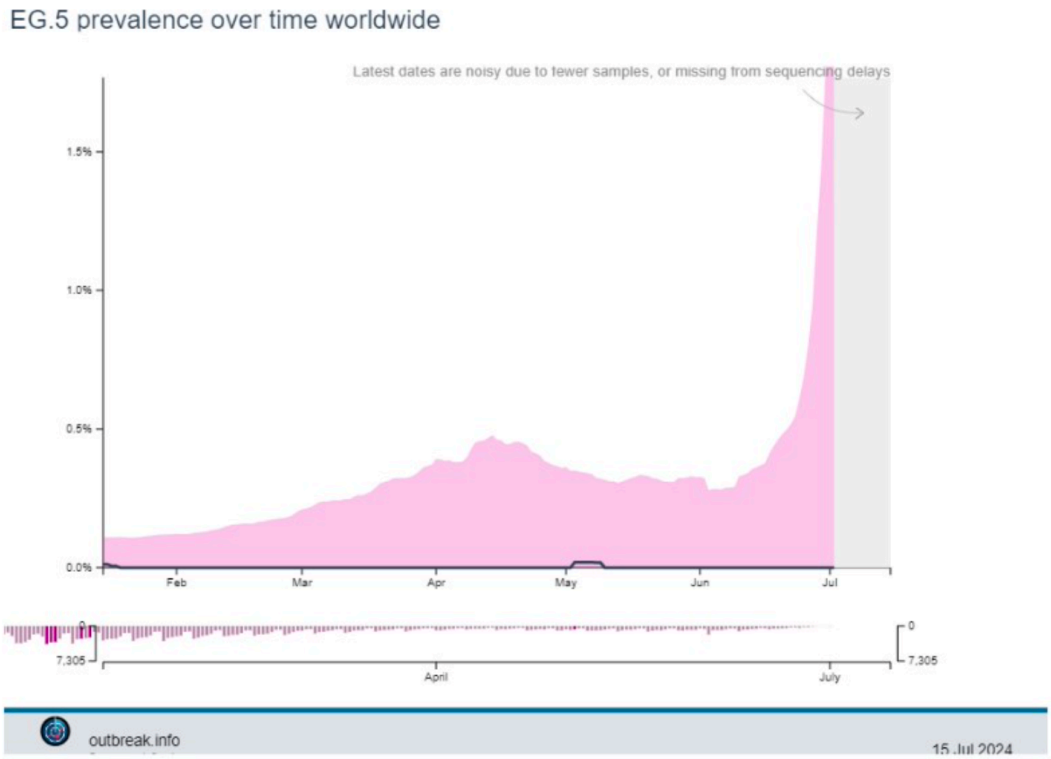

Figure 2.

Statements and Declarations

Author Contributions

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Data Availability

This review is based on previously published studies and publicly available data sources cited within the text. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Publicly available datasets analyzed during the study (e.g., from GISAID, WHO) are cited appropriately in the manuscript.

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