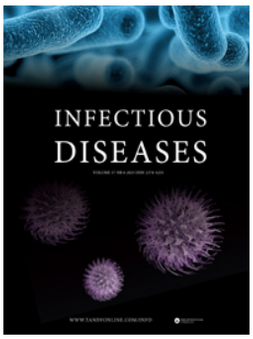

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Francesco Branda, Massimo Ciccozzi & Fabio Scarpa

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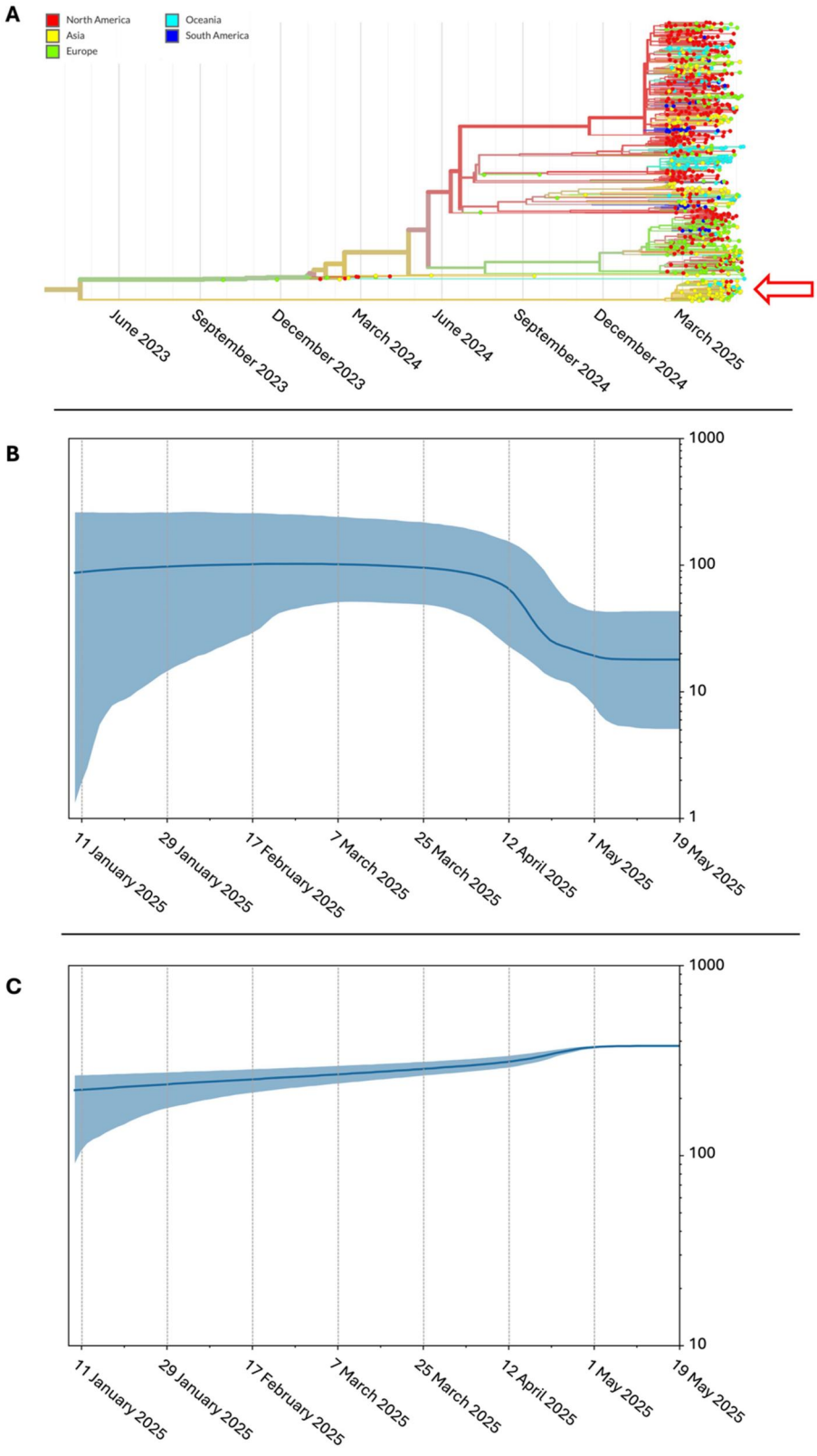
COMMENT

Genome-based analyses of SARS-CoV-2 NB.1.8.1 variant reveals its low potential

In the past few years, the world has grappled with the COVID-19 pandemic, caused by the SARS-CoV-2 virus [1]. SARS-CoV-2 is a positive-sense, single-stranded RNA virus known for its high mutation rate due to the error-prone nature of RNA replication [2]. All of these mutations can affect how the virus responds to neutralising antibodies developed through infection or vaccination, as well as its transmissibility. Consequently, the virus underwent continuous genetic changes throughout the pandemic, leading to the development of multiple distinct lineages and sub-lineages with varying levels of contagiousness. Indeed, since the beginning of the pandemic, countless variants of the virus have emerged and circulated, gradually becoming less virulent and aggressive as SARS-CoV-2 transitioned towards endemicity. In recent times, we have observed a global pattern in which a dominant variant remains prevalent for several months—often influenced by seasonal factors—before being replaced by a newly emerging one [3]. This process reflects a kind of succession, where the newer variant tends to outcompete and displace the previous one [3]. The most recent emerged variant is the one labelled NB.1.8.1, nicknamed *Nimbus*, which has been designated VuM (Variant under Monitoring) on 23 May 2025 [4]. Phylogenomic reconstruction here presented (Figure 1a) indicates that NB.1.8.1 (Nextstrain clade 25B) does not represent a monophyletic group. Instead, it clusters within a heterogeneous clade that also includes specimens of XDV (Nextstrain clade 24). This is a particularly interesting aspect, as NB.1.8.1 is in fact a descendant of XDV, which in turn originates from NJ.1—just like all variants that have circulated since late 2023. However, NB.1.8.1 does not yet appear to have differentiated enough to form a distinct genetic cluster.

Compared to JN.1, this variant carries the following mutations in the spike protein: T22N, F59S, G184S, A435S, F456L, T478I, and Q493E—none of which are currently classified as Mutations of Concern (MoC) or Mutations of Interest (MoI). Among these, particular attention should be paid to S:F456L, which is considered a FLip mutation. This mutation has been shown—especially when paired with another FLip, L455F—to notably enhance the spike protein's binding affinity to the ACE2 receptor [7]. This increased binding capability could, in theory, enable the virus to tolerate additional mutations that favour immune evasion. Nevertheless, F456L appears alone in NB.1.8.1 for now, though it remains worth monitoring. From an evolutionary perspective, it is noteworthy that the clade from which this new lineage emerged lies on a very long branch, which is typically indicative of an evolutionary dead end. This pattern suggests a lineage that required a long period to accumulate the defining mutations, which is generally not characteristic of a variant of concern. The evolutionary rate here estimated of NB.1.8.1 aligns with that of recent variants, estimated at 2.8×10^{-4} substitutions per site per year [95% HPD: $1.4 \times 10^{-4} - 4.1 \times 10^{-4}$]. This is a relatively low rate and does not suggest a rapidly expanding or dangerous variant. In fact, a rate on the order of 10^{-4} has become typical of circulating variants since SARS-CoV-2 began transitioning into endemicity. By comparison, during the early phase of the pandemic, the original SARS-CoV-2 lineage had an evolutionary rate of approximately 6.58×10^{-3} substitutions per site per year [8], meaning that NB.1.8.1 is evolving about ten times more slowly than the original Wuhan-Hu-1 strain. Indeed, as shown in the Bayesian Skyline Plot (BSP) graph in Figure 1b, NB.1.8.1 peaked its genetic diversity in the first half of April. Afterward, diversity declined, hitting a low in early May, and has since entered a plateau phase that continues to the present day. It is also worth noting that even during its initial expansion, the variant did not show exponential growth in genetic variability (Figure 1b), or in the number of lineages (Figure 1c). Instead, it displayed a flattened genetic variability that quickly stabilised into a plateau lasting approximately three months from its estimated origin around early January 2025—which aligns with the earliest documented sample, dated 22 January 2025. This further reinforces the notion that NB.1.8.1 does not exhibit the characteristics of a high-risk variant. A dangerous variant would have


A
North America
Asia
Europe
Oceania
South America
June 2023
September 2023
December 2023
March 2024
June 2024
September 2024
December 2024
March 2025
B
1000
100
10
1
11 January 2025
29 January 2025
17 February 2025
7 March 2025
25 March 2025
12 April 2025
1 May 2025
19 May 2025
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1000
100
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11 January 2025
29 January 2025
17 February 2025
7 March 2025
25 March 2025
12 April 2025
1 May 2025
19 May 2025

Figure 1. (a) Time-calibrated phylogenomic tree on all SARS-CoV-2 genomes available in GISAID collected between september 2023 and may 2025 (last updated 29 may 2025). Reconstruction was carried out using the nextstrain/ncov pipeline (https://github.com/nextstrain/ncov). The red arrow indicates the heterogenous clade composed by specimens of XDV and NB.1.8.1. (b) Bayesian skyline plot (BSP) of all available SARS-CoV-2 NB.1.8.1 genomes in GISAID (https://gisaid.org/) as of 24 may 2025 ($n = 378$; collection dates: 2 february 2025 – 19 may 2025). For details on analysed genomes (https://doi.org/10.55876/gis8.250524rc) see supplementary file S1. The graph shows changes in the genetic variability over time. (c) Lineages through time (LTT) on the same daset used for BSP. The graph shows the changes of the number of lineages overtime. Analyses in panels a and B have been performed by using the software beast V.1.10.4 [5] and tracer v.1.7.2 [6]. the entire image was edited using GIMP 2.8 (https://www.gimp.org/downloads/oldstable/).

shown rapid exponential growth and a surge in cases shortly after its emergence, rather than a delayed and modest increase.

Currently, the number of NB.1.8.1 infection cases is increasing. As of 18 May 2025, NB.1.8.1 sequences had been reported in GISAID from 22 countries, representing 10.7% of the globally available sequences in epidemiological week 17 of 2025 (21–27 April 2025) [9]. However, considering that the current global case numbers are comparable to those observed in July 2024 [9], the situation does not appear alarming. It is normal for the virus to continue evolving, with a kind of variant replacement favouring newer variants that exhibit higher transmissibility. Indeed, in early 2025, XEC was the most widespread variant reported globally, followed closely by KP.3.1.1, the former dominant variant. In February, XEC began to decline, while LP.8.1 increased in prevalence. By mid-April, LP.8.1 showed a slight decline, coinciding with a growing number of NB.1.8.1 detections [9]. It is important to highlight that, despite showing higher transmissibility, the genomic data presented here classify NB.1.8.1 as a less aggressive variant compared to recent ones. In addition, it should always be remembered that the vaccine—developed based on its predecessor JN.1—combined with immune memory from past infections, is expected to provide adequate protection. However, this does not mean we can lower our guard or relax our vigilance regarding the study of new variants. The data presented reflect the situation as it stands, but since the virus is constantly mutating, our only effective tool remains continuous and comprehensive genome-based surveillance. This is essential to detect any significant changes in the viral genome and to develop timely and appropriate response strategies.

Authors' contributions

Francesco Branda: Conceptualisation, Formal analysis, Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing. **Massimo Ciccozzi**: Conceptualisation, Formal analysis, Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing. **Fabio Scarpa**: Conceptualisation, Formal analysis, Investigation, Resources, Data curation, Writing - Original Draft, Writing - Review & Editing.

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

[1] Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270–273. doi:10.1038/s41586-020-2012-7.

[2] Hillen HS, Kokic G, Farnung L, et al. Structure of replicating SARS-CoV-2 polymerase. Nature. 2020;584(7819):154–156. doi:10.1038/s41586-020-2368-8.

[3] Branda F, Ciccozzi M, Scarpa F. Genetic variability of the recombinant SARS-CoV-2 XEC: is it a new evolutionary dead-end lineage? New Microbes New Infect. 2024;62:101520. doi:10.1016/j.nmni.2024.101520.

[4] WHO. Risk evaluation for SARS-CoV-2 Variant Under Monitoring: NB.1.8.1; 2025 May 23. Available from: https://www.who.int/publications/m/item/risk-evaluation-for-sars-cov-2-variant-under-monitoring-nb.1.8.1

[5] Drummond AJ, Rambaut A. BEAST: Bayesian evolutionary analysis by sampling trees. BMC Evol Biol. 2007;7(1):e214. doi:10.1186/1471-2148-7-214.

[6] Rambaut A, Drummond AJ, Xie D, et al. Posterior summarisation in Bayesian phylogenetics using Tracer 1.7. Syst Biol. 2018;67(5):901–904. doi:10.1093/sysbio/syy032.

[7] Focosi D, Spezia PG, Gueli F, et al. The era of the FLips: how spike mutations L455F and F456L (and A475V) are shaping SARS-CoV-2 evolution. Viruses. 2023;16(1):3. doi:10.3390/v16010003.

[8] Benvenuto D, Giovanetti M, Salemi M, et al. The global spread of 2019-nCoV: a molecular evolutionary analysis. Pathog Glob Health. 2020;114(2):64–67. doi:10.1080/20477724.2020.1725339.

[9] WHO. Disease outbreak news COVID-19 - global situation; 2025 May 28. Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2025-DON572

Francesco Branda and Massimo Ciccozzi
Unit of Medical Statistics and Molecular Epidemiology, University Campus Bio-Medico of Rome, Rome, Italy
f.branda@unicampus.it

Fabio Scarpa
Department of Biomedical Sciences, University of Sassari, Sassari, Italy