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RESEARCH ARTICLE

Primary assessment of the diversity of Omicron sublineages and the epidemiologic features of autumn/winter 2022 COVID-19 wave in Chinese mainland

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Abstract **With the recent ongoing autumn/winter 2022 COVID-19 wave and the adjustment of public health control measures, there have been widespread SARS-CoV-2 infections in Chinese mainland. Here we have analyzed 369 viral genomes from recently diagnosed COVID-19 patients in Shanghai, identifying a large number of sublineages of the SARS-CoV-2 Omicron family. Phylogenetic analysis, coupled with contact history tracing, revealed simultaneous community transmission of two Omicron sublineages dominating the infections in some areas of China (BA.5.2 mainly in Guangzhou and Shanghai, and BF.7 mainly in Beijing) and two highly infectious sublineages recently imported from abroad (XBB and BQ.1). Publicly available data from August 31 to November 29, 2022 indicated an overall severe/critical case rate of 0.035% nationwide, while analysis of 5706 symptomatic patients treated at the Shanghai Public Health Center between September 1 and December 26, 2022 showed that 20 cases (0.35%) without comorbidities progressed into severe/critical conditions and 153 cases (2.68%) with COVID-19-exacerbated comorbidities progressed into severe/critical conditions. These observations shall alert healthcare providers to place more resources for the treatment of severe/critical cases. Furthermore, mathematical modeling predicts this autumn/winter wave might pass through major cities in China by the end of the year, whereas some middle and western provinces and rural areas would be hit by the upcoming infection wave in mid-to-late January 2023, and the duration and magnitude of upcoming outbreak could be dramatically enhanced by the extensive travels during the Spring Festival (January 21, 2023). Altogether, these preliminary data highlight the needs to allocate resources to early diagnosis and effective treatment of severe cases and the protection of vulnerable population, especially in the rural areas, to ensure the country's smooth exit from the ongoing pandemic and accelerate socio-economic recovery.**

Keywords SARS-CoV-2; COVID-19; Omicron; genomic epidemiology

Introduction

Since November 2021, Omicron (Pango lineage B.1.1.529), the current WHO-designated variant of concern (VOCs) of SARS-CoV-2, has driven large waves of COVID-19 outbreak around the globe [1,2]. Compared to ancestral SARS-CoV-2 VOCs (Alpha, Beta, Gamma, and Delta), Omicron is more infectious and capable of evading immunity established by previous vaccination or

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infections [3,4]. In part due to convergent evolution of the viral genome impacting the function of virus-host entry and immune response factors, a series of Omicron sublineages have appeared within the past 12 months, many of which possess even greater infectivity and immune-evasion abilities [5,6]. Although Omicron sublineages are reportedly less virulent than ancestral strain and VOCs such as the prototype and Delta (e.g., Omicrons are less likely to infect the lung or cause severe disease) [3,7], rapid transmission and breakthrough infections increasingly strain the public health system, which calls for more flexible strategies to ameliorate impact of the pandemic.

Because of strong non-pharmaceutical public health intervention (NPI) measures—including mass testing, quarantining and travel restrictions—to prevent large outbreaks, only a small portion of the people in Chinese mainland were exposed to SARS-CoV-2 prior to November 2022. In the meantime, over 90% of the population were vaccinated by at least two doses of inactivated vaccines, and among the elderly people population over 60 or 80 years old, the coverage of a third booster dose vaccination reached 86.6% and 66.4%, respectively, by December 13, 2022 [8]. Analysis of the previous immunized COVID-19 patients have also shown that full and booster doses of inactivated vaccines achieved strong efficacy against severe disease [9,10]. These achievements led to major adjustment of COVID-19 control measures between November 11 to December 7, 2022 [11], for example, to encourage voluntary stay-at-home quarantine of asymptomatic, mild, or moderate cases, gradual replacement of nucleic acid screening by antigen detection, and the lift of travel restrictions, while keeping close monitoring and care of people at higher risk of developing severe diseases (e.g., seniors, patients with co-morbidities, pregnant women, and preschool children). On December 26, 2022, it was announced by the National Health Commission that the status of COVID-19 in China will be changed from category B infectious disease with management of category A to category B disease with management of category B starting from January 8, 2023 [12].

Nevertheless, a sudden rise of a variety of Omicron sublineages brought new challenges to the public health system. In particular, the majority of the Chinese population would experience first-time or breakthrough infections in the coming months. Even though a full two-dose schedule and/or a booster dose could induce neutralizing antibodies (NAbs), such humoral immunity only lasts for about six months [13–15]. In addition, most widely applied SARS-CoV-2 vaccines in China were based on the prototype strain, and NAbs induced appear to be largely ineffective against several new Omicron sublineages such as BA.4/5, XBB, and BQ.1 [4,6,16]. Thus, strength of population-wide immunity could be sub-optimal when confronted with the coming waves of Omicron infection. As large Omicron waves have already been reported in many cities in China and are likely going to reach rural areas, evidence-based evaluation and knowledge-based prediction of the magnitude of the coming infection waves shall be of critical value to guide the public and public health systems to navigate through the pandemic.

Thus far, we have closely monitored and analyzed the past two major COVID-19 outbreaks in Shanghai, the first in early 2020 when the original SARS-CoV-2 strain was imported to local community [17], and the second in spring 2022 when BA.2.2.1, a subvariant of Omicron BA.2.2 sublineage, drove a large community outbreak lasting three months [18–22]. Our analysis of the impact of those early outbreaks was based on three different lines of investigation: (1) genomic epidemiology study of the viral genome sampled during different phases of the outbreak; (2) analysis of the pathophysiological features of COVID-19 patients with distinct severities of symptoms; (3) mathematical modeling of trend of the ongoing infection wave. In this study, we aim to use these methods to assess the on-going Omicron wave of SARS-CoV-2 in Shanghai and extend the assessment to other places in China.

Methods

Ethics statement and sample collection

This study was approved by the Shanghai Public Health Clinical Center (SHPHC) Ethics Committee and Shanghai Ruijin Hospital Ethics Committee. For this study, 378 patients, who had tested positive for SARS-CoV-2 RNA, were admitted to the SHPHC between November 16 and December 12, 2022. For clinical presentation analysis, a total of 5706 symptomatic patients treated at SHPHC between September 1 and December 26, 2022 were analyzed, and the disease severities were classified according to the ninth edition of the COVID-19 diagnosis and treatment protocol [23].

SARS-CoV-2 targeting sequencing and phylogenetic analysis

Swabs and sputum samples were collected for nucleic acid extraction using an automatic magnetic extraction device and accompanying kit (Shanghai Bio-Germ) and screened using a semiquantitative RT-PCR kit (Shanghai Bio-Germ) with amplification targeting the ORF1a/b and N genes. The SARS-CoV-2 amplicon library were obtained with the Illumina COVIDSeq ARTIC V4.1 kit according to the manufacture's instruction (Illumina). The libraries were sequenced at the Illumina NovaSeq 6000 platform (Illumina) according to a PE 150bp protocol in

the National Research Center for Translational Medicine (Shanghai).

Sequencing reads were trimmed with fastp (version 0.23.2) [24] to remove low-quality regions, adaptor sequences, and sequencing primers prior to subsequent analysis. Host sequences was screened by a preprocess of Kraken2 (version 2.1.2) [25], and valid reads were mapped to reference genome (NCBI Accession: NC_045512.2) by bowtie2 (version 2.4.4). Samples with amplicon coverage greater than 80% passed QC process and entered downstream analysis. All mapped reads were piled up for consensus assembly and variation calling with iVar (version 1.3.1). The assembled genome sequences were evaluated on clade assignment, mutation calling, and assembly quality with Nextclade (ver 2.9.1) and validated genomes undertook lineage analysis by Pangolin (ver 4.1.1) [26]. The resulting phylogeny tree was visualized using auspice (v2.42.0) from the Nextstrain package (version 3.0.3) [27]. Bioinformatics analysis were performed with viralrecon (version 2.5) pipeline along with Nextflow (version 22.10.4) [28] management software on the ASTRA supercomputing platform with DAOS high-performance filesystem in the National Research Center for Translational Medicine (Shanghai).

Statistical analysis

Two sided Mann–Whitney U tests and Kruskal–Wallis tests were used to compare two and more than two groups of variables, respectively. χ^2 and Fisher's exact test were used for analyzing contingency tables. Spearman's rank correlation test was used to evaluate correlations. No statistical methods were used to predetermine sample size. Investigators were not blinded to patient group during experiments and outcome assessment.

Mathematical modeling

The differential equation used in the mathematical modeling is an update of the equation used in our previous study [20]:

$$\frac{dp(t)}{dt} = k \cdot [p(t) - u \cdot p(t-\tau) - p(t-T)]$$

Briefly, parameters k, u, and τ represent the average spreading coefficient, the average quarantine ratio, and the average detection interval, respectively. Apart from the original three parameters, the new equation takes an addition parameter T into account, and the $p(t-T)$ in the equation represent infected people who are already healed, which allows long-term epidemiological prediction. Numbers of COVID-19 cases used in data fitting were collected from officially released reports and moving averages were then calculated.

Results

Genomic epidemiological analysis of SARS-CoV-2 sublineages and variants circulating in Shanghai or imported from other places in autumn/winter 2022

We used whole-genome targeted sequencing technology to obtain SARS-CoV-2 genome assemblies from a cohort of 378 randomly selected COVID-19 patients who were admitted to SHPHC between November 16 and December 12, 2022. The patients of this cohort all developed common mild/moderate COVID-19 symptoms such as fever, headache, and cough, and none have progressed toward severe symptoms at the time of writing. After stringent quality check, 369 samples with more than 80% genome coverage were used for subsequent analysis (see Methods for details).

To characterize the lineages of these viral genomes, we called mutations in each sequenced genome and combined them with a reference set of SARS-CoV-2 genomes at the Global Initiative on Sharing All Influenza Data (GISAID) database for an unsupervised phylogeny analysis (Fig. 1A). The results revealed 30 Pango-nomenclature-system-named subvariants with varying representations in the sequenced genomes, and 353 (95.66%) out of the 369 genomes were clustered into four main sublineages: BA.5.2 (172, 46.61%), BA.5.3 (118, 31.98%), BA.2.75 (36, 9.76%) (Fig. 1B) and recombined strains (27, 7.32%). Moreover, one or two subvariants accounted for the large fraction of each main sublineage, including BQ.1 for the BA.5.3 sublineage (112/118, 94.92%), BF.7 for the BA.5.2 sublineage (43/172, 25%), XBB for the recombined strain sublineage (25/27, 92.59%), BN.1 for the BA.2.75 sublineage (22/36, 61.11%) (Fig. 1B). By contrast, the remaining subvariants were only represented by 1–4 genomes, which could be recently imported minor strains circulating in the community.

After the last community outbreak of COVID-19 in Shanghai during spring 2022, only sporadic cases appeared among Shanghai residents before the relaxation of NPI measures. To infer the likely origin(s) of the viruses, we questioned each patient of our study cohort about their own travels or contact history with other recent SARS-CoV-2-infectd cases. Using these data, we analyzed the geographical distribution of each main sublineages in our genome data set (Fig. 1C). The results indicated that 94% of BQ.1 cases (105/112) and 96% of XBB cases (24/25) recently came to Shanghai from outside Chinese mainland. Considering that both BQ.1 and XBB were newly emerged VOCs in Europe and North America, the very high representation in imported cases suggested that these two sublineages were probably imported to Shanghai only recently. In comparison, for the BA.5.2 sublineage, including its progeny sublineage

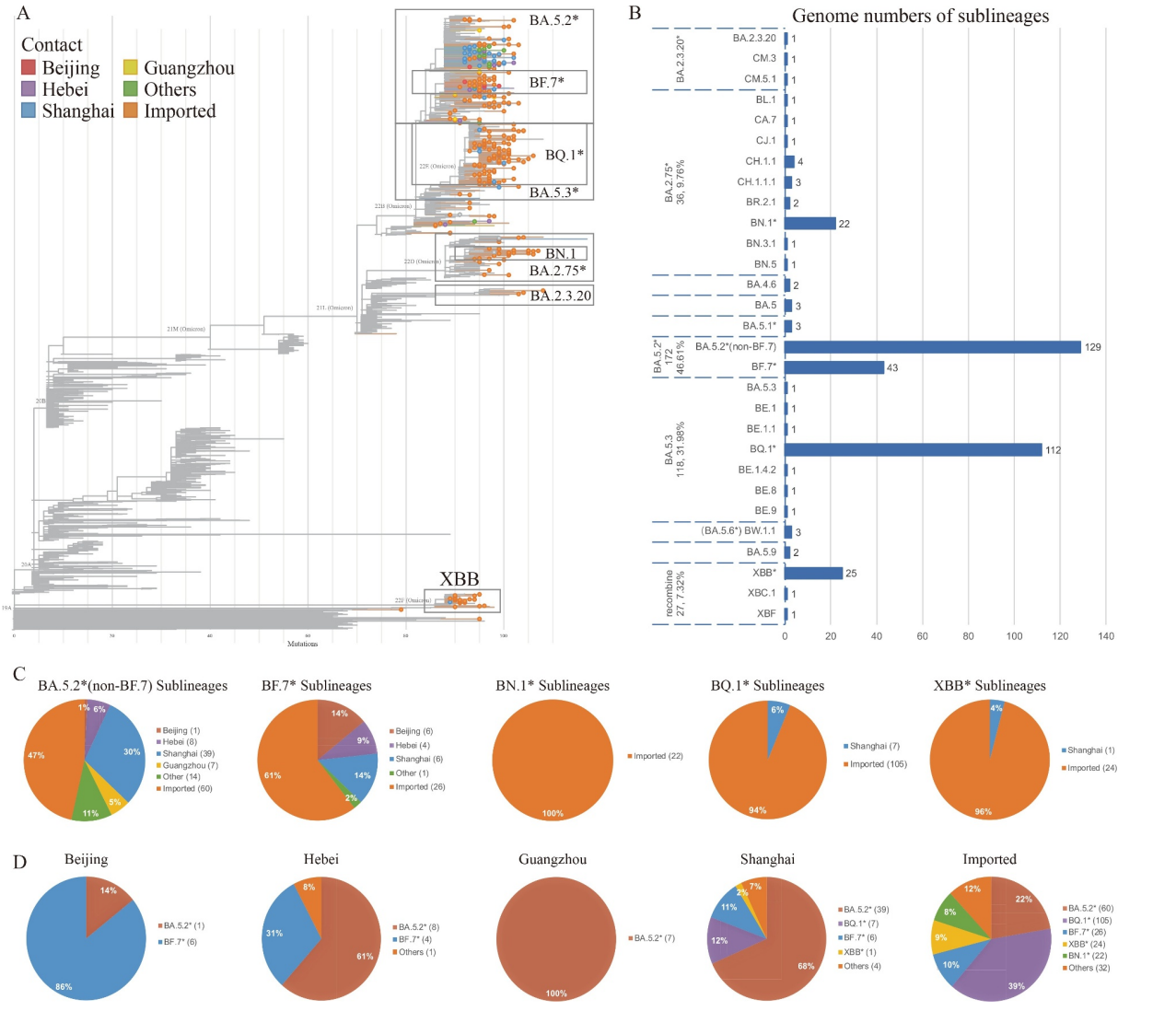

Fig. 1 Genomic epidemiology analysis of the SARS-CoV-2 genomes sampled from patients diagnosed during the outbreak of autumn/winter 2022. (A) Phylogenetic tree of recently sequenced viral genomes in Shanghai cases. Major sublineages are indicated by squares. (B) Bar plot of the number of genomes for different Omicron sublineages. (C) Pie charts of inferred origin-of-infection for indicated sublineages. (D) Pie charts of the relative fractions of Omicron sublineages per inferred origin-of-infection. Asterisk indicates all known subvariants grouped under each sublineage. The BF.7 sublineage was not included in counting of the BA.5.2 sublineage in (D).

BF.7, only 38%–64% could be classified as imported cases, whereas the rest cases were traced to parts of Chinese mainland, suggesting that BA.5.2 and BF.7 might have already broadly circulated in many places prior to their appearance in Shanghai.

Furthermore, we examined cases that could be traced to each city, and found that Beijing and Guangzhou cases were respectively dominated by BF.7 and BA.5.2, respectively (Fig. 1D). By contrast, cases originated from Hebei (a province adjacent to Beijing) and Shanghai (at similar distances from Beijing and Guangzhou) showed larger diversity of Omicron sublineages, with Shanghai cases having a larger representation of imported BQ.1 and XBB sublineages (Fig. 1D). On one hand, these were consistent to recent suggestions that BF.7 and BA.5.2 were dominant sublineages causing recent COVID-19 outbreaks in Beijing and Guangzhou, respectively [29]. On the other hand, they suggested that outbreaks in other regions such as Hebei and Shanghai were caused by multiple viral variants, belonging to several distinct Omicron sublineages that likely simultaneously appeared in local communities.

Symptomatic COVID-19 patients during the autumn/winter 2022 outbreak

Mass nucleic acid testing was widely implemented in Chinese mainland prior to the end of November 2022 as a way to screen the SARS-CoV-2-infected cases. Based on the data released by the National Health Commission, it

was evident that, since progression of the autumn/winter 2022 wave and more recently the lift of lockdown and travel restrictions as part of the revision of NPI measure, there was a rapid rise of laboratory confirmed SARS-CoV-2-infections nationwide (Fig. 2A, upper panel), which was associated with a gradual increase of severe/critical cases reported from hospitalized symptomatic COVID-19 patients (Fig. 2A, lower panel). As of November 29, the overall rate of severe/critical cases was 0.035%. We note that severe/critical COVID-19 symptoms only become apparent until about one to two weeks after infection, and thus the severe/critical rate should be continuously monitored and based on up-to-date public health records.

Because mass nucleic acid screening was gradually withdrawn from community outbreak surveillance and are kept only in hospitals, nursing homes, and pregnancy and childcare centers, the precise number of asymptomatic cases would likely remain unknown henceforth. To estimate the portions of severe/critical cases among hospitalized symptomatic patients, we carefully examined all 5706 symptomatic patients admitted to SHPHC between September 1 and December 26, 2022, and classified them into four groups based on symptomatic severities and pre-existing conditions (see Method for details). As of December 26, 2022, a total of 5533 patients (96.97%) were classified as mild/moderate cases, whereas the rest (173; 3.03%) cases progressed toward severe/moderate conditions. Among the 173 severe/critical cases, 153 cases had severe-COVID-19-related comorbidities, suggesting that those with or without comorbidities respectively represented 2.68% and 0.35% of total symptomatic cases in the ongoing outbreak. Furthermore, of our patient cohort, the disease severity was significantly associated with age ($P < 0.0001$, Kruskal–Wallis test; Table 1): the media ages (range) were 66 (55–79) years for severe/critical cases without comorbidities, 59 (46–73) years for severe/critical cases with comorbidities exacerbated by COVID-19, and 39 (28–53) years for mild/moderate cases, respectively.

Mathematical modeling of the duration of magnitude of coming waves of Omicron in Chinese mainland

To assess the magnitude and duration of the current Omicron outbreaks across Chinese mainland, we mathematically modeled the curves of daily new COVID-19 cases and accumulated total cases starting from the beginning of October 2022, before the onset of surges of local outbreaks in major cities in Chinese mainland. Specifically, we applied a time-delayed differential equation to describe the spreading of Omicron in several major cities in China (i.e., Beijing, Shanghai, Guangzhou, and Chongqing), as well as several provinces in inner China (i.e., Gansu, Qinghai, Shaanxi, and Sichuan) with deduction of their capital cities so that the situations could be analyzed mainly for countryside and small and medium size towns. Based on recently reported cases in different areas in Chongqing, we also modeled the trend of the waves in urban vs. suburban areas to approximate the impact of the wave in city vs. rural areas. To obtain values of parameters in the differential equation, we used the number of reported cases before November 29, when nationwide community nucleic acid data were available, in the data fitting (Fig. 3A). We found the apparent R0 values (calculated by multiplying the spreading coefficient k and the detection interval τ) in the cities were different. For example, the apparent R0 of ~2.18 in Beijing was the largest, followed by ~1.91 in Shanghai, and the smallest was ~0.91 in Chongqing suburbs. The results showed that Guangzhou already passed the recent wave, while Beijing, Shanghai, and Chongqing urban

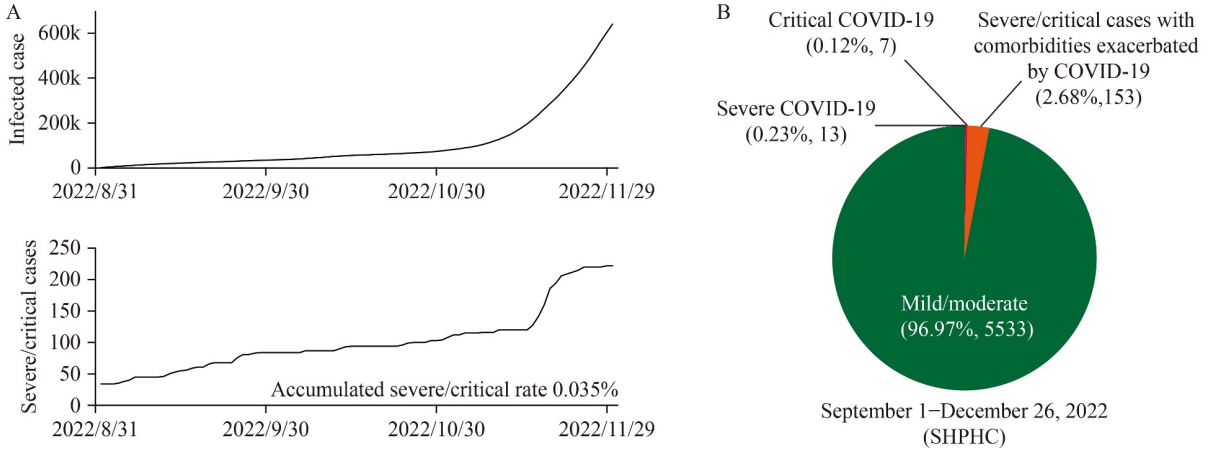

Fig. 2 Symptomatic patients during autumn/winter COVID-19 outbreaks in Chinese mainland. (A) Count of all infected cases (upper panel) and severe/critical cases (bottom panel) in Chinese mainland. (B) Pie chart of symptomatic patients with different severities treated in Shanghai Public Health Center (SHPHC).

Table 1 Clinical features of enrolled patients as of December 26, 2022

	Severe/critical cases (n = 20)	Severe/critical cases with comorbidities exacerbated by COVID-19 (n = 153)	Mild/moderate cases (n = 5533)	P value
Age (year)				$P < 0.0001$[a]
Median (range)	66 (55–79)	59 (46–73)	39 (28–53)	
< 10, *n* (%)	0 (0%)	0 (0%)	179 (3.22%)	
10–19, *n* (%)	0 (0%)	2 (1.31%)	289 (5.20%)	
20–29, *n* (%)	0 (0%)	13 (8.50%)	1052 (18.94%)	
30–39, *n* (%)	2 (10.00%)	19 (12.42%)	1284 (23.12%)	
40–49, *n* (%)	2 (10.00%)	10 (6.54%)	1052 (18.94%)	
50–59, *n* (%)	5 (25.00%)	33 (21.57%)	909 (16.37%)	
60–69, *n* (%)	3 (15.00%)	28 (18.30%)	531 (9.56%)	
70–79, *n* (%)	4 (20.00%)	29 (18.95%)	201 (3.62%)	
80–89, *n* (%)	3 (15.00%)	16 (10.46%)	48 (0.86%)	
⩾ 90, *n* (%)	1 (5.00%)	3 (1.96%)	8 (0.14%)	
Gender				$P < 0.0001$[b]
Female, *n* (%)	6 (30%)	52 (33.99%)	3231 (41.82%)	
Male, *n* (%)	14 (70%)	101 (66.01%)	2322 (58.18%)	

[a]Kruskal–Wallis test; [b]Fisher exact test.

areas are in the midst of the current wave that would likely pass by the end of 2022 (Fig. 3B). As for Chongqing suburban areas, an infection wave is projected to appear in early February, 2023. Of note, a great number of migrant workers will likely return home from cities to rural areas during the coming Spring Festival (January 21, 2023), ensuing travel rush in mid-January, 2023. To figure out to what extent this large-scale migration could affect COVID-19 spreading in rural areas in Chinese mainland, we manually decreased u of Chongqing suburbs to mimic a more dynamic situation during a holiday travel rush. The results indicated that the Spring Festival travel rush could accelerate the onset of the upcoming COVID-19 wave by 15–30 days (Fig. 3B). Last, the outbreak wave appears to just get started in middle and western provinces, with the peak projected to reach Sichuan slightly earlier than in Shaanxi, Gansu, and Qinghai (Fig. 3B).

Discussion

In this study, we performed a primary assessment of the diversity of Omicron sublineages circulating in Shanghai between November 15 and December 15. These samples were obtained from COVID-19 samples randomly selected upon hospitalization, shortly after recent nationwide relaxation of NPI measures in Chinese mainland. Though our sample size is relatively small, it reveals at least four notable sublineages (i.e., BF.7, BA.5.2, XBB, and BQ.1) that have been reported as drivers of new infection waves in other regions. Specifically, BF.7 and BA.5.2 were implicated as dominant sublineages in Beijing and Guangzhou, respectively, and XBB and BQ.1 are emerging VOCs whose infected cases are overtaking older Omicron subvariants in north America and Europe. In consistence with geographical distribution of these sublineages, contact history tracing of the patients of our samples showed that most BF.7 and BA.5.2 cases in Shanghai were linked to people who recently traveled to Shanghai from Beijing and Guangzhou, respectively, whereas most of the XBB and BQ.1 samples were from those who recently came to Shanghai from aboard. These observations suggested that the ongoing outbreak in Shanghai might still be in the middle of a course, wherein multiple recently imported variants intermingle and co-circulate in the community.

Of note, the current surge of SARS-CoV-2 infection in Shanghai is markedly different from an earlier community outbreak in spring 2022, wherein more than 90% of the infected Shanghai residents were infected by BA.2.2.1, which quickly overtook non-BA.2.2.1 sublineages in less than three weeks [18,30]. Because BA.2.2.1 was only a minor strain outside Chinese mainland prior to its appearance in Shanghai, its dominance in the spring outbreak and relatively quick disappearance could be, at least in part, attributed to strict NPI measures implemented at that time, which might have prevented other sublineages from competing with BA.2.2.1 then. By contrast, the presence of multiple Omicron subvariants in the current outbreak in Shanghai likely result from non-restricted interminglement and/or competition of various strains. Nevertheless, as the infected cases increase over time, the shrinking non-infected population might put

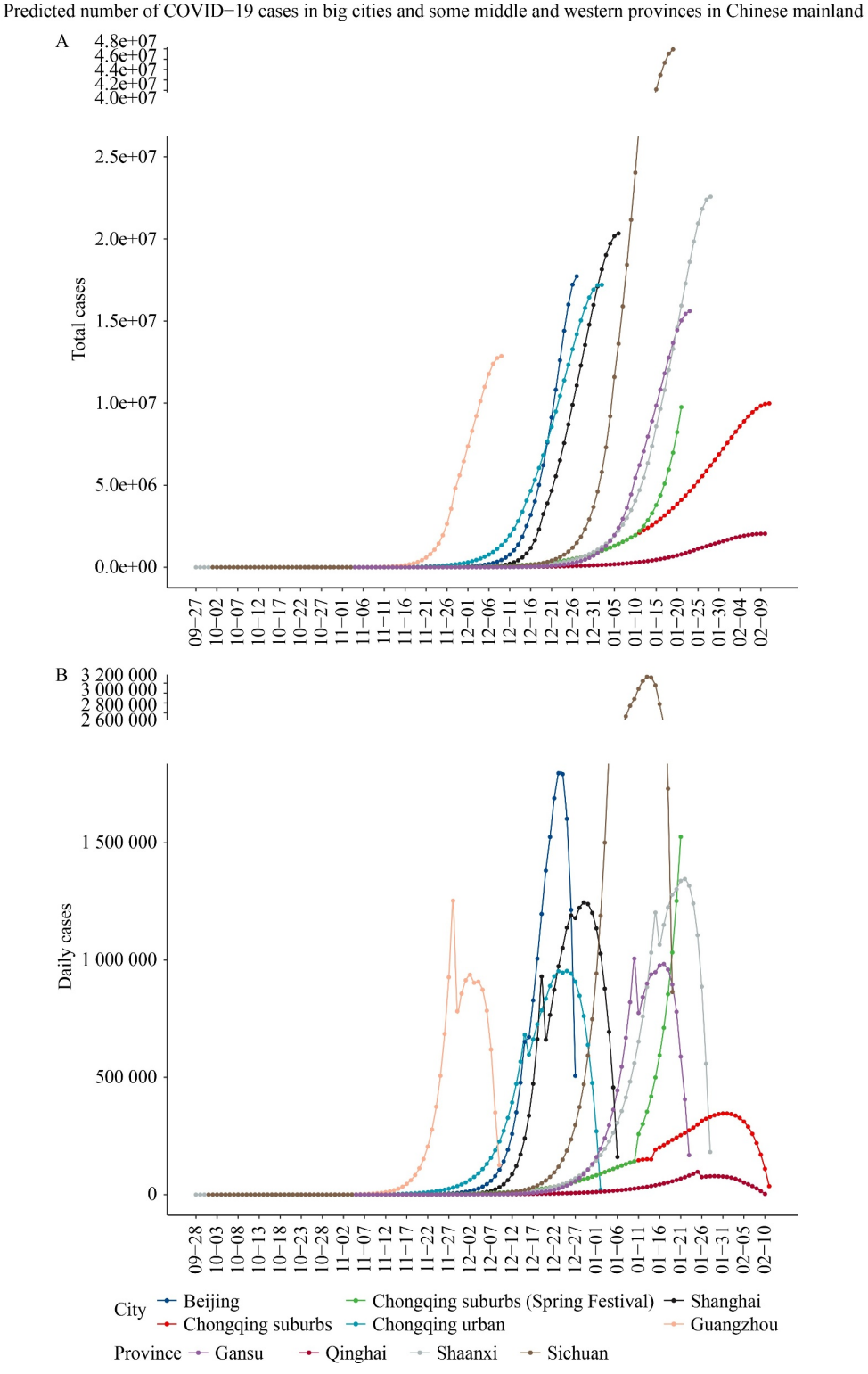

Fig. 3 Mathematical modeling of the ongoing Omicron outbreak in representative areas in Chinese mainland. (A) Plot of accumulated total COVID-19 cases in the modeling of the autumn/winter Omicron infection waves in selected regions (cities or provinces). (B) Plot of predicted number of daily COVID-19 cases and accumulated total cases as in (A). Total cases in each region were used for simulation except for Chongqing, where the cases in urban or suburban areas were separated. For Chongqing suburban cases, two independent simulations were performed to estimate the influence of Spring Festival travel rush on the rural areas.

competition pressure on currently circulating strains and enable selection of strains with higher infectivity or immune-evasion capability. Thus, vigilance shall be placed on evaluating the infectivity, transmissibility, and immune-evasion capabilities of the strains that become dominant drivers of future outbreaks.

To better understand how the current outbreak is developing in Chinese mainland after the lifting of COVID-19 restrictions, we also mathematically described and predicted the spreading of COVID-19 in various places in China, using an updated version of a differential equation that was successfully used in the prediction of dynamics of the Omicron outbreak in Shanghai during spring 2022 [20]. Based on the mathematical prediction, Beijing, Shanghai, and Chongqing urban areas would likely see localized spikes of COVID-19 by the end of 2022. In comparison, Guangzhou has already passed the main peak of the recent infection wave. Furthermore, we took the suburbs of Chongqing as an example to depict the COVID-19 spreading in China rural areas. After decreasing the value of the parameter u, which was obtained from data fitting, to mimic the COVID-19 spreading during Spring Festival travel rush, we found that the peak of infections during the holiday travel rush could occur 2–4 weeks earlier in rural areas in some inner provinces. To be noticed, we only predicted the current outbreak in each city or rural/small-medium town areas in each inner province, and the final stage of each wave was discarded (the predicted curves of total infections did not exhibit the shape of an S-like curve), since we mainly focused on estimating the time when 80%–85% of people would be infected. However, we note that the real-world situation is far more complicated—for example, several regions such as Hong Kong and Taiwan and countries like Japan had already experienced multiple waves of COVID-19. Of note, partly due to the dwindling of the level of COVID-19 antibody obtained from vaccination or real-life infection, it is reasonable to speculate that the Omicron outbreak in Chinese mainland might appear in multiple waves, with re-appearance of new local surges possibly in late 2023. The importance of regular monitoring of circulating SARS-CoV-2 sublineages and variants across China shall not be overestimated in the months and years to come.

Numerous studies so far have implicated that age and several comorbidities (e.g., high blood pressure, cardiovascular disease, diabetes, cancer) as leading risk factor for severe COVID-19. Given the rapid transmission of Omicron infection, senior population, especially those with pre-existing health conditions, in remoted regions in China are at greater risk of developing severe disease in the next few weeks or months. This issue is particularly worrisome because of short supply of medicine and ICU facilities even in the early phases of current Omicron infection wave in some areas especially in the countryside. To have an estimation of how many ICUs could be needed among infected population, we analyzed the data of all confirmed COVID-19 cases in Chinese mainland till November 29, 2022 and obtained a crude accumulative severe/critical case rate of 0.035%, which suggested that if half of the population in China (approximately 700 million) is infected within a relatively narrow time window (for example, within four to six weeks), then around 200 000 to 250 000 ICUs should be required for severe/critical cases. Indeed, based on an analysis of 5706 hospitalized patients at SHPHC, 173 cases (3.03%) were diagnosed as severe/critical cases. Though no death was reported yet at the time of writing, some patients were in critical conditions that could be fatal, highlighting urgent requirement for ICU in places like Shanghai where the outbreak is still under way. Hence, risk communication/public health education and categorical treatment should be the key to dealing with current challenges. And reporting system based on antigen detection at home should be set up immediately through community medicine centers/stations in urban and rural areas to collect information of the COVID-19 infected people. At present, emergency measures should be directed at delivering over-the-counter medicine to symptomatic patients of low-risk populations (i.e., vaccinated people under 60 years without comorbidities) and timely treatment of high-risk populations (i.e., people older than 60 years, especially those with comorbidities or without receiving full vaccinations) with effective antiviral drugs such as Paxlovid or VV116 [31,32]. In particular, emergency use administration (EUA) should be authorized to VV116, a new drug developed by Chinese medical and pharmaceutical scientists recently [31]. In parallel, NPI of precision including N95 mask wearing, social distancing in close spaces, increased number of means of transportation to avoid traffic congestion, should be carried out for infection peak clipping to relieve heavy pressure on the healthcare system. Storage and supply of specific and symptom-relieving drugs should be also speeded up for coming waves in rural areas to avoid delayed-treatment-related disease deterioration and death. In addition, recently approved inhalable vaccine should be applied to protect people who have not yet be infected by Omicron subvariants, while new Omicron variants-(such as BA.4/5)-specific vaccines should be subject to EUA for 4th shot booster among health professionals and people providing basic services in different sectors of the society. Last, it is critical to record the number of excessive deaths, including those who die from or with COVID-19, and the timeliness and accuracy of these data are required for up-to-date evaluation and prediction of the trend of the ongoing pandemic to ensure evidence-based policy-making.

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Compliance with ethics guidelines

Gang Lu, Yun Ling, Minghao Jiang, Yun Tan, Dong Wei, Lu Jiang, Shuting Yu, Fangying Jiang, Shuai Wang, Yao Dai, Jinzeng Wang, Geng Wu, Xinxin Zhang, Guoyu Meng, Shengyue Wang, Feng Liu, Xiaohong Fan, and Saijuan Chen declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000(5). Informed consent was obtained from all patients for being included in the study.

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