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Microbiology Section

Genomic Characterisation and Epidemiology of XBB Recombinant Variant of Severe Acute Respiratory Syndrome Coronavirus 2 in Uttarakhand using Next Generation Sequencing: A Retrospective Cross-sectional Study

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ABSTRACT

Introduction: Following the surge of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in late 2019, there was an 11-month period of relative evolutionary stability. However, since late 2020, SARS-CoV-2 evolution has been characterised by the emergence of mutation sets impacting virus characteristics like transmissibility and antigenicity, termed "variants of concern." This shift likely responds to changing immune profiles within the human population. There is mounting evidence suggesting that post-vaccination serum is less effective in neutralising certain SARS-CoV-2 genotypes. XBB is a recombinant variant comprising sublineages BA.2.10.1 and BA.2.75 of the Omicron variant.

Aim: To investigate the genomic characterisation and epidemiology of the XBB recombinant variant of SARS-CoV-2 in Uttarakhand, India.

Materials and Methods: A retrospective cross-sectional study was conducted at the Viral Research Diagnostic Laboratory (VRDL Lab), Government Doon Medical College (GDMC), Dehradun, Uttarakhand, India. A total of 1,162 nasopharyngeal swabs received between September 2022 and February 2023 from various healthcare facilities were included for Next Generation Sequencing (NGS) of coronavirus. NGS was performed and all results were forwarded to the Indian SARS-CoV-2 Genomics Consortium (INSACOG) and the Indian Biological Data Centre (IBDC) for variant determination. Data collection occurred from March to April 2023, with data analysis following from May to June 2023. Statistical analysis was conducted using Microsoft Excel and Omnicalculator.

Results: Among the 1,162 processed samples, 41 (3.53%) were identified as the XBB variant of Omicron. Within the XBB variants, XBB.2 was predominant 22 (53.7%). Maximum XBB samples (38, 92.7%) originated from District Dehradun, Uttarakhand, India.

Conclusion: SARS-CoV-2 has been evolving and advancing with each new variant coming across. As XBB is impacting both previously infected individuals and those vaccinated, there is an imperative to develop new and efficacious vaccines against circulating variants to reduce associated risks of morbidity and mortality.

Keywords: Coronavirus variants, Coronavirus disease-2019 vaccines, Omicron variants

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by SARS-CoV-2 that was first identified in Wuhan City, Hubei Province, China, in December 2019, is still raging due to the emergence of the Omicron variant and its descendant sublineages [1,2]. The Omicron Variant of Concern (VOC), which first emerged in November 2021, has since emerged to be the most widespread and dominant variant worldwide [3]. On January 30, 2020, the first case of COVID-19 was reported in Kerala, India [4]. Subsequent lockdowns were announced on March 23, 2020, in Kerala and on March 25, 2020, across the nation [5]. Infection rates started to decline after September- October 2020 [6]. The daily reported cases peaked in mid-September 2020, exceeding 90,000, before falling to under 15,000 by January 2021 [7]. The second wave, commencing in March 2021, was markedly more destructive than the initial wave, leading to shortages of vaccines, hospital beds, oxygen cylinders, and other medical essentials in various regions [8]. The third wave hit India in January 2022, lasting until March 2022, with 22,487 cases nationwide as of March 2022 [9,10]. Since the onset of the pandemic, the coronavirus has undergone various mutations globally. Several COVID-19 patients have experienced reinfections due to the persistent nature of the pandemic [11]. With Omicron variants, reinfections are anticipated to rise due to diminishing immune responses from earlier Omicron infection and the ongoing evolution of Omicron variants [12]. Omicron's mutation enhances its ability to bind more strongly to Angiotensin-Converting Enzyme 2 (ACE2) host cell receptors compared to other identified variants [13]. Additionally, it evades many (though not all) of the virus- blocking or "neutralising" antibodies produced by vaccinated individuals or those exposed to other variants [14].

The original Omicron BA.1 was replaced by the BA.2 sublineage, leading to further sublineage evolution like BA.2.12.1, BA.2.75, BA.2.75.2, BA.4, and BA.5, with BA.5 holding the majority in several nations [15]. XBB was initially detected in mid-August 2022 in India and swiftly became predominant in India, Singapore, and other Asian regions [1]. XBB is a recombinant of the BA.2.10.1 and BA.2.75 sublineages [16]. Besides XBB and XBB.1, XBB.1.5 represents another Omicron subvariant [17]. The "X" denotes that these subvariants resulted from the recombination of two or more sublineages, specifically BA.2.10.1 and BA.2.75.2 [18,19].

Against this backdrop, present study aim was to explore the genomic characterisation and epidemiology of the XBB recombinant variant of SARS-CoV-2 in Uttarakhand, India. The study aims to investigate the epidemiological trends and genetic characteristics of recombinant variant identified at the VRDL lab, Government Doon Medical College, Dehradun, Uttarakhand, India.

This research will enhance our understanding of the genome of the newly emerged XBB recombinant variant of the coronavirus. It will contribute to the existing data on the epidemiology of various coronavirus variants circulating in Uttarakhand and adjacent regions during the study period. Given the rapid genomic alterations in the coronavirus and its impact on fully vaccinated individuals, a comprehensive comprehension of the viral genome and unique mutations in the circulating variants is crucial.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted at the VRDL lab, Government Doon Medical College, Dehradun, Uttarakhand, India from September 2022 to February 2023. Data collection took place from March 2023 to April 2023, and data analysis was conducted from May 2023 to June 2023. Ethics approval was obtained from the Institutional Ethical Committee (Approval No. GDMC/IEC/2023/39).

Inclusion criteria: All samples that tested positive for SARS-CoV-2 by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) across all age groups were included in the study.

Exclusion criteria: Samples included samples that tested negative for SARS-CoV-2 by RT-PCR were excluded from the study.

Sample size: A total of 1,162 upper respiratory tract samples (nasopharyngeal and oropharyngeal swabs) from all age groups were included in the study. These samples were received for SARS-CoV-2 sequencing during the study period and comprised samples from inpatients, outpatients, and community surveillance. Sample size calculation was not performed as this was a retrospective study, and all samples received during the study period for sequencing were considered the study population.

Study Procedure

Samples were collected in 3 mL viral transport media tubes following standard protocols for sequencing [20]. These samples were tested positive by RT-PCR in the set-up. Samples obtained from other hospitals were received in cryovials after testing positive for SARS-CoV-2 at Viral Research Diagnostic Laboratory (VRDL), Government Doon Medical College, Dehradun, Uttarakhand, India. RNA isolation was extracted using an automated magnetic bead-based extraction process in a Biosafety Level 2 (BSL) laboratory. RNA extraction was carried out using a 200 µL sample of viral transport media transferred to a 96-well deep well cartridge plate, following the manufacturer's instructions with the QIA Symphony instrument. Library preparation and sequencing were conducted using the Ion AmpliSeq™ library kit plus, according to the manufacturer's instructions. The Ion AmpliSeq™ SARS-CoV-2 Research Panel library was created, covering all possible serotypes and offering >99% coverage of the SARS-CoV-2 genome. The MagMAX™ Viral/Pathogen Nucleic Acid Isolation Kit was used for RNA isolation, and TaqMan™ 2019-nCoV Assay Kit v1 was used for quantification and normalisation of RNA.

Sequenced findings were analysed using the Torrent Suite™ Software with COVID-19 Annotate SnpEff, IRMA report, and Assembler Trinity SARS-CoV-2 plugins. Sequences from libraries with the highest concentration were used in FASTQ files and sent to the INSACOG for variant determination. Overall, the study followed a systematic approach in sample collection, processing, and analysis to identify SARS-CoV-2 variants in the study population.

STATISTICAL ANALYSIS

Microsoft Excel and Omnicalculator were used for the statistical analysis.

RESULTS

A total of 1,162 samples were processed for NGS of the coronavirus from September 2022 to February 2023. Out of the 1,162 processed samples, 41 (3.53%) samples were found to be the XBB variant of SARS-CoV-2 [Table/Fig-1].

Result of sequencing	n (%)
XBB and its sublineage	**41 (3.53)**
Omicron variant other than XBB	960 (82.62)
Sequencing failed	142 (12.22)
Lineage not detected	19 (1.63)

[Table/Fig-1]: Results of Next Generation Sequencing (NGS) of 1162 processed samples.

Among patients infected with the XBB variant of the coronavirus and its sublineages, 26 (63.4%) were males and 15 (36.6%) were females. In the case of both males and females, young adults were affected more (age group 21-30 years) as shown in [Table/Fig-2].

Age (in years)	Total XBB and its sublineages detected, n (%)	Males, n (%)	Females, n (%)
11-20	3 (7.3)	3 (7.3)	0
21-30	13 (31.7)	7 (17.07)	6 (14.7)
31-40	4 (9.8)	4 (9.76)	0
41-50	8 (19.5)	5 (12.2)	3 (7.3)
51-60	10 (24.4)	5 (12.2)	5 (12.2)
61-70	1 (2.4)	1 (2.4)	0
71-80	1 (2.4)	0	1 (2.4)
>80	1 (2.4)	1 (2.4)	0
Total	**41 (100)**	**26 (63.4%)**	**15 (36.6%)**

[Table/Fig-2]: Age and gender wise distribution of patients infected with XBB and its sublineages.

The XBB and its sublineages were identified from patients in three districts of Uttarakhand, India. 38 (92.7%) of patients were from district Dehradun, followed by 2 (4.9%) in Haridwar and 1 (2.4%) in Uttarkashi. Among the patients with XBB and its sublineages, 8 (19.51%) patients were vaccinated, 19 (46.34%) were not vaccinated, and the vaccination status was unknown in 14 (34.15%) patients. Among vaccinated individuals, 6 (75%) were vaccinated with Covishield, 1 (12.5%) was vaccinated with Covaxin, and 1 (12.5%) was vaccinated with Moderna.

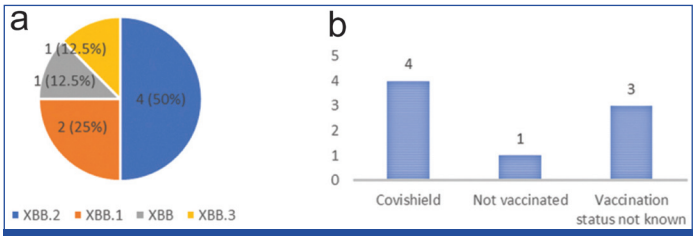
Eight (19.5%) patients were hospitalised, 31 (75.6%) patients were not hospitalised, while the hospitalisation status was unknown for 2 (4.9%) patients. All the patients with the XBB or its sublineages were symptomatic for SARS-CoV-2 infection. Five variants of XBB and its sublineages was found during the study period-XBB, XBB.1, XBB.1.5, XBB.2, and XBB.3. Majority of the patients 22 (53.7%) were affected by XBB.2, other variants are shown in [Table/Fig-3].

Omicron variant name (XBB and related lineages)	n (%)
XBB	9 (21.9)
XBB.1	5 (12.2)
XBB.1.5	2 (4.9)
XBB.2	22 (53.7)
XBB.3	3 (7.3)

[Table/Fig-3]: XBB and its variants detected in study population.

Eight hospitalised patients and their vaccination details are shown in [Table/Fig-4]. Two patients with XBB.2 and XBB.3 sublineages were reported to have died. Both patients who passed away were elderly males who had been hospitalised in the Intensive Care

Unit (ICU) for the management of severe COVID-19 disease. Death was not reported among the rest of the hospitalised patients during the study period. The genetic makeup of XBB, XBB.1, XBB.1.5, XBB.2, and XBB.3 lineages of the Omicron variant were studied, and the differences in mutations among the various lineages were analysed. [Table/Fig-5] depicts the differences in mutations in XBB and its sublineages. There were some mutations that were unique in the case of XBB, XBB.1, XBB.1.5, XBB.2, and XBB.3 lineages of the Omicron variant.



[Table/Fig-4]: (a) Details of hospitalised patients (n=8) affected with XBB and related variants. (b) Vaccination details of hospitalised patients.

XBB.3 is most reported from Tamil Nadu and least from Madhya Pradesh [21].

In present study, 13 (31.7%) COVID-19 positive patients infected with XBB and its sublineages were from the age group of 21-30 years, followed by 10 patients (24.4%) in the age group 51-60 years and eight (19.5%) from the age group 41-50 years. The age group least affected by the XBB variant and sublineages in present study were 61-70 years, 71-80 years, and >80 years with one patient (2.4%) each. In present study population, five variants of XBB and its sublineages were found-XBB, XBB.1, XBB.1.5, XBB.2, and XBB.3. Out of the 41 patients with XBB and its sublineages, 8 (19.5%) were hospitalised (four patients were affected with XBB.2, two patients with XBB.1, and one patient each with XBB and XBB.3 lineages of the Omicron variant), 31 (75.6%) patients were not hospitalised whereas hospitalisation status was unknown for two (4.9%) patients. The majority of the patients with XBB strains were not hospitalised signifying that the circulating XBB variant and its sublineages do not cause significant morbidity and mortality in the majority of the patients.

XBB		XBB.1		XBB.1.5		XBB.2		XBB.3	
Gene	AA	Gene	AA	Gene	AA	Gene	AA	Gene	AA
S	***Q94H***	***S***	***G252V***	S	R408S	***S***	***D253G***	***ORF1a***	***G82D***
ORF3a	***T2231***	S	R408S	S	K417N	S	R408S	***ORF1b***	***I1998V***
		S	K417N	***S***	***F486P***	S	K417N	S	F486S
		S	F486S	S	D614G	S	F486S	S	D614G
		S	D614G	S	Q954H	S	D614G	E	T9I
		E	T9I			S	Q954H	E	T11A
		E	T11A					M	Q19E
		M	Q19E					M	A63T
		M	A63T					ORF6	D61L
		ORF6	D61L					ORF8	S84L
		ORF8	***G8***						
		ORF8	S84L						
		S	Q954H						

[Table/Fig-5]: Differences between mutations in XBB and its variants.
*Unique sequences have been written in Italics and bold

DISCUSSION

Conducted over a six-month period, this study involved NGS of SARS-CoV-2 positive samples, indicating that among the 1162 processed samples, the majority (82.62%) belonged to the Omicron variant, excluding XBB, while 3.53% (41 samples) were identified as XBB and its sublineages, as illustrated in [Table/Fig-1]. Lineage detection was unsuccessful in 19 samples (1.63%), and sequencing failed in 142 samples (12.22%), with potential reasons for sequencing failure including issues such as improper sample collection, delayed transport of collected samples, or inadequate transport procedures for the collected samples. A total of 41 patients (3.53% of 1162) were identified with the XBB variant and its sublineages, predominance (63.4%). In contrast, a study by Selvavinayagam ST et al., in Tamil Nadu revealed that the XBB variant affected both male and female populations almost equally (males: 52.5%), indicating no gender based preference for the virus [19]. According to Indian Biomedical Data Centre data, the maximum number of patients suffering from the XBB variant of SARS-CoV-2 were from Gujarat, and the minimum cases were seen in Assam, Bihar, and Uttarakhand. Patients with the XBB.1 sublineage were the maximum in Maharashtra and the minimum in Jharkhand. Six cases of XBB.1 sublineage infection have been reported from Uttarakhand. XBB.1.5 sublineage was least reported from Tripura and maximum from Maharashtra. There were three reported XBB.1.5 variants from Uttarakhand. XBB.2 sublineage was found in the maximum numbers in Gujarat and the minimum from Tripura, Punjab, Himachal Pradesh, and Manipur. Eleven samples were reported with XBB.1.5 sublineage from Uttarakhand.

Among the eight hospitalised patients, four patients were vaccinated with Covishield (both doses), one was not vaccinated, and vaccination status was not known for three patients. Among the hospitalised patients, 50% were previously vaccinated with the Covishield vaccine (two doses), which signifies the potentiality of the XBB variants and its sublineages to enter vaccinated hosts and cause disease. Findings from a study conducted by Tamura T et al., in Japan indicate that XBB exhibits enhanced fitness and displays resistance against the antiviral humoral immunity triggered by breakthrough infections of the previous Omicron variant. All vaccinated individuals took two complete doses of the vaccine [22].

Death was reported in two patients affected by XBB.2 and XBB.3 sublineages. Both patients who succumbed to death were elderly males and were admitted to the ICU for severe COVID-19 disease management. This points towards the virulent nature of XBB.2 and XBB.3 sublineages compared to other XBB sublineages. Although elderly patients were least affected by the XBB sublineages, deaths were only reported in the elderly age group. This could be because of their already compromised immune systems due to old age. In present study, hospitalised patients with the XBB.1 variant did not experience any mortality, consistent with the results of a study conducted by Selvavinayagam ST et al., in Tamil Nadu, which demonstrated a significant association between XBB.1 and the development of mild disease [19].

Present study analysed the mutations in XBB and its sublineages in terms of mutated amino acids, and found that the XBB variant

differed from its sublineages by having two unique mutations. One was at amino acid Q94H of the S gene, and the other was at amino acid T2231 in the ORF3a gene. The unique mutations in the XBB sublineages are highlighted in [Table/Fig-5]. Although the ORF3a in SARS-CoV is not essential for virus replication, it contributes to pathogenesis by regulating the Spike (S protein) trafficking [23].

All the mutations found in the XBB variant were shared by one or more of the four sublineages of the XBB variant. Two unique mutations were identified in XBB.1: one in the G252V amino acid of the S gene and the other in the G8 amino acid of the ORF8 gene. The unique mutation in the G252V amino acid of the S gene in the XBB.1 variant was also reported by Selvavinayagam ST et al., from Tamil Nadu [19]. The wide array of S-protein mutations in the XBB and XBB.1 sublineages raises significant concerns regarding the potential compromise in the efficacy of existing vaccines and antibodies (mAbs, neutralising antibodies) used as therapeutics against COVID-19 [17]. There was one unique mutation in the XBB.1.5 sublineage in the F486P amino acid of the S gene. The unique mutation in the S gene of XBB.1.5 at position F486P may enhance its infectivity and pave the way for future evolutionary advancements and the acquisition of further mutations [24].

A unique mutation for the XBB.2 sublineage was observed in the D253G amino acid of the S gene. The XBB.3 sublineage had two unique mutations: one in the G82D amino acid of the ORF1a gene and the other in the I1998V amino acid of the ORF1b gene. The unique mutation in the I1988V amino acid of the ORF1b in the XBB.3 variant was also reported by Selvavinayagam ST et al., from Tamil Nadu [19]. These unique mutations in various genes of SARS-CoV-2 may potentially help the virus develop resistance against vaccination, further complicating disease outcomes.

The involvement of F486P in antibody escape post-vaccination in COVID-19 infection, uniquely mutated in the XBB.1.5 sublineage, has been a topic of discussion [25]. According to the US Centers for Disease Control and Prevention (CDC), the doubling time of the XBB.1.5 proportion is nine days, and the CDC's nowcast algorithm estimates the variant's current prevalence in the US to be around 27.6% (95% prediction interval 14.0- 46.5%). The effect of the spike modification S486P, along with the existing high degree of immune escape by XBB, is likely the reason for its growth advantage [26]. XBB.1.5 is identified as one of the Omicron subvariants with the largest immune escape based on pseudotyped viral neutralisation assays [27]. The requirement of two nucleotide changes in the same codon to convert from phenylalanine to proline has made this mutation uncommon throughout the pandemic. The fact that XBB.1.5 exhibits a higher ACE2 affinity than XBB.1, without a more pronounced reduction in neutralisation by vaccines and convalescent sera, suggests that the advantage of XBB.1.5 over XBB.1 may be due to an increase in intrinsic transmissibility [28].

Limitation(s)

Vaccination history was not available for all cases, as our laboratory received samples for sequencing from various remote areas. A complete clinical history of patients could have shed better light on the clinical significance of various coronavirus variants. Follow-up was not feasible for all patients, which could have provided a clearer understanding of the disease outcomes caused by various coronavirus variants. Data on XBB and its sublineages could not be compared with other studies due to a lack of existing data on the same.

CONCLUSION(S)

SARS-CoV-2 has been changing and advancing throughout the ongoing COVID-19 outbreak. With the ability to potentially reduce the efficacy of the existing vaccinations, XBB has rapidly emerged as a global public health concern. Despite this situation, it is still vital to advocate for widespread immunisation using available vaccines and to stress the need of booster shots, as the XBB variant and its sublineages are infecting both previously infected as well as vaccinated individuals. Conducting representative testing and genomic surveillance of each SARS-CoV-2 variant is essential for effectively developing mRNA vaccines, identifying new variants, and predicting their potential for immune evasion. Maintaining a robust level of immunity across all age groups, preventing reinfections, and reducing the risk of protracted COVID-19 are essential. Research efforts like this should be ongoing to monitor novel coronavirus variants, enabling proactive measures to potentially prevent another pandemic.

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REFERENCES

[1] Wang Q, Iketani S, Li Z, Liu L, Guo Y, Huang Y, et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. Cell [Internet]. 2023;186(2):279-86.e8. Available from: http://dx.doi.org/10.1016/j.cell.2022.12.018.

[2] Chauhan S. Comprehensive review of Coronavirus Disease 2019 (COVID-19). Biomed J. 2020;43(4):334-40.

[3] Aleem A, Samad A, Vaqar AB. Emerging variants of SARS-CoV-2 and Novel Therapeutics against Coronavirus (COVID-19). StatPearls Treasure Island. 2023; Available from: http://www.ncbi.nlm.nih.gov/books/NBK570580/.

[4] Andrews MA, Areekal B, Rajesh KR, Krishnan J, Suryakala R, Krishnan B, et al. First confirmed case of COVID-19 infection in India: A case report. Indian J Med Res [Internet]. 2020;151(5):490-92. Available from: http://dx.doi.org/10.4103/ijmr.IJMR_2131_20.

[5] Ajayakumar A, Shagufta AM, Joseph R. COVID-19 management and control: The Kerala story. [cited 2023 May 18].

[6] Tamrakar V, Srivastava A, Saikia N, Parmar MC, Shukla SK, Shabnam S, et al. District level correlates of COVID-19 pandemic in India during March-October 2020. PLoS One. 2021;16(9):e0257533.

[7] Chauhan N, Manjunath BC, Kumar JS. Rise and fall of COVID-19 cases in India: A review. J Evid Based Med Healthc. 2022;9(11):8431-37.

[8] Samarasekera U. India grapples with second wave of COVID-19. Lancet Microbe [Internet]. 2021;2(6):e238. Available from: http://dx.doi.org/10.1016/s2666-5247(21)00123-3.

[9] Mishra PP, Kumar A, Garg A, Mahaur P, Bhatnagar G, Upadhyay D, et al. Evolution of the COVID-19 pandemic: An analysis of the brunt of the second and third waves on patients in western Uttar pradesh. Cureus:14(9):e29251. Doi 10.7759/cureus.29251. Available from: http://dx.doi.org/10.7759/cureus.29251.

[10] COVID cases in India and total vaccination [Internet]. Ministry of health and family welfare. Government of India; [cited 2023 May 16]. Available from: https://www.mohfw.gov.in/.

[11] Sironi M, Hasnain SE, Rosenthal B, Phan T, Luciani F, Shaw MA, et al. SARS-CoV-2 and COVID-19: A genetic, epidemiological, and evolutionary perspective. Infect Genet Evol [Internet]. 2020;84(104384):104384. Available from: http://dx.doi.org/10.1016/j.meegid.2020.104384.

[12] Vitiello A, Ferrara F, Auti AM, Di Domenico M, Boccellino M. Advances in the Omicron variant development. J Intern Med [Internet]. 2022;292(1):81-90. Available from: http://dx.doi.org/10.1111/joim.13478.

[13] Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 Omicron variant: Recent progress and future perspectives. Signal Transduct Target Ther [Internet]. 2022;7(1):141. Available from: http://dx.doi.org/10.1038/s41392-022-00997-x.

[14] Morales-Núñez JJ, Muñoz-Valle JF, Torres-Hernández PC, Hernández-Bello J. Overview of neutralizing antibodies and their potential in COVID-19. Vaccines (Basel) [Internet]. 2021;9(12):1376. Available from: http://dx.doi.org/10.3390/vaccines9121376.

[15] Chatterjee S, Bhattacharya M, Nag S, Dhama K, Chakraborty C. A detailed overview of SARS-CoV-2 Omicron: Its sub-variants, mutations and pathophysiology, clinical characteristics, immunological landscape, immune escape, and therapies. Viruses. 2023;15(1):167. Available from: http://dx.doi.org/10.3390/v15010167.

[16] Brandolini M, Gatti G, Grumiro L, Zannoli S, Arfilli V, Cricca M, et al. Omicron sub-lineage BA.5 and recombinant XBB evasion from antibody neutralisation in BNT162b2 vaccine recipients. Microorganisms. 2023;11(1):191. Available from: http://dx.doi.org/10.3390/microorganisms11010191.

[17] Chakraborty C, Bhattacharya M, Chopra H, Islam MA, Saikumar G, Dhama K. 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? Int J Surg [Internet]. 2023;109(4):1041-43. Available from: http://dx.doi.org/10.1097/JS9.0000000000000246.
[18] Virological [Internet]. 2021. Pango Lineage Nomenclature: Provisional rules for naming recombinant lineages- SARS-CoV-2 coronavirus. [cited 2023 May 16]. Available from: https:// virological.org/t/pango-lineage-nomenclature-provisional-rules-for-naming-recombinant-lineages/657.
[19] Selvavinayagam ST, Karishma SJ, Hemashree K, Yong YK, Suvaithenamudhan S, Rajeshkumar M, et al. Clinical characteristics and novel mutations of omicron subvariant XBB in Tamil Nadu, India - A cohort study. The Lancet Regional Health - Southeast Asia. 2023;19:100272.
[20] Interim Guidelines for Collecting and Handling of Clinical Specimens for COVID-19 Testing. [cited 2023 May 16]. Centres for Disease Control and Prevention. Updated.
[21] Indian SARS-CoV-2 Genomics Consortium (INSACOG) Dashboard [Internet]. [cited 2023 May 16]. Available from: https://inda.rcb.ac.in/insacog/ statisticsinsacog.
[22] Tamura T, Ito J, Uriu K, Zahradnik J, Kida I, Anraku Y, et al. Virological characteristics of the SARS-CoV-2 XBB variant derived from recombination of two Omicron subvariants. Nat Commun. 2023;14(1):2800.
[23] Michel CJ, Mayer C, Poch O, Thompson JD. Characterization of accessory genes in coronavirus genomes. Virol J. 2020;17(1):131. Available from: http://dx.doi.org/10.1186/s12985-020-01402-1.
[24] Callaway E. Coronavirus variant XBB.1.5 rises in the United States- Is it a global threat? Nature [Internet]. 2023;613(7943):222-23. Available from: http://dx.doi.org/10.1038/d41586-023-00014-3.
[25] Guenthoer J, Lilly M, Starr TN, Dadonaite B, Lovendahl KN, Croft JT, et al. Identification of broad, potent antibodies to functionally constrained regions of SARS-CoV-2 spike following a breakthrough infection. Proc Natl Acad Sci USA [Internet]. 2023;120(23):e2220948120. Available from: http://dx.doi.org/10.1073/pnas.2220948120.
[26] Update on SARS-CoV-2 variants: ECDC assessment of the XBB.1.5 sub-lineage [Internet]. 2023 [cited 2024 Jan 16]. Available from: https://www.ecdc.europa.eu/en/news-events/update-sars-cov-2-variants-ecdc-assessment-xbb15-sub-lineage.
[27] Wang X, Jiang S, Jiang S, Li X, Ai J, Lin K, et al. Neutralization of SARS-CoV-2 BQ.1.1, CH.1.1, and XBB.1.5 by breakthrough infection sera from previous and recent waves in China. Cell Discov [Internet]. 2023;9(64):01-04. Available from: http://dx.doi.org/10.1038/s41421-023-00569-5.
[28] Yue C, Song W, Wang L, Jian F, Chen X, Gao F, et al. ACE2 binding and antibody evasion in enhanced transmissibility of XBB.1.5. Lancet Infect Dis [Internet]. 2023;23(3):278-80. Available from: http://dx.doi.org/10.1016/S1473-3099(23)00010-5.

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