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Editorial: The XBB.1.5 ('Kraken') Subvariant of Omicron SARS-CoV-2 and its Rapid Global Spread

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Abstract In November 2021, the World Health Organization (WHO) first identified the Omicron variant of SARS-CoV-2, B.1.1.529, as a variant of concern (VOC). By early 2022, the Omicron variant and its five lineages, BA.1, BA.2, BA.3, BA.4. and BA.5, had become the predominant cause of COVID-19 in most countries. The Omicron XBB.1.5 subvariant is a sublineage of the XBB variant, a recombinant of two BA.2 sublineages, with the F486P mutation in the spike protein that increases infectivity due to increased binding affinity to the angiotensin-converting enzyme 2 (ACE2) receptor. On the week ending 21 January 2023, the XBB.1.5 subvariant caused 49.1% of cases of COVID-19 in the US. The rapid rise in the prevalence of this subvariant may be explained by immune escape to previous infection or vaccines, spike mutations in F486P, and increased affinity for the ACE2 receptor. Also, current booster vaccines may not provide adequate protection from infection from this subvariant, which has been named by the media as the 'Kraken' subvariant. This Editorial aims to present the current status of the XBB.1.5 subvariant of Omicron SARS-CoV-2 and the reasons for, and implications of, its rapid global spread.

Keywords: XBB.1.5 • Subvariant • Omicron • SARS-CoV-2 • Editorial

In November 2021, the World Health Organization (WHO) first identified the Omicron variant of SARS-CoV-2, B.1.1.529, as a variant of concern (VOC) [1-3]. In early 2022, the Omicron variant and its five lineages, BA.1, BA.2, BA.3, BA.4. and BA.5, became the predominant cause of COVID-19 in most countries [4]. From August 2022, Omicron became classified into five main lineages, including BA.1, BA.2, BA.3, BA.4, BA.5, and several sublineages including, BA.1.1, BA.2.12.1, BA.2.11, BA.2.75, and BA.4.6 [4]. Between July and December 2022, the BA.5 subvariant of the Omicron was the dominant subvariant causing COVID-19 in most countries and showed significant escape from antibody neutralization when compared with previous SARS-CoV-2 variants [5,6]. Within one year, several new Omicron subvariants have been identified in patients with COVID-19, including the BA.4 sublineage BA.4.6, the BA.2 sublineage BA.2.75.2, the BA.2 lineage recombinant XBB.1, and the BA.5 sublineages BF.7 and BQ.1.1 [5,6]. These variants have the R346T mutation in the spike (S) protein [5,6]. From late 2022, the BQ.1.1 subvariant spread rapidly to replace BA.5 as the dominant subvariant of SARS-CoV-2 [5,6].

The start of 2023 brings a new subvariant of the Omicron variant of SARS-CoV-2, known as XBB.1.5 [7]. The Omicron XBB.1.5 subvariant is a sublineage of the XBB variant, a recombinant of two BA.2 sublineages, with an additional spike receptor-binding domain (RBD) change, S486P [7,8]. The F486P mutation in the spike protein increases infectivity due to increased binding affinity to the human cell receptor for SARS-CoV-2, ACE-2 [7,8]. Currently, there are more than 600 Pango lineages of the Omicron variant of SARS-CoV-2, B.1.1.529, which means that there are now too many to identify alphabetically by name [8]. However, following the rise in cases of COVID-19 due to infection with the XBB.1.5 Omicron subvariant in the US, it has been named the 'Kraken' subvariant in the media [9]. 'Kraken' is the name of a legendary northern European giant sea monster, which was the topic of the apocalyptic poem by Lord Alfred Tennyson, published in 1830 [10]. The poem, 'The Kraken,' symbolizes the fear and doubt of advances in science in the 19th century, which might be realized when they were allowed to 'awake' and spread [10].

Below the thunders of the upper deep,
Far, far beneath in the abysmal sea,
His ancient, dreamless, uninvaded sleep
The Kraken sleepeth.....[10]

Aside from the emotive but increasingly popular name, the reasons for the rapid spread of this Omicron subvariant, XBB.1.5, and the predicted increase in cases may be explained by its mutation lineage [7,8]. The daily growth advantage between XBB and XBB.1.5, of approximately 12%, in the US, when compared with other circulating variants, may be explained by a

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difference in transmissibility of XBB.1.5 [7,8]. There is also concern that because XBB and XBB.1 have shown the highest levels of immune escape among all the Omicron sublineages currently identified and have shown significant reductions in the neutralizing capacity of serum from vaccinated individuals, XBB.1.5 might have these properties [7,8]. Also, the F486P mutation in XBB.1.5 has been proposed to enhance the binding of SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2) receptor, which may be an important factor in its transmission and infection rates [7,8].

On 6 January 2023, the US Centers for Disease Control and Prevention (CDC) identified the increased prevalence of the XBB.1.5 subvariant of Omicron in the US [11]. Data for Omicron sublineage XBB.1.5 are now displayed separately from XBB data on the CDC COVID Data Tracker, which identified that on the week ending 21 January 2023, the XBB.1.5 subvariant caused 49.1% of cases of COVID-19 in the US [12]. The CDC recognizes XBB.1.5 as a variant of concern (VOC) [12].

On 11 January 2023, a rapid risk assessment from the WHO noted the unusually accelerated rate of increase in cases of COVID-19 due to infection with the XBB.1.5 Omicron subvariant [13]. On 5 January 2023, the Technical Advisory Group on Virus Evolution (TAG-VE) of the World Health Organization (WHO) met to discuss the latest evidence on the XBB.1.5 subvariant and the risk to public health [14]. The opinion given by the WHO at that time was that based on the genetic characteristics and the early estimates of its rate of spread, XBB.1.5 might contribute to an increase in the incidence of COVID-19 in early 2023, but that estimates on transmissibility and prevalence were based only from the US [13,14]. The WHO reported that between 22 October 2022 and 11 January 2023, 5,288 sequences of the Omicron XBB.1.5 variant were identified in 38 countries [14]. Most of these sequences were from the US (82.2%), the UK (8.1%), and Denmark (2.2%) [14]. Therefore, on 11 January 2023, the WHO and the TAG-VE recommended that countries prioritize studies to address uncertainties relating to the spread of this subvariant, antibody escape, and disease severity of COVID-19 from infection with the XBB.1.5 subvariant [14].

On 13 January 2023, the European Centre for Disease Prevention and Control (ECDC) reported that the proportion of cases of COVID-19 due to XBB.1.5 in the European Union/European Economic Area (EU/EEA) was less than 2.5% during the final two weeks of 2022 [15]. The ECDC reports that while there are no current vaccine effectiveness (VE) estimates for XBB.1.5, it should be assumed that available vaccines are effective in preventing severe COVID-19 from currently circulating SARS-CoV-2 variants in Europe [15]. There are no specific data on the effectiveness of antiviral agents, such as remdesivir or nirmatrelvir/ritonavir for XBB.1.5. Mathematical modeling studies are ongoing by the ECDC to determine when XBB.1.5 can be expected to become dominant in the EU/EEA by causing >50% of infections [15]. On 11 January 2023, a technical briefing released by the UK Health Security Agency (UKHSA) reported that the XBB.1.5 subvariant of Omicron had a weekly growth advantage of 38.9% compared to the recently dominant BQ1.1 sublineage of Omicron in the UK [16].

The WHO and the CDC await data on transmission advantage and immune escape from previous infection and vaccination for XBB.1.5. However, on 18 January 2023, Miller and colleagues reported preliminary data that the BQ.1.1 and XBB.1 subvariants of SARS-CoV-2 escaped neutralizing antibodies more effectively compared to the BA.5 variant by factors of 7 and 17, respectively, after monovalent mRNA vaccine boosting [17]. Also, the BQ.1.1 and XBB.1 subvariants of SARS-CoV-2 escaped neutralizing antibodies more effectively than the BA.5 variant by factors of 7 and 21, respectively, after bivalent mRNA vaccine boosting [17]. Also, modeling studies using deep mutational scanning (DMS) profiles of evolution trends for BA.2.75 and BA.5 subvariants have shown that convergent RBD mutations could lead to evasion of immunity from infections with previous SARS-CoV-2 variants and that Omicron BA.4/BA.5-adapted COVID-19 vaccine boosters may not efficiently prevent infection from Omicron convergent variants [18].

Conclusions

As a new year begins, from January 2023, the XBB.1.5 ('Kraken') subvariant of the Omicron variant of SARS-CoV-2 is set to become the cause of the majority of cases of COVID-19 in the US. The rapid rise in the prevalence of this subvariant may be explained by immune escape to previous infection or vaccines, spike mutations in F486P, and increased affinity for the ACE2 receptor that binds SARS-CoV-2. Also, current SARS-CoV-2 booster vaccines may not provide adequate protection from infection due to the XBB.1.5 ('Kraken') subvariant.

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