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Cover Photo: Nucleic acid sampling in the rain in Guangzhou City, in the early morning of May 26, 2021 (photo adapted from Chinanews.com).

Preplanned Studies

Perception of the COVID-19 Epidemic and Acceptance of Vaccination Among Healthcare Workers Prior to Vaccine Licensure — Beijing Municipality, China, May–July 2020

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Summary

What is already known about this topic?

The coronavirus disease 2019 (COVID-19) vaccine development has been progressing, but acceptance of the new vaccines by healthcare workers (HCWs) was not well known prior to approval of COVID-19 vaccines in China.

What is added by this report?

This study found that before vaccine approval, Beijing HCWs expressed moderate willingness to get vaccinated. Factors positively influencing willingness included free vaccination and belief that the vaccine had been fully evaluated. A negatively influencing factor was presence of an underlying disease. Trust in vaccines, in general, was positively associated with willingness to get new vaccines.

What are the implications for public health practice?

COVID-19 vaccines should be provided at no cost to HCWs. Effective measures should be taken to enhance the acceptance of COVID-19 vaccination among HCWs in China.

The coronavirus disease 2019 (COVID-19) vaccines are expected to be widely used, but awareness and acceptance of the new COVID-19 vaccines by healthcare workers (HCWs) was not well known prior to approval by China's vaccine regulatory authority. The research conducted a cross-sectional survey in Beijing to assess HCWs' perceptions of the COVID-19 epidemic and attitudes towards vaccination before COVID-19 vaccines were approved. Multivariate analyses were used to evaluate factors associated with willingness to get vaccinated. A total of 8,040 HCWs were recruited; 67.1% reported they would get vaccinated, while the rest were unsure or indicated they would not get vaccinated. Factors associated with willingness to get vaccinated included the epidemic situation and its prognosis, perception of disease severity, and perceived risk of getting infected. Multivariate analyses found two factors strongly associated with willingness, "wanting the vaccine to be free of charge" (OR: 5.78, 95% CI: 5.05–6.60, $P<0.001$) and "belief that the vaccine was fully evaluated prior to licensure" (OR: 4.45, 95% CI: 3.81–5.20, $P<0.001$). One factor, "presence of an underlying disease" was found to be negatively associated with willingness (OR: 0.74, 95% CI: 0.61–0.90, $P<0.001$). The results supported a free vaccination policy and use of effective measures to remove barriers and convey accurate information about COVID-19 vaccines to enhance acceptance of the vaccines among HCWs in China.

The COVID-19 pandemic, caused by the COVID-19 virus also known as SARS-CoV-2, has resulted in global public health and economic crises (*1*). The general consensus is that successful vaccines should be developed to reduce morbidity and mortality caused by the disease (*2*). Many countries have been promoting vaccine research and achieving landmark results over the past months (*3*). Several vaccines completed Phase III clinical trials and have been put into extensive use.

Based on previous experience, it is highly likely that HCWs will be recommended as a priority population for vaccination. Experience has shown that even if vaccines are successfully developed, the acceptance may not be ideal (*4*). In China, where non-pharmacological interventions (*5*) have been strictly implemented and the epidemic effectively controlled, awareness and acceptance by HCWs of the new vaccines are not well known. This study conducted a cross-sectional survey in Beijing to provide a reference for formulating rational vaccination strategies.

The setting was 6 (Chaoyang, Fengtai, Changping, Daxing, Miyun, and Huairou) of the 16 districts in Beijing. Overall, ten hospitals, including two Level III general hospitals, two Level II general hospitals, and six Level I hospitals or communities health centers were selected in each district by a systematic sampling method. These hospitals were responsible for diagnosis and treatment of COVID-19 cases, community population screening, and nucleic acid sampling during the epidemic. All doctors, nurses, and technicians in high-risk departments/units were included. In non-high-risk departments, at least five doctors and five nurses were included, unless there were fewer than five doctors or nurses, in which case all were included.

The investigation began in early May 2020 and ended in mid-July 2020 (prior to emergency use authorization of any COVID-19 vaccine in China). An anonymous questionnaire was administered through a WeChat App. Questions included demographic characteristics, perceptions of risk towards the COVID-19 epidemic and severity of the disease, attitudes towards COVID-19 vaccination, and past vaccination history. Five-point Likert scales were used, and responses were classified into three categories — positive, negative, and uncertain. The research implemented quality control measures to ensure achieving target numbers of respondents.

Univariate analysis included frequency and ratio calculations and Pearson's chi-squared test for differences. Multivariate stepwise logistic regression was used to evaluate factors associated with intention to accept vaccination. All variables significant at the $P<0.1$ level in univariate logistic regression were included in multivariable stepwise logistic regression analyses. Odds ratios and 95% confidence intervals were calculated. Alpha was set at 0.05. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS/PASW, version 19.0, SPSS Inc, Chicago, IL, USA.).

A total of 8,040 HCWs participated in the survey; 3,844 (47.8%) were nurses; 2,836 (35.3%) were doctors; and 1,360 (16.9%) were technicians. Most (90.4%) respondents were less than 50 years old and most were female (80.4%); 70.3% had participated in prevention and control of the COVID-19 epidemic; 34.4% came from departments directly involved in diagnosis and treatment of COVID-19 patients; 35.1% reported having received other vaccines in the past three years; and 10.9% reported presence of an underlying disease.

Most respondents considered that consequences of COVID-19 infection were "serious", and 80.1% perceived they might become infected by the virus; 57.5% indicated that they were at greater risk of COVID-19 virus infection than others. Nearly half were unsure whether the outbreak would come back and thought the global epidemic would last a long time; 67.6% agreed that the epidemic could be prevented by vaccination, and a slightly lower proportion believed in the safety and effectiveness of the vaccine; 73.0% reported their life had been seriously disturbed by the epidemic in the past months; 43.6% estimated life and work would continue to be disturbed in the next six months (Table 1).

Respondents believed more in professional staff advice (94.1%) compared with statements from media (80.4%); 80.0% of HCWs were convinced the vaccine had been fully evaluated in clinical trials, and 77.4% wanted the vaccine to be free of charge; 67.1% of the respondents reported they would get vaccinated, while 7.9% said they would not, and 25.0% were unsure. The percentage of respondents who would advise family members to get vaccinated (68.2%) was similar to their own willingness to be vaccinated; however, fewer (61.9%) were willing to vaccinate their children. Among willing respondents, vaccination campaigns organized by their hospital (75.3%) were more acceptable than vaccination offered by community clinics (24.7%). Doctors, nurses, and technicians answered questions similarly (Table 2).

Results of univariate logistic regression of intention to accept COVID-19 vaccination and related variables are shown in Table 3. In multiple logistic regression models, positive factors significantly associated with intention to get vaccinated included "received other vaccines in the past three years," "received seasonal influenza vaccine," agreed with "suffering from COVID-19 virus infection is serious," "China's epidemic will come back," "the global epidemic will last for a long time," "COVID-19 can be prevented by vaccination", "the vaccine is safe," and "the vaccine is effective." Overall, two factors showed stronger positive associations — "wanting the vaccine to be free of charge" (OR: 5.78, 95% CI: 5.05–6.60, $P<0.001$) and "believing the vaccines approved for license have been fully evaluated" (OR: 4.45, 95% CI: 3.81–5.20, $P<0.001$); one factor was negatively associated — "presence of an underlying disease" (OR: 0.74, 95% CI: 0.61–0.90, $P<0.001$). Gender, age, occupational cohort, ward type, hospital level, academic degree, salary, participation in prevention and control of the epidemic, and perception of infection risk were not associated with intention to be vaccinated.

DISCUSSION

This study, which was conducted before completion of Phase III vaccine clinical trials, found that HCWs in Beijing were moderately willing to accept COVID-19 vaccination and that their willingness was strongly associated with perception of whether the vaccine is free and safe. Our results supported implementation of

TABLE 1. Healthcare worker perceptions of the COVID-19 epidemic by occupation category, Beijing Municipality, China.

Question	Total, n=8,040 (%)	Doctors, n=2,836 (%)	Nurses, n=3,844 (%)	Technicians, n=1,360 (%)	*P* value*
Q1 Is suffering from SARS-CoV-2 infection serious?					
Not serious	33(0.4)	14(0.5)	10(0.3)	9(0.7)	<0.001
Little serious	307(3.8)	176(6.2)	95(2.5)	36(2.6)	
Serious	7,700(95.8)	2,646(93.3)	3,739(97.3)	1,315(96.7)	
Q2 Are you likely to be infected by SARS-CoV-2?					
Unlikely	2,135(26.6)	612(21.6)	1,000(26.0)	523(38.5)	<0.001
Likely	4,382(54.5)	1,646(58.0)	2,094(54.5)	642(47.2)	
Very likely	1,523(18.9)	578(20.4)	750(19.5)	195(14.3)	
Q3 Are you at greater risk of SARS-CoV-2 infection than other people?					
Agree	4,627(57.5)	1,815(64.0)	2,277(59.2)	535(39.3)	<0.001
Disagree	1,353(16.8)	480(16.9)	542(14.1)	331(24.3)	
Unsure	2,060(25.6)	541(19.1)	1,025(26.7)	494(36.3)	
Q4 If you were infected by SARS-CoV-2, do you think you will suffer from more serious symptoms than others?					
Agree	1,247(15.5)	420(14.8)	643(16.7)	184(13.5)	0.004
Disagree	2,034(25.3)	759(26.8)	912(23.7)	363(26.7)	
Unsure	59.2(59.2)	1,657(58.4)	2,289(59.5)	813(59.8)	
Q5 Do you think China's COVID-19 epidemic will come back?					
Agree	1,850(23.0)	788(27.8)	850(22.1)	212(15.6)	<0.001
Disagree	2,144(26.7)	726(25.6)	951(24.7)	467(34.3)	
Unsure	4,046(50.3)	1,322(46.6)	2,043(53.1)	681(50.1)	
Q6 Do you think the global COVID-19 epidemic will last for a long time?					
Agree	3,996(49.7)	1,679(59.2)	1,738(45.2)	579(42.6)	<0.001
Disagree	1,141(14.2)	378(13.3)	539(14.0)	224(16.5)	
Unsure	2,903(36.1)	779(27.5)	1,567(40.8)	557(41.0)	
Q7 Do you think COVID-19 can be prevented by vaccination?					
Agree	5,439(67.6)	1,976(69.7)	2,556(66.5)	907(66.7)	<0.001
Disagree	450(5.6)	181(6.4)	208(5.4)	61(4.5)	
Unsure	2,151(26.8)	679(23.9)	1,080(28.1)	392(28.8)	
Q8 Do you think COVID-19 vaccines are safe?					
Agree	4,929(61.3)	1,727(60.9)	2,363(61.5)	839(61.7)	0.902
Disagree	101(1.3)	34(1.2)	47(1.2)	20(1.5)	
Unsure	3,010(37.4)	1,075(37.9)	1,434(37.3)	501(36.8)	
Q9 Do you think COVID-19 vaccines are effective?					
Agree	5,024(62.5)	1,761(62.1)	2,401(62.5)	862(63.4)	0.213
Disagree	48(0.6)	24(0.8)	20(0.5)	4(0.3)	
Unsure	2,968(36.9)	1,051(37.1)	1,423(37.0)	494(36.3)	
Q10 How disrupted has your work and life been in the past three months due to the epidemic?					
Not serious	253(3.1)	62(2.2)	137(3.6)	54(4.0)	<0.001
Little serious	1,921(23.9)	588(20.7)	1,003(26.1)	330(24.3)	
Serious	5,866(73.0)	2,186(77.1)	2,704(70.3)	976(71.8)	
Q11 In the next period of time (six months), how much do you expect your work and life to be disrupted by the epidemic?					
Not serious	792(9.9)	269(9.5)	377(9.8)	146(10.7)	0.638
Little serious	3,746(46.6)	1,308(46.1)	1,802(46.9)	636(46.8)	
Serious	3,502(43.6)	1,259(44.4)	1,665(43.3)	578(42.5)	

* χ^2 test.

TABLE 2. Healthcare worker attitudes toward COVID-19 vaccination by occupation category, Beijing Municipality, China.

Questions	Total, n=8,040 (%)	Doctors, n=2,836 (%)	Nurses, n=3,844 (%)	Technicians, n=1,360 (%)	*P* value*
Q1 Do you trust the official statements from the media?					
Believe	6,462(80.4)	2,385(84.1)	2,983(77.6)	1,094(80.4)	<0.001
Disbelieve	319(4.0)	99(3.5)	171(4.4)	49(3.6)	
Unsure	1,259(15.7)	352(12.4)	690(18.0)	217(16.0)	
Q2 Do you trust professional staff advice?					
Believe	7,563(94.1)	2,663(93.9)	3,634(94.5)	1,266(93.1)	0.266
Disbelieve	31(0.4)	13(0.5)	14(0.4)	4(0.3)	
Unsure	446(5.5)	160(5.6)	196(5.1)	90(6.6)	
Q3 If the COVID-19 vaccine is approved for licensure, do you want it to be free of charge?					
Yes	6,221(77.4)	2,125(74.9)	3,043(79.2)	1,053(77.4)	<0.001
No	293(3.6)	127(4.5)	115(3.0)	51(3.8)	
Either is OK	1,526(19.0)	584(20.6)	686(17.8)	256(18.8)	
Q4 Do you believe that COVID-19 vaccine approved for licensure will have been fully evaluated in clinical trials?					
Believe	6,431(80.0)	2,220(78.3)	3,118(81.1)	1,093(80.4)	<0.001
Disbelieve	144(1.8)	75(2.6)	49(1.3)	20(1.5)	
Unsure	1,465(18.2)	541(19.1)	677(17.6)	247(18.2)	
Q5 Will you get vaccinated with a COVID-19 vaccine?					
Yes	5,395(67.1)	1,849(65.2)	2,636(68.6)	910(66.9)	<0.001
No	632(7.9)	269(9.5)	251(6.5)	112(8.2)	
Unsure	2,013(25.0)	718(25.3)	957(24.9)	338(24.9)	
Q6 Where would you like to get the COVID-19 vaccine?†					
Community vaccination clinic	1,331(24.7)	478(25.9)	570(21.6)	283(31.1)	<0.001
Vaccination campaign organized by hospital	4,064(75.3)	1,371(74.1)	2,066(78.4)	627(68.9)	
Q7 Will you advise your family members to get the COVID-19 vaccine?					
Yes	5,486(68.2)	1,857(65.5)	2,682(69.8)	947(69.6)	0.001
No	514(6.4)	213(7.5)	214(5.6)	87(6.4)	
Unsure	2,040(25.4)	766(27.0)	948(24.7)	326(24.0)	
Q8 Will you take your children to get the COVID-19 vaccine?§					
Yes	2,643(61.9)	995(59.5)	1,221(62.3)	427(67.0)	0.02
No	359(8.4)	154(9.2)	159(8.1)	46(7.2)	
Unsure	1,267(29.7)	523(31.3)	580(29.6)	164(25.7)	
Q9 Who do find most trustworthy for offering COVID-19 vaccine information (multiple choice)?					
Official media	6,862(85.3)	2,379(83.9)	3,346(87.0)	1,137(83.6)	<0.001
Medical specialist	7,134(88.7)	2,427(85.6)	3,511(91.3)	1,196(87.9)	<0.001
Relatives and friends	317(3.9)	76(2.7)	155(4.0)	86(6.3)	<0.001
Colleagues	415(5.2)	96(3.4)	243(6.3)	76(5.6)	<0.001
Medical literature	4,786(59.5)	1,844(65.0)	2,282(59.4)	660(48.5)	<0.001
Online media	492(6.1)	105(3.7)	264(6.9)	123(9.0)	<0.001

* χ^2 test;

† only for those who are willing to be vaccinated;

§ only for parents with children under 18 years old.

TABLE 3. Multiple logistic regression model for healthcare worker intention to accept COVID-19 vaccination, Beijing Municipality, China.*

Variable	Value	Univariate logistic regression model		Multiple logistic regression model	
		Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Gender	Female	Reference			
	Male	1.07(0.95–1.20)	0.279		
Age group	<40 years old	Reference		Reference	
	≥40 years old	0.82(0.74–0.91)	<0.001	0.90(0.77–1.06)	0.197
Occupational cohort (three largest categories)	Doctors	0.88(0.80–0.97)	0.007	1.06(0.86–1.30)	0.617
	Nurses	1.14(1.04–1.25	0.007	1.01(0.84–1.22)	0.883
	Technicians and others	0.99(0.87–1.12)	0.87		
Ward type	Other	Reference			
	COVID-19 related department	0.99(0.80–1.09)	0.802		
Hospital level	Level I	0.99(0.90–1.10)	0.911		
	Level II	1.21(1.04–1.35)	<0.001		
	Level III	0.85(0.78–0.94)	0.001	1.04(0.918–1.179)	0.538
Academic degree	Junior college and below	Reference	0.001	Reference	
	Undergraduate	1.82(1.33–2.50)	<0.001	1.24(0.80–1.94)	0.34
	Masters	1.37(1.00–1.87)	0.048	0.97(0.64–1.47)	0.877
	Doctor or above	1.19(0.86–1.66)	0.296	0.95(0.62–1.45)	0.801
Salary	Less than 5,000 CNY	Reference		Reference	
	5,000–9,999 CNY	1.74(1.06–2.85)	0.029	1.06(0.54–2.06)	0.874
	10,000–19,999 CNY	1.42(0.87–2.31)	0.163	0.99(0.52–1.91)	0.98
	More than 20,000 CNY	1.30(0.78–2.14)	0.314	1.13(0.59–2.20)	0.709
Professional ranks and titles	No title	Reference		Reference	
	Junior	1.62(1.29–2.04)	<0.001	1.21(0.85–1.72)	0.302
	Intermediate	1.45(1.24–1.69)	<0.001	1.30(1.01–1.69)	0.044
	Senior	1.03(0.88–1.21)	0.723	0.88(0.71–1.12)	0.279
Underlying disease	No	Reference	<0.001	Reference	
	Yes	0.71(0.62–0.82)	<0.001	0.74(0.61–0.90)	0.002
Participated in the prevention and control of epidemic	No	Reference		Reference	
	Yes	0.87(0.78–0.96)	0.005	1.08(0.95–1.23)	0.232
Received other vaccines in the past 3 years	No	Reference	<0.001	Reference	
	Yes	1.69(1.53–1.87)	<0.001	1.28(1.05–1.56)	0.015
Received seasonal influenza vaccine	No	Reference		Reference	
	Yes	1.85(1.65–2.08)	<0.001	1.43(1.15–1.80)	0.002
Perception Q1 answer	Not serious and little serious	Reference	<0.001	Reference	
	Serious	1.75(1.41–2.18)	<0.001	1.34(1.01–1.79)	0.046
Perception Q2 answer	Unlikely	Reference		Reference	
	Likely and Very likely	1.12(1.01–1.25)	0.029	1.14(0.99–1.31)	0.074
Perception Q3 answer	Disagree and unsure	Reference		Reference	
	Agree	1.21(1.10–1.32)	<0.001	1.06(0.93–1.21)	0.363
Perception Q4 answer	Disagree and unsure	Reference		Reference	
	Agree	1.16(1.02–1.32)	0.029	1.07(0.90–1.27)	0.463

TABLE 3. (Continued)

Variable	Value	Univariate logistic regression model		Multiple logistic regression model	
		Odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Perception Q5 answer	Disagree and unsure	Reference		Reference	
	Agree	1.13(1.01–1.26)	0.034	1.33(1.13–1.56)	<0.001
Perception Q6 answer	Disagree and unsure	Reference		Reference	
	Agree	1.32(1.20–1.45)	<0.001	1.19(1.05–1.36)	0.008
Perception Q7 answer	Disagree and unsure	Reference		Reference	
	Agree	4.40(3.98–4.87)	<0.001	1.74(1.52–2.01)	<0.001
Perception Q8 answer	Disagree and unsure	Reference		Reference	
	Agree	5.60(5.06–6.19)	<0.001	1.91(1.61–2.27)	<0.001
Perception Q9 answer	Disagree and unsure	Reference		Reference	
	Agree	5.29(4.78–5.85)	<0.001	1.38(1.16–1.65)	<0.001
Perception Q10 answer	Not serious and little serious	Reference		Reference	
	Serious	1.11(1.00–1.23)	0.049	1.04(0.91–1.19)	0.583
Perception Q11 answer	Not serious and little serious	Reference			
	Serious	1.07(0.98–1.18)	0.137		
Attitudes Q1 answer	Disbelieve and unsure	Reference		Reference	
	Believe	2.90(2.59–3.24)	<0.001	1.23(1.04–1.44)	0.015
Attitude Q2 answer	Disbelieve and unsure	Reference		Reference	
	Believe	6.33(5.13–7.80)	<0.001	1.24(0.94–1.65)	0.133
Attitudes Q3 answer	No and either is OK	Reference		Reference	
	Yes	8.12(7.23–9.13)	<0.001	5.78(5.05–6.60)	<0.001
Attitudes Q4 answer	Disbelieve and unsure	Reference		Reference	
	Believe	9.59(8.46–10.88)	<0.001	4.45(3.81–5.20)	<0.001

*: Regression analyses were performed on 8,040 individuals who answered the question about their intention to get vaccinated. For the dependent variable “accept COVID-19 vaccination,” answer “Yes” is assigned as 1, answer “No” or “Unsure” is assigned as 0. If the independent variable is an unordered categorical variable, such as “Occupational cohort” and “Hospital level,” it is assigned to be a dummy variable.

a policy of free vaccination and removal of barriers to vaccination, and conveyance of accurate information through appropriate channels to further enhance awareness and improve acceptance of COVID-19 vaccination of HCWs.

By the end of 2020, COVID-19 epidemic in China had gone through several stages: prevention and control of outbreaks in Wuhan City and Hubei Province; prevention and control of overseas importation-associated cases; and control of local outbreaks in Beijing, Dalian, and Urumqi. We conducted our investigation in Beijing and found that one-third of HCWs would not get vaccinated or were unsure of whether they would get vaccinated. This finding is particularly surprising in a city facing continuous risk of COVID-19 and experiencing local outbreaks.

Two factors were strongly associated with intention to get vaccinated — a policy of free vaccination and a belief that approved vaccines have been fully evaluated. Other positively associated factors included the epidemic situation, disease severity, self-risk of infection, and the disease being preventable by vaccine. These factors make common sense and are logical. Previous vaccination with influenza or other vaccines can be interpreted as a high degree of trust in vaccines. Concerns about the safety and effectiveness of vaccines found in this study were similar to the factors reported in pandemic influenza A (H1N1) vaccine studies (*6*–*8*).

A factor negatively associated with willingness to get vaccinated was presence of underlying disease; the association was not strong but is noteworthy. People with an underlying disease are usually a priority group for vaccination — for example, for influenza vaccination. Some countries recommend that people with underlying diseases such as controlled hypertension and diabetes receive COVID-19 vaccination. Perhaps due to confidence in the effectiveness of non-pharmacological interventions, Beijing HCWs who had underlying diseases tended to be more cautious - a finding worthy of further study.

A systematic review of the willingness of HCWs to receive pandemic influenza A (H1N1) vaccination in 2009 found that willingness ranged from 13% to 89% by country and stage of the pandemic and that ultimate vaccination rates were lower than predicted (*4*). The main reason for lower than predicted uptake was that perception of the seriousness of the disease less than the expected seriousness (*9*). Under Beijing's free and voluntary influenza A (H1N1) vaccination strategy, coverage among HCWs was 71%, which was considerably higher than coverage in the general population (12.6%) (*10*).

HCWs are a high-risk population for infection and potentially can serve as transmission bridges for nosocomial infection. HCWs are also important professionals for recommending vaccines to the general population. Measures should be taken to improve vaccine acceptance. Results of Phase III clinical trials and post-licensure studies should be published in peer-reviewed journals to maintain openness and transparency; evidence-based evaluations should be conducted; technical guidelines from China's National Immunization Advisory Committee and professional physician associations should be widely used to provide authoritative information. Accurate information should be transmitted to leaders of professional medical associations to mobilize providers to participate fully in the vaccination effort.

Since December 2020, China has been conducting COVID-19 vaccination in key populations that include HCWs. As of the publication of this article, the vaccination rate among HCWs in Beijing exceeded the acceptance rate predicted by this survey. In addition to the free vaccination policy, timely disclosures of clinical trials results, extensive publicity of academic research by the media, and highly credible medical authorities leading the vaccination effort played important, positive roles and provided confidence in the COVID-19 vaccines and vaccination efforts. A combination of repeated social mobilizations and multiple, readily accessible vaccination opportunities further encouraged individuals who were uncertain about vaccination to choose to be vaccinated.

The study was subject to at least two limitations. First, specialist hospitals, including traditional Chinese medical hospitals, children's hospitals, maternity hospitals, dental hospitals, and hospitals closed during the epidemic were not included in the survey. Second, for each hospital sampled, only high-risk departments/units, including emergency departments, fever clinics, respiratory system disease departments, intensive care units, medical imaging departments, and laboratory testing departments were required to be included in the study; other departments were not required to participate, and therefore participated less fully. Thus the rates of willingness to get vaccinated that we found in our survey only represent the sampled population and do not necessarily extend to all HCWs.

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Preplanned Studies

Integrated Approaches for COVID-19 Case Finding and Their Impact on Timeliness for Disease Containment — Changning District, Shanghai Municipality, China, January–July, 2020

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Summary

What is already known on this topic?

The demand for containing the virus and protecting the economy is high on the agenda of policymakers during the coronavirus disease 2019 (COVID-19) pandemic. Modelling studies indicated that highly effective contact tracing and case isolation were enough to contain the spread of COVID-19 at the early stages, but this has not been validated in real world contexts.

What is added by this report?

Integrated case finding approaches, including outpatient monitoring, exposed people quarantining, and contact tracing, effectively contained the spread of COVID-19 in a densely populated district in Shanghai Municipality, China. Active case-finding involving quarantine of exposed persons and contact tracing could reduce the time from symptom onset to COVID-19 diagnosis, thus reducing the risk of local transmission.

What are the implications for public health practice?

Active case-finding should be prioritized as an effective approach to minimize the risk of local transmission in future pandemics. Integrated COVID-19 case finding approaches applied in Shanghai may inform public health policy in other regions where strict lockdown is not applicable.

The new wave of coronavirus disease 2019 (COVID-19) has been threatening the global efforts on disease containment since late 2020. This study aimed to delineate the approaches for COVID-19 case finding in its early outbreak stage in a district of Shanghai Municipality, China, and to evaluate the impact of timeliness on COVID-19 containment. The records of case investigations in Changning District were retrospectively reviewed up to July 2020. Case-finding approaches for local transmission included outpatient monitoring, exposed people quarantining, and contact tracing. The paths of detection of all domestic COVID-19 cases in Changning District in 2020 were analyzed. Overall, 22 local COVID-19 cases were identified. From the 6,160 outpatient visits to designated fever clinics, 58 suspected cases were identified and 8 were subsequently confirmed. The number of people travelling to/from epidemic locations and quarantining within the district was 1,570. During the 14-day quarantine, 9 reported symptoms and 8 were confirmed. Of the 27 close contacts living in the district, 8 reported symptoms during quarantine, and 6 were confirmed. The median time from symptom onset to COVID-19 diagnosis was 6 and 2 days for outpatient monitoring and active case-finding (*P*=0.003), thus reducing the risk of local transmission. The effective containment in Shanghai may inform public health policy in other regions where strict lockdown is not applicable.

As a respiratory infectious disease, the spread of COVID-19 is influenced by human mobility, population density, and age structures (*1*). The Changning District of Shanghai possesses a population of nearly 690,000 and the population density is as high as around 18,000 per square kilometer. Apart from the high population density, it is also the home to the Hongqiao Integrated Transportation Hub, which handles a large volume of civil aviation, high-speed and interurban railways, long-distance passenger transportation, subways, ground buses, and taxis (*2*). As the forefront for COVID-19 containment in Shanghai, Changning District faces substantial threats.

Many regions in the world have moved into a period where the new wave of COVID-19 has been threatening the efforts on disease containment since late 2020. The demand for containing the virus and protecting the economy is high on the agenda for policymakers. However, there are few studies yet to help us understand what works, what is necessary, what is sufficient, and what is too much. Modelling studies showed that highly effective contact tracing and household quarantine were enough to achieve disease containment (*3–4*), but these studies need to be validated in real-world contexts.

This study was a secondary data analysis based on the records of COVID-19 case investigations in Changning District, Shanghai, from January 16 up to July 14 2020. Three case-finding approaches were applied simultaneously to rapidly identify COVID-19 cases from the district. The first approach was to strengthen outpatient monitoring. In Changning District, 5 fever clinics in 3 general hospitals, 1 traditional Chinese medicine hospital, and 1 community health center were designated for COVID-19 case finding. The second approach was to quarantine individuals with travel history to Hubei Province (within which Wuhan City is located) over the past 14 days since they were suspected to have possible exposure to COVID-19. The third approach was contact tracing for confirmed COVID-19 cases. The latter two approaches were collectively called active case finding. A 14-day home quarantine was required and recommended for all exposed people and identified close contacts. During quarantine, if an individual reported suspected symptoms, they were promptly transferred to a designated fever clinic for clinical examination. (Figure 1)

Quarantine data were collected from January 25 to February 27, 2020 since no local transmission was reported 2 weeks after the diagnosis of last local case, i.e., February 12, in Changning District. Information for individuals who visited designated fever clinics, suspected COVID-19 cases, and confirmed cases were extracted through medical records at the aforementioned 5 hospitals, from January 16 to February 27, 2020. Field epidemiological reports were obtained from Changning District Center for Disease Control and Prevention to extract epidemiological and laboratory data of confirmed cases and their close contacts. Mann-Whitney U test was applied to identify the difference on time from symptom onset to COVID-19 diagnosis between outpatient monitoring and active case-finding in IBM SPSS 22.0 (IBM Corp., Armonk, NY).

A total of 22 local COVID-19 cases and 19 imported cases were detected in Changning District up to July 14, 2020. Of the 22 local cases, 8 (36.4%) were detected by quarantining the people with Hubei Province travel history, 8 (36.4%) were found by outpatient monitoring at designated fever clinics, and 6 (27.3%) were identified by contact tracing (Figure 2). Of the 11 cases with travel history to Hubei Province, 4 arrived in Shanghai before the implementation of quarantine and were identified by outpatient monitoring. For those with close contacts with confirmed cases, 2 had suspected symptoms before their index cases confirmed with COVID-19, thus were found through other approaches rather than contact tracing.

From onset of symptoms to COVID-19 diagnosis, the median time for cases detected from outpatient monitoring, exposed people quarantining, and contact tracing was 6 days [Interquartile Range(IQR): 4–8], 2.5 days (IQR: 2–3) and 2 days (IQR: 1.5–3), respectively. Compared to outpatient monitoring, active case finding approaches significantly reduced the time from symptom onset to diagnosis (P=0.003).

Local COVID-19 cases detected by outpatient monitoring were interspersed between January 27 and February 9, 2020. The total number of outpatient visits to designated fever clinics was 6,160 from January 16 to February 27, and 58 were identified as suspected cases. As a result, 8 (13.8%) patients were confirmed with COVID-19, including one asymptomatic infection. The median duration from their first outpatient visit to diagnosis was 2.5 days (range, 0–10.0).

A total of 2,591 individuals reported themselves having a travel history to the Hubei Province over the past 14 days. Of them, 1,570 (60.6%) were quarantined in Changning District while the rest were quarantined in other districts of Shanghai. During the 14-day quarantine, 0.6% of them (9/1,570) reported fever, cough, diarrhea, or other symptoms, and 8 were confirmed as COVID-19 cases.

Overall, 6 (22.2%) cases were detected from the 27 close contacts who resided in Changning District, including one confirmed after 2 reverse-transcription polymerase chain reaction tests. During the 14-day quarantine, 6 (22.2%) of them reported fever and 3 were confirmed as COVID-19 cases. Another 2 (7.4%) close contacts reported diarrhea or other respiratory symptoms without fever and were subsequently confirmed as COVID-19 cases. One asymptomatic infection was confirmed in a 1-year-old child, who was the youngest COVID-19 case in Changning District. (Figure 3)

DISCUSSION

This study delineated the COVID-19 case finding approaches at the earliest outbreak stage in Changning District with regard to key time points and

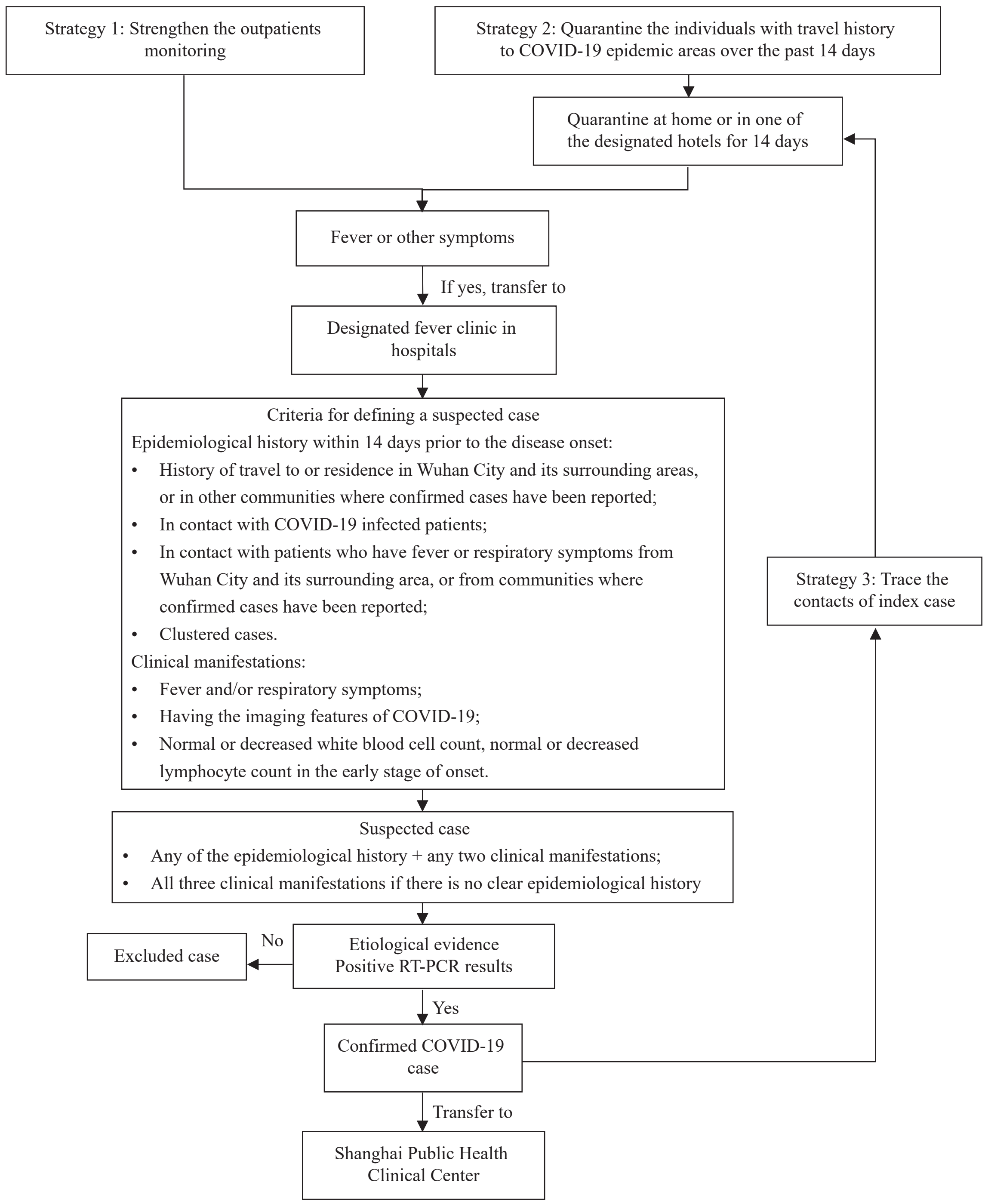

FIGURE 1. Flowchart for case finding approaches and case management of coronavirus disease 2019 (COVID-19) in Changning District, Shanghai Municipality.
Abbreviation: RT-PCR=reverse-transcription polymerase chain reaction.

epidemiological links. Compared to outpatient monitoring at designated fever clinics, active case-finding approaches, including quarantine of people with travel history to/from high-risk locations and contact tracing, significantly shortened the time from symptom onset to COVID-19 diagnosis, thereby reducing the risk of disease transmission in the population.

Experiences from the severe acute respiratory syndrome (SARS) epidemic suggested that the primary mode of SARS transmission was close contact with a symptomatic patient (*5–6*). As the pathogens for SARS and COVID-19 belong to the same coronaviridae family, it is reasonable to consider the close contacts of

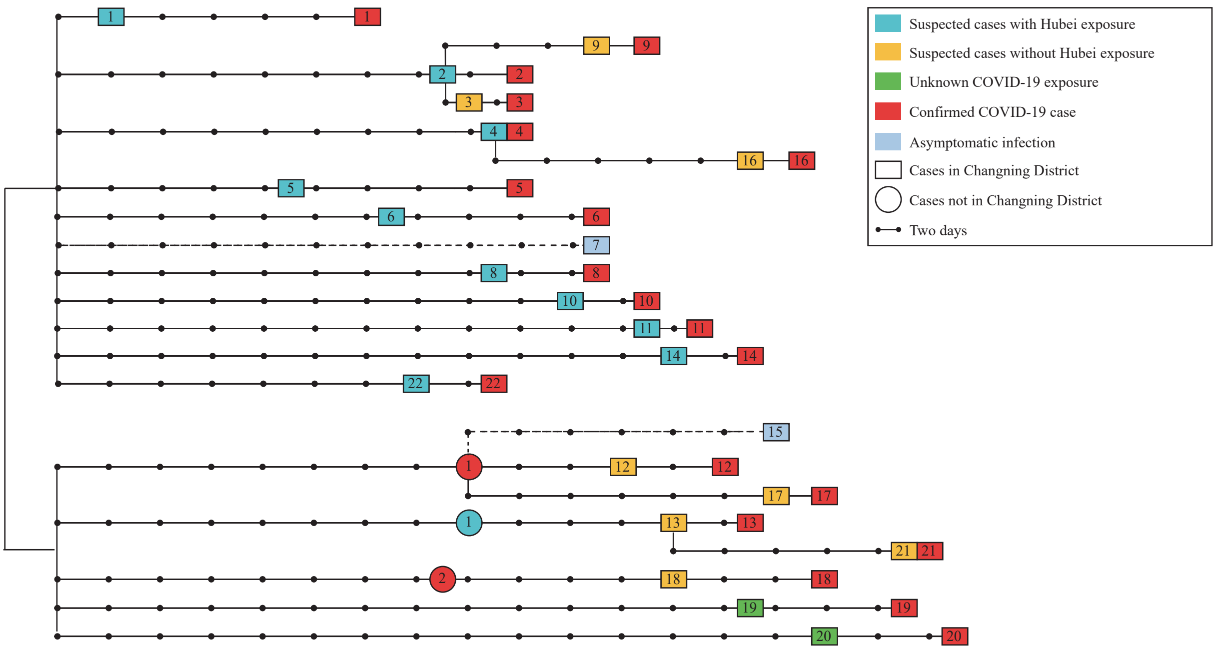

FIGURE 2. Epidemiological links of coronavirus disease 2019 (COVID-19) in Changning District, Shanghai Municipality.

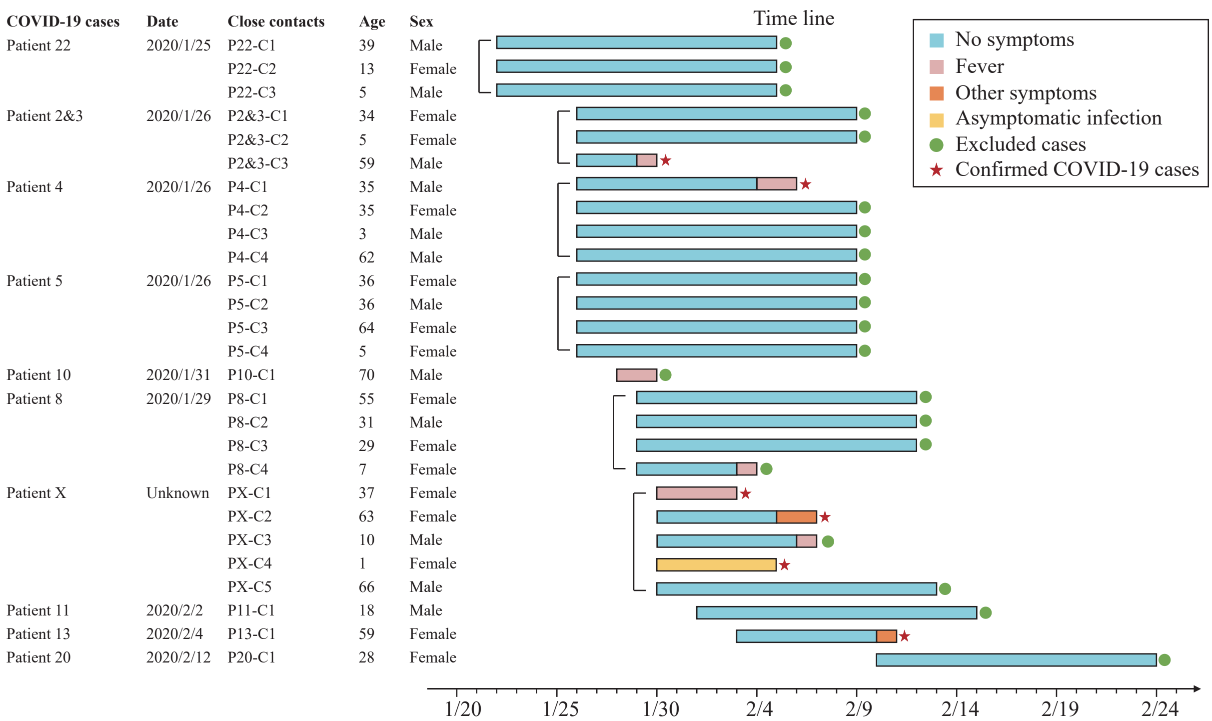

FIGURE 3. Contact tracing for confirmed coronavirus disease 2019 (COVID-19) cases in Changning District, Shanghai Municipality.

Note: Date of COVID-19 diagnosis was shown for each index cases. Patient X was detected in another district of Shanghai and thus lacked a COVID-19 diagnosis date. Excluded cases included those who completed 14-day quarantine without any symptoms and those who had suspected symptoms during quarantine but received negative reverse-transcription polymerase chain reaction results twice.

COVID-19 cases as a high-risk population for quarantine, especially with confirmed evidence on human-to-human transmission (*7–8*). In this study, 20.0% of close contacts were subsequently confirmed with COVID-19, supporting the high risk of infection in this population. It would be ideal to provide pathogenic testing for all identified close contacts, especially at the early stage of COVID-19 outbreak.

In this study, outpatient monitoring at designated fever clinics and quarantining people who had travelled to COVID-19 epidemic areas also played an important role in disease containment. Despite the requirement of a substantial amount of time and labor to implement quarantine, this approach effectively detected nearly one-third of COVID-19 cases. Another one-third of cases were detected by outpatient monitoring, although it was associated with a longer time from symptom onset to COVID-19 diagnosis. The unique strength of outpatient monitoring is its ability to identify early cases before quarantining exposed people and contact tracing are implemented. In addition, outpatient monitoring can provide additional assurance by catching patients who might have been missed by the active case-finding approaches.

This study was subject to some limitations. First, this study only had exposure and diagnosis information, and therefore, was unable to prove the epidemiological links between COVID-19 cases at the genomic level. Second, due to the presence of mild symptoms and asymptomatic infection, some COVID-19 cases might have been missed, resulting in under-ascertainment. However, since the last case was reported on February 12, there had been no new domestic cases detected since then, indicating that the case-finding approaches implemented in Changning District were probably effective to achieve disease containment.

In conclusion, contact tracing of confirmed COVID-19 cases was effective to find new cases. Compared to outpatient monitoring at designated fever clinics, active case-finding approaches significantly reduced the time from symptom onset to COVID-19 diagnosis, therefore reducing the risk of disease transmission. The case-finding approaches implemented in Changning District was effective in rapid COVID-19 containment and may help inform public health policy in other regions where strict lockdown is not applicable.

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Perspectives

Progress of Active Surveillance for Vaccine Safety in China

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Vaccination is one of the most cost-effective interventions for saving lives and promoting public health. The coronavirus disease 2019 (COVID-19) pandemic is providing a stark reminder of the importance and power of vaccines (*1*). However, vaccines can cause harm, and their rare safety concerns have increased in relative visibility as successful control and prevention of vaccine preventable diseases has diminished awareness of these diseases. Vaccine hesitancy — the reluctance or refusal to be vaccinated despite the accessibility of vaccines — has been called one of the top ten threats to global health (*2*). This threat has stalled or even reversed some progress in preventing disease through immunization. To address public concern and maintain confidence in vaccines, comprehensive and reliable evidence is crucial, including evidence from clinical trials, passive safety surveillance, and active safety surveillance (*3*). Among the methods used to monitor the safety of vaccines, active surveillance is the predominant means to discover and assess causal association between vaccines and adverse events. In this article, we briefly summarize policies, capabilities, and influences of active vaccine safety monitoring in China.

POLICIES FOR ACTIVE SURVEILLANCE

In 2019, the World Health Organization (WHO) Global Vaccine Safety Blueprint 2.0 initiated a Global Vaccine Safety Ecosystem and prioritized active surveillance and causality assessments for the next ten years (*4*). The WHO also upgraded evaluations of the National Regulatory Systems (NRS) with a new Global Benchmarking Tool, highlighting risk — benefit balance and active vigilance for vaccine safety concerns. Additionally, the first and overarching strategic priority in the new Immunization Agenda 2030 (IA2030) is to ensure that immunization programs are an essential part of primary healthcare and universal health coverage (*1*). A key focus of IA2030 is continuous monitoring of vaccine safety with effective responses to vaccine safety concerns.

In China in 2019, the Law on Drug Administration underwent a major revision that strengthened regulation of pharmacovigilance, market authorization holders (e.g., manufacturers), and market authorization application procedures. The Law on Vaccine Administration of China, enacted in 2019, stipulates strict management of vaccine safety by requiring whole-process, end-to-end supervision and a secure digital tracking system. To enforce these laws, the State Council of China launched a new campaign — Opinions of Comprehensively Strengthening the Capacity of Drug Supervision — that includes the construction and promotion of NRSs, digital supervision throughout the life cycles of vaccines, and scientific action planning for supervision. It is laudable that the "14th Five-Year Plan" of China expressly continues the national Expanded Program on Immunization and appeals to the health community to achieve IA2030 goals.

PROGRESS IN ACTIVE SURVEILLANCE

Active vaccine safety surveillance is the active monitoring of post-vaccination clinical manifestations of each dose administered in a defined population; it enables precise estimation of the incidence of adverse events relative to baseline levels and assessment of potential casual relationships (*5*). Given the shortcomings of passive surveillance, researchers began turning to electronic health data for monitoring vaccine safety starting in the late 1980s. A few countries established national active surveillance systems as integral parts of their immunization program. According to the characteristics of their electronic health data, these systems can be categorized into three groups: population-, hospital-, and vaccination-based systems.

Population-Based Active Surveillance

The Vaccine Safety Datalink (VSD) was the first large-scale population-based active surveillance (PBAS) system in the world. VSD has well-defined target populations that include vaccinated and unvaccinated persons with individual-level linking of comprehensive medical records to vaccination histories (*6*). In VSD, all essential information is available from Health Maintenance Organizations' records systems. Thus, the denominator of cohorts, vaccination statuses, and occurrences of clinical events are all captured through database linkages. In addition to VSD, in 2009, the United States developed another nationally-representative program, called for Post-Licensure Rapid Immunization Safety Monitoring program (PRISM), which used 9 immunization information systems and 4 national health insurers' data to cover 38 million individuals in active safety surveillance of influenza H1N1 pandemic vaccine (*7*).

In China, a study demonstrated that the regional health information platform (RHIP) of Ningbo City could actively monitor human papillomavirus (HPV) vaccine safety; however, due to low HPV vaccine coverage, the system was limited to hypothesis testing (*8*). In the future, strength-of-association analyses will be conducted for vaccines having high coverage levels among Ningbo infants, and, for vaccines with low coverage, by integrating data from multiple RHIPs to provide sufficient sample sizes for assessment of causal relationships. Fortunately, the number of RHIPs having similar capabilities as Ningbo's has increased to 38 cities this year. For methodology- and information-intensive PBAS analyses, active vaccine safety monitoring research organizations should offer maximum methodological support to regulatory departments-up to and including leading or assisting with specific studies, as VSD often does in the US.

Hospital-Based Active Surveillance

Due to limitations of enhanced passive surveillance, Canada determined in the 1980s that monitoring serious vaccination-related adverse events could be conducted at hospitals, and thus became a pioneer of hospital-based active surveillance (HBAS) for vaccine safety (*9*). However, at that time, it was not feasible to start open-ended monitoring of all events due to the tremendous workload and paucity of readily-available timely vaccination records. The project therefore initially targeted surveillance of acute neurological hospital admissions and discharges. Cases-only study designs were usually used to evaluate associations because data collection could be limited to cases of interest and their vaccination histories — both of which could be obtained using case report forms. Some studies proved to be alternatives to cohort designs, especially for high-coverage vaccines (*10*).

In China, a nested case-control study to assess risk of Guillain-Barre Syndrome (GBS) following influenza vaccination was conducted in 74 hospitals in Jiangsu Province; the study showed no association of GBS within the six months of vaccination (*11*). Some national hospital-based sentinel networks for active surveillance of influenza-like illness or adverse drug reactions (ADR) have existed for several years. It is commendable that the innovative China Hospital Pharmacovigilance System for ADR discovery uses intelligent search and reports assistance to promote efficiency and quality. In the future, these networks may become foundations for active vaccine safety surveillance, especially when records can be linked with individual-level immunization information system data.

Vaccination-Based Active Surveillance

Some projects have created an electronic vaccination follow-up system using email, text messages, or smartphone APPs to obtain potential adverse event reports following each dose of vaccine (*12*). Such a system can be considered a single-arm cohort study facilitated by novel information techniques for vaccination follow-up, or an active extension to passive vaccine safety surveillance augmenting data access for key stakeholders.

In China, cohort-based adverse event monitoring studies are widely used, especially for new vaccines like COVID-19 vaccines (*13*). These studies have clear advantages because they provide complete and valid vaccination records coupled with a full range of adverse events reporting — like clinical trials do. In developing and using these systems in the future, it will be essential to ensure sensitivity, data quality, and validity of captured events. For example, the efficiency of detecting rare, serious adverse events could be frustratingly low, challenging validity of estimates. Thus far, however, these systems play the basic role of signal detection, and few have clarified causal relationships between vaccines and rare or serious adverse events. However, these vaccination follow-up designs have only recently been developed and validated as good options for assessing associations in cohorts (*10*).

OPPORTUNITIES AND THE WAY FORWARD

It is imperative to establish robust national active vaccine safety surveillance in China, especially in an era of global attention to efficacy, adverse events, licensing, and roll-out of COVID-19 vaccines. Long-term success depends on sustained support from regulations, policies, and finance, as well as collaborative efforts of regulatory departments, research organizations, and data owners. Considering the potential of available databases and the merits of various methods, we believe that in China today, vaccination-based models can be used for signal detection, and population- and hospital-based models are more reliable and practical for evaluating causality.

Without doubt, active surveillance for vaccine safety in China can and will make a difference in global health. The entire world is becoming a community with a shared destiny in public health. China, as the world's largest country, would make a great contribution to global disease prevention by achieving all IA2030 goals. Evidence from active vaccine safety surveillance in China would not only boost confidence in vaccines around the world but also would support use of Chinese vaccines to further increase global vaccine availability and vaccination coverage. Therefore, with the goal of improving global public health, let us build upon lessons learned and set out on a course to make active vaccine safety surveillance a reality in China.

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Notes from the Field

Transmission Dynamics of an Outbreak of the COVID-19 Delta Variant B.1.617.2 — Guangdong Province, China, May–June 2021

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On May 21, 2021, a local case of coronavirus disease 2019 (COVID-19) was confirmed in a 75-year-old woman (experienced onset of symptoms on May 18) in Liwan District, Guangzhou City, Guangdong Province, China. The number of infections has increased in the following 10 days and led to 5 generations of transmission. As of June 23, a total of 167 locally transmitted cases related to this outbreak were observed in 4 cities (Guangzhou, Maoming, Foshan, and Zhanjiang) in Guangdong (Figure 1A). The cases identified have been found to share the same RNA sequence as the highly infectious Delta variant strain (B.1.617.2) which was first found in India (*1*).

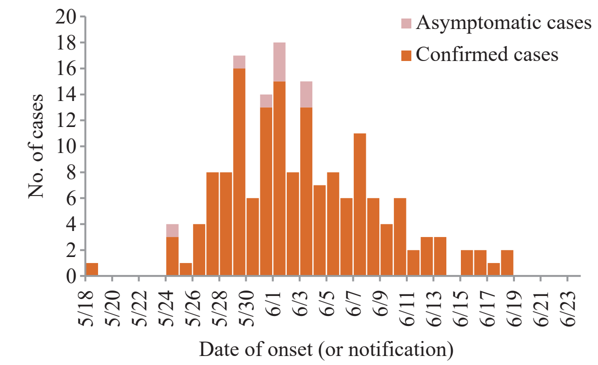
The rapid spread of the epidemic highlighted the high transmissibility of this variant strain. Based on the initial 68 infections belonging to 24 clusters that had a clear chain of transmission, we investigated the key transmission parameters including the incubation period (the period of time from infection to illness onset), the generation time (GT, the interval between infection of the primary case and secondary cases), and the serial interval (the interval between the onset of symptoms in a primary case and secondary cases). The result showed that the mean incubation period was 4.4 days [95% confidence interval (CI): 3.9–5.0] (Figure 1B), which was shorter than that reported by Li et al. (4.4 *vs.* 5.2) in Wuhan City, Hubei Province, China (*2*). The mean generation time was 2.9 days (95% CI: 2.4–3.3), which was much shorter than that reported by Hu et al. in Hunan Province (2.9 *vs.* 5.7) (*2*). The mean serial interval was 2.3 days (95% CI: 1.4–3.3), which was also shorter than that reported by previous reports (*2*–*3*), and 21.6% (11/51) of serial intervals were negative (Figure 1C). We observed that 64.7% (44/68) of transmission events occurred during the pre-symptomatic phase, which was higher than that reported by Hu et al. (64.7% *vs.* 59.2%) (*3*). The transmission parameters suggested that suppressing the rapid spread and hidden transmission of this mutant virus is of high priority.

Based on the data of the cases with illness onset (or notification) between May 18 and May 29, and the GT of 2.9 days, the basic reproductive number (R_0) was estimated, which was defined as the expected number of additional cases that one case will generate. The estimated R_0 (maximum likelihood method) was 3.2 (95% CI: 2.0–4.8), which was much higher than 2.2 from Li et al. (*2*). Based on the GT and R_0 estimated, the epidemic growth rate (r, which represents transmission rate of epidemic with the formula of $r=[R_0 -1]/GT$) for the early stage of the outbreak was estimated as approximately 0.76 per day, which was about 100% higher than findings from previous epidemic strains (*4*). This result was in line with the Finlay et al. report that the transmissibility of Delta variant was increased by 97% (95% CI: 76%–117%) (*5*).

We further estimated the effective reproduction number (R_t) as of June 23 (*6*). R_t was an indicator to measure transmission before and after the interventions (*7*). In this epidemic, the R_t increased from 3.0 to 3.5 from May 27 to May 29, then decreased after May 30, reached a value of 1 on June 6, and fluctuated near 1 from June 7 to June 15. The R_t was lower than 1 from June 16 (Figure 1D), and there were no new cases reported from June 19 to June 23. To respond to the unprecedented threat, Guangdong Province has taken a series of rigorous intervention measures including mass testing, active cases finding, community management, travel restrictions, and affected area lockdown to contain this outbreak. The evidence indicated that the public health measures taken by Guangdong have had an effect on the epidemic.

In conclusion, we observed that the transmission of this COVID-19 outbreak in Guangdong was faster and more severe than that of previous epidemics. Presently, the non-pharmaceutical interventions deployed against this epidemic have been working and should be sustained in the affected area until this epidemic is fully contained. Recently, several cases

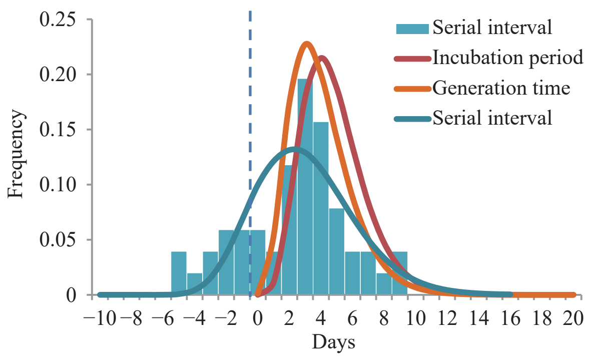
A



B

Transmission parameters	Mean	Median	SD	95% CI
Incubation period	4.4	4.0	1.9	3.9–5.0
Generation time	2.9	3.0	1.9	2.4–3.3
Serial interval	2.3	3.0	3.4	1.4–3.3

C



D

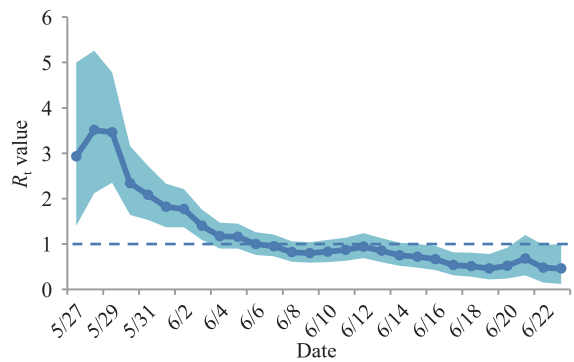


FIGURE 1. The key transmission parameters and transmission dynamics of an outbreak of the COVID-19 delta variant B.1.617.2 in Guangdong Province, China, 2021. (A) The epidemic curve of 167 COVID-19 cases in Guangdong Province — China, May and June, 2021; (B) The mean, median, standard deviation (SD), and the 95% confidence interval (CI) of the incubation period, generation time, and serial interval; (C) The histogram of serial intervals, and the estimated distributions of the incubation period, generation time, and serial interval; (D) The effective reproduction number (R_t) of the ongoing COVID-19 epidemic in the scenarios of strict intervention measures have been implemented in Guangdong from May 27 to June 23, 2021.

Note: Distribution of the incubation period (the period of time from infection to illness onset) was estimated by log-normal distributions based on 47 confirmed cases that have a clear date of exposure and symptom onset. Distribution of the generation time (the interval between infection of the primary case and secondary cases) was estimated by gamma distributions based on 55 transmission pairs. Distribution of the serial interval (the interval between the onset of symptoms in a primary case and secondary cases) was estimated by gamma distributions based on 51 transmission pairs. In Figure 1C, the left of blue dotted line indicated serial intervals were negative, which means that the symptoms of the infectees precedes their infectors.

The daily number of reported COVID-19 cases from May 21 to June 23 and the generation time [mean: 2.9 days (SD: 1.9 days)] were used to estimate the effective reproduction number (R_t) and its 95% credible interval on each day via a 5-day moving average using the Bayesian framework. In Figure 1D, the blue dotted line indicates R_t=1, below which sustained transmission is unlikely so long as intervention measures are sustained, indicating that the outbreak is under control.

R software (version 3.6.0, R Core Team, Austria) was used for the data analyses, "*fitdistrplus*" package was used for fitting the distributions, and "*EpiEstim*" package was used for estimating R_t.

infected by other Delta variant were observed in Shenzhen and Dongguan cities of Guangdong Province. The experience in Guangdong suggested that the emergence of variant strains would be a great threat for COVID-19 response in the scenarios of global pandemic. We should pay close attention to the prevalence of the variant strains, and non-pharmaceutical interventions should be maintained even after ongoing COVID-19 vaccination.

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Notes from the Field

Genome Characterization of the First Outbreak of COVID-19 Delta Variant B.1.617.2 — Guangzhou City, Guangdong Province, China, May 2021

Zhencui Li[1,2,&]; Kai Nie[3,&]; Kuibiao Li[4]; Yao Hu[1,2]; Yang Song[3]; Min Kang[1,2]; Meng Zhang[1,2]; Xiaoling Deng[1,2]; Jun Yuan[4]; Wenbo Xu[3,#]; Baisheng Li[1,2,#]

On May 20, 2021, 75-year-old female (Case A) went to a local hospital due to pharyngeal pain and low-grade fever in Liwan District, Guangzhou City, Guangdong Province. The oropharyngeal swab from Case A tested preliminarily positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/coronavirus disease 2019 (COVID-19) virus using a quantitative real-time reverse transcription polymerase chain reaction (RT-qPCR) method after a hospital visit. In the early morning of May 21, 2021, the re-collected specimens were confirmed to be positive for COVID-19 for this patient with RT-qPCR tests by Guangdong Provincial CDC and Guangzhou City CDC. Subsequently, Guangdong Province began immediately taking a series of rigorous intervention measures including social distancing, community management, and lockdown to contain this outbreak. A total of 4 cases were confirmed with COVID-19 infections between May 23 and May 26 (Table 1). These patients were transported immediately to the local designated treatment hospital for isolated treatment by ambulance after COVID-19 virus infection was confirmed.

The viral ribonucleic acid (RNA) was extracted directly from 200-μL swab samples with Viral RAN/DNA Mini Kit (Invitrogen, USA). High-throughput sequencing was performed for 5 COVID-19 virus samples using Illumina (USA) and MGI Tech Co., Shenzhen, China. Nucleotide (nt) and amino acid (AA) differences between the 5 virus genome sequences from this study and the reference sequence Wuhan-Hu-1 were analyzed using the programs BioEdit and online tool "Nextclade" (https://clades.nextstrain.org/) (*1*).

The 5 specimens from Case A, Case B, Case C, Case D, and Case E were tentatively designated as XG5138-Case A-GZ-2021-05-21, XG5370-Case B-GZ-2021-05-23, XG5571-Case C-MM-2021-05-24, XG5647-Case D-GZ-2021-05-26, and XG5645-Case E-GZ-2021-05-26, respectively, in this study. Compared with the reference genome sequence Wuhan-Hu-1 (*2–3*), the genome sequences coverage of these 5 strains were 99.89%, 99.85%, 99.86%, 99.86%, and 99.87%, respectively. Based on the "Pango lineages" rule, the 5 virus strains from this study were assigned to delta (B.1.617.2), which was also known as variant of

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

Case ID	Sample number	Gender	Age (years)	Report city	Date of first positive detection of COVID-19 virus	Ct value (ORF1ab/N) by RT-qPCR			
						Specimen type	Daan	Bojie	Mingde
Case A	XG5138-Case A-GZ-2021-05-21	Female	75	Guangzhou	May 21, 2021	Nasopharyngeal swab	17/16	N/A	18/21
						Oropharyngeal swab	20/19	N/A	18/21
Case B	XG5370-Case B-GZ-2021-05-23	Male	75	Guangzhou	May 23, 2021	Nasopharyngeal swab	21/22	N/A	26/26
						Oropharyngeal swab	21/21	N/A	23/23
Case C	XG5571-Case C-MM-2021-05-24	Female	47	Maoming	May 25, 2021	Nasopharyngeal swab	16/13	14/15	N/A
						Oropharyngeal swab	20/18	19/20	N/A
Case D	XG5647-Case D-GZ-2021-05-26	Male	11	Guangzhou	May 26, 2021	Nasopharyngeal swab	16/13	N/A	16/15
Case E	XG5645-Case E-GZ-2021-05-26	Female	73	Guangzhou	May 26, 2021	Nasopharyngeal swab	19/17	N/A	19/19

Note: N/A=not applicable.

Abbreviation: RT-qPCR=quantitative real-time reverse transcription PCR.

concern (VOC) Delta (Figure 1) (*4*–*6*).

Compared with the reference genome sequence Wuhan-Hu-1, 5 strains shared 35 nucleotide variation sites (G210T, C241T, C1191T, C1267T, C3037T, C5184T, T6023C, C9598T, C9891T, T11418C, T12946C, C14408T, G15451A, C16466T, C18176T, A20262G, A21137G, C21618G, G21987A, T22917G, C22995A, A23403G, C23604G, G24410A, G25088T, C25469T, A25562G, T26767C, T27638C, C27739T, C27752T, A28461G, G28881T, G29402T, and G29742T) and 7 deletion mutations (22029–22035, 28248–28254, and 28274). Except for the mutations above, another variation site (C27092T) was observed in genome of the strain XG5571-Case C-MM-2021-05-24, XG5647-Case D-GZ-2021-05-26, and XG5645-Case E-GZ-2021-05-26. XG5370-Case B-GZ-2021-05-23 had a unique variation site (T21673C), but not the C27092T variation.

By comparing deduced amino acid sequences, the 5 strains displayed 29 AA variation sites (M:I82T; N:D63G, R203M, D377Y; ORF1a:P309L, P1640L, Y1920H, A3209V, V3718A; ORF1b:P314L, G662S, P1000L, P1570L, K2557R; ORF3a:S26L, Q57R; ORF7a:V82A, L116F, T120I; ORF9b:T60A; S:T19R, G142D, R158G, L452R, T478K, D614G, P681R, D950N, and V1176F) and 4 deletion mutations (ORF8:D119del, F120del; S:F156del, and R157del).

The delta (B.1.617.2) was first identified in India in October 2020 and its spike protein had 9–10 characteristic mutations: T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, and

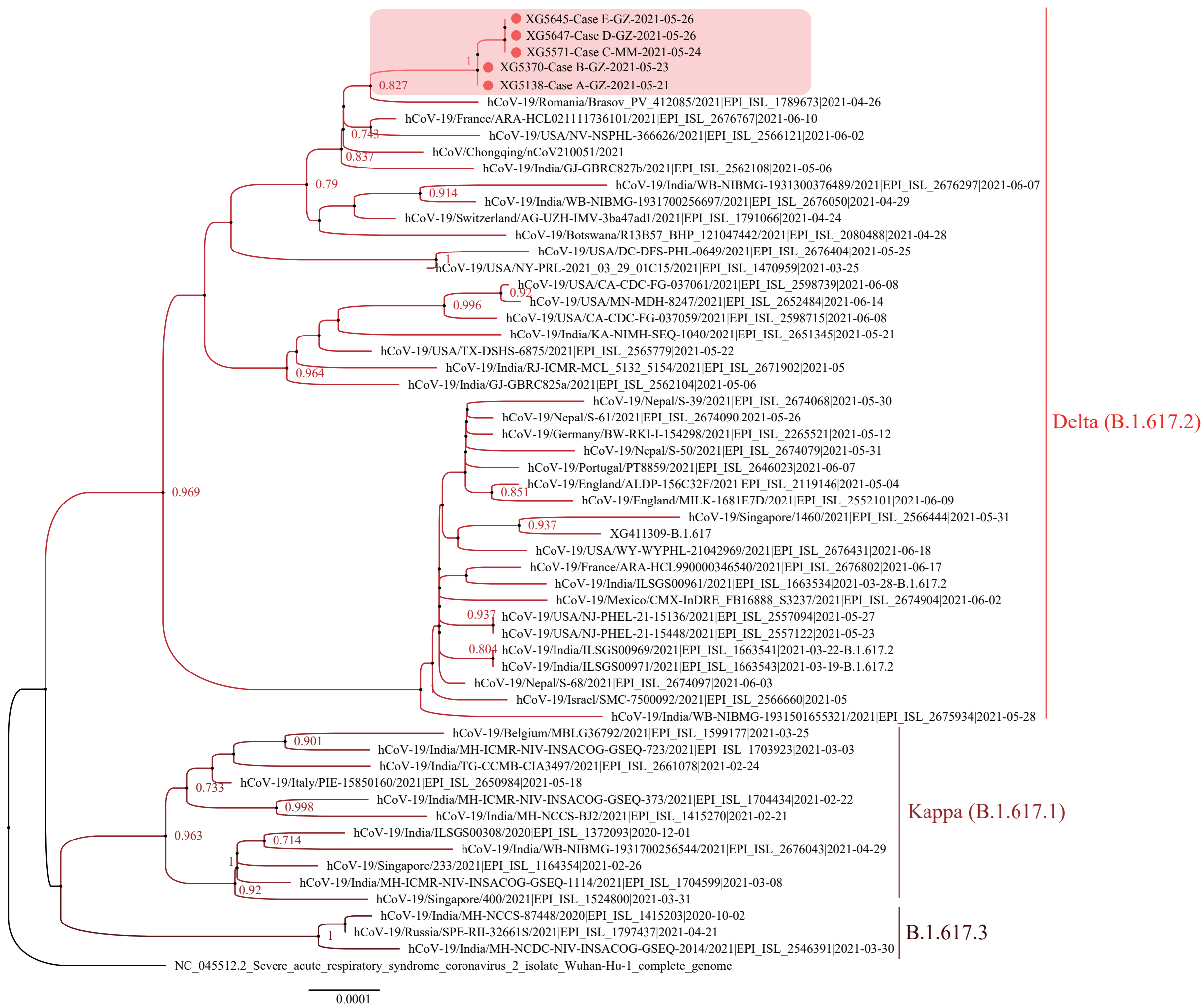

FIGURE 1. Neighbor-joining phylogenetic tree based on the whole-genome sequences of the delta (B.1.617.2) COVID-19 virus representative strains.

Note: The delta (B.1.617.2), kappa (B.1.617.1) and B.1.617.3 strains were marked on the right side. The five Guangzhou delta strains were indicated by red dots and highlighted by light red background. The tree was rooted using the Wuhan reference strain.

D950N (*4–5,7*). According to the current data of the World Health Organization (WHO), the delta (B.1.617.2) spread rapidly to 74 countries, areas, or territories (December 2019–June 8, 2021) (*5*). The epidemiological investigation showed that Case A was the index case and Case B (husband) was a close contact of Case A. Furthermore, Case C and Case E were at high risk of exposure due to Case A’ s activities (Case C as a waiter served Case A in a restaurant, and Case E went to same restaurant for dinner at the same time). Lastly, Case D was the grandson of Case E and was therefore a close contact. The whole gene sequencing results showed that Case C, Case D, and Case E added a common mutation site (C27092T) based on the sequence of Case A, and Case B possessed a new mutation site (T21673C) compared with Case A’s sequence.

This Guangzhou outbreak is the first local transmission caused by delta (B.1.617.2) in China. The transmissibility and pathogenicity of these mutant variants urgently need more attention.

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