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Editorial: A Rapid Global Increase in COVID-19 is Due to the Emergence of the EG.5 (Eris) Subvariant of Omicron SARS-CoV-2

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Abstract A new variant of SARS-CoV-2 has currently achieved global domination. EG.5 (Eris) was first reported by the World Health Organization (WHO) on February 17, 2023, and designated as a variant under monitoring (VUM) on July 19, 2023. EG.5 (Eris), and its sublineages, EG.5.1, EG.5.1.1, and EG.5.2, is a descendent lineage of XBB.1.9.2, which has the same spike amino acid profile as XBB.1.5 (Kraken). However, EG.5 (Eris) has an additional F456L amino acid mutation in the spike protein compared to these parent subvariants, and the subvariant EG.5.1 has another spike mutation, Q52H. Following risk evaluation by the WHO, EG.5 (Eris) and its sublineages were designated as a variant of interest (VOI) on August 8, 2023. In the US, the Centers for Disease Control and Prevention (CDC) provides two-weekly monitoring data on the incidence and mortality from COVID-19 and SARS-CoV-2 variants. The most recent CDC data for August 19, 2023, showed an increase in cases in the past two weeks, with hospitalizations for COVID-19 increasing by 14.3% and mortality from COVID-19 rising by 8.3%. In the US, the most common COVID-19 cases have been due to three new SARS-CoV-2 Omicron variants: EG.5 (Eris) (20.6%); FL.1.5.1 (Fornax) (13.3%); and XBB.1.16 (Arcturus) (10.7%). This Editorial aims to highlight the importance of rapid virus genomic sequencing and continued global SARS-CoV-2 surveillance to identify rapidly emerging SARS-CoV-2 Omicron variants, such as EG.5 (Eris).

Keywords: COVID-19 • SARS-CoV-2 • Omicron • EG.5 • Eris • Editorial

Since 2020, there has been an acceleration in the diversity and changing prevalence of variants of SARS-CoV-2 due to mutations in the spike protein of SARS-CoV-2, some of which have resulted in significant changes in the disease profile and outcome of COVID-19 [1,2]. The World Health Organization (WHO) began to identify SARS-CoV-2 variants of concern (VOC) and variants of interest (VOI) within one year, in response to the recognition of evolving genotypes, with the recognition of the Alpha (B.1.1.7), Beta (B.1.351), and Gamma (P.1) variants [3]. With the development and regulatory approval of the first vaccines for SARS-CoV-2, initial hope changed to uncertainty and concerns that vaccine development might not match the rapidity of changes in the virus and become ineffective [2,4,5]. Also, concerns were raised that vaccines may also be a driver of spike mutations in the virus [2,4,5].

A major landmark in understanding the 'evolution' of the SARS-CoV-2 virus was identifying the Omicron variant, which became a WHO VOC on November 26 2021 [5]. In only three months, Omicron had spread to become the dominant variant in several countries [5]. By October 2022, the WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution (TAG-VE) considered that the Omicron variant was the only circulating variant of concern (VOC) [6]. However, it soon became apparent that Omicron had a propensity for developing mutations in the spike protein, possibly driven by epidemiological evolutionary pressures, resulting in increasing numbers of subvariants that have been identified and are increasingly competing for prevalence [6,7]. By January 2022, the original Omicron strain BA.1 was replaced by subvariants that included BA.2, BA.3, BA.4, BA.5, XBB, and BQ.1 [7].

Rapidly, and unexpectedly, by the week ending January 21, 2023, the XBB.1.5 (Kraken) subvariant was identified as the cause of 49.1% of cases of COVID-19 in the US [8]. The Omicron XBB.1.5 (Kraken) subvariant is a sublineage of the XBB Omicron variant, a recombinant of two BA.2 sublineages, with an F486P mutation in the spike protein [8]. This new spike protein mutation may have explained the rapid dominance in the prevalence of this subvariant, resulting in immune escape to previous SARS-CoV-2 infection and possibly to the then-current vaccines [8]. However, XBB.1.5 (Kraken) did not dominate for long. Since January 2023, new subvariants of Omicron have emerged rapidly and with a global pattern of prevalence and dominance that appears to change within weeks [9]. This rapid rate of mutations and the emergence and changing prevalence of new Omicron variants is clearly shown in the twice-weekly monitoring data from the US Centers for Disease Control and Prevention (CDC) (**Table 1**) [9]

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Table 1. Centers for Disease Control and Prevention (CDC) estimates for Omicron variants of SARS-CoV-2 infection in the US. Week ending 19th August 2023 [9].

SARS-CoV-2 Pango lineage number	Percentage of cases of COVID-19 in the US
EG.5 (Eris) (subvariants: EG.5.1, EG.5.1.1, & EG.5.2)	20.6%
FL.1.5.1 (Fornax)	13.3%
XBB.1.16 (Arctura)	10.7%
XBB.2.3 (Acrrux)	10.6%
XBB.1.16.6	8.0%
XBB.1.16.1	5.9%
XBB	5.1%
XBB.1.5 (Kraken)	4.7%
XBB.1.9.1	4.1%
XBB.1.5.70	2.4%
EG.6.1	2.3%

SARS-CoV-2 Pango lineage number	Percentage of cases of COVID-19 in the US
XBB.1.6.11	1.9%
XBB.1.5.72	1.9%
XBB.1.9.2	1.8%
GE.1	1.8%
XBB.1.5.10	1.0%
FE.1.1	0.9%
FD.1.1	0.8%
CH1.1	0.8%
XBB.1.5.68	0.6%
XBB.1.5.59	0.4%
EU.1.1	0.2%
XBB.1.5.1	0.1%

Two-week estimates of variant proportions calculated as weighted estimates and Nowcast estimates. Modified from [9]: Centers for Disease Control and Prevention (CDC). COVID Data Tracker. August 19, 2023.
Available at: https://covid.cdc.gov/covid-data-tracker/#variant-proportions.

In the US, the CDC provides two-weekly monitoring data on the incidence and mortality from COVID-19 and SARS-CoV-2 variants [9]. The CDC uses genomic surveillance to identify and track SARS-CoV-2 variants with sequencing of patient samples through the National SARS-CoV-2 Strain Surveillance (NS3) program, combined with sequencing data from contracted academic and commercial laboratories to identify the SARS-CoV-2 lineages [9]. The most recent data for the two weeks ending August 19, 2023, showed an increase in cases of COVID-19, with total cumulative hospitalizations for COVID-19 of 6,244,216 and a recent rise of +14.3% [9]. Total cumulative deaths from COVID-19 of 1,137,742 showed an increase of +8.3% [9]. By August 19, 2023, the total number of bivalent SARS-CoV-2 vaccine doses in the US was 152,508,4650 [9]. As of August 19, 2023, the most common causes of COVID-19 have been due to new SARS-CoV-2 Omicron variants: EG.5 (Eris) (20.6% of cases); FL.1.5.1 (Fornax) (13.3% of cases); and XBB.1.16 (Arcturus) (10.7% of cases) (**Table 1**) [9].

'Eris' was the name of the mythical Greek Goddess of Discord, who may have started the Trojan War, and was mentioned in Homer's Iliad [10]. Eris is also the name of a dwarf planet in the solar system. The SARS-CoV-2 subvariant, EG.5 (Eris), is derived from the XBB Omicron strain of SARS-CoV-2 with a clinical presentation similar to other Omicron subvariants [11]. This subvariant is now the most prevalent cause of COVID-19 in the US, and its prevalence is rising in many other countries [11]. Worldwide, EG.5 (Eris) is one of the fastest-growing subvariants, possibly due to a mutation in the spike protein that increases its transmission compared to other variants and subvariants [11]. EG.5 (Eris), and its sublineages, EG.5.1, EG.5.1.1, and EG.5.2, is a descendent lineage of XBB.1.9.2, which has the same spike amino acid profile as XBB.1.5 (Kraken) [11]. However, EG.5 (Eris) has an additional F456L amino acid mutation in the spike protein compared to these parent subvariants [11]. Within the EG.5 (Eris) lineage, the subvariant EG.5.1 has an additional spike mutation, Q52H, representing 88% of the available sequences for EG.5 and its descendent lineages. EG.5 (Eris) was first reported by the WHO on February 17, 2023, and designated as a variant under monitoring (VUM) on July 19, 2023 [11]. Following risk evaluation by the WHO, EG.5 (Eris) and its sublineages (EG.5.1, EG.5.1.1, and EG.5.2) were designated as VOI on August 8, 2023 [11].

In addition to data from the US CDC, the WHO reports that the most significant number of EG.5 (Eris) sequences are currently from China (30.6%, 2,247 sequences) [11]. Countries with at least 100 sequences include the US (18.4%, 1,356 sequences); the Republic of Korea (14.1%, 1,040 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) [11]. The WHO reported that between June 19 to July 23, 2023, the reported VOIs and VUMs of SARS-CoV-2 with the F456L spike mutation, EG.5 (Eris) was most reported (49.1%), compared to XBB.1.16 (Arcturus) (4.88%), FL.1.5.1 (Fornax) (4.41%), XBB.1.5.10 (4.06%), XBB.1.5.72 (3.52%),

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EG.6.1 (3.26%), FD.1.1 (3.07%), EG.5.2 (3.06%), FE.1.1 (2.58%), FL.15 (2.47%), FE.1.2 (2.09%), XBB.1.5.70 (1.91%), GK.1 (1.83%), FE.1.1.1 (1.68%), XBB.1.5.59 (1.31%), XBB.1.5 (Kraken) (1.27%), GN.1 (1.26%), XBB.1.16.9 (1.15%), FL.1.5 (1.08%), and XBB.1.9.1 (1.07%) [11].

Worldwide, there has been a steady increase in the proportion of reported cases of EG.5 (Eris) [11]. The global prevalence of COVID-19 due to EG.5 (Eris) up to June 25, 2023, was 7.6%, which rose rapidly to 17.4% by August 9, 2023 [11]. However, at this time, the WHO has stated that, based on the available evidence, the public health risk from EG.5 (Eris) is similar to other VOIs and is low [11]. However, the WHO and the Technical Advisory Group on SARS-CoV-2 Evolution (TAG-VE) recommend that Member States continue to share information on the growth advantage of EG.5 (Eris) and provide sequence information weekly or monthly and conduct neutralization assays using human sera and regularly assess the impact of variants such as EG.5 (Eris) on the performance of COVID-19 vaccines [11].

From August 18, 2023, medical journals and the medical media began to note the WHO and CDC data on EG.5 (Eris) and its status as a new VOI associated with increased hospitalizations and mortality from COVID-19 in the US [12,13]. Notably, this surge in cases from EG.5 (Eris) appeared long before the expected autumn and winter surge in what was previously assumed to be an endemic and seasonal viral infection [12,13]. The rapid spread of EG.5 (Eris) indicates at least a moderate growth advantage and reproductive (R) number, which also shows that EG.5 (Eris) and its sublineages will continue to predominate in the coming months [12,13]. There is also concern regarding protection from infection by current vaccines, as EG.5 (Eris) has the spike protein mutation F456L [12,13]. In laboratory experiments, spike protein mutation F456L has resulted in immune evasion from most XBB.1.5 (Kaken)-neutralizing antibodies [14]. The EG.5.1 subvariant, which accounts for 88% of available EG.5 sequences, also contains an additional spike protein mutation, Q52H, which may have a similar effect on immune evasion [12,13]. However, there may be some hope regarding updated COVID-19 vaccine boosters, including monovalent XBB.1.5 (Kraken) boosters, which will offer protection against EG.5, provided they receive regulatory approval before the end of 2023 [15]. Although Moderna, Pfizer, and Novavax are all developing vaccines for this autumn aimed at Omicron XBB.1.5 (Kraken), the new boosters may not match EG.5 (Eris) [15]. However, in August 2023, Moderna announced that early clinical trials showed that its booster vaccine could effectively target the EG.5 (Eris) and FL.1.5.1 (Fornax) subvariants [15].

Conclusions

The importance of rapid virus genomic sequencing data, published online every two weeks by the CDC and also by the WHO, has recently been highlighted by clearly showing the rapid emergence and current dominance of XBB sublineages of the SARS-CoV-2 the Omicron variants EG.5 (Eris), and also of FL.1.5.1 (Fornax), and XBB.1.16 (Arcturus). Autumn and winter will soon arrive in the northern hemisphere, and booster vaccination programs are being planned for COVID-19. Therefore, these updates on emerging and dominant SARS-COV-2 variants will determine whether COVID-19 testing, treatments, vaccine development, and authorization will be effective against emerging SARS-CoV-2 variants, including EG.5 (Eris), FL.1.5.1 (Fornax), XBB.1.16 (Arcturus), and other new Omicron variants.

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