Virus Evolution, 2024, **10(1)**, veae035
DOI: https://doi.org/10.1093/ve/veae035
Advance Access Publication 7 May 2024
Research Article

Emergence and dissemination of SARS-CoV-2 XBB.1.5 in New York

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Abstract

The recombinant SARS-CoV-2 Omicron XBB.1.5 variant was first detected in New York City (NYC) and rapidly became the predominant variant in the area by early 2023. The increased occurrence of circulating variants within the SARS-CoV-2 XBB-sublineage prompted the modification of COVID-19 mRNA vaccines by Moderna and Pfizer-BioNTech. This update, implemented in mid-September 2023, involved the incorporation of a monovalent XBB.1.5 component. Considering that NYC probably played a central role in the emergence of the XBB.1.5 variant, we conducted phylogeographic analysis to investigate the emergence and spread of this variant in the metropolitan area. Our analysis confirms that XBB.1.5 emerged within or near the NYC area and indicates that XBB.1.5 had a diffusion velocity similar to that of the variant Alpha in the same study area. Additionally, the analysis of 2,392 genomes collected in the context of the genomic surveillance program at NYU Langone Health system showed that there was no increased proportion of XBB.1.5, relative to all cocirculating variants, in the boosted compared to unvaccinated individuals. This study provides a comprehensive description of the emergence and dissemination of XBB.1.5.

Keywords: SARS-CoV-2; viral phylogeography; molecular epidemiology.

Introduction

The emergence of SARS-CoV-2 Omicron XBB.1.5 variant, resulting from a recombination event between Omicron BA.2.75 and BA.2.10 lineages, has gained significant attention within the scientific community. This is due to its rapid dissemination and its designation as the primary variant for the annual vaccine update in 2023. It was first identified in New York City (NYC) in October 2022, and by the beginning of 2023, the variant had quickly spread, accounting for 81 per cent and 26 per cent of the sequenced samples in NYC and the country, respectively (Luoma 2023). Globally, as of early January 2023, it had been detected in 38 countries, with a notable prevalence in the USA (82.2 per cent), the UK (8.1 per cent), and Denmark (2.2 per cent) (WHO 2023).

The rapid dissemination of Omicron XBB.1.5 has been associated with strong immune evasive properties, likely akin to its parental lineages. This rapid spread is further attributed to enhanced transmissibility resulting from the acquisition of the S486P substitution, which enhances its binding affinity to the ACE2 receptor (Uriu et al. 2023). Today, of particular concern are the XBB.1.5-related lineages, especially those exhibiting an additional amino acid change, F456L, which have witnessed a rapid surge in circulation, now dominating global SARS-CoV-2 infections (European Centre for Disease Prevention and Control 2023).

Because NYC was likely the epicentre of XBB.1.5 emergence in the USA, we capitalised on the pre-existing genomic surveillance infrastructure within the NYU Langone Health (NYULH) system, a large health care system in the NYC metropolitan area, to investigate the spread of the XBB.1.5 variant in this metropolitan area. Here, we examined 2,397 XBB.1.5 genomes collected from the NYC area in the context of a set of background sequences including global SARS-CoV-2 XBB.1.5 and other variants. We estimate and compare the introduction and dispersal dynamics of the XBB.1.5 variant with previous circulating SARS-CoV-2 variants in the study area (Dellicour et al. 2023). Additionally, we assessed the relative prevalence of the XBB.1.5 variant compared

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to other cocirculating variants over time in both vaccinated individuals who received a booster shot and those who remained unvaccinated.

Results and discussion

The potential emergence of XBB.1.5 in New York state (Supplementary Figs S1A and S2), and specifically in the NYC area, was studied in the context of the observational genomic surveillance program in the multicentre NYULH system. The three centres include the Langone hospital in Manhattan, Midtown East, the Winthrop hospital on Long Island, Nassau County, and the Lutheran hospital in Brooklyn. The cross-sectional study was based on the sequencing of all SARS-CoV-2-positive cases (nasopharyngeal swabs from SARS-CoV-2-exposed or diagnosed individuals) with a Ct value <30, up to our maximum sequencing capacity of 94 cases per week.

XBB.1.5 belongs to the XBB lineage, a recombinant between BA.2.75 (BM.1.1.1) and BA.2.10 (BJ.1) with a breakpoint in the RBD region of spike, which additionally acquired the spike mutations G252V and F/S486P and a stop codon in ORF8 (Supplementary Fig. S1B). XBB.1.5, which dominated the first half of 2023 in the USA and globally, is closely related to XBB.1.9 and XBB.1.16 lineages (Supplementary Fig. S1B), which dominated the second half of 2023 (Khare et al. 2021).

Our recent study showed that booster vaccine pressure can be associated with increased prevalence of one variant over others (Duerr et al. 2023). To study this for XBB.1.5, we estimated the proportion of the XBB.1.5 variant relative to all cocirculating variants over time for the boosted and unvaccinated groups on the full NYULH data, which comprised a total of 2,392 sequences. Of these sequences, 24 per cent corresponded to the XBB.1.5 variant and 15 per cent to BQ.1.1. These sequences were collected from 1 August 2022, up to 4 February 2023 (Fig. 1A and Supplementary Fig. S2). We found a similar increase of XBB.1.5 detection rates relative to all cocirculating variants in boosted and unvaccinated individuals (Fig. 1B). When juxtaposing the findings of our present research with those of Duerr and colleagues (Duerr et al. 2023), we discerned a notable superiority of the emergent Omicron (BA.1) over coexisting lineages, predominantly Delta, in individuals who have received a booster shot. Conversely, the emergent XBB.1.5 did not exhibit any superiority over its coexisting lineages, which were primarily other Omicron variants. Thus, although XBB.1.5 has been previously described as highly immune evasive *in vitro* (Hoffmann et al. 2023), we did not observe any heightened detection rates compared to contemporaneous variants under booster vaccine pressure within this New York cohort.

In line of these findings, a differential mutation analysis from boosted vs unvaccinated individuals across all residues of the full genome of XBB.1.5 study viruses (multiplicity corrected Fisher's exact test) exclusively identified the synonymous T120204C mutation in ORF1a significantly enriched in boosted individuals ($P = 0.04$) and the nucleocapsid deletion NRS31-33del enriched in unvaccinated individuals ($P = 0.01$; Fig. 1C); two mutations with no evidence of immune escape. While spike mutations K417N and H655Y were by ≥4 per cent more abundant in boosted individuals, these differences did not reach statistical significance ($P \geq 0.1$). Adaptive evolution in XBB.1.5 spike was studied using a Fast Unconstrained Bayesian Approximation (FUBAR) for inferring selection based on the difference of non-synonymous and synonymous mutation rates per site (dN-dS). Two of the three sites of strong diversifying selection were identical in boosted (sites 417, 408, and 655) and unvaccinated (sites 417, 655, and 614) individuals, with site 417 being the most prominent (Fig. 1D). Furthermore, in both groups, site 1,146 was under strong purifying selection. In addition to the pervasive selection studies using FUBAR, we also employed the Mixed Effects Model of Evolution (MEME) to screen for instances of episodic positive selection. MEME aids in identifying sites evolving under positive selection across a proportion of branches (Supplementary Table S1). We found evidence of episodic positive selection in the XBB.1.5 spike at five sites in individuals who received a booster (sites 408, 417, 477, 486, and 1,181) and at two sites in unvaccinated individuals infected with XBB.1.5 (sites 417, 486). Notably, sites 417 and 486 exhibited positive selection in both groups, with site 417 involved in the highest number of branches in both boosted (10 branches) and unvaccinated individuals (6 branches). Sites 408, 477, and 1,181 were only positively selected in individuals who received a booster, not in unvaccinated individuals, for both pervasive (FUBAR) and episodic (MEME) positive selection.

Overall, this analysis indicates that there are only minor signs of immune pressure when comparing sequences derived from boosted and unvaccinated individuals. The roles of these subtle differences still need to be further investigated and validated using larger datasets. Our data imply that XBB.1.5's rise was predominantly independent of booster vaccine pressure.

To understand the emergence of XBB.1.5 in the NYC area, we investigated a total of 2,397 XBB.1.5 genomes collected in this study area by the NYULH and other laboratories, together with a set of 'background' sequences comprising global SARS-CoV-2 genomes deposited in the GISAID database (Khare et al. 2021) from 1 August 2022, up to 4 February 2023 ($n = 24{,}060$; see the Methods section). We initially performed a discrete phylogeographic analysis considering only the two discrete locations, 'NYC area' and 'other', to delineate XBB.1.5 clades circulating within the study area. Following Dellicour et al. (2023), a XBB.1.5 clade circulating in the NYC area was defined as a clade introduced into the study area and connecting at least three sampled viral genomes.

We identified a total of 617 distinct XBB.1.5 clades that were introduced into the study area. The vast majority of these clades, 73.4 per cent, consisted only of one sequence each. Notably, we observed one particularly large clade, encompassing 49 per cent of the XBB.1.5 sequences collected in the NYC area (1,168 sequences out of 2,397). This clade, referred to as 'clade 1', has been circulating since the beginning of September 2022, nearly 1 month before the detection of XBB.1.5 variant circulation in the NYC area. Furthermore, XBB.1.5 clade 1 appears dispersed throughout the phylogeny of XBB.1.5 sequences and basal to the other XBB.1.5 clades identified in the NYC area. The complementary discrete phylogeographic analysis, which exclusively includes XBB.1.5 sequences, consistently suggests that the inferred location for XBB.1.5 clade 1 is the NYC area (with a location probability of 0.99; Supplementary Fig. S3). This suggests that XBB.1.5 clade 1 initially emerged within or at least in the close vicinity of the NYC area. In contrast, the other clades likely originated from XBB.1.5 viruses that had left the NYC area and subsequently re-entered it. It is essential to acknowledge that while each lineage represents a local transmission chain, either originating within or introduced to the study area, we expect this number to be underestimated. Very likely, lineages could have remained unobserved due to incomplete or uneven subsampling, or they might have become aggregated into

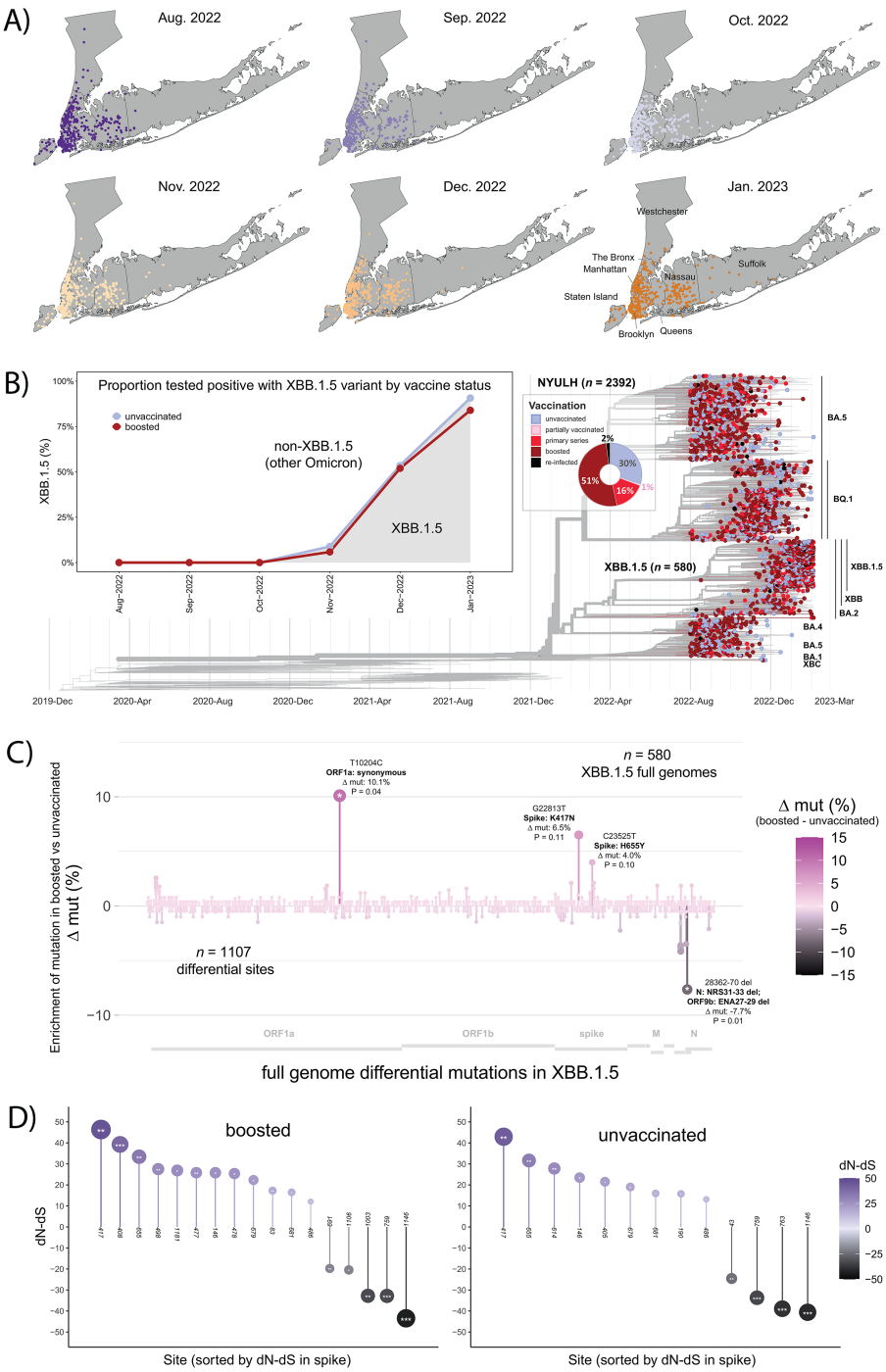

Figure 1. XBB.1.5 global distribution, lineage prevalence, and mutation analyses by vaccine status. (A) Geographic distribution of SARS-CoV-2 samples collected by the NYULH genomic surveillance effort between 1 August 2022 and 4 February 2023 in the NYC area per month. The last plot corresponds to the month of January 2023 until 4 February 2023. (B) Time-calibrated maximum-likelihood tree of North America-focused global SARS-CoV-2 sequences, filtered for the 2,392 NYULH sequences collected in the state of New York and annotated by vaccination/re-infection status. Pie chart indicates distribution by vaccination/re-infection status. Box: probability of detection of XBB.1.5 by month in boosted (red) individuals compared to unvaccinated individuals (grey), adjusted for month of test, sex, and age of the participants. (C) Site-specific spike mutation analysis in SARS-CoV-2 booster vaccine breakthrough sequences compared to unvaccinated controls. The Wuhan-Hu-1 sequence served as the reference for mutation calling. The mirror plot displays differences in mutation frequencies per full genome residue between boosted and unvaccinated groups, shown along the x-axis. Bars facing up and down refer to elevated mutation frequencies in boosted and unvaccinated individuals, respectively. Study number, observed differential mutation sites (muts), and most enriched mutations are indicated. (D) Adaptive evolution analysis of all spike residues using a fast, unconstrained Bayesian approximation for inferring selection (FUBAR, Datamonkey) based on the differences of non-synonymous (dN) and synonymous (dS) mutation rates per site. The analyses were done for boosted and unvaccinated individuals infected with XBB.1.5. All sites with significant positive (facing up) and negative (facing down) selection are shown along the x-axis. The dots are coloured in a gradient based on the dN-dS value, as indicated in the legend. Their size corresponds to the absolute value of the dN-dS value. The y-axis displays the difference of non-synonymous and synonymous mutation rates per site. Posterior probabilities (PP) > 0.9 are considered significant (*PP > 0.9; **PP > 0.95; ***PP > 0.99) and are indicated by asterisks inside the circles.

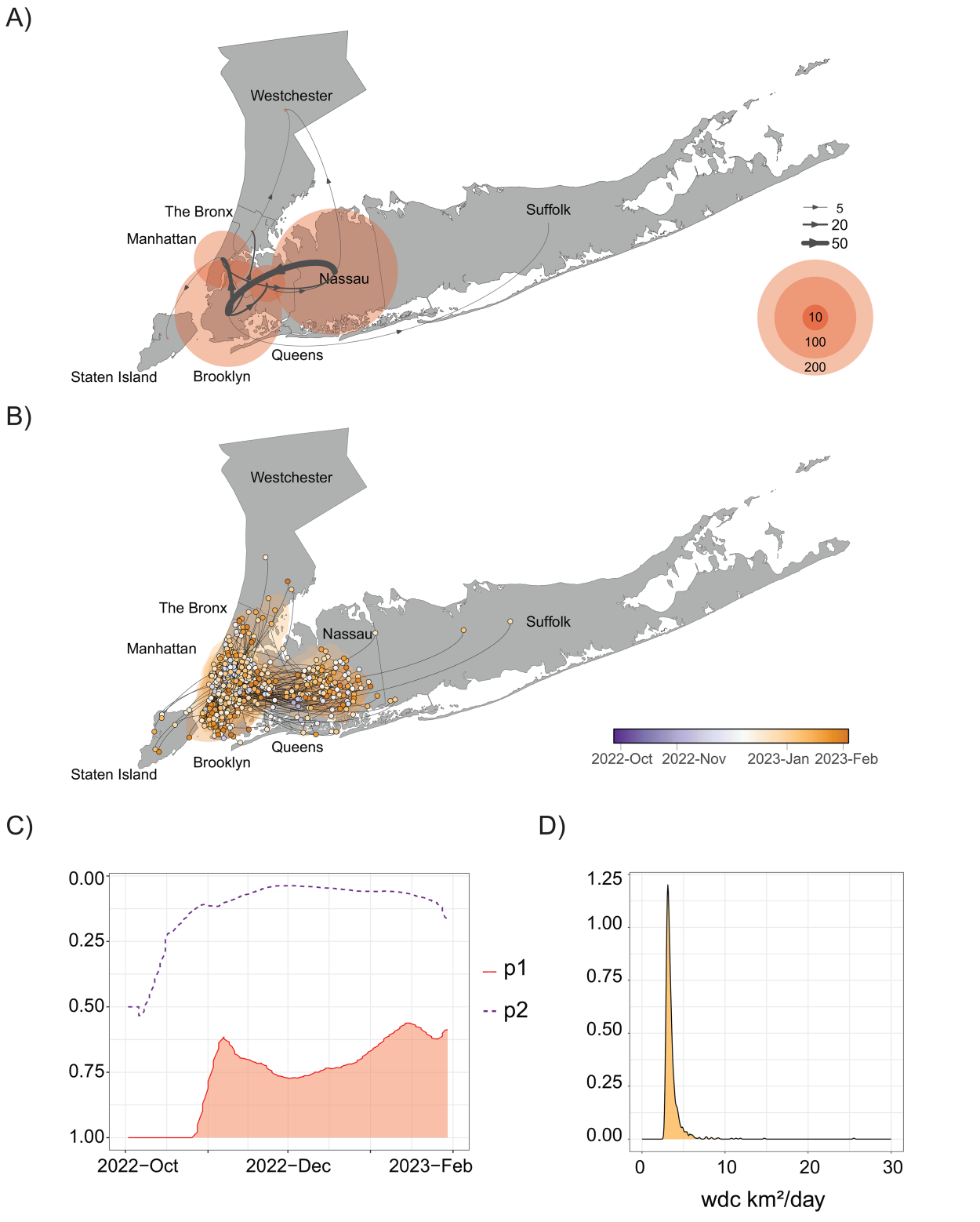

Figure 2. Dispersal dynamics of XBB.1.5 lineages in the NYC area. (A) Discrete phylogeographic reconstruction showing the dispersal patterns of XBB.1.5 within the area. Arrows represent inferred transition events between different counties/boroughs, while the circles show transitions within the same county/borough. Only transition events with an adjusted Bayes Factor (BF) >3 are shown. (B) Dispersal history of XBB.1.5 lineages inferred by continuous phylogeographic analysis. The maximum clade credibility (MCC) tree is shown, along with the 80 per cent high posterior density (HPD) regions, illustrating the uncertainty associated with phylogeographic inference. (C) Evolution of the probability p_1 that two randomly selected circulating lineages belong to the same clade independently introduced into the study area (solid curve), and the proportion p_2 calculated as the ratio of circulating clusters to phylogenetic branches occurring concurrently across the study area (dashed curve). (D) Posterior distribution of the weighted diffusion coefficient (km^2/day).

a lower number due to the low genetic diversity displayed upon the emergence of a new variant.

We also studied the dispersal dynamic of the XBB.1.5 lineages within the NYC area. To this end, we conducted discrete and continuous phylogeographic analyses, including viral genomes for which we had county-level sampling location information (totalling 377 XBB.1.5 genomes; Fig. 2). During the initial month of XBB.1.5 variant circulation in the NYC area, the probability that two circulating viruses belong to the same clade, as measured by metric p_1, approached a value of 1 (Fig. 2C). Subsequently, this probability declined, indicating an increase in the number of circulating clades. Nevertheless, over time, the number of circulating clades relative to the total number of circulating viruses remained consistently low, as indicated by the metric p_2 (Fig. 2C). This pattern of p_1 and p_2 metrics mirrors the dynamics of the SARS-CoV-2 Iota variant. This variant has been suggested to have emerged in the vicinity or even within the NYC area as described in a previous study (Dellicour et al. 2023). This similitude further supports the hypothesis that XBB.1.5 likely emerged within or in close proximity to the NYC area.

On average, each XBB.1.5 clade invaded three counties (corresponding to distinct NYC boroughs), with a 95 per cent high posterior density (HPD) of [3.73–3.82]. In general, viral lineages tended to migrate between counties that were geographically close to each other, with Nassau to Brooklyn (Kings County) and Brooklyn (Kings County) to Manhattan (New York County) being most prominent among-county dispersal events (Fig. 2A). We estimated that the proportion of phylogenetic branches associated with a transition event between counties, a metric referred to as p_3, was 0.37 (95 per cent HPD = [0.35–0.41]). Notably, this proportion was found to be higher in comparison to what was observed for the Alpha and Omicron BA.1 variants that were studied in the same area (Dellicour et al. 2023). Yet, the weighted diffusion coefficient for XBB.1.5 was estimated at 3.3 km^2/year (95 per cent HPD = [2.74–4.97]), an estimate comparable to that of the Alpha variant but four times lower than that of the Omicron BA.1 variant (Dellicour et al. 2023) (Fig. 2D).

We acknowledge two main limitations in our study. Firstly, we did not jointly infer the phylogenetic tree and the ancestral locations of its internal nodes, which hinders to fully account for the uncertainty associated with the Bayesian phylogenetic inference in the phylogeographic reconstruction. However, we opted for this approach due to the computational constraints imposed by the large data set in our study (n = 24,060 sequences). Secondly, it is important to note that our estimation of the various circulating XBB.1.5 lineages relies on the currently available data, and these numbers are likely underestimated. Similarly, the discrete and continuous Bayesian phylogeographic analyses relied on a subset of genomes (n = 377) for which associated zip code data were available.

In summary, we here applied phylogeographic methods to investigate the emergence and to reconstruct the dispersal history of the XBB.1.5 variant in the NYC area, in a discrete and continuous space, which allowed us to investigate the capacity of this variant to establish local transmission chains and to spread through the geographic area. These insights are key to understanding the pathogens dispersal dynamics, establishing the basis for retrospective conclusions that could inform future intervention strategies. Our study supports that the XBB.1.5 variant likely originated within or in close proximity to the NYC area. Similar to the emergence patterns observed with the Iota variant within NYC, XBB.1.5 initially circulated as a single lineage, and subsequently, smaller lineages emerged, very likely, corresponding to re-introductions events in the NYC area. While XBB.1.5 displayed a higher capacity to spread across different counties (shown by the p_3 metric), the preceding BA.1 variant exhibited a higher diffusion velocity, as indicated by the weighted diffusion coefficient metric.

Data availability

R scripts, sequence data, metadata file, and BEAST XML files associated with the phylogeographic analyses are all available at https://github.com/FabiGambaro/XBB.1.5_NYC.

Supplementary data

Supplementary data is available at *VEVOLU* Journal online.

Acknowledgements

We acknowledge the authors, originating laboratories, and submitting entities responsible for providing the sequences obtained from GISAID (Supplementary Table S1). FG and SD acknowledge support from the *Fonds National de la Recherche Scientifique* (F.R.S.-FNRS, Belgium; grant n°F.4515.22). SD also acknowledges support from the Research Foundation—Flanders (*Fonds voor Wetenschappelijk Onderzoek—Vlaanderen*, FWO, Belgium; grant n°G098321N) and from the European Union Horizon 2020 project MOOD (grant agreement n°874850). We thank NYU Langone Health DataCore for supporting the extraction of the data for this study from clinical databases and the clinical laboratory technicians for assistance in testing, saving, and retrieving specimens, especially Joanna Fung and Dawn Ip. We also thank Dr Joan Cangiarella and Dr Dafna Bar-Sagi for their continuous support of genomic surveillance for SARS-CoV-2 at NYULH, including providing institutional funding for this study. The NYULH Genome Technology Center is partially supported by the Cancer Center Support Grant P30CA016087 at the Laura and Isaac Perlmutter Cancer Center and the National Institutes of Health Clinical and Translational Science award 3UL1TR001445-06A1S1. This research was also funded in part by the National Institutes of Health (grant number AI148574) and NIAID contract funding via 75N93021C00014 to M.J.M.

Conflict of interest: Mark J. Mulligan reports potential competing interests: clinical trials and laboratory research contract funding for vaccines and monoclonal antibodies for SARS-CoV-2 with Lilly, Pfizer, and Sanofi; personal fees for Scientific Advisory Board service from Merck, Meissa Vaccines, Inc., and Pfizer. All other authors declare no conflicts of interest.

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Virus Evolution, 2024, **10(1)**, veae035
DOI: https://doi.org/10.1093/ve/veae035
Advance Access Publication 7 May 2024
Research Article

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