GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Characterization of Omicron XBB subvariants in Vietnam

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GSC Biological and Pharmaceutical Sciences, 2023, 24(03), 337–343

Publication history: Received on 16 August 2023; revised on 27 September 2023; accepted on 29 September 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.24.3.0400

Abstract

SARS-CoV-2, an RNA virus that causes COVID-19, is known for its high mutation rate. Its latest variant, Omicron, has raised concerns due to several amino acid substitutions in the spike protein that could increase its transmissibility and virulence. Omicron has also produced subvariants with specific nucleotide mutations to evade antibodies and enhance infectivity. One of these subvariants, XBB, has become prevalent in Vietnam. Therefore, it is essential to accurately assess the genetic diversity of this emerging variant. This study analyzed the April 15th, 2023 updated data and identified nine XBB and subvariants in Vietnam, with XBB.1.5 being the most common. Phylogenetic analysis revealed that the original XBB variant was related to BA.2.75, and XBB.1.5 had a close relationship with XBB.1.2. A crucial mutation, G22317T (G252V), played an essential role in the emergence of the XBB subvariant, and XBB.1.5 split from XBB.1.2 with an A22405T (E281D) mutation, as shown by the mutation network.

Keywords: Spike gene; SARS-CoV-2; Genetic diversity; Omicron; Vietnam; XBB

1. Introduction

COVID-19 continues to be the primary global health threat, causing millions of deaths worldwide. As a viral RNA, SARS-CoV-2 possesses a single-stranded RNA that can mutate rapidly [1], resulting in the emergence of thousands of variants all over the world. The World Health Organization has categorized SARS-CoV-2 variants into three groups based on their potential public health impact. Variants of Concern (VOC) are of particular interest as they have higher transmissibility and virulence and can resist current antibody and therapeutic therapies. Notable VOC variants include Alpha, which originated in England and spread globally [2], Beta, which appeared in South Africa and was highly infectious [3], and Delta, which emerged in India and rapidly became the dominant variant globally [4].

The success of the VOC variants in particular and the contrast in the pandemic hierarchy of COVID-19 with the previous SARS-CoV is attributed to several mutations in the Spike (S) gene, which is coding for the spike protein that directly interacts with hACE2 [5]. The S genomic region of SARS-CoV-2 carries a PRRAR insertion at the furin cleavage region (FCS) of the S protein that has not been observed in previous coronavirus families [6]. In addition, the amino acid changes in the Receptor Binding Domain (RBD) of SARS-CoV-2 also contribute to this virus having a 10-20 fold binding affinity when compared with SARS-CoV [7]. Certainly, the strong infectivity of the variant: Alpha, Beta, Gamma, or Delta is attributed above all to the mutations in RBD, such as L452R, T478K, E484K/Q, Q498R, N501Y that enhance the affinity to the receptor [8-11]. In addition, mutations in the FCS also showed a positive effect on infectious efficiency. P681H/R mutations are the primary mutation support for the hit of the Alpha and Delta variants [12, 13]. Following the success of Delta, a new variant is B.1.1.529, which was classified B.1.1.529 into the VOCs group based on this variant containing more than 30 amino acid substitutions in the S protein by WHO. Many previous studies have demonstrated that Omicron

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had the highest binding affinity and transmission rate compared to Delta [14, 15]. Therefore, Omicron quickly replaced Delta as the most prevalent variant globally. Omicron has given rise to many subvariant variants that carry high transmissibility and cause re-infection, such as BA.2.75, BA.5, BQ.1, XBB and subvariants.

As the Omicron variant continues to spread, Vietnam is not immune to its migration. A previous study from May 2022 revealed that BA.2 was the dominant subvariant of Omicron in Vietnam, and there was a high level of genetic diversity within the Omicron variant. However, the situation changed when Vietnam started reporting more dangerous variants, including BA.4 and BA.5. Of particular concern is the subvariant XBB (also known as Kraken by WHO), which caused significant outbreaks in Hanoi in mid-April 2023. As a result, there is a need to investigate the genetic diversity of XBB and its subvariants in Vietnam to gain insights for epidemiological investigations.

2. Materials and Methods

2.1. Data collection

The whole genome of SARS-CoV-2 XBB variants isolated in Vietnam were extracted from the GISAID database on April 15th, 2023. The SARS-CoV-2 full-length MSA tool of the MAFFT [16] server was used to split the S gene base on the S of Wuhan-hu-1 reference sequence (accession number NC_045512.2) in GenBank. The in-house software was used to number the nucleotide and identify the single-nucleotide polymorphism in the S gene.

2.2. The phylogenetic tree

The IQtree software ver 2.2.0 was used to build the Maximum-Likelihood (ML) phylogenetic tree [17]. In order to build the ML tree, we chose the HKY+F+I as the best model based on the BIC scores and set the Wuhan-hu-1 as the tree's root. A 2000 bootstrap values were used to provide consistency in the ML tree. Then, the iTOL web tool was used to display the ML tree.

2.3. Examination of genetic diversity and haplotype network drawing

The genetic diversity measures were determined by Arlequin ver 3.5 [18], and PopART [19] software based on the Median Joining Network method built the mutation network in the S gene.

3. Results and Discussions

3.1. Haplotype diversity

To 18th April 2023, we collected 34 S gene sequences of XBB variants that appeared in Vietnam (Table S1) and were classified into 15 haplotypes with high diversity at 0.8913 ± 0.0345. Vietnam recorded XBB and subvariant XBB.2, XBB.1, XBB.1.9, XBB.1.9.1, XBB.1.8, XBB.1.5, XBB.1.2, XBB.1.1 (Table 1). The XBB.1.5 had the highest frequency in Vietnam (Table 1). Tracking by the time, we indicated the XBB, XBB.1, and XBB.1.2 emerging from November to December 2022 (Figure 1). Then, in March 2023, multiple subvariants of XBB, including XBB.1.5, XBB.1.8, and XBB.1.9, entire to Vietnam and XBB.1.5 prevailed in April 2023 (Figure 1).

For the ML phylogenetic tree in the S gene of XBB, we set Wuhan-hu-1 as the root tree and other variants: Alpha, Delta, Omicron subvariant: BA.2.75, BA.4, BA.5 as the group to indicate a relationship with XBB variant (Figure 2). The outcome showed that the XBB related to the BA.2.75 with a high bootstrap value of 99.7. This initial result correlates to the previous study based on the whole genome phylogenetic tree. In addition, we also note the XBB.1.5 variants diverged into a particular group on the ML tree with a corresponding bootstrap value of 87.1 and closely related to XBB.1.2 (Figure 2).

Table 1 XBB and subvariants frequently in Vietnam

	Variant	Frequency	First Collection
1	XBB	9%	2022-11-04
2	XBB.2	3%	2023-04-04
3	XBB.1	6%	2022-11-07

4	XBB.1.9	9%	2023-03-09
5	XBB.1.9.1	6%	2023-04-04
6	XBB.1.8	12%	2023-03-02
7	XBB.1.5	32%	2023-03-07
8	XBB.1.2	12%	2022-11-28
9	XBB.1.1	12%	2022-12-06

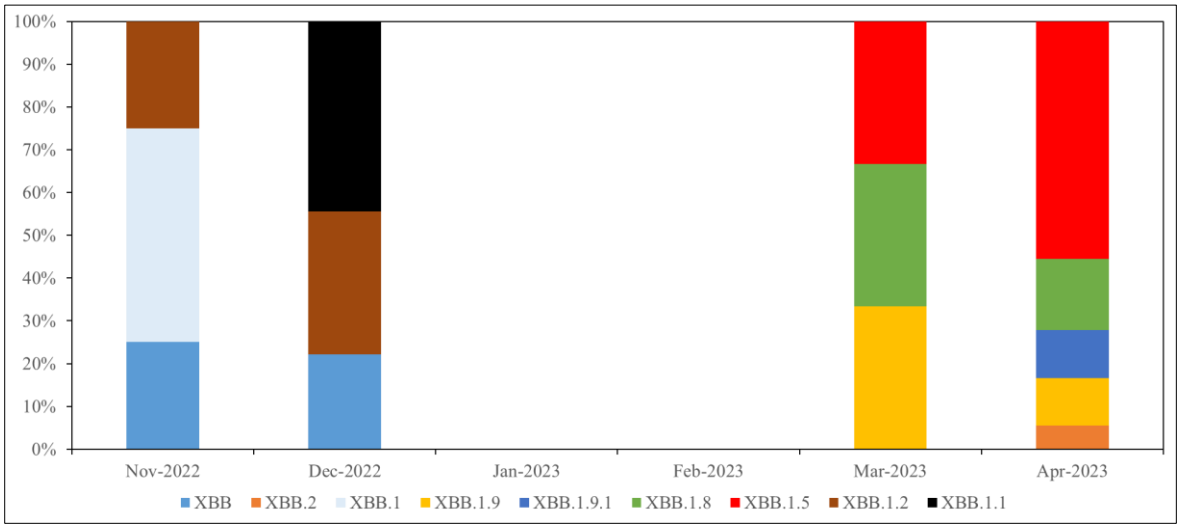

Figure 1 The timeline of XBB and subvariants appeared in Vietnam

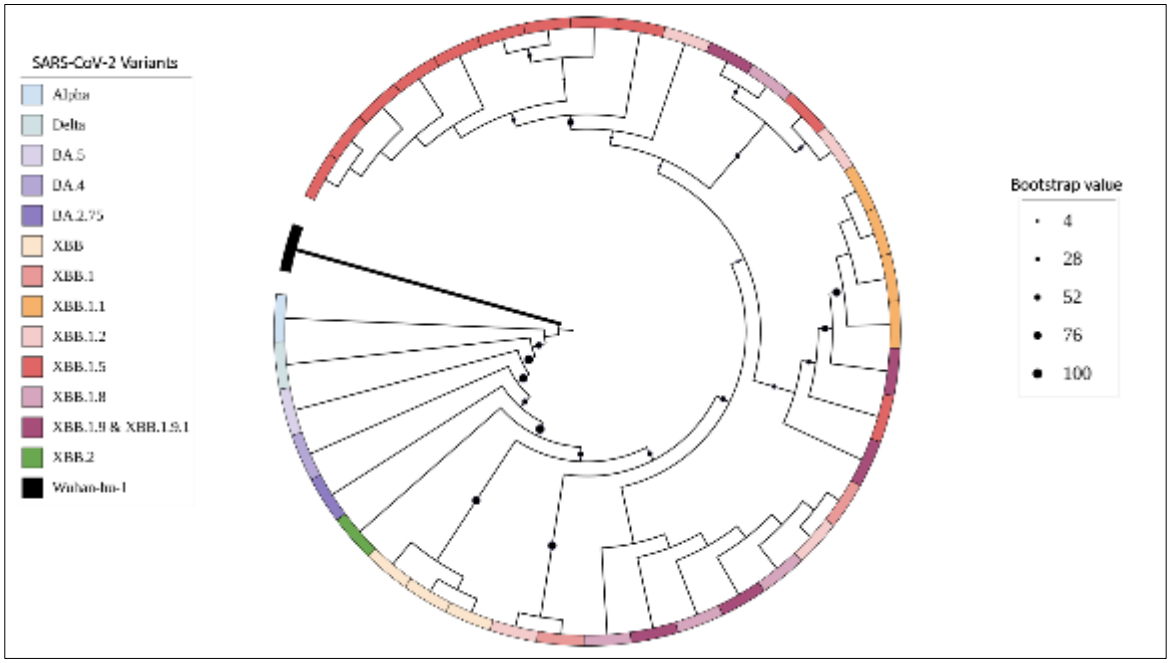

Figure 2 The Maximum-Likelihood tree of the S gene of XBB and subvariants in Vietnam

(In this figure, each variant was colored by each color. Each middle node on the brach is displayed for bootstrap, and the node's size indicated value.)

3.2. Nucleotide diversity

Nucleotide diversity analysis showed that the XBB and subvariants recorded 73 polymorphic sites, and 12 deletions were 21633-41TACCCCTGC, leading to deletion amino acid 24-26LPP (Del 24-26LPP and 21991-93 TTA (Del 144Y). In addition, we discovered the nucleotide difference between the XBB haplotypes at 3.032086 ± 1.619934, implying that these variants generate new mutations in the S gene. To evaluate in detail the mutations appearing on the S gene, we built a mutation in the S gene. The network analysis showed that the XBB and subvariant were developed from the G22317T (changes amino acid G252V) mutation of the XBB origin variant (Figure 3), a conserved mutation of the XBB and subvariants. The G252V mutation has enhanced XBB infectivity through antibody evasion [20]. Subsequently, variant XBB.1.1 was derived from mutation C23123T (P521S), which has not been extensively investigated in previous studies but shown to decrease infectivity [21].

Based on the ML tree and mutation network analysis, XBB.1.5 is closely related to XBB.1.2 and was derived from A22405T (E281D) mutation (Figure 2 and 3). The XBB.1.5 variant generated new offspring, which other subvariants have not recorded. It was shown that the A22405T (E281D) mutation seems to contribute to the viability of the XBB.1.5 variant. However, the XBB.1.5 variants appearing in Vietnam did not record the S486P mutation on the S protein. The S486P mutation appearing commonly in XBB.1.5 variant worldwide is thought to enhance the transmissibility of XBB.1.5 [22]. Therefore, it is very likely that XBB.1.5, with a higher transmission rate, will be recorded in Vietnam. In addition, XBB.1.8 is also derived from mutation T21726A (F55Y) – this mutation has not been recorded in previous publications. In addition, XBB.1 generated XBB.1.2 with two mutations, C22109G (Q183E) and C24797T (P1079S) (Figure 3).

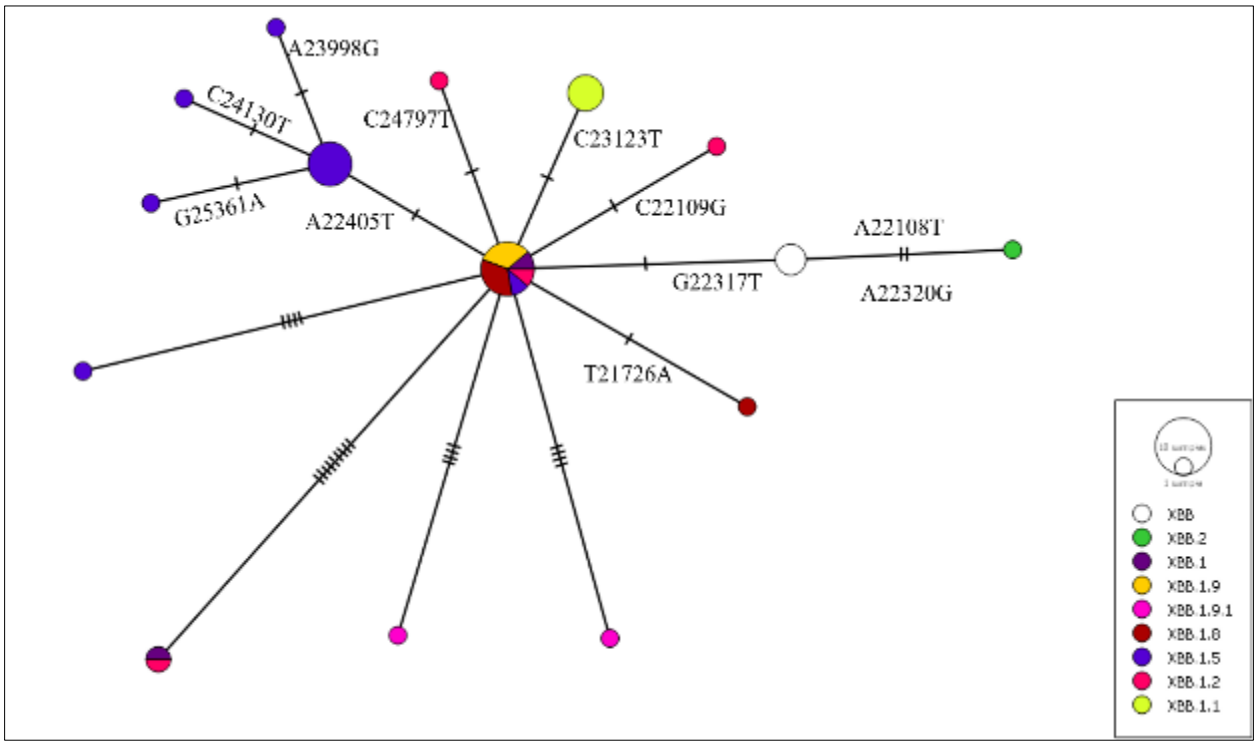

Figure 3 The mutation network in the S gene of XBB and subvariants in Vietnam

(In this figure, each node is present for each haplotype, and the color is displayed respectively for each subvariants. The edge between two nodes related to nucleotide changes of these nodes and the hatch mark displays for the number of mutations.)

4. Conclusion

Our study provides the phylogenetics of XBB and subvariants in general. First, we recorded the migration of various XBB subvariants from two waves in November 2022 and March 2023, in which the XBB.1.5 variant predominated in the second wave. Phylogenetic analysis revealed that the XBB and subvariants were taken from the G22317T (G252V) mutation. Then, the XBB.1.5 variant was closely related to XBB.1.2 and originated from the A22405T mutation (E281D).

This study has partly evaluated the revolution of changes in the S gene region of XBB in general and identified important mutations for each subvariant in particular. This result is a premise for further studies on the evolution of SARS-CoV-2, especially the XBB variant, and furnishes essential information for the following research. Finally, our study is limited in that it has not yet evaluated the impact of mutations on the S protein as well as the effect on receptor binding. Therefore, further studies are needed to evaluate in detail the mutations appearing on the S protein, especially the two mutations G252V and E281D.

Compliance with ethical standards

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

References

[1] Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, *et al.* Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus. Cell.2020/08/20/ 2020;182(4):812-27.e19.

[2] Walker AS, Vihta K-D, Gethings O, Pritchard E, Jones J, House T, *et al.* Tracking the Emergence of SARS-CoV-2 Alpha Variant in the United Kingdom. New England Journal of Medicine.2021/12/30 2021;385(27):2582-5.

[3] Duong D. Alpha, Beta, Delta, Gamma: What's important to know about SARS-CoV-2 variants of concern? CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.Jul 12 2021;193(27):E1059-e60.

[4] Earnest R, Uddin R, Matluk N, Renzette N, Turbett SE, Siddle KJ, *et al.* Comparative transmissibility of SARS-CoV-2 variants Delta and Alpha in New England, USA. Cell Reports Medicine.2022/04/19/ 2022;3(4):100583.

[5] Ovsyannikova IG, Haralambieva IH, Crooke SN, Poland GA, Kennedy RB. The role of host genetics in the immune response to SARS-CoV-2 and COVID-19 susceptibility and severity. Immunological reviews.Jul 2020;296(1):205-19.

[6] Segreto R, Deigin Y, McCairn K, Sousa A, Sirotkin D, Sirotkin K, *et al.* Should we discount the laboratory origin of COVID-19? Environ Chem Lett2021;19(4):2743-57.

[7] Hartenian E, Nandakumar D, Lari A, Ly M, Tucker JM, Glaunsinger BA. The molecular virology of coronaviruses. The Journal of biological chemistry.Sep 11 2020;295(37):12910-34.

[8] Han P, Li L, Liu S, Wang Q, Zhang D, Xu Z, *et al.* Receptor binding and complex structures of human ACE2 to spike RBD from omicron and delta SARS-CoV-2. Cell.2022/02/17/ 2022;185(4):630-40.e10.

[9] Di Giacomo S, Mercatelli D, Rakhimov A, Giorgi FM. Preliminary report on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike mutation T478K. Journal of medical virology.Sep 2021;93(9):5638-43.

[10] Cherian S, Potdar V, Jadhav S, Yadav P. SARS-CoV-2 Spike Mutations, L452R, T478K, E484Q and P681R, in the Second Wave of COVID-19 in Maharashtra, India.Jul 20 2021;9(7).

[11] Liu Y, Liu J, Plante KS, Plante JA, Xie X, Zhang X, *et al.* The N501Y spike substitution enhances SARS-CoV-2 infection and transmission. Nature.Feb 2022;602(7896):294-9.

[12] Kumar V, Singh J, Hasnain SE, Sundar D. Possible Link between Higher Transmissibility of Alpha, Kappa and Delta Variants of SARS-CoV-2 and Increased Structural Stability of Its Spike Protein and hACE2 Affinity. International journal of molecular sciences2021;22(17):9131.

[13] Fan L-Q, Hu X-Y, Chen Y-Y, Peng X-L, Fu Y-H, Zheng Y-P, *et al.* Biological Significance of the Genomic Variation and Structural Dynamics of SARS-CoV-2 B.1.617. Frontiers in microbiology2021;12:750725-.

[14] Hwang S, Baek S-H, Park D. Interaction Analysis of the Spike Protein of Delta and Omicron Variants of SARS-CoV-2 with hACE2 and Eight Monoclonal Antibodies Using the Fragment Molecular Orbital Method. Journal of Chemical Information and Modeling.2022/04/11 2022;62(7):1771-82.

[15] Kumar S, Thambiraja TS, Karuppanan K, Subramaniam G. Omicron and Delta variant of SARS-CoV-2: A comparative computational study of spike protein. Journal of medical virology.Apr 2022;94(4):1641-9.

[16] Katoh K, Standley DM. MAFFT Multiple Sequence Alignment Software Version 7: Improvements in Performance and Usability. Molecular Biology and Evolution2013;30(4):772-80.

[17] Minh BQ, Schmidt HA, Chernomor O, Schrempf D, Woodhams MD, von Haeseler A*, et al.* IQ-TREE 2: New Models and Efficient Methods for Phylogenetic Inference in the Genomic Era. Molecular Biology and Evolution2020;37(5):1530-4.

[18] Excoffier L, Lischer HE. Arlequin suite ver 3.5: a new series of programs to perform population genetics analyses under Linux and Windows. Mol Ecol Resour.May 2010;10(3):564-7.

[19] Leigh JW, Bryant D. popart: full-feature software for haplotype network construction. Methods in Ecology and Evolution.2015/09/01 2015;6(9):1110-6.

[20] Lasrado N, Collier AY, Miller J, Hachmann NP, Liu J, Sciacca M*, et al.* Waning Immunity Against XBB.1.5 Following Bivalent mRNA Boosters. bioRxiv : the preprint server for biology.Jan 23 2023.

[21] Li Q, Wu J, Nie J, Zhang L, Hao H, Liu S*, et al.* The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell.Sep 3 2020;182(5):1284-94.e9.

[22] Parums DV. Editorial: The XBB.1.5 ('Kraken') Subvariant of Omicron SARS-CoV-2 and its Rapid Global Spread. Medical science monitor : international medical journal of experimental and clinical research.Feb 1 2023;29:e939580.

Supplementary information

Table S1 The subsequent information of XBB variants isolated in Vietnam

Sequence number	GISAID ID	Collection date	Lineage
1	EPI_ISL_16201138	2022-11-04	XBB
2	EPI_ISL_16201086	2022-11-07	XBB.1
3	EPI_ISL_16377104	2022-11-17	XBB.1
4	EPI_ISL_16342385	2022-11-28	XBB.1.2
5	EPI_ISL_16377109	2022-12-05	XBB.1.2
6	EPI_ISL_17198165	2022-12-05	XBB.1.2
7	EPI_ISL_16342412	2022-12-06	XBB.1.1
8	EPI_ISL_16342423	2022-12-07	XBB.1.1
9	EPI_ISL_16342424	2022-12-07	XBB.1.1
10	EPI_ISL_16342425	2022-12-07	XBB.1.1
11	EPI_ISL_16342427	2022-12-08	XBB
12	EPI_ISL_17198184	2022-12-12	XBB.1.2
13	EPI_ISL_16377098	2022-12-16	XBB
14	EPI_ISL_17481600	2023-03-02	XBB.1.8
15	EPI_ISL_17481603	2023-03-07	XBB.1.5
16	EPI_ISL_17481621	2023-03-09	XBB.1.9
17	EPI_ISL_17481608	2023-04-04	XBB.1.5

18	EPI_ISL_17481605	2023-04-04	XBB.1.9.1
19	EPI_ISL_17481607	2023-04-04	XBB.2
20	EPI_ISL_17481624	2023-04-06	XBB.1.9.1
21	EPI_ISL_17481625	2023-04-10	XBB.1.5
22	EPI_ISL_17481609	2023-04-12	XBB.1.5
23	EPI_ISL_17481613	2023-04-12	XBB.1.5
24	EPI_ISL_17481614	2023-04-12	XBB.1.5
25	EPI_ISL_17481615	2023-04-12	XBB.1.5
26	EPI_ISL_17481616	2023-04-12	XBB.1.5
27	EPI_ISL_17481618	2023-04-12	XBB.1.5
28	EPI_ISL_17481619	2023-04-12	XBB.1.5
29	EPI_ISL_17481620	2023-04-12	XBB.1.5
30	EPI_ISL_17481610	2023-04-12	XBB.1.8
31	EPI_ISL_17481612	2023-04-12	XBB.1.8
32	EPI_ISL_17481626	2023-04-12	XBB.1.8
33	EPI_ISL_17481611	2023-04-12	XBB.1.9
34	EPI_ISL_17481617	2023-04-12	XBB.1.9