Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Genetic and structural genome-based survey reveals the low potential for epidemiological expansion of the SARS-CoV-2 XBB.1.5 sublineage

Dear Editor,

We read with interest the Letter to the Editor *Evolution of SARS-CoV-2 Omicron subvariants BF.7 and XBB.1.5: Time to follow Africa and abort all COVID restrictions* by Kelleni,[1] on the need, for the global health care authorities, to carefully consider the African COVID-19 safe and effective early treatment approach. In such a context, here we report on the global epidemic trajectory of SARS-CoV-2 XBB.1.5 lineage that we believe the above Authorities should consider in taking their decisions.

The phylogenomic reconstruction, available at https://gisaid.org/phylodynamics/global/nextstrain/, depicts an evolutionary pattern of XBB.1.5 very similar to that of previous, recent variants such as BA.2.75,[2] BA.2.12.1 and BQ.1[3] that appeared as an evolutionary blind background. Notably, this pattern has also been identified for the original recombinant XBB and its first descendant XBB.1,[4] which are now known not to exhibit characteristics of epidemiologically dangerous lineages. Actually, the XBB.1.5 lineage represents the first descendant of the recombinant XBB for which threats on public health impact originally arose. As of now, it has been detected in 54 countries and its speed of diffusion prompted the WHO to revise the confidence level of the risk assessment from low (January 11, 2023) to moderate (January 25, 2022).[5] However, the Bayesian Skyline Plot (BSP) in Fig. 1 (estimated on all high-quality genomes and coverage available on January 13, 2023 form the GSAID portal (https://gisaid.org/) by following Scarpa et al.[2,4,6]), indicates quite a low level of genetic variability with very few fluctuation points over time. The viral genetic variability and the population size peaked reaching the plateau around November 24, 2022. This substantial lack of genetic variation during the time (also depicted by branches' length in the phylogenetic tree shown in Fig. S1) is not the trend of a lineage that is about to explode in terms of population size and, accordingly, in terms of contagiousness. Indeed, at the beginning of the pandemic, the genetic variability of SARS-CoV2 ancestral strain was shortly and quickly increasing with a very vertical curve.[7] Conversely, XBB.1.5 seems to be quite typical of an evolutionary lineage that presents new features in comparison to its direct progenitor and to other recent variants, but unable to promote an abnormal expansion. The estimated evolutionary rate for XBB.1.5 (6.9×10^{-4} subs/site/year) further accounts for the low genetic variability and limited capacity for strong demographic expansion. The evolutionary rate of the variant BA.5, which remained dominant worldwide for several months in 2022, was slightly higher (7.4×10^{-4} subs/site/year),[2] but BA.5 had been circulating for several months before peaking, and its plateau phase presented several fluctuations of the viral population size.[2] A direct comparison of evolutionary rates of recent versus early SARS-CoV-2 strains should be taken cautiously because of the different population susceptibilities to infection among unvaccinated, vaccinated and preinfected subjects. Nonetheless, it remains noteworthy that the evolutionary rate of the pandemic starting, SARS-CoV-2 Wuhan-Hu-1 strain, was around 6.58×10^{-3} subs/site/year,[8] i.e., roughly 10 times faster than XBB.1.5.

The lineage XBB.1.5 presents the same point mutations of interest in the spike protein sequence as its progenitor XBB (i.e., K417N, S477N, N501Y and P681H),[4] except for mutation at position 486.[9] Indeed, the NTD domain is identical for XBB.1 and XBB.1.5 whereas their RBDs only differ for the mutations at position 486, where the original Wuhan Phe (conserved in BA.2) is replaced by a Ser in XBB and XBB.1,[4] and a Pro in XBB.1.5. The predicted net electrostatic charges of the RBD and NTD domains, the changes of which have been reported to impact on virus transmissibility and infectivity, are reported in Table 1. While the three XBB descendants differ from BA.2 for their negative net charge on NTD, being in this similar to the first Omicron variant, the BA.1,[10] no evident differences between lineages XBB/XBB.1 and XBB1.5 are present in the distribution of the electrostatic surface potential of NTD and RBD. The conserved F486 in BA.2 can establish Van der Waals contacts with residues in a hydrophobic pocket on the ACE2 receptor. The substituting Ser in XBB and XBB.1 tends to destabilize the RBD-ACE2 interface by disrupting hydrophobic interactions. Consistently, the interaction BA.2 RBD-ACE2 is inferred to be the most stable among the four tested variants.

It should also pointed out that XBB.1.5, as all these recent, BA.2 and BA.5-derived Omicron subvariants, have remained so far confined to selected regional areas of the USA, despite its high transmissibility and immune-evasion potential, as reported by "COVID data tracker" of the Centers for Disease Control and Prevention (CDC).[3] Thus, the data reported here and our interpretation of a limited expansion potential of XBB.1.5 appear to be well in keeping with the current epidemiological, real-world observations.

In conclusion, genetic and structural analyses here presented do not provide evidence for a particularly high risk of XBB.1.5 expansion to become a new, global public health threat. The Omicron variant of concern, and more specifically BA.5 and its descendant lineages, remain the dominant variants circulating globally.[5] The variant XBB.1.5 appears to spread even more slowly than the last subvariants that have caused concerns in 2022. However, it cannot be excluded that new mutations will occur and make XBB.1.5 more dangerous. In this context, extensive genome-based monitoring must continue uninterruptedly because it is the only way to identify and/or predict important changes in the genomic composition of SARS-CoV-2.

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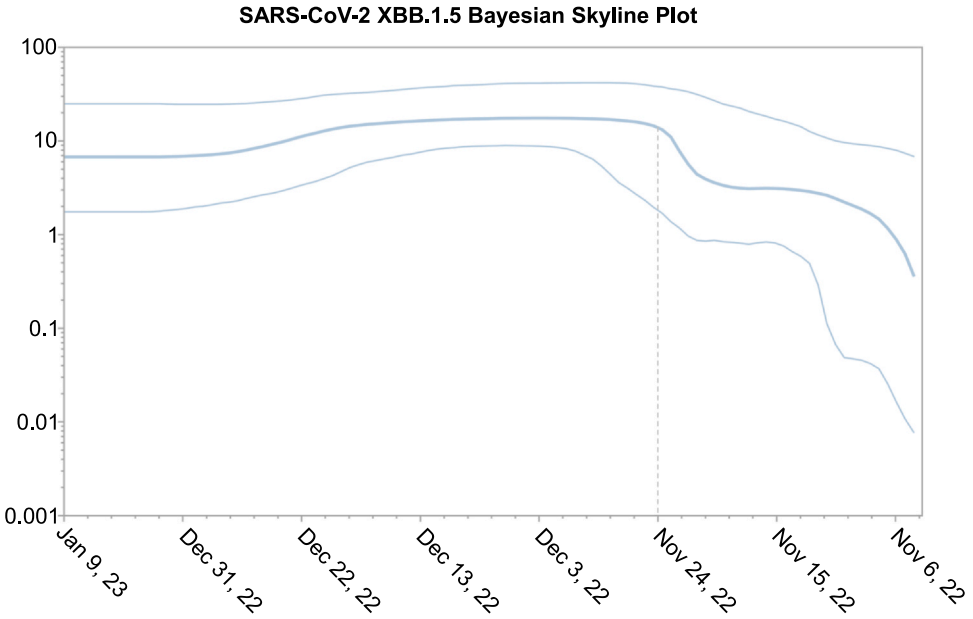

Fig. 1. Bayesian skyline plot of SARS-CoV-2 XBB.1.5 variant. The viral effective population size (y-axis) is shown as a function of days (x-axis). Solid area represents the 95% high posterior density (HPD) region. Demographic analysis has been performed by using BEAST 1.10.4 [27] following Scarpa et al.[3] Figure has been edited by using the software GIMP 2.8 (available at https://www.gimp.org/downloads/oldstable/).

Table 1
Net charge of NTD and RBD for BA.2, XBB, XBB.1, and XBB.1.5.

	BA.2	XBB	XBB.1	XBB.1.5
NTD	0.95 ± 0.04	1.14 ± 0.04	1.18 ± 0.04	1.18 ± 0.04
RBD	5.19 ± 0.01	5.45 ± 0.02	5.45 ± 0.02	5.42 ± 0.01

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Author contributions

FS and MC (Massimo Ciccozzi) developed the study design. FS, AV, and SP analyzed data. FS and MC (Massimo Ciccozzi) wrote the original draft manuscript. All of the authors revised the manuscript. All authors read and approved the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.02.039.

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