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Source: Environmental Health Insights, 17(1)

Published By: SAGE Publishing

URL: https://doi.org/10.1177/11786302231217805

The Many Mutations of the COVID-19 Variant: Current Perspectives on EG.5/Eris

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Environmental Health Insights
Volume 17: 1–5

DOI: 10.1177/11786302231217805

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ABSTRACT: Viral diseases pose a significant threat to public health around the world. SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was originally identified in Wuhan, China, in 2019. Throughout the epidemic, SARS-CoV-2 has continually changed genetically, giving rise to variants that are distinct from the original virus. SARS-CoV-2 has a high-frequency mutation rate, resulting in more genetic diversity. EG.5/Eris is a subvariant and descendant of Omicron, which remains the world's most prevalent coronavirus strain of current concern. The percentage of EG.5 recorded has steadily increased across the board. Epidemiological week 29 (17-23 July 2023) saw a 17.4% global prevalence of EG.5. Mutations in the virus's genome can cause false-negative results in molecular detection and cause increased transmissibility, morbidity, and mortality due to a reduction in vaccine efficiency. Furthermore, these changes in S-protein structure alter the neutralising ability of neutralising antibodies (Nabs), resulting in a reduction in vaccine efficiency. Therefore, all countries should take efficient infection prevention and control measures as per the guidelines of the world, continental, and their country's health organisations, along with vaccine and treatment investigations.

KEYWORDS: EG.5, Eris, SARS-CoV-2, COVID-19, Omicron, Coronavirus variants

RECEIVED: August 30, 2023. **ACCEPTED:** November 6, 2023.

TYPE: Review

FUNDING: The author received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Background

Viral diseases pose a significant threat to public health around the world.[1] SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was originally identified in Wuhan, China, in 2019. In practically every nation, the COVID-19 pandemic caused significant morbidity and mortality.[2-4] The most recent coronavirus variant pandemics are the third-highest cause of death in comparison to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV, 2003) and Middle East respiratory syndrome coronavirus (MERS-CoV, 2012).[5] From a slightly symptomatic sickness to a severe disease necessitating admission to an intensive care unit (ICU), the infection may present with a variety of clinical presentations.[3,6]

Viruses are continually changing owing to mutation, and changes in the SARS-CoV-2 virus have been seen all over the world as a result of evolution and adaptation processes (Figure 1).[1] Some mutations or combinations of mutations may give the virus a selective advantage, such as greater transmissibility or the capacity to avoid the host immune response, despite the fact that the majority of newly discovered mutations will not have a substantial impact on the virus's ability to spread.[7] Since the SARS-CoV-2 virus, the virus that causes COVID-19, has been spreading globally, variants have emerged and been identified in many countries around the world. SARS-CoV-2 has a high-frequency mutation rate, resulting in more genetic diversity.

According to reports, the environment, humans, and animals spread SARS-CoV-2. SARS-CoV-2 gets mutations when it spreads to new areas. These mutations help SARS-CoV-2 acclimatise better within the hosts and in new geographical locations. Different researchers[9-11] establish the existence of a causal link between the climatic conditions and the number of new positive cases and deaths. According to Menebo,[9] temperature and precipitation are correlated with the incidence rate of daily cases of COVID-19, at maximum and normal temperatures and positively associated with COVID-19 while precipitation is negatively associated. Chan et al[10] investigated that coronaviruses do not survive in high-temperature countries such as Malaysia, Indonesia, and Thailand, while the spread is intensive in low-temperature countries. Scientists must closely monitor and track SARSCoV-2 dynamics, mutations and genetic diversity in different areas to produce more active vaccines. Despite various research studies, the effects of the host's genetic variables and the genetic variations of SARS-CoV-2 remain unknown.

Characteristics of the Current Omicron EG.5 COVID-19 Variant

As modifications to the genetic code (either from genetic mutations or viral recombination) take place during genome replication, viruses like SARS-CoV-2 continue to change and evolve as they spread between people over time. Throughout the epidemic, SARS-CoV-2 has continually changed, giving rise to variants that are distinct from the original virus.[12] Alpha, Beta, Gamma, Delta, Epsilon, Eta, Iota, Kappa, Omicron, Zeta and Mu are some of the variants recognised by the Centers for Disease Control and Prevention (CDC). EG.5/Eris is a subvariant and descendant of omicron, which remains the world's most prevalent coronavirus strain.[7]

The spike amino acid profile of XBB.1.9.2, from which EG.5 is descended, is identical to that of XBB.1.5. The first instance of EG.5 was reported on February 17, 2023, and it was classified as a variant under monitoring (VUM) on July 19, 2023. The World Health Organisation (WHO) categorises

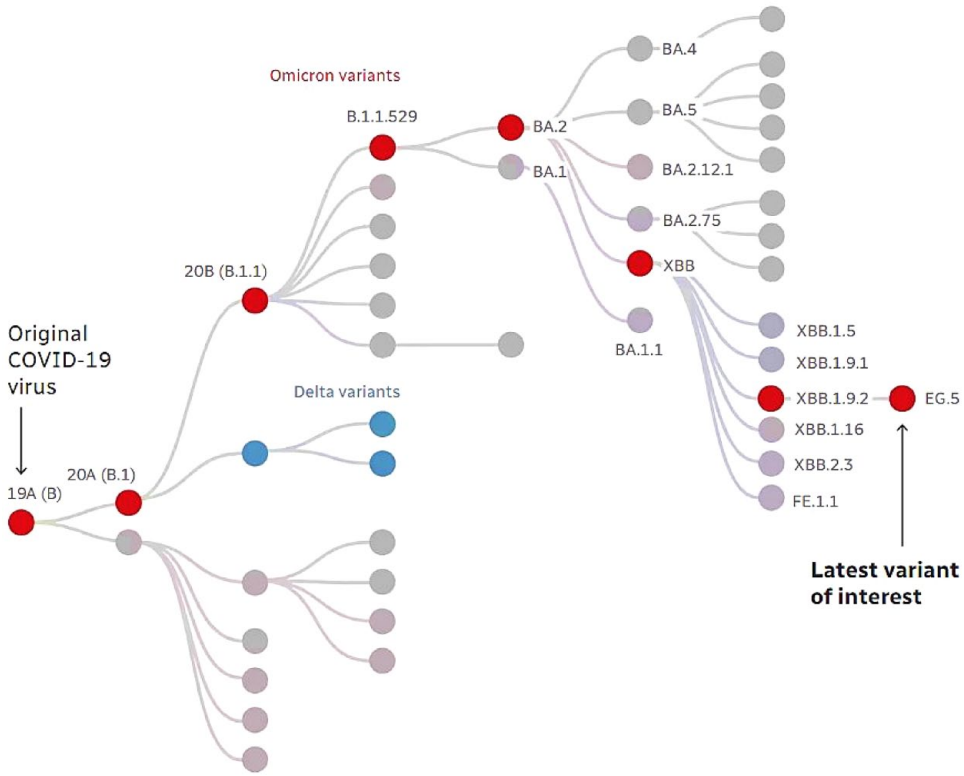

Figure 1. The many mutations of the COVID-19 variant.[8]

EG.5 and its sub-lineages as variants of interest (VOI) based on their risk assessment. Comparing EG.5 to its parent XBB.1.9.2 subvariant and XBB.1.5, the spike protein of EG.5 has an extra F456L mutation. The subvariant EG.5.1 of the EG.5 lineage contains an extra spike mutation Q52H and accounts for 88% of the sequences that are currently available for EG.5 and its offspring lineages.[13]

Health Threat of the Current Omicron EG.5 COVID-19 Variant

The percentage of EG.5 recorded has steadily increased across the board. Epidemiological week 29 (17-23 July 2023) saw a 17.4% global prevalence of EG.5. The global prevalence of EG.5 was 7.6% 4 weeks earlier (from June 19 to 25, 2023), which represents a significant increase.

As of August 7th, 2023, 7354 EG.5 sequences from 51 different nations had been submitted to the Global Initiative on Sharing All Influenza Data (GISAID). The largest portion of EG.5 sequences are from China (30.6%, 2247 sequences). The other countries with at least 100 sequences are the United States of America (18.4%, 1356 sequences), the Republic of Korea (14.1%, 1040 sequences), Japan (11.1%, 814 sequences), Canada (5.3%, 392 sequences), Australia (2.1%, 158 sequences), Singapore (2.1%, 154 sequences), the United Kingdom (2.0%, 150 sequences), France (1.6%, 119 sequences), Portugal (1.6%, 115 sequences) and Spain (1.5%, 107 sequences).[13]

Mutations of SARS-CoV-2 and Their Impact on Disease Diagnosis and Severity

The genetic diversity of SARS-CoV-2 affects the effectiveness of the molecular tests used for virus diagnosis. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) is a molecular test that uses primer probes that are precisely designed to bind to one of the highly conserved regions of the structural genes of SARS-CoV-2's envelope, nucleocapsid and RNA-dependent RNA polymerase (RdRp) genes.[14] Numerous diagnostic RT-PCR kits have been developed and are used as trustworthy assays to identify a variety of SARS-CoV-2 nucleotide sequences.[15]

Vogels et al[16] discovered some variations that include just one base and are less frequent in the binding sites of primers and probes. The GGG-to-AAC mutation at genome locations 28 881 to 28 883, which coincides with the first 3 CDC N gene forward primer 5′ ends, is the exception.[16] This emphasises how crucial it is for diagnostic assays to focus on various viral genomic locations.

One factor contributing to misleading negative results could be the sequence variation at the primer binding sites. The high rate of virus mutation may be the cause of the false negatives in RT-PCR assays. However, as stated, there is little chance that this probe's strains and variation with mutations in 2 targets will alter the sensitivity of an assay. As a result, it is more likely that mutations at the 3′ ends of the primers will influence the assay's sensitivity.[17]

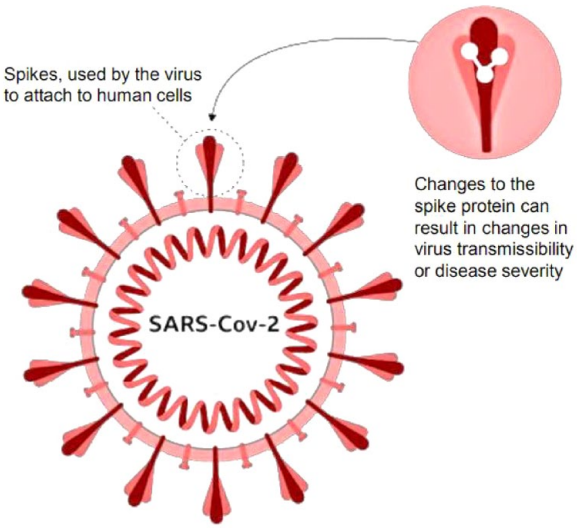

Figure 2. The genetic mutations in the spike protein contribute to the newly emerging SARS-CoV-2 variants.

Currently, the Omicron variant has about 50 mutations, most of which are in the spike proteins, which leads to an S-gene target failure.[18] This led to increased false-negative RT-PCR test results due to a 69-70del mutation, mainly in the PCR tests with S-gene target failure. Changes in viral nucleic acid and protein sequences jeopardise the accuracy of various in vitro diagnostic procedures. Negative findings will arise from a mismatch in the regions where primers bind if a virus mutation occurs in that region, which is crucial for a primer in RT-PCR.[19] Generally, mutations in SARS-CoV-2 have a great impact on disease diagnosis, along with increasing the severity of the variants.

Current Challenges in the Control of Newly Emerging SARS-CoV-2 Variants Using Vaccines

All these variants involve genetic mutations of the spike protein (Figure 2). Among these mutations, D614G (aspartate to glycine in protein position 614) is the most prominent. Mutations in the S protein and proteins comprising the RNA-dependent RNA polymerase were the most common. This mutation leads to different variant expansions.[20] Van Dorp et al[21] discovered that the S protein is responsible for nearly 80% of SARS-CoV-2 mutations. Because of its adaptability, the Orf1ab gene expresses a significant number of mutations in its regions, resulting in alterations in this protein and the structural and nonstructural proteins Nsp-6, Nsp-11 and Nsp-13, indicating that it is a heavy evolutionary agent. According to Abulsoud et al,[22] the mutations and new variants of SARS-CoV-2 cause increased transmissibility, morbidity, and mortality. They can also escape detection by escaping diagnostic tests, show lower susceptibility to therapy with antivirals and antibodies, and finally, reinfect previously recovered and vaccinated people.

Regarding the Omicron variant's mutation, the spike protein represents the primary target for current vaccines.[23] The SARS-CoV-2 vaccines that Pfizer-BioNTech developed – Moderna, Janssen, and AstraZeneca – are created on a spike (S) glycoprotein version and vary in efficacy against SARS-CoV-2.[19] The vaccine's efficacy against severe coronavirus disease was low for Omicron variants compared to previous SARS-CoV-2 variants after 1 month of vaccination. For the Omicron variant, the vaccine's effectiveness declined rapidly from the first to the sixth months after the initial vaccine series was finished.[24]

A study by Andrews et al[25] in England was designed to evaluate vaccine efficacy against symptomatic disease, which is triggered by the Delta (B.1.617.2) and Omicron variants, after being immunised with 2 dosages of BioNTech-Pfizer (BNT162b2), AstraZeneca (ChAdOx1 nCoV-19) or Moderna (mRNA-1273) vaccine after a supporter dosage of BNT162b2, or ChAdOx1 nCoV-1. The vaccine's efficacy against symptomatic disease tended to be lower for the Omicron than for the Delta variant. After the 2 doses (ChAdOx1 and nCoV-19), no response for the Omicron variant was reported after 20 weeks. In contrast, vaccine efficacy after 2 doses of BNT162b2 was 65.5% at 2 to 4 weeks, declining to 8.8% (95% CI, 7.0-10.5) after 25 weeks or more.[25]

The recent Novavax vaccine from phase III clinical trials of the NVX-CoV2373 against the 2 Omicron variants was evaluated, and the protective efficacy of 501Y. V1 (B.1.1.7) and 501Y. V2 (B.1.351) is apparently different. The effectiveness of 501Y.V.1 is more than 85%, and the efficacy of 501Y.V.2 is less than 50%.[26] This finding indicated that SARS-CoV-2 variants also challenge recombinant protein vaccines.[27] In general, the available data have indicated that the variant of SARS-CoV-2 may have the ability to resist vaccine-induced immunity (a reduction in vaccine efficiency due to these mutations). These studies suggest that we should try to update the therapeutic strategy and vaccine design against the challenges of variants.

New Perspectives on Future Approaches in Combating SARS-CoV-2

There are several emerging therapeutic approaches to combat COVID-19. One such approach is the use of antiviral drugs such as remdesivir (binds to the viral-RNA dependent RNA polymerase, inhibiting the replication of the virus by terminating transcription of viral-RNA),[28] favipiravir (destroys the conservative catalytic domain of RNA-dependent RNA polymerase [RdRp], interrupting the nucleotide incorporation process, thus interfering with the life cycle of the virus),[29] umifenovir (blocks the fusion of virus to the cell/endosome by interfering with the hydrogen bond network in the phospholipid),[30] Lopinavir/Ritonavir (inhibits the protein 3CLpro, required for cleaving poly protein into RNA dependent RNA polymerase and helicase,

helps in transcription of Viral RNA),[31] and hydroxychloroquine (increases the endosomal pH inhibiting the fusion of SARS-CoV-2 with the host cell membrane)[32] which have shown efficacy against SARS-CoV-2.

Another promising approach is the use of peptide-based vaccines, which have shown potential in preclinical studies. The same article also highlights the potential of nano-based approaches to combat COVID-19.[33] Other innovative approaches include the use of CRISPR-Cas13 technology to detect and destroy SARS-CoV-2 RNA in human cells and the use of monoclonal antibodies to treat COVID-19 patients.[34] Furthermore, scientists are studying the potential of convalescent plasma therapy, which involves transfusing plasma from recovered COVID-19 patients into those who are currently infected. This therapy has shown some promise in treating COVID-19 patients with severe symptoms.[35] It is important to note that these approaches are still in the experimental stage and require further testing before they can be widely implemented.

Recommendations for the Management of the Current Omicron EG.5 COVID-19 Variant

This genetic variation may impact the virus's properties, such as transmission (eg, it may spread more easily) or the severity of symptoms in infected individuals (eg, it may cause a more severe disease). Therefore, the experts stress the importance of taking preventative measures to safeguard yourself and stop the spread of COVID-19, such as (i) frequent hand washing with soap and water, (ii) staying home when ill, (iii) avoiding contact with sick people, (iv) improving ventilation, (v) wearing a mask in crowded indoor areas and finally (vi) covering coughs and sneezes.[36]

Conclusions

Throughout the COVID-19 epidemic, numerous SARS-CoV-2 mutations have been discovered both domestically and internationally. The omicron coronavirus, which is still the most common coronavirus strain in the world, is a subvariant and ancestor of the EG.5 coronavirus. A descendant of Omicron, EG.5, often known as 'Eris', is now thought to account for 17.4% of cases across the globe. Generally, mutations in SARS-CoV-2 have a great impact on disease diagnosis and severity, as well as vaccine efficiency. Future research and studies should focus on integrative methodologies that combine human and environmental efforts to better understand the various components of this disease system and provide suitable solutions to protect the public's health.

Acknowledgements

The author would like to thank all the scientists who are working to create a viable global healthcare system in light of the COVID-19 outbreak.

Author Contributions

Abayeneh Girma: Conceptualisation; formal analysis; project administration; supervision; writing – original draft; writing – review and editing.

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