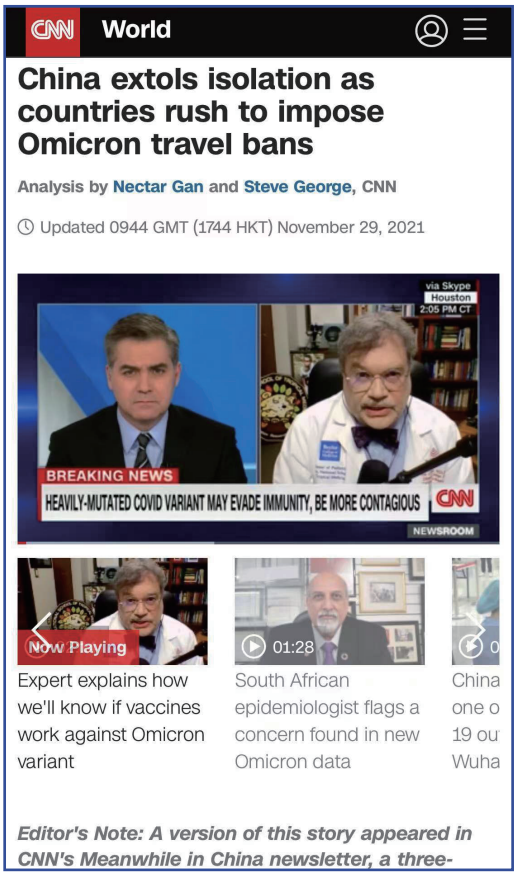
ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 3 No. 50 Dec. 10, 2021

中国疾病预防控制中心周报



COVID-19 ISSUE (21)

ISSN 2096-7071
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China CDC Weekly

Cover Photo: An article published this week named 'On Coexistence with COVID-19: Estimations and Perspectives' that was referenced by CNN on November 29, 2021 (https://edition.cnn.com/2021/11/29/china/china-covid-omicron-response-mic-intl-hnk/index.html).

Perspectives

On Coexistence with COVID-19: Estimations and Perspectives

Yuan Zhang[1,2,#]; Chong You[3,&]; Xin Gai[4,&]; Xiaohua Zhou[2,3,4,#]

Given the harsh reality faced by the global effort to contain coronavirus disease 2019 (COVID-19) and the virtual impossibility of its worldwide eradication in the foreseeable future, global human coexistence with fast mutating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have to occur, for the time being, irrespective of the wishes and aspirations of our people. Therefore, for China, the risk associated with small to medium scale outbreaks induced by imported cases and the corresponding need to continuously and promptly suppress domestic infections would persist for a certain period of time. However, such reality would not imply that we can deviate from our existing effective COVID-Zero strategy on entry-exit quarantine measures and community non-pharmaceutical interventions (NPIs) containment measures and embrace certain "open-up" strategies without reservation, resting solely on the hypothesis of the success of herd immunity induced by vaccination advocated by certain western countries. In this article, we found that even in a highly underestimated outbreak scenario under the most optimistic assumptions, once China adopts the control and prevention strategies of some typical western countries, the number of the daily new confirmed cases in China would likely rise up to hundreds of thousands of cases, and among which >10,000 cases would present with severe symptoms. Particularly, the number of standing severe cases would exceed the peak number nationwide in early 2020 within 1–2 days, which would have a devastating impact on the medical system of China and cause a great disaster within the nation.

Estimation on A Lower Bound of The Number of Newly Reported Cases

In this article, we used the real-world pandemic scenario in the following countries: the United States, the United Kingdom, Israel, Spain, and France, as a reference group to evaluate the corresponding potential consequences if pandemic response strategies in the aforementioned countries were to be adopted in China. In order to obtain a conservative estimation/lower bound, we hereby recalled a series of census data and key epidemiology characteristics of each of these countries below.

The population of the mainland of China is 1,411,778,724 based on the 7th National Census (*1*), which yields a countrywide population density of 147 people/km^2 (*1–2*). In particular, the population of the eastern region, which includes the provincial-level administrative divisions (PLADs) of Hebei, Shandong, Jiangsu, Zhejiang, Fujian, Guangdong, Hainan, Beijing, Tianjin, and Shanghai accounts for 39.9% of the total population, which is 563,300,220 (*1*), yielding a much higher population density of 661 people/km^2 (*1,3–4*). According to the latest report (*5*), a population of 777,046,000 has been fully vaccinated in the mainland of China, which represents a full vaccination ratio of roughly 55.04%. Natural immunity ratio is negligible in China considering the small number of cases with respect to its huge population size (*6*). The epidemiological information of the countries in our reference group has been collected and summarized in Table 1.

Note that the cumulative number of confirmed cases can serve as a very conservative estimate on the population with natural immunity. Thus, we can see that for each country in the reference group, their vaccination coverage together with natural immunity ratio are higher than in China. As for the population density, the United States, Spain, and France all have population densities lower than China. At the same time, none of these reference countries have their population densities as high as that of the eastern region in China.

For now, we assumed that the immunity induced by inactivated vaccines used in China is as strong as the one induced by vaccines used in the reference countries and also as strong as natural immunity in terms of providing protection against infection/symptoms. The following over-optimistic assumptions were used: 1) the vaccination rate in China is as high as the reference countries; and 2) the population density of China or China's eastern region is as low as the reference

TABLE 1. Epidemiology profiles of the reference countries.

Reference country	Population	Population density	Vaccination ratio-full	Confirmed cases-cumulative	Confirmed cases-averaged in 7 days
US	332,580,000 (*7*)	36.2 (*8*)	51.16% (08/23) (*9*)	37,939,641 (*10*)	150,098 (*10*)
UK	67,081,000 (*11*)	280.6 (*8*)	61.59% (08/22) (*9*)	6,555,419 (*10*)	32,843 (*10*)
Israel	9,289,800 (*12*)	400.0 (*8*)	62.94% (08/23) (*9*)	999,110 (*10*)	7,293 (*10*)
Spain	47,330,000 (*13*)	93.7 (*8*)	67.26% (08/22) (*9*)	4,794,352 (*10*)	10,727 (*10*)
France	67,347,241 (*14*)	119.2 (*8*)	55.57% (08/22) (*9*)	6,708,163 (*10*)	21,667 (*10*)

countries (see detailed explanation below) if pandemic response strategies and community activity patterns in the reference countries were adopted in China, the ratio of infection would be similar to these countries. While in reality, such a rate should be much higher.

According to the dynamic transmission models in epidemiology, for example the well-known susceptible-infected-removed (SIR) model and its variants, the daily increment in pandemic size can be estimated by $\beta SI/N$, where β is the transmission rate, S is the susceptible population, I is the infected population and N is the total population. If β and the ratio of infection I/N are fixed, the number of new infections is proportional to S, which is in turn approximately proportional to the population size N.

We could hence scale the size of S to estimate the daily confirmed cases in China if the same strategies in the reference countries would have been adopted, under the aforementioned assumptions. Note that the estimates would be most likely over-optimistic due to the nature of assumptions (*1*–*2*), but still serve their purpose of obtaining a plausible lower bound of pandemic sizes.

To ensure that assumption (*2*) was always a conservative one and thus led to a universally over-optimistic estimate if China adopted response strategies of all the reference countries, we estimated various lower bounds of national-wide daily new infection sizes using the national population if the corresponding reference countries have a population density lower than China (i.e., the United States, Spain, and France). Otherwise, the lower bounds of daily new infection sizes in the eastern region were calculated using only the population within that part of China (i.e., Britain and Israel). Recall that the population in the eastern region of China is significantly higher than any of the reference countries, ensuring that assumption (*2*) remains conservative. Estimations of the lower bound in the two scenarios above are precisely calculated in the following Equations:

(i) Population density of reference country < Overall population density of China

$$lowerboundestimate = \frac{Population\ of\ China}{Population\ of\ Reference\ Country} \times \bar{C}\left(Reference\ Country\right) \quad (1)$$

(ii) Population density of reference country > Overall population density of China

$$lowerboundestimate = \frac{Population\ of\ Easternregion}{Population\ of\ Reference\ Country} \times \bar{C}\left(Reference\ Country\right) \quad (2)$$

Remark 1: In Equation (1)–(2), $\bar{C}\left(Reference\ Country\right)$ stands for the average of confirmed cases reported in the reference country, August 17–August 23, 2021.

Based on Equation (1)–(2), the conservative estimates on hypothetic daily new infections in China can be obtained under strategies in the reference countries in Table 2. We can see that even with the aforementioned over-optimistic assumptions, the size of daily new infection in China would be very likely of hundreds of thousands if China adopted the strategies in these reference countries.

Estimation on a Lower Bound of Daily New Severe Cases

There have been recent arguments that a higher infection size is now more tolerable provided that severe cases of COVID-19 have been substantially reduced under the large-scale vaccination campaign, preventing the medical system from being overrun. While vaccination has been proved to significantly reduce the development of severe symptoms after infection from the original and mutated strain of the virus, the emergence of new mutated strains would potentially disrupt such protection. In order to depict the combined effect from vaccine coverage rate, vaccine protection efficiency, and the characteristics of the Delta strain on the current rate of severe cases, we used real-world data in the most recent outbreak in Yangzhou, China and modified it based on nationwide age structure.

By midnight of August 23, 2021, there have been a

TABLE 2. Estimates on the lower bound of daily new infections in China under strategies in the reference countries.

Reference country	Population in the reference country	Confirmed cases-averaged in 7 days in the reference country	Estimated lower bound of daily new cases in China
US	332,580,000	150,098	637,155
UK	67,081,000	32,843	275,793
Israel	9,289,800	7,293	442,221
Spain	47,330,000	10,727	319,969
France	67,347,241	21,667	454,198

total of 568 cases reported in Yangzhou (*15*). Moreover, as of August 16, the city had 27 standing severe cases and 17 critical cases (*16*) Thus, the cumulative number of cases who had ever developed severe symptoms is at least 44 (27+17), which yields a ratio of 7.7%. Note that the outbreak in Yangzhou was still in a moderate scale without medical overloading, the observed rate can be considered as an optimistic estimate on the rate of severe cases for larger scale outbreaks.

However, it is worth noting that the outbreak in Yangzhou was mainly induced by the spread of COVID-19 in Mahjong clubs and that the elderly accounted for 41.0% of the total reported infections. Noting that the elderly is known to have a higher risk of developing severe symptoms, we had to rescale the rate of severe cases by adjusting the age structure in Yangzhou to match that of the whole population of China as follows.

The rate of severe cases in Yangzhou can be expressed as

$$\rho^s = \rho_1 p_1^s + \rho_2 p_2^s = 7.7\%,$$

where ρ^s is the rate of severe cases in Yangzhou, $\rho_1 = 1 - \rho_2 = 41.0\%$ is the proportion of elderly in total infection in Yangzhou while p_1^s and p_2^s are the unknown rates of severe cases for elderly and non-elderly. In a same way, the rate of severe cases in the whole population of China can be expressed as

$$q^s = q_1 p_1^s + q_2 p_2^s,$$

where q^s is the rate of severe cases over the whole Chinese population, $q_1 = 1 - q_2$ is the proportion of elderly in total infection in China. Under the massive outbreak hypothesized in the previous section, we assumed that q_1 equals the proportion of the elderly in the population in China, that is 18.7% (*17*), we have

$$q^s = q_1 p_1^s + q_2 p_2^s \geq \frac{18.7}{41}\left(\rho_1 p_1^s + \rho_2 p_2^s\right) = 3.5\%.$$

Note that lower bound was calculated based on a reasonable assumption on $p_1^s > p_2^s$. Here, we took 3.5% to be a reasonable lower bound for the rate of severe cases under the combined effects of current population age structure, vaccination coverage and protection rate, medical resources, and the characteristics of the Delta strain.

Remark 2: Considering the possibly lower vaccination coverage, protection, and the immunity to COVID-19 in elderly group, as well as higher aging level in eastern region of China, the aforementioned lower bound is likely to be underestimated again.

Remark 3: As most of the reference countries do not conduct community-level screening and contact tracing to the same lengths and strength as in China, the ascertainment rate is probability lower than that in Yangzhou (many asymptomatic/mild cases detected in Yangzhou might not be ascertainable in the reference countries). This implies that the rate of severe cases would be higher when applying the criterion of confirmed cases found in the reference countries to the reported cases in Yangzhou, and hence the fraction of severe cases was likely to be underestimated.

Note that all the aforementioned estimates are uniformly on the conservative side. Combining these over-optimistic estimates, we found the number of daily new severe cases or sickbed demand was as follows in Table 3 if we adopt the "open-up" strategies of these reference countries. We can see if strategies in these reference countries were adopted, the number of severe cases might exceed the peak of standing severe cases nation-wide in early 2020 [11,977, on February 18, 2020 (*18*)] within 1–2 days, and thus would pose an unaffordable burden to the medical system in this country.

DISCUSSION

How to safely open up is one of the most interesting issues at present, which has been discussed in many studies (*19–20*). Among which, Foo et al. proposed four insightful key tenets for the safe transition from elimination strategies to open-up strategies: 1) retain flexible NPIs based on the changing epidemiology and hospital capacities; 2) maximize vaccination coverage; 3) shield industries and vulnerable groups from the

TABLE 3. Estimates on the lower bound of daily severe cases in China under strategies in the reference countries.

Reference country	Estimated lower bound of daily severe cases in China
US	22,364
UK	9,680
Israel	15,522
Spain	11,231
France	15,942

unintended consequences resulting from NPIs; and 4) detect and isolate COVID-19 promptly using extensive surveillance and stronger community social responsibility. However, due to the large population and relatively scarce health resources per capita in China, it is difficult to fully achieve tenets 1, 3, and 4, especially during a large-scale outbreak; therefore, China needs to be cautious about the decision on the open-up. Nevertheless, our suggestions towards China might not necessarily be applicable to other countries.

To be noted again, our results were based on elementary arithmetic calculations to provide quick estimates on the lower bound of the daily new infections and severe cases should China adopt coexistent or open-up policies seen in the reference countries. As a result, there were some limitations in our study, for example: 1) the estimates here were only the conservative lower bounds of, and not the actual number of cases, which is not possible to predict, but the order of magnitude seems reasonable; and 2) the effects on different vaccination strategies were not able to be incorporated into the estimations. More sophisticated dynamic models are needed to study the evolution of the pandemic and the risk if travel restrictions were lifted, various vaccination strategies were implemented together, different levels of NPI containment intensities, all of which are works in progress.

CONCLUSION

To summarize, in this article we estimated a plausible lower bound on the outbreak size and sickbed demands if the pandemic response strategies in the reference countries were applied in China. The estimates revealed the real possibility of a colossal outbreak which would almost certainly induce an unaffordable burden to the medical system. Our findings have raised a clear warning that, for the time being, we are not ready to embrace "open-up" strategies resting solely on the hypothesis of herd immunity induced by vaccination advocated by certain western countries. More efficient vaccinations or more specific treatment, preferably the combination of both, are needed before entry-exit quarantine measures and other COVID-19 response strategies in China can be safely lifted.

According to the celebrated dynamic models in epidemiology and Grönwall's Inequality in math, an epidemic decays exponentially when the reproductive number $R<1$, but may also blow up in the same exponential manner once $R>1$. In the past year, many in the world have suffered by overconfidently jumping into the latter scenario. China should not, and cannot afford to, be the next.

Conflicts of interest: No conflicts of interest.

Funding: National Natural Science Foundation of China grant 8204100362 and The Bill & Melinda Gates Foundation (INV-016826).

doi: 10.46234/ccdcw2021.245

[#] Corresponding authors: Yuan Zhang, zhangyuan@math.pku.edu.cn; Xiaohua Zhou, azhou@math.pku.edu.cn;.

[1] School of Mathematical Sciences, Peking University, Beijing, China; [2] Center for Statistical Sciences, Peking University, Beijing, China; [3] Beijing International Center for Mathematical Research, Peking University, Beijing, China; [4] Department of Biostatistics, School of Public Health, Peking University, Beijing, China.
[&] Joint first authors.

Submitted: October 18, 2021; Accepted: October 25, 2021

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Perspectives

Papua New Guinea Under the COVID-19 Pandemic and Public Health Support from the World Health Organization

Wenwen Lei[1,#]

On March 20, 2020, the first positive case of coronavirus disease 2019 (COVID-19) was detected in Papua New Guinea (PNG). That same day, a state of emergency was declared in the country, thereby halting all incoming and domestic flights and limiting travel between provinces. Meanwhile, the PNG government established the National Control Centre (NCC) to specifically respond to the pandemic. The pandemic's second wave struck local areas in February 2021, with a corresponding surge in the number of positive cases (Figure 1A). As of March 15, 2021, 54,410 nasal samples had been collected and tested nationwide, with 2,351 confirmed positive cases and 26 deaths.

While these numbers are still lower than that in some other countries, there has been a sharp increase in cases and the World Health Organization (WHO) is highly concerned about the pandemic's potential to spread much wider (*1*). Due to low testing capacity and a shortage of testing personnel and reagents, the actual number of infections in PNG may be far higher than the reported number (*2*). The pandemic in PNG is suspected to be underestimated and has spread rapidly nationwide (Figure 1B). The number of cases in the capital city of Port Moresby has accounted for 47% of the country's total. Port Moresby General Hospital, the country's largest hospital, was overwhelmed at that time (*2*). In terms of health security threats, PNG is one of the most at-risk countries in the world (*3*). Dengue, tuberculosis, malaria, HIV, and diarrhea are present and ongoing threats for PNG (*2*). PNG also has a relatively weak healthcare system (*3*) and one of the world's lowest ratios of doctors; the World Bank figures for 2018 show the country had only 0.07 physicians per 1,000 people. This is well below the 2017 average for Pacific Small Island Developing States (0.5), the 2017 world average (1.6), and the 2017 level in the United States (2.6) (*4*). As of April 2, 2021, the country had 500 doctors, fewer than 4,000 nurses, fewer than 3,000 community health workers, and roughly 5,000 hospital beds for 9 million people (*4*).

From the early stages of the COVID-19 pandemic in 2020, the WHO deployed experts to the PNG government to provide technical support for case management, epidemiology, infection prevention and control, laboratory support, and information management (*1*). The WHO and related personnel worked in the NCC's Incident Management Team (IMT) framework under the leadership of the PNG National Department of Health (NDoH) staff. Global Outbreak Alert and Response Network (GOARN) experts were located within the IMT pillar areas, assisting in daily work, providing technical assistance, and supporting special projects. From November 4, 2020 to March 30, 2021, the WHO invited me, as a laboratory technical expert in response to the COVID-19 pandemic, to provide technical assistance for PNG. I am the first person successfully dispatched by GOARN from China during the COVID-19 pandemic, and the first Chinese expert to be deployed by an international organization to PNG for assistance in this pandemic.

During nearly 5 months of work, I engaged in communication with and coordinated with various organizations and departments such as the WHO Headquarters, WHO Western Pacific Region, local governments and the NDoH, and provincial health authorities, and I worked in accordance with the PNG Response Plan for COVID-19. My colleagues and I have successfully held a series of national workshops on enhancing the diagnosis of and response to COVID-19 and aimed to improve PNG laboratories' diagnosis and detection capabilities. During January 20–23, 2021, I traveled to East New Britain Province to conduct theoretical and practical training in Nonga General Hospital for rapid detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigens. The methods taught were later implemented nationwide. My colleagues and I have also evaluated and certified the laboratories in PNG with nucleic acid detection capacity. We have reviewed and assessed the COVID-19 real-time reverse transcription polymerase chain reaction (rRT-PCR) assay and instrument platform, and laboratory design and space, for three private

laboratories in the capital — Aspen Medical Laboratory, Sky Health & Medical Services COVID-19 Laboratory, and Pacific International Hospital. We issued an evaluation report providing suggestions on the diagnostic algorithm, test verification, and reporting process regarding COVID-19. The WHO Regional Director for the Western Pacific, upon learning of my work in PNG, expressed great pleasure and strong affirmation that WHO experts were supporting pandemic prevention and control in PNG.

I already engaged in COVID-19 pandemic control in Wuhan, Suifenhe, and Shulan cities and the Beijing Xinfadi Wholesale Market in China in 2020. The experience acquired there provided me with a vital foundation for my work in PNG. I believe communication, sharing, and learning are pivotal for controlling infectious diseases at the global scale.

As of September 28 2021, a total of 191,925 vaccine doses had been administered in PNG. The situation in PNG is excellent proof of the vital importance of vaccine fairness. Vaccines have contained the COVID-19 pandemic for a long time, but with the increase in

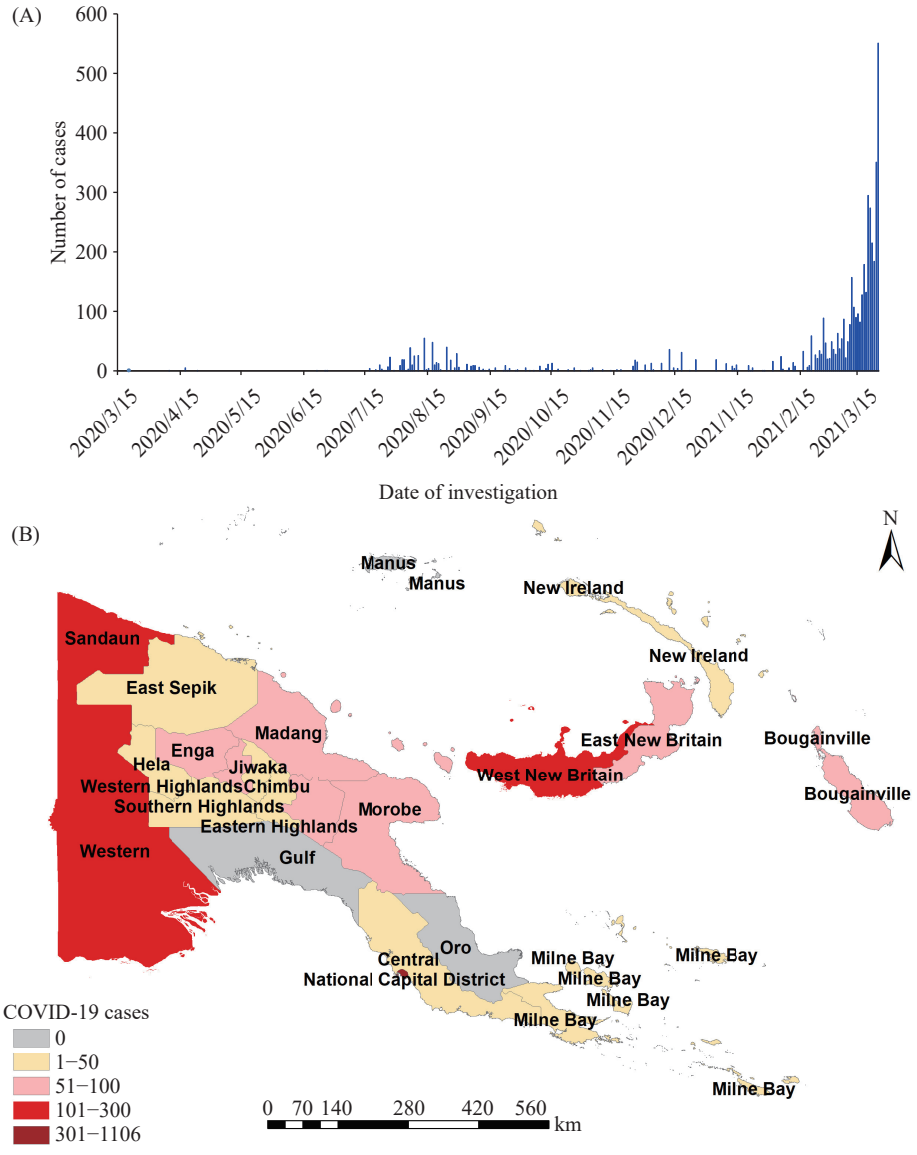

FIGURE 1. Coronavirus disease 2019 (COVID-19) pandemic in Papua New Guinea. (A) Papua New Guinea confirmed cases from March 15, 2020, to March 15, 2021. (B) Distribution of COVID-19 cases in Papua New Guinea as of March 15, 2021.
Note: The map was created using ArcGIS (version 10.4, Esri, Redlands, CA, USA). Data were collected from WHO website: https://covid19.who.int/region/wpro/country/pg.

the number of infections, fatigue from social restrictions, low levels of people's immunity, and fragile health systems, it is crucial to obtain more vaccines as soon as possible. In the future, vaccinations should be vigorously promoted in PNG, laboratory testing and monitoring capabilities strengthened at the same time — i.e., to strengthen the whole genome sequencing and RT-PCR infrastructure in the national public health plan–early detection and monitoring of new SARS-CoV-2 mutant strains strengthened, and detection capabilities expanded. These measures will play a greater role in controlling the epidemic.

Since the COVID-19 outbreak was declared a Public Health Emergency of International Concern, the WHO, through GOARN, has deployed more than 130 experts to 26 countries to provide support in enhancing laboratory capacity, epidemiology, infection prevention and control, case management, and data management (*5*). All these experts have greatly contributed to controlling the COVID-19 pandemic. Meanwhile, public health experts from China have been to countries including Iran, Iraq, Russia, and Italy to support local COVID-19 control and technique training, just as the supportive work in Western Africa during the Ebola epidemic (*6*–*7*). China is collaborating with different countries on Phase III clinical trials of the vaccines, and Chinese vaccines against COVID-19 have been shared with more than 100 countries and international organizations. Working together with experts from different countries under the WHO's coordination, China's public health experts are increasingly participating in global public health efforts to improve governance in this area and build a community concerned with the health of greater mankind.

Acknowledgments: Dr. Dapeng Luo, Dr. Anna Maalsen, Dr. George F. Gao, Dr. Guizhen Wu, Dr. William J. Liu, Dr. Xianyuan Du, and Dr. Idrissa Laybohr Kamara.

Conflicts of interest: No conflicts of interest.

doi: 10.46234/ccdcw2021.214

Corresponding author: Wenwen Lei, leiww@ivdc.chinacdc.cn.

[1] National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: August 16, 2021; Accepted: September 08, 2021

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Outbreak Reports

Exploring the Bridge Cases' Role in the Transmission of the SARS-CoV-2 Delta Variant — Ruili City, Yunnan Province, China, July–September 2021

Xiangyu Yan[1,&]; Litao Chang[2,&]; Zekun Wang[1]; Linhui Hao[2]; Zhongwei Jia[1,3,4]; Bo Zhang[1,#]; Tiejun Shui[2,#]

Summary

What is already known about this topic?

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant has proved to have increased transmissibility, and mutations that can cause partial immune escape, which makes its transmission more insidious.

What is added by this report?

This study showed that probable cases who had negative results in nucleic acid testing but had positive IgM test result and/or IgG test value of over 20 S/CO in antibodies testing, might serve as bridges in the Delta variant's transmission chain.

What are the implications for public health practice?

In border inspection and quarantine, tests for SARS-CoV-2 IgM and IgG antibodies should be strengthened alongside nucleic acid tests to prevent probable cases with transmission potential from crossing the land border into China. In contact tracing investigations, the bridging role of probable cases should be considered to reconstruct the transmission chain.

On July 4, 2021, 3 confirmed coronavirus disease 2019 (COVID-19) patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.617.2 (Delta) variant were found through regular nucleic acid screening in Jiegao Community, Ruili City, Yunnan Province (*1*). During the epidemiological investigation conducted by local CDCs and the Yunnan Provincial CDC from July to September, 2021, many of the confirmed cases were found to have no clear history of contact to other cases, which made difficult the tracing of the source of cases and effective control of the recent outbreak. In a retrospective analysis of the epidemiological investigation and laboratory test data, we reported a phenomenon for the first time that the probable index case, who had a negative nucleic acid test but had a positive IgM test result and/or IgG test value of over 20 S/CO in antibodies testing, might have acted as a bridging case for SARS-CoV-2 transmission. Based on this finding, probable cases were considered as clues of case tracing in the following epidemiological investigation, and serological antibody monitoring was strengthened to include the probable cases. Our evidence indicated that strengthening the management of probable cases is essential to effectively control transmission, especially in border areas that may have increased contact with COVID-19 prevalent regions.

INVESTIGATION AND RESULTS

The confirmed COVID-19 cases were diagnosed and classified according to severity (mild, moderate, severe, and critical) based on guidelines issued by the National Health Commission (*2*), which the local CDC confirmed. The biological samples of these cases were also sent to the China CDC for further virus genotyping. A detailed epidemiological investigation was conducted for these patients, including collecting their sociodemographic information, residential address, and history of travel, work, contacts, and activities. These patients were immediately transported to a designated quarantine site. Close contacts of these COVID-19 patients were found through epidemiological investigation and travel history big data and were quarantined for at least 14 days. Regular SARS-CoV-2 nucleic acid testing and antibody testing (IgM and IgG) was conducted on the COVID-19 patients and their close contacts. Their COVID-19 vaccination records were obtained from the vaccination database using ID numbers and names as unique identifiers. Compared with the confirmed COVID-19 cases, whose nucleic acid testing results were positive, we defined the probable cases as individuals who had negative results in nucleic acid testing but had positive

IgM test results and/or IgG test values of over 20 S/CO in antibody testing. We set a value limit of 20 S/CO for the IgG test because the positive IgG value was common among people who have been vaccinated against COVID-19, and the value of 20 S/CO was a conservative limit that was about two times higher than the 98% quantile value (10.810 S/CO) of the 117 confirmed COVID-19 cases' IgG test results in the one-month follow-up in Ruili City. Therefore, the probable cases had a high probability of infection but had not been detected by nucleic acid testing.

For laboratory testing, Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) targeting of ORF1ab and N genes was conducted on the viral RNA extracted from the nasopharyngeal swabs using the Novel Coronavirus 2019 Nucleic Acid Test Kit (manufactured by Bojie Medical Technology, Shanghai Municipality and Daan Gene Company, Guangzhou City, China). The detection limit of cycle threshold (Ct) of the above tests was 40, a Ct value of less than 40 was considered as a positive nucleic acid test result. The nucleic acid test reading positive or not was the key to distinguishing between the confirmed cases and the probable cases. Serum samples collected from confirmed COVID-19 patients and their close contacts were tested for antibodies IgM and IgG using Anti-SARS-CoV-2 Rapid Test Kit (manufactured by Antubio Diagnostics Company, Zhengzhou, China). A value of over 1 S/CO was considered a positive result for IgM and IgG tests.

Retrospective analysis was conducted based on the epidemiological investigation data from July to September 2021. Contact networks of confirmed COVID-19 patients and their close contacts were formed. The nodes in the contact networks represent the confirmed COVID-19 patients and their close contacts. Edges of the networks represent the contacts among these persons, including work and household contacts, environmental contacts, and so on. Statistical analysis was performed with IBM SPSS (version 21.0, IBM Corp., Armonk, NY, US). Network visualization was done with Cytoscape (version 3.5.1, NIH Biomedical Technology Research Center, Bethesda, MD, US).

In this study, we showed a representative example that 2 confirmed COVID-19 cases (C1 and C2) and their contact networks were linked by two probable cases (P1 and P2) that acted as bridges, which constituted a potential chain of Delta variant transmission (Figure 1). C1 was the first index case of the "July 4" COVID-19 outbreak in Ruili City, Yunnan Province and occurred in a 51-year-old Chinese man who lived in Jiegao Community. C2 occurred in a 25-year-old Chinese male diagnosed on August 2, 2021. The two confirmed cases were both infected with SARS-CoV-2 Delta variant, and the amino acid mutation sites in the S protein of the two patients' viruses were the same, including T19R, G142D, R158G, L452R, T478K, D614G, P681R, D950N, E156del, and F157del. The two patients all declared that they had no contact with other COVID-19 patients or anyone with suspected symptoms before they were diagnosed (Table 1). A total of 238 close contacts were found through epidemiological investigation, of whom 85 were close contacts of C1, and 153 were close contacts of C2. The mean age of the contacts was 31.2±13.5 years, and most of them were aged 18–45 years (73.9%). C1 had more contacts with people in Myanmar than C2 (50.6% *vs.* 1.3%); 75.2% of the close contacts were vaccinated against COVID-19 (Table 2).

P1 (a 34-year-old man from Myanmar) and P2 (a 25-year-old Chinese man) were two close contacts of the two patients. P1 was a close contact of C1, and P2 was a close contact of P1 and C2. All four patients had been vaccinated against COVID-19 before (Table 1, Figure 1). The detailed transmission chain was described in the following three stages (Figure 1).

Stage 1: P1's contact with C1

P1 had sustained environmental exposure to C1 due to sharing stairs until July 4, 2021. He had a high-level IgG value of 21.139 S/CO tested on July 5, 2021. The quarantine began on July 4, 2020, and he was repatriated to Myanmar on August 2, 2021. C1 also had extremely high antibody values tested on the same day (July 5, 2021), of which IgM value was 11.773 S/CO, and IgG value was 64.768 S/CO (Table 1). The potential transmission path might exist between the two cases (Figure 1).

Stage 2: P2's contact with P1

P2 had contact with P1 through shopping on June 27, 2021, and the quarantine period lasted from July 6 to 20, 2021. He had a positive IgM test result, and a relatively high IgG value of 11.552 S/CO tested on July 7, 2021. Considering that the infection of P1 occurred earlier (IgM negative and IgG positive) at the same period, there was a high probability that the virus transmitted from P1 to P2. (Table 1, Figure 1)

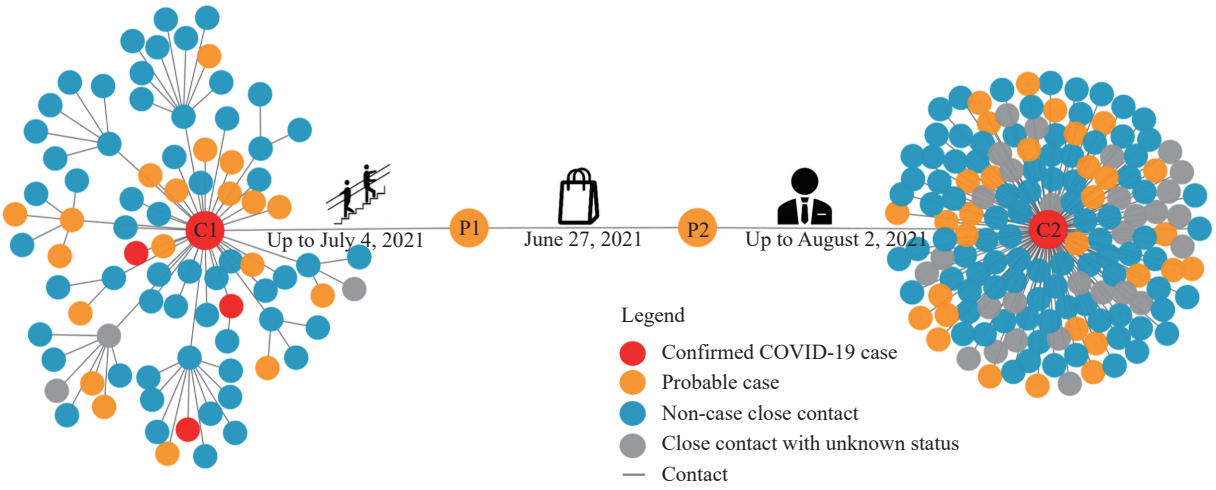

FIGURE 1. Contact network of two confirmed COVID-19 cases (C1 and C2) and two corresponding probable cases (P1 and P2) in Ruili City, Yunnan Province, China, July–September 2021.

Stage 3: C2's contact with P2

After P2 left the first quarantine on July 20, 2021, he was quarantined a second time on August 3, 2021 because he had work and daily life contact with C2. The last contact between P2 and C2 was on August 2, 2021. C2 was diagnosed as a confirmed COVID-19 case on August 2, 2021, and the first antibody test results were negative for both IgM and IgG tested on August 3, 2021, but then both were revealed to be positive in subsequent tests. The three antibodies test results of P2 during this quarantine were all double-positive for IgM and IgG until August 17, 2021. It was possible that P2's latent infection status continued from July to August after the contact with P1, in which the virus was transmitted to C2. (Table 1, Figure 1)

In the ongoing outbreak of COVID-19 in Ruili, antibody tests were carried out among almost all of the close contacts to identify potential probable cases. The epidemiological investigation and case tracing was carried out using the clue of probable cases. In addition, serological antibody monitoring and follow-up were strengthened for the probable cases.

DISCUSSION

In this study, we constructed a hidden chain of transmission between two confirmed COVID-19 patients connected by two probable cases acting as bridges. This finding could help solve the difficulties faced in the front-line epidemiological investigation in tracing the source of cases. Both confirmed patients had no contact history with other COVID-19 patients and anyone with suspected symptoms before, but the virus they were infected with had the same amino acid mutation sites. Without considering the probable cases' effect, it was possible that the two cases were separate, and the transmission links were hard to be established.

Of the two probable cases, P2 was the most critical bridge case in the transmission chain. His double-positive antibodies status lasted for over one month and covered his first 14-day quarantine after he had contact with P1. A previous study had indicated that the SARS-CoV-2 Delta variant contained mutations that could cause partial immune escape (*3*). A special confirmed COVID-19 case with virus variation has been reported to have continuous negative results for routine PT-PCR detection in Guangzhou and was finally diagnosed using Nanopore Sequencing combined with antibody testing (*4*). P2 might have a similar situation with the special case. A study from Todsen et al. also indicated that the oropharyngeal swabs showed relatively lower sensitivity for lower respiratory tract infections of SARS-CoV-2 (*5*). It was possible that the virus existed in the lower respiratory tract infections of P2. In addition, the intermittent virus shedding between two regular nucleic acid tests, which were conducted every three days, made it possible for P2 to transmit the virus to other persons but could not be detected by regular nucleic acid tests. Another potential reason is that the SARS-CoV-2 variant might have a longer latent period than previously thought. Recent evidence provided by Guangzhou's outbreak showed a latent period of 4.0 days and an incubation period of 5.8 days (*6*). However, the report of the Hebei's outbreak showed an incubation period of more than 22.0 days (*7*).

TABLE 1. Characteristics of the two confirmed COVID-19 cases and two probable cases in Ruili City, Yunnan Province, China, July–September 2021.

Case*	Sex	Age (years)	Community	Nationality	Date of symptom onset	Date of positive nucleic acid test	Severity	Date of COVID-19 vaccination		Antibody test results (S/CO)			
										First time		Last time	
								First Dose	Second Dose	Date	Results	Date	Results
C1	Male	51	Jiegao	China	Jul 2, 2021	Jul 3, 2021	Moderate	May 5, 2021†	–	Jul 5, 2021	IgM: 11.773(+); IgG: 64.768(+)	Aug 5, 2021	IgM: 7.684(+); IgG: 7.154(+)
C2	Male	25	Jiegao	China	Aug 2, 2021	Aug 2, 2021	Mild	Mar 18, 2021	Apr 1, 2021	Aug 3, 2021	IgM: 0.032(−); IgG: 0.343(−)	Aug 23, 2021	IgM: 24.428(+); IgG: 8.227(+)
P1	Male	34	Jiegao	Myanmar	–	–	–	Apr 25, 2021	May 26, 2021	Jul 5, 2021	IgM: 0.373(−); IgG: 21.139(+)	–	–
P2	Male	25	Jiegao	China	–	–	–	May 6, 2021†	–	Jul 7, 2021	IgM: 1.695(+); IgG: 11.139(+)	Aug 17, 2021	IgM: 2.426(+); IgG: 5.001(+)

* C1=confirmed COVID-19 case 1; C2=confirmed COVID-19 case 2; P1=probable case 1, P2=probable case 2.
† The COVID-19 vaccine they received has only one dose.

Therefore, more comprehensive epidemiological and laboratory data collection is needed to verify this phenomenon. In addition, it has been proved that the Delta variant had increased transmissibility (*8*). Though the virus was not detected in P2's respiratory tract samples, it did not rule out that he transmitted the virus to other people or the environment in some other routes. Considering that he was vaccinated against COVID-19, the total shedding period of the virus might be longer than the evidence provided by Chen et al. (*9*).

Although we only showed a representative example, the phenomenon that probable cases acted as bridges in the transmission chain is not rare. This study also finds other potential transmission between two probable cases regardless of P1 and P2's connection in C1's contact network (Figure 1). A previous study in Liaoning Province also showed a phenomenon in an outbreak that made it difficult to determine the first index case, persons who were double-positive for IgM and IgG but negative for nucleic acid testing were also found, which supported our finding (*10*).

Our finding has strong practical implications. Great importance needs to be attached to the role of latent infections and probable cases in the transmission chain. First, considering that Ruili City is an important border port city bordering Myanmar in western Yunnan Province, refugees caused by the war in north Myanmar and border trade increased the difficulty of COVID-19 control and management in China's border. In this study, P1, who was a man from Myanmar, became an important link in the chain of transmission. Therefore, in border inspection and quarantine, tests for SARS-CoV-2 antibodies (IgM and IgG) should be carried out alongside nucleic acid tests to prevent probable cases with transmission potential from crossing the land border into China. Second, in case tracing investigations, not only the connections among confirmed COVID-19 patients and asymptomatic cases, but also the bridging role of probable cases should be considered to reconstruct the transmission chain. In addition, in the process of close contacts management, the probable cases need to be treated the same as confirmed cases to reduce the risk of transmission.

In conclusion, this is a pioneering study to reveal the bridging role of latent infection in the spread of the SARS-CoV-2 Delta variant. However, there were some limitations in the process of building the transmission chain. First, because the situation of the border port in Ruili City was so complex, there might be some

TABLE 2. Characteristics of close contacts of the two confirmed COVID-19 cases in Ruili City, Yunnan Province, China, July–September 2021.

Characteristics	Total (n=238), n (%)	C1* (n=85), n (%)	C2† (n=153), n (%)
Age (years)			
Mean±SD	31.2±13.5	30.7±17.7	31.4±10.4
<18	22/234 (9.4)	19/84 (22.6)	3/150 (2.0)
≥18 to <45	173/234 (73.9)	49/84 (58.3)	124/150 (82.7)
≥45 to <65	37/234 (15.8)	14/84 (16.7)	23/150 (15.3)
≥65	2/234 (0.9)	2/84 (2.4)	0/150 (0.0)
Sex			
Male	164/236 (69.5)	35/84 (41.7)	129/152 (84.9)
Female	72/236 (30.5)	49/84 (58.3)	23/152 (15.1)
Nationality			
China	193 (81.1)	42 (49.4)	151 (98.7)
Myanmar	45 (18.9)	43 (50.6)	2 (1.3)
COVID-19 vaccination			
Yes	179 (75.2)	60 (70.6)	119 (77.8)
No	59 (24.8)	25 (29.4)	34 (22.2)
Infection status			
Confirmed COVID-19 case	3 (1.3)	3 (3.5)	0 (0)
Probable case	53 (22.3)	21 (24.7)	32 (20.9)
Non-case close contact	150 (63.0)	58 (68.2)	92 (60.1)
Unknown status	32 (13.4)	3 (3.5)	29 (19.0)

* C1=confirmed COVID-19 case 1.
† C2=confirmed COVID-19 case 2.

incompleteness in the process of close contact tracing and epidemiological investigations. The bridging role of the probable cases needed to be verified by strengthening investigations of the detailed co-exposure history of close contacts in further case tracing because the possible co-exposure with confirmed cases during one's infectious period might not imply a definite transmission chain linkage. Second, though we set a very conservative limit for the antibody test results to prevent the inclusion of unreasonable probable cases, the standard of selecting probable cases from confirmed cases' close contacts needed to be further explored in deliberately designed representative research. In future studies, more abundant and detailed epidemiological investigations should be carried out to give a more precise definition of probable case with latent infection and verify their possible bridging role. It is also needed to strengthen basic virology research to explain the biological mechanism of latent infections' transmission capacity.

Conflicts of interest: No conflicts of interest.

Acknowledgements: Ruili City CDC, Yunnan Province CDC, and China CDC; the confirmed COVID-19 patients and their close contacts.

Funding: The National Key Research and Development Program of China (2020YFC0849200), National Natural Science Foundation of China (No. 91546203, 91846302).

doi: 10.46234/ccdcw2021.239

Corresponding authors: Bo Zhang, zhangbo0136@pku.edu.cn; Tiejun Shui, 67637539@qq.com.

[1] School of Public Health, Peking University, Beijing, China; [2] Yunnan Center for Disease Control and Prevention, Kunming, Yunnan, China; [3] Center for Intelligent Public Health, Institute for Artificial Intelligence, Peking University, Beijing, China; [4] Center for Drug Abuse Control and Prevention, National Institute of Health Data Science, Peking University, Beijing, China.
& Joint first authors.

Submitted: October 07, 2021; Accepted: November 01, 2021

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Methods and Applications

Feasibility of Booster Vaccination in High-Risk Populations for Controlling Coronavirus Variants — China, 2021

Kangguo Li[1]; Zeyu Zhao[1,2]; Hongjie Wei[1]; Jia Rui[1]; Jiefeng Huang[1]; Xiaohao Guo[1]; Yichao Guo[1]; Shiting Yang[1]; Guzainuer Abudurusuli[1]; Li Luo[1]; Xingchun Liu[1]; Yao Wang[1]; Jingwen Xu[1]; Yuanzhao Zhu[1]; Meng Yang[1]; Tianlong Yang[1]; Weikang Liu[1]; Bin Deng[1]; Chan Liu[1]; Zhuoyang Li[1]; Peihua Li[1]; Shanshan Yu[1]; Zimei Yang[1]; Yanhua Su[1]; Benhua Zhao[1]; Yan Niu[3,#]; Tianmu Chen[1,#]

ABSTRACT

Introduction: Vaccination booster shots are completely necessary for controlling breakthrough infections of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China. The study aims to estimate effectiveness of booster vaccines for high-risk populations (HRPs).

Methods: A vaccinated Susceptible-Exposed-Symptomatic-Asymptomatic-Recovered/Removed (SEIAR) model was developed to simulate scenarios of effective reproduction number (R_{eff}) from 4 to 6. Total number of infectious and asymptomatic cases were used to evaluated vaccination effectiveness.

Results: Our model showed that we could not prevent outbreaks when covering 80% of HRPs with booster unless R_{eff}=4.0 or the booster vaccine had efficacy against infectivity and susceptibility of more than 90%. The results were consistent when the outcome index was confirmed cases or asymptomatic cases.

Conclusions: An ideal coronavirus disease 2019 (COVID-19) booster vaccination strategy for HRPs would be expected to reach the initial goal to control the transmission of the Delta variant in China. Accordingly, the recommendation for the COVID-19 booster vaccine should be implemented in HRPs who are already vaccinated and could prevent transmission to other groups.

INTRODUCTION

Currently, countries with sufficient vaccine supply, such as Israel, are working towards a policy to promote booster vaccination. Israel began offering booster vaccines to the elderly on July 30, 2021 and offered these booster shots to the rest of the population starting on October 3, 2021 (*1*). The United States, Spain, Britain, China, and other countries have also reported planning to implement booster vaccinations.

One study of fully vaccinated over 60-year-olds in Israel found the rate of confirmed infection was lower in booster groups than in the two dose groups after 12 days, relative ratio: 11.3 (95% CI: 10.4–12.3) (*2*). China has administered more than 2.2 billion doses of COVID-19 vaccines as of October 6, 2021 (*3*), but still has a high risk of being attacked by variants of SARS-CoV-2 through international trade. More than 40 outbreaks, which were started with the high-risk population (HRPs), such as health workers and airport staff, have been reported in China. In the latest outbreaks in Nanjing City in Jiangsu Province, high transmissibility of the breakthrough infection of the Delta variant was reported among the more vaccinated population. This evidence may point out that the current vaccination status cannot address the challenge presented by the Delta variant independently. Accordingly, a booster vaccination is necessary for China to better cope with imported cases. Based on our previous studies, we developed a mathematical model (*4*) to estimate the effectiveness when getting a COVID-19 booster shot among HRPs in China.

METHODS

Model Development

Based on the natural history of COVID-19 and our previous studies (*5*–*6*), we developed a Susceptible-Exposed-Symptomatic-Asymptomatic-Recovered/Removed (SEIAR) model with R (version 4.1.0, R Foundation, Vienna, Austria) to predict the cumulative case outcome of booster vaccines on 50 million high-risk individuals (making up 1.43% of the total population), who were fully vaccinated. In the model, HRPs who had been fully vaccinated were divided into five categories: Vaccinated but still Susceptible (S) due to breakthrough infection, Exposed (E), Symptomatic (I), Asymptomatic (A), and Removed (R) including recovered and death. Booster vaccinated HRPs were

also divided into five categories and denoted as S_1, E_1, I_1, A_1, and R_1, respectively.

The model was based on the following assumptions:

a) Susceptible HRPs would be infected by contact with symptomatic/asymptomatic infections with a transmission relative rate of β.

b) The latent period of an exposed person was $1/\omega$, the latent period of an asymptomatic person was $1/\omega$'.

c) Parameter p ($0 \leq p \leq 1$) gave the proportion of individuals who had asymptomatic infections.

d) The transmission rates of S were β and $\kappa\beta$ after effective contact with I and A ($0 \leq \kappa \leq 1$).

e) Individuals in categories I and A were transferred into category R after an infectious period of $1/\gamma$ and $1/\gamma$', respectively.

f) Case fatality rate was 0 and was not simulated in the model because vaccines were highly protective against death.

g) We assumed that the infectivity and susceptibility would be reduced after vaccination (*7*–*8*). Vaccine efficacy against infectivity (VEI) and against susceptibility (VES) (*7*) due to booster vaccination were denoted as (1 - x) and (1 - y), respectively.

The flowchart of the booster vaccination SEIAR model was shown in Figure 1.

The equations of the model were as follows:

$$\frac{dS}{dt} = -\left(\frac{\beta S(I+\kappa A)}{N} + \frac{x\beta S(I_1+\kappa A_1)}{N}\right)$$

$$\frac{dE}{dt} = \left(\frac{\beta S(I+\kappa A)}{N} + \frac{x\beta S(I_1+\kappa A_1)}{N}\right) - p\omega' E - (1-p)\omega E$$

$$\frac{dI}{dt} = (1-p)\omega E - \gamma I$$

$$\frac{dA}{dt} = p\omega' E - \gamma' A$$

$$\frac{dS_1}{dt} = -\left(\frac{y\beta S_1(I+\kappa A)}{N} + \frac{xy\beta S_1(I_1+\kappa A_1)}{N}\right)$$

$$\frac{dE_1}{dt} = \left(\frac{y\beta S_1(I+\kappa A)}{N} + \frac{xy\beta S_1(I_1+\kappa A_1)}{N}\right) - p\omega' E_1 - (1-p)\omega E_1$$

$$\frac{dI_1}{dt} = (1-p)\omega E_1 - \gamma I_1$$

$$\frac{dA_1}{dt} = p\omega' E_1 - \gamma' A_1$$

$$\frac{dR_1}{dt} = \gamma I_1 + \gamma' A_1$$

$$N = S + E + I + A + R + S_1 + E_1 + I_1 + A_1 + R_1$$

N was defined as the total population. The left side of the equation indicated the instantaneous change rate of each department at time t.

Parameter Estimation

Most parameter settings were based on our previous study (*8*). Considering the changes of the Delta variant, we edited the value of some parameters according to the latest research (*9*), including latent relative rates. The effective reproduction number (R_{eff}) was defined as the number of secondary cases an infected person can cause in a population after some interventions (*8*). In the study, R_{eff} was adjusted from 4 to 6 based on the current immune barrier in China and β was calculated by R_{eff}; $1-x$ and $1-y$ based on simulations; ω and ω' were set as 0.33 and 0.20, respectively; γ was set as 0.2; γ' was set as 0.1; κ was set as 0.6; and p was set as 0.5 (Supplementary Table S1, available in http://weekly.chinacdc.cn/).

Based on our previous studies (*4*,*8*), the equation of R_{eff} from the SEIAR model was shown as follows:

$$R_{eff} = \frac{\beta}{(1-p)\omega + p\omega'}\left(\frac{(1-p)\omega}{\gamma} + \frac{\kappa p\omega'}{\gamma'}\right)$$

Sensitivity Analysis

In this study, 6 parameters were used to analyze the

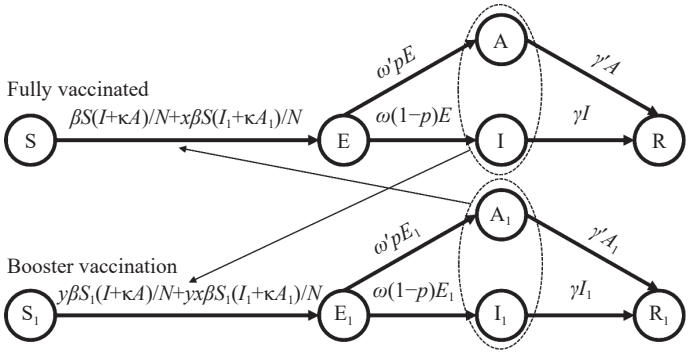

FIGURE 1. Flowchart of the booster vaccination susceptible-exposed-symptomatic-asymptomatic-recovered/removed (SEIAR) model.

sensitivity of the model: κ (0–1), ω (0.056–0.500), ω' (0.056–0.500), γ (0.111-0.333), γ' (0.048-1.000), and p (0–1). Each parameter was split into 20 values according to its range.

RESULTS

Our model showed that under the current vaccination strategy, there still existed a high risk of a outbreak in Chinese HRPs. Further simulation showed that we could not prevent outbreaks when 80% of HRPs were covered with a booster vaccine, unless the effective reproduction number (R_{eff}) =4.0 and the effectiveness of the booster (EB) was high, indicated by VES and VEI exceeding 90% (Figure 2A). Furthermore, when 90% of HRPs were covered with a booster vaccine, only an EB with the values of VES and VEI exceeding 60% were required (Figure 2B), and with 99% coverage of HRPs was needed for the VES and VEI to only have to exceed 50% (Figure 2C). However, VES and VEI both needed to exceed 70% at 99% coverage of HRPs under high transmissibility conditions (R_{eff}=6.0) (Figure 2I).

To estimate the reality as closely as possible, we selected high transmissibility (R_{eff}=6.0) and covered 99% of HRPs with booster shots and assumed the VES and VEI were both 50%. Cumulative cases did not seem to be sensitive to the six parameters (κ, ω, ω', γ, γ', p), but the proportion of cases was sensitive to

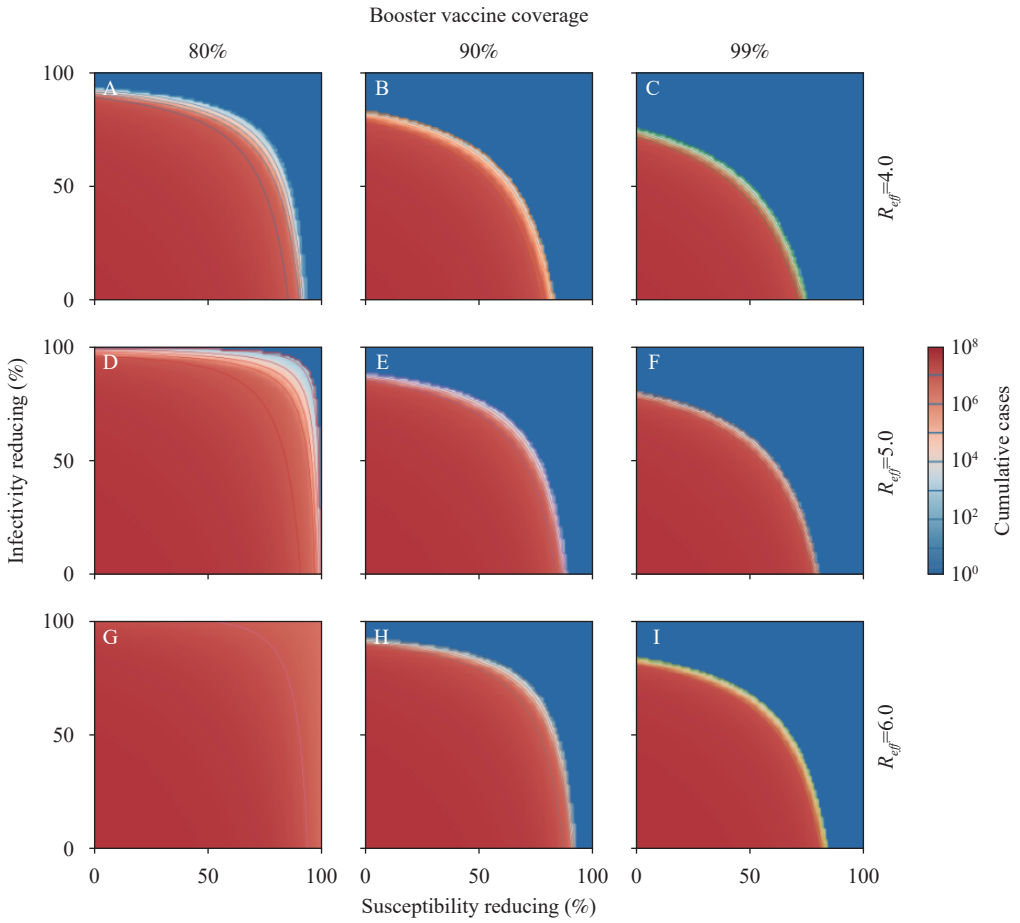

FIGURE 2. Simulated cumulative cases of COVID-19 for different effective reproduction numbers (R_{eff}) and booster vaccine coverage. (A) Booster vaccine coverage of 80% and R_{eff} at 4.0, (B) Booster vaccine coverage of 90% and R_{eff} at 4.0, (C) Booster vaccine coverage of 99% and R_{eff} at 4.0, (D) Booster vaccine coverage of 80% and R_{eff} at 5.0, (E) Booster vaccine coverage of 90% and R_{eff} at 5.0, (F) Booster vaccine coverage of 99% and R_{eff} at 5.0, (G) Booster vaccine coverage of 80% and R_{eff} at 6.0, (H) Booster vaccine coverage of 90% and R_{eff} at 6.0, (I) Booster vaccine coverage of 99% and R_{eff} at 6.0.
Note: We estimate the effectiveness of booster shots in high-risk populations, simulated by setting R_{eff} from 4 to 6 and booster vaccine coverage with 80%, 90%, and 99%, respectively. We assume that infectivity and susceptibility would be reduced after vaccination (*7–8*), with scenarios that booster vaccine can further reduce infectivity (0–100%) and susceptibility (0–100%). Logarithmic contour was adopted to display the outcome of this study because the outcome varies considerably between different conditions.

latent periods and the proportion of asymptomatic cases (Supplementary Figure S1, available in http://weekly.chinacdc.cn/).

We adjusted parameters and re-ran the SEIAR model to simulate a different scenario, which presented a similar result (Supplementary Figure S2, available in http://weekly.chinacdc.cn/). Considering COVID-19 cases were regularly divided into confirmed cases and symptomatic cases, we also re-ran the SEIAR model to predict the dynamic evolution of COVID-19 with outcomes of confirmed cases and symptomatic cases (Supplementary Figures S3–S4, available in http://weekly.chinacdc.cn/). The results were consistent with our findings where cumulative cases were selected as the outcome index.

DISCUSSION

We used the SEIAR model to consider the infectivity of asymptomatic cases and previously described parameters to discover whether the hypotheses that had been put forward was feasible. All else being equal, low booster vaccine coverage cannot sustain the barrier of immunity, let alone against increased infectivity variant over time. Our finding suggests that the VES and VEI of both at least 70% are required when covering 99% of HRPs under high transmissibility (R_{eff}=6.0). However, 90% coverage at equal conditions can generate a hundredfold increase, despite lower coverage of the booster vaccine.

Undoubtedly, current vaccines had high effectiveness to reduce severe and dead cases. However, it could not control the transmission of the Delta variant in China due to breakthrough infection. Two strategies, including improving the vaccine effectiveness (VE) and adding the booster dose among HRPs, should be simultaneously applied for controlling the high transmission of coronavirus variants. Therefore, it is essential to assess the VES and VEI of current vaccines for the booster. Considering substantial differences in VE, further application of booster shots in HRPs should be based on high VE to increase antibody concentrations, including selecting other kinds of vaccines and administration of booster doses (*10*).

This study was subject to some limitations. First, our model did not consider the transmission between HRPs and non-HRPs which was widely happening in current outbreaks. Second, although our model represents HRPs in China, our initial population size (N=50,000,000) did not consider the influence of occupation in which contact rates and susceptibility were different.

Under the current vaccination strategy, which could not control the transmission of the Delta variant in China due to breakthrough infection, there was still a high risk of outbreaks of HRPs in China. Therefore, we recommend booster vaccination in HRPs.

Conflicts of interest: No conflicts of interest reported.

Funding: Bill & Melinda Gates Foundation (INV-005834).

doi: 10.46234/ccdcw2021.259

[#] Corresponding authors: Yan Niu, niuyan@chinacdc.cn; Tianmu Chen, chentianmu@xmu.edu.cn.

[1] State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health, Xiamen University, Xiamen, Fujian, China; [2] Université de Montpellier, Montpellier, France; CIRAD, Intertryp, Montpellier, France; IES, Université de Montpellier-CNRS, Montpellier, France; [3] Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: October 14, 2021; Accepted: October 21, 2021

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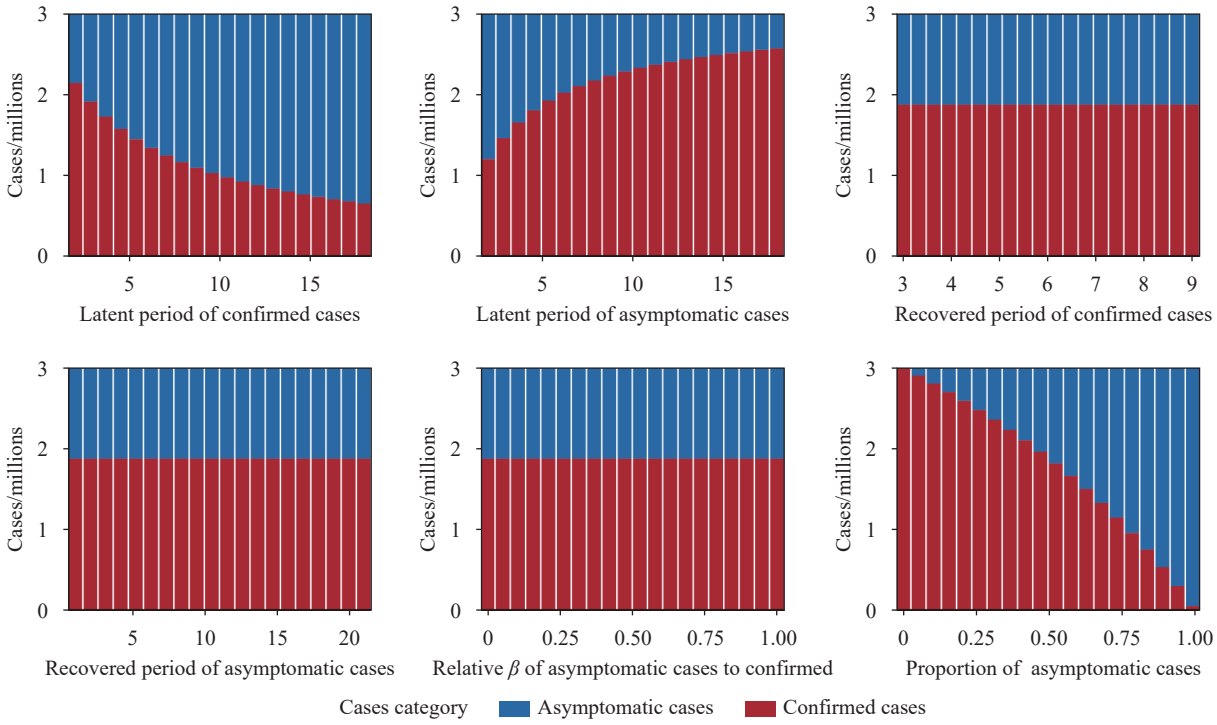
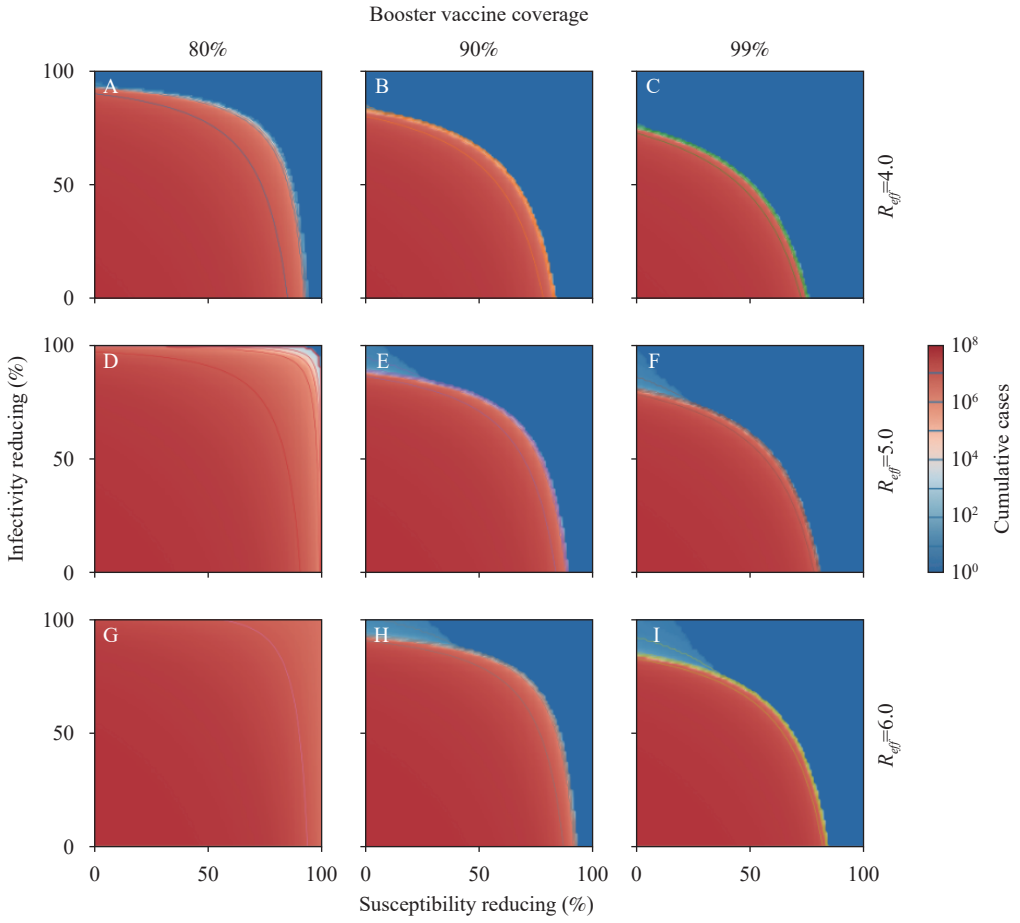
SUPPLEMENTARY TABLE 1. Parameters in the booster vaccination SEIAR model.

Parameter	Definition	Unit	Value	Range	Method
β	Transmission relative rate	/(Individuals·days)	–	≥0	Basing on different R_{eff} values
$1-x$	VEI	1	–	0–1	Simulated
$1-y$	VES	1	–	0–1	Simulated
ω	Latent relative rate of the confirmed case	/days	0.33	0.056–0.500	Reference[1]
ω'	Latent relative rate of the asymptomatic case	/days	0.2	0.056–0.500	Reference[1]
γ	Recovered/Removed rate of the confirmed case	/days	0.2	0.111–0.333	Reference[2]
γ'	Recovered/Removed rate of the asymptomatic case	/days	0.1	0.048–1.000	Reference[2]
κ	Relative transmissibility rate of asymptomatic to confirmed cases		0.6	0–1	Reference[2]
p	Proportion of the asymptomatic cases		0.5	0–1	Reference[2]

Abbreviations: SEIAR=Susceptible-Exposed-Symptomatic-Asymptomatic-Recovered/Removed; VEI=vaccine efficacy against infectivity; VES=vaccine efficacy against susceptibility; R_{eff} =effective reproduction number.

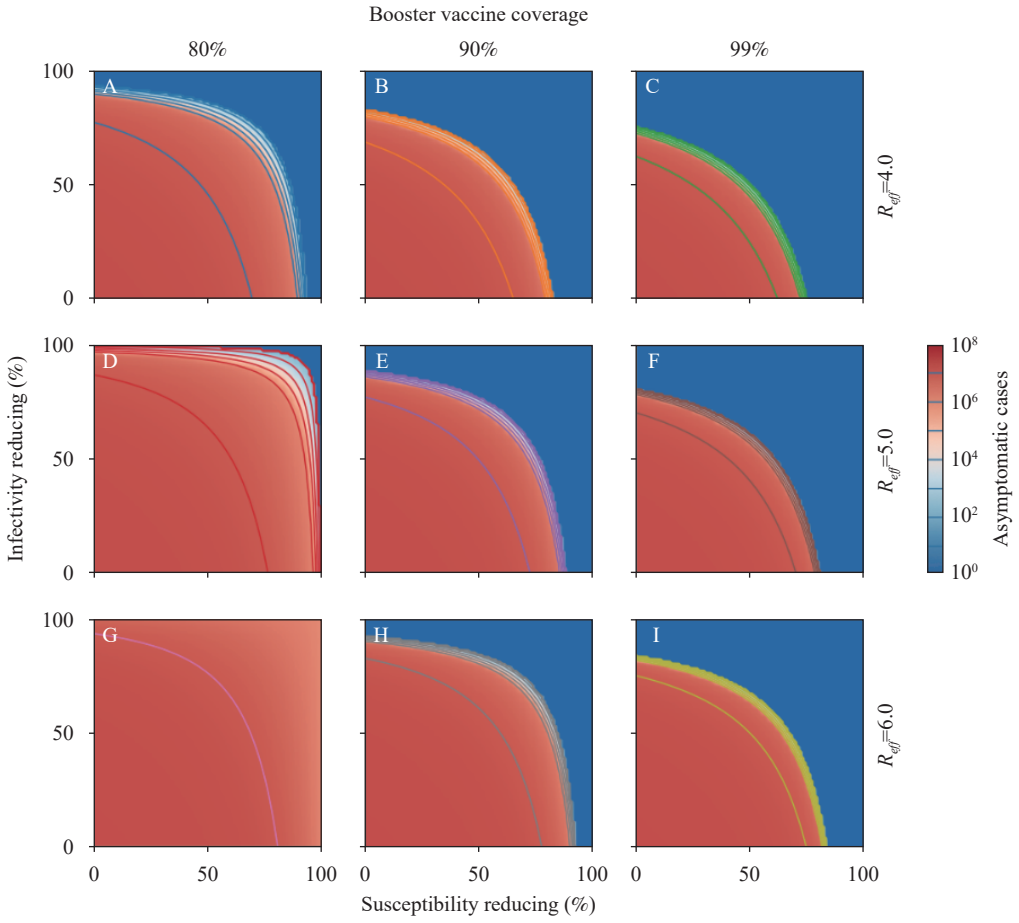


SUPPLEMENTARY FIGURE S1. Sensitivity analysis of SEIAR model.
Note: Variable parameters will influence the proportion of asymptomatic cases and confirmed cases. However, cumulative cases do not seem to be influenced by parameters.
Abreviation: SEIAR=Susceptible-Exposed-Symptomatic-Asymptomatic-Recovered/Removed.



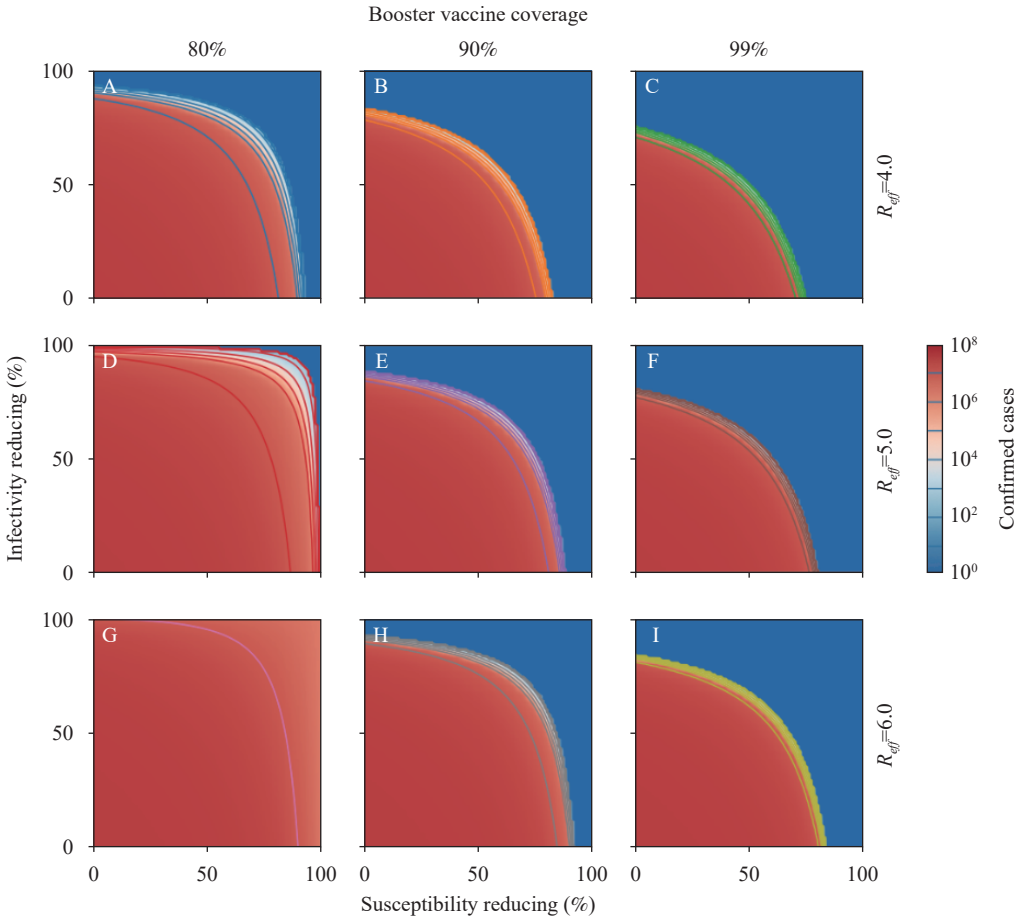
SUPPLEMENTARY FIGURE S2. Simulated cumulative cases of COVID-19 for different effective reproduction numbers (R_{eff}) and booster vaccine coverage. (A) Booster vaccine coverage of 80% and R_{eff} at 4.0, (B) Booster vaccine coverage of 90% and R_{eff} at 4.0, (C) Booster vaccine coverage of 99% and R_{eff} at 4.0, (D) Booster vaccine coverage of 80% and R_{eff} at 5.0, (E) Booster vaccine coverage of 90% and R_{eff} at 5.0, (F) Booster vaccine coverage of 99% and R_{eff} at 5.0, (G) Booster vaccine coverage of 80% and R_{eff} at 6.0, (H) Booster vaccine coverage of 90% and R_{eff} at 6.0, (I) Booster vaccine coverage of 99% and R_{eff} at 6.0.

Note: We re-run the model based on adjusting parameters ($\omega^{'}$ and ω both are 1 days^{-1}, $\gamma^{'}$ and γ both are 0.5 days^{-1}, κ is 0.25 and p is 0.5). Logarithmic contour is adopted to display the outcome of this study because the outcome varies considerably between different conditions.



SUPPLEMENTARY FIGURE S3. Simulated asymptomatic cases and index case of COVID-19 for different effective reproduction numbers (R_{eff}) and booster vaccine coverage. (A) Booster vaccine coverage of 80% and R_{eff} at 4.0, (B) Booster vaccine coverage of 90% and R_{eff} at 4.0, (C) Booster vaccine coverage of 99% and R_{eff} at 4.0, (D) Booster vaccine coverage of 80% and R_{eff} at 5.0, (E) Booster vaccine coverage of 90% and R_{eff} at 5.0, (F) Booster vaccine coverage of 99% and R_{eff} at 5.0, (G) Booster vaccine coverage of 80% and R_{eff} at 6.0, (H) Booster vaccine coverage of 90% and R_{eff} at 6.0, (I) Booster vaccine coverage of 99% and R_{eff} at 6.0.

Note: Adding index case, instead of only asymptomatic cases, was selected as the outcome index of this study. Because asymptomatic cases do not generate in our model in some situations and logarithmic transform cannot deal with 0 asymptomatic case.



SUPPLEMENTARY FIGURE S4. Simulated confirmed cases of COVID-19 for different effective reproduction numbers (R_{eff}) and booster vaccine coverage. (A) Booster vaccine coverage of 80% and R_{eff} at 4.0, (B) Booster vaccine coverage of 90% and R_{eff} at 4.0, (C) Booster vaccine coverage of 99% and R_{eff} at 4.0, (D) Booster vaccine coverage of 80% and R_{eff} at 5.0, (E) Booster vaccine coverage of 90% and R_{eff} at 5.0, (F) Booster vaccine coverage of 99% and R_{eff} at 5.0, (G) Booster vaccine coverage of 80% and R_{eff} at 6.0, (H) Booster vaccine coverage of 90% and R_{eff} at 6.0, (I) Booster vaccine coverage of 99% and R_{eff} at 6.0.

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Notes from the Field

Whole-Genome Sequences Analysis Displays Relationship of SARS-CoV-2 Delta Variant Between Four Local Cases and Passengers of a Flight from South Africa — Shenzhen City, Guangdong Province, China, June 2021

Yaqing He[1,2]; Renli Zhang[1,2]; Qiuying Lyu[3]; Bo Peng[1,2]; Shujiang Mei[3]; Ying Sun[1,2]; Dongfeng Kong[3]; Chaoqiong Peng[4]; Ziquan Lyu[5]; Xinyi Wei[1,2]; Can Zhu[1,2]; Xiaoliang Xiao[1,2]; Shimin Li[1,2]; Qingju Lu[1,2]; Jiancheng Chen[1,2]; Hang Zhang[4]; Xuan Zou[4,#]; Tiejian Feng[2,4,#]; Long Chen[1,2,#]

On June 14, 2021, a customs officer (Case A) went to the infirmary at Baoan International Airport in Shenzhen due to a runny nose and fever. He was admitted to the Central Hospital of Baoan immediately. This patient preliminarily tested positive for coronavirus disease 2019 (COVID-19) infection, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), using a quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) method in this hospital. Then, a mixed specimen of nasopharyngeal swab, oropharyngeal swab, and anal swab was sent to the virology laboratory of Shenzhen Center for Disease Control and Prevention (Shenzhen CDC) and was confirmed positive for SARS-CoV-2 by a qRT-PCR method simultaneously implemented in two commercial kits (Daan, Guangzhou, China and Bojie, Shanghai, China) (Supplementary Table S1, available in http://weekly.chinacdc.cn/). This patient tested negative for SARS-CoV-2 on June 8, 2021 and participated in an epidemiological investigation and sampling in a flight from South Africa that arrived at Baoan International Airport on June 10, 2021. Between June 10, 2021 and June 25, 2021, a total of 39 passengers (Case 1 to 39) from this flight were confirmed to be infected with SARS-CoV-2 in the virology laboratory of Shenzhen CDC.

On June 17, 2021, a third-party laboratory detected SARS-CoV-2 in a mixed specimen of 10 swabs from ten individuals by qRT-PCR method, and the preliminary result was positive. This mixed specimen and one (Case B) of ten nasopharyngeal swabs from ten individuals were confirmed positive for SARS-CoV-2 in the virology laboratory of Shenzhen CDC. Case B was a 22-year-old female who worked in a restaurant at Baoan International Airport. The third case (Case C) lived in Dongguan City and worked in Nanshan District in Shenzhen City. He presented symptoms of chills, dry cough, diarrhea, and fever on June 12, 2021 and was confirmed to be infected with SARS-CoV-2 on June 18, 2021. The fourth case (Case D) lived and worked in Baoan District, Shenzhen. She was confirmed to be infected with SARS-CoV-2 during screening of key populations on June 20, 2021.

High-throughput sequencing was performed for 4 local SARS-CoV-2 strains and 39 imported SARS-CoV-2 strains by Illumina Sequencing Technology. First, viral RNA was extracted directly from 200-μL swab samples using a High Pure Viral RNA Kit (Roche, Germany). Second, viral RNA was reverse-transcribed and amplified using ULSEN® 2019-nCoV Whole Genome Capture Kit V-090418 (Beijing MicroFuture Technology Co., Ltd, Beijing, China). Third, the sequencing libraries were prepared using the Nextera® XT Library Prep Kit FC-131-1001(Illumina, Inc., San Diego, USA). The final viral-enriched libraries were sequenced using the MiSeq platform (Illumina, USA). The viral genome was assembled by MicronCoV® Analyzer M-881027 (Beijing MicroFuture Technology Co., Ltd, Beijing, China). Genome sequences of the 4 local SARS-CoV-2 strains and 28 of 39 imported SARS-CoV-2 strains were successfully determined. Virus strains from this study were genotyped using the online Pangolin COVID-19 Lineage Assigner (www.pangolin.cog-uk.io/). The evolutionary relationship of local SARS-CoV-2 strains and imported SARS-CoV-2 strains was inferred with the program MEGA version X (www.megasoftware.net) (*1*). Nucleotide difference between viral genome sequences from this study and the reference sequence Wuhan-Hu-1 (GenBank no. NC_045512.2) was analyzed using the programs BioEdit 7.1.9 (www.bioedit.software.informer.com) and MEGA version X.

The 4 local SARS-CoV-2 strains and 26 of 28 imported SARS-CoV-2 strains from this study were assigned to lineage B.1.617.2 (Supplementary Table S2, available in http://weekly.chinacdc.cn/), which was the fourth variant of concern (VOC) (Delta variant). The other two imported SARS-CoV-2 strains were assigned to lineage B.1.351 and lineage C.1.2. Molecular phylogeny indicated that 30 SARS-CoV-2 Delta variants (lineage B.1.617.2) from this study formed 2 distinct clades (Figure 1). The imported strain hCoV-19/Shenzhen/IVDC-0610-01/2021 (Case1) clustered in clade A and showed the closest relationship to the Indian strain hCoV-19/India/GJ-NCDC-NIV-INSACOG-24095/2021 by an Audacity Instant search in Global initiative on sharing all influenza data (GISAID). The 4 local SARS-CoV-2 strains of lineage B.1.617.2 and 25 imported SARS-CoV-2 strains of lineage B.1.617.2 clustered in clade B and showed the closest relationship or showed only one nucleotide difference to the British strain hCoV-

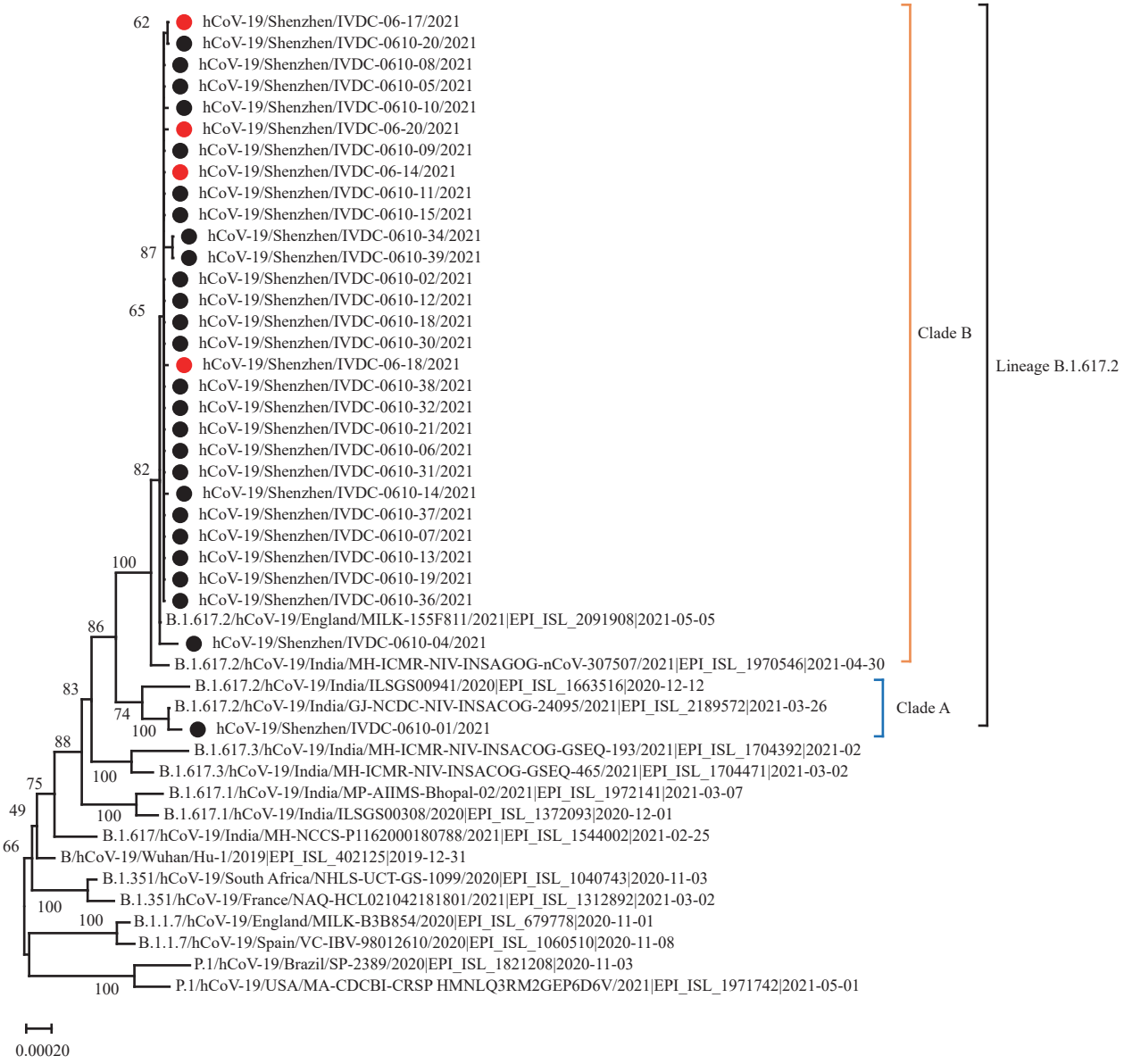

FIGURE 1. Evolutionary relationships of 30 SARS-CoV-2 strains of lineage B.1.617.2 from this study.
Note: Maximum likelihood phylogenetic tree was reconstructed for 30 SARS-CoV-2 strains from this study and 16 reference strains based on the whole-genome sequences. The best fit nucleotide substitution model used for phylogenetic reconstruction was TN93+G5+I. The scale bar represents a genetic distance of 0.0002 nucleotide substitutions per site. Bootstrap analysis (1,000 replicates) was used for statistical support of the tree. The 4 local strains were indicated by red dots, and 26 imported strains were indicated by black dots.

TABLE 1. Nucleotide differences between 30 SARS-CoV-2 strains of lineage B.1.617.2 from this study and the reference strain Wuhan-Hu-1 (NC_045512.2).

Clade	Case	Nucleotide variation	Nucleotide deletion mutation
Clade A	Case 1	G210T, C241T, C799T, C3037T, G4181T, C6402T, C7124T, C8986T, G9053T, C10029T, A11201G, A11332G, G13812T, C14408T, G15451A, C16466T, C19220T, C21618G, G21987A, T22917G, C22995A, A23403G, C23604G, G24410A, C25413T, C25469T, T26767C, T27638C, C27752T, C27874T, A28461G, G28881T, G28916T, G29402T, and G29742T	del22029-22034, del28248-28253, del28271
Clade B	Case A, Case 2, Case 5–9, Case 11–15, Case 18, Case 19, Case 21, Case 30–32, Case 36, Case 38	31 variation sites: G210T, C241T, G410T, C3037T, C5184T, A5584G, T9429C, C9891T, T11418C, C11514T, C13019T, C14408T, G15451A, C16466T, C21618G, G21987A, C22227T, T22917G, C22995A, A23403G, C23604G, G24410A, C25469T, T26767C, T27638C, A27677C, C27752T, A28461G, G28881T, G29402T, and G29742T	del510-518, del22029-22034, del28248-28253, del28271
	Case B, Case 20	31 variation sites + C21575T	del510-518, del22029-22034, del28248-28253, del28271
	Case C	31 variation sites + C18431T	del510-518, del22029-22034, del28249, del28253, del28271
	Case D	31 variation sites + C10605A	del510-518, del22029-22034, del28248-28253, del28271
	Case 4	31 mutations – G210T – G410T – G21987A0 – C22227T + G174T + C1059T + A5839G	del28249, del28253, del28271
	Case 10	31 mutations + C11665T	del510-518, del22029-22034, del28248-28253, del28271
	Case 34, Case 39	31 mutations + G3875A + G6476T	del510-518, del22029-22034, del28248-28253, del28271
	Case 37	31 mutations + A28249T + C28253A	del510-518, del22029-22034, del28271

19/England/MILK-155F811/2021. These 29 SARS-CoV-2 strains of lineage B.1.617.2 showed at least 23 nucleotide differences to the strain hCoV-19/Shenzhen/IVDC-0610-01/2021 (Case 1). In clade B, the imported strain hCoV-19/Shenzhen/IVDC-0610-04/2021 (Case 4) showed a certain degree of genetic distance to the other 28 virus strains from this study, which was also indicated by comparative analysis of genome sequences in Table 1. The local B.1.617.2 strain hCoV-19/Shenzhen/IVDC-06-14/2021 (Case A) showed 100% sequence identity to 19 imported B.1.617.2 strains (Table 1). These 20 SARS-CoV-2 strains of lineage B.1.617.2 shared 31 nucleotide variation sites and 22 deletion mutations compared with the reference strain Wuhan-Hu-1. Except for the variation sites above, an additional variation site was observed in genomes of the 3 local strains hCoV-19/Shenzhen/IVDC-06-17/2021 (Case B), hCoV-19/Shenzhen/IVDC-06-18/2021 (Case C), and hCoV-19/Shenzhen/IVDC-06-20/2021 (Case D). The local strain hCoV-19/Shenzhen/IVDC-06-17/2021 (Case B) showed 100% sequence identity to the strain hCoV-19/Shenzhen/IVDC-0610-20/2021 from imported Case 20.

Among imported SARS-CoV-2 strains, genome sequences of 19 SARS-CoV-2 strains from imported passengers showed 100% sequence identity to each other, and these 19 passengers had no common exposure history before boarding. It suggested that at least one virus transmission occurred among the 19 passengers after boarding. The only strain from Case 1 belonged to clade A within lineage B.1.617.2, which indicated that Case 1 was not related to the infection in the cabin. Based on phylogenetic relationship and comparative analysis of genome sequences, we deduced that 3 virus strains from local cases (Cases B to D) and 5 virus strains from imported passengers (Cases 10, 20, 34, 37, and 39) were progeny viruses.

According to the report by Li et al (*2*), SARS-CoV-2 Delta variant strains from this study showed 18 to 28 nucleotide differences to those from the first outbreak of COVID-19 in Guangzhou, May 2021, which suggested that the SARS-CoV-2 Delta variant that caused local outbreaks of COVID-19 in Guangzhou and Shenzhen came from different sources. At present, the SARS-CoV-2 Delta variant is becoming the dominant variant worldwide and has been detected in at least 142 countries as of August 10, 2021. The SARS-CoV-2 Delta variant is posing new challenges on the control and prevention of COVID-19 due to its increased transmissibility compared with Alpha variant (lineage B.1.1.7) and capacity of immune escape (*3*–*7*).

In conclusion, whole-genome sequencing (WGS) confirmed that 4 local SARS-CoV-2 strains and 26 of

28 imported SARS-CoV-2 strains from this study were Delta variants, and phylogenetic and comparative genome analyses showed close relationship between the four local SARS-CoV-2 strains of Delta variant and imported SARS-CoV-2 strains of Delta variant introduced from South Africa.

Acknowledgements: Baoan CDC, Nanshan CDC, and Shenzhen Third People's Hospital.

Conflicts of interest: No conflicts of interest.

Funding: Shenzhen Science and Technology Innovation Commission Key project (no. JSGG20200225152648408), the Shenzhen Science and Technology Innovation Commission COVID-19 Special Fund (no. JSGG20200207161926465), and Sanming Project of Medicine in Shenzhen (No.SZSM202011008).

doi: 10.46234/ccdcw2021.215

[#] Corresponding authors: Long Chen, chen_l_2011@163.com; Tiejian Feng, fengtiej@126.com; Xuan Zou, 914494557@qq.com.

[1] Institute of Pathogen Biology, Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China; [2] Shenzhen Center for Infectious Disease Control and Prevention, Chinese Academy of Medical Sciences, Shenzhen, Guangdong, China; [3] Department of Communicable Diseases Control and Prevention, Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China; [4] Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China; [5] Laboratory of Molecular Epidemiology, Shenzhen Center for Disease Control and Prevention, Shenzhen, Guangdong, China.

Submitted: August 28, 2021; Accepted: September 29, 2021

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SUPPLEMENTARY TABLE S1. Demographic characteristics of 4 local cases and 39 imported cases, and specimen testing information.

Case	Gender	Age (years)	Date of first positive detection of COVID-19 virus	Ct value (ORF1ab/N) of specimen used for sequencing	
				Daan	Bojie
Case A	Male	30	June 14, 2021	14/18	16/18
Case B	Female	21	June 17, 2021	23/21	22/22
Case C	Male	35	June 18, 2021	24/22	22/24
Case D	Female	64	June 20, 2021	30/30	35/28
Case 1	Male	36	June 11, 2021	31/31	30/31
Case 2	Male	35	June 11, 2021	31/31	26/28
Case 3	Female	42	June 11, 2021	33/34	34/34
Case 4	Female	58	June 11, 2021	30/27	27/28
Case 5	Male	53	June 13, 2021	17/16	16/17
Case 6	Male	32	June 14, 2021	24/23	24/23
Case 7	Male	52	June 14, 2021	17/17	16/17
Case 8	Male	33	June 15, 2021	17/15	15/17
Case 9	Male	47	June 15, 2021	16/16	15/16
Case 10	Male	64	June 15, 2021	21/20	20/21
Case 11	Male	40	June 15, 2021	15/14	14/15
Case 12	Male	50	June 15, 2021	18/17	16/18
Case 13	Male	33	June 15, 2021	28/26	27/28
Case 14	Female	31	June 15, 2021	19/17	18/17
Case 15	Male	61	June 15, 2021	14/14	15/15
Case 16	Female	38	June 15, 2021	35/34	36/33
Case 17	Male	39	June 15, 2021	37/40	Undet/35
Case 18	Female	50	June 15,2021	14/15	14/14
Case 19	Male	35	June 15, 2021	17/16	16/17
Case 20	Male	58	June 15, 2021	16/15	15/16
Case 21	Female	47	June 15, 2021	29/25	26/26
Case 22	Male	29	June 15, 2021	35/35	38/Undet
Case 23	Male	32	June 15, 2021	38/36	Undet/35
Case 24	Male	63	June 15, 2021	35/34	35/32
Case 25	Female	63	June 15, 2021	35/33	33/33
Case 26	Male	45	June 15, 2021	38/35	Undet/Undet
Case 27	Male	44	June 15, 2021	Undet/38	Undet/35
Case 28	Male	61	June 15, 2021	Undet/37	37/Undet
Case 29	Male	58	June 15, 2021	37/Undet	Undet/36
Case 30	Male	9	June 15, 2021	21/21	22/22
Case 31	Female	45	June 15, 2021	28/28	27/28
Case 32	Male	42	June 15, 2021	15/15	14/15
Case 33	Male	35	June 16, 2021	26/24	23/26
Case 34	Male	1	June 16, 2021	30/27	27/29
Case 35	Female	24	June 17, 2021	34/30	32/30
Case 36	Male	25	June 17, 2021	19/18	19/18
Case 37	Female	32	June 19, 2021	22/19	19/20
Case 38	Male	38	June 19, 2021	31/29	28/30
Case 39	Female	28	June 25, 2021	18/16	17/18

Note: There were 43 subjects in total, and the male/female ratio and mean age of subjects was 2.58∶1 and 40.9 years, respectively.
Abbreviations: Undet=Undetected; Ct=Cycle threshold; COVID-19=Coronavirus disease 2019.

SUPPLEMENTARY TABLE S2. Genome sequence information for 30 SARS-CoV-2 strains of lineage B.1.617.2 from this study.

Case	Virus name	Length in nt (% GC content)	Closest strain by an audacity instant search in GISAID
Case A	hCoV-19/Shenzhen/IVDC-06-14/2021	29,813nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case B	hCoV-19/Shenzhen/IVDC-06-17/2021	29,562nt (37.98)	hCoV-19/England/MILK-155F811/2021
Case C	hCoV-19/Shenzhen/IVDC-06-18/2021	29,428nt (37.98)	hCoV-19/England/MILK-155F811/2021
Case D	hCoV-19/Shenzhen/IVDC-06-20/2021	29,612nt (37.98)	hCoV-19/England/MILK-155F811/2021
Case 1	hCoV-19/Shenzhen/IVDC-0610-01/2021	29,702nt (37.96)	hCoV-19/India/GJ-NCDC-NIV-INSACOG-24095/2021
Case 2	hCoV-19/Shenzhen/IVDC-0610-02/2021	29,813nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case 4	hCoV-19/Shenzhen/IVDC-0610-04/2021	29,836nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 5	hCoV-19/Shenzhen/IVDC-0610-05/2021	29,555nt (37.99)	hCoV-19/England/MILK-155F811/2021
Case 6	hCoV-19/Shenzhen/IVDC-0610-06/2021	29,657nt (38.00)	hCoV-19/England/MILK-155F811/2021
Case 7	hCoV-19/Shenzhen/IVDC-0610-07/2021	29,814nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case 8	hCoV-19/Shenzhen/IVDC-0610-08/2021	29,824nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case 9	hCoV-19/Shenzhen/IVDC-0610-09/2021	29,831nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 10	hCoV-19/Shenzhen/IVDC-0610-10/2021	29,833nt (37.95)	hCoV-19/England/MILK-155F811/2021
Case 11	hCoV-19/Shenzhen/IVDC-0610-11/2021	29,830nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 12	hCoV-19/Shenzhen/IVDC-0610-12/2021	29,830nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 13	hCoV-19/Shenzhen/IVDC-0610-13/2021	29,710nt (37.99)	hCoV-19/England/MILK-155F811/2021
Case 14	hCoV-19/Shenzhen/IVDC-0610-14/2021	29,551nt (37.98)	hCoV-19/England/MILK-155F811/2021
Case 15	hCoV-19/Shenzhen/IVDC-0610-15/2021	29,834nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 18	hCoV-19/Shenzhen/IVDC-0610-18/2021	29,820nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 19	hCoV-19/Shenzhen/IVDC-0610-19/2021	29,828nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 20	hCoV-19/Shenzhen/IVDC-0610-20/2021	29,820nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 21	hCoV-19/Shenzhen/IVDC-0610-21/2021	29,574nt (37.99)	hCoV-19/England/MILK-155F811/2021
Case 30	hCoV-19/Shenzhen/IVDC-0610-30/2021	29,827nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case 31	hCoV-19/Shenzhen/IVDC-0610-31/2021	29,829nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 32	hCoV-19/Shenzhen/IVDC-0610-32/2021	29,849nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 34	hCoV-19/Shenzhen/IVDC-0610-34/2021	29,809nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case 36	hCoV-19/Shenzhen/IVDC-0610-36/2021	29,819nt (37.96)	hCoV-19/England/MILK-155F811/2021
Case 37	hCoV-19/Shenzhen/IVDC-0610-37/2021	29,827nt (37.97)	hCoV-19/England/MILK-155F811/2021
Case 38	hCoV-19/Shenzhen/IVDC-0610-38/2021	29,553nt (37.99)	hCoV-19/England/MILK-155F811/2021
Case 39	hCoV-19/Shenzhen/IVDC-0610-39/2021	29,797nt (37.94)	hCoV-19/England/MILK-155F811/2021

Abbreviation: nt=Nucleotide.

Indexed by PubMed Central (PMC) and Emerging Sources Citation Index (ESCI).

The inauguration of *China CDC Weekly* is in part supported by Project for Enhancing International Impact of China STM Journals Category D (PIIJ2-D-04-(2018)) of China Association for Science and Technology (CAST).

CCDC weekly

Vol. 3 No. 50 Dec. 10, 2021

Responsible Authority
National Health Commission of the People's Republic of China

Sponsor
Chinese Center for Disease Control and Prevention

Editing and Publishing
China CDC Weekly Editorial Office
No.155 Changbai Road, Changping District, Beijing, China
Tel: 86-10-63150501, 63150701
Email: weekly@chinacdc.cn

CSSN
ISSN 2096-7071
CN 10-1629/R1