



The SARS-CoV-2 Omicron recombinant subvariants XBB, XBB.1, and XBB.1.5 are expanding rapidly with unique mutations, antibody evasion, and immune escape properties – an alarming global threat of a surge in COVID-19 cases again?

Chiranjib Chakraborty, PhD^{a,*}, Manojit Bhattacharya, PhD^b, Hitesh Chopra, PhD^c, Md. Aminul Islam, MSc^{e,f,*}, Gutulla Saikumar, MVSc, PhD^d, Kuldeep Dhama, MVSc, PhD^d

Dear Editor,

Several subvariants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant have evolved very quickly and are also evolving continuously. Notably, some significant subvariants such as BF.7, BA.2, BA.2.75, BA.2.75.2, BQ, XBB, etc., are potentially expanding in the brief period of current times^[1,2]. These significant subvariants were circulating throughout the globe, eventually became dominant, and are creating surges in coronavirus disease 2019 (COVID-19) cases from time to time in different countries across the world. They have acquired some exclusive characteristics like enhanced immune evasion, higher transmissibility, additional spike mutations, distinct viral signatures, epidemiological, and clinical features, and are leading to vaccine breakthrough infections and reinfections^[3,4]. Recently, it has become very apparent that BQ, and XBB family members are noteworthy subvariants, which were described as the ‘variant soup’ by the scientists and are posing fears of unpredictable surges in some cases this winters^[5]. Researchers have tried to analyze and unfold the receptor-

binding domain (RBD) mutations over time^[6]. These new subvariants, BQ and XBB, are currently overgrowing in different countries, owing to which COVID-19 cases are increasing significantly in Europe, North America, India, Singapore, and other countries^[5,7].

Among the ‘variants soups’, XBB and its offspring, such as XBB.1 and XBB.1.5, are playing a significant role in the recent surges observed in different nations. XBB is a recombinant sublineage, and the offspring XBB.1 resulted from recombination between two lineages of BA.2, which are BA.2.75 and BJ.1 (BA.2.10.1) and sublineages (Fig. 1A). Researchers have reported that the subvariant is increasing very fast in the USA, Singapore, France, and India^[7]. These sublineages have several unique mutations that help them acquire antibody escape mechanisms and overpower the protection rendered by neutralizing antibodies and monoclonal antibodies (mAbs).

The newly emerged Omicron sublineages XBB and XBB.1 were first identified in India in August 2022. Subsequently, these spread rapidly in several Asian countries and are now predominant in Singapore and India, as well as other countries in Asia, and are rising worldwide. The spike (S) protein of XBB has 14 mutations additionally found in BA.2, precisely nine mutations in the RBD regions (Fig. 1B). XBB.1 contained an additional mutation (G252V) in comparison to XBB. The wide range of S-protein mutations in these two sublineages signifies major concerns about the compromising efficacy of existing vaccines and antibodies (mAbs, neutralizing antibodies) in use as therapeutics against COVID-19^[8]. The mutations may cause antigenic shifts in newly emerging sublineages that facilitate the vaccine escape phenomena^[5].

Previously, it was noted that the substitution mutation in Omicron S-protein R346T confers therapeutic antibody resistance^[3,9]. Researchers have also evidenced that the XBB and XBB.1 share the R346T and N460K mutations, holding the evolutionary convergence targeted to the escape of antibodies engaged to the S-protein regions^[10]. The mutations N460K and F486S show resistance to the RBD region’s mAbs (classes 1 and 2). Moreover, the mutations F490S, R346T, G446S, and V455P are considered for revealing resistance to the mAbs of RBD class 3. It has also been noted that the substitution of V445P in XBB and XBB.1 might employ a comparable effect as the mutation of K444T. This mutation is responsible for the steric hindrance as well as the breaking

^aDepartment of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, West Bengal, ^bDepartment of Zoology, Fakir Mohan University, VyasaVihar, Balasore, Odisha, ^cChitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, ^dDivision of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Bareilly, Uttar Pradesh, India, ^eAdvanced Molecular Lab, Department of Microbiology, President Abdul Hamid Medical College, Karimganj, Kishoreganj and ^fCOVID-19 Diagnostic Lab, Department of Microbiology, Noakhali Science and Technology University, Noakhali, Bangladesh

C.C. and M.B.: contributed equally for this study.

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*Corresponding author. Address: COVID-19 Diagnostic Lab, Department of Microbiology, Noakhali Science and Technology University, Noakhali 3814, Bangladesh. Tel: +91-9871608125. E-mail address: aminulmbg@gmail.com (M.A. Islam); Department of Biotechnology, School of Life Science and Biotechnology, Adamas University, Kolkata, West Bengal 700126, India. E-mail address: drchiranjib@yahoo.com (C. Chakraborty).

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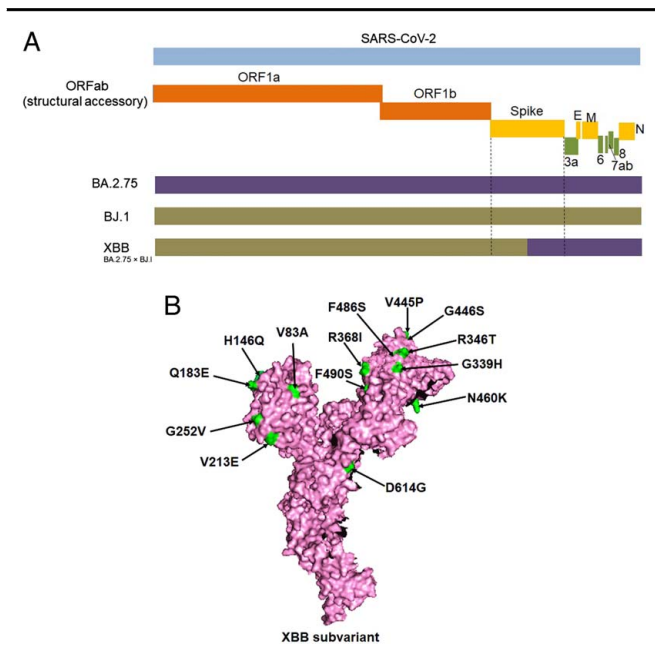


Figure 1. Origin and significant spike mutations of the XBB subvariant. (A) the schematic diagram depict the recombinant origin of the XBB subvariant, which was resulted from recombination between two lineages of BA.2, which are BA.2.75 and BJ.1(BA.2.10.1). (B) Significant spike mutations of the XBB subvariant including receptor-binding domain (RBD) mutations.

of the hydrogen bond with mAbs, resulting in the incapability of the antibody neutralization mechanism^[8].

R346S/K mutations were detected in the sublineages of Omicron; specifically, the mutation in the position of R346 has been suggested to show a superior impact in the context of the other Omicron mutations according to the amino acid interaction networks model developed by Miller *et al.*^[8]. However, the researchers have also pointed out that the mutation R346 has also been associated with the epitope network of S309 with other mutations^[8]. In the position of R346, R→K is observed as a conservative mutation. However, different researchers, such as Liu *et al.*^[11] and Cameroni *et al.*^[12], have assessed the R346K + Omicron and noted no significant extra reduction in antibody neutralization.

The XBB and its offspring have acquired some exclusive characteristics, such as enhanced immune evasion, higher transmissibility, and additional spike mutations, which helped in the natural selection of the XBB, making them ‘great escapist and more transmissible’, a significant subvariant candidate of the Omicron family. Uraki and colleagues have tried to understand the current humoral immunity status of the XBB and BQ.1.1 by performing an experiment using three different groups using these isolates. The first group was made with the persons ($n = 20$) who received third doses of the monovalent mRNA vaccines mRNA-1273 (Moderna) or BNT162b2 (Pfizer–BioNTech) both. The second group was made up of individuals who received four doses of the monovalent mRNA vaccine, mRNA-1273 BNT162b2. Another group was made up of individuals who received these three vaccine doses before the BA.2 infection ($n = 10$). The researchers found a 50% reduction in the neutralization titer of the plasma samples against XBB and suggested that the subvariant efficiently evades the recently acquired humoral immunity induced by natural infection or the mRNA vaccine. They also concluded that

clinical isolates of XBB have superior immune evasion capability compared to the subvariant of Omicron variants such as BA.2 and BA.5^[7]. Similarly, Kurhade *et al.*^[13] reported reduced neutralization activity of XBB.1 against the mRNA vaccine-induced immunity with different doses.

Recently, cases of the newly identified XBB.1.5 subvariant (an offshoot of XBB) have been seen significantly rising in the USA, and its prevalence is increasing in other countries; however, much is yet to be known about XBB.1.5. It is presently not clear whether it will lead to any high surge in COVID-19 cases or increased hospitalizations, and eventually might pose a global threat as a dominant subvariant outcompeting other previous subvariants in coming time^[14,15]. It was reported that this recombinant subvariant has one additional mutation, F486P (substitution) a rarely seen amino acid change, in the spike protein, compared to XBB.1. The rarely seen mutation in XBB.1.5 might enhance its infectivity and facilitate opportunities for further evolutionary gains and acquiring new mutations^[14]. XBB.1.5 has gained enhanced transmissibility and a strong immune evasion property. A recent report indicated that the robust ACE2 receptor-binding affinity and antibody evasion properties might significantly increase the transmissibility XBB.1.5^[16]. Antibody-evading mutations have allowed new lineages to overcome immune defenses gained from vaccination and previous infection waves with different variants and subvariants. One recent study has suggested that individuals who have been vaccinated with updated bivalent booster doses are better protected against the XBB, possibly including offspring such as XBB.1.5, than those who have not taken up such booster shots^[17].

In the current changing scenario, there is an urgent need to enhance surveillance and tracking of emerging novel Omicron subvariants, understand the protective levels of humoral and cellular immunity against these new subvariants, explore the beneficial effects of booster doses, and design newer and more efficacious vaccines and mAbs for the clinics for prophylaxis and treatment of COVID-9 patients. The global concerns of a surge in COVID-19 cases ahead need to be countered by promoting booster uptake and raising awareness against relaxed disease-mitigation measures and by adopting COVID-19 appropriate behavior and safety measures, including the wearing of face masks, hand washing, hygiene, and social distancing norms. Finally, we urge policymakers to implement adequate proactive control measures, formulate preparedness plans and appropriate infection prevention and control measures, and implement necessary strategies to prevent the transmission and spread of newly emerging Omicron subvariants so as to ameliorate the fears of a surge of a new COVID-19 pandemic.

Ethical approval

This article does not require any human or animal subjects to acquire such approval.

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C.C. and K.D.: designed the study. C.C., M.B., H.C., A.I.: made the first draft. C.C., K.D., G.S.: updated the manuscript. C.C. and K.D.: reviewed the final draft. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Md. Aminul Islam, COVID-19 Diagnostic Lab, Department of Microbiology, Noakhali Science and Technology University, Noakhali 3814, Bangladesh

Data statement

The data in this correspondence article is not sensitive in nature and is accessible in the public domain. The data is therefore available and not of a confidential nature.

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