Emerging Microbes & Infections
2023, VOL. 12, 2191738 (5 pages)
https://doi.org/10.1080/22221751.2023.2191738

ARTICLE COMMENTARY

OPEN ACCESS Check for updates

Impact of National Omicron Outbreak at the end of 2022 on the future outlook of COVID-19 in China

Liwei Zheng[a], Shuying Liu[b] and Fengmin Lu[a,c]

[a]Department of Microbiology & Infectious Disease Center, School of Basic Medicine, Peking University Health Science Center, Beijing, People's Republic of China; [b]SL Consulting, Thousand Oaks, CA, USA; [c]Beijing Key Laboratory of Hepatitis C and Immunotherapy for Liver Diseases, Peking University People's Hospital, Peking University Hepatology Institute, Beijing, People's Republic of China

ARTICLE HISTORY Received 28 February 2023; Revised 7 March 2023; Accepted 8 March 2023

The sudden change of public health policy in containing COVID-19 in China around 7 December 2022 and the subsequent immediate large-scale outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the entire country across different age groups with various baseline health conditions raised the critical question on how such major event would impact the future COVID-19 status in the country and even to the world. The current commentary attempts to use the global COVID-19 data and information accumulated in the last 3 years to analyse the interactions between evolving virus strains and human immunity, which will shape the scenarios of COVID-19 in the coming year.

Awaken by the initial outbreak of SARS-CoV-2 in Wuhan, China took a strict lockdown approach in the whole country, which was successful in controlling the outbreak of the first SARS in 2002–2003. This approach succeeded again in putting down SARS-CoV-2 outbreaks in Wuhan and other major cities in the country in early 2020. However, SARS-CoV-2 evolving into a global pandemic forced China to adopt a zero-COVID policy for more than 2 years during which international travel was severely restricted with anyone coming to China being heavily screened for COVID along with lengthy quarantine after entering the country. Any isolated domestic cases of COVID would trigger a full-scale lockdown for the local district or even expanding to the whole city. While the economic cost for such policy was high, the zero-COVID-19 policy during the 2020–2021 period made China a rare country with infrequent confirmed COVID cases and limited mortality while the rest of the world suffered a full scale of SARS-CoV-2 spread with millions of cases of deaths.

However, situation changed upon Omicron variants of SARS-CoV-2 emergence by the end of 2021. Omicron variants have an enhanced ability to cause faster transmission on a scale larger than early SARS-CoV-2 variants [1]. Immune responses elicited by COVID vaccines developed against the ancestral viral strains were not as effective against Omicron variants [2]. Omicron variants quickly entered China in early 2022. Multiple cities in China had seen a much higher number of Omicron cases in the Spring of 2022 than early variants identified in the previous 2 years. It took much harder effort to put down local outbreaks than before. For example, a full-scale lockdown of up to 3 months was needed to finally control the COVID outbreak in Shanghai, the most populated city in China with 28.5 million residents. Even so, the lower scale but continuous spread of Omicron variants persisted in China, reaching more provinces and more local areas throughout 2022. The resources and cost required to hold a zero-COVID policy were becoming unattainable and the national GDP also suffered accordingly. By early December 2022, reported daily cases were growing at an alarming rate nationwide which further disrupted normal economic and social life (https://www.chinacdc.cn/). At the same time, Omicron variants were shown to be much less pathogenic than ancestral viral strains based on extensive studies of the global scientific community and clinical data [3].

A major shift in zero-COVID policy was announced around 7 December 2022. Local governments were given more authority to decide how to modify the screening practice of COVID cases, and within a few days, such screening was largely terminated nationwide except under certain specific situations. Almost immediately huge numbers of

CONTACT Fengmin Lu lu.fengmin@hsc.pku.edu.cn Department of Microbiology & Infectious Disease Center, School of Basic Medicine, Peking University Health Science Center, Beijing 100191, People's Republic of China

symptomatic COVID cases were reported everywhere across the country. While the precise number was missing, it was estimated that 60–80% of people at least in major cities were infected in this major outbreak (let's call it "National Omicron Outbreak") [4]. China had achieved over 90% coverage of vaccination with its inactivated COVID vaccines (https://www.chinacdc.cn/). Such vaccination status did not appear to protect against the National Omicron Outbreak although the wide vaccination was expected to limit the total number of severe cases or deaths in this round of infection, considering its previously reported effectiveness in Hong Kong [5]. As typical for a large-scale human outbreak of a self-limiting viral infection, the downward slope of the National Omicron Outbreak was just as steep as its upward slope. Within 4–6 weeks, new cases of SARS-CoV-2 infections stopped appearing in many communities. Healthcare facilities re-emerged from heavy COVID caseloads to return to regular services of treating common illness.

Given the fact that the majority of 1.4 billion people in China escaped early viral variants such as Alpha, Beta, Gamma, and Delta isolates for 2 years but quickly got infected with Omicron variants within 1.5 months, there were serious questions on how such a viral dynamic process in China would affect the next wave of COVID in the country and what would be the impact to the world.

What variants caused the National Omicron Outbreak?

The first question is whether the National Omicron Outbreak was truly caused by Omicron variants or were there some early and more pathogenic SARS-CoV-2 variants involved? When a large number of symptomatic COVID cases, including a considerable number of severe cases and even quick deaths, were reported in China shortly after the lifting of the zero-COVID policy, people were questioning if the outbreak was only caused by Omicron strains because Omicron is supposed to lead to mild diseases. Some even wondered if the original Wuhan ancestral isolate was re-emerging. However, the outbreak was quickly coming down and the most recent report indicated that the leading viral strains in this round of outbreak were mainly BA.5.2 and BF.7, the sublineages of Omicron, representing about 90% cases (https://www.chinacdc.cn/), although the founder effect could not be excluded. There were no new emerging variants in the short period of outbreak [6]. This report was reassuring. It would confirm that the sudden rising of severe cases especially in Beijing was the result of quick and large-scale infection while the spread of Omicron variants outside China was a gradual process that would reduce the number of severe cases at any given time. Hong Kong also saw a similarly high number of severe cases when Omicron variants first entered Hong Kong in early 2022. Such surge was brief, only seen shortly after the opening of society and quickly subsided within a few weeks, similar to what had been observed in the National Omicron Outbreak in mainland China.

Chance for new variants to be created dramatically different from the world after the National Omicron Outbreak

Knowing that only a few Omicron variants caused the National Omicron Outbreak in China and the very fact that no novel variants occurred during that period [6] helps answer the next question: will China become the place after opening up to produce future unknown variants which will be vastly different from current circulating variants in the world?

Recent studies reported that SARS-CoV-2 infection-induced immunity reduced rates of reinfection and hospitalization caused by later variants [7]. It is not clear how long such immunity may last but such infection-induced-immunity can supplement vaccine-induced-immunity, by forming the "hybrid immunity" as being described in recent literature [8].

In 2022, new COVID cases in the world outside China were mainly caused by various Omicron variants, including those who had been vaccinated with three or even four doses of COVID vaccines which were developed against the ancestral viral strains. In this sense, China is re-joining the global community with its people previously receiving a nationwide vaccination plus the National Omicron Outbreaks to create a hybrid immunity as the rest of the world. With the loosening of previous screening and lengthy quarantine policy for inbound visitors, China is expected to allow more international exchange from now on. Chinese tourists are returning to the world with international booking already going up quickly as reported by many travel agencies. With such globalization of COVID, China is less likely to be a site to create its variants different from the world.

Threat of newer Omicron variants to China once China is re-open

Seeing the continuous viral mutations within the Omicron lineage and the non-stopping reports of Omicron-caused human diseases including deaths in the world, people in China are concerned whether more dangerous variants are going to enter China to cause more rounds of infections and more cases of severe diseases.

Inaccurate media reports may be responsible for not providing a full picture of the evolution of Omicron variants. Basic virologists used the in-vitro

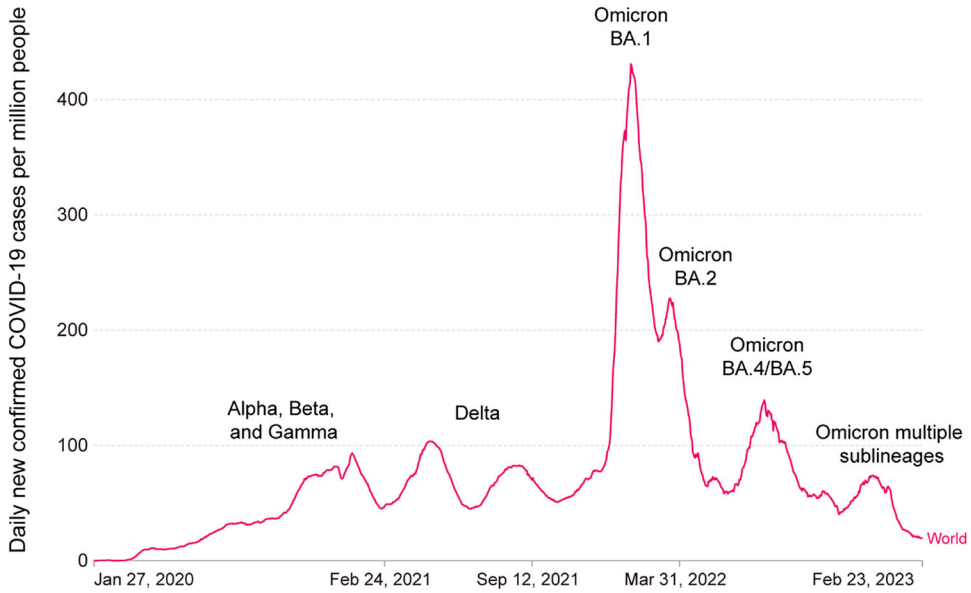

Figure 1. World new confirmed COVID-19 cases per million people (7-day rolling average). Source: Our World in Data and Johns Hopkins University CSSE COVID Data [13,14].

neutralizing antibody assay to demonstrate the escape of new Omicron variants from the antibodies generated by vaccines/infections targeting the early viral strains or variants, implying the existing immunity in the human population was no more protective [9,10]. Similarly, biologists demonstrated that the new variants would have a relative stronger binding to the viral receptor, implying stronger viral infection ability [11,12].

However, such information should be verified in the context of actual human COVID-19 epidemiology data. First, data collected from the world demonstrated the magnitude of each infection wave associated with key Omicron variants had been coming down over 2022 (Figure 1) [13,14]. The widely reported Omicron sublineage mutations were very restricted within a narrow scope of its molecular mutations, much different from the early SARS-CoV-2 mutations which created several major subtypes with a much larger span of molecular mutations (Figure 2) [11]. This would imply that by the time Omicron was first reported in November 2021, the global herd immunity, developed by both the quick

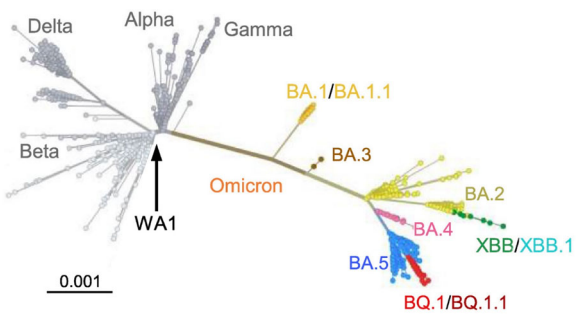

Figure 2. Unrooted phylogenetic tree of Omicron subvariants along with other main SARS-CoV-2 variants [11].

and large-scale human population vaccination and the wide spread of viral infections in many countries, had created such a broad barrier that all other major subtypes of SARS-CoV-2 were not able to survive much longer but instead replaced by the Omicron variants.

Omicron had more amino acid mutations inside the receptor binding domain than the early mutated subtypes, basically creating a new lineage of the SARS-CoV-2 virus [15]. Such mutations led to the predominance of the endocytic pathway in Omicron infection instead of that enhanced by TMPRSS2 as early subtypes [16], accounting for less pathogenesis nature of Omicron than the ancestral virus.

More significantly, none of the evolving Omicron variants was able to dominate the world for too long before being replaced by newer Omicron variants, as shown by the US CDC tracking of SARS-CoV-2 viral strains circulating in the US for the entire 2022 (Figure 3) [17]. It would suggest that herd immunity, especially the immunity created by Omicron infections, was able to quickly narrow down the community dominance of previous circulating Omicron variants. By the end of 2022, multiple Omicron variants rather than one dominating strain are needed to keep the viral survival in the community. This is quite different from the published predictions that some highly powerful viral mutants might be dominating the world [11].

If we use the global viral evolution data as a guide, there should not be too much concern about the invasion of newer Omicron variants into China, especially considering the fact the entire nation was just infected by the recent circulating Omicron variants in the world. SARS-CoV-2-induced immunity should protect the hosts for at least 6 months which will provide

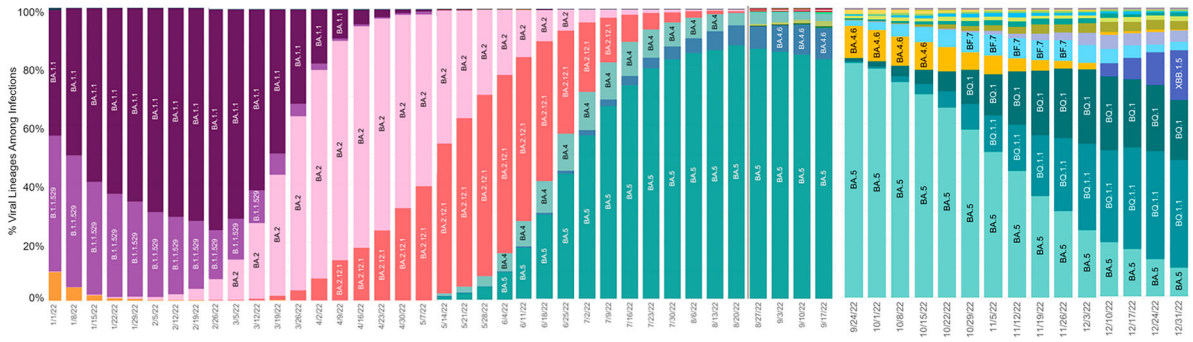

Figure 3. 2022 Tracking of Omicron strains in the US (1/1/2022 to 12/31/2022) [17].

time for Chinese people to establish enough herd immunity to face the next Omicron variants.

There is some concern about the XBB variant as well as its sublineage XBB.1.5 variant which has spread rapidly across several countries including Singapore and the United States in the past few months [12]. Such concern may be exaggerated. The numbers of cases, severe cases, and deaths have been decreasing in the US despite XBB dominance there [12], not to mention other countries where XBB was less detected. Neutralizing antibodies with high titres still works, despite XBB-derived variants' superior immune evasion capacities from neutralizing antibodies induced by previous vaccination or breakthrough infections [9,18]. Moreover, neither higher pathogenicity nor any peculiar clinical manifestations have been observed in XBB-infected animals [18]. Indeed, viral characteristics of emerging variants in the past 3 years have revealed that SARS-CoV-2 evolution conforms to the same Darwinian principle that generally variants with increased transmissibility and decreased pathogenicity are selected eventually. Notably, antiviral drugs remdesivir, molnupiravir, and nirmatrelvir showed equal efficacy for the XBB variant [19]. Additionally, vaccination or infection-induced humoral and cellular immunity systemically and at mucosal surface are orchestrated to shield hosts from reinfection or symptomatic reinfection in vivo [20,21], further offsetting the concerns on potential XBB outbreak in China.

The value of hybrid immunity against COVID

While original vaccines (no matter whether mRNA vaccines, viral vector vaccines, or inactivated vaccines) using ancestral Spike immunogen would not have generated sufficient antibody responses to cross-neutralize the Omicron variants, there is still some low level of cross-protection in real-life situations. More significantly, animal studies showed that further boost with either the original vaccine or other heterologous vaccines could increase the antibody responses against Omicron variants even by the inactivated vaccine [22]. Such findings are significant as they indicate that the original vaccination, no matter how low the responses, may serve as an important prime to the immune system. A subsequent viral infection would be able to boost the primed immune system to elicit higher protective immune responses.

Herd immunity or population immunity is referred when a sufficient proportion of the population acquires immunity to a certain contagious disease, either through vaccination or natural infection. With the development and approvals of several SARS-CoV-2 vaccines, it had been thought that herd immunity through vaccination would be the best way to curb the SARS-CoV-2 infection. Therefore, many countries have attempted to reach the herd immunity threshold as early as possible since the commencement of vaccination at the end of 2020. The hope faded with the COVID-19 pandemic continuing with the emerging Omicron variants, and the bivalent COVID-19 vaccines were developed and used in Western countries. Bivalent vaccine containing mRNAs encoding Spike protein of both the ancestral strain and Omicron strain of SARS-CoV-2 was supposed to elicit an immune response of higher coverage against various variants. Nonetheless, the value of such bivalent vaccines was questioned [23]. There are basic design questions to be answered: (1) whether the second immunogen, covering one particular variant of Omicron, would be outdated by the time such vaccine is used in large populations as newer Omicron variants would have already emerged and (2) by one injection of the bivalent COVID-19 vaccine, it is questionable whether the body's immune system will provide a strong immune response toward the first immunogen but not the second immunogen, a phenomenon well known as "original antigenic sin" [24].

In contrast, natural infection by the Omicron virus would provide immunity against future Omicron variants [21,25]. More reports are emerging that infection by a previous Omicron strain would play a meaningful role in real-life protection from subsequent Omicron infections. The fact that most people in China now have been synchronously infected with the recent

Omicron variants around the end of 2022 will provide a valuable test to find out how long and to which degree such infection-induced immunity will protect the nation against future Omicron variants. Some low-level Omicron infections may persist as observed in the world, the key question is whether the large-scale outbreak can be prevented in China in the coming year due to the National Omicron Outbreak at the end of 2022. Continued monitoring is warranted for any emerging variants which may be more pathogenic than current Omicron variants.

Acknowledgments

This work was partially supported by grants from the Natural Science Foundation of China (grant number 8214100646). The information used in Figure 3 was collected from the US CDC website. The use of the material, including any links to the materials on the CDC website, does not imply endorsement by the CDC or the United States Government of work presented in this commentary. The material is otherwise available on the agency website for no charge.

Disclosure statement

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

Funding

This work was supported by National Natural Science Foundation of China [Grant Number 8214100646].

References

[1] Araf Y, Akter F, Tang Y-D, et al. Omicron variant of SARS-CoV-2: genomics, transmissibility, and responses to current COVID-19 vaccines. J Med Virol. 2022;94(5):1825–1832.
[2] Andrews N, Stowe J, Kirsebom F, et al. COVID-19 vaccine effectiveness against the Omicron (B.1.1.529) variant. N Engl J Med. 2022;386(16):1532–1546.
[3] Suzuki R, Yamasoba D, Kimura I, et al. Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. Nature. 2022;603(7902):700–705.
[4] Bureau CsB. China says 80% of population have had Covid-19, as millions travel for Lunar New Year. Cable News Network. 2023 January 22 [cited 2023, Feb 23]. Available from: https://edition.cnn.com/2023/01/22/china/china-covid-80-lunar-new-year-intl-hnk/index.html.
[5] McMenamin ME, Nealon J, Lin Y, et al. Vaccine effectiveness of one, two, and three doses of BNT162b2 and CoronaVac against COVID-19 in Hong Kong: a population-based observational study. Lancet Infect Dis. 2022;22(10):1435–1443.
[6] Pan Y, Wang L, Feng Z, et al. Characterisation of SARS-CoV-2 variants in Beijing during 2022: an epidemiological and phylogenetic analysis. Lancet. 2023.
[7] de La Vega M-A, Polychronopoulou E, Ara, et al. SARS-CoV-2 infection-induced immunity reduces rates of reinfection and hospitalization caused by the Delta or Omicron variants. Emerg Microbes Infect. 2023: 2169198.
[8] Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. Lancet Infect Dis. 2023.
[9] Cao Y, Jian F, Wang J, et al. Imprinted SARS-CoV-2 humoral immunity induces convergent Omicron RBD evolution. Nature. 2023;614(7948):521–529.
[10] Qu P, Evans JP, Faraone JN, et al. Enhanced neutralization resistance of SARS-CoV-2 Omicron subvariants BQ.1, BQ.1.1, BA.4.6, BF.7, and BA.2.75.2. Cell Host Microbe. 2023;31(1).
[11] Wang Q, Iketani S, Li Z, et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. Cell. 2023;186(2).
[12] Yue C, Song W, Wang L, et al. ACE2 binding and antibody evasion in enhanced transmissibility of XBB.1.5. Lancet Infect Dis. 2023;23(3):278–280.
[13] Our World in Data [Internet]. Johns Hopkins University. 2020 [cited 2023, Feb 23]. Available from: https://ourworldindata.org/coronavirus.
[14] Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533–534.
[15] Kandeel M, Mohamed MEM, Abd El-Lateef HM, et al. Omicron variant genome evolution and phylogenetics. J Med Virol. 2022;94(4):1627–1632.
[16] Zhao H, Meng X, Peng Z, et al. Fusion-inhibition peptide broadly inhibits influenza virus and SARS-CoV-2, including Delta and Omicron variants. Emerg Microbes Infect. 2022;11(1):926–937.
[17] COVID Data Tracker [Internet]. Atlanta, GA: US Department of Health and Human Services, CDC. [cited 2023, Feb 21]. Available from: https://covid.cdc.gov/covid-data-tracker.
[18] Tamura T, Ito J, Uriu K, et al. Virological characteristics of the SARS-CoV-2 XBB variant derived from recombination of two Omicron subvariants. bioRxiv. 2022.2022.12.27.521986.
[19] Imai M, Ito M, Kiso M, et al. Efficacy of antiviral agents against Omicron subvariants BQ.1.1 and XBB. N Engl J Med. 2023;388(1):89–91.
[20] Moss P. The T cell immune response against SARS-CoV-2. Nat Immunol. 2022;23(2):186–193.
[21] Chemaitelly H, Ayoub HH, AlMukdad S, et al. Protection from previous natural infection compared with mRNA vaccination against SARS-CoV-2 infection and severe COVID-19 in Qatar: a retrospective cohort study. Lancet Microbe. 2022;3(12):e944–e955.
[22] He Q, Mao Q, An C, et al. Heterologous prime-boost: breaking the protective immune response bottleneck of COVID-19 vaccine candidates. Emerg Microbes Infect. 2021;10(1):629–637.
[23] Offit PA. Bivalent Covid-19 vaccines – A cautionary tale. N Engl J Med. 2023;388(6):481–483.
[24] Gao B, He L, Bao Y, et al. Repeated vaccination of inactivated SARS-CoV-2 vaccine dampens neutralizing antibodies against Omicron variants in breakthrough infection. Cell Res. 2023;33(3):258–261.
[25] Stein C, Nassereldine H, Sorensen RJD, et al. Past SARS-CoV-2 infection protection against re-infection: a systematic review and meta-analysis. Lancet. 2023;401(10379):833–842.