

Research Article

The spatiotemporal analysis of SARS-CoV-2 transmission in China since the termination of the dynamic zero-COVID policy

Jiaying Li^a, Jingqi Yang^a, Xiao Ding^a, Hangyu Zhou^a, Na Han^a, Aiping Wu^{a,b,*}^a State Key Laboratory of Common Mechanism Research for Major Diseases, Suzhou Institute of Systems Medicine, Chinese Academy of Medical Sciences & Peking Union Medical College, Suzhou 215123, China^b Key Laboratory of Pathogen Infection Prevention and Control (Peking Union Medical College), Ministry of Education, Beijing 100730, China

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ABSTRACT

China's dynamic zero-COVID policy has effectively curbed the spread of SARS-CoV-2, while inadvertently creating immunity gaps within its population. Subsequent surges in COVID-19 cases linked to various SARS-CoV-2 lineages post-policy termination necessitate a thorough investigation into the epidemiological landscape. This study addresses this issue by analyzing a comprehensive dataset of 39,456 high-quality genomes collected nationwide over an 11-month period since policy termination. Through lineage assignment, phylogenetic analysis, pandemic pattern comparison, phylodynamic reconstruction, and recombination detection, we found that China's post-epidemic period could be divided into three stages, along with dynamic changes in dominant lineages. Geographical clustering of similar lineages implies the importance of cross-border cooperation among neighboring regions. Compared to the USA, UK, and Japan, China exhibits unique trajectories of lineage epidemics, characterized by initial lagging followed by subsequent advancement, indicating the potential influence of diverse prevention and control policies on lineage epidemic patterns. Hong Kong, Shanghai, and Hubei emerge as pivotal nodes in the nationwide spread, marking a shift in the transmission center from east to central regions of China. Although China hasn't experienced significant variant emergence, the detection and validation of the novel recombination event, XCN lineage, underscore the ongoing virus evolution. Overall, this study systematically analyzes the spatiotemporal transmission of SARS-CoV-2 virus in China since the termination of the dynamic zero-COVID policy, offering valuable insights for regional surveillance and evidence-based public health policymaking.

1. Introduction

Since the outbreak of COVID-19 in late 2019, SARS-CoV-2 has spread widely and evolved around the world (Markov et al., 2023; Tan et al., 2020). Accompanied by the emergence of multiple variants of concern (VOCs), the virus has engendered at least five waves of infection in numerous countries (Levi et al., 2024; Markov et al., 2023). Notably, China has adhered to a dynamic zero-COVID policy for over two years, aiming for short-term eradication of cases (Moeti et al., 2022; Zhou et al., 2020). This stringent strategy, marked by robust containment and isolation measures, effectively suppressed the spread of SARS-CoV-2, resulting in a substantial reduction in COVID-19 cases and fatalities (Ba et al., 2023). While this dynamic zero-COVID policy has safeguarded public health to a certain extent, it has concurrently posed immune challenges for the Chinese population. Given that a significant proportion of individuals lack natural infection experience or passive immunity from

diverse variants, the immune system's proficiency in recognizing and combating novel SARS-CoV-2 variants is relatively compromised (Andrews et al., 2022; Liu and Liu, 2023). In comparison to countries experiencing multiple infection waves, China exhibits a "cleaner" immune landscape (Liu and Liu, 2023).

On December 7, 2022, the Chinese government announced the relaxation of strict social isolation and the cessation of mandatory polymerase chain reaction (PCR) testing, signifying the conclusion of the dynamic zero-COVID policy. Subsequently, various SARS-CoV-2 lineages, such as BA.5 and BF.7 in the early stages (China CDC, 2023), swiftly spread across the nation, leading to a transient upswing in COVID-19 cases in China (Goldberg et al., 2023; Pan et al., 2023). To discern the specific lineages propelling this rapid epidemic, several studies have focused on monitoring or estimating the epidemiological condition (Huang et al., 2023; Ioannidis et al., 2023; Li et al., 2023; Zhou et al., 2023), transmission dynamics (Goldberg et al., 2023; Liu and Xu, 2023;

* Corresponding author.

E-mail address: wap@ism.cams.cn (A. Wu).<https://doi.org/10.1016/j.virs.2024.09.003>

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Pan et al., 2023), or clinical symptoms (Liu et al., 2024) of SARS-CoV-2 lineages in China after the policy termination. However, these studies were predominantly concentrated in a few cities (Huang et al., 2023; Li et al., 2023; Liu et al., 2024; Pan et al., 2023), a limited number of lineages (Leung et al., 2023; Pan et al., 2023), or a period of less than three months (Leung et al., 2023; Liu and Xu, 2023). These studies provided a partial mirror image of the China's post-epidemic era and initially addressed the concerns regarding the potential emergence of entirely new variants. However, a comprehensive examination of the composition and replacement dynamics of SARS-CoV-2 lineages over an extended period following the cessation of the dynamic zero-COVID policy is notably lacking. Additionally, considering the distinctive immune status of the Chinese population, it remains unknown whether there are discernible differences in the epidemic characteristics of these lineages compared to other countries during the same period.

In this study, we retrieved and analyzed 39,456 high-quality Chinese SARS-CoV-2 sequences sampled within eleven months since the termination of China's dynamic zero-COVID policy. Leveraging these genomes and corresponding metadata, we analyzed and described the co-epidemic characteristics of multiple SARS-CoV-2 lineages across various provincial-level administrative regions in China. We then conducted a comparative analysis with the United States (USA), the United Kingdom (UK), and Japan. Our findings revealed that China's post-epidemic period could be divided into three stages, during which the virus transmission centers changed. Additionally, we found that geographically neighboring regions usually shared similar epidemic lineages. Moreover, we observed a unique feature in the pandemic dynamics of these lineages in China - an initial lag followed by subsequent advancement - when compared to other countries. Finally, we identified a novel recombination event, the XCN lineage that was first detected in China. In all, this study systematically elucidates the epidemiological characteristics of SARS-CoV-2 in China since the termination of the dynamic zero-COVID policy.

2. Materials and methods

2.1. Data acquisition and preprocessing

To ensure the reliability of genomic epidemiological information and the integrity of regional sources in China, we retrieved the “Accession ID” of all Chinese sequences starting with “EPI_ISL” from the National Genomics Data Center (NGDC), which stands as one of China's largest and official genome databases under the China National Center for Bioinformation (CNCB) (CNCB-NGDC Members and Partners, 2023). This retrieval process was executed by setting the collection date range from December 1, 2022, to October 31, 2023. Following this, we downloaded genomes from the Global Initiative on Sharing All Influenza Data (GISAID) database (Shu and McCauley, 2017). These sequences were then subjected to a thorough quality control process using the Nextclade (Aksamentov et al., 2021) CLI 2.14.0 pipeline. Only sequences with a coverage exceeding 97% and deemed “good” in “qc.overallStatus” were retained. Furthermore, all qualified genomes were required to have complete collection dates and accurate province information. For sequences collected from the USA, UK, and Japan, the corresponding meta-files were accessed from the GISAID database (Supplementary Table S1) and subjected to the same screening criteria.

In addition, we gathered Chinese and global genome frequencies from the CoV-Spectrum (Chen et al., 2022) website (<https://cov-spectrum.org/>) for eight representative lineages. This batch of data served to verify the accuracy of our Chinese dataset, thereby enhancing the reliability of our epidemiological findings.

It is crucial to note that in this study, the term “provinces” collectively refers to the provincial-level administrative regions in China, encompassing 23 provinces, four direct-administered municipalities, two special administrative regions, and five autonomous regions. This

clarification ensures a comprehensive understanding of the geographical scope in our analysis.

2.2. Lineage assignment

For samples collected in China, lineage assignment was carried out with the Nextclade CLI 2.14.0, employing the Pango lineage designation. For sequences from the USA, UK, and Japan, we retained the Pango lineage as listed in the GISAID meta file. To manage the extensive sub-lineages, we grouped them into eight representative ancestor lineages or the “others” category. The selection criteria for these representative lineages were based on three principles: ensuring mutually exclusive evolutionary relationships, including as detailed lineage names as possible, and maximal inclusion of genomes. Guided by the Pango lineage designation rules and the monthly count of genomes for each lineage (Supplementary Table S2), we ultimately selected the following clusters as representatives: BA.5.2.48*, BF.7.14*, BA.2.75*, XBB.1.5*, XBB.1.9.1*, XBB.1.22.1*, XBB.1.16*, and EG.5.1* (Supplementary Table S3), with the asterisk (*) denoting their respective sub-lineages. This classification method effectively encompassed over 90% of the genomes in total (Supplementary Table S3).

2.3. Phylogenetic analysis

To display the relationship between lineages in China and the world, we estimated a maximum likelihood phylogenetic tree of all the enrolled Chinese sequences using Nextclade CLI tool. The generated “auspice.json” file was then put into the Auspice (Hadfield et al., 2018) web-based tool (<https://auspice.us>) to visualize the phylogenetic placement of the isolates. Secondly, to demonstrate the details of genetic evolutionary relationships more clearly among various lineages, we subsampled a small dataset comprising 300 sequences and conducted a phylogenetic analysis for them (Supplementary Table S4). Here, the covSampler (Cheng et al., 2022) v2.0.0 tool, a subsampling method with balanced genetic diversity developed for large-scale SARS-CoV-2 genome dataset, was used to accomplish the subsampling task. In covSampler, we set the minimum sequence length to 27,000 and applied the subsampling strategy as a comprehensive method. It provides a more uniform geographic distribution, and a relatively higher genetic diversity compared to the representative strategy, reducing the sampling bias across provinces and provide a more comprehensive reflection of lineages in Chinese dataset. The phylogenetic analysis was performed using the IQ-TREE (Minh et al., 2020) v2.1.4 method, while the best-fit model was determined as GTR + F + R2 (General Time Reversible, Empirical Base Frequencies, Two Gamma Rate Categories) nucleotide substitution model by its ModelFinder, with the reference (Wuhan-Hu-1) rooted. Finally, the phylogenetic tree was visualized by the R package ggtree (Yu et al., 2017) v3.0.4.

2.4. Pandemic pattern analysis

Based on the epidemiological information, we analyzed the spatio-temporal distribution of lineages using custom scripts available in our GitHub repository. The genomic distribution in China, as depicted in Fig. 1A, was generated using the hchinamap v0.1.0 R package. Province maps, illustrated in Fig. 1D, were plotted using the mapChina v0.1.0 R package. For each lineage, the “peak occurrence interval days” represented the interval days of the first peak occurrence time between China and other countries, while the “peak duration days” denoted the date duration of the middle 50% genomes of a lineage collected from each country. Lineage distribution in provinces was visualized using the pheatmap R package and clustered with the Manhattan method.

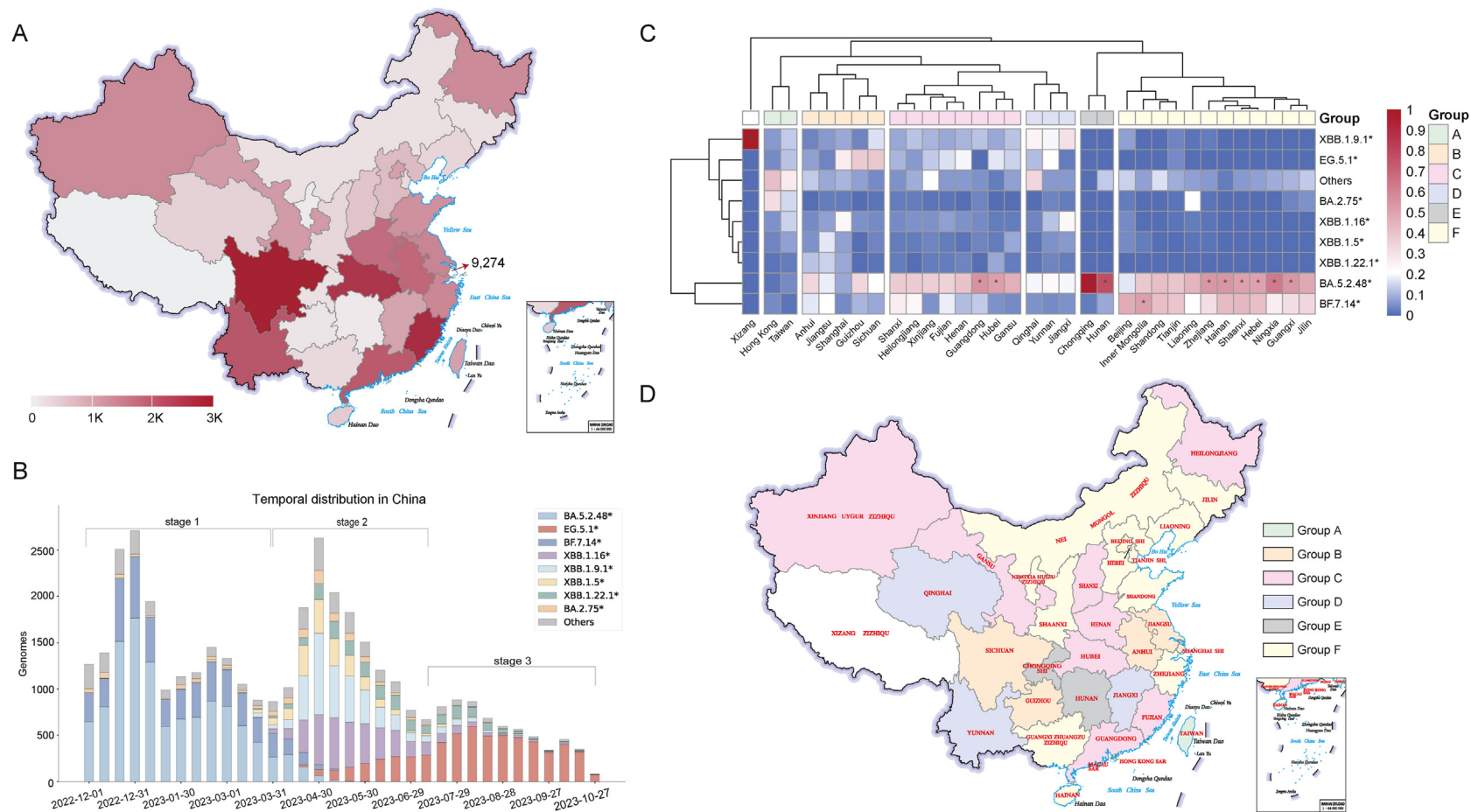


Fig. 1. Spatiotemporal distribution of lineages in China. **A** Spatial distribution of 39,456 genomes collected in China from December 1, 2022, to October 31, 2023. Colors indicate the absolute number of genomes per province. Shanghai, with 9274 sequences, is highlighted separately for clarity (marked by text and red arrows). **B** Temporal distribution of the 39,456 genomes during the pandemic in China. The y-axis represents the absolute number of genomes for different lineages within ten-day intervals. The post-termination period of the dynamic zero-COVID policy is divided into three stages based on the total sample size. **C** Distribution and clustering of Chinese epidemic lineages across provinces. The clustering pattern reveals at least six distinct groups (Group A–F). Since the absence of data from Macao, the province is not shown here. **D** Geographic distribution of the six pandemic pattern groups identified in (C).

2.5. Phylodynamic analysis

To retrospectively analyze the spatiotemporal dispersal patterns of the lineages pandemic in China after the termination of the dynamic zero-COVID policy, we subsampled one-tenth of Chinese genomes (Supplementary Table S5) using the covSampler tool, employing the comprehensive strategy to mitigate the sampling bias and ensure the maximum coverage across provinces.

Subsequently, we generated time-scaled tree phylogenies and inferred ancestral sequences with FastTree (Price et al., 2010) v.2.1.11 and TreeTime (Sagulenko et al., 2018) tools, as the method employed in previous studies (Tegally et al., 2022, 2023; Zhu et al., 2022). Specifically, FastTree generated Maximum-likelihood tree topologies with a General Time Reversible (GTR) model of nucleotide substitution. The resulting tree underwent inspection using the `-reroot` flag for “least-squares”, and the `-confidence` flag to establish 90% maximum posterior bounds for divergence times and state transition confidence levels, which is critical for the subsequent migration analysis. We then utilized the migration package extension of TreeTime to map province locations to tips and infer internal node locations under the GTR model. Additionally, R scripts were generated to quantify source-sink dynamics and viral movement patterns, available in our GitHub repository. We visualized transmission paths among provinces using rworldmap (South, 2011) v1.3-6 and ggplot2 v3.4.2 R packages, representing provinces by their respective capital city coordinates.

Furthermore, to analyze dynamic changes in inferred transmission paths during different periods, we divided a year into three stages based on genome number fluctuations and identified the first 20 main transmission paths for each stage to showcase their respective characteristics.

The map data of China presented in Figs. 1 and 3 and Supplementary Fig. S5 was obtained from the Ministry of Natural Resources Standard Map Service website GS (2019) 1680 and GS (2019) 1676, accessed on July 3, 2024.

2.6. Recombination analysis

Three methods were employed to detect potential recombination events that have occurred in China, including Nextclade CLI, rebar (Eaton, 2023), and CovRecomb (Li et al., 2024). CovRecomb was specifically utilized to determine the putative parental lineages for candidate recombinants, with maximum breakpoint number set at two and the minimum sequential feature mutation number set at four. The first collected recombinants were selected as ancient-like events for genomes with the same parental lineages, verified by searching sequences of parental lineages collected a month prior. Thus, all identified recombination events were validated from both genomic and epidemiological standpoints.

3. Results

3.1. Spatiotemporal lineage distribution in China

In total, 39,456 qualified sequences were downloaded from the GISAID dataset, covering the period from December 1, 2022, to October 31, 2023 (Fig. 1A, Supplementary Table S2). However, it is worth noting that due to the unavailability of genome data from Macao (also known as Macau), sequences from only 33 out of 34 provinces in China were included in the dataset. Shanghai contributed the most genomes (9,274, 24%), followed by Sichuan (2,862, 7%), Fujian (2,636, 7%), and Hubei (2,456, 6%) provinces (Fig. 1A, Supplementary Fig. S1A).

From the standpoint of lineage replacement, spanning almost a year, the majority of genomes were attributed to the BA.5.2.48 (29.12%), EG.5.1 (15.6%), BF.7.14 (13.92%), XBB.1.16 (9.73%), and XBB.1.9.1 (9.6%) lineages, along with their sub-lineages (Supplementary Fig. S1B). The composition of the dominant lineage(s) underwent approximately three phases (Fig. 1B, Supplementary Fig. S1C). The first stage, from

December 2022 to March 2023, witnessed the dominance of BA.5.2.48* and BF.7.14* lineages in China. The second stage, spanning from April 2023 to early July 2023, involved simultaneous pandemics of three or four lineages, including XBB.1.9.1*, XBB.1.16*, and XBB.1.5* or XBB.1.22.1*. The third stage, post-early July 2023, saw EG.5.1* emerging as the unequivocally dominant strain (Fig. 1B, Supplementary Fig. S1C).

Examining lineages within provinces revealed distinct compositions, with Xizang, Chongqing, and Hunan displayed notable dominant lineages, while others exhibited closer frequency and greater genetic diversity, exemplified by provinces such as Jiangsu and Shanghai. Additionally, at least six lineage pandemic patterns were discernible in China (Fig. 1C and D). Three of them had a concentrated distribution range, showing distinct geographical proximity (Fig. 1D, Groups A, B and E), while two of them distributed across more provinces with a relatively discrete distribution range, yet still displayed a tendency of geographical agglomeration (Fig. 1D, Groups C and F).

3.2. Dynamic shifts in lineage frequencies

As illustrated in Fig. 1B, the temporal evolution of SARS-CoV-2 lineages underwent discernible changes over the year following the conclusion of the dynamic zero-COVID policy. When compared to the publicly available Chinese dataset from Cov-Spectrum, our dataset exhibited a congruent trend (Supplementary Figs. S2A and B), though the trajectory observed in China markedly deviated from global patterns (Supplementary Fig. S2C). To further elucidate this distinction, the USA, UK, and Japan were chosen as representative countries of other countries for comparative analysis. The findings indicated a substantial prolongation of the overall periods of epidemic peaks for SARS-CoV-2 infection in China post dynamic zero-COVID policy termination, particularly notable during the second stage of concurrent pandemics involving multiple lineages from April 2023 to July 2023 (Fig. 2A).

Analyzing individual lineage epidemic cycles, we observed that in the initial six months post-policy termination, the peak dates for lineages (BA.5.2.48*, BF.7.14*, BA.2.75*, and XBB.1.5*) in China lagged behind those in other countries, with average intervals of 64.5 days (USA), 50.5 days (UK), and 34.25 days (Japan) (Fig. 2B and C). However, this trend was gradually broken while the XBB.1.9.1* appeared, and the trend was completely reversed after more than half a year, the peak dates for lineages XBB.1.22.1*, and XBB.1.16* in China generally preceding those in the USA, UK, and Japan, with average interval days of 85 days (USA), 128 days (UK), and 77 days (Japan) (Fig. 2B and C). By the appearance of EG.5.1* lineages in the second half of 2023, epidemic peak dates in various countries were basically similar. Importantly, there was no statistical disparity in the duration of the peak epidemic period for lineages across countries (Fig. 2D, Supplementary Fig. S2D). Certain lineages (e.g., BA.5.2.48*, XBB.1.5*, XBB.1.9.1*, and XBB.1.16*) displayed pandemic periods in Japan that fell between those in China and the USA or the UK (Fig. 2B).

From a phylogenetic aspect, lineages prevalent in China exhibited similarity to those worldwide (Supplementary Fig. S3A), suggesting no significant emergence of diverse variants within China. Additionally, the genetic relationships between lineages in China aligned with their chronological appearance and pandemic progression (Supplementary Fig. S3B, Fig. 2A).

3.3. Province-to-province transmission path inference

In addition to examining the overall spatiotemporal distribution of lineages, we conducted a comprehensive analysis of the dynamic transmission process of SARS-CoV-2. A total of 2101 transmission paths were deduced from 3945 comprehensively sampled sequences within the pool of 39,456 Chinese genomes (Supplementary Table S6). Due to the absence of Xizang genomes and the data from Macao, these two provinces were excluded from the inferred paths. The remaining 32 provinces

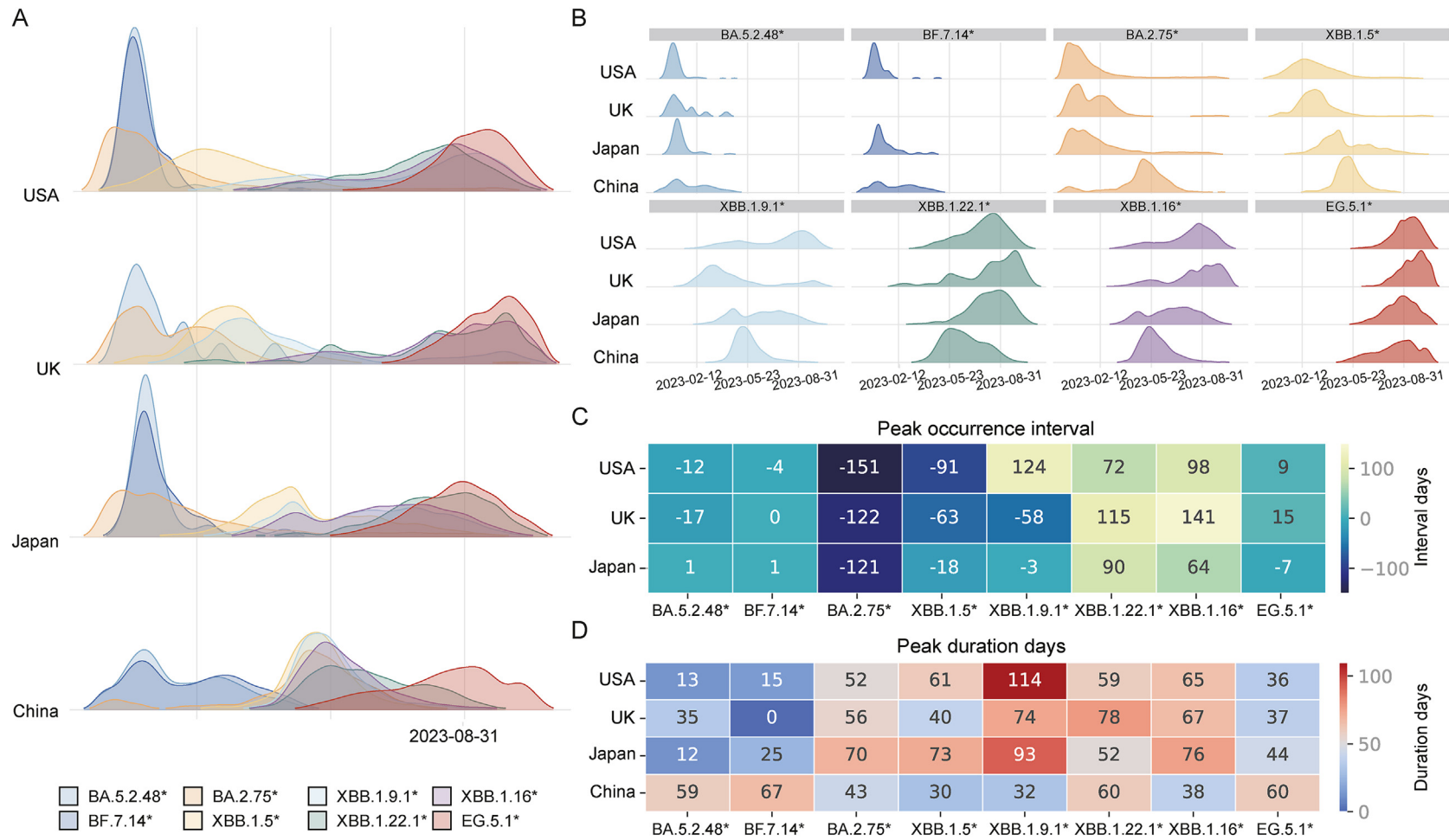


Fig. 2. Cross-country disparities in lineage pandemic patterns. **A, B** Temporal distribution of eight lineages in the United States (USA), the United Kingdom (UK), Japan, and China, presented on a unified horizontal axis (**A**) and categorized by lineages (**B**). **C** Derived from (**B**), the comparison of the first peak occurrence date for each lineage in the United States (USA), the United Kingdom (UK), and Japan with the corresponding dates in China. Negative values indicate a later occurrence in China, while positive values indicate an earlier occurrence. Numerical values represent the absolute number of interval days. **D** In concordance with (**B**), the calculation of the time span for genomes collected in the middle 50% of each lineage in each country, designated as the duration days for each respective country.

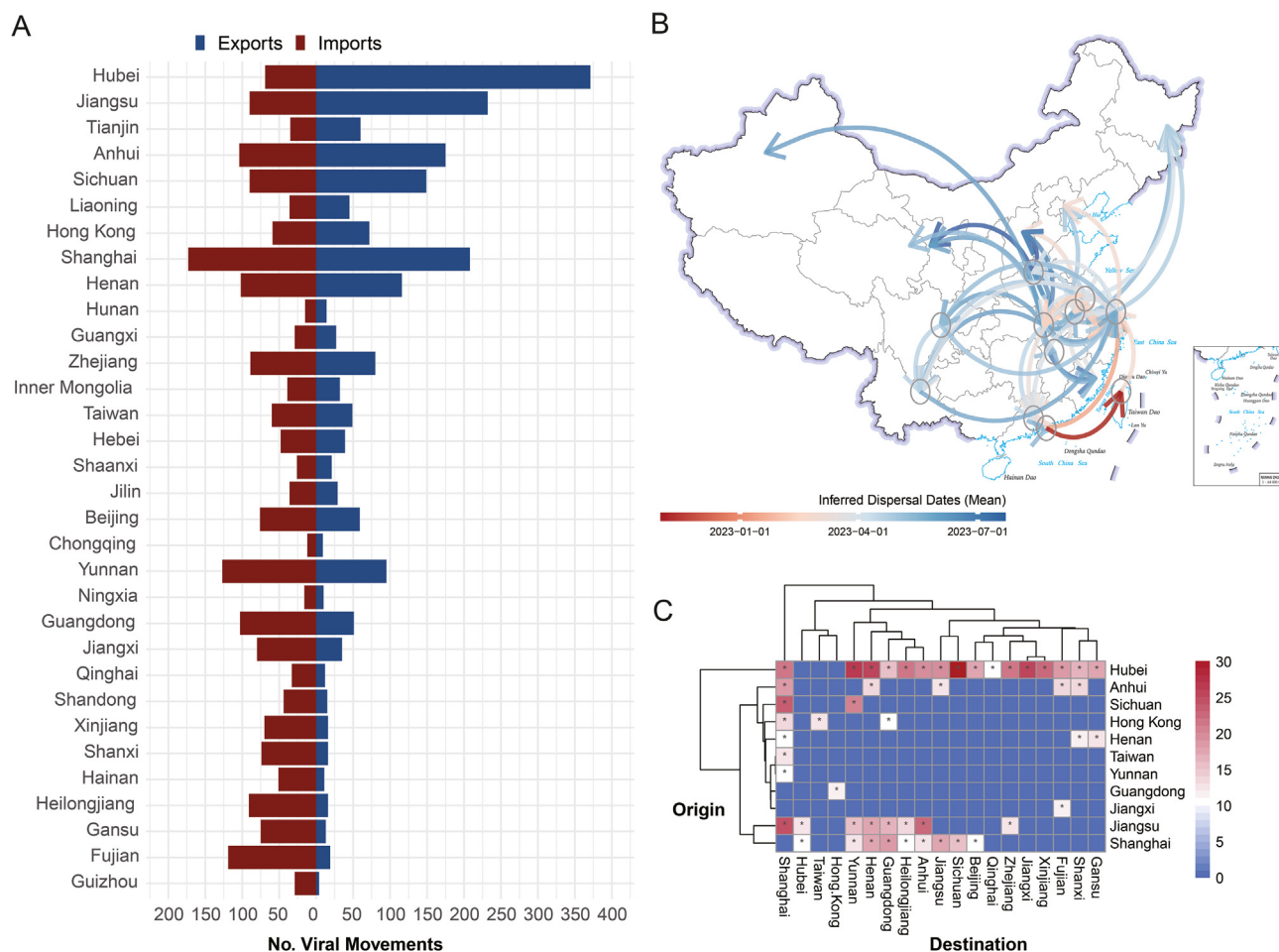


Fig. 3. Inference of provincial transmission paths. **A** Horizontal bar chart illustrating the absolute numbers of viral movements for provinces engaging in both exports and imports among the 2101 inferred transmission routes. Regions are sorted based on the ratio of exports to imports. Since genomes from Xizang and Macao of China are not included in the 3945 subsampled dataset, these two provinces are not displayed in the bar chart. **B** Top 50 enriched routes derived from the spatiotemporal dispersal pattern of the 3945 subsampled sequences in China. The presentation includes dissemination and source-sink dynamics aggregated in provinces, determined through ancestral state reconstruction analysis. The arrows signify the direction of virus movement, and curves connecting locations are color-coded based on the mean dates of inferred viral movements along the route. **C** Clustered heatmap displaying the exports (Origin) and imports (Destination) of the top 50 enriched routes between provinces as depicted in (B). Provinces with more than 11 routes for each province-pair are marked with an asterisk (*).

actively participated in both virus imports and exports. Among them, Hubei, Shanghai, Jiangsu, and Anhui exhibited the most significant viral movements (Fig. 3A). Regions with the highest net exports included Hubei, Jiangsu, Tianjin, Anhui, and Sichuan, while Guizhou, Fujian, Gansu, Heilongjiang, and Hainan had the most net imports (Fig. 3A).

Over the course of a year, despite 32 provinces involved in the network comprising 2101 inferred transmission paths, most of them exhibited no more than 11 connections between pairs (Supplementary Fig. S4). Employing a stringent threshold of 11 paths, we filtered and visualized the principal 50 transmission paths across China (Fig. 3B and C). Notably, 11 provinces emerged as focal points of significant dissemination, namely Hong Kong, Shanghai, Anhui, Hubei, Jiangsu, Taiwan, Guangdong, Henan, Sichuan, and Yunnan (Fig. 3B, Supplementary Table S7). The genesis of transmission routes can be traced to Hong Kong, radiating to diverse provinces encompassing Shanghai, Guangxi, Yunnan, Jiangsu and Taiwan, evolving into a pervasive multi-center pattern across the mainland of China (Supplementary Fig. S4, Supplementary Table S6).

Based on the genomic dynamics (Fig. 1B), we demarcated the temporal boundaries of March 31, 2023, and July 10, 2023, to systematically analyze the evolution of transmission paths across discrete stages. During the inaugural stage, the dissemination of SARS-CoV-2 originated from focal points such as Hong Kong and Taiwan region, with Shanghai emerging as a pivotal hub orchestrating subsequent spreading events

throughout eastern China. Additionally, regions in eastern China, including Jiangsu, Anhui, and Beijing, constituted primary centers for viral transmission (Supplementary Fig. S5A, Supplementary Table S7). However, in the subsequent second and third stages, the epicenter of transmission shifted to central China, notably Hubei, serving as a conduit for the widespread distribution of the virus to diverse provinces across the nation. Simultaneously, regions such as Sichuan, Henan, and Yunnan gradually transitioned into notable areas for viral dissemination, as elucidated in Supplementary Fig. S5C–F and documented comprehensively in Supplementary Table S7.

3.4. Uncovering a recombination event in China

Although no novel variant with widespread prevalence has been identified in China, the detection of a new recombination event may offer a unique opportunity to gain insights into potential risks. Initial screenings using the rebar and Nextclade methods identified no and 105 potential recombinants, respectively. Subsequently, the CovRecomb method validated six recombinants by identifying their parental lineages as FR.1.1 and EG.5.1.1 from a genetic standpoint (Supplementary Table S8). These recombinants were also confirmed epidemiologically, as their parental lineages co-circulated at the same time (August 1, 2023) and place (Shanghai) as the first sampled sequence (EPI_ISL_18105656). Meanwhile, the first sampled sequence, collected from a Chinese 27-year-

old male via pharyngeal swab technique, was considered an ancient-like recombinant genome resulting from the recombination event between FR.1.1 and EG.5.1.1 lineages. However, given that only six recombinants were detected and their relatively large time ranges (more than two months), further research is needed to determine whether there was a transmission chain among these genomes.

By comparing the exact mutations between the six recombinants and their closest putative parental sequences (EPI_ISL_18074780 and EPI_ISL_18105651), the mosaic composition of these recombinants was evident. Except for around nine mutations with uncertain sources, at least 23 nucleotide variations or 12 amino acid replacements near the 5' end of these recombinants were inherited from the FR.1.1 lineage, while the other 10 nucleotide or five amino acid mutations near the 3' end were derived from the EG.5.1.1 lineage (Fig. 4A, Supplementary Table S8). Therefore, the recombination breakpoint was inferred to be distributed between 22,630 nt and 22,663 nt, within the Spike genome (21,563–25,384) and after the receptor-binding domain (RBD, 21,881–22,103) region (Fig. 4A). Moreover, each genome segment contained no mutations from its non-corresponding parental lineages, confirming the reliability of the recombination event. Phylogenetic scrutiny of regions both preceding and succeeding the breakpoint revealed intricate genomic mosaic structures, underscoring their phylogenetic congruence with the respective lineages (Fig. 4B and C).

Subsequently, we discovered that this recombination event had already been designated as the XCN lineage in the pangolin-designation system (Roemer, 2020) and was also inferred to originate from China. Remarkably, the assigned parental lineages and breakpoint position concurred with our results. Apart from samples collected in Anhui and Shanghai reported online, we also discovered an additional sequence in Gansu province, collected on October 6, 2023, which supplements the lack of scattered online reports.

4. Discussion

Prior to December 2022, China adhered to a stringent dynamic zero-COVID policy. However, despite these measures, imported cases were regularly detected. In Beijing, the incidence of local cases was markedly lower than that of imported cases, with all monitored genomes from Delta and Omicron VOCs (Pan et al., 2023). In Weihai, a coastal city in Shandong province, a local cluster of cases linked to the Gamma variant in Jun 2022 was speculated to have originated from overseas through cold chain seafood shipments (Li et al., 2024; Yu et al., 2022). Notably, before the substantial surge in local infections caused by BA.5.2* and BF.7* in late November 2022, which were detected in certain cities (Li et al., 2024; Liu et al., 2024; Pan et al., 2023), there was only a minor peak in local cases between April and June 2022, mainly attributed to the BA.2* lineage (Pan et al., 2023).

This study reveals a compelling spatiotemporal distribution pattern of SARS-CoV-2 lineages post December 1, 2022, in China, elucidating a remarkable evolutionary trajectory. The dominant lineages in China underwent a transition from dual to triple or four lineage co-circulation, ultimately converging into a single lineage pandemic. This transition correlates with fluctuations in collected genomes (Fig. 1B), echoing findings from previous studies based on patient sampling (Colson et al., 2023; Pan et al., 2023). This shift may be attributed to a new wave of infections arising from the emergence of variants or sub-lineages with enhanced adaptability (Pan et al., 2023). Significant disparities exist in the lineage composition among various provinces, where some provinces showcase a predominant single lineage while others present a more varied lineage composition, mirroring observations from the early stages of the COVID-19 epidemic (Alteri et al., 2021; Franceschi et al., 2021). However, caution is warranted in interpreting these findings due to divergent surveillance density and capabilities across provinces. We advocate for provinces with higher genetic diversity to share surveillance

experiences with those exhibiting less diversity. Provinces such as Jiangsu and Anhui, with significant genetic diversity, could possibly serve as representative snapshots of the national pathogen landscape. Moreover, geographically adjacent countries shared similar epidemic lineage compositions, for example, compared to the USA and the UK, the spatiotemporal distributions of BA.5.2.48*, XBB.1.5*, XBB.1.9.1*, and XBB.1.16* lineages in China align more closely with Japan (Fig. 2B), potentially due to similar climate, environment, population flow, and other regional characteristics. The regional clustering of virus lineages underscores the importance of cross-border cooperation among neighboring regions to collectively address potential epidemics and enhance overall health prevention and control capabilities at the regional or national level (Suk et al., 2014).

A comparative analysis of global lineage epidemic cycles sheds light on the impact of the dynamic zero-COVID policy. Following the policy's cessation, China experienced a delayed peak occurrence of each lineage compared to other countries, attributed to stringent social control measures before December 2022, hindering the entry of global pandemic lineages. For the unique lineages epidemic pattern of firstly lagging and then advancing in China, we propose an explanatory hypothesis based on the Chinese “immune gap” (Messacar et al., 2022; Xia et al., 2020) background. That is, Chinese individuals were not only vulnerable to already widespread global lineages (BA.5.2.48*, BF.7.14*, BA.2.75*, and XBB.1.5*) but also to newly evolved lineages (XBB.1.9.1*, XBB.1.22.1*, XBB.1.16*, and EG.5.1*), leading to a delayed peak of infection for early lineages, an early outbreak for late lineages, an increase in genetic diversity, and a prolonged peak of the early epidemic stage in China. This hypothesis raises a possible causal interpretation of the relationship between Chinese immunity and lineage prevalence. However, its validity requires further investigation. Furthermore, the overall similarity of the lineages between China and the world highlights the global connection of virus diversity and dispels concerns about the emergence of new variants in China due to distinct immune backgrounds.

Understanding the epidemiology and transmission dynamics of viruses can help improve public health decision-making and develop comprehensive control strategies (Ryu et al., 2022). The inferred virus transmission paths among Chinese provinces underscore a complex network of spread, with Hong Kong, Shanghai, and Hubei assuming primary roles in the virus's import and export. Initially, following the cessation of the dynamic zero-COVID policy, the transmission route from Hong Kong or Taiwan to Shanghai became the starting point for virus transmission to other provinces in the mainland of China. Notably, Anhui and Jiangsu, proximate to Shanghai, emerged as significant areas for viral dissemination during the first stage. Post-May 2023, a paradigm shift occurred in the transmission center, relocating from eastern China to densely populated inland provinces in central China, exemplified by regions such as Sichuan and Henan. Simultaneously, Hubei, acting as a crucial transportation hub in central China, played a pivotal role in the extensive spread of SARS-CoV-2 across the mainland of China. This pattern reveals a cross-provincial transmission trajectory in the evolution of SARS-CoV-2, that is, provinces with heightened virus transmission were concentrated in densely populated or highly mobile regions. This aligns with our expectations and, to some extent, demonstrates concordance with socio-economic factors. Consequently, we recommend considering stringent social isolation measures and enhanced pathogen surveillance in key areas during a pathogenic pandemic to effectively mitigate overall harm. Importantly, the number of inferred transmission pathways in each province shows no correlation with the uploaded genome count (Supplementary Fig. S1A, Fig. 3A), indicating minimal impact of sampling bias on our inferred pathways.

The discovery of novel recombinants enhances China's genomic landscape, emphasizing the critical need for continuous surveillance of viral evolution. Genetic recombination, a pivotal driver of viral diversity, assumes a central role in shaping the trajectory of SARS-CoV-2 (Turakhia

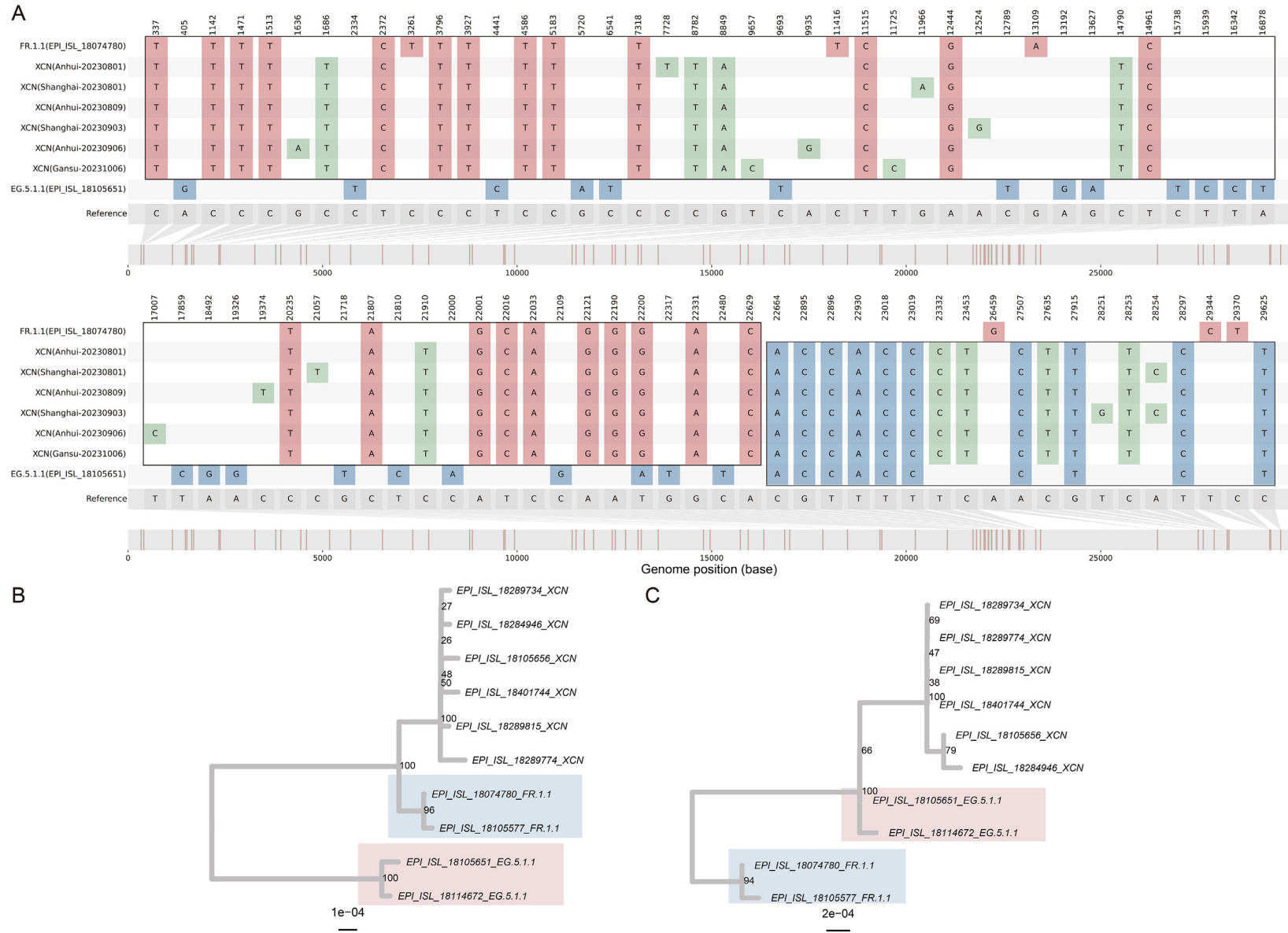


Fig. 4. The XCN recombination event in China. **A** Nucleotide variations relative to the reference sequence (Wuhan-Hu-1, bottom) for the identified XCN recombinants (six genomes in the middle, corresponds to [Supplementary Table S8](#)) and their parental lineages, namely, FR.1.1 (EPI_ISL_18074780, top colored genome) and EG.5.1.1 (EPI_ISL_18105651, bottom colored genome). Mutations for FR.1.1 and EG.5.1.1 lineages are indicated in red and blue, respectively, while unique mutations for the XCN recombinants are denoted in green. The black box marks the origin of each genome segment of the recombinant. **B, C** Phylogenetic analysis of different segments (B: 1–22, 629 bp; C: 22, 664 bp–29903 bp) encompassing all detected XCN recombinants and their parental sequences. Numbers in black text at the nodes represent the bootstrap percentages (%).

et al., 2022). The XCN lineage, a recombination event involving the FR.1.1 and EG.5.1.1 lineages, exhibits a breakpoint within the Spike protein region. This region, recognized for its pivotal involvement in viral entry and host cell recognition, signifies potential implications for virus transmissibility, antibody escape, and vaccine efficacy, as substantiated by previous researches (Letko et al., 2020; Shang et al., 2020.). Fortunately, the XCN recombination event did not culminate in an epidemic, being limited to merely six sequences in three provinces in China. In tandem with the XCN lineage, the pango-designation (Roemer, 2020) introduces another recombination event, denoted as XDL lineage, which occurred after the policy cessation. As documented in an online source (<https://github.com/cov-lineages/pango-designation/issues/2351>), accessed on April 23, 2024, XDL is a putative recombination featuring parental lineages of EG.5.1.1 and non-EG.5, with a breakpoint between 25,573 nt and 29,624 nt (NS3–NS10 region). It was initially identified in an oropharyngeal swab sample from a 42-year-old female in Yunnan Province, China, on July 30, 2023, with the accession ID “EPI_ISL_18111103”. Diverging from the limited impact of XCN, XDL has manifested itself in 186 sequences across 23 countries. Notably, while the XCN and XDL recombinants were initially detected and designated in China, their precise natural origin remains unconfirmed. Nevertheless, this observation highlights the ongoing evolutionary dynamics of SARS-CoV-2 within the Chinese population. Despite the absence of conspicuous emergences of new variants within China following the termination of the dynamic zero-COVID policy, the genome heterogeneity within the population underscores the imperative for sustained vigilance. Therefore, to identify potentially deleterious mutations or variants and preempt their widespread transmission, continuous sampling and monitoring of SARS-CoV-2 remain indispensable.

The findings hold both theoretical and practical significance. Firstly, they unveil a unique outbreak pattern in China after the cessation of the policy, distinguishing it from other nations, particularly in the emergence of the lineage peak date. This illuminates the profound impact of the dynamic zero-COVID policy on the epidemic dynamics in China, offering crucial insights into the effects of diverse prevention and control strategies on virus transmission. Secondly, the study extrapolates the spread of SARS-CoV-2 among provinces in China, identifying major transmission centers and discovers the evolution of these centers over time. Such insights bear practical importance for devising targeted prevention and control measures and orchestrating prompt responses to epidemic flare-ups in diverse regions. Additionally, the identification of a potential viral recombination event underscores the dynamic evolution process within the Chinese population, emphasizing the significance of vigilant monitoring of viral evolution and emerging mutations.

Acknowledging inherent limitations is crucial for interpreting and generalizing our findings. Firstly, the nationwide decrease in the sampling rate of COVID-19 infected patients following the termination of the dynamic zero-COVID policy has introduced potential deviations in data sampling and uploading rates across provinces. Consequently, the inclusion of 39,456 samples may not fully reflect the actual epidemic situation, thereby impacting the distribution of lineages at the provincial level. While our comprehensive sampling method mitigated some of these impacts during the transmission inference analysis, additional comprehensive data is required for validation in this aspect of the results. Secondly, the absence of detailed and reliable social and natural ecological data, such as population and traffic flow data, poses challenges for further verifying transmission routes and assessing risk factors for regional virus spread. Moreover, the inability to quantify the population immunity status of different regions makes it difficult to establish a causal relationship between China's unique lineage evolution pattern and disparities in herd immunity.

5. Conclusions

In conclusion, our study delved into the post-dynamic zero-COVID policy evolution of SARS-CoV-2 in China. Through genomic analysis, we

delineated three stages with shifting dominant lineages and transmission patterns across provinces. China's epidemic trajectory, initially lagging then advancing, and its intricate interprovincial transmission network underscore the profound influence of public health policies on virus dynamics. The transition of transmission centers from east to central regions highlights the importance of adaptable strategies in response to evolving epidemiological landscapes. Additionally, novel recombinant events signify ongoing virus evolution, emphasizing the need for continuous genomic surveillance to prepare for harmful variants. These findings offer valuable insights for evidence-based public health interventions and regional cooperation. We stress the importance of further quantitative research to measure the intensity of policy impacts.

Data availability

All the SARS-CoV-2 genomes in this study are accessible through the GISAID dataset (<https://www.gisaid.org/>). The accession IDs of the 39,456 qualified Chinese genomes are presented online (https://epicov.org/epi3/epi_set/240301ye?main=true). The GISAID accession IDs of the United States, the United Kingdom, and Japan analyzed in this study are provided in [Supplementary Table S1](#). The Chinese or global genome frequencies are also sourced from the CoV-Spectrum website (<https://cov-spectrum.org/>). The genomic mosaic structure of recombinants was visualized by snipit (<https://github.com/aineniamh/snipit>). All scripts utilized in this study were written in Python and R and are readily accessible in our GitHub repository (https://github.com/Sonia-Ljy/China_Epi_Post_Policy).

Ethics statement

This article does not contain any studies with human or animal subjects performed by any of the authors.

Author contributions

Jiaying Li: conceptualization, acquisition, statistical analysis of data, methodology, visualization, writing-original draft. Jingqi Yang: investigation, data curation, visualization, validation. Xiao Ding: methodology, reviewing and editing. Hangyu Zhou: investigation, acquisition of data. Na Han: investigation, methodology. Aiping Wu: conceptualization, project administration, funding acquisition, writing, reviewing, and editing. All authors have revised and approved the submitted manuscript.

Conflict of interest

All authors declare that there are no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.virs.2024.09.003>.

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