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Cover Photo: The 'double mutant' COVID-19 variant first emerging in India has spread around the world and has been discovered in more than 20 countries.

Outbreak Reports

Mild Breakthrough Infection in a Healthcare Professional Working in the Isolation Area of a Hospital Designated for Treating COVID-19 Patients — Shaanxi Province, China, March, 2021

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Summary

What is already known about this topic?

Healthcare workers are at high risk of acquiring COVID-19 from occupational exposure to COVID-19 virus during their daily medical service work. Excellent infection prevention and control measures and adequate personal protective equipment (PPE) are essential to reduce the risk of hospital-acquired COVID-19.

What is added by this report?

On March 17, 2021, a female healthcare professional who already received both doses of the COVID-19 vaccination and was working in the isolation area of a designated COVID-19 hospital was diagnosed with COVID-19 in Xi'an city. Her exposure likely occurred five days before illness onset when she obtained nasopharyngeal and oropharyngeal swabs from the two imported cases that were identified as belonging to the B.1.1.7 lineage, the variant first detected in the United Kingdom.

What are the implications for public health practices?

Since the healthcare worker had been fully vaccinated and had mild symptomatology, it is considered a mild breakthrough infection. All vaccines are associated with breakthrough infections. In addition to rigorous adherence to infection prevention and control measures, use of adequate PPE, and using good clinical practices, the potential role of chronic upper respiratory infection in acquiring COVID-19 during medical procedures deserves further consideration.

The coronavirus disease 2019 (COVID-19) pandemic, caused by COVID-19 virus also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared by the World Health Organization (WHO) on March 11, 2020 (*1–2*). To date, more than 130 million confirmed cases and 2.8 million deaths have been reported worldwide for a crude case-fatality rate of 2.2%. COVID-19 vaccines made with several technologies are currently being used in many countries. China has a national policy to provide COVID-19 vaccines free of charge, and by the end of March 2021, nearly one hundred million people have been vaccinated. However, China's overall population immunity is far from established, and healthcare workers at the frontline of the fight against COVID-19 are at high-risk of acquiring COVID-19 during medical procedures (*3–4*). In many countries, healthcare workers, together with elderly people, residents and personnel in long-term care facilities, social care personnel, and workers in essential public services are prioritized for COVID-19 vaccination. We report the first domestic COVID-19 breakthrough infection in China — a vaccinated healthcare professional working in the isolation ward of a designated COVID-19 hospital.

INVESTIGATION AND FINDINGS

On March 17, 2021, Xi'an Health Commission reported a domestic COVID-19 case. The patient was a 36-year-old female laboratorian working in a hospital designated for treatment of imported COVID-19 cases. That day she was febrile, with a temperature of 37.9 °C; she had a cough and headache. She reported no dyspnea or shortness of breath. Chest computed tomography (CT) revealed flocculent shadows in both lungs. Throat swabs and blood samples were immediately obtained. Throat swabs were positive by COVID-19-specific quantitative reverse-transcription polymerase chain reaction (qRT-PCR), with the cycle threshold (*Ct*) values of 34 for N gene and 35.27 for ORF1ab fragment (Figure 1). Rapid COVID-19 antibody tests were weakly positive for IgG and negative for IgM. She was diagnosed as a confirmed COVID-19 case (regular type).

An epidemiological investigation was immediately launched. She had been healthy without fever or other relevant abnormalities during the 14 days before starting work in the isolation area on March 4. She had been vaccinated with inactivated COVID-19 vaccine (Beijing Institute of Biological Products Co. LTD) on December 30, 2020 and again on January 20, 2021. She and her 33 workmates were working in the isolation area for a 3-week period. She lived in the dormitory in an area separate from the isolation wards. She lived and shared a bathroom in the dormitory with one colleague. On March 2 and March 11, she tested negative for COVID-19 by qRT-PCR in the hospital's routine testing of staff. Her main work was obtaining throat swabs for COVID-19 cases in the isolation wards and conducting blood, urine, and feces testing in the isolation area's BSL-2 laboratory. She alternated every other day with another laboratorian for this work. Medical history review showed that she has chronic rhinitis and usually breathes by mouth when wearing a mask.

After diagnosis, she was immediately transferred to the isolation ward for medical treatment and observation. Her highest temperature was 37.2 °C, recorded on March 19. Her cough increased slightly. She described dry mouth and mildly decreased sense of smell. Rapid testing for COVID-19 virus antibody showed IgG positive and IgM weakly positive. Chemiluminescence assay for total COVID-19 virus antibody appeared strongly positive with a cutoff index (COI) of 1,368 (Figure 1). On March 20, her temperature was normal, and her sense of smell improved slightly. Viral qRT-PCR was positive for N gene (*Ct*: 37) and negative for ORF1ab. Her temperature remained normal and all other symptoms disappeared in the following days. Her oxygen saturation was never below 98% and she never required supplemental oxygen. The patient remained in the isolation hospital due to weakly positive qRT-PCR. On April 9, she recovered and was discharged from the isolation ward.

Whole viral genome sequencing was conducted on an insolate from a throat swab specimen obtained on March 17. Due to the low viral load of the sample, sequences covering only 82% of the entire genome were obtainable. Sequence analysis revealed that the

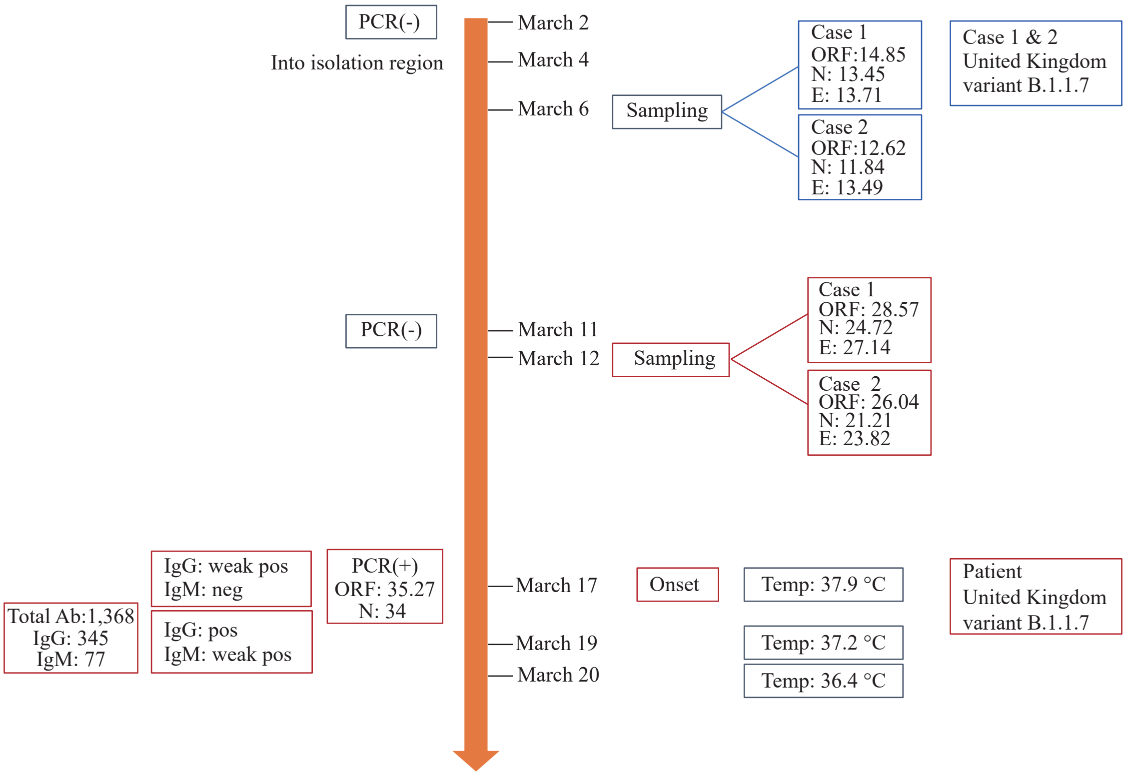

FIGURE 1. Timeline of the patient's medical work, her clinical course, and her virological testing.
Abbreviations: PCR=polymerase chain reaction; Total Ab=Total antibody; IgG=Immunoglobulin G; IgM=immunoglobin M; ORF1ab=open reading frame 1ab gene; N=nucleocapsid gene; E=envelope gene; Temp=temperature; neg=negative; pos=positive.

virus was a COVID-19 variant B.1.1.7 lineage virus and that it had high homology with isolates from 2 COVID-19 patients in the isolation ward who had returned to China from Uzbekistan on March 5.

The patient had two close contacts with both of the returnees from Uzbekistan. With assistance from other nurses, she obtained nasopharyngeal swabs (left and right nares) and an oropharyngeal swab from each returnee on March 6 and again on March 12. As shown in Figure 1, the 2 returnees had strongly positive qRT-PCR test results, with *Ct* values of the 3 targeted genes ranging from 11.84 to 14.85 in the March 6 samples and from 21.21 to 28.57 in the March 12 samples. During interviews with her and her colleagues, she indicated that she was well trained in use of personal protective equipment (PPE) and conducted medical procedures precisely, according to standard operating procedures.

The 33 colleagues on her team were transferred to another designated hospital for quarantine. Three serial qRT-PCR tests, conducted between March 17 and March 19, were all negative. None of the team members became febrile or ill. Prior to working in the isolation are, all 33 staff had been vaccinated with the same type of inactivated COVID-19 vaccine; 30 staff completed 2-dose regimens, while 3 received only 1 dose due to personal reasons. Blood samples from all 33 staff were obtained on March 19 and the levels of COVID-19 virus total antibody, IgG, and IgM were measured by chemiluminescence. As shown in Figure 2, all 30 fully vaccinated staff were positive in total antibody with an average COI of 19.77 (ranging from 1.7 to 150.83) and positive in IgG with an average COI of 20.29 (ranging from 3.69 to 64.33). The 3 staff who received 1 dose of vaccine tested negative (COI<1.0) in total antibody; 2 of the 3 were also IgG negative; 15 of the 30 fully vaccinated individuals were positive in IgM, while the 3 recipients that received 1-dose were negative. On Day 6, 13, 20, and 27 after quarantine, the 33 staff were tested again with qRT-PCR and all tested negative.

More than 3,000 healthcare workers and their family members were asked to stay at their work place or at home. All tested negative by qRT-PCR. Hundreds of environmental samples were obtained, including in the dormitory, isolation area, and other buildings of the hospital. Other than positive samples from the patient's room, all environmental samples were negative by qRT-PCR.

DISCUSSION

This case is the first infection of a healthcare professional working in an isolation region of a designated COVID-19 hospital since March 2020. Based on viral sequencing, this laboratorian clearly acquired infection from hospitalized, imported COVID-19 cases. There was no outbreak of COVID-19 in Xi'an at the time, and the only domestic case reported since January was an imported case from Hebei Province who had been infected by a different strain of COVID-19 virus. Routine viral qRT-PCR testing before and 7 days after she entered the isolation area imply that it is extremely unlikely that she was infected outside of the isolation area. Due to a rapid and timely response, transmission into the community was prevented.

Based on the epidemiological investigation, we believe that the laboratorian was likely infected on March 12 when she obtained throat swabs for the 2 imported cases of COVID-19. She was negative by qRT-PCR on March 11, and on March 12, when she obtained swabs from the 2 returnees, both returnees had high viral loads of the B.1.1.7 variant. Simultaneously obtaining two nasopharyngeal swabs and one oropharyngeal swab is a high-risk procedure. People being sampled often sneeze or retch, expelling virus. The laboratorian's chronic rhinitis may have

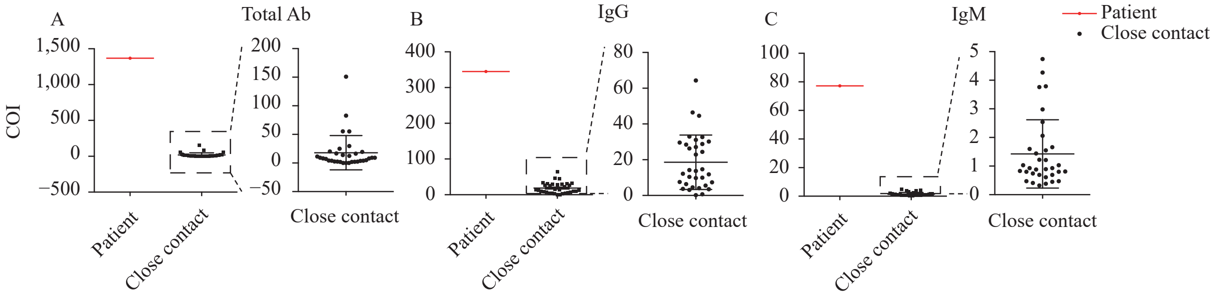

FIGURE 2. Serological assays for COVID-19 virus antibody for the patient and her 33 colleagues (shown as close contacts). Antibody titers were measured with commercial chemiluminescence kits for COVID-19 virus. Cutoff index (COI) values are indicated on the Y-axis. (A) Total antibody (Total Ab); (B) Immunoglobulin G (IgG); (C) Immunoglobin M (IgM).

contributed to her propensity for mouth breathing, which may increase risk inhaling virus around a mask. Although the potential influence of chronic rhinitis on susceptibility to COVID-19 remains unknown, one study has showed that allergic rhinitis and asthma confer a greater risk of susceptibility to COVID-19 virus infection (*5*). We believe that a combination of factors may contribute to risk of infection.

The patient and 30 of her teammates had completed the full COVID-19 vaccination regimen by the beginning of February. Their serological assays confirmed COVID-19 virus seroconversion. Three individuals had received only one dose of vaccine; their serological tests showed low antibody levels. Unlike for the other staff, the patient's whole antibody, IgG, and IgM titers were all very high — an observation that implies that the patient had been immunized against by the vaccine, since the high titers are consistent with a boosting response. There are several types of COVID-19 vaccines on the market worldwide; all are effective, but none is 100% effective. One study showed lower efficacy in a high-risk population that had a high force of infection — healthcare professionals — compared with a community population (*6*). Our case report serves as a reminder of the importance of appropriate PPE for medical staff, even after vaccination. Globally-available COVID-19 vaccines have been demonstrated to prevent severe COVID-19 (*7*). Although it is not possible to prove by a single case study, the clinical course of the patient is consistent with a COVID-19 vaccination benefit — making the illness mild and short.

The COVID-19 vaccines in use in China have very good efficacy, all meeting or exceeding the WHO Target Product Profile efficacy requirements. Breakthrough infections happen with all vaccines, and these breakthroughs merit study. We suggest conducting routine, systematic study of every fully vaccinated breakthrough case. Such study should include tracing the source of the virus, identifying the virus lineage to find variants, measuring antibody levels, and assessing for vaccine-associated enhancement of disease (VAED). Systematic study requires controls matched to breakthrough cases for assessing severity of illness (for VAED) and characteristics of the viruses and the vaccines (for effectiveness). Systematic study will help ensure that vaccination continues to be the safest and most effective way to prevent COVID-19.

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Outbreak Reports

A COVID-19 Outbreak — Nangong City, Hebei Province, China, January 2021

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Summary

What is known about this topic?

Coronavirus disease 2019 (COVID-19) is widespread globally. In China, COVID-19 has been well controlled and has appeared only in importation-related cases. Local epidemics occur sporadically in China and have been contained relatively quickly.

What is added by this report?

Epidemiological investigation with genome sequence traceability analysis showed that the first case of COVID-19 in Nangong City acquired infection from a confirmed case from Shijiazhuang City; infection subsequently led to 76 local cases. All cases were associated with the index case, and most were located in Fenggong Street and did not spread outside of Nangong City. The main routes of transmission were family clusters, intra-unit transmission, and nosocomial transmission.

What are the implications for public health practice?

This study highlights new techniques for rapidly tracing cases and identifying COVID-19 transmission chains. The different epidemiological characteristics in Nangong City, from the earliest stages of the outbreak, suggest that allocation of health sources for prevention and treatment were reasonable. Preventing transmission within medical institutions and isolation facilities and strengthening management in the community should be priorities for COVID-19 control during a city lockdown.

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus (also known as severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) that was declared a pandemic by the World Health Organization (WHO) in March 2020. COVID-19 is widespread globally but has been well controlled in China with only scattered, importation-related local outbreaks following containment in April 2020.

On January 3, 2021, Nangong City (part of Xingtai City, Hebei Province with 484,000 residents in 2017) reported its first symptomatic case of COVID-19. China CDC, Hebei CDC, and Xingtai CDC jointly carried out a field epidemiological investigation and traced the outbreak. On January 6, Nangong City started its first round of population-wide nucleic acid screening. On January 9, Nangong City was locked down by conducting control and prevention measures that included staying at home and closing work units for seven days. As of January 27, 2021, 76 cases had been reported in Nangong City; among these, 8 were asymptomatic. No additional cases have been reported to date, and there were no COVID-19-related deaths in the outbreak.

INVESTIGATION AND FINDINGS

The index COVID-19 case in Nangong City is a 34-year-old male office worker (Patient A) when he noticed a fever and took his temperature, finding it to be 38.1 ℃ at 14∶00 on January 1, 2021. At 15∶30, he drove to the fever clinic of Nangong People's Hospital for evaluation and treatment and was screened for COVID-19 by nucleic acid testing. Patient A was informed on January 2 that his nucleic acid test was positive. On January 3, Patient A was diagnosed as a confirmed case of symptomatic COVID-19 and treated in isolation.

The field epidemiological investigation and case tracing found that Patient A went to the respiratory department of Hebei Children's Hospital in Shijiazhuang City on December 25, 2020 and had close contact with a symptomatic case of COVID-19 in a waiting area. The contact, Patient B, female, from Gaocheng District, Shijiazhuang City, had asthma and was febrile on December 25 (highest temperature 38.5 ℃). Video monitoring showed Patient A and B were in a room 4.5 meters apart from each other for 16 minutes. During this period, they did not talk or touch the same objects. Patient B removed her face mask twice to eat, and Patient A pulled down his face mask to make phone calls. Whole genome sequence traceability analysis from Hebei CDC found that the viral nucleic acid sample from Patient A, compared with the Wuhan reference strain (NC_045512), had mutation characteristics of the gene locus of the European family of the L genotype and was on the B.1.1.123 branch. The genome sequence has 21 nucleotide mutations that are same as virus samples from Gaocheng District cases. The genetic sequences of Patient A's and Patient B's viruses were highly homologous, presumably representing a common transmission source.

Considering dates of illness onset identified by the field epidemiological investigation and the sampling date of the first positive nucleic acid test, the first COVID-19 infection in Nangong City occurred on January 1. Since then, the number of cases reported each day increased rapidly and peaked on January 13 with 12 cases reported. Following the peak, the number of cases reported each day decreased until the last case was reported on January 23. The cumulative number of cases increased fastest from January 9 to January 13 (Figure 1). Among all 76 cases, 46 (60.5%) were among males; 63 (82.9%) were among young to middle-aged (15–59 years old) individuals; the ages ranged from 2 to 83 years with a median of 34.5 years; 34 (44.7%) were farmers, 11 (14.5%) were office staff, and 10 (13.2%) were health care workers; 59 (77.6%) came from Fenggang Street, and 17 (22.4%) came from seven other streets or townships (there are 15 streets and townships in Nangong City) (Figure 2, Table 1). Symptoms among the 68 symptomatic cases were generally moderate or mild.

Two cases, including the index case, were identified by fever clinics; 16 were found by community-wide nucleic acid screening; 5 were detected by daily routine tests for medical staff conducted by hospitals; and 53 were discovered by regular, confirmatory nucleic acid screening of close contacts or sub-close contacts including 48 (63.2%) identified during centralized isolation or quarantine.

Transmission chains were characterized by mixed existence of intra-unit transmission, family clusters, nosocomial infections, and community transmission associated with the index case Patient A. There was 1 intra-unit transmission with 23 (30.3%) people infected, 2 family clusters (identified by ≥5 people infected) with 17 (22.4%) people infected, 3 re-transmissions in medical institutions with 8 (10.5%) people infected, and 1 community cluster (identified by ≥5 people infected) with 6 (7.9%) people infected. There was the possibility of cross-infection in isolation places, but there is no definitive supporting evidence. All COVID-19 cases in Nangong City were related to the index case, Patient A; eight generations of infection were observed in the transmission chains.

DISCUSSION

This was a local outbreak of COVID-19, with the first case coming from a known epidemic area (Gaocheng District, Shijiazhuang City). The epidemic was confined to a limited area — mainly Fenggang Street — and did not spread outside Nangong City, indicating that the strategies used in Nangong City

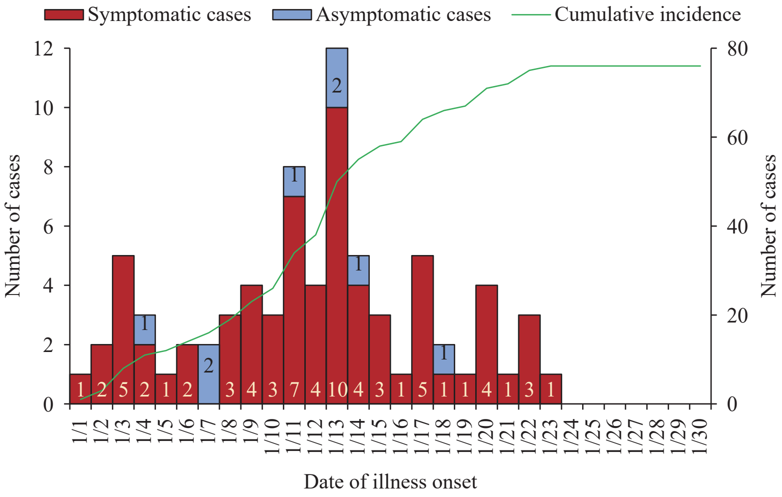

FIGURE 1. Distribution of date of illness onset based on field epidemiological investigation and cumulative incidence of COVID-19 cases from January 1 to January 23, 2021 in Nangong City, Hebei Province, China.

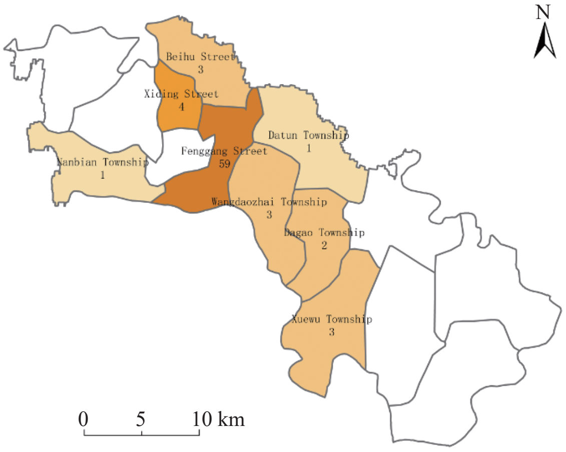

FIGURE 2. Geographic distribution of the 76 COVID-19 cases reported in Nangong City, Hebei Province, China, January 3 to January 27, 2021.

were highly effective.

Compared with the earliest cases in China during 2019–2020 (*1–2*), the epidemic in Nangong City was characterized by milder symptoms and faster and more insidious transmission and occurred mainly young and middle-aged adults. These characteristics suggest reasonable allocation of health sources and effective prioritization of health policies in the control, prevention, and treatment of COVID-19.

Application of new technologies and new investigation methods were crucial for case tracing and identification of transmission chains. For various reasons, it can sometimes be difficult to provide exact information in field epidemiological investigation reports. When possible, we should integrate digital techniques, big data, trajectory tracking systems, monitoring videos, and sensitive and timely laboratory detection technologies into field investigations. Indeed, in the Nangong City outbreak, source identification for the first case and transmission chain identification for subsequent cases were accomplished with the assistance of monitoring video surveys.

Early and proactive measures are highly effective and

TABLE 1. Epidemiological characteristics of the 76 COVID-19 cases reported in Nangong City, Hebei Province, China, January 3 to January 27, 2021.

Characteristics	**Symptomatic cases**		**Asymptomatic cases**		**Total**	
	N	**Percentage (%)**	**N**	**Percentage (%)**	**N**	**Percentage (%)**
Total	68	89.5	8	10.5	76	100.0
Gender						
Female	29	42.6	1	12.5	30	39.5
Male	39	57.4	7	87.5	46	60.5
Age group (years)						
<15	5	7.4	1	12.5	6	7.9
15–29	17	25.0	2	25.0	19	25.0
30–44	20	29.4	3	37.5	23	30.3
45–59	19	27.9	2	25.0	21	27.6
≥60	7	10.3	0	0	7	9.2
Occupation						
Farmer	31	45.6	3	37.5	34	44.7
Office staff	11	16.2	0	0	11	14.5
Health care worker	8	11.8	2	25.0	10	13.2
Workman	5	7.4	1	12.5	6	7.9
Teacher	5	7.4	0	0	5	6.6
Student	4	5.9	1	12.5	5	6.6
Child	2	2.9	1	12.5	3	3.9
Business services	2	2.9	0	0	2	2.6
Location						
Fenggang Street	52	76.5	7	87.5	59	77.6
Other streets	16	23.5	1	12.5	17	22.4

play an important role in rapid control of infectious diseases (*3*) as was seen in the COVID-19 outbreak in Nangong City. First cases are usually identified in medical institutions, suggesting the necessity of continuously improving the sensitivities of symptom surveillance, fever screening, and disease diagnosis in hospitals, private clinics, and even pharmacies. We should therefore strengthen and routinize standardized construction and management of fever clinics and their training of professionals. We should work to avoid nosocomial infection of COVID-19, and we should carry out rapid and accurate risk assessments in outbreaks, using nucleic acid testing for close contacts and people at high risk to provide evidence to further improve evaluation and implementation of measures.

When vaccines and effective medicines are not available on-demand, strictly implementing containment and suppression public health strategies (*4*) is urgently needed once an outbreak happens. However, it is challenging to prevent transmission in community and isolation points under a city lockdown. For communities, in addition to implementation of relevant control measures, we should ensure supplies for normal living, strengthen management of service providers and volunteers, and promote health education. In isolation points, we should take strict prevention measures, such as staying in separate rooms, not allowing visitors, ensuring adequate ventilation, employing sensitive fever screening, and properly disinfecting the environment.

Personal protection is one of the most effective ways to prevent infection. Measures should include maintaining social distance, hand hygiene, respiratory etiquette, face mask use, and not smoking. In the Nangong City epidemic, the index case, Patient A, was likely infected after he pulled down his face mask to make a phone call. Case number 75 was likely infected when removing his or her face mask for smoking while in the presence of a COVID-19 carrier.

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Outbreak Reports

Index and First-Generation Cases in a COVID-19 Outbreak — Jilin Province, China, 2021

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Summary

What is already known on this topic?

Contact tracing and testing with isolated medical care of identified cases is a key strategy for interrupting chains of transmission of COVID-19 and reducing mortality associated with COVID-19. At the early phases of the COVID-19 pandemic, due to test capacity limitations, case finding often started from suspected cases.

What is added by this report?

The index patient infected 74 individuals who were close contacts that were identified through contact tracing, and exposed individuals were monitored in quarantine with daily polymerase chain reaction (PCR) testing. All individuals were asymptomatic initially, but all PCR-positive individuals eventually developed symptoms. Infectivity was documented up to 8 days before being confirmed as a symptomatic case, approximately 4 days before turning PCR positive.

What are the implications for public health practice?

During an outbreak, we suggest tracing close contacts from both PCR-positive individuals and suspected cases, rather than from suspected cases alone. Due to the long period of infectivity before turning PCR positive or developing symptoms, close contacts that had contact with a newly PCR positive case within 4 days should be judged as at risk of being infected; close contacts that had contact within 8 days of a newly symptomatic case should be judged as at risk being infected.

Contact tracing — along with robust testing, isolation, and care of cases — is a key strategy for interrupting chains of transmission of coronavirus disease 2019 (COVID-19), caused by COVID-19 virus also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and reducing mortality associated with COVID-19 (*1–2*). Close contacts are defined as individuals who have had contact, without effective protection, with one or more suspected or confirmed COVID-19 cases any time starting 2 days before onset of the suspected or confirmed cases' symptoms or 2 days before sampling for laboratory testing of asymptomatic infected persons (*3–4*). At the early phases of COVID-19 pandemic, the finding of COVID-19 cases usually began from suspected cases due to delayed testing capabilities (*5*).

On January 9, 2021, the first case (Patient A) of a COVID-19 outbreak arrived unknowingly infected in Dongchang District, Tonghua City, Jilin Province, China. He gave three product promotion lectures in Location A and infected audience members during the lectures. By January 31, 2021, 74 lecture participants were confirmed to have been infected and were considered first-generation cases. The Tonghua CDC led an investigation of this outbreak that ultimately identified 140 cases (*6*). In this article, we focused on the 74 first-generation cases, which all had known exposure times and locations. Once Patient A had been diagnosed using polymerase chain reaction (PCR) testing as being infected, lecture participants were located and placed in quarantine where they were tested with PCR and evaluated for COVID-19 symptoms every day. This careful observation period under quarantine provided an opportunity to assess infectivity period, incubation time, the time between becoming PCR positive and developing symptoms. We report results of our study of first-generation cases to further improve investigation and management of close contacts of COVID-19 cases.

INVESTIGATION AND RESULTS

We obtained data about the index case and first-generation cases from the National Infectious Diseases Reporting System (NIDRS) and the Tonghua CDC outbreak investigation. In response to the outbreak, close contacts were quarantined, and nucleic acid testing was conducted daily to determine whether the contacts had been infected. Contacts who turned PCR positive were transferred from quarantine to a hospital and were reported to NIDRS within 2 hours. CDC staff would complete an epidemiological report within 24 hours. As soon as PCR-positive individuals developed symptoms, they would be classified by physicians as confirmed cases, and their NIDRS record would be updated with their new status as a confirmed COVID-19 case.

On January 10 and 11, Patient A gave three lectures in Site A in Tonghua City. As of January 31, 74 close contacts were diagnosed as COVID-19 confirmed cases. All were first-generation PCR-positive cases, and all were PCR-positive, first-generation infected individuals ultimately became symptomatic. The median age was 72 (inter-quartile range, 60–87) years (Figure 1A); 12 (16.22%) were critical cases, 10 (13.51%) were severe cases, 47 (63.51%) were moderate cases, and 5 (6.76%) were mild cases.

All first-generation cases had attended lectures by Patient A on January 10 or 11. The average time between exposure (lecture) and turning PCR-positive while in quarantine was 6.15 days (95%CI: 5.65–6.65) (Figure 1B). The average time between exposure and being diagnosed as confirmed (symptomatic, PCR-positive) cases was 8.64 days (95%CI: 8.04–9.23) (Figure 1C). The average time between turning PCR-positive and being diagnosed as confirmed cases was 2.49 days (95%CI: 2.00–2.92).

Patient A had been infected by an adjacent passenger on train K350 on January 5, 2021 (*7*). He tested PCR-positive on January 12, 2021 and was diagnosed as a confirmed (symptomatic) case on January 16. He infected participants who attended his lecture in Changchun City, Jilin Province on January 8. Therefore, the earliest date that Patient A had documented infectivity was January 8, 4 days before Patient A tested PCR-positive and 8 days before his diagnosis as a confirmed case (Figure 2).

DISCUSSION

During the earliest phase of the COVID-19 pandemic in China, the finding of COVID-19 cases was often delayed due to insufficient laboratory capacity, with long times between development of symptoms (i.e., a suspected case) and being confirmed as COVID-19 cases by PCR (*4*). Markedly improved PCR testing capacity was instrumental in stopping the

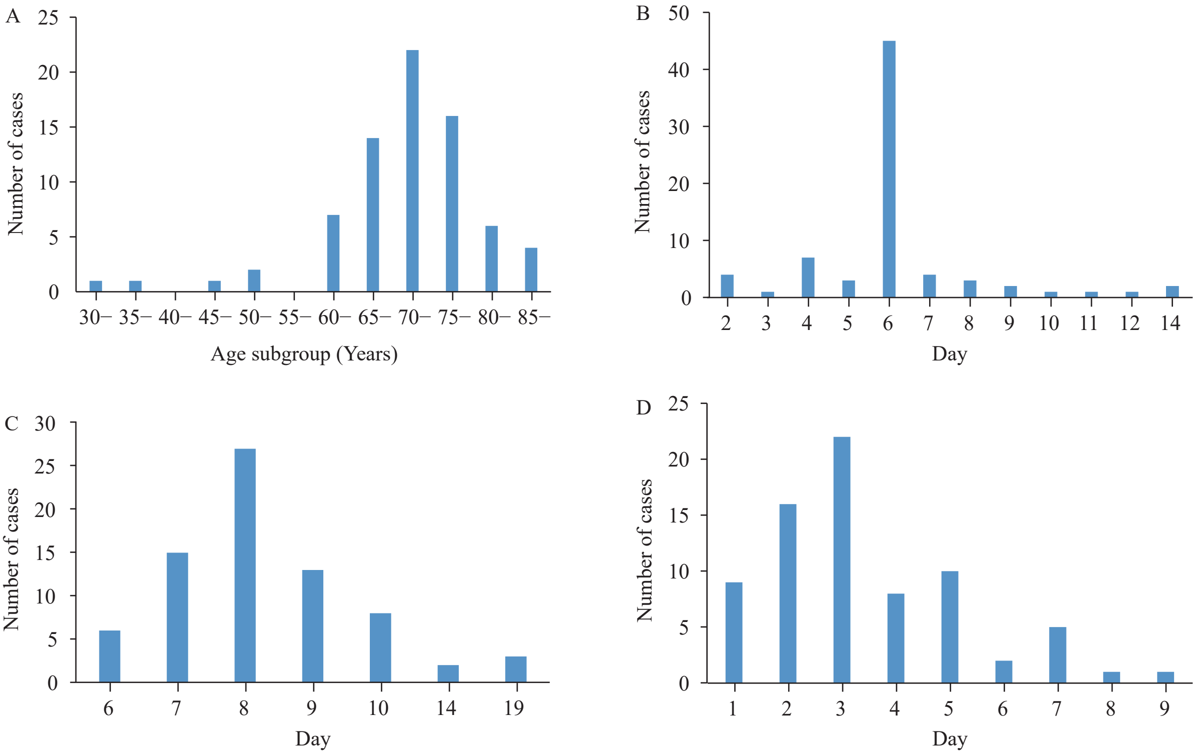

FIGURE 1. Observations during quarantine of the 74 first-generation COVID-19 cases infected by Patient A on either January 10 or January 11, 2021, Jilin Province, China. (A) Age distribution. (B) Period between exposure to Patient A and turning PCR positive. (C) Period between exposure to Patient A and being confirmed as a COVID-19 case. (D) Period between turning PCR-positive and being confirmed as a COVID-19 case.

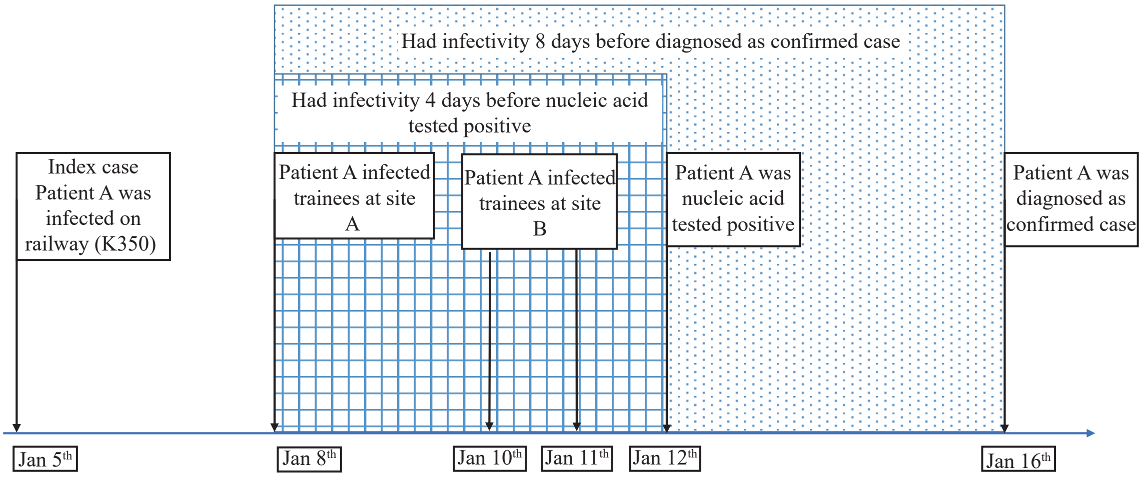

FIGURE 2. Timeline of infectivity of Patient A before and after testing positive with PCR and being confirmed as a COVID-19 case, January, 2021, Jilin Province, China.

Tonghua outbreak (*6*). By the time of the Tonghua outbreak, samples from close contacts of cases could be tested, and laboratory results obtained within 24 hours. Higher PCR throughput helped to efficiently find infected individuals among close contacts in order to quarantine contacts and stop chains of transmission. Based on the case finding with population-wide PCR testing used in this outbreak, we suggest that during an outbreak response, close contacts should be traced from PCR-positive individuals and suspected cases, rather than from suspected cases only.

Patient A caused a large cluster of COVID-19 cases infected during his lectures. Many cases were serious — 39% of cases were classified as critical or severe. All 74 of the first-generation cases developed symptoms, possibly indicating that Patient A was at an early stage of illness and secreting large amounts of virus (*6*). His lectures were lengthy and were held in small, non-ventilated spaces, possibly increasing inhalation of virus. One recent study found viral loads among index cases to be a leading determinant of SARS-CoV-2 transmission. In that study, risk of transmission from symptomatic cases and shorter incubation times were strongly associated with viral loads during contact, in a dose-dependent manner (*8*).

Local CDC staff traced his close contacts once Patient A tested positive by PCR on January 12. The close contacts were quarantined and tested with PCR daily. Once PCR-positive, they were transferred to fixed point medical institutions for medical observation and treatment, when indicated. If a PCR-positive case developed symptoms, clinicians would diagnose him or her as a confirmed COVID-19 case. All times were well documented, allowing precise analysis. We measured the incubation periods of the confirmed cases and found the average to be 8.64 days. We found that the time between turning PCR positive and developing symptoms was 2.49 days.

Patient A’s infection timeline was clear: he was infected on January 5; gave lectures and infected participants on January 8, 10, and 11; turned PCR-positive on January 12; and diagnosed as a confirmed COVID-19 case on January 16. The clear timeline enabled determination of infectivity before diagnosis. Patient A was infectious at least eight days before being diagnosed as a confirmed case and was infectious at least four days before turning PCR-positive. This timing implies that using two days between close contact and PCR positivity as the risk period for infection is too short of a time interval as many infections would be missed. One report in China found transmission as early as five days before onset of symptoms in an index case (*9*). Our investigation suggests that the close contact tracing period should be four days before samples are obtained for PCR testing of asymptomatic infected persons, and even longer for confirmed cases with symptoms.

This report was subject to at least two limitations. First, all subjects were elderly; the corresponding time periods and degrees of infectivity may be different for younger people. Second, all subjects were first-generation cases; subsequent generation cases may differ by infectivity or timing. However, studying first-generation cases while under quarantine or medical observation allowed precise timing of infection or illness events.

(Data updated on February 1, 2021)

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Notes from the Field

Emerging Variants of B.1.617 Lineage Identified Among Returning Chinese Employees Working in India — Chongqing Municipality, China, April 2021

Sheng Ye[1,&]; Yongjun Zhang[2,&]; Xiang Zhao[3]; Zhen Yu[1]; Yang Song[3]; Zhangping Tan[1];
Yun Tang[1]; Shuang Chen[1]; Mingyue Wang[1]; Hua Ling[1,#]

On April 22 and 23, 2021, 3 confirmed COVID-19 cases in passengers on an arriving airplane from Nepal were reported by Chongqing Public Health Medical Center. Preliminary epidemiological investigation revealed these 3 patients, males aged 20–30 years, were coworkers of a cellphone company that has a manufacturing base in Noida, India, where they worked with their Indian colleagues since late 2019. They were well protected at the workplace, where a dust-free environment was required as a cellphone making industry standard, and they took relevant precaution measures against the coronavirus disease 2019 (COVID-19) pandemic in their daily life in India.

According to epidemiological investigation reports, their business trip started since April 19, when they were escorted from Noida to New Delhi in a chartered car. On the same day, with protective clothes, N95 respirators, goggles, and gloves equipped throughout the trip, they flew to Kathmandu, Nepal. They arrived at hotels in a chartered cab and lived there until April 21. Then they went to the airport in a chartered cab in the morning and flew to Chongqing Municipality, China, with full protective measures. Their COVID-19 tests were negative on multiple occasions in India, and the latest negative results for Patient A and Patient B were on April 17, and for Patient C was on April 19. However, their nucleic acid results for COVID-19 were positive at Chongqing Customs on April 21 and subsequently confirmed by local CDC laboratories.

Patients were transferred to the designated COVID-19 hospital, the Chongqing Public Health Medical Center. Clinical manifestation of three patients included normal body temperature, blood tests, and liver-kidney functions. Abnormalities in chest computed tomography (CT) suggested infectious lesions, classified as common type of COVID-19.

Specimens of the confirmed patients were sent to Chongqing CDC and sequenced on April 28 and 30. In comparison with the COVID-19 reference strain (GenBank Accession: NC_045512), also known as SARS-CoV-2, these isolates possessed 34–36 variation sites in nucleic acids, including 8–10 variations in the spike protein. Phylogenetic analysis of genome sequences indicated these isolates belonged to the Pangolin lineage B.1.617, an emerging variant in India first identified in October 2020 and has recently been designated as variants of interest (VOIs) by the World Health Organization (WHO) (Figure 1) (*1*–*2*). Notably, 6 variation sites of amino acid residuals (T19R, L452R, T478K, D614G, P681R, and D950N), which were identical to those in Indian B.1.617.2 variants, were observed in the 3 isolates, supporting that the COVID-19 infection on these 3 patients probably occurred in India. Since most of B.1.617 variants reported in 17 countries contained 2 key mutations, L452R and E484Q, these imported cases in Chongqing Municipality were excluded from such double mutant variants. Constant surveillance of genome sequences in imported cases are required to track transmission and evolution of COVID-19 virus during the ongoing COVID-19 pandemic.

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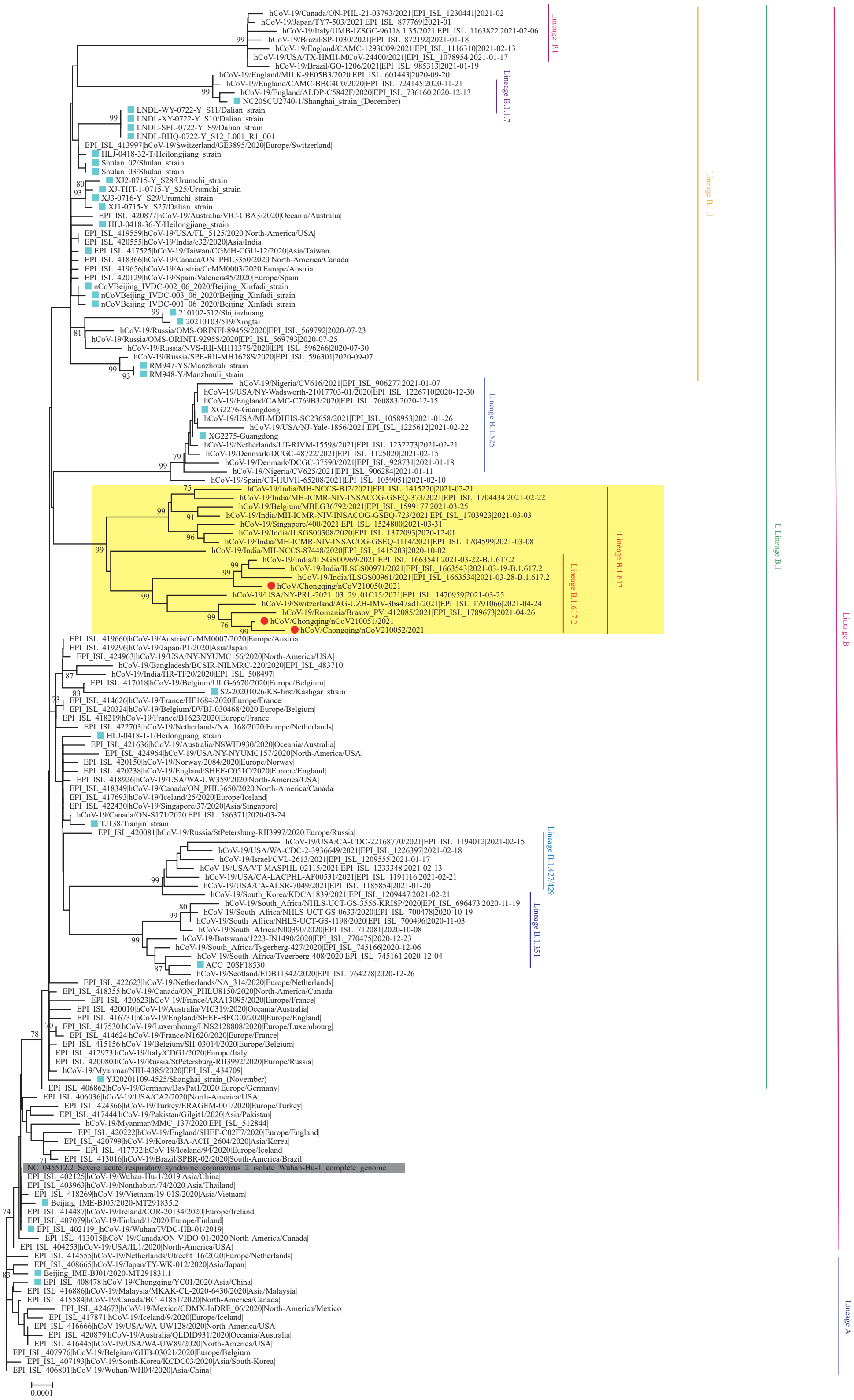

FIGURE 1. Neighbor-joining phylogenetic tree based on the whole genome sequences of COVID-19 representative strains. The 3 Chongqing strains are indicated by red dots; the representative strains from B.1.617 lineage are highlighted with a yellow background; strains associated with specific outbreaks in China are indicated by blue squares; and the Wuhan reference strain is shaded in gray. The PANGOLIN lineages were marked and colored on the right. The tree was rooted using strain WH04 (EPI_ISL_406801) in accord with the root of PANGOLIN tree.

Notes from the Field

Two Imported Cases of New Variant COVID-19 First Emerging in Nigeria — Guangdong Province, China, March 12, 2021

Yao Hu[1]; Xiang Zhao[2]; Zhencui Li[1]; Min Kang[1]; Xiaoling Deng[1]; Baisheng Li[1,#]

On February 19, 2021, a 48-year-old male (Case A, XG2275) returning from Nigeria and a 38-year-old female (Case B, XG2276) returning from Ukraine via airplane were tested by the laboratory of Guangzhou Customs using nose swabs to test for coronavirus disease 2019 (COVID-19). Both of them tested positive and were transported by ambulance from the isolation point to Guangzhou Eighth People's Hospital. They are still undergoing centralized medical observation in the hospital after recovery.

On March 5, Guangdong CDC received the samples and began virus isolation and genome sequencing analysis. On March 10, the 2 samples were sequenced using Nanopore GridION. On March 12, the sequencing analysis concluded that the 2 virus genomes belonged to lineage B.1.525, a new COVID-19 variant first emerging in Nigeria, which was first detected by genome sequencing in mid-December in Nigeria but was also quickly found in cases in the United Kingdom, France, and elsewhere. As of March 8, 2021, a total of 577 counted sequences in 30 countries were found in the world (*1*).

Compared with the Wuhan reference sequence (EPI_ISL_402119) (*2*–*3*), the strain from Case A (XG2275) displayed 24 nucleotide variation sites (C241T, C1498T, A1807G, G2659A, C3037T, C6285T, T8593C, C9565T, C14407T, C14408T, C18171T, A20724G, A21717G, C21762T, G23012A, A23403G, G23593C, T24224C, C24748T, T26767C, C28308G, A28699G, C28887T, and G29543T) including the single nucleotide polymorphisms (SNPs) that defined the L-lineage European branch and belonged to the Pangolin lineage B.1.525 (Figure 1). Furthermore, 10 amino acid mutation sites (E:L21X, M:I82T, N:A12G, N:T205I, S:Q52R, S:A67V, S:E484K, S:D614G, S:Q677H, and S:F888L) and 3 amino acid deletions (H69del, V70del, and Y144del) were detected in the protein that corresponded to the features of the Nigerian variant (B.1.525) (*4*).

Compared with the Wuhan reference sequence (EPI_ISL_402119) (*2*–*3*), the Case B (XG2276) strain displayed 22 nucleotide variation sites (C241T, C1498T, A1807G, C3037T, C6285T, T8593C, C9565T, C14407T, C14408T, C18171T, A20724G, C21762T, G23012A, A23403G, G23593C, T24224C, C24748T, T26767C, C28308G, A28699G, C28887T, and G29543T) including the SNPs that defined the L-lineage European branch and belonged to the Pangolin lineage B.1.525 (Figure 1). Furthermore, 9 amino acid mutation sites (E:L21X, M:I82T, N:A12G, N:T205I, S:A67V, S:E484K, S:D614G, S:Q677H, and S:F888L) and 3 amino acid deletions (H69del, V70del, and Y144del) were detected in the protein that corresponded to the features of the Nigerian variant (B.1.525).

The variant first emerging in Nigeria (B.1.525) shares the same 3 amino acid deletions (H69del, V70del, and Y144del) with the 501Y.V1 variant (also known as the B.1.1.7). The mutation E484K is also present in the 501Y.V2 variant first emerging in South Africa (also known as the B.1.351) and Brazilian strains (501Y.V3). The amino acid substitution at position 677 (Q677H) is identical to that found in variants recently described in the United States. The amino acid substitutions Q52R and A67V are unique to the B.1.525 (*4*). This is the third recent detection of a major international variant following the detection of the United Kingdom 501Y.V1 variant and the South African 501Y.V2 variant. The transmissibility and pathogenicity of these mutant variants urgently needs further study (*5*–*6*).

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FIGURE 1. Phylogenetic tree based on the full-length genome sequences of the COVID-19 virus. The Nigerian variants (B.1.525) are highlighted in yellow and the Guangdong imported B.1.525 variant cases are marked with red dots. The strains associated with specific outbreaks in China are marked with blue squares. The Wuhan reference strain is shaded in gray. The 5 distinguished COVID-19 mutants are marked and colored on the right. The L(A)- or L(B)-lineage and sublineages of the COVID-19 virus were marked and colored on the right.

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Profiles

Xiaoping Dong, China CDC's Chief Expert of Virology

Yu Chen[1]; Peter Hao[1]; Nankun Liu[1]; Zhenjun Li[1]; Jingjing Xi[1,#]; Feng Tan[1,#]

Xiaoping Dong is the Chief Expert of Virology of China CDC, Adjunct Professor at Beijing University and Xi'an Jiaotong University, and Adjunct Principal Investigator (PI) at the Chinese Academy of Science and China Academy of Chinese Medical Sciences. He is a syndic of the Chinese Society of Microbiology and the Head of the Group of Medical Virology. During his roughly 40-year career, he has dedicated himself to the studies of medical virology and molecular biology, particularly in the fields of prions, human papillomavirus (HPV), and many emerging infectious diseases. He has also participated in emerging responses and controls of many viral infectious diseases domestically and internationally.

In the period of 1980's and 1990's, his major research interest focused on human papillomavirus (HPV). With the help of DNA hybridization, Dong and his colleagues identified high positive rate of HPV DNAs in the tissues of cervical cancer. During 1991 to 1997, he went to Germany and explored the HPV carcinogenesis under the supervision of Prof. H. Pfister. Dong and the colleagues successfully mapped the binding sites of YY1, a new host factor, in viral long control region (LCR) and confirmed it as a negative regulator for the activity of HPV early promoter. This finding and several others supplied valuable evidence for carcinogenesis of HPV.

Under the guidance of Prof. T Hung, a famous senior Chinese virologist, Dong shifted his research to prion diseases (PrD), when he returned from Germany in 1998. At that time, PrD was not widely recognized in China, and there was almost no capacity to diagnose human PrDs. Dong and his team started a mission to address this challenge by establishing various laboratory diagnostic tools. Chinese National Surveillance for Creutzfeldt-Jacob disease (CNS-CJD) was set up a couple of years later under the leadership of China CDC. With the innovative surveillance methodologies and working mechanism, as well as dozens of training programs, the annual number of suspected CJD cases increased from a small dozen in the beginning to more than 500 cases currently. More than 2,000 cases were diagnosed as sporadic CJD (sCJD) and about 250 cases were diagnosed as genetic PrD (gPrD). Such groundbreaking work supplies not only the platform for diagnosis of human PrDs, but also contributed to the recognition of China as a bovine spongiform encephalopathy (BSE)-free country. The accumulated data over the past roughly 20 years of CJD surveillance have helped explain the features of PrDs in China for the first time systematically and precisely.

Dong's team identified 19 different gPrD-associated mutations in Chinese people for the first time. The top 5 most frequent gPrDs in Chinese were T188K-gCJD (29.8%), D178N-FFI (25.7%), E200K-gCJD (18.8%), E196A-gCJD (7.3%) and P102L-GSS (6.4%). Such pattern of *PRNP* mutants in Chinese gPrDs was not only completely distinct from that of Caucasian, but also different from Japanese and Korean. Some types of gPrDs showed geographic relationship, e.g., more D178N-FFI patients came from Henan and Guangdong, and more T188K-gCJD cases lived in the northern provinces. These findings and others of Chinese gPrDs enriched the knowledge of gPrDs worldwide.

After years of efforts, Dong and his team successfully set up two *in vitro* prion replication techniques, protein misfolding cyclic amplification (PMCA), and real-time quaking-induced conversion (RT-QuIC), which are already widely used in various studies. RT-QuIC has been used in the diagnosis for human PrDs, with specimens of the brain, cerebrospinal fluid (CSF), and skin. Additionally, a series of infectious cell models, animal models, and transgenic mice models infected with different prion strains had been established. Those techniques form the solid and unique research platform for prions in the levels of molecules, cells, tissues, and animals *in vitro* and *in vivo*.

In addition to human CJD surveillance, Dong and his team have several achievements in prion-related research including the following: 1) identification of autophagy activation in the brains of human PrDs and prion-infected rodent models; 2) global omics profiles that identified differentially expressed proteins and affected biological pathways; 3) aberrant alterations of biological functions in brains; 4) activation of brain native immunity;

5) abnormal changes of protein post-translation modifications; and 6) cross-species transmission demonstrated by PMCA assisting prion strains to overcome species barriers. These accomplishments helped enrich the knowledge of prion biology and pathology.

In the past 20 years, Dong participated actively in the emerging response and control for many infectious diseases. In 2003, he dedicated himself to the fight against SARS. He went many times to the front lines in Guangdong, Beijing, and Shanxi for case investigation, epidemiological survey, and laboratory diagnosis. Working together with Sinovac and the Chinese Academy of Medical Science, he contributed greatly to the research and development (R&D) of an inactivated SARS vaccine that was the first SARS vaccine to finish Phase I clinical trials worldwide. In an outbreak of human cases infected with H5N1 influenza virus in 2005, as the team leader from China side, he worked closely with the experts of the World Health Organization (WHO) for the investigations of the first two cases. He worked as a co-PI in the R&D of an inactivated vaccine of H5N1 virus for human use, which successfully finished Phase I and II clinical trials. In 2015, he went to Sierra Leone as China CDC's team leader for Ebola disease. He and his colleagues set up a biosafety laboratory level III (BSL-3) in Freetown and conducted thousands of sample testing. Since the emergence of coronavirus disease 2019 (COVID-19) in 2020, Dong has fully dedicated himself to the national and international responses. He attended numerous domestic and international consultant Webinars, went the front lines in Beijing, Heilongjiang, Shaanxi, etc., contributed to the biweekly reports of the global COVID-19 pandemic, consulted for the R&D of COVID-19 vaccines, and had several other contributions.

Dong has rich experience in international cooperation, which has led to his appointment as Director of Center for Global Public Health of China CDC since 2018. He and his colleagues visited many countries in Africa and Asia, communicated with different international organizations, drafted China CDC's global health strategic and development plan, created training programs, dispatched short- and long-term Chinese experts to different countries, and implemented international collaborating projects. New communication platforms have been developed and gradually recognized internationally, such as annual Consultation on Public Health Development (CPHD), roundtable of Belt & Road Public Health Cooperation Network, program of Molecular Diagnosis and Pathogen Determination (ModPad), etc. The collaborating fields cover major infectious diseases, emerging responses, public health events, training and education, task-force capacity building, laboratory capacity, and others.

Dong has rich experience in medical virology and public health based on his long-term work in clinical medicine, laboratory, disease surveillance, and field emerging response. He has contributed significantly to academic research as a PI for more than 30 national and international projects and published more than 220 SCI-cited papers. Dong's international collaborative experience has provided him with wider perspective on medical virology and public health, and he will continue to use this expertise as China CDC's Chief Expert of Virology.

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