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Preplanned Studies

Antibody Response to COVID-19 Virus — Heilongjiang Province and Gansu Province, China, 2020

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Summary

What is already known about this topic?

Coronavirus disease 2019 (COVID-19) has become a global pandemic, while the profile of antibody response against the COVID-19 virus has not been well clarified.

What is added by this report?

In this study, 210 serum samples from 160 confirmed COVID-19 cases with different disease severities were recruited. The IgM, IgA, IgG, and neutralizing antibodies (NAb) against COVID-19 virus were determined. Our findings indicated that four antibodies could be detectable at low levels within 2 weeks of disease onset, then rapidly increasing and peaking from the 3rd to 5th Weeks. NAb decreased between 5th and 9th Weeks, and a higher IgM/IgA level was observed in the groups with mild/moderate severity within 2 weeks ($p < 0.05$), while all 4 types of antibodies were higher in the group with severe/critical severity after 4 weeks ($p < 0.05$).

What are the implications for public health practice?

Our study on the dynamics of serological antibody responses against COVID-19 virus among COVID-19 patients complements the recognition regarding the humoral immune response to COVID-19 virus infection. The findings will help in the interpretation of antibody detection results for COVID-19 patients and be beneficial for the evaluation of vaccination effects.

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease, and the ongoing quick spread of COVID-19 cases has become a global pandemic (1). Detecting serum-specific antibodies has become one of the key approaches for the identification of COVID-19 virus infection. However, the interpretation of antibody detection largely depends on understanding host antibody responses

during infection, but the profiles of the antibody responses and the relationship between IgM, IgA, IgG, and the neutralizing antibodies (NAb) among COVID-19 patients with different disease severity is not yet clearly understood. Therefore, the purpose of this study was to supplement the knowledge regarding the human immune response to COVID-19 virus infection.

In this study, the confirmed COVID-19 patients by real-time reverse transcription polymerase chain reaction (real-time RT-PCR) were included. A total of 210 sera were collected from 160 COVID-19 patients based on varying course of disease in Gansu and Heilongjiang provinces of China during January to March in 2020. The age of the cases ranged between 1–98 years (median age: 46 years). The sampling time of all the sera ranged from 0 to 64 days after onset of illness (median days: 28 days). According to disease classifications outlined in the “Guidelines on the Novel Coronavirus-Infected Pneumonia Diagnosis and Treatment (Seventh Edition)” issued by the National Health Commission of China (NHC), the majority of the COVID-19 cases (76.7%) belonged to the mild (39 cases/45 samples) and moderate (83 cases/109 samples) categories, and the remainder were classified as either severe (34 cases/52 samples) or critical (4 cases/4 samples); 81% of the severe and critical cases were older than 40 years old.

After the sera were inactivated at 56 °C for 30 minutes, the IgM, IgA, and IgG antibodies against COVID-19 virus were detected by using a commercial magnetic chemiluminescence enzyme immunoassay (MCLIA) kit (Bioscience, China) (2). The luminescence value of each sample was positively correlated with the antibody concentration to evaluate the level of IgM/IgA/IgG antibodies against COVID-19 virus in the serum samples. NAb was evaluated using the microneutralization assay (3). Antibody titers greater than or equal to 1:8 indicated a positive result in this study. To calculate the geometric mean titer

(GMT), antibody titers of $<1:8$ and $>1:256$ were assigned as $1:4$ and $1:256$, respectively, and the 95% confidence interval (95% CI) was calculated. The median and interquartile range (IQR) were used for statistical analysis of IgM/IgA/IgG/NAb levels. The Kruskal-Wallis test and Pearson chi-square test were used to test the differences among groups, including age, days after onset of disease, and clinical classification by using R software (version 3.5.2, Lucent Technologies, FL, USA). A p -value less than 0.05 was considered statistically significant.

The dynamics analysis for four types of antibodies showed that the positive rate of IgM/IgA was slightly higher than that of IgG/NAb within the first two weeks after onset. The positive rate of the 4 antibodies successively reached 100% after two weeks. The dynamics of positive rates of IgM and IgA was generally consistent reaching 44.4% and 38.9%, respectively, within 4–7 days followed by a peak after 2 weeks. The positive rate between IgG and NAb was consistent throughout the course of the disease, except for the 6th week, when the positive rate was 81.8% and 95.5% for NAb and IgG, respectively. The low positive rate of NAb in the 6th week might be associated with the low level of IgG in three cases with negative NAb (Table 1). The levels of IgM/IgA/IgG/NAb were also analyzed based on days after onset. All antibodies could be detected at low levels within 0–3 days. The levels of the 4 antibodies were similar within 2 weeks, followed by a rapid increase and the maintenance of a high level from the 3rd and 4th weeks. Similar to the positive rate, the levels of IgM and IgA were consistent throughout the course of the disease. In contrast, the NAb antibody rapidly decreased from a GMT of $1:62$ during the 5th week to $1:31$ by the 9th week, while IgG remained at a

relatively stable level (Figure 1).

All 160 cases in this study were divided into 3 age groups: 1–39 years, 40–59 years, and ≥ 60 years. Due to the limited number of cases aged 1–19 years, all cases younger than 40-year-old were classified into 1 group for statistical analysis in this study. The levels of IgA, IgG, and NAb antibodies showed significant differences among the 3 age groups between the 3rd and 4th weeks ($p < 0.05$), and the level of IgM and NAb showed significant differences among 3 age groups between the 5th and 9th weeks ($p < 0.05$). No obvious differences were observed for all four types of antibodies among different age groups within two weeks after onset (Figure 2).

Variable responses among the four different disease types were observed for the four types of antibodies. The antibody levels of IgM and IgA showed significant differences among the different disease types within two weeks of onset ($p < 0.05$), and higher antibody levels were observed in the mild and moderate groups than those in the severe and critical groups. While the antibody levels of IgM, IgA, IgG, and NAb showed significant differences among the different disease severities after 4 weeks of onset ($p < 0.05$), higher levels were observed in the severe and critical groups. Persistently higher levels of IgG and NAb were observed from the beginning of disease onset among the four critical-type cases in this study compared to other types of disease classification (Figure 3).

DISCUSSION

In this study, IgM, IgA, and IgG antibodies and NAb were detected in 210 serum samples from 160 confirmed COVID-19 cases. The changes in the levels

TABLE 1. The positive detection rate of antibodies against COVID-19 Virus in different course of disease.

Days after onset	No. of samples	IgA		IgM		IgG		Neutralization antibody	
		No. of positive samples	Detection rate (%)	No. of positive samples	Detection rate (%)	No. of positive samples	Detection rate (%)	No. of positive samples	Detection rate (%)
0–3	26	7	26.9	10	38.5	5	19.2	4	15.4
4–7	18	7	38.9	8	44.4	6	33.3	7	38.9
8–14	13	8	61.5	8	61.5	6	46.2	6	46.2
15–21	21	20	95.2	21	100.0	20	95.2	20	95.2
22–28	27	25	92.6	27	100.0	27	100.0	26	96.3
29–35	33	33	100.0	30	90.9	31	93.9	31	93.9
36–42	22	20	90.9	22	100.0	21	95.5	18	81.8
43–64	50	48	96.0	45	90.9	50	100.0	47	94.0
Total	210	168	80.0	171	81.4	166	79.0	159	75.7

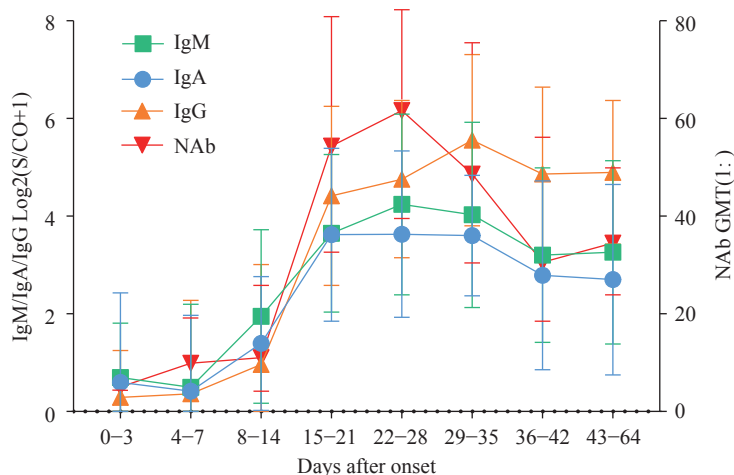


FIGURE 1. The changes in levels of antibodies, including IgM, IgA, IgG, and NAb, against COVID-19 virus after symptom onset. COVID-19 patients from the cross-sectional cohort were grouped based on days after disease onset (0–3 days, 4–7 days, 8–14 days, 15–21 days, 22–28 days, 29–35 days, 36–42 days, 43–64 days). The left Y-axis indicated the S/CO values of the IgM, IgA, and IgG antibodies converted by $\text{Log}_2(\text{S}/\text{CO}+1)$, and the antibody levels of all the groups were shown with the median values. The right Y-axis indicated the geometric mean titer (GMT) level of the neutralizing antibody.

of the 4 types antibodies against COVID-19 virus were analyzed. Our results confirmed findings from previous reports that the positive rate of COVID-19 virus antibodies was lower among patients within the first week of onset, then rapidly increasing and remaining at a high level after two weeks of onset (4). Similar antibody responses were also observed from severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), where the antibody against the SARS coronavirus (CoV) appeared within approximately two weeks of onset and gradually increased over the course of the disease (5) and the anti-MERS-CoV antibody occurred between days 14–21 after infection (6). However, this was different from the measles virus, in which 90% of measles cases showed detectable levels of IgM 3 days following rash onset (7).

Although the sensitivity of nucleotide acid detection was high in samples collected within the first week after onset, it decreased up to 45.5% in those collected after two weeks (4). The dynamics of the COVID-19 virus-specific antibody responses found in this study indicated their roles in the diagnosis of suspected COVID-19 cases. As a supplement to nucleotide acid detection, IgM, IgA, and IgG antibodies could be useful biomarkers for the confirmation of COVID-19 cases, particularly in the later stages of the disease (after two weeks of onset). However, prolonged antibody response raises challenges in diagnosis and the management of COVID-19 patients.

The levels of 4 types of COVID-19 virus specific

antibodies were consistent with the positive rate of detection. A low level of the antibodies was detected within 2 weeks of onset, the levels subsequently increased rapidly and reached a peak between the 3rd and 4th weeks, and then the levels maintained a plateau. A similar trend has also been found in other studies, which showed that the antibody titer peaks at 10–15 days after onset (8). However, the results of this study showed that the level of NAb rapidly decreased between the 5th and 9th weeks after onset while IgG maintained a stable level. Considering that the IgG antibody is the major protective antibody, its ability to offer protection from the virus might decrease due to significant decreases in the NAb titer at the later stages of the disease. Therefore, reinfection might occur if the level of the NAb wanes persistently below the protective level. In addition, the persistence of immunity is a key issue in the development of safe and effective antiviral therapy and vaccines (9). For other coronaviruses, immunity was maintained for several months after infection and then began to wane (10–11). In this study, because the longest period of specimen collection for COVID-19 patients was around nine weeks after disease onset, the persistence of the antibodies remains unclear due to the short observation period. Therefore, more sera of convalescent patients should be collected for further study on the long-term dynamics of COVID-19 virus antibodies.

No obvious differences were observed for antibodies among different age groups within 2 weeks, while

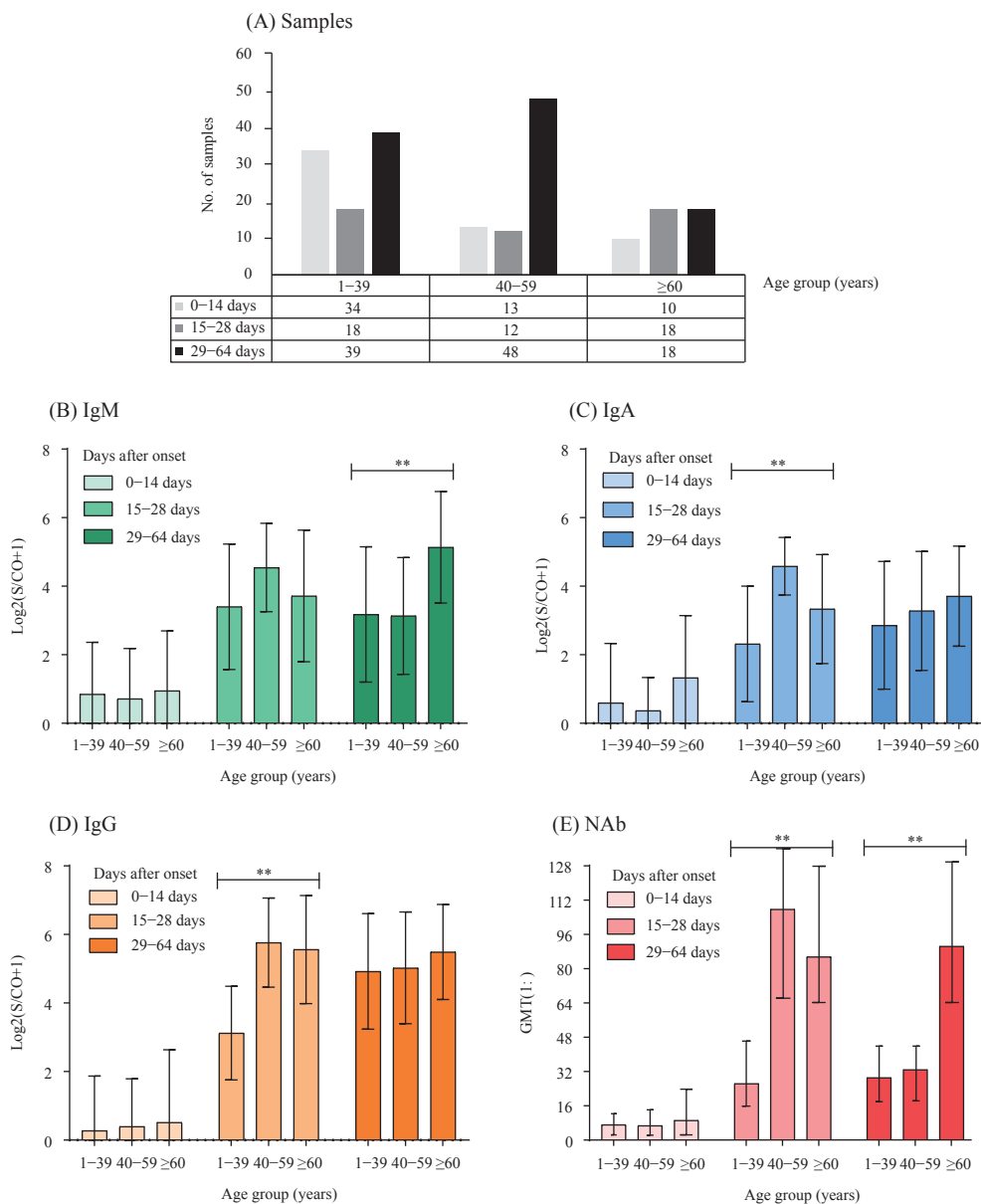


FIGURE 2. The changes in levels of antibodies, including IgM (B), IgA (C), IgG (D), and NAb (E), against COVID-19 virus after disease onset based on the age distribution of the COVID-19 cases. (A) showed the number of samples in age groups including those aged 1–39 years, those aged 40–59 years, and those over 60 years of age. The symbol “**” indicated statistical significance ($p < 0.05$) across the age groups. Scatter and histogram plots were created with GraphPad Prism (version 8.0.2, GraphPad Software, San Diego, CA, USA). GMT=geometric mean titer.

higher NAb level were found among the older age groups (≥ 40 years) after 2 weeks, which was consistent with a previous report (3). However, variable antibody responses among the COVID-19 cases with different disease severity were observed for the four types of antibodies. The higher antibody levels of IgM and IgA were found in the early stage of the disease in the mild and moderate groups, while higher levels of IgM, IgA, IgG, and NAb were observed in the later stages of the disease in the severe and critical groups. Our findings

suggested that the antibody response was closely related to the severity of disease. In addition, persistently high levels of IgG/NAb were observed from the onset among four critical cases. This phenomenon was also found in previous reports that SARS patients with more severe symptoms had stronger serological responses (12–13). Antibody-dependent enhancement (ADE), as a possible underlying mechanism, has been proposed recently (14). Thus, extensive viral replication, cellular damage, and ADE might be

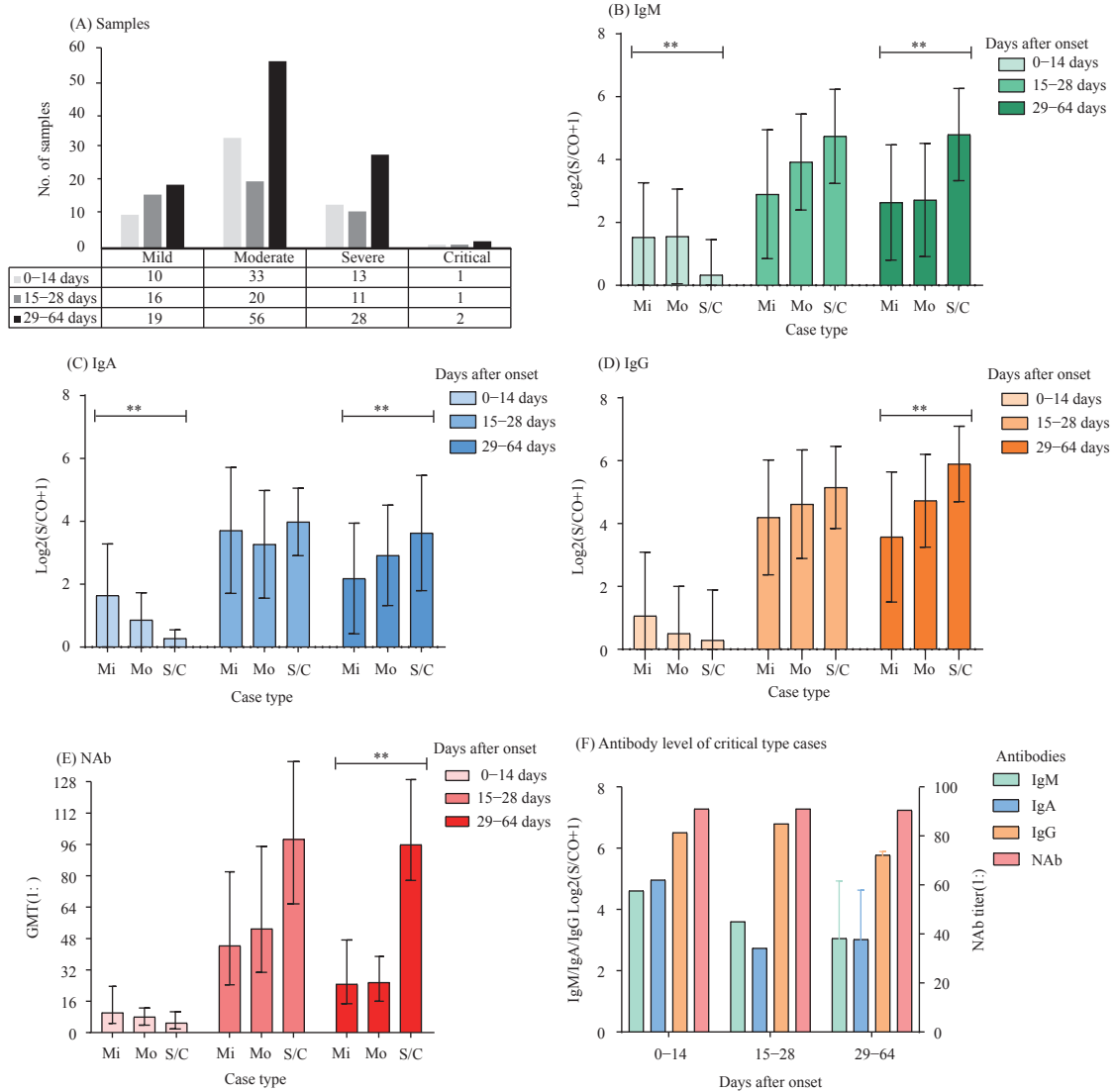


FIGURE 3. The antibody response of IgM (B), IgA (C), IgG (D), and NAb (E) against COVID-19 virus among COVID-19 patients with different disease severity. (A) showed the number of samples in the different disease severities of COVID-19 cases, including mild (Mi), moderate (Mo), and severe and critical types (S/C). (F) showed the antibody levels of critical-type cases based on number of days after disease onset. The level of NAb was shown by the titer of the NAb, instead of geometric mean titer (GMT), due the limited number of critical cases. The symbol “***” indicated statistical significance ($p < 0.05$) across age groups. Scatter and histogram plots were created with GraphPad Prism (version 8.0.2, GraphPad Software, San Diego, CA, USA).

responsible for the aggressive inflammation caused by the COVID-19 virus (14–15).

This study was subject to some limitations. Although the sera in this study were obtained at various times following illness onset, more serial sera were recommended to be collected from patients with the different disease severity, in order to study the long-term dynamic of COVID-19 virus antibodies response.. In addition, sample collection should be strengthened among child patients to supplement the knowledge regarding the pediatric immune response against COVID-19 virus.

Our study on the dynamics of serological antibody responses against COVID-19 virus among COVID-19 patients complements the recognition regarding the humoral immune response to COVID-19 virus infection. Our study will help in the interpretation of antibody detection results for COVID-19 patients and be beneficial for the evaluation of vaccination effects.

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Preplanned Studies

Effectiveness of Interventions to Control Transmission of Reemergent Cases of COVID-19 — Jilin Province, China, 2020

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Summary

What is already known about this topic?

COVID-19 has a high transmissibility calculated by mathematical model. The dynamics of the disease and the effectiveness of intervention to control the transmission remain unclear in Jilin Province, China.

What is added by this report?

This is the first study to report the dynamic characteristics and to quantify the effectiveness of interventions implemented in the second outbreak of COVID-19 in Jilin Province, China. The effective reproduction number of the disease before and after May 10 was 4.00 and $p < 0.01$, respectively. The combined interventions reduced the transmissibility of COVID-19 by 99% and the number of cases by 98.36%.

What are the implications for public health practice?

The findings of this study would add data on the transmission of COVID-19 and provide evidence to prepare the second outbreak transmission of the disease in other areas of China even in many other countries.

China has successfully controlled the first outbreak of the coronavirus disease 2019 (COVID-19) due to the strictly implemented public health policy including active case finding with case management (1). However, it has become an essential public health concern that whether there would be a second outbreak of COVID-19 in China, and how to control the second outbreak? Jilin Province, locating in the north east of China, has also controlled its first outbreak of COVID-19 successfully (2). On May 7, 2020, an outbreak of COVID-19 was reported in Shulan City, Jilin Province, China. The outbreak is the second outbreak in the province. Therefore, it has public health significance to quantify the transmissibility, to assess the effectiveness of

interventions, and to provide experience for other provinces or cities in China, or even for other countries to deal with the second outbreak of COVID-19 outbreaks.

Based on our previous study (2–5), we developed a Susceptible-Exposed-Infectious-Asymptomatic-Removed (SEIAR) model to fit the data in Jilin Province and to perform the assessment. In the SEIAR model, individuals were divided into five compartments: Susceptible (*S*), Exposed (*E*), Infectious (*I*), Asymptomatic (*A*), and Removed (*R*), and the equations of the model were shown as follows:

$$\frac{dS}{dt} = -\beta S(I + \kappa A) \quad (1)$$

$$\frac{dE}{dt} = \beta S(I + \kappa A) - p\omega' E - (1-p)\omega E \quad (2)$$

$$\frac{dI}{dt} = (1-p)\omega E - \gamma I - fI \quad (3)$$

$$\frac{dA}{dt} = p\omega' E - \gamma' A \quad (4)$$

$$\frac{dR}{dt} = \gamma I + \gamma' A \quad (5)$$

There are eight parameters (β , κ , ω , ω' , p , γ , γ' , and f) in the model. The transmission rate, β , was estimated by fitting the reported data. Since only limited secondary transmission was observed due to *A*, in this study, we assumed that the transmissibility of *A* was 5% of that of *I*. Therefore, the parameter κ , the relative transmissibility coefficient of *A* compared with *I*, was set as 0.05 in this study. According to the reported data in the outbreak, we investigated the following parameters: A) the incubation period ($1/\omega$) and the latent period ($1/\omega'$) was 8 days and 6 days, respectively; B) the infectious periods of *A* and *I* were both set as 3 days; C) the parameter p , the proportion of *A*, was 6.52%; D) and the parameter f , the case fatality rate, was 2.17%.

Commonly, we used the basic reproduction number (R_0) to assess the transmissibility of COVID-19. R_0

was defined as the expected number of secondary infections that result from introducing a single infected individual into an otherwise susceptible population(4). However, if intervention was implemented, R_0 should be replaced as effective reproduction number (R_{eff}) which could be calculated by the following equation:

$$R_{eff} = \beta S \left(\frac{1-p}{\gamma+f} + \frac{\kappa p}{\gamma'} \right) \quad (6)$$

Berkeley Madonna 8.3.18 (developed by Robert Macey and George Oster of the University of California at Berkeley; Copyright © 1993–2001 Robert I. Macey & George F. Oster, University of California, Berkeley, CA) was employed to perform the curve fitting and simulation.

The data were collected including all reported cases in Jilin Province from April 25, 2020 to June 4, 2020. The data included the basic information (sex, age, occupation, address), the classification (asymptomatic infection and confirmed cases), key date point (contact date, symptom onset date, hospitalization date, and diagnosed date), and the number of close contacts of each case.

From April 25, 2020 to June 4, 2020, a total of 43 confirmed cases and 3 asymptomatic infections were reported in the province. The epidemic peak was during May 8 to May 10 (Figure 1). The outbreak lasted 7 generations. The secondary attack rate (TAR) of the index case and its following generations was 40.00%, 2.59%, 4.55%, 5.09%, 1.19%, and 0.55%, respectively. Based on the information of some cases which had the exact

exposure date and symptoms onset date, the median incubation period of the cases was calculated as 6 days (range: 2–11 days). The epidemic spread to five districts and cities in Jilin Province (Shulan, Fengman, Chuanying, Changyi, and Gaoxin). About 48.84% confirmed cases had an age of 25–46 years. The main occupation of patients was housework and unemployment, cadres and staff, and business services (Table 1).

The SEIAR model fitted the data well ($R^2=0.29$, $p<0.01$). The value of R_{eff} before and after May 10 was 4.00 and $p<0.01$, respectively. Therefore, the combined interventions reduced the transmissibility of COVID-19 by 99% in the area (Figure 1). According to the simulation results, if the comprehensive intervention measures were not taken on May 10, as of June 4, the predicted cumulative number of cases would be 2,833.

Three further scenarios were simulated as follows: Scenario A: the duration from onset to diagnosed date was shortened by 50% after May 10; Scenario B: the value of R_{eff} was shortened by 50% after May 10; Scenario C: all the cases (exception asymptomatic infections) were isolated after May 10. The results showed that: under the circumstance of Scenario A, the number of cumulative cases would be 503 with a reduction of 82.24%; under the circumstance of Scenario B, the number of cumulative cases would be 309 with a reduction of 89.09%; under the circumstance of Scenario C, the number of cumulative cases would be 211 with a reduction of 92.55%. The reported cumulative number of cases was 46 (43

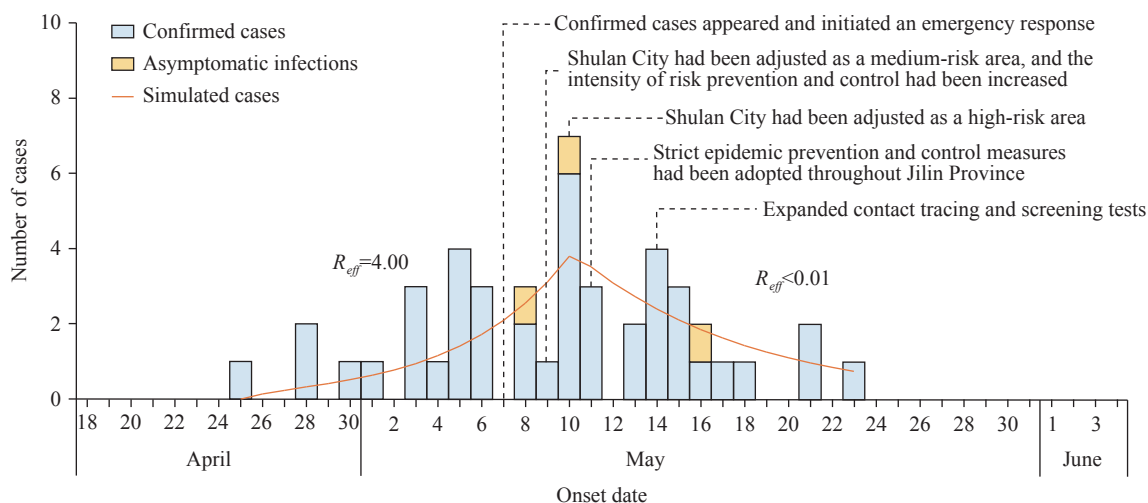


FIGURE 1. Curve fitting results of Susceptible-Exposed-Infectious-Asymptomatic-Removed (SEIAR) model to fit the data of COVID-19 cases in Jilin Province, China.

TABLE 1. The epidemiological characteristics of 46 COVID-19 cases or infections in Jilin Province, China.

Variables	Confirmed cases		Asymptomatic infections	
	n	%	n	%
Areas				
Shulan City in Jilin City	20	46.51	0	0.00
Fengman District in Jilin City	16	37.21	2	66.67
Chuanying District in Jilin City	3	6.98	0	0.00
Changyi District in Jilin City	1	2.32	0	0.00
Gaoxin District in Jilin City	3	6.98	0	0.00
Kuancheng District in Changchun City	0	0.00	1	33.33
Sex				
Male	19	44.19	1	33.33
Female	24	55.81	2	66.67
Age (years)				
≤24	3	6.98	2	66.67
25–46	21	48.84	1	33.33
47–68	12	27.90	0	0.00
≥69	7	16.28	0	0.00
Occupation				
Housework and unemployment	14	32.56	0	0.00
Cadres and staff	8	18.60	1	33.33
Business services	6	13.95	0	0.00
Retired personnel	5	11.63	0	0.00
Farmer	5	11.63	0	0.00
Teacher	2	4.64	0	0.00
Scattered children	1	2.33	2	66.67
Student	1	2.33	0	0.00
Medical staff	1	2.33	0	0.00

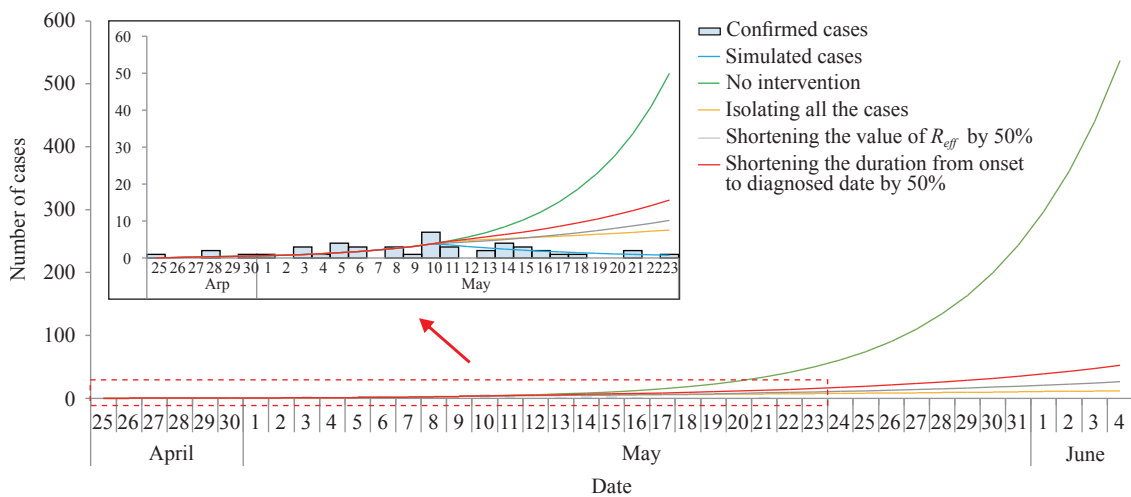


FIGURE 2. Simulating the effectiveness of interventions to control the transmission of COVID-19 in Jilin Province, China.

confirmed cases and 3 asymptomatic infection). The number of cases was reduced by 98.38% by

comprehensive prevention and control measures (Figure 2).

DISCUSSION

Most of the cases in this outbreak were clustered in Shulan City and Fengman District and transmitted through family and work contact, which shows that close contacts were the main transmission route in the spread of the outbreak. The distribution characteristics of cases in region, age and occupation further confirmed the transmission route.

The value of R_{eff} was 4.00 and p -value was below 0.01 before and after May 10, respectively, which indicates that one case can transmit more than four new cases before May 10 and the transmissibility of COVID-19 was decreased to a low level due to the interventions implemented by the authorities. Most of the cases, which got symptoms after May 10, were probably infected before the date and were in their incubation periods.

Our three simulation scenarios showed that case finding and case isolation has the highest effectiveness followed by shortening R_{eff} and the duration from onset to diagnosed date. The simulation results also showed that the comprehensive countermeasures in Jilin Province including emergency response in time, enhancing the risk level of Shulan City, and improving the ability of case finding, had reduced the number of infected people by 98.38% (Figure 2).

The successful control of this outbreak has provided a good experience to control the COVID-19 transmission in future. High transmissibility of the disease calls for a sensitive surveillance system to find out the infected people at the early stage of the transmission. It is also essential to improve the ability of local public health departments on epidemiologic field investigation, laboratory test to screen the infection in a large area, and implementing the interventions such as case isolation, wearing face mask, and keeping social distance. However, the transmission route of this outbreak was person-to-person. More researches are needed to explore the control of the other routes such as environment-to-person and food-to-person.

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Notes from the Field

A Hospital Superspreading Event of COVID-19 — Qingdao City, Shandong Province, China, 2020

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Superspreaders were defined as the minority of individuals who infect disproportionately more susceptible contacts, especially when compared to the majority of individuals who infect few or no others. Superspreading events, i.e. events involving superspreaders, highlight the limitations of basic reproduction number (R_0), which represented the average dynamics of transmission. Previous reports of superspreading events of COVID-19 indicate that these events contributed significantly to the rapid transmission of infections (1). During recent severe outbreaks of the severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and Ebola virus disease, superspreading events were associated with explosive growth early in an outbreak and sustained transmission in later stages (2). To determine how the virus may have spread in a superspreading event of COVID-19 associated with a hospital in Qingdao City, Shandong Province, China, we monitored and traced close contacts and hypothesized possible transmission modes. Real-time reverse transcription polymerase chain reaction (real-time RT-PCR) diagnosis based on nasopharyngeal swab was used for confirmation of this disease (3). The study was approved by Qingdao CDC, and all patients in this study were anonymized.

EPIDEMIOLOGICAL FINDINGS

On February 2, 2020, a 28-year-old man (patient B) was isolated and treated in a designated hospital based on his high body temperature (39 °C) during a visit to his grandmother (Patient A), who was an inpatient in this hospital. On February 4, COVID-19 was confirmed for both patient B and Patient A.

Patient A, an 85-year-old woman with multiple underlying diseases including coronary heart disease, hypertension, diabetes, and pulmonary interstitial fibrosis, was the only patient who indicated that she had been in contact with people from Hubei Province

(the suspected origin of COVID-19 within China). She had been hospitalized due to repeated pulmonary interstitial fibrosis since January 2, 2020. On January 23, she presented symptoms of shortness of breath, of fever (37.8 °C) on January 26, and of chest distress, dyspnea, and cough on January 30. She was classified as a critical case beginning on February 3 and died on February 8. Epidemiological investigations revealed that between January 16 and 21, 2 individuals from Hubei Province went to this hospital to visit their family member, a trauma patient in the same ward as Patient A, and all 3 individuals developed no symptoms. Asymptomatic carrier transmission had been reported for COVID-19 (4), and Patient A was possibly infected by asymptomatic carriers from Hubei Province. To exclude the possibility of Patient A becoming infected through close contact with unknown infected persons, such as the asymptomatic carriers in the hospital, we sampled all 674 persons (including 497 staff members, 177 inpatients, and their family members) who were not classified as close contacts of Patient A and who had been in the hospital from 14 days before the onset of Patient A's symptoms. These persons were tested from February 21 and February 23 for PCR test and serological test, and all were negative for COVID-19 nucleic acids and antibodies. However, we could not determine whether these individuals from Hubei were asymptomatic carriers because they returned to Hubei Province on January 21, but our evidence suggests that these individuals are the most likely source of transmission.

A total of 44 close contacts had contact history with Patient A without appropriate personal protective measures and were traced and sampled every 2 days. These close contacts included 30 medical workers, 10 patients and visitors in the same ward, and 4 family members of Patient A. Overall, 8 confirmed and asymptomatic cases (as of the date of testing) were identified between February 4 and 18 among these close contacts (Patients B–I; overall attack rate: 18.2%)

including 2 medical workers (attack rate: 6.7%), 4 patients and visitors in the same ward (attack rate: 40.0%), and 2 family members (attack rate: 50%) of Patient A. Local CDCs traced and tested close contacts of Patients B–I, and on February 7 and 9, 2 confirmed cases (Patients J and K) were detected.

Overall, 12 (Patients A–L) COVID-19 confirmed and asymptomatic patients were identified in this cluster (Figure 1 and Table 1) and none of them had a history of travel outside Qingdao 14 days before the onset of illness. The incubation period ranged from 1 to 11 days. Patient A was defined as having the initial case; among the 11 secondary cases (Patients B–L), 8 (Patients B–I) were second-generation cases and were likely infected from Patient A; 2 (Patients J and K) were third-generation cases and were infected from Patients B and C; and 1 (Patient L) case had an undetermined generation.

Based on the dates of illness onset of 5 pairs of cases in this cluster, we fitted a gamma distribution by using data from field investigations to estimate the serial interval distribution and estimated that the serial interval distribution had a mean of 7.0 ± 4.4 days. A total of 11 cases occurred in the hospital and only 1 case (Patient J) occurred during a family dinner: Patient J was a 59-year-old man who joined a family dinner with Patient B and Patient C on January 24, and he experienced a runny nose on February 4 and tested positive for COVID-19 on February 7. Patient J had no contact history with other suspected cases 14

days before illness onset. Patients B and C did not have symptoms until January 25, so the source of infection for Patient J was most likely Patients B and C during their incubation period. A total of 5 persons participated in this family dinner, and only patient J developed disease so the attack rate was 20%.

Of the 3 medical workers (Patients G, I, and L) that were infected (Table 1, Figure 1), 2 (Patients G and I) had a history of direct contact with Patient A and were an attending doctor and nurse of Patient A. Patient G performed nursing services for Patient A on January 24 and was laboratory-confirmed for COVID-19 on February 8 (without symptoms as of the test date). Patient I carried out nasal catheterization for Patient A on February 2, and he developed suspected positive result for COVID-19 nucleic acid on February 13 and was laboratory-confirmed on February 18. Patients G and I wore disposable surgical masks, caps, and isolation gowns but did not wear medical gloves when in contact with Patient A. Patient L was a doctor in the hospital laboratory and had no contact history with Patient A and other patients in the hospital, and most likely became infected through performing two routine blood examinations for Patient A (without contact with samples of other confirmed cases) in the hospital laboratory with a primary level of personal protection, including disposable surgical mask, latex gloves, disposable medical cap, and gown. However, we cannot exclude the possibility that Patient L became infected through indirect contact with other COVID-

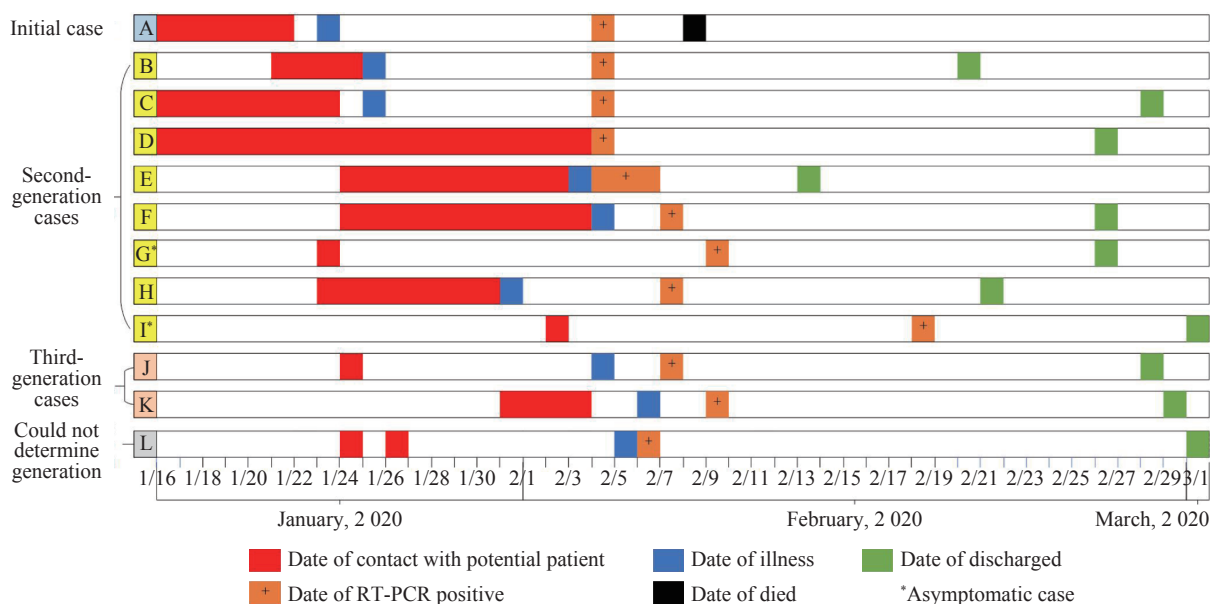


FIGURE 1. Cluster of COVID-19 cases associated with a hospital in Qingdao, China, 2020.

TABLE 1. Demographic features of the cluster infected with COVID-19 in a hospital of Qingdao, 2020.

	Patient												
	A	B	C	D	E	F	G	H	I	J	K	L	
Relationship	Grandma of patient B	Grandson of Patient A	Daughter of Patient A	Same ward as Patient A	Daughter of Patient D	Daughter of Patient D	Daughter of Patient D	Nurse of Patient A	Adjacent ward of Patient A	Doctor of Patient A	Brother of Patient C	Same ward with Patient C	Lab physician of Patient A
Age (years)	85	28	60	70	45	43	22	50	38	59	46	48	
Sex	Female	Male	Female	Female	Female	Female	Female	Female	Male	Male	Female	Female	Male
Occupation	Retired	Work at home	Retired	Retired	Housework	Pharmacist	Medical staff	Patient care	Medical staff	Housework	Office worker	Medical staff	
Underlying disease	Coronary heart disease, hypertension, diabetes, pulmonary interstitial fibrosis	-	Myocarditis	Diabetes	-	Hypertension	-	-	-	Diabetes	-	Hypertension	

Note: "-" represents without underlying disease.

19 cases in this cluster (5) based on the existence of confirmed and asymptomatic cases in this hospital. No COVID-19 cases had been reported before this cluster in this hospital, and all 4 family members and neighbors of Patient L tested negative for COVID-19 RNA.

PRELIMINARY CONCLUSIONS

Based on the findings from this study, a superspreading event of COVID-19 associated with a hospital occurred in Qingdao City with multiple populations experiencing the risk of infection. In addition, people who are pre-symptomatic can transmit COVID-19 virus and asymptomatic carriers may also transmit the disease. Targeted control measures include rapid identification, diagnosis, and isolation of all potentially infected patients, including a high index of suspicion for transmissible diseases and implementation of universal infection control procedures in all areas of the healthcare facilities.

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Notes from the Field

Reemergent Cases of COVID-19 — Dalian City, Liaoning Province, China, July 22, 2020

Xiang Zhao¹; Lingling Mao²; Jianqun Zhang³; Yong Zhang¹; Yang Song¹; Zhijian Bo³; Hong Wang¹; Ji Wang¹; Cao Chen¹; Jinbo Xiao¹; Tianjiao Ji¹; Qian Yang¹; Wenbo Xu¹; Dayan Wang^{1,†}; Wenqing Yao^{2,‡}

From July 22–23, 3 local COVID-19 cases were reported in Dalian City, Liaoning Province, China. All 3 patients reported that they did not leave Dalian 14 days before the onset of disease and had no COVID-19 case contact history and no foreign personnel contact history. Epidemiological investigation, medical isolation, and nucleic acid detection was immediately carried out in Dalian, and 12 asymptomatic infections were detected in close contacts of Patient 1. Because asymptomatic infections made up a large proportion of total infections, the outbreak was likely observed in the beginning stages. Most newly confirmed cases that had been detected were those that had been diagnosed as asymptomatic infections but had onset of symptoms during quarantine.

Throat swab samples were taken from COVID-19 patients and asymptomatic infections. Full length genomic sequences were acquired from the first four COVID-19 cases and found to have lower Ct values. The 4 SARS-CoV-2 genomes were completely identical and showed nucleotide similarity of 99.95% when compared to a reference strain (GenBank No. NC_045512). According to the phylogenetic tree based on the full-length genome of COVID-19 virus, all 4 genome sequences belonged to the L-Lineage European Branch 1. Using the latest classification principle (1), the Dalian strain could be defined as a new branch B.1.1.34 (Figure 1). This further confirmed that this outbreak in Dalian may have been caused by the introduction of an infectious source as it was found to be different from the virus that was prevalent in Wuhan in December 2019 that belonged to the S(A)-lineage and was likely not related to the continuous transmission of that virus.

Compared with the reference strain (GenBank No. NC_045512), all the four genome sequences shared the same substitutions at nt241 (C→T), nt3037 (C→T), nt14408 (C→T), nt23403 (A→G), nt28881 (G→A), nt28882 (G→A), and nt28883 (G→C), among which nt14408, nt23403, and nt28881-nt28883 were nonsynonymous substitutions in the

ORF 1ab gene, S gene, and N gene, respectively. All 7 nucleotide substitutions were characteristic nucleotide substitutions of European Branch 1. All 4 genome sequences also shared another 7 unique nucleotide substitutions, nt2091 (C→T), nt5128 (A→G), nt8360 (A→G), nt13860 (C→T), nt19839 (T→C), nt19999 (G→T), and nt28905 (C→T), which were the characteristic nucleotide substitutions of COVID-19 virus in Dalian.

No other COVID-19 virus sequences with nucleotide substitutions at these 7 characteristic sites was found in the published databases at home and abroad, suggesting that the outbreak was caused by a new branch B.1.1.34 of L-Lineage European Branch 1, which was imported from abroad and likely from Europe. The complete genome sequence analysis of the COVID-19 virus in Dalian further confirmed that the source of the epidemic was not a new crossover event from a natural host or intermediate host. According to the dynamic variation rule of the COVID-19 viral genome and the characteristics of nucleotide substitutions in the genome, it was preliminarily judged that associations between this outbreak in Dalian and those in Beijing Xinfadi (2), Shulan (3), and Heilongjiang (4) were excluded.

With the continuous emergence of next generation sequencing platforms and the rapid development of bioinformatics analytic technology, genomics has entered the field of epidemiological research and played an important role. Genomic epidemiology is a research method combining epidemiology with genomic information to evaluate the epidemiological significance of genomic information on infectious diseases. Cases of COVID-19 had not been reported in Dalian for more than 100 days before the first reemergent case occurred on June 22, 2020. Judging from the timing and phylogenetic analysis, the virus was likely imported from outside. According to the genomic epidemiological analysis, there was no clear relationship between the outbreak in Dalian and that in Beijing, and there was no evidence to suggest a

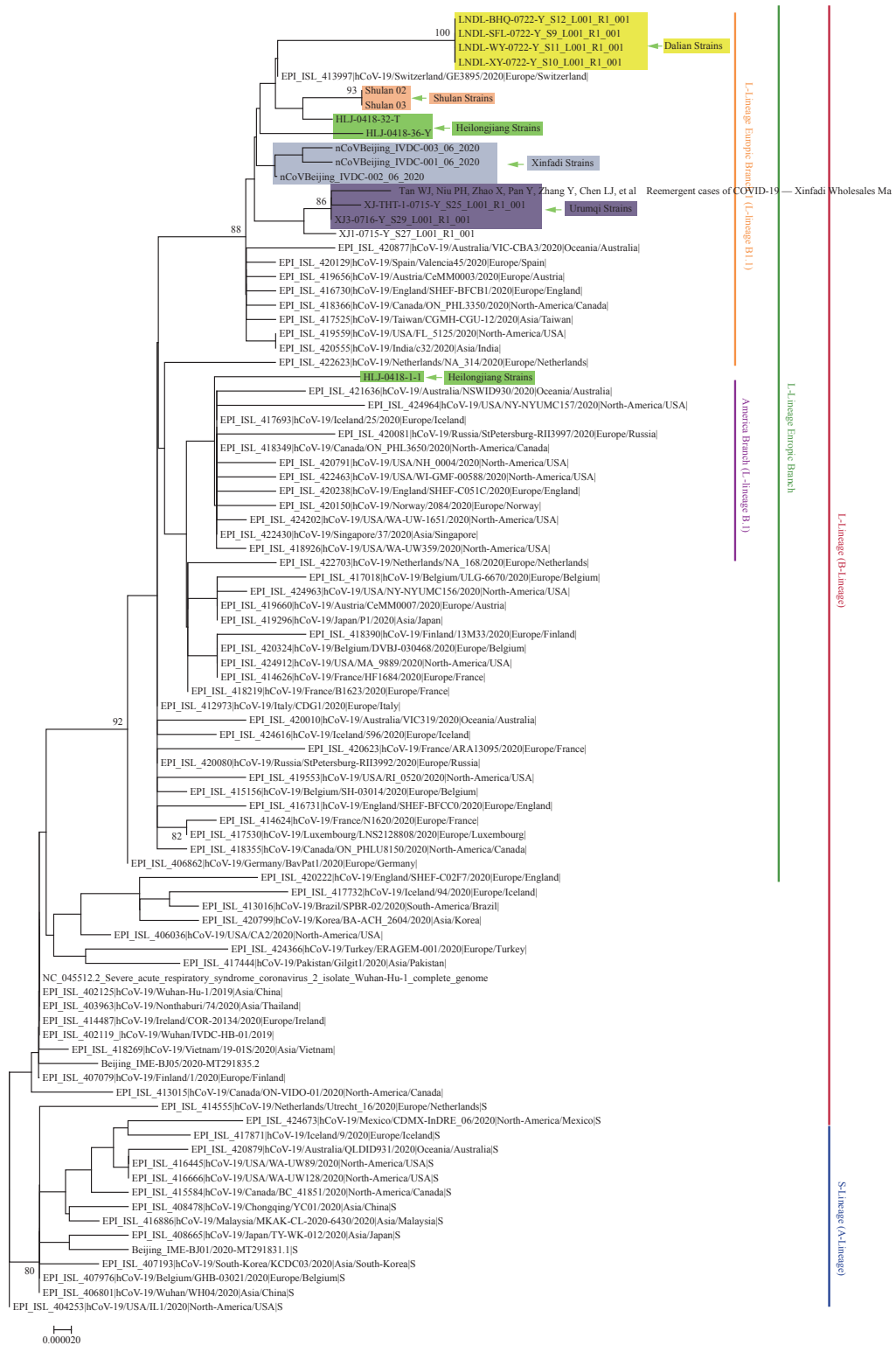


FIGURE 1. Phylogenetic tree based on the full-length genome sequences of the COVID-19 virus. The genomes of the COVID-19 virus from Dalian were highlighted in shades of yellow. The genomes of the reference COVID-19 virus from Wuhan (December 2019) were highlighted in shades of grey. The recent reemergence of COVID-19 virus in Beijing XinfaDi and Urumqi were highlighted in shades of green and blue, respectively, and the recent reemergence of COVID-19 virus in northeastern China (Shulan City and Heilongjiang Province) that was associated with imported cases was highlighted in shades of brown and ochre red, respectively. S(A)- or L(B)-lineage of the COVID-19 virus were marked and colored on the right.

definite link between the imported cases from other countries and Dalian.

The Dalian outbreak was likely related to the processing of cold chain seafood products, especially imported contaminated products. Therefore, the surveillance of imported COVID-19 should be strengthened, especially the detection and monitoring of nucleic acids of COVID-19 virus in imported foods, and a scientific and routine mechanism for entry detection should be implemented.

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Vaccination Guidelines During and After the COVID-19 Epidemic in China

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In late December 2019, clinicians in Hubei Province noticed and reported to health authorities a cluster of cases of pneumonia of unknown etiology (PUE) that turned out to be the start of the coronavirus disease 2019 (COVID-19) pandemic (1). By January 29, 2020, all provincial-level administrative divisions (PLADs) across the country had launched their highest public health emergency responses (Level 1 responses) (2–3). Vaccination service delivery was impeded by social distancing measures and restrictions on gatherings of people required in the Level 1 response protocols. Although vaccination services continued to be available in some areas, and four vaccines — rabies vaccine for post-exposure prophylaxis, the birth doses of hepatitis B vaccine and bacille calmette-guerin (BCG) vaccine, and tetanus toxoid for wound prophylaxis — continued to be administered on time in all areas, most vaccination services were stopped as part of the response (4–6). On February 3, China CDC published interim guidelines for vaccinations during the COVID-19 epidemic based on local epidemiological circumstances (7).

In early March 2020, the COVID-19 epidemic in PLADs outside of Hubei Province was coming under control, and in mid-march, China's National Health Commission issued a notice to resume routine vaccination services in an orderly manner (8). Eighty percent of the country's vaccination venues (China CDC, unpublished data) had suspended immunization services for up to two months for vaccines other than BCG, the first dose of hepatitis B, rabies, and tetanus toxoid for wound management. China CDC developed guidelines for resumption of routine immunization services and catch-up vaccinations for children who missed or delayed vaccine doses due to COVID-19. We describe the China CDC guidelines for during and after the COVID-19 epidemic in

China.

VACCINATION SERVICES DURING THE COVID-19 EPIDEMIC

During the COVID-19 epidemic, community transmission of the COVID-19 virus increased risk of infection in gatherings of people including in vaccination clinic settings. Considering the risk of COVID-19 infection and the risk of vaccine preventable diseases, China CDC made the following guidelines (7,9).

1) Hepatitis B vaccine and BCG vaccine should be administered to newborn infants in birth hospitals and centers on time in accordance with routine National Immunization Program recommendations. The second and third doses of hepatitis B vaccine for infants whose mothers were hepatitis B surface antigen positive should be administered on time at vaccination clinics.

2) Vaccines for post-exposure prophylaxis (PEP), e.g. rabies vaccines and tetanus toxoid, should be administered on time based on standard PEP guidelines. Patients should go to the nearest medical institution with a dog-related injury treatment clinic for timely administration of rabies PEP.

3) If COVID-19 virus is not circulating in a community (urban and rural communities and villages under the jurisdiction of sub-district offices or township people's governments), individuals can receive vaccination services during clinic operation times in accordance with local health authorities or local CDC guidelines.

4) If the COVID-19 virus is circulating in a community, administration of vaccines other than the urgent vaccinations described above can be suspended. Attention must be given to ensuring that children can be caught up on vaccinations as soon as possible once community circulation of the COVID-19 virus has ended.

5) Individuals seeking vaccination services should make an appointment with their vaccination clinic through the Internet or by telephone. Appointments allow clinics to minimize the number of children and parents waiting to receive vaccinations or waiting to be released from observation after vaccination.

6) All people coming to a vaccination clinic should ensure they do not have a fever or other illness symptom. Children with symptoms or signs of illness will not be vaccinated. Children must be accompanied by their parents or guardians, who must also not have symptoms or signs of illness.

7) At home, following vaccination, the child's physical condition should be monitored. If the child feel hot or feverish then their temperature should be taken. Post-vaccination adverse reactions like fever and local swelling will generally resolve without treatment. If there are symptoms other than mild, local reactions or fever that can be relieved, medical advice should be sought in a timely manner.

8) To learn about personal protective measures for going to vaccination clinics, please refer to the "Provisional Guidelines for Public Medical Care During the COVID-19 Pandemic" issued by China CDC (10).

CATCH-UP VACCINATION AFTER COVID-19 EPIDEMIC CONTROL

To reduce risk of COVID-19 virus transmission during the epidemic, most vaccination clinics in China suspended vaccination services for vaccines other than BCG, hepatitis B vaccines, rabies, and tetanus toxoid, as described above. As the level of control over the COVID-19 pandemic in China improves, local vaccination clinics should resume routine immunization services and provide catch-up vaccinations based on the following technical guidelines.

Premises

Vaccination clinics should consider requirements and anticipated staffing needs for COVID-19 prevention and control efforts as they arrange vaccination services (8).

In counties and districts where there have been no cases or all imported cases have been controlled (i.e. no new confirmed or suspected infections within 14 days after the last case and close contacts have been released from quarantine), vaccination clinics should restart

routine immunization and implement catch-up vaccination in an orderly manner.

Who should or should not receive catch-up vaccinations?

1) Anyone whose vaccinations have been postponed due to the COVID-19 pandemic;

2) Anyone who missed any vaccinations or is not completely up-to-date on vaccinations based on the National Immunization Program schedule;

3) Appointments and catch-up immunization shall be suspended for individuals in the following circumstances:

Anyone confirmed to have COVID-19 and asymptomatic infected individuals who have not been quarantined for 14 days after leaving the hospital; those who have come into contact with someone infected with COVID-19 virus within 14 days; anyone who has been present in an epidemic area within 14 days or whose family members have had symptoms like fever and cough within 14 days.

Catch-up vaccination principles and procedures

Principles and guidelines for catch-up immunization

Vaccines that are covered by the National Immunization Program including hepatitis B, BCG, polio, MMR, DTaP, Japanese encephalitis, meningococcal, and hepatitis A vaccines, shall be considered priority vaccines. Vaccines that are not covered by the National Immunization Program should be caught up in a timely manner. Program and non-program vaccines can be administered together in the same clinic visit.

Individuals who have missed doses prescribed by the National Immunization Program schedule only need to complete the missed doses; there is no need to restart the vaccination series for any vaccine.

Individuals who have missed vaccines prescribed by the National Immunization Program should complete the vaccination schedule based on their age and vaccination procedures, including minimum vaccination intervals and number of doses described in the catch-up immunization section.

If it is not feasible to complete a vaccination series with vaccines from the same manufacturer, the same vaccine type from a different manufacturer can be administered instead.

Catch-up immunization of vaccines covered by the National Immunization Program

Hepatitis B vaccine. Newborns who were not vaccinated within 24 hours of birth should receive their first dose of hepatitis B vaccine as an urgent priority. Newborns whose mothers are hepatitis B surface antigen positive must receive the second and third doses in a timely manner. The interval between the first and second dose should be at least 28 days, and the interval between the second and third dose should be at least 60 days.

BCG vaccine. Newborns who did not receive BCG vaccine within 24 hours of birth should be vaccinated as a priority. Infants below 3 months of age who did not receive the BCG vaccine can be vaccinated immediately; children between 3 months and 3 years who have tested negative for tuberculin pure protein derivatives (TB-PPD) or BCG protein derivatives (BCG-PPD) shall receive a catch-up vaccination; children older than 4 years do not need to receive catch-up BCG vaccination.

Polio vaccine. Children younger than 4 years old should receive 3 doses of polio vaccine, and those who are 4 years or older should receive 4 doses. IPV should be administered first, followed by bOPV. Children born after October 1, 2019 should receive IPV for the first 2 doses, and bOPV for the second 2 doses.

DTaP and DT. Children aged between 3 months and 5 years old who have not received DTaP vaccine should complete 4 doses of DTaP vaccine. The interval between the first 3 doses should be at least 28 days, and the interval between the third dose and the fourth dose should be at least 6 months. Children aged 6 years or older who have received less than 3 doses of DTaP and DT vaccines should receive DT vaccine to complete 3 doses, children aged between 6 and 11 years old should receive adsorbed diphtheria and tetanus combined vaccines (for children), while children aged 12 years or older should receive adsorbed diphtheria and tetanus combined vaccines (for adults and adolescents). The interval between the first dose and the second dose should be 1–2 months, and the interval between the second dose and the third dose should be 6–12 months.

Measles and rubella vaccine and MMR vaccine. Children aged at least 8 months old should receive measles and rubella vaccine or MMR vaccines (to be selected according to the recommendations of the local immunization program); and children aged at least 18 months old should receive the MMR vaccine. Children aged 24 months and older who have not received 2 doses of measles-containing vaccines shall receive measles and rubella vaccines or MMR vaccine. The

interval between the two doses shall be at least 28 days.

Japanese encephalitis vaccine. Children who have not received Japanese Encephalitis vaccines according to the national immunization schedule and who are aged less than 15 years old should receive 2 doses of live attenuated Japanese Encephalitis vaccines with an interval of at least 12 months between doses; or 4 doses of inactivated Japanese Encephalitis vaccines. For inactivated JE vaccine, the interval between the first dose and the second dose should be 7–10 days, the interval between the second dose and the third dose should be 1–12 months, and the interval between the third dose and the fourth dose should be at least 3 years.

Group A meningococcal polysaccharide vaccine and group A+C meningococcal polysaccharide vaccine. Children who have not received group A meningococcal polysaccharide vaccines and are aged less than 24 months of age should receive 2 doses of group A meningococcal polysaccharide vaccines with an interval of at least 3 months between doses; children aged 24 months or older should receive 2 doses of group A+C meningococcal polysaccharide vaccines with an interval of at least 3 years between doses. No group A meningococcal polysaccharide vaccines will be administered as catch-up doses. The interval between the first dose of group A+C meningococcal polysaccharide vaccines and the second dose of group A+C meningococcal polysaccharide vaccines should be at least 12 months.

Hepatitis A vaccine. Children aged older than 24 months who have not received Hepatitis A vaccine should receive 1 dose of attenuated live hepatitis A vaccine or 2 doses of inactivated hepatitis A vaccines with an interval of at least 6 months between doses of inactivated hepatitis A vaccine. Children who have received the first dose of inactivated hepatitis A vaccines but are unable to receive the second dose of inactivated hepatitis A vaccines can receive 1 dose of attenuated live hepatitis A vaccines with an interval of at least 6 months between the inactivated vaccine dose and the live vaccine dose.

Catch-up immunization of vaccines not covered by National Immunization Program

After prioritization of vaccines that are covered by the National Immunization Program, vaccine recipients whose non-covered vaccinations have been postponed are encouraged to complete all subsequent doses using the same category of non-covered vaccines.

If a vaccination is postponed due to the COVID-19 epidemic, and the age of vaccine recipients exceeds the

limits set out in vaccine package inserts, vaccinations can still be completed with informed consent of the vaccine recipient or their guardians with the exception of oral rotavirus vaccine. If the recipients or their custodians do not consent, the vaccination should be cancelled.

Technical requirements of catch-up immunization

Preparation before vaccination

Local vaccination clinics can work with rural government officials, sub-district offices (resident committees) and community service centers, as well as kindergartens and school teachers, to inform parents and supervise vaccination efforts through the epidemic joint prevention and control mechanism.

Vaccination clinics should increase the number of vaccination doctors and nurses, appropriately increase the workdays for vaccination, and provide vaccination appointment services. By consolidating the vaccination information of recipients, vaccination clinics should accurately identify individuals who have delayed or missed a vaccination, and arrange catch-up immunization through telephone, SMS, or WeChat based on the service area of vaccination clinics and number of vaccination doctors and nurses.

Vaccination clinics should reduce the number of persons accompanying vaccine recipients, check the health conditions of the vaccine recipients and the persons accompanying them, and inquire, inspect, and report their health conditions before they enter the vaccination clinics as required by local health authorities.

Vaccination clinics shall clean, ventilate, and disinfect the internal environment appropriately.

Specific measures during vaccination

Based on local regulations on COVID-19 prevention and control, vaccination doctors and nurses shall use personal protective equipment, and wear surgical masks, work clothes, caps, and gloves as recommended.

Vaccination doctors and nurses shall strictly implement verification procedures and confirm the consistency of information on vaccination certificates and vaccine packages before administering vaccines.

Vaccination doctors and nurses shall disinfect their hands with hand sanitizers before administering vaccines.

Treatment after vaccination

After administering vaccines, vaccination doctors

and nurses shall disinfect their hands again with hand sanitizers.

After administering vaccines, vaccination doctors and nurses shall make appointments with vaccine recipients or their guardians for upcoming vaccinations. Vaccine recipients should stay for an observation period of 30 minutes while avoiding crowded areas.

Evaluation of catch-up immunization

Goals

The catch-up immunization should be completed within 2 months with a completion rate of at least 95% for vaccines covered by the National Immunization Program.

Investigation and registration of individuals who have missed vaccination should be completed within 2 months with a completion rate of at least 90% for vaccines covered by the National Immunization Program.

The vaccination rate of vaccines covered by the National Immunization Program should be at least 90%.

Evaluation methods and data reporting

After the COVID-19 epidemic has stabilized for 2 months, 2–3 counties from every city, as well as 1 community and 2 township from every county should be selected at random for evaluation of catch-up immunization to ensure that the catch-up immunization has achieved the expected results.

Existing immunization information systems can be used to evaluate catch-up immunization, and places without such systems can implement on-site surveys.

Within one month after catch-up immunization, local vaccination clinics should analyze their catch-up immunization data, draft their reports, summarize the data at different levels and submit the reports to their upper-level disease control agencies and health authorities.

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Perspectives

Tuberculosis Infection Control Project Management Experience and Its Application in COVID-19 Response

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The outbreak of COVID-19 resulted in many infections, including patients in health care settings (1). Although the main mode of transmission of COVID-19 is by droplets, both tuberculosis (TB) and COVID-19 are respiratory infections that can be spread by airborne transmission. Therefore, a set of systematic and comprehensive nosocomial infection control policies is necessary to control infectious sources, block transmission, and protect people at risk in health care settings.

Surveys showed that the TB infection prevention and control (IPC) status in health care centers were poor resulted from absence of policy support, unreasonable environmental layout, insufficiency of IPC knowledge, shortage of protective appliances (2). Elevated capacity and improved practice, profiting from a systematic training and intervention, would be very useful for better IPC in facilities. In order to improve IPC work based on the strengthened knowledge and skill of staff, a set of IPC activities were designed and conducted in a collaborated project named Building and Strengthening Infections Control Strategies for TB (TB BASICS), developed by China CDC and US CDC. Chongqing Public Health Medical Center (CPHMC), being an infectious disease and public health emergency designated hospital at provincial level, took the responsibility to cooperate with other hospitals during the implementation of this project. TB BASICS has been carried out from July 2018 to June 2019.

Since the outbreak of COVID-19, CPHMC improved its COVID-19 epidemic response by using the experience and lessons learned from implementing this infection control project, to reach the goal of zero infections among healthcare staff who were battling COVID-19 in frontline.

TB BASICS PROJECT IMPLEMENTATION

TB IPC measures are categorized into three hierarchical groups of measures: administrative,

environmental, and personal protection (3–4). The facility-wide administrative measures focus on activities and policies that will support the implementation of systematic IPC in the entire facility. The other administrative measures focus on reducing the risk of exposure by implementing systems and policies to quickly detect, separate, and effectively treat TB cases as well as respiratory hygiene. Environmental measures, such as sufficient ventilation and germicidal ultraviolet, focus on reducing the concentration of *M. tuberculosis* droplet nuclei and prevent their spread. Personal protection measures, mainly using respirator, serve as a complement to the previous two measures to further reduce the risk of exposure of healthcare workers to *M. tuberculosis* (3,5).

TB BASICS is a continuous quality improvement project that aims to implement and strengthen sustainable TB IPC strategies in health facilities through continuous practice, evaluation, and improvement. The CPHMC initiated TB-BASICS project in July 2018, covering 16 areas of the facility deemed to be at risk for TB transmission, including the infection control unit, tuberculosis clinics, in-patient wards, laboratories, and other specialized departments. To realize continuous improvements of TB IPC measures in all parts, the CPMHC conducted baseline assessments, established intervention control teams, and developed a TB IPC improvement plan and standard operation procedure (SOP) during a 12-month time period.

RESULTS AND REFLECTIONS OF THE PROJECT

Evidence points to TB BASICS having improved our expertise in and attention to IPC. First, support from the facility leadership guaranteed the successful implementation and improvement of TB IPC. Implementing TB BASICS elevated leadership's understanding and support for TB IPC including supporting an investigation of the status of TB

infection and disease among health care workers (HCWs) in CPHMC since 2013, strengthening the supply of disinfection equipment, improving patients' pathway, and increasing financial support, and providing disposable surgical masks free of charge for all ambulatory and hospitalized TB patients. Second, hospital layouts and patient diagnosis procedures have been improved, such as better ventilation in sputum collection rooms, an online appointment registration system was developed that assigns patients to consultation times in order to reduce waiting times and waiting room crowding. Third, increased awareness of TB IPC among HCWs has led many of them to take the initiative to improve their daily practice of diagnosis and treatment through multiple methods, especially training (5–6), with increased correct rate from 40% at baseline to 70% at final evaluation. Fourth, daily material and equipment meetings are held to discuss the availability of personal protective equipment (PPE), in particular respirators, which give priority to frontline HCWs in isolation areas. Furthermore, HCWs became more attentive to personal protection. It has been observed that all staff starting work on the isolation ward actively ask for respirator fit-testing and use the respirators properly at work.

IMPACT OF TB BASICS PROJECT ON COVID-19 RESPONSE

CPHMC was designated as a COVID-19 hospital in Chongqing on January 21, 2020, and diagnosed and treated its first confirmed COVID-19 patient on January 24, 2020. Up to March 15, 2020, 224 patients (14 critical, and 17 severe), have been admitted. All patients were admitted to three isolation buildings with six wards (including one negative pressure ward) and a total of 430 HCWs from 61 departments of CPHMC worked in these isolated areas.

The participation of TB BASICS project laid a solid foundation for us to manage this challenge. COVID-19 is a respiratory infectious disease like tuberculosis. Tuberculosis is mainly airborne, but COVID-19 is mainly spread by droplets and contact. Based on the current view point, both of them can be spread by aerosols. The management of COVID-19 response was enhanced by the lessons learned from TB BASICS. Scientific and rational COVID-19 response strategy was established and more than 20 standardized workflows were developed including access to the

COVID-19 isolation area, patient transfer, disinfection of emergency vehicles, donning and doffing of PPE, among others, which covered administrative control, environmental control and personal protection equipment. Several IPC guidelines were compiled to guide the epidemic response and printed for easy access by facility staff.

After receiving the task of treating COVID-19 patients, the CPHMC, based on its experience learnt in TB BASICS, offered personnel and financial support, established COVID-19 Emergency Team. All staff of the infection control department engaged in workflow development. The function of each room and pathway of HCWs were discussed thoroughly and the best way was determined to avoid cross contamination. Some physical barriers were built for protecting HCWs from infection. In addition, in order to make all staff familiar with new workflow, training and drills were carried out, and further revisions were made to improve feasibility. After several rounds of drills, an optimized pathway was agreed upon which guaranteed smooth workflow and reduced transmission risk for all HCWs.

Since January 20, 2020, more than 20 intensified IPC trainings and workflow rehearsals were conducted. Before participating in the treatment of patients with COVID-19, all HCWs must receive IPC training and pass the assessment before entering the isolation ward. These training courses were based in part on information learned from TB BASICS, covered IPC guidelines and best practices, and helped HCWs comply strictly with the requirements that aim to reduce the risk of COVID-19 transmission. Trainings on standard prevention measures based on transmission mode (6) were strengthened.

Using principles and techniques learned from TB BASICS, environmental measures in isolation area were improved. Before COVID-19 patients were moved into isolation wards, a transmission risk assessment was performed in each area. The air changes per hour (ACH) were measured to assess the ventilation with the goal of achieving 12 ACH in all isolation areas. For areas with poor ventilation (did not meet 12 ACH criteria), upper room GUV fixtures were installed to supplement poor ventilation. One hundred sets of upper-room GUV fixtures were purchased for replenishment, and a robotic disinfection machine and other disinfection facilities were acquired and used. HCWs were assigned to sterilize the isolation area every day at least twice. Work in isolation area being completed, infection control department has taken

samples from the isolation area. And bacterial cultures of 200 samples were all negative.

In personal protection, N95 respirator fit-testing was provided. The respirators for all staff were selected based on fit testing results. Every staff who was assigned to the isolation area was given one-on-one training on respirator use to guarantee their correct use of the respirator without leakage. A total of 428 staff were given fit-testing to make sure that each staff wore his/her own respirator suitably (7). Moreover, the CPHMC provided surgical masks for all COVID-19 patients without charge.

After completing all work in the isolation area, all HCWs tested negative for COVID-19 using RT-PCR tests for SARS-CoV-2. In addition, after a 14-day quarantine, all HCWs had 2–3 follow up specimens and tested by RT-PCR for SARS-CoV-2, all of which were negative. However, a small investigation of PPE outer surfaces including 5 sets of randomly selected goggles and respirators using environmental sampling methods illustrated detection of SARS-CoV-2 on 1 of the five sampled sets. These results and the fact that none of our HCWs were infected with SARS-CoV-2 highlights the protective effectiveness and proper doffing of PPE among our HCWs.

CONCLUSION

Benefiting from the establishment of new IPC concepts and technical measures introduced by TB BASICS, the IPC measures in CPHMC were systematically improved as was the knowledge, awareness, and practices of IPC among HCWs. The capacity enhancement through TB BASICS project has laid a solid foundation for us to make correct strategies for fighting COVID-19, and to successfully complete the various IPC tasks, achieving the goal of “zero infection” for HCWs. The IPC team won the highest trust of all staff, and was known as the “guardian” by the HCWs.

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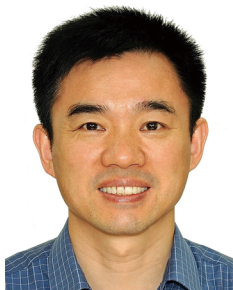
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Zunyou Wu, China CDC's Chief Expert of Epidemiology

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Zunyou Wu is the Chief Expert of Epidemiology of China CDC, an Adjunct Professor of Epidemiology at the University of California, Los Angeles (UCLA), and a member of the UNAIDS Evaluation Expert Advisory Committee. He has made significant contributions in the field of infectious diseases control, particularly for HIV/AIDS, severe acute respiratory syndrome (SARS), and coronavirus disease 2019 (COVID-19).

Zunyou Wu's work over the past 30 years in HIV research, health policy, and public health practice in China has saved countless lives through improvements in both treatment and prevention that extend far outside China's borders. He has been a strong leader in both the implementation and expansion of a comprehensive HIV response in China and the development of internationally collaborative efforts to bring the global HIV epidemic under control.

From the very beginning, Zunyou Wu has been a leader in China's HIV response. After completing his Ph.D. in the United States at UCLA in 1995, Zunyou Wu returned to China and quickly became involved in a major HIV outbreak investigation in rural Anhui province. The investigation revealed the greatest public health tragedy China has faced in a century — the widespread HIV infection of paid plasma donors in villages throughout central China. Zunyou Wu was the epidemiologist on the team that identified unsafe plasma collection procedures as the common origin of a large number of newly-identified HIV cases. This timely discovery spurred immediate actions to end unsafe plasma collection methods and prevented thousands of donors from acquiring HIV infections.

Immediately following the conclusion of the outbreak investigation, Zunyou Wu started to promote HIV testing as a control strategy. He conducted the first HIV survey among former commercial plasma donors in 1996, which revealed that HIV prevalence in this population was 12.5%. He then pushed for the rapid expansion of treatment services for those who had become infected with HIV through plasma donation and the implementation of pre-marital health screening to prevent the spread of infection. From 1997 to 1999, Zunyou Wu spearheaded China's first large-scale HIV training program for healthcare workers in rural areas, and from 2003 to 2007, he led a US National Institutes of Health (NIH)-funded, community-based, intervention trial to reduce HIV/AIDS-related stigma for infected former plasma donors.

To realize these successes, Zunyou Wu worked vigorously within China CDC and across sectors to push for changes in the national HIV response that required a significant shift in long-standing social and political paradigms. For example, China's HIV epidemic originated and grew rapidly early on among people who use drugs (PWUD) in southwestern China as a result of unsafe injecting behavior. Using implementation science strategies to scale-up harm reduction programs for reducing HIV transmission among people who inject drugs (PWID) in China, Zunyou Wu led the design, pilot testing, and scale-up of methadone maintenance treatment (MMT) and needle exchange programs in China. These harm reduction programs have become national strategies and resulted in the continuing decline of HIV incidence and prevalence among PWUD in China. The harm reduction programs in China led by Zunyou Wu have become internationally-recognized best practices for controlling HIV among PWUD. Zunyou Wu has become a preeminent expert on the control of HIV epidemics among drug users. He has shared lessons learned and best practices with delegates from Russia, the Ukraine, Myanmar, Vietnam, and Thailand, thereby contributing directly to the testing, treatment, and prevention of HIV among PWUD globally.

Zunyou Wu used implementation science strategies to pilot and scale-up a simplified protocol for HIV testing and treatment initiation. Although HIV testing has been expanded and more people living with HIV (PLWH) are being diagnosed, a considerably high proportion of HIV infections are diagnosed at late clinical stages and patients were dying shortly after diagnosis. The complexity of multiple stages and multiple institutes involved in HIV diagnosis and treatment had made the process from initially screening HIV reactivity to finally starting antiretroviral therapy (ART) difficult and slow, resulting in unacceptably high rates of loss to follow-up in the pre-ART period.

He pilot tested a structural intervention called the “One4All” strategy, which simplified HIV diagnosis and treatment initiation. He first used a pre/post study design, and then conducted a cluster-randomized trial, supported by the US National Institute on Drug Abuse (NIDA) of the NIH. Both approaches demonstrated that the simplified protocol significantly shortened the time interval between screening for HIV-reactivity and initiating ART and significantly reduced mortality among newly-diagnosed HIV cases. The “One4All” strategy has since been adopted as China’s national strategy and written into the 13th Five-Year Action Plan as a key control strategy for China’s national HIV/AIDS response.

Zunyou Wu continued his promotion of HIV testing as an important HIV/AIDS control strategy starting from the mid-2000s. More recently, it had become apparent that a very high proportion of HIV-infected individuals who remained undiagnosed, which meant they not only failed to receive the medical care they needed but were also contributing to ongoing transmission. Zunyou Wu led several studies demonstrating the importance of promoting HIV testing. He has also provided strong evidence for the importance of improving retention in the care continuum from diagnosis to treatment to viral suppression both for individuals’ clinical benefit and for communities’ public health benefit. Zunyou Wu’s strong and steadfast advocacy for expanded HIV testing coverage and strategies has meant that HIV testing remains a key control strategy in China’s national HIV/AIDS response programs still today.

Zunyou Wu created the National HIV/AIDS Comprehensive Response Information Management System (CRIMS) in 2008. CRIMS is a nationwide online electronic medical record system that integrates data on HIV case reporting, surveillance, testing, prevention, ART, and MMT. CRIMS is a key tool for monitoring HIV/AIDS strategy implementation in China.

Participating in the response to the SARS outbreak in Beijing in 2003, Zunyou Wu discovered long time delays from onset of illness to patient isolation and proposed to shorten the time between the first clinic visit and hospitalization as an important containment strategy. His proposed changes to case management protocols were immediately adopted, helping achieve control of SARS in Beijing. Zunyou Wu attended the 56th World Health Assembly and contributed to drafting the international resolution on SARS (WHA56.28 Revision of the International Health Regulations; WHA56.29 Severe acute respiratory syndrome, SARS).

Zunyou Wu has participated in China’s response to COVID-19 since January 16, 2020. He analyzed epidemic data in real time as it was collected in the early days of the outbreak in Wuhan and has since monitored epidemic trends closely. He has made significant contributions to the global understanding of COVID-19 epidemiology, particularly the heightened vulnerability of the elderly and people with underlying chronic conditions, and has also studied and reported on the important role of asymptomatic and pre-symptomatic infection in transmission. Zunyou Wu was involved in the World Health Organization (WHO) — China Joint Mission on COVID-19 from February 16–24, 2020. He worked with WHO technical experts and leaders, participated in field visits, and contributed to drafting the final Joint Mission report. Additionally, Zunyou Wu was involved in investigating the COVID-19 outbreak in Beijing in June and July 2020 and found that the cause of the outbreak may have been associated with contamination of imported seafood products.

As China CDC’s Chief Expert of Epidemiology, Zunyou Wu continues to lead the country’s response to infectious diseases by providing critical insight and experience. His experiences addressing HIV/AIDS, SARS, and COVID-19 demonstrate his invaluable contributions to academic research and to informing the public.

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