Journal of Medical Virology

WILEY

JOURNAL OF MEDICAL VIROLOGY

RESEARCH ARTICLE OPEN ACCESS

Integrated Genomic and Epidemiological Surveillance to Monitor SARS-CoV-2 Variants in Italy: Insights From the JN.1 Case Study (2023–2024)

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Received: 9 June 2025 | **Revised:** 21 November 2025 | **Accepted:** 14 December 2025

Funding: NextGenerationEU-MUR, Grant/Award Numbers: PE00000007, CUP H93C22000640007; SeCOV+, Grant/Award Number: 101102366

Keywords: epidemiology | Genetics | SARS coronavirus | Virus classification

ABSTRACT

The epidemiology of SARS-CoV-2 is marked by the continuous emergence of new lineages. Early detection and assessment of their transmissibility can be challenging for surveillance systems that rely solely on case time series data. Genomic surveillance, focusing on identifying and characterizing circulating variants, can provide early insights into their epidemiological impact. Phylogenetic and phylodynamic methods were applied to sequence data collected between October 2023 and January 2024 to study the transmission of the JN.1 variant in Italy. The genomic surveillance encompassed two data flows: flash surveys estimating variant prevalence and continuous sampling to identify emerging variants. We estimated the effective reproduction number (R_e) of JN.1 using a phylodynamic birth-death model. Results were compared with the daily net reproduction number (R_t) of SARS-CoV-2 estimated from time series of hospital admissions recorded through epidemiological surveillance. We traced back the appearance of JN.1 in Italy to October 2023, with subvariants emerging and co-circulating shortly thereafter. JN.1 became dominant nationwide by the end of 2023. According to phylodynamic analysis, the R_e of JN.1 was 1.73 (95% CI: 1.36–2.28) in mid-November, and its transmissibility declined over the following months. This trend aligned with R_t estimates from epidemiological surveillance, encompassing all co-circulating lineages. The high transmissibility of JN.1 anticipated the rise in its prevalence in the population and showed a temporal correlation with a transient increase in COVID-19 hospitalizations. Integrating genomic and epidemiological surveillance enhances pathogen monitoring and the assessment of new lineages' transmissibility, providing complementary evidence to patterns observed through standard surveillance.

1 | Introduction

The evolution of SARS-CoV-2 has become a highly dynamic process, marked by the relentless emergence of new variants and subvariants [1, 2]. The selective pressure exerted on the circulating lineages can favor mutations enhancing the viral transmissibility and/or immune evasion, thereby promoting their spread [3–5]. The epidemiology of SARS-CoV-2 infections has been characterized by successive waves of COVID-19 cases of varying intensity and associated with potentially different morbidity rates, driven by the genetic characteristics of the spreading variants.

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A standard approach for monitoring viral transmissibility relies on estimating the net reproduction number by applying the renewal equation to the time series of cases that test positive for the infection, exhibit symptoms, or are hospitalized [6, 7]. However, intensive surveillance efforts are costly and may not be sustainable in the long term. As a result, under conditions of relatively low disease burden and stable pressure on the healthcare system, surveillance efforts are typically scaled back and adapted to monitor warning signs of changing conditions, rather than continuously tracking every detectable case. Additionally, estimates based on the time series of confirmed cases can be strongly affected by fluctuations in case reporting, often biased towards more severe cases, and are unable to provide separate transmissibility estimates for co-circulating variants due to the availability of genetic characterization only for a limited set of identified infections.

Since 2021, genomic surveillance has been successfully applied to monitor SARS-CoV-2 variants. Genetic, phylogenetic, and phylodynamic analyses have enabled public health systems to rapidly identify and characterize emerging variants [8–10], as well as trace their origins and patterns of spread [11]. These efforts have contributed to the development of effective mitigation and containment strategies to counter new epidemic waves [8, 12]. In Italy, surveillance of SARS-CoV-2 is currently conducted through two complementary data flows: epidemiological and genomic.

In this study, we investigated how genetic and phylodynamic methods can successfully integrate the epidemiological analysis of new emerging SARS-CoV-2 variants. To this aim, as a proof of concept, we focused on the emergence and spread of the JN.1 variant in Italy, between 16 October 2023 and 31 January 2024. Internationally, the first confirmed case of JN.1 variant was identified in France in August 2023 [13]. The variant rapidly spread across American and European countries, eventually becoming prevalent globally at the beginning of 2024. JN.1 is a descendant of the Omicron lineage's BA.2.86 subvariant, characterized by more than 30 distinctive mutations in the spike protein [14]. JN.1 has subsequently given rise to multiple sublineages that dominate the current global circulation of SARS-CoV-2 variants [15].

During the study period, genomic surveillance of SARS-CoV-2 virus was conducted following two sequencing flows: 1) genomic surveys (hereafter denoted as "flash surveys") aimed at estimating variant prevalence by sequencing a representative sample of ascertained cases across the national territory on a given week of the month; and 2) continuous sequencing, applied to a subset of hospitalized patients with confirmed SARS-CoV-2 infection, enabling the early detection of variants or mutations. We analyzed the emergence of the JN.1 variant and its descendants, which together we refer to as JN.1*, as identified according to the Pango designation criteria as of 16 May 2024. The analysis of its temporal dynamics serves as an illustrative example of how the spread of new SARS-CoV-2 lineages can be assessed by integrating data from epidemiological and genomic surveillance.

2 | Materials and Methods

2.1 | Epidemiological Surveillance

Since February 2020, Italy notifies all laboratory-confirmed SARS-CoV-2 human infections to a national case-based surveillance system (hereby indicator-based surveillance) as previously described in Riccardo et al. [16]. The surveillance collects also the date of eventual hospitalization admissions. We analyzed the epidemiology of SARS-CoV-2 in Italy in the period September 2023–January 2024. We extracted epidemiological records, consolidated as of 27 May 2024, and we calculated the number of hospital admissions by day and week during the study period. We then estimated the net reproduction number (R_t) as previously described in [6] at national and at Region/Autonomous Province (AP) levels. Estimates of R_t assume that the generation time of newly emerging variants is comparable to that of pre-circulating variants and consistent across different lineages.

2.2 | Genomic Surveillance

In Italy, SARS-CoV-2 genomic surveillance and monitoring are regulated by official communications of the Minister of Health, updated according to the epidemiological situation (n. 0017975-17/03/2022-DGPRE-DGPRE-P, 0014186-05/05/2023-DGPRE-DGPRE-P, 0019476-01/07/2024-DGPRE-DGPRE-P and subsequent amendments, available at https://www.trovanorme.salute.gov.it/) and coordinated by ISS, in collaboration with the Ministry of Health. During the study period, in line with the national recommendations, sequencing data were collected, analyzed, and stored within the Italian COVID-19 genomic (I-Co-Gen) platform by a network of around 70 laboratories distributed across the country and involving all 19 Regions and two Autonomous Provinces (APs) of Italy. The sequencing was carried out using different NGS technologies according to protocols established by the originating laboratories. Lineage assignment was confirmed using Nextclade (https://clades.nextstrain.org/ accessed on 16/05/2024).

During the study period, three flash surveys were conducted: 13–19 November 2023, 11–17 December 2023, and 15–21 January 2024. Out of 820, 913, and 433 sequences collected in the three surveys, 52 (6.3%), 372 (40.7%), and 333 (76.9%) were identified as belonging to the JN.1* lineage (including JN.1 and its subvariants), respectively. A generalized linear model with a binomial distribution was applied to estimate the increase in JN.1* prevalence over time (day of the year).

Genomes collected through both flash surveys and continuous sequencing of COVID-19 hospitalized patients, covering all variants circulating between 16 October 2023 and 31 January 2024, were uploaded to GISAID [17]. From this dataset, we selected all sequences belonging to the JN.1* lineage that met minimal quality criteria, which included the absence of sporadic insertions or deletions and a coverage (i.e., the percentage of the genome sequenced) > 90%. The resulting dataset consisted of 1217 genomes, which were further analyzed using genomic modeling approaches.

2.3 | Genomic Diversity and Phylogenetic Analysis

To calculate the genetic diversity within and between JN.1 and JN.1 subvariants, the selected genomes were aligned using MAFFT V.7.520 [18]. Pairwise genetic distances were calculated using the p-distance model and 500 bootstrap repetitions with Mega 11. The distribution of JN.1 and JN.1 subvariants across

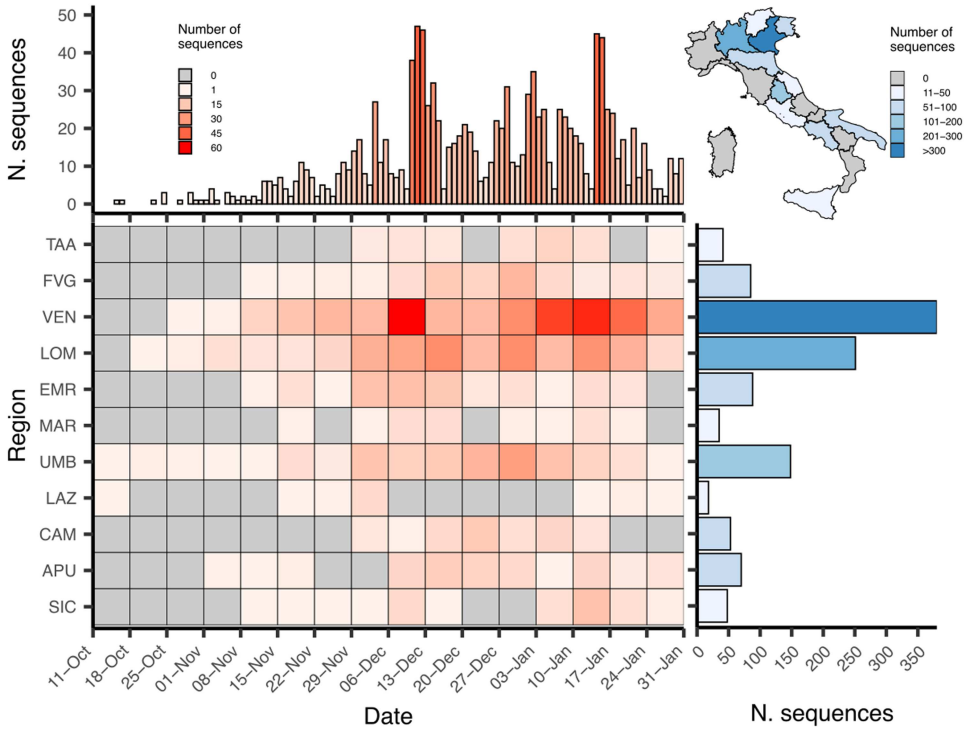

FIGURE 1 | Number of analyzed JN.1* (JN.1 and JN.1 subvariants) sequences collected in Italy from 16 October 2023 to 31 January 2024. Upper left panel) Number of sequences by date of collection. Lower left panel) Heatmap of the number of sequences by week of collection. Upper right panel) Map of Italian region contributing the sequences. Lower right panel) Number of sequences by region of collection. (Region name abbreviations: APU = Apulia, CAM = Campania, EMR = Emilia-Romagna, FVG = Friuli Venezia Giulia, LAZ = Lazio, LOM = Lombardy, MAR = Marche, SIC = Sicily, TAA = Trentino-South Tirol, UMB = Umbria, VEN = Veneto.

the Italian regions were evaluated by means of a maximum likelihood phylogenetic tree constructed using IQ-TREE v1.6.9 [19]. The phylogenetic tree included all the JN.1* genomes that met our inclusion criteria and was rooted to reference 'BA.2.86' (using the Nextclade reference Wuhan-Hu-1 with BA.2.86 SNPs), with bootstrap support values calculated from 1,000 replicates. The tree was built using the best substitution model (GTR + F) as identified through ModelFinder and visualized using TVBOT [20].

2.4 | Phylodynamic Analysis

To provide quantitative epidemiological insights on the new emerging variant, we performed a Bayesian phylodynamic analysis of the JN.1 sequences, using a birth-death skyline model (BDSKY) [21]. We used the BEAST2 software (v2.7.5) for the phylodynamic analysis and the R package "beastio" to inspect the parameter posterior distributions and assess convergence and sufficient sampling (effective sample size > 200).

This modeling approach enabled us to estimate key epidemiological indicators, including the variant specific reproduction number (R_e), representing its transmissibility potential; the 'uninfectious rate', which directly relates to the variant-specific generation time; the 'time of most recent common ancestor', informing on the time of initial (potentially unobserved) variant emergence; and the 'sampling proportion', which provides insights into the overall number of individuals infected by the variant during the study period. The phylodynamic model assumes a general time reversible (GTR) + G4 nucleotide substitution model and an uncorrelated, lognormally distributed, relaxed molecular clock, implying that every branch in a phylogenetic tree may evolve at different evolutionary rates. To investigate temporal changes of the variant's transmissibility, we assumed a prior Gamma-distributed R_e (shape = 2, scale = 1) to be piecewise constant over five intervals. For the uninfectious rate parameter, we assumed a lognormal prior distribution with a mean of 90 and a standard deviation of 0.4; for the origin parameter, we assumed a uniform prior distribution ranging from 0 to 5 years. Finally, for the sampling proportion, we assumed a Beta distributed prior (alpha = 1, beta = 3).

We applied the model to JN.1 sequences collected in Italy between 16 October 2023 and 31 January 2024. Specifically, based on the results of genomic diversity and phylogenetic analyses, JN.1 subvariant sequences were excluded from our baseline phylodynamic analysis to reduce computational time and complexity. To assess the model's robustness under this approach while accounting for computational constraints, we conducted a sensitivity analysis by comparing results from one illustrative Italian region using either all JN.1* sequences or only JN.1 sequences (i.e., with and without JN.1 subvariants). To do this, we selected the Veneto region because it shared the highest number of sequences and accounted for approximately one third (31.2%, $n = 380$) of all JN.1* sequences collected in Italy (Figure 1). An additional sensitivity analysis was conducted by considering that every branch in a phylogenetic tree evolves according to the same evolutionary rate, assuming a strict molecular clock with uninformative uniform prior. For each analysis, we carried out 100 million independent MCMC

runs, sampling every 1000 steps and discarding 10% of the initial iterations to account for the burn-in period. Finally, we compared the estimated reproductive number (R_e) of the JN.1 variant obtained from the phylodynamic model to the overall SARS-CoV-2 reproduction number (R_t), as inferred from the time series of hospitalized COVID-19 cases during the same period.

3 | Results

During the study period, 49089 hospitalizations were reported to the Italian National surveillance of SARS-CoV-2 infections. The median age was 79 (IQR: 67–86) and 49.2% ($n = 24152$) were women. Weekly cases almost steadily increased up to the middle of December 2023 and then continuously decreased at the minimum level in the last week of January 2024 (Figure 2). Figure S1 shows the temporal distribution of hospitalizations by Region/Autonomous province. In all cases, the peak was observed in December, with most of them showing a temporal trend similar to the one observed at the national level.

The JN.1 variant was first detected through the genomic flash survey in November 2023, with a point prevalence of 5.97% at the national level, when adjusted by the number of cases by region (see Figure 2). According to data collected through the flash surveys, JN.1 became the predominant SARS-CoV-2 variant circulating in Italy by the end of 2023, reaching a 77% national point-prevalence in the third week of January 2024 (see Figure 2).

Based on analyzed genomic data collected in Italy during the study period and shared on GISAID, according to the lineage assignment confirmed using Nextclade (accessed 16 May 2024) we retrospectively traced back the earliest JN.1 sequence to a case sampled on 16 October 2023 (Figure 1), before the official identification of the JN.1 variant through the national surveys. However, only later, during the week of 23–29 October 2023, distinct subvariants of JN.1 (i.e. with a limited number of mutations from JN.1 [22]) emerged and began to co-circulate with the original JN.1 (Table S1 for a complete list of JN.1 subvariants).

The proportion of JN.1 among JN.1* sequences remained approximately constant throughout the study period (Figure 3), resulting in 635 (52.1%) JN.1 sequences out of the 1217 JN.1* sequences analyzed.

All analyzed sequences reported the region of collection (Figure 1, Figure S2), while information regarding the age class and the admission in hospital of the sequenced cases was available for 75.8% ($n = 922$) and 43.2% ($n = 526$) of sequences, respectively. Similar percentages were observed between JN.1 and JN.1 subvariants (age class: 489 out of 635, 77.0% JN.1 vs 433 out of 582, 74.4% JN.1 subvariants; hospitalization: 276 out of 635, 43.5% JN.1 vs 250 out of 582, 43.0% JN.1 subvariants). Almost half of the sequenced cases for which the age class was reported were between 70 and 90 years of age; no differences were observed between JN.1 and JN.1 subvariants (Figure S3).

To evaluate the genetic distance between genomes belonging to JN.1 and JN.1 subvariants and to determine to what extent they should be considered as two distinct groups, inter and intra-group distances were calculated. The JN.1 group exhibited an

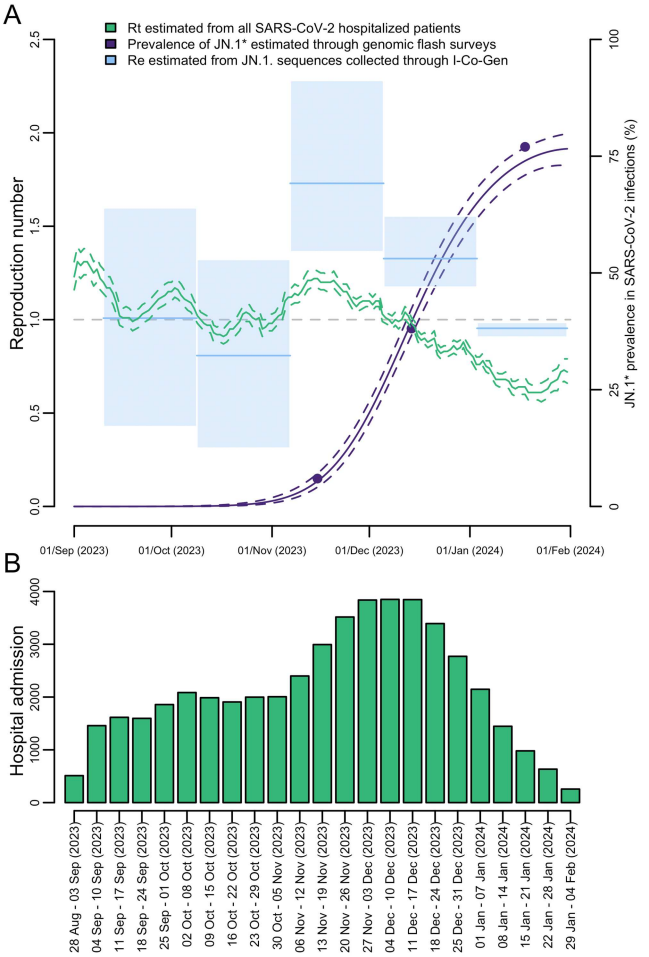

FIGURE 2 | (A) Estimated JN.1 transmissibility from the birth-death model applied to genomic data (blue lines: mean; shaded areas: 95% credible interval), and from the time series of cases testing positive for SARS-CoV-2 as collected through epidemiological surveillance (green line: mean; dashed lines: 95% credible interval). JN.1 prevalence as estimated by the flash surveys (purple line: mean; dashed lines: 95% confidence interval). (B) Total number of SARS-CoV-2 hospitalized patients by admission week.

internal distance with a standard deviation of $2.3 \times 10^{-4} \pm 1.5 \times 10^{-5}$, while the JN.1 subvariants group had a slightly higher internal distance of $3.3 \times 10^{-4} \pm 3.5 \times 10^{-5}$. The inter-group distance between JN.1 and JN.1 subvariants was calculated to be $3.0 \times 10^{-4} \pm 2.8 \times 10^{-5}$. This overall similarity among sequences is further supported by the phylogenetic tree, where only small clusters with significant bootstrap values (> 80) were identified. Additionally, Figure 4 shows how all sequences from different regions are interspersed and to what extent sequences from individual regions contributing a substantial number of sequences (e.g. the Veneto region corresponding to orange interconnections) are mixed with those of other regions without forming a distinct cluster.

Results from the phylodynamic model revealed a relatively high transmissibility of JN.1 during mid-November, with an estimated R_e of 1.73 (95% CI: 1.36–2.28). This finding aligns with evidence coming from flash surveys conducted at the same time, showing a progressive increase in the prevalence of JN.1 (see Figure 2). R_t estimates obtained from epidemiological

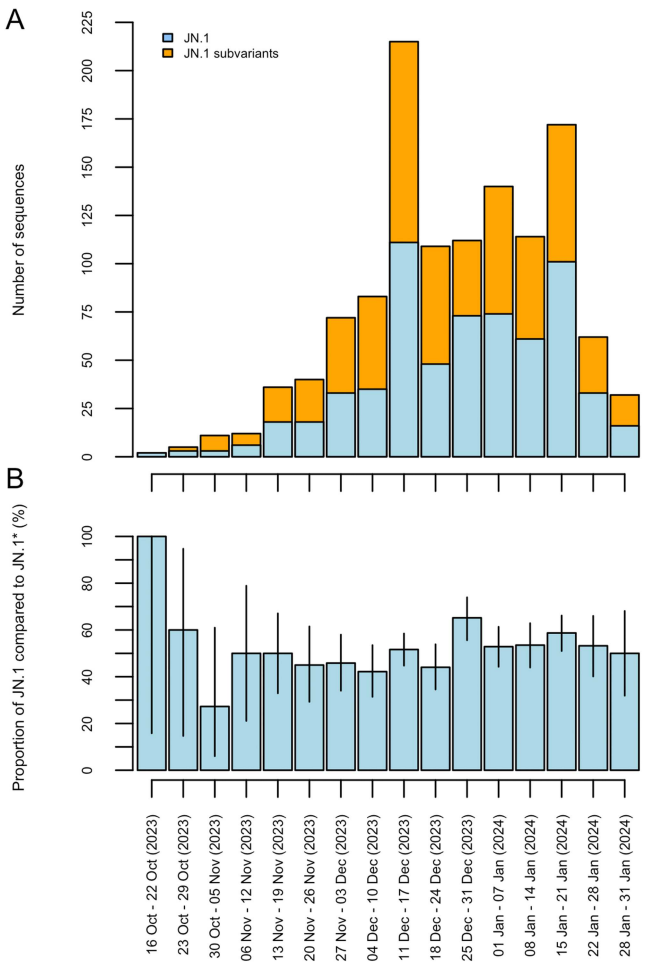

FIGURE 3 | (A) Temporal trend of JN.1 and JN.1 subvariants. Bars represent the number of sequences of JN.1 (light blue) and JN.1 subvariants (orange). (B) Proportion of JN.1 genomes identified among JN.1* (including both JN.1 and JN.1 subvariants) SARS-CoV-2 sequences collected in Italy between 16 October 2023 and 31 January 2024. The vertical lines represent the binomial 95% confidence interval of the estimated proportion.

surveillance records collected in the same period show a downward trend lasting until October 2023, followed by a sharp upsurge in November (from 0.98 to 1.22). A similar dynamic was observed in the number of hospital admissions associated with SARS-CoV-2 infection (see Figure 2).

R_e estimates obtained from the phylodynamic model show a decline in transmissibility in December 2023, reaching estimated values below the epidemic threshold (0.95, 95% CI: 0.91–0.99) at the beginning of 2024. This pattern coincided with JN.1* becoming the predominant SARS-CoV-2 variant circulating in Italy by the end of 2023 (Figure 2). The increased prevalence of JN.1, coupled with an estimated decrease in its reproduction number, correlated with a decline in R_t based on hospitalized cases. Specifically, R_t dropped below the epidemic threshold towards the end of 2023 and ranged between 0.61 and 0.82 in January 2024 (Figure 2).

The phylodynamic model also yielded a mean estimated duration of infectiousness of 5.4 days (95% CI: 2.9–9.2 days), which is consistent with available estimates for previous Omicron lineages (mean estimates ranging between 5.7 and 8.6 days [23]). The time to the most recent common ancestor (tMRCA) was estimated to fall between 15 August and 24 September 2023, in line with the emergence of JN.1 in Europe [13]. Our analysis also suggests that analyzed sequences represented the 0.22% (95% CI: 0.06%–0.58%) of all JN.1 infections occurred in the country during the reconstructed epidemic, suggesting that as of 31 January 2024, the circulation of the JN.1 variant might have caused approximately 110–1095 thousand SARS-CoV-2 infections in Italy. Similar estimates were obtained under the assumption of a strict molecular clock, with a mean duration of infectiousness of 5.38 days, a tMRCA falling between 15 August and 24 September, and approximately 113–985 thousand JN.1 infections occurring during the study period (Table S2). The temporal dynamics of the JN.1 reproduction number were also consistent, showing a peak of approximately 1.72 in early December, followed by a decrease in transmissibility that led to Re estimates below 1 in early February (Figure S4). A considerable overlap in the estimated trajectory of transmissibility was found when restricting the analysis to the sequences obtained from the Veneto region, either including or not JN.1 subvariants (see Figure S5 and Table S1).

4 | Discussion

In Italy, JN.1 and its subvariants rapidly became predominant between December 2023 and January 2024, almost replacing previously circulating variants. Our analysis reveals a high degree of genetic homogeneity among all JN.1* genomes analyzed, including both JN.1 and its subvariants. Although, as expected, the JN.1 group exhibited slightly lower diversity compared to the JN.1 subvariants, the phylogenetic tree analysis did not reveal well-supported bootstrap clusters, likely due to the high sequence similarity. This suggests an ongoing evolutionary process marked by a high degree of genetic relatedness among circulating variants. These findings support the assumption that JN.1 can serve as a representative of the entire JN.1* group for phylodynamic analyses, thereby reducing computational constraints.

The rapid spread of JN.1* observed over a relatively short period – about 1 month and a half from emergence to dominance – underscores its high transmissibility compared to pre-circulating strains. We found that the temporal expansion of JN.1* correlates with a swift, albeit brief, wave of hospital admissions detected by monitoring epidemic trends from epidemiological surveillance data. This surge was relatively short-lived, with the variant's specific transmissibility peaking in early November and subsiding within a couple of months. In principle, the increasing prevalence of JN.1* and the high transmissibility we estimated for JN.1 in early November could also be associated with the development of new immune escape mechanisms or an increased ability to infect specific niches of susceptible individuals [13, 24, 25]. During the 2023–2024 season, the Italian Ministry of Health recommended administration of the updated monovalent XBB.1.5 mRNA vaccine as a booster for individuals aged ≥ 60 years and for younger people with high frailty due to underlying medical conditions, with priority given to those aged ≥ 80 years, residents of long-term care facilities, and individuals with chronic diseases [26]. However, vaccination coverage among the elderly remained modest, with 11.7% of individuals aged 70–79 years and 15.8% of those aged ≥ 80 years receiving a

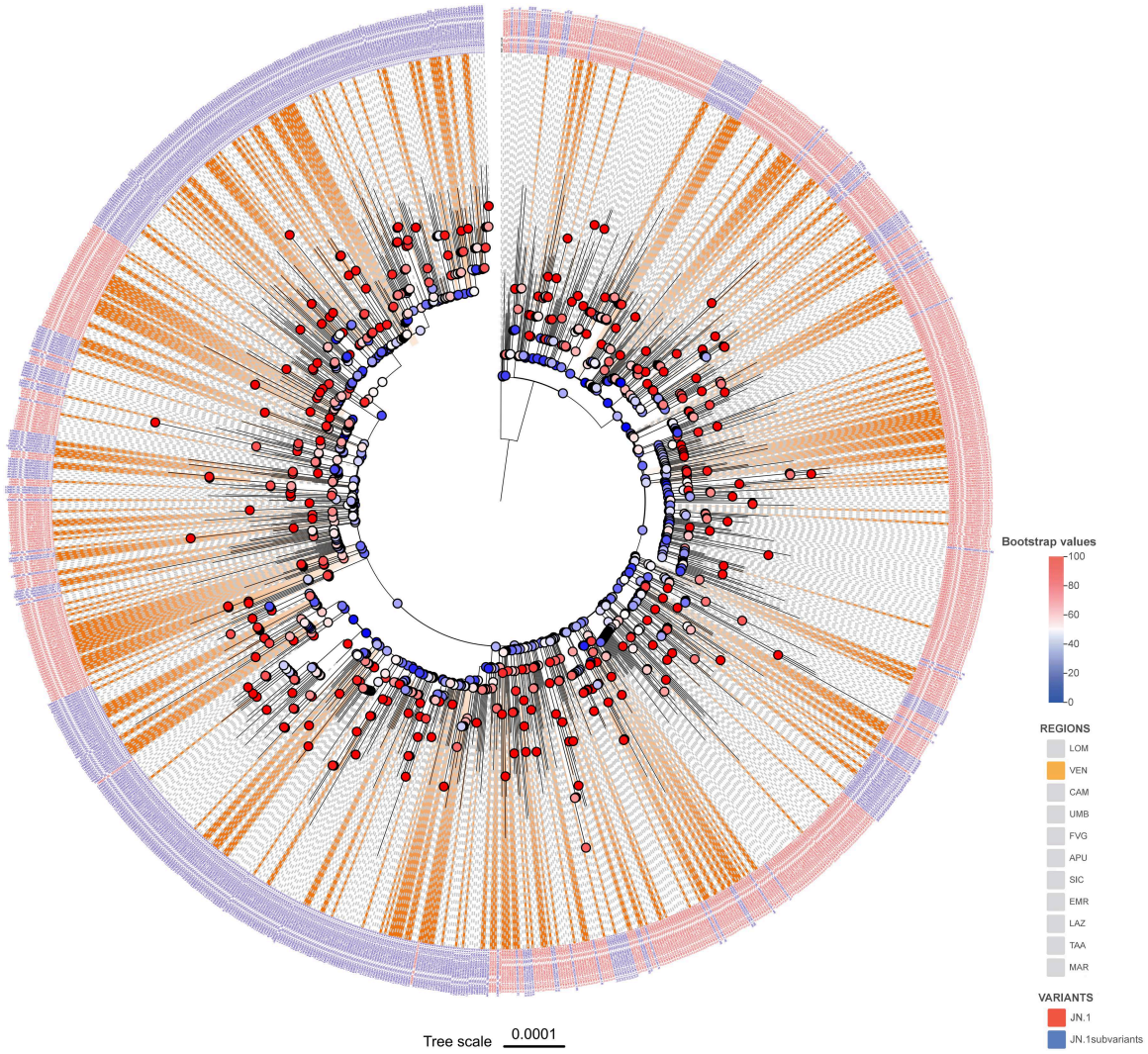

FIGURE 4 | Phylogenetic analysis of JN.1 and JN.1 subvariants used in this study. Maximum likelihood phylogenetic tree of full-length genomes of JN.1 (names in red) and JN.1 subvariants (names in blue). The orange interconnections highlight the genomes coming from the Veneto region. Bootstrap values are represented by colored circles on the nodes, with the color gradient blue to red shown in the legend corresponding to low to high confidence. The tree scale is 0.0001 and quantifies the genetic differences (nucleotide substitutions per site) shown by branch lengths (black lines).

booster between September 2023 and July 2024 [27]. Although vaccination may have partially influenced transmission dynamics, its overall impact was likely limited. During this period, no age-specific social distancing measures were in place, and most COVID-19–related restrictions in Italy had already been lifted. Given the complex epidemiological landscape associated with SARS-CoV-2, including uncertainties surrounding the current levels of both natural and vaccine-induced immunity within the considered population, it is not possible to draw definitive conclusions about the factors driving the temporary epidemiological success of JN.1 based only on the results presented here. Multiple lines of evidence – such as results from immune surveillance and severity data – would be required to provide a robust interpretation of the observed pattern.

Our estimates suggest that, following its rapid surge, the transmissibility of JN.1 began to decrease significantly. This pattern aligns well with the temporal qualitative trajectory of the (overall) SARS-CoV-2 net reproduction number, as estimated from the time series of hospitalized patients. However, our analysis reveals that transmissibility estimates differ significantly when comparing a phylogenetic approach applied to the spread of JN.1 (average R_e~1.7) with the assessment of overall SARS-CoV-2 transmissibility encompassing all co-circulating lineages based on epidemiological data (average R_t~1.2). This underscores the value of integrating diverse approaches to characterize the spread of new variants. The observed progressive decrease in the transmission potential of JN.1 could be due to several alternative or coexisting factors [28–30]. Firstly saturation, i.e. the reduction of susceptible because of acquired immunity. Secondly competition, i.e. the emergence or persistence of other circulating variants limiting the component of overall SARS-CoV-2 transmission due to JN.1. Thirdly, since we are measuring this decrease among hospitalized patients, the observed reduction in severity might reflect decreased JN.1 circulation only within hospitalized cases, and not necessarily in the general population or be a distinctive seasonal recurring pattern in SARS-CoV-2 epidemiology in Italy [31].

Moreover, limited evidence suggest that JN.1* exhibits either increased or reduced pathogenicity compared to other circulating variants [32].

Accurately characterizing specific SARS-CoV-2 variants in terms of transmissibility and attack rates remains a significant challenge due to the availability of samples eligible for the sequencing and the testing policy. However, phylodynamic analyses may effectively integrate and increase the granularity to data collected through epidemiological surveillance. Here we show that combining these two sources can provide valuable insights into transmission patterns by allowing the production of estimates that are associated with specific lineages significantly reducing uncertainties underlying complex epidemiological dynamics. For instance, by leveraging the estimated sampling proportion, we also derived an approximate estimate of the infection attack rate of JN.1 during the considered period. Despite the uncertainty of the obtained estimates, such a result is well beyond what can be estimated using data collected only through routine epidemiological surveillance [8]. More in general, when testing is predominantly limited to hospitalized patients – as in the case for SARS-COV-2 in Italy in 2024 – combining genetic and phylodynamic methods with standard analyses of epidemiological surveillance data may become essential for monitoring complex epidemiological patterns and epidemic trends occurring in the general population.

Nonetheless, several limitations need to be considered when interpreting our results. First, we neglected any geographical pattern in the spread of the infection and therefore considered the progressive expansion of JN.1 as an epidemic occurred at national scale. This may have introduced a bias in our analysis due to potentially different sampling efforts carried out across regions, different local transmission patterns, or the likely heterogeneous representativeness of collected samples of the viral diversity cocirculating during the study period. However, the phylogenetic tree of full-length genomes of JN.1 and JN.1 subvariants demonstrated that circulating variants were not geographically restricted but rather exhibited a uniform distribution across different regions. This supports the idea that individual regions contributing a substantial number of sequences may serve as arbitrary yet representative proxies of nationally circulating variants when applying phylodynamic approaches, which are computationally intensive and may become impractical when applied to very large sequence datasets. Specifically, as an illustrative example, we show that phylodynamic analyses conducted using samples exclusively from one region yielded estimates consistent with those obtained when including data from all regions. Second, we should acknowledge that genetic epidemiology is highly dynamic, with the classification of variants and their subvariants being continuously revised as new information becomes available. This means that estimates obtained from sequencing data should be progressively and carefully revised over time. Although our results highlight the potential of phylodynamic approaches in providing complementary evidence on the epidemiological patterns detected through standard surveillance of cases, non-negligible computational challenges may still arise from the analysis of large datasets of sequences gathered during large and widespread epidemics.

The approach described here will be valuable in illustrating the spread mechanisms of SARS-CoV- 2 variants that may emerge in the future, during a time when the virus is no longer considered pandemic but endemic. Given the complex and ever-evolving immunity landscape associated with SARS-CoV-2, maintaining and enhancing the integration of different surveillance systems is required to equip public health systems with multiple and adaptive strategies to control and monitor new variants as they emerge.

Author Contributions

Mattia Manica, Emanuela Giombini, Paola Stefanelli, Stefano Merler, Piero Poletti, and Patrizio Pezzotti conceived the study. Piero Poletti, Paola Stefanelli, and Stefano Merler supervised the study. Mattia Manica, Emanuela Giombini, Martina Del Manso, Carla Molina Grané, and Daniele Petrone performed analysis. All authors contributed to interpreting the results; and read, reviewed, and approved the final version and the submission of the manuscript.

Acknowledgments

We gratefully acknowledge all data contributors, i.e., the Authors and their Originating laboratories responsible for obtaining the specimens, and their Submitting laboratories for generating the genetic sequence and metadata and sharing via the GISAID Initiative, on which this research is based (https://doi.org/10.55876/gis8.250411yo). The authors especially thank: Stefano Morabito, Arnold Knijn, Gabriele Vaccari, Ilaria Di Bartolo, Luca De Sabato (Department of Food Safety, Nutrition, and Veterinary Public Health, Istituto Superiore di Sanità, Rome, Italy) as well as the Italian Genomic Laboratory Network (I-Co-Gen) and Regional/AP epidemiological representatives. This work is supported by R.I.Pr.E.I-ISS (as per art. 34bis, Law. 106 - 23 July 2021) and NextGenerationEU-MUR PNRR Extended Partnership Initiative on Emerging Infectious Diseases (project no. PE00000007 - Missione 4 Componente 1 CUP H93C22000640007) and funded by the European Union under Grant Agreement no. 101102366 for the project Enhancing whole genome sequencing (WGS), national infrastructures and capacities for COVID-19 and surveillance of other respiratory viruses in Italy (SeCOV +). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HADEA). Neither the European Union nor the granting authority can be held responsible for them.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The genomic data that support the findings of this study are openly available in GISAID at https://doi.org/10.55876/gis8.250411yo. The epidemiological data contain confidential information, and public data deposition is not permitted. Due to the sensitive nature of these data, limited epidemiological data are available at the link https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Figure S6.