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Cover Photo: College Entrance Exam (Gaokao) examinees of a high school in Guangzhou City waiting to enter the exam rooms during the epidemic in Guangdong Province, June 7, 2021.

Policy Notes

Interpretation of the Protocol for Prevention and Control of COVID-19 in China (Edition 8)

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BACKGROUND

Since the release of *Protocol for Prevention and Control of COVID-19* (Edition 7), coronavirus disease 2019 (COVID-19) control and prevention has been facing new challenges in China with evolving domestic and global epidemiological situations. Since September 2020, China has experienced more than 20 local outbreak waves, all of which were able to be contained within a few weeks. Investigation and response to these importation-related outbreaks not only resulted in the accumulation of rich experience, but also exposed new problems requiring remediation. First, rural areas are potential weak links in epidemic prevention and control. Second, prevention of coronavirus importation and transmission risk is not limited to incoming travelers from overseas, as imported cold-chain food and goods and people with occupational exposure to these goods are now known to be able to cause local outbreaks. Third, there are weaknesses in the management of centralized quarantine. In addition to these three identified risks, another major change since publication of the seventh edition is that several COVID-19 vaccines developed by China have been granted conditional market authorization or emergency use approval by the National Medical Products Administration. In December 2020, China officially launched a large-scale vaccination campaign using the approved vaccines (*1*). Vaccination adds strength and new characteristics to the prevention and control of COVID-19.

The National Health Commission (NHC) and external experts worked together to update the seventh edition of the prevention and control protocol to an eighth edition based on carefully evaluated experience with the previous containment measures, and with anticipation of matters related to COVID-19 vaccination. In this article, we provide our interpretation of key revisions and updates to the seventh edition that can be found in the eighth edition of the protocol.

STRUCTURE

The new edition strengthens technical guidance for grassroots-level work. The protocol now has nine sections that describe work requirements, including general requirements, the etiological and epidemiological characteristics, public measures, epidemic surveillance methods, outbreak response, laboratory-based detection, prevention and control of imported viruses, strengthen the prevention and control of key links, and organizational responsibilities. The new protocol also includes 12 detailed technical guidelines as attachments that provide information for prevention and control personnel in a variety of occupations.

IMPROVEMENTS IN EPIDEMIC CONTAINMENT

The protocol emphasizes early prevention, detection, reporting, quarantine, and treatment; adheres to the principle of preventing simultaneous transmission from people and goods; and enhances prevention of transmission from contaminated, imported cold-chain food and goods. It strengthens epidemic prevention and control during key periods of time, including holidays, and in key areas, including rural areas, to detect sporadic cases and clusters of cases as early as possible and to achieve precise, powerful, orderly, and effective outbreak response.

STRENGTHEN VACCINATION AND PREVENTION AND CONTROL AFTER VACCINATION

Vaccination is the most effective method for preventing, controlling, and ultimately defeating COVID-19 virus, also known as severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2). The new edition emphasizes vaccination in the sections on "public measures" and "prevention and control of key populations." The current work and strategies for COVID-19 vaccination in China are to complete vaccination of key population aged 18 years or above at high risk of occupational exposure to SARS-CoV-2; to continue vaccination of citizens traveling abroad to areas with ongoing transmission; to vaccinate domestic populations at high risk of transmission in key regions of the country, service industry workers, and workers in labor-intensive industries; and to offer vaccination to all individuals 18 years or above who would like to be vaccinated and have no contraindications to vaccination. Domestic vaccination strategies and their management will be adjusted and improved in a timely manner based on progress of vaccine research and results of clinical trials and observational studies.

Because COVID-19 vaccination results in an antibody response in the person vaccinated, the current diagnostic and exclusion criteria for cases have been adjusted so that serum IgM and IgG antibody tests are no longer used as indicators for diagnosis or exclusion. To continuously monitor COVID-19 vaccine protection effectiveness and safety, the eighth edition of the protocol includes gathering vaccine administration data on anyone identified as infected, regardless of the presence of symptoms. Additionally, sequencing viruses isolated from infected individuals will enable the study of SARS-CoV-2 variants and the ability of COVID-19 vaccines to provide protection from variants.

STRENGTHEN EPIDEMIC SURVEILLANCE AND PROMPTLY IDENTIFY RISK FACTOR

Sensitive monitoring and early warning systems are essential for early detection and effective outbreak response. To further improve detection, identification, and early warning of cases, the protocol continues to strengthen case detection sensitivity of medical institutions, multi-channel surveillance, and early warning mechanisms. The previous outbreaks indicated that index cases in the outbreaks were best detected by medical institutions. Examples of medical institutions identifying outbreak index cases include the Xinfadi Wholesales Market outbreak in Beijing and the Dalian, Shanghai Pudong Airport, Qingdao, and Manchuria outbreaks that occurred in 2020 (*2*). In contrast, it was found that community health service stations, village clinics, and private clinics did not have nucleic acid testing capabilities and were weak links in case detection in the outbreaks that occurred in Shijiazhuang and Shenyang. To address this weakness, the eighth protocol expands the scope of nucleic acid testing for patients attending any medical institution — nucleic acid testing is required for all patients with fever. For individuals without fever who have COVID-19-related symptoms such as dry cough, weakness, sore throat, hyposmia/hypogeusia, or diarrhea, nucleic acid testing is to be performed for those with an epidemiological history compatible with COVID-19 and those working in high-risk occupations (e.g., medical staff receiving patients with fever or infectious diseases, individuals engaged in cold-chain food supervision and related work, and management and service personnel at quarantine sites).

When patients with fever or other COVID-19 related symptoms are identified in community health services stations, village clinics, or private clinics, patient information is required to be reported to the community healthcare center or township health center within 2 hours. A nucleic acid testing strategy of "reporting by village level medical institutions, sampling by township level medical institutions, and detecting by county level medical institutions" is to be implemented to ensure the earliest possible case detection.

To promptly identify risks and early warning signs and guide local government implementation of multi-channel monitoring, the protocol refines requirements and methods for monitoring of people, goods, and the environment. The scope includes patients attending medical institutions, individuals engaged in occupations with infection risk, health monitoring of key populations, monitoring of key institutions, monitoring of imported goods, and environmental sample monitoring in centralized quarantine sites, medical institutions, and wet markets and sewage from large processing facilities for imported frozen goods.

To facilitate understanding of the prevalence of SARS-CoV-2 variants and their influence on laboratory detectability and vaccine effectiveness, the new protocol strengthens pathogen monitoring and includes monitoring variants of concern and variants of interest, as designated by the World Health Organization (*3*).

STANDARDIZE OUTBREAK MANAGEMENT AND RESPONSE

The protocol summarizes outbreak response experiences and standardizes relevant information in ten aspects: infection source control, epidemiological investigation and tracing to the infectious source, close contact tracing and management, nucleic acid testing of key populations, patients and close contact transportation, centralized quarantine site management, community (village) management and control, disinfection, mental health services, and release of epidemic information. In response to rural area issues, such as poor medical conditions, inadequate capacity for nucleic acid testing, and limited quarantine sites, the updated protocol provides guidance for containment measures targeted to rural areas.

STRICT MANAGEMENT OF QUARANTINE FOR MEDICAL OBSERVATION

A few incoming international travelers test nucleic-acid-positive after 14 days of centralized quarantine. To prevent this residual transmission risk, the eighth edition protocol enhances management of quarantine for travelers entering China and the close contacts of COVID-19 virus infected cases based on a comprehensive analysis of possible causes. Incoming travelers from overseas and all the close contacts of COVID-19 virus infected cases are still required to be quarantined for 14 days in designated centralized quarantine sites. Nucleic acid tests are performed using nasopharyngeal swab samples on days 1, 4, 7, and 14 of quarantine. Two nasopharyngeal swabs are to be collected at the time of discharge or release from quarantine and tested using different reagents and by different institutions in principle. After release from quarantine, travelers and close contacts are required to stay at home for seven days of health monitoring, with the nucleic acid tests performed on days 2 and 7. During the household health monitoring period, individuals should adhere to health monitoring, personal protection, staying at home, and not participating in any activities involving gatherings of people.

PRECISE MANAGEMENT OF CLOSE CONTACTS OF CLOSE CONTACTS

Due to the relatively low risk of infection and transmission from close contacts of close contacts (secondary close contacts) and to ensure the effectiveness of epidemic prevention and control, the protocol adjusts management of close contacts of close contacts to reduce pressure on quarantine sites and management tasks for clusters of infection. The duration of quarantine is determined from the actual situations of close contacts of close contacts. If a close contact is released from quarantine, his/her close contacts may also be released from quarantine; if a close contact has negative results from the first two nucleic acid tests, his/her close contracts may be released from quarantine if they have negative nucleic acid tests on days 1, 4, and 7.

SIMULTANEOUS PREVENTION OF INFECTION FROM PEOPLE AND GOODS

The global pandemic situation remains severe, as epidemics have rebounded in some countries. Additionally, virus variants have increased pressure on preventing importation of the virus in China. The tracing to the infectious source of previous outbreaks indicated that imported cases and cold-chain foods and goods can cause local spread and epidemics. In addition to the management of oversea travelers entering China, the new protocol requires management of imported goods, management of persons in direct contact with imported goods, and control measures for positive testing goods and people in contact with these goods.

Specific measures are as follows: 1) strengthen sampling and testing of imported cold-chain foods, their processing environments, transportation, storage, and sales, and strictly implement prevention and control and tracing management during the entire process; 2) strengthen sampling, testing, and preventive disinfection of imported, high-risk, non-cold-chain goods at ports; 3) in addition to regular health education and health monitoring, nucleic acid testing is required to be conducted once a week and before leaving a job for people in direct contact with imported goods at ports; 4) when imported good are identified as positive for COVID-19 virus, temporary storage and safe disposal should be practiced, and the working area

is required to be disinfected. According to a transmission risk assessment, health monitoring and nucleic acid testing will be conducted for personnel contacting goods that test positive. Centralized medical quarantine can be used for contacts when necessary.

DISCUSSION

Building on the previous seven editions of the protocol for prevention and control of COVID-19, the eighth edition adheres to an overall containment strategy of "preventing imported virus and domestic resurgence," and summarizes relevant technical documents issued previously and the experience in managing local outbreaks. The protocol covers all aspects of containment measures and integrates administrative management with technical implementation. It is a practical reference book to guide all localities in their response to COVID-19.

The seventh edition of the protocol played an important role in the prevention and control of the epidemic during autumn and winter of 2020. However, factors such as vaccine availability, discoveries of SARS-CoV-2 variants, and resurgences in other countries have brought new challenges for continued epidemic containment in China. The eighth edition improves and revises key containment measures, including vaccination, epidemic surveillance, outbreak response, quarantine management, management of close contacts of close contacts, and prevention and control of imported virus. The protocol will continue to be updated to provide technical support for achieving China's goals for containment of COVID-19 based on epidemic situations at home and abroad, vaccination in China, and scientific advances on variants of SARS-CoV-2, development of drugs, and other topics relevant to ending the pandemic and returning to a more normal global societal situation.

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Preplanned Studies

Willingness of the General Public to Receive the COVID-19 Vaccine During a Second-Level Alert — Beijing Municipality, China, May 2020

Rui Ma[1]; Luodan Suo[1]; Li Lu[1,#]; Xinghuo Pang[1]

Summary

What is already known on this topic?

Preclinical trials showed the effectiveness of domestic inactivated vaccine candidates for coronavirus disease 2019 (COVID-19). However, it is necessary to evaluate the willingness of the public to receive future domestic vaccines and to understand factors associated with willingness at the early stages of vaccine development.

What is added by this report?

Through May 25, 2020, 70.48% were willing to receive future domestic COVID-19 vaccines. Confidence in vaccines had the largest impact on public willingness, while age and presence of underlying chronic disease did not significantly increase public willingness.

What are the implications for public health practice?

It is necessary to increase awareness of COVID-19 vaccines among people with high risk of severe infection and to build public confidence in vaccines. Releasing accurate, timely, and reliable data to the public can help increase willingness to get vaccinated.

Preclinical animal studies showed that domestic inactivated vaccine candidates induced coronavirus disease 2019 (COVID-19) specific neutralizing antibodies, raising the possibility that mass vaccination with domestic vaccines might be used in the future to end the pandemic. This research conducted a survey among the public with a WeChat mini program (an application within WeChat) to determine intention to get vaccinated. Approximately 70.48% were willing to be vaccinated. Concerns about vaccine safety and effectiveness were the most important factors influencing willingness. Older age and presence of underlying chronic disease were not shown to significantly increase public willingness. Timely and accurate scientific data are greatly needed to build public confidence in vaccines, especially among people at high risk of severe COVID-19 infection. Immunization clinics may need increased resources to ensure high vaccination coverage.

On April 16, 2020, Beijing reported the city's first locally transmitted COVID-19 case. By April 30, 2020, Beijing reported no new cases for 14 consecutive days and lowered the COVID-19 emergency response from the highest level to the second highest level. As COVID-19 began spreading globally, Beijing faced an increasing risk of transmission of imported COVID-19 virus, also known as SARS-CoV-2. In May, 2020, domestic inactivated vaccines entered Phase Ⅱ clinical trials in healthy adults 18 years of age and older (*1*). Preclinical animal studies had shown that inactivated vaccines induced COVID-19-specific neutralizing antibodies in animals and had a protective effect with no observed antibody-dependent enhancement of infection (ADE) (*2*). The research conducted a survey between May 12, 2020 and May 25, 2020 to determine willingness of the general public to get a future COVID-19 vaccine.

The study was an exploratory cross-sectional survey in 2 urban districts and 3 rural districts of Beijing. Respondents were classified into 5 age groups: 18–30, 31–40, 41–50, 51–60, and >61 years old. We assumed an intention to get vaccinated (p) to be 50%, a maximum permissible error (δ) to be 10%, and an allowable α error of 5%. The estimated sample size for each age group was 385 according to the formula $n = \left(\frac{u_{\alpha}^{2} \times p \times (1-p)}{\delta^{2}} \right)$. The study surveyed at least 77 adults per age group in each district. We selected three townships with the largest population sizes. In each selected township, we selected the community with the largest population. Subjects were recruited by community committees. Two-dimensional barcodes were distributed to residential groups in WeChat, the mostly widely and frequently used mobile app for social communication in China (*3*). Respondents

scanned the barcodes and completed the questionnaire on WeChat. The survey was brief to help ensure response quality and completeness — it took subjects only two minutes to answer all questions, decreasing the survey abandonment rate. Each mobile phone could only be used once to answer questions. The number of respondents was tallied daily. The survey ended when the number of subjects in each age group and each district reached their targets.

The questionnaires were designed to obtain information on respondent willingness to be vaccinated with a future domestic COVID-19 vaccine, the most trusted sources of information, preferred vaccination venue, and demographics. Logic skip patterns and data completeness checks were set in WeChat. Study procedures were approved by the Institutional Review Board and Human Research Ethic Committee of Beijing Center for Disease Prevention and Control. Informed consent was obtained at the beginning of the survey. Intention to receive a future vaccine was the primary outcome of the survey, scored as "No", "Uncertain", or "Yes". Descriptive statistics was used to summarize results. Multinomial logistic regression was used to identify factors associated with intention to receive a future vaccine. The main outcome of "Yes" (willing) was used as the referent. Statistical analyses were conducted with SPSS software (version 18.0, SPSS Inc, Chicago, IL, USA).

A total of 3,208 adults were surveyed. More than 30% of respondents were not sure that domestic COVID-19 vaccines were safe and effective. Among all respondents, 70.48% (2,261/3,208) were willing to get vaccinated, 23.66% (759/3,208) were uncertain, and 5.86% (188/3.208) were not willing to get vaccinated. Willingness varied by demographics, perception of COVID-19 disease, and vaccine characteristics. Among people aged >60 years, 74.41% were willing to get vaccination. Among people with underlying chronic disease, 73.02% were willing to get vaccinated. The 3 factors associated with the highest rate of willingness (above 80%) were belief that vaccines were safe, belief that vaccines were effective, and whether they had received influenza vaccination during the most recent 3 years. Among people who thought vaccines were unsafe or ineffective, approximately 40% were unwilling to get vaccinated (Table 1).

TABLE 1. Demographic characteristics, perceptions of disease and domestic COVID-19 vaccines, and willingness to get a future vaccine in Beijing, China.

Variable	Number of interviewees (%)	Willingness to accept vaccination			*P* value*
		"No", n (%)	"Uncertain", n (%)	"Yes", n (%)	
Gender					
Female	1,950 (60.79)	111 (5.70)	500 (25.64)	1,339 (68.67)	0.004
Male	1,258 (39.21)	77 (6.12)	259 (20.59)	922 (73.29)	
Age (years)					
18–30	571 (17.80)	30 (5.25)	135 (23.64)	406 (71.10)	
31–40	1,050 (32.73)	56 (5.33)	284 (27.05)	710 (67.62)	
41–50	666 (20.76)	36 (5.41)	152 (22.82)	478 (71.77)	<0.001
51–60	456 (14.21)	34 (7.46)	101 (22.15)	321 (70.39)	
>60	465 (14.50)	32 (6.88)	87 (18.71)	346 (74.41)	
Highest education					
Secondary school or lower	474 (14.78)	25 (5.27)	94 (19.83)	355 (74.89)	
3-years of college	1,301 (40.55)	69 (5.30)	278 (21.37)	954 (73.33)	<0.001
Undergraduate or higher	1,433 (44.67)	94 (6.56)	387 (27.01)	952 (66.43)	
Living area					
Urban	1,821 (56.76)	97 (5.33)	491 (26.96)	1,233 (67.71)	<0.001
Suburban	1,387 (43.24)	91 (6.56)	268 (19.32)	1,028 (74.12)	
Income					
<5,000 CNY (700 USD)	1,526 (47.57)	92 (6.03)	337 (22.08)	1,097 (71.89)	0.134
≥5,000 CNY (700 USD)	1,682 (52.43)	96 (5.71)	422 (25.09)	1,164 (69.20)	

TABLE 1. (Continued)

Variable	Number of interviewees (%)	Willingness to accept vaccination			*P* value*
		"No", n (%)	"Uncertain", n (%)	"Yes", n (%)	
Underlying chronic disease					
Yes	430 (13.40)	37 (8.60)	79 (18.37)	314 (73.02)	0.002
No	2,778 (86.60)	151 (5.44)	680 (24.48)	1,947 (70.09)	
Seasonal flu vaccination within 3 years					
Yes	488 (15.21)	32 (8.44)	41 (10.82)	306 (80.74)	<0.001
No	2,720 (84.79)	156 (5.51)	718 (25.38)	1,955 (69.11)	
Perception of seriousness of COVID-19 disease					
Very serious	2,227 (69.42)	117 (5.25)	494 (22.18)	1,616 (72.56)	
Serious	869 (27.09)	55 (6.33)	234 (26.93)	580 (66.74)	<0.001
Not serious	112 (3.49)	16 (14.29)	31 (27.68)	65 (58.04)	
Perception of risk of contracting COVID-19					
Very likely	276 (8.60)	18 (6.52)	46 (16.67)	212 (76.81)	
Likely	1,467 (45.73)	73 (4.98)	355 (24.20)	1,039 (70.82)	0.020
Unlikely	1,465 (45.67)	97 (6.62)	358 (24.44)	1,010 (68.94)	
If infected, my symptoms would be more severe than other people's					
Yes	417 (13.00)	21 (5.04)	68 (16.31)	328 (78.66)	
Uncertain	1,847 (57.57)	74 (4.01)	484 (26.20)	1,289 (69.79)	<0.001
No	944 (29.43)	93 (9.85)	207 (21.93)	644 (68.22)	
Perception of impact of COVID-19 pandemic on own life within the past 3 months					
Very serious	835 (26.03)	112 (5.56)	437 (21.68)	1,467 (72.77)	
Serious	1,181 (36.81)	49 (5.08)	263 (27.28)	652 (67.63)	<0.001
Not serious	1,192 (37.16)	27 (11.84)	59 (25.88)	142 (62.28)	
Perception of impact of COVID-19 pandemic on own life in the next 6 months					
Very serious	390 (12.16)	86 (6.35)	295 (21.79)	973 (71.86)	
Serious	964 (30.05)	69 (4.72)	357 (24.42)	1,036 (70.86)	0.039
Not serious	1,854 (57.79)	33 (8.42)	107 (27.30)	252 (64.29)	
Perception of vaccine safety					
Safe	2,147 (66.93)	85 (3.96)	307 (14.30)	1,755 (81.74)	
Uncertain	1,028 (32.04)	87 (8.46)	444 (43.19)	497 (48.35)	<0.001
Unsafe	33 (1.03)	16 (48.48)	8 (24.24)	9 (27.27)	
Perception of vaccine effectiveness					
Effective	2,189 (68.24)	87 (3.97)	314 (14.34)	1,788 (81.68)	
Uncertain	1,000 (31.17)	93 (9.30)	440 (44.00)	467 (46.70)	<0.001
Ineffective	19 (0.59)	8 (42.11)	5 (26.32)	6 (31.58)	
Perception of rebound of COVID-19 infection in China					
Likely	632 (19.70)	63 (9.97)	121 (19.15)	448 (70.89)	
Uncertain	1,596 (49.75)	73 (4.57)	448 (28.07)	1,075 (67.36)	<0.001
Unlikely	980 (30.55)	52 (5.31)	190 (19.39)	738 (75.31)	
Perception of continuity of global COVID-19 transmission					
Likely	1,555 (48.47)	107 (6.88)	337 (21.67)	1,111 (71.45)	
Uncertain	1,195 (37.25)	50 (4.18)	327 (27.36)	818 (68.45)	<0.001
Unlikely	458 (14.28)	31 (6.77)	95 (20.74)	332 (72.49)	

*: χ^2 test.

Compared with the referent (willing) group, belief that vaccines were not safe was the most strongly associated factor for vaccine hesitancy and refusal, with adjusted odds ratio (OR) values of 2.86 and 13.33, respectively. People who had chronic diseases, who thought COVID-19 infection was not serious, who thought their symptoms would be less severe than others if infected, who thought their life had not been seriously affected during the previous three months, or who thought COVID-19 was likely to rebound in China, were more likely to refuse vaccines. Being uncertain of vaccine effectiveness was the second most associated factor for vaccine hesitancy, with an adjusted OR value of 2.68 (Table 2).

TABLE 2. Factors associated with intention to get a future domestic COVID-19 vaccine in Beijing, China.

Variable	Unwillingness*		Uncertainty*	
	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Gender				
Female	1	1	1	1
Male	1.01 (0.74–1.36)	0.91 (0.65–1.26)	0.75 (0.63–0.89)	0.88 (0.72–1.06)
Age (years)				
18–30	1	–†	1	–†
31–40	1.07 (0.67–1.69)	–†	1.20 (0.95–1.53)	–†
41–50	1.02 (0.62–1.68)	–†	0.96 (0.73–1.25)	–†
51–60	1.43 (0.86–2.39)	–†	0.95 (0.70–1.27)	–†
>60	1.25 (0.75–2.10)	–†	1.20 (0.95–1.53)	–†
Highest education				
Secondary school or lower	1	1	1	1
3-years of college	1.03 (0.64–1.65)	1.54 (0.92–2.59)	1.10 (0.85–1.43)	1.06 (0.79–1.43)
Undergraduate or higher	1.40 (0.89–2.22)	1.26 (0.75–2.13)	1.54 (1.19–1.98)	1.39 (1.03–1.86)
Living area				
Urban	1	1	1	1
Suburban	1.13 (0.84–1.52)	1.28 (0.92–1.79)	0.66 (0.55–0.78)	0.79 (0.65–0.96)
Income				
<5,000 CNY (700 USD)	1	1	1	1
≥5,000 CNY (700 USD)	0.98 (0.73–1.32)	–†	1.18 (1.00–1.39)	–†
Underlying chronic disease				
Yes	1	1	1	1
No	0.66 (0.45–0.96)	0.50 (0.32–0.78)	1.39 (1.07–1.80)	1.17 (0.86–1.58)
Seasonal flu vaccination within 3 years				
Yes	1	1	1	1
No	0.76 (0.51–1.14)	0.69 (0.44–1.07)	2.74 (1.96–3.84)	2.28 (1.59–3.27)
Perception of seriousness of COVID-19 disease				
Very serious	1	1	1	1
Serious	1.31 (0.94–1.83)	1.25 (0.88–1.79)	1.32 (1.10–1.58)	1.33 (1.08–1.63)
Not serious	3.40 (1.91–6.06)	2.27 (1.18–4.37)	1.56 (1.01–2.42)	1.39 (0.86–2.27)
Perception of risk in contracting COVID-19				
Very likely	1	1	1	1
Likely	0.83 (0.48–1.42)	0.86 (0.48–1.56)	1.58 (1.12–2.21)	1.17 (0.80–1.70)
Unlikely	1.13 (0.67–1.91)	1.12 (0.61–2.07)	1.63 (1.16–2.30)	1.31 (0.89–1.93)
If infected, my symptoms would be more severe than other people's				
Yes	1	1	1	1

TABLE 2. (Continued)

Variable	Unwillingness*		Uncertainty*	
	Unadjusted OR (95%CI)	Adjusted OR (95%CI)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Uncertain	0.90 (0.54–1.48)	1.22 (0.70–2.12)	1.81 (1.37–2.40)	1.38 (1.01–1.91)
No	2.26 (1.38–3.69)	3.05 (1.71–5.45)	1.55 (1.14–2.10)	1.23 (0.86–1.76)
Perception of impact of COVID-19 pandemic on own life within the past 3 months				
Very serious	1	1	1	1
Serious	0.98 (0.70–1.39)	1.16 (0.75–1.80)	1.35 (1.13–1.62)	1.28 (1.01–1.61)
not serious	2.49 (1.58–3.92)	2.54 (1.35–4.78)	1.40 (1.01–1.92)	1.17 (0.77–1.78)
Perception of impact of COVID-19 pandemic on own life in the next 6 months				
Very serious	1	1	1	1
Serious	0.75 (0.54–1.05)	0.77 (0.51–1.16)	1.14 (0.95–1.36)	1.07 (0.85–1.34)
Not serious	1.48 (0.97–2.27)	1.06 (0.58–1.95)	1.40 (1.08–1.82)	1.39 (0.97–1.97)
Perception of vaccine safety				
Safe	1	1	1	1
Uncertain	3.61 (2.64–4.95)	2.35 (1.44–3.83)	5.11 (4.28–6.09)	2.50 (1.91–3.27)
Unsafe	36.71 (15.77–85.47)	13.33 (4.83–36.80)	5.08 (1.95–13.27)	2.86 (1.02–7.96)
Perception of vaccine effectiveness				
Effective	1	1	1	1
Uncertain	4.09 (3.00–5.58)	2.52 (1.55–4.10)	5.37 (4.50–6.40)	2.68 (2.05–3.50)
Ineffective	27.40 (9.30–80.73)	3.52 (0.94–13.17)	4.75 (1.44–15.64)	3.28 (0.92–11.77)
Perception of rebound of COVID-19 infection in China				
Likely	1	1	1	1
Uncertain	0.48 (0.34–0.69)	0.57 (0.37–0.89)	1.54 (1.23–1.94)	1.23 (0.93–1.62)
Unlikely	0.50 (0.34–0.74)	0.56 (0.35–0.92)	0.95 (0.74–1.23)	1.08 (0.79–1.48)
Perception of continuity of global COVID-19 transmission				
Likely	1	1	1	1
Uncertain	0.64 (0.45–0.90)	0.63 (0.41–0.97)	1.32 (1.10–1.57)	0.96 (0.77–1.20)
Unlikely	0.97 (0.64–1.47)	1.16 (0.70–1.92)	0.94 (0.73–1.22)	1.12 (0.83–1.52)

*: Being willing to get vaccine was selected as reference category in multinomial logistic regression.
†: Variables that were not statistically significant in univariate analyses were excluded from the multinomial logistic regression model.

Respondents' most popular sources of information about COVID-19 vaccines were social media (86.94%, 2,789/3,208), medical doctors (78.68%, 2,524/3,208), and professional papers (34.57%, 1,109/3,208). Among the 2,261 respondents who were willing to get vaccinated, 58.29% (1,318/2,261) preferred getting vaccinated in immunization clinics.

DISCUSSION

This study found that 70% of the general public were willing to be vaccinated with a COVID-19 vaccine, a rate close to the 74% willingness found in a study conducted in France at about the same time as our survey (*4*). A study in Wuhan city showed that the basic reproduction number (R_0) of COVID-19 was 2.24–3.58 (*5*) in the early phase of the epidemic, indicating that 55.36%–72.07% of the population needs to be immune to the virus to prevent sustained transmission. Based on that result, the future COVID-19 vaccination rate should be at least 70% in Beijing, assuming that COVID-19 vaccines are 70%–80% effective in preventing disease. In our study, about 70% were willing to get COVID-19 vaccines, which is close to that target. We also found that 20% of the general public was uncertain whether they would get a COVID-19 vaccine. Among people who believed vaccines were safe and effective, 81% were willing to get vaccinated. Therefore, achieving the goal of no sustained spread of COVID-19 seems not far off in Beijing through use of a mass vaccination program. In

January 2021, Beijing started a COVID-19 vaccination campaign targeting people aged 18–59 years old, and shortly thereafter extended the age range to 60 years and above. At the time of publication of this article, coverage of the 1st dose of COVID-19 vaccine has exceeded the 70% coverage level that was predicted in our study, as more than 80% of people over 18 years of age have already received at least one dose of COVID-19 vaccine in the ongoing campaign (*6*).

Among interviewees, more than 30% were not confident in COVID-19 vaccines — a finding that may be due to lack of scientific data at the time the survey was conducted. "Vaccine hesitancy" (*7*) could be another reason. Our multivariable analyses showed confidence in vaccine safety had the highest impact on public willingness. Although belief that the vaccine was ineffective did not significantly increase the unwillingness rate, the OR value was 27.40, and statistically significant in univariate analyses. Being uncertain of vaccine effectiveness was also significantly associated with vaccine hesitancy (Table 2). Therefore, building confidence in domestic vaccines should be a priority. It was noteworthy that age had no significant impact on willingness. It is therefore important to increase awareness of vaccines among people ≥60 years of age, who were more likely to have severe COVID-19 (*8*). People who thought COVID-19 was serious or who thought their symptoms would be more severe than others if infected, were more willing to get vaccinated. This finding implies that social mobilization, especially among people with high risk of severe COVID-19, could increase vaccine acceptance. If vaccines are shown to be effective against severe infection, willingness to get vaccines may significantly increase. Presence of underlying chronic diseases was associated with an increased possibility to refuse vaccination. That could be due to concerns that vaccination may exacerbate the disease. It is difficult to explain our finding that people who believed COVID-19 might rebound in China were more likely to refuse vaccination. Further study on this point is needed. The finding does suggest that social mobilization is necessary among people believing that COVID-19 will rebound in China.

More than 70% of the general public received vaccine information from social media or medical doctors. Media reports therefore should be objective and fair. Increased willingness of medical doctors to get vaccinated could be another key factor. Around one third of the public received information from professional literature. Hence, accurate, timely, and reliable data about vaccines should be released to the general public through social media and medical doctors.

Over half of respondents preferred getting vaccinated in clinics that provide routine immunization for children aged 0–14 years. Increased resources and personnel for immunization clinics would be necessary to avoid decreases in coverage of routine vaccines during mass COVID-19 vaccination.

Social mobilization has played an important role in achieving high coverage in Beijing's vaccination campaign. Consistent with findings in our study, building public confidence in vaccines through publicity of the COVID-19 vaccine clinical trials that showed the vaccines to be safe and effective, making vaccination convenient by establishing temporary vaccination clinics, and using social media to increase awareness of the importance of immunization have been instrumental in building high coverage levels.

Our study has some limitations. First, our result could not be generalized to the entire adult population. Second, our results can only be applied to when Beijing set its public health emergency response to the second level and data of Phase I clinical trials of domestic COVID-19 vaccines were available. Continued monitoring will be important. Third, self-reported data may have introduced information bias.

Our study showed a high level of willingness of the general public to be vaccinated with domestic COVID-19 vaccines. Building public confidence in vaccines through social media and medical doctors is needed. It is also necessary to increase awareness of vaccines among people with high risk of severe COVID-19 infections. Increased personnel and resources for routine immunization clinics should be considered to prepare for mass vaccination efforts.

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Perspectives

Caution About Truncation-By-Death in Clinical Trial Statistical Analysis: A Lesson from Remdesivir

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In an effort to combat coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), clinicians across the globe have been working tirelessly to find effective treatments. In 2020, inspiring drug trials have focused on treating COVID-19 with the antiviral drug remdesivir. Beigel et al. conducted a well-designed multicenter randomized trial, where 541 patients were assigned to receive remdesivir, and 522 patients were assigned to receive placebo treatment (*1*). They reported that those who received remdesivir had a median recovery time of 11 days [95% confidence interval (CI): 9–12], as compared with 15 days (95% CI: 13–19) in those who received a placebo (P<0.001).

Another multicenter randomized trial was conducted by Wang et al. at 10 hospitals in Hubei Province, China (*2*). They reported that remdesivir use had a positive but insignificant effect compared with standard care in the time to clinical improvement [hazard ratio (HR)=1.23, 95% CI: 0.87–1.75]. Due to early suspension of the trial because of adverse events, this study was underpowered, and the findings were deemed to be inconclusive (*3*). Discrepant findings between these two studies show that a small sample size may fail to achieve the predetermined power or make an expected conclusion. Despite the small sample size, the remdesivir studies for COVID-19 can still also provide a lot of valuable information under more careful statistical analysis.

First, we must be cautious whether remdesivir is safer than placebo. Beigel et al. found serious adverse events among 114 of the 541 (21.1%) patients in the remdesivir group and 141 of the 522 (27%) patients in the placebo group, while Wang et al. reported adverse events in 102 of 155 (66%) remdesivir recipients versus 50 of 78 (64%) placebo recipients. This difference in adverse events may be attributable to underlying medical diseases among patients included in the studies. As Wang et al. described in their article, the remdesivir group included more patients with hypertension, diabetes, or coronary artery disease than the placebo group, which led to an imbalance between the two treatment groups. Although this study was randomized at baseline, randomization alone does not guarantee balance between the treatment and placebo groups. The consequence of clinical trials relying on pure randomization has been discussed in some statistics literature: the treatment effect estimate may be far from the true value if the sample size is not large enough (*4*–*6*). Thus, the causal effect of underlying medical diseases on recovery rate or safety outcomes may be confounded by the severity of underlying diseases. By comparing these two studies, we have reason to think that remdesivir has different effects on populations with different baseline status.

Another topic related to treatment imbalance is the statistical analysis for the truncated-by-death individuals. Beigel et al. reported that the Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (HR for death=0.70, 95% CI: 0.47–1.04). An analysis with adjustment for baseline ordinal score as a stratification variable showed a HR for death of 0.74, 95% CI: 0.50–1.10. Wang et al. also found insignificant differences in mortality between the remdesivir group and the placebo group. Similar with adverse events, the possibility that death was associated with underlying diseases cannot be excluded. If patients with underlying diseases were more likely to develop adverse events or die, then the treatment effect of remdesivir versus placebo would have been underestimated (*7*).

It is worth noting that handling the truncation-by-death problem is different from censoring. That is to say, the Kaplan-Meier approach, which is commonly adopted in survival analysis with censoring, should be used with great care if the target of a study is the time to clinical improvement or recovery instead of mortality. Censoring can be understood as a missing data problem: the time to clinical improvement or recovery does exist but is longer than the study period. For example, if a patient recovered at Day 35 but the study ended at Day 28, then the time to recovery was censored. In the methodology, partial likelihood is calculated for at-risk individuals at each time point.

However, truncation-by-death is a completely different issue. If a patient was truncated by death, then his/her outcome (time to clinical improvement or recovery) is undefined. In the classical survival analysis, every individual would experience the failure event at some day. But by definition, a patient that dies at Day 21, for example, should not be treated as censored at any day because he/she has lost the ability to experience the failure event (referring to clinical improvement or recovery here), and the failure event would never occur no matter how long the follow-up is. To be brief, treating death as censoring would confuse different types of outcomes. Different statistical procedures should be adopted in dealing with the truncation-by-death problem.

In fact, comparing treatment effects is a question about causal inference. Under the potential outcome framework, each individual has two potential outcomes: one under the treatment, the other under the control. The treatment effect is the difference of these two potential outcomes. By principal stratification, one can divide the whole population into four strata (*8*):

(1) LL, always survivor, alive either if treated or untreated.

(2) LD, protected, alive if treated but dead if untreated.

(3) DL, harmed, dead if treated but alive if untreated.

(4) DD, doomed, dead either if treated or untreated.

The fundamental problem in causal inference is that one can only observe one of these two potential outcomes, since a patient can either be treated or untreated, but not both. Thus, the observed alive individuals at Day 28 come from mixed strata: LL and LD for the treatment group and LL and DL for the placebo group. However, the treatment effect is only meaningful in the LL stratum, since the pair of potential outcomes, clinical improvement, or recovery, are only well defined in the LL stratum.

Since common clinical analyses considered death as right censoring at the endpoint, we cannot conclude whether the estimates represent a meaningful parameter. In order to identify the LL stratum, a substitutional variable for survival is needed (*9*–*10*). Since the information of baseline covariates and COVID-19 is still insufficient, we do not know whether a qualified substitutional variable exists or not. Analysis based on observed survivors may underestimate the true treatment effect due to the positive correlation between the severity of underlying diseases and death, so principal stratification or baseline adjustment for underlying diseases is recommended for better statistical analysis.

To address the truncation-by-death problem, we use generated simulation data (see Supplementary Material for simulation details, available at weekly.chinacdc.cn) that mimics the findings of Beigel et al. to show the grave consequence of considering death as right censoring. Suppose that 500 patients are enrolled into the treatment group and 500 patients are enrolled into the placebo group. The probability of possessing underlying disease is 0.4 in the treatment group and 0.3 in the placebo group. The probability of death is 0.3 with underlying diseases and 0.1 with no underlying diseases. Thus, by assuming that death is independent of treatment course, the probability of being alive is 0.82 in the treatment group and 0.84 in the placebo group. Suppose the time to recovery (or clinical improvement) follows an exponential distribution with mean 11 days if receiving treatment and 15 days if receiving placebo, so the true HR is 1.36. Recovery time of more than 30 days is considered as right censored. We simulate for 500 runs and use the Cox proportional hazard model to analyze the data. The procedures and codes are listed in the Appendix.

(1) If the dead individuals are regarded as right censored at Day 30, the average estimated HR is 1.27 (s.e.=0.09, average *P*-value=0.012).

(2) If conditioning on the alive individuals, the estimated HR is 1.37 (s.e.=0.10, average *P*-value 0.002).

(3) If conditioning on the alive subsample and weighting the alive individuals by the survival probability in each group, the estimated HR is 1.37 (s.e.=0.10, average *P*-value=0.001).

(4) If dividing the sample into 2 subsamples of possessing underlying diseases and not possessing underlying diseases, and regarding the dead individuals as right censored at Day 30, the estimated HR is 1.27 (s.e.=0.13, average *P*-value=0.125) in the former subsample and 1.33 (s.e.=0.11, average *P*-value=0.017) in the latter subsample.

(5) If dividing the sample into 2 subsamples of possessing underlying diseases and not possessing underlying diseases and conditioning on the alive individuals, the estimated HR is 1.38 (s.e.=0.19, average *P*-value=0.099) in the former subsample and 1.38 (s.e.=0.13, average *P*-value=0.013) in the latter subsample.

One can see that regarding death as right censoring

would underestimate the treatment effect, even if stratifying the severity of underlying diseases. The second and third approaches yield similar estimates and are close to the true value, because the survival probability is similar in the two groups. The fourth and fifth approaches have larger standard errors and *P*-values due to the decline of sample size by dividing the observed sample.

At the very least, to make the assumption of truncation-by-death at random (i.e., death is independent of treatment) more convincing, baseline covariates such as disease severity (baseline score) and underlying diseases should be adjusted if the imbalance in enrollment is obvious, as Beigel and his colleagues did in their work. Furthermore, a better experimental design at the design phase would allow for a more hassle-free analysis at the analysis phase. It is true that randomization for recruitment is a commonly adopted approach to eliminate the effects of confounding. Still, there are some approaches to improve the randomization at the design phase that can minimize the impact of confounding and treatment imbalance if a few critical covariates exist. For example, rerandomization can be used to balance the covariates between the treatment and placebo groups (*11*). By iteratively trying to randomize the assignment, only the assignment that satisfies some criterion (for example, the distance of covariates between the treatment and the placebo groups is lower than a threshold) can enter into the experiment. It is encouraging that statistical inference under rerandomization is still valid with a little adjustment (*12*). Therefore, in future clinical studies, we suggest that greater attention should be given to the design phase, so that problems that may occur in the analysis phase can be avoided.

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Supplementary Material

We conduct a simulation study to show truncation-by-death is different from censoring. The simulation is conducted using R statistical software (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria). The following R code lists the procedure of model fit in each iteration.

(1) Generate the recovery time with right censoring of treatment group and placebo group.

```
n1=500
n0=500
t1=round(rexp(n1,1/11),0)
t0=round(rexp(n0,1/15),0)
t1[t1>30]=30
t0[t0>30]=30
c1=as.numeric(t1<30)
c0=as.numeric(t0<30)
```

(2) Consider two strata: with and without underlying medical diseases. Generate the survival status.

```
s1=rbinom(n1,1,0.4)
s0=rbinom(n0,1,0.3)
d1=-(s1×rbinom(n1,1,0.3)+(1-s1)×rbinom(n1,1,0.1))
d0=1-(s0×rbinom(n0,1,0.3)+(1-s0)×rbinom(n0,1,0.1))
```

(3) The observed recovery time T, observability R, underlying diseases S, survival status D, treatment X.

```
T1=t1×d1+30×(1-d1)
T0=t0×d0+30×(1-d0)
R1=apply(rbind(c1,c1),2,min)
R0=apply(rbind(c0,c0),2,min)
X=c(rep(1,n1),rep(0,n0))
R=c(R1,R0)
T=c(T1,T0)
S=c(s1,s0)
D=c(d1,d0)
W=1/c(rep(0.82,n1),rep(0.84,n0))
```

(4) Fitting the Cox proportional hazard model.

```
library(survival)
res.cox1<-coxph(Surv(T,R)~X)
res.cox2<-coxph(Surv(T,R)~X, subset=(D==1))
res.cox3<-coxph(Surv(T,R)~X, weights=W, subset=(D==1))
res.cox41<-coxph(Surv(T,R)~X, subset=(S==1))
res.cox42<-coxph(Surv(T,R)~X, subset=(S==0))
res.cox51<-coxph(Surv(T,R)~X, subset=(D==1&S==1))
res.cox52<-coxph(Surv(T,R)~X, subset=(D==1&S==0))
```

Notes from the Field

Genome Characterization of COVID-19 Lineage B.1.1.7 Detected in the First Six Patients of a Cluster Outbreak — Shenzhen City, Guangdong Province, China, May 2021

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Screening for coronavirus disease 2019 (COVID-19) virus, also known as SARS-CoV-2, infection every seven days was performed for high-risk populations who worked at the Yantian Port in Yantian District, Shenzhen City, Guangdong Province. On May 20, 2021, an oropharyngeal swab from a 44-year-old male (Case A) tested preliminarily positive for COVID-19 by a quantitative real-time reverse transcription polymerase chain reaction (RT-qPCR) method in a third-party laboratory. On May 21, 2021, 3 types of specimens (nasopharyngeal swab, oropharyngeal swab, and anal swab) from this case were collected by Yantian CDC and were confirmed positive for COVID-19 virus by a RT-qPCR method simultaneously implemented in two commercial kits (Daan, Guangzhou, China and Bojie, Shanghai, China) in the virology laboratory of Shenzhen CDC (Table 1). Then, screening was initiated for employees from the Yantian Port and close contacts. A total of 5 cases were confirmed with COVID-19 infections between May 22, 2021 and May 24, 2021 (Table 1). These cases were transported immediately to the Shenzhen Third People's Hospital for isolated treatment by ambulance after COVID-19 virus infection was confirmed. Specimens from the cases above collected by the Shenzhen Third People's Hospital were sent to the virology laboratory of Shenzhen CDC for discharge assessment.

High-throughput sequencing was performed for six COVID-19 virus strains from this study. First, viral RNA was extracted directly from 200-μL swab samples with the lowest Ct value in RT-qPCR tests using a High Pure Viral RNA Kit (Roche, Germany). Second, libraries were prepared using a Nextera® XT Library Prep Kit (Illumina, USA), and the resulting DNA libraries were sequenced on a MiSeq platform (Illumina) using a 300-cycle reagent kit (*1*). Last, mapped assemblies were generated using the COVID-19 virus/SARS-CoV-2 reference sequence Wuhan-Hu-1 (GenBank no. NC_045512.2). Nucleotide (nt) and amino acid (AA) differences between the six virus genome sequences from this study and the reference sequence Wuhan-Hu-1 were analyzed using the programs BioEdit 7.19 and MEGA version7 (*2*).

The 6 strains from Case A, Case B, Case C, Case D, Case E, and Case F were designated as hCoV-19/Guangdong/IVDC-05-01-2/2021, hCoV-19/Guangdong/IVDC-05-02-2/2021, hCoV-19/Guangdong/IVDC-05-03/2021, hCoV-19/Guangdong/IVDC-05-04/2021, hCoV19/Guangdong/IVDC-05-05/2021, and hCoV-19/Guangdong/IVDC-05-06/2021, respectively, in this study. The genome sequences of these 6 strains were 29,844 nt, 29,867nt, 29,808 nt, 29,846 nt, 29,760 nt, and 29,832nt in length, respectively. Based on the "Pango lineages" rule (*3*), the 6 virus strains from this study were assigned to lineage B.1.1.7, which was also known as Variant of Concern 202012/01 (VOC-202012/01) or 20B/501Y.V1. The lineage B.1.1.7 was first identified in the UK in September 2020 and had 24 characteristic mutations (ORF1a: T1001I, A1708D, I2230T, del3675-3677; ORF1b: P314L; S: del69/70, del144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H; ORF8:Q27stop, R52I, Y73C; N: D3L, R203K, G204R, S235F).

Compared with the reference genome sequence Wuhan-Hu-1, 5 strains (hCoV-19/Guangdong/IVDC-05-01-2/2021, hCoV-19/Guangdong/IVDC-05-02-2/2021, hCoV-19/Guangdong/IVDC-05-03/2021, hCoV-19/Guangdong/IVDC-05-04/2021, and hCoV-19/Guangdong/IVDC-05-06/2021) displayed 38 nucleotide variation sites (C241T, C643T, C913T, C2536T, A2784G, C3037T, C3267T, C5388A, C5986T, T6954C, C7851T, G13975T, C14408T, C14676T, T15096C, C15279T, T16176C, C17430T, G17944T,

TABLE 1. Demographic characteristics of the cases and specimen testing information.

Case	Age (year)	Date of first positive detection of COVID-19 virus	Ct value (ORF1ab/N) by RT-qPCR		
			Specimen type	Daan	Bojie
Case A	44	May 21, 2021	Nasopharyngeal swab	17/20	18/19
			Oropharyngeal swab	19/22	20/22
			Anal swab	40/37	Undet/36
Case B	46	May 22, 2021	Nasopharyngeal swab	18/16	17/18
			Oropharyngeal swab	23/20	22/23
			Anal swab	37/35	Undet/37
Case C	49	May 23, 2021	Nasopharyngeal swab	25/20	21/22
			Oropharyngeal swab	35/30	30/31
			Anal swab	Undet/Undet	Undet/Undet
Case D	48	May 23, 2021	Nasopharyngeal swab	37/34	32/34
			Oropharyngeal swab	31/26	27/28
			Anal swab	Undet/Undet	Undet/Undet
Case E	33	May 23, 2021	Nasopharyngeal swab	22/16	19/19
			Anal swab	Undet/Undet	Undet/Undet
Case F	44	May 24, 2021	Nasopharyngeal swab	17/16	16/17
			Oropharyngeal swab	37/33	34/34
			Anal swab	39/34	Undet /35

Note: All the reported cases were male. The reported Ct value was the lowest value of several tests as of May 27, 2021.
Abbreviations: Undet=Undetected; RT-qPCR=quantitative real-time reverse transcription PCR.

G21578T, A23063T, C23271A, A23403G, C23604A, C23709T, T24506G, G24914C, C27972T, G28048T, A28111G, G28280C, A28281T, T28282A, G28739T, G28881A, G28882A, G28883C, and C28977T) and 18 deletion mutations (ORF1a: del11288-11296/TCTGGTTTT; S: del21766-21771/ACATGT, del21994-21996/TTA). Except for the mutations above, other two variation sites (ORF1a: C884T and S: A23898T) were observed in genome of the strain hCoV-19/Guangdong/IVDC-05-05/2021 (Case E).

By comparing deduced amino acid sequences, the 5 SARS-CoV-2 strains (hCoV-19/Guangdong/IVDC-05-01-2/2021, hCoV-19/Guangdong/IVDC-05-02-2/2021, hCoV-19/Guangdong/IVDC-05-03/2021, hCoV-19/Guangdong/IVDC-05-04/2021, and hCoV-19/Guangdong/IVDC-05-06/2021) displayed 24 AA variation sites (ORF1a: N840S, T1001I, A1708D, I2230T, A2529V; ORF1b: G170C, P314L, V1493L; S: V6F, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H; ORF8: Q27stop, R52I, Y73C; N: D3L, A156S, R203K, G204R, and S235F) and 6 deletion mutations (ORF1a: S3675del, G3675del, and F3677 del; S: H69del, V70del, and Y144del). Except for the mutations above, 2 other variation sites (ORF1a: R207C; S: Q779L) were observed in amino acid sequence of the strain hCoV-19/Guangdong/IVDC-05-05/2021 (Case E). All of the characteristic mutations belonging to SARS-CoV-2 variant B.1.1.7 were found in genomes of the 6 SARS-CoV-2 strains from this study.

Whole-genome sequencing (WGS) confirmed that all SARS-CoV-2 strains from this study were VOC 202012/01-lineage B.1.1.7, suggesting a common source of exposure at the Yantian Port. SARS-CoV-2 lineage B.1.1.7 is of growing concern because it has shown to be significantly more transmissible than other variants (*4*–*7*). As of now, the 4 SARS-CoV-2 VOCs (B.1.1.7, B.1.351, P.1, and B.1.617.2) have been imported into mainland China (*8*–*11*). There is a high risk that imported SARS-CoV-2 VOCs may cause local outbreaks and epidemics.

In this study, we focused on laboratory testing and genome characterization of the pathogen. Detailed epidemiological investigation is essential in a follow-up report.

Data availability: The six SARS-CoV-2 genome sequences determined in this study have been deposited in GISAID (www.gisaid.org) under the accession numbers EPI_ISL_2405168, EPI_ISL_2405169, EPI_ISL_2432955, EPI_ISL_2405170, EPI_ISL_2405171, and EPI_ISL_2405172.

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Notes from the Field

Three Cases of COVID-19 Variant Delta With and Without Vaccination — Chengdu City, Sichuan Province, April–May, 2021

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On April 26, 2021, a 33-year-old male Chinese sailor returning from India via Kathmandu, Nepal, tested positive for the coronavirus disease 2019 (COVID-19) by Chengdu Customs and was confirmed positive by Chengdu CDC (Case A).

On May 2, 2021, a housewife in the same flight tested positive for COVID-19 by Pengzhou CDC in Sichuan Province during her quarantine period and was confirmed positive by Chengdu CDC the next day (Case B).

On May 9, 2021, a male worker at a cement company in a different flight tested positive for COVID-19 by a third-party testing laboratory during his quarantined period and was confirmed positive by Chengdu CDC the next day (Case C).

Epidemiological investigations revealed that Case A arrived in Kathmandu on April 19 from New Delhi, India and Case B arrived in Kathmandu on April 21 from Uttar Pradesh, India. Case C had been working in Kathmandu before returning. They all tested negative for polymerase chain reaction (PCR) tests and antibody tests of COVID-19 before boarding.

Case A had been fully vaccinated with two doses of inactivated COVID-19 vaccine (Beijing Institute of Biological Products Co. LTD) with the first dose on January 25 and the second on February 8, 2021. In addition, Case C was vaccinated (Sinovac Biotech Co. LTD) on October 19 and November 4, 2020. Case B was not vaccinated.

The samples of nasopharyngeal swabs from the three cases were sequenced by Illumina MiniSeq Sequencing platform with commercial kits on April 27 and May 11, then the whole genome sequences of 29,858, 29,732, and 29,877 bp by length with depth over 3000X were obtained. Compared to the Wuhan reference sequence (MN908947) (*1*–*2*), they shared 20 nucleotide variation sites containing the characteristic spike mutations of T19R, L452R, T478K, D614G, P681R, and D950N listed in the sub-lineage of B.1.617.2 (variant Delta) that was assigned by a web analytical tool as B.1.617.2 (*3*), which had been circulating in India since December 2020 and was designated as one of the variants of concern (VOCs) by the World Health Organization (WHO) (*4*). The phylogenetic tree by CLC Main Workbench 11.0 (QIAGEN, Dusseldorf, Germany) was shown in Figure 1.

Cases A, B, and C of COVID-19 were transferred to the Public Health Clinical Center of Chengdu for treatment in isolation on April 26, May 3, and May 10, 2021, separately (the main clinical events are shown in Figure 2). Soon after the admission, they all were found to have an increase in lung lesions according to chest computed tomography (CT) abnormalities. During the isolation treatment period, 3 differences were found between the vaccinated and unvaccinated patients: 1) The IgG\IgM\total antibodies tests were positive for Case A on the 4th day, positive for Case C on the 1st day with high titer, and negative for Case B even on the 7th day (negative for IgM during the entirety of hospitalization and positive for IgG and total antibodies on the 13th day with low titer), which suggested that the time from diagnosis to antibody positivity was shorter in vaccinated cases than in unvaccinated cases [Figure 3 shows the results of IgM and total antibodies results with chemiluminescence immunoassay (CLIA)]. 2) The cycle threshold (Ct) value of fluorescent PCR seems lower in samples from unvaccinated patients than those from the vaccinated ones [Figure 4 shows the results of Ct values of the open reading frame (ORF)]. There is a similar finding that a significant increase in Ct in vaccinated individuals than matched unvaccinated control group infections (n=1,888) from days 12–37 after vaccination was reported (*5*). 3) The length of hospitalization was shorter for vaccinated

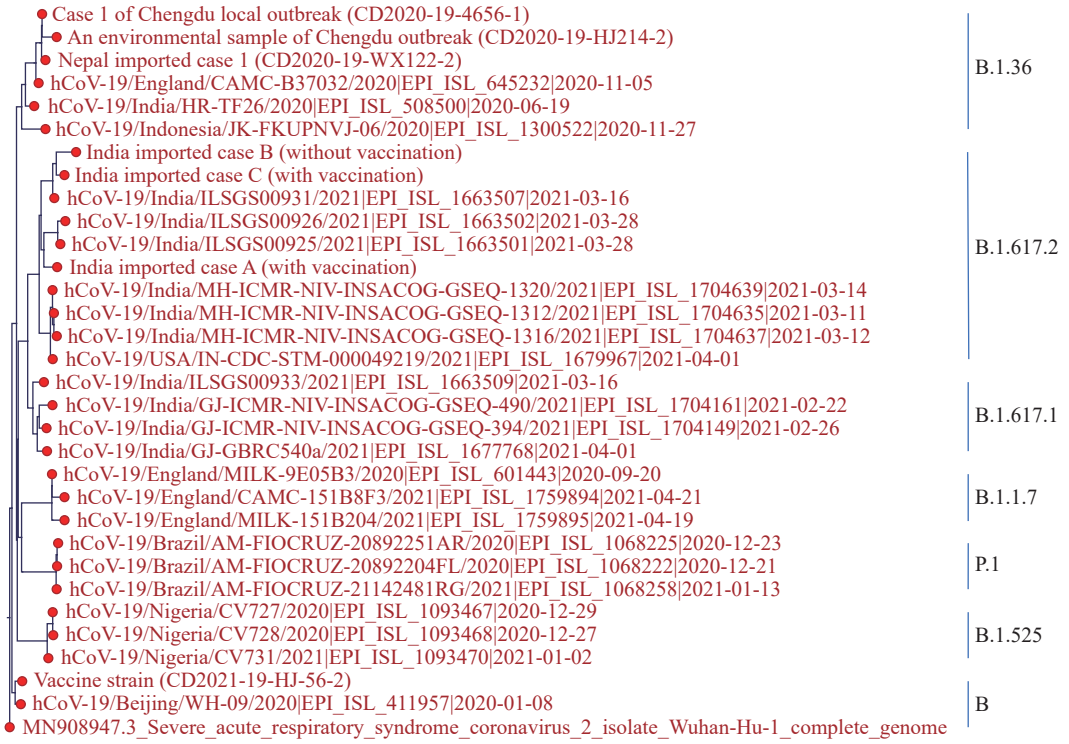

FIGURE 1. Phylogenetic tree based on the full-length genome sequences of the COVID-19 virus.
Note: The main mutations: C241T, C3037T, C14408T, G15451A, C16466T, C21618G, T22917G, C22995A, A23403G, C23604G, G24410A, C25469T, T26767C, T27638C, C27752T, A28461G, G28881T, G29402T, and G29742T.

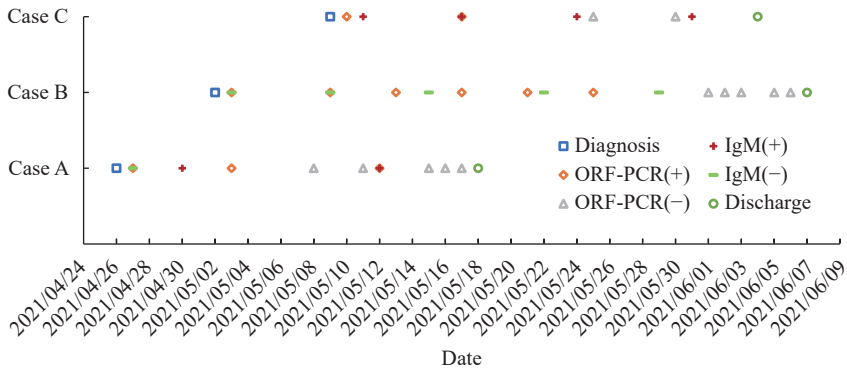

FIGURE 2. The timeline of the main clinical events of the cases.
Note: Cases A and C had been vaccinated while Case B was not vaccinated.
Abbreviations: ORF=the open reading frame, PCR=polymerase chain reaction.

patients than for unvaccinated one. Case A and Case C were discharged after 21 and 25 days in the hospital, respectively, and Case B was discharged on June 7 after 36 days.

The variant Delta strains were imported into China and exerted a great threat to the prevention and control of COVID-19. Further studies looking into the epidemiological impacts of the variants and the effects of the vaccine are urgently needed. As local outbreaks of COVID-19 are still reported in Anhui, Liaoning, and Guangdong, vaccination should be taken as the first strategy and promoted efficiently for the disease control for COVID-19.

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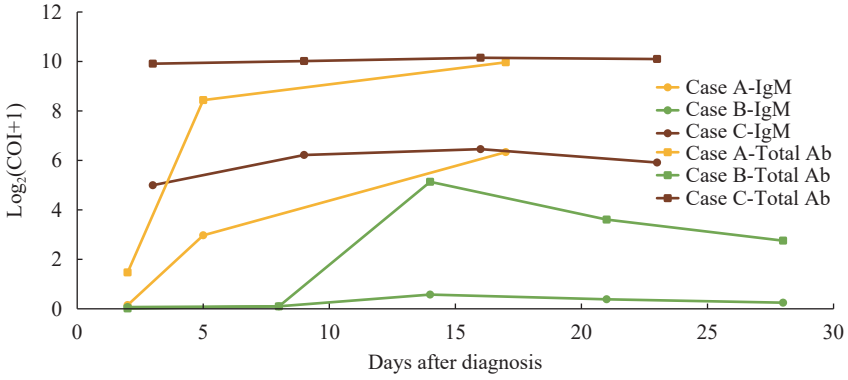

FIGURE 3. The antibody titer of IgM and total antibodies analyzed using chemiluminescence analysis (CLIA) during the isolation treatment period.
Note: Cases A and C had been vaccinated while Case B was not vaccinated. All cases were negative for IgM with ELISA on Day 1, which is not shown in this figure.
Abbreviations: Total Ab=total antibodies, COI=cut off index.

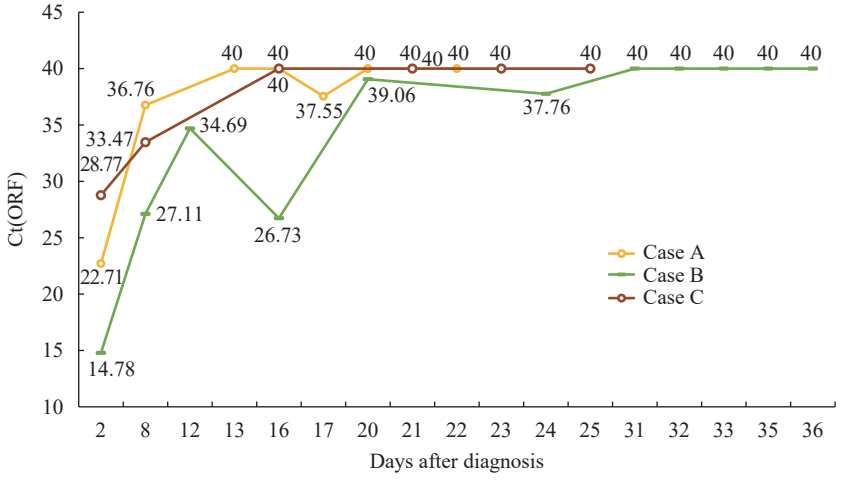

FIGURE 4. The CT values of ORF with PCR during the isolation treatment period.
Note: Cases A and C had been vaccinated while Case B was not vaccinated. A CT value of 40 was used to assume a negative result.
Abbreviations: CT=computed tomography; ORF=open reading frame; PCR=polymerase chain reaction.

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Notifiable Infectious Diseases Reports

Reported Cases and Deaths of National Notifiable Infectious Diseases — China, April, 2021

Diseases	Cases	Deaths
Plague	0	0
Cholera	0	0
SARS-CoV	0	0
Acquired immune deficiency syndrome	5,283	1,363
Hepatitis	137,828	38
Hepatitis A	1,142	0
Hepatitis B	110,385	32
Hepatitis C	22,613	4
Hepatitis D	31	0
Hepatitis E	2,797	2
Other hepatitis	860	0
Poliomyelitis	0	0
Human infection with H5N1 virus	0	0
Measles	69	0
Epidemic hemorrhagic fever	510	2
Rabies*	17	21
Japanese encephalitis	0	0
Dengue	4	0
Anthrax	19	0
Dysentery	3,945	1
Tuberculosis	80,548	117
Typhoid fever and paratyphoid fever	522	0
Meningococcal meningitis	3	1
Pertussis	308	0
Diphtheria	0	0
Neonatal tetanus	1	0
Scarlet fever	2,790	0
Brucellosis	7,848	1
Gonorrhea	10,874	0
Syphilis	49,113	4
Leptospirosis	3	0
Schistosomiasis	6	0
Malaria	74	0
Human infection with H7N9 virus	0	0
COVID-19†	454	0
Influenza	31,535	0
Mumps	11,501	0

Continued

Diseases	Cases	Deaths
Rubella	107	0
Acute hemorrhagic conjunctivitis	2,808	0
Leprosy	34	0
Typhus	105	0
Kala azar	27	0
Echinococcosis	304	0
Filariasis	0	0
Infectious diarrhea[§]	110,751	0
Hand, foot, and mouth disease	144,167	1
Total	**601,558**	**1,549**

[*] Of the 21 reported death cases of rabies, there were 10 reported in April, the other were reported previously.
[†] The data were extracted from the website of the National Health Commission of the People's Republic of China.
[§] Infectious diarrhea excludes cholera, dysentery, typhoid fever and paratyphoid fever.
The number of cases and cause-specific deaths referred to data recorded in National Notifiable Disease Reporting System (NNDRS) in China, which includes both clinically-diagnosed cases and laboratory-confirmed cases. Only reported cases of the 31 provincial-level administrative divisions in the mainland of China are included in the table, whereas data of Hong Kong Special Administrative Region, Macau Special Administrative Region, and Taiwan, China are not included. Monthly statistics were calculated without annual verification, which is usually conducted in February of the next year for de-duplication and verification of reported cases in annual statistics. Therefore, 12-month cases could not be added together directly to calculate the cumulative cases because the individual information might be verified via NNDRS according to information verification or field investigations by local CDCs.

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