ISSN 2096-7071
CN 10-1629/R1

CHINA CDC WEEKLY

Vol. 2 No. 47 Nov. 20, 2020

CCDC weekly

中国疾病预防控制中心周报

ISSN 2096-7071

Cover Image: On September 24, 2019, staff of the National Institute of Occupational Health and Poison Control, China CDC were collecting benzene sample in a coking plant, Jiangsu Province (Photographer: Caihong Xing, National Institute of Occupational Health and Poison Control, China CDC).

Preplanned Studies

Characteristics in the Distribution of Chronic Benzene Poisoning Associated Industries — 6 PLADs, China, 2005−2019

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Summary

What is already known on this topic?

Starting in the early 1950s, the main industries in China associated with chronic benzene poisoning (CBP) included painting, pharmaceuticals, and shoemaking. However, because of rapid socioeconomic development, the distribution of industries associated with CBP likely changed.

What is added by this report?

From 2005 to 2019, CBP has become an increasingly important type of chronic occupational poisoning (COP) in China. CBP was mainly found to have occurred in manufacturing industries, especially private enterprises and small and medium-sized enterprises. The sub-industry with the highest proportion of CBP cases was general and special equipment manufacturing, followed by chemical raw materials and chemical manufacturing.

What are the implications for public health practice?

CBP was found to be the main component of COP in China, so the supervision and management in manufacturing, especially in the medium-sized and small enterprises, need to be strengthened. Occupational benzene exposure limits should also be adjusted accordingly.

Chronic exposure to benzene causes poisoning, acute myeloid leukemia (AML), and other hematopoietic malignancies. While benzene exposure has an overall 7-fold risk for development of leukemia, chronic benzene poisoning (CBP) is associated with a 71-fold risk for development of AML or myelodysplastic syndromes in humans (*1*–*2*). CBP patients experience a strong and prolonged hematotoxicity characterized by significantly reduced white blood cell counts. Malignant transformation in these CBP patients can take place in a short period of time (*3*). In this study, CBP data were obtained from the Occupational Disease and Occupational Health Monitoring Information System, a subsystem of the China Information System for Disease Control and Prevention. CBP patients from 6 provincial-level administrative divisions (PLADs)* were analyzed and characterized by age, enterprise scale†, ownership of the enterprise §, and industry¶ distribution. There was a total of 3,836 CBP patients across China during 2005–2019, of which 1,861 CBP in 6 PLADs were included in the analysis. This study suggests that a targeted occupational health survey is needed to determine the number of industries with CBP changes and strengthen the supervision and management of the industry with CBP.

CBP had been reported in China in the early 1950s with the main industries associated with CBP at the time being painting, pharmaceuticals, and distillation of coal and coal tar. In the 1970s, the prevalence of CBP was 1.1% (*4*). With the reduction of maximum allowable concentration (MAC) of benzene to 40 mg/m^3 in 1979 and the improvement of hygiene conditions of workplaces, the prevalence of CBP decreased to 0.5%. The annual mean number of CBP cases decreased from 892 cases during 1979–1982 to 594 cases during 1984–1993 and 223 cases during 1996–2003. Correspondingly, the main industries associated with CBP had shifted to light industry and machinery (*5*–*6*). The permissible concentration-time weighted average (PC-TWA) of benzene in workplace in China was reduced to 6 mg/m^3 in 2002. So far, whether the industrial distribution of CBP has changed with decreasing PC-TWA is unknown.

* Guangdong Province, Jiangsu Province, Shandong Province, Sichuan Province, Beijing Municipality, and Tianjin Municipality.

† Large, medium, small, and mini-sized enterprises.

§ State-owned, collective, pooling, private, foreign, stock, and Hong Kong, Macao, and Taiwan of mainland China.

¶ Chemical raw materials and chemical products manufacturing, general and special equipment manufacturing, non-mental mineral product industry, etc. More information about industry category is available at http://www.stats.gov.cn/tjsj/tjbz/hyflbz/201710/t20171012_1541679.html.

The 6 PLADs of Guangdong, Jiangsu, Shandong, Sichuan, Beijing, and Tianjin were selected because the number of CBP cases increased from 2005 to 2019 and accounted for more than half of the total number of new CBP patients in China after 2013. All CBP patients were diagnosed by local occupational disease diagnostic teams. To further refine the distribution of CBP in specific industries, the occupations of CBP patients in these PLADs were standardized using the *Industrial classification for national economic activities* (GB/T 4754–2017). Data were processed using Excel software (version Home and Student 2019, Microsoft Office).

From 2005 to 2019, the annual mean number of CBP cases increased to 256 and the proportion of CBP in chronic occupational poisoning (COP) increased and reached 46% in 2019 (Figure 1A). As shown in Table 1, the number of medium-sized enterprises with CBP cases increased rapidly in the 6 PLADs from 2005 to 2012 and subsequently remained at a high level from 2009 to 2019. The number of small businesses with CBP cases continued to rise, and both small and medium enterprises eventually comprised 71% of all enterprises with CBP cases from 2017 to 2019. When enterprises with CBP cases were categorized according to ownership type, the number of CBP cases reported by private enterprises was the highest and increased rapidly. It was followed by foreign enterprises and

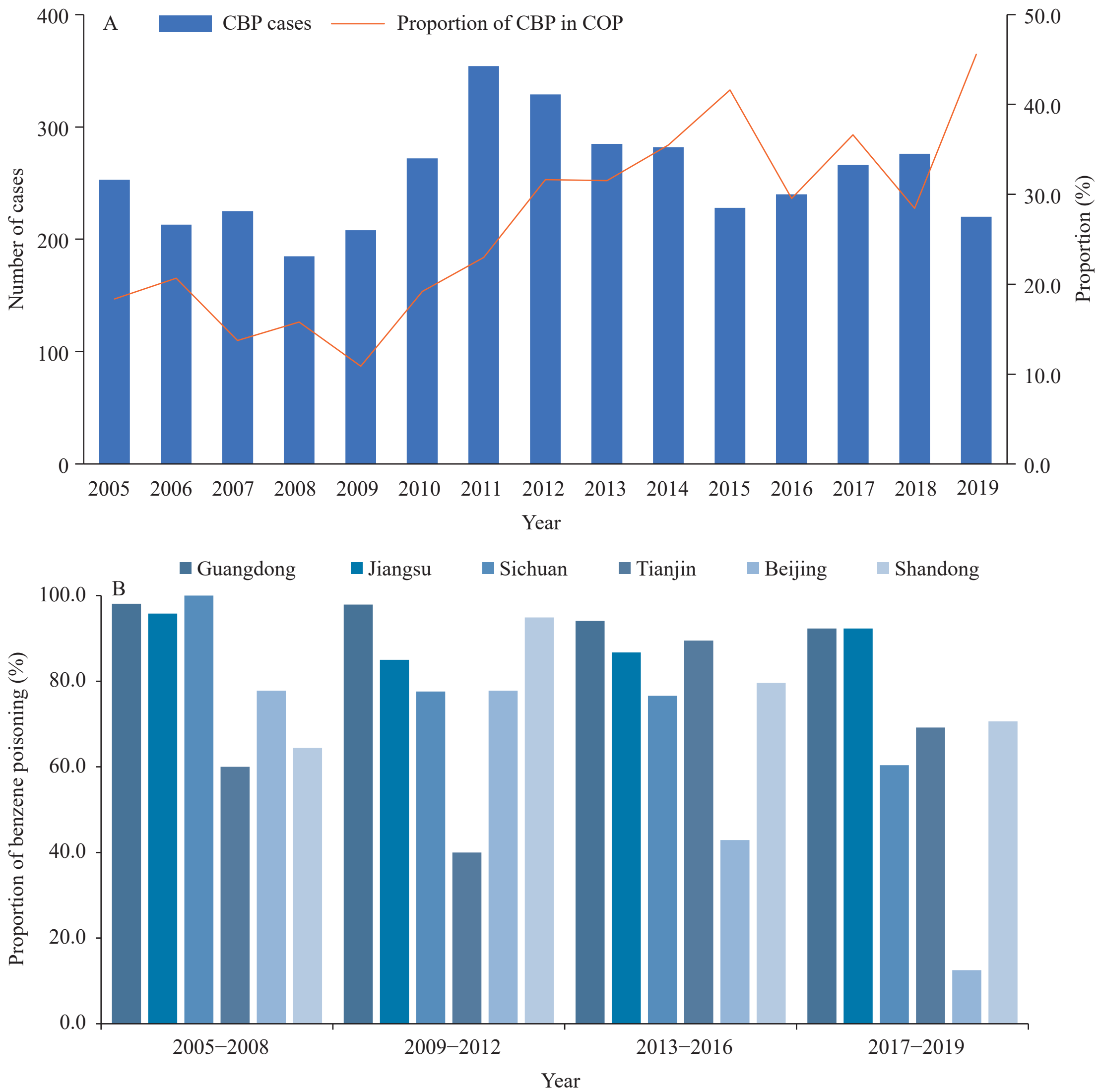

FIGURE 1. CBP in China, and manufacturing with CBP in 6 PLADs, 2005−2019. (A) New cases and proportion of reported CBP in China, 2005−2019; (B) The proportion of manufacturing with CBP in 6 PLADs in 4 periods of 4-years (2005−2008, 2009−2012, 2013−2016, 2017−2019).

TABLE 1. Distribution of enterprise scale and ownership type with chronic benzene poisoning (CBP) cases in 6 provincial-level administrative divisions (PLADs), 2005−2019.

Item	Number of CBP (%)			
	2005−2008	2009−2012	2013−2016	2017−2019
Total	252	464	595	550
Enterprise scale				
Large	59(23.4)	119(25.6)	157(26.4)	126(22.9)
Medium	73(29.0)	193(41.6)	190(31.9)	197(35.8)
Small	52(20.6)	111(23.9)	195(32.8)	195(35.5)
Mini-sized	0	0	6(1.0)	12(2.2)
Unrevealed	68(27.0)	41(8.8)	47(7.9)	20(3.6)
Ownership type				
State-owned	78(31.0)	74(16.0)	82(13.8)	38(6.9)
Collective	17(6.7)	20(4.3)	25(4.2)	4(0.7)
Pooling	9(3.6)	42(9.1)	46(7.7)	0
Private	72(28.6)	151(32.6)	237(39.8)	183(33.3)
Foreign	34(13.5)	77(16.6)	42(7.1)	140(25.5)
Hong Kong, Macao, and Taiwan of mainland China	16(6.3)	6(1.3)	6(1.0)	131(23.8)
Stock	0	20(4.3)	20(3.4)	22(4.0)
Unrevealed	26(10.3)	73(15.8)	137(23.0)	32(5.8)

Abreviation: CBP=chronic benzene poisoning.

Hong Kong, Macao, and Taiwan of mainland China enterprises, they showed a sharp increase from 2017 to 2019.

For industry distribution, manufacturing was the industry in the 6 PLADs with the highest number of CBP cases during 2005–2008, accounting for 60% up to 100% of all cases. In 2009, the number of CBP cases related to manufacturing decreased in all PLADs except Shandong, but manufacturing was still the primarily associated industry. During 2013–2019, the proportion of CBP cases in 5 PLADs, excluding Beijing, related to manufacturing exceeded 60%, ranging from 60.4% to 94.1% (Figure 1B).

During 2005–2019, CBP mainly occurred in general and special equipment manufacturing, followed by raw chemical materials and chemical product manufacturing. Compared with the previous periods from 2005 to 2016, the number of CBP cases in these 2 industries decreased from 2017 to 2019, but they remain the main industries associated with CBP.The distribution of associated industries and characteristics of CBP in PLADs often differed: 1) in Jiangsu, chemical raw materials and chemical products manufacturing was always found to be the main industry associated with CBP during 2009–2019 (2009–2012: 11 cases, 27.5% of the total; 2013–2016: 26 cases, 35.6% of the total; 2017–2019: 9 cases, 34.6% of the total), followed by general and special equipment manufacturing (2009–2012: 10 cases, 25.0% of the total; 2013–2016: 13 cases, 17.8% of the total; 2017–2019: 7 cases, 26.9% of the total); 2) in Sichuan, the main industries associated with CBP were general and special equipment manufacturing during 2013–2016 (22 cases, 34.4% of the total) and was outpaced by paper products manufacturing and electrical equipment manufacturing during 2017–2019 (both 9 cases, 17.0% of the total); 3) in Shandong, the main industry associated with CBP was general and special equipment manufacturing during 2005–2008 (30 cases, 30.0% of the total)—which increased during 2009–2012 (39 cases, 33.3% of the total) and decreased during 2013–2016 (11 cases, 11.8% of the total) and during 2017–2019 (5 cases, 14.7% of the total) — and several industries were associated with CBP as 34 cases occurred in 25 industries during 2017–2019; and 4) in Tianjin, several industries were also associated with CBP, but transportation equipment manufacturing gradually became the most associated with CBP (2013–2016: 5 cases, 26.3% of the total; 2017–2019: 7 cases, 26.9% of the total) (Table 2).

TABLE 2. Characteristics in distribution of the top three industries with the most chronic benzene poisoning (CBP) cases in Jiangsu, Sichuan, Shandong, and Tianjin, 2005−2019.

PLAD	Year	Industry	Number of CBP (%)
Jiangsu	2005−2008	Leather, fur, feather products and shoemaking manufacturing	9(36.0)
		Plastics and rubber products manufacturing	5(20.0)
		General and special equipment manufacturing	5(20.0)
	2009−2012	Chemical raw materials and chemical products manufacturing	11(27.5)
		General and special equipment manufacturing	10(25.0)
		Non-mental mineral product industry	3(7.5)
	2013−2016	Chemical raw materials and chemical products manufacturing	26(35.6)
		General and special equipment manufacturing	13(17.8)
		Metal product manufacturing	6(8.2)
	2017−2019	Chemical raw materials and chemical products manufacturing	9(34.6)
		General and special equipment manufacturing	7(26.9)
		Transportation equipment manufacturing	2(7.7)
Sichuan	2005−2008	Computer and electronic product manufacturing	6(60.0)
		General and special equipment manufacturing	3(30.0)
		Chemical raw materials and chemical products manufacturing	1(10.0)
	2009−2012	Transportation equipment manufacturing	13(27.5)
		Weapon and ammunition manufacturing	8(16.3)
		General and special equipment manufacturing	6(12.4)
	2013−2016	General and special equipment manufacturing	22(34.4)
		Transportation equipment manufacturing	9(14.1)
		Metal product manufacturing	5(7.8)
	2017−2019	Paper and paper products Manufacturing	9(17.0)
		Electrical equipment manufacturing	9(17.0)
		General and special equipment manufacturing	5(9.4)
Shandong	2005−2008	General and special equipment manufacturing	30(30.0)
		Transportation equipment manufacturing	11(11.0)
		Petroleum processing industry	9(9.0)
	2009−2012	General and special equipment manufacturing	39(33.3)
		Transportation equipment manufacturing	20(17.1)
		Chemical raw materials and chemical products manufacturing	10(8.5)
	2013−2016	Chemical raw materials and chemical products manufacturing	13(14.0)
		General and special equipment manufacturing	11(11.8)
		Transportation equipment manufacturing	6(6.5)
	2017−2019	General and special equipment manufacturing	5(14.7)
		Computer and electronic product manufacturing	5(14.7)
		Chemical raw materials and chemical products manufacturing	3(8.8)
Tianjin	2005−2008	Chemical raw materials and chemical products manufacturing	5(33.3)
		Petroleum processing industry	5(33.3)
		General and special equipment manufacturing	2(13.3)
	2009−2012	Petroleum processing industry	8(54.3)
		Computer and electronic product manufacturing	2(13.3)
		General and special equipment manufacturing	2(13.3)

TABLE 2. (Continued)

PLAD	Year	Industry	Number of CBP (%)
	2013−2016	Transportation equipment manufacturing	5(26.3)
		Metal product manufacturing	2(10.5)
		General and special equipment manufacturing	2(10.5)
	2017−2019	Transportation equipment manufacturing	7(26.9)
		General and special equipment manufacturing	3(11.5)
		Petroleum exploitation	3(11.5)

DICSUSSION

The number of new cases of CBP and the increased proportion of CBP in COP during 2005–2019 suggested that CBP may be the most important diseases in COP in China. The increasing number of cases may result from an increase in benzene-exposed workers; the increasing proportion of CBP in COP may result from a decrease in other occupational poisonings. The number of CBP cases needs to be further reduced due to the carcinogenicity of benzene.

In this study, we found that CBP mainly occurred in manufacturing industries, especially in private enterprises and small and medium-sized enterprises. The number of CBP cases in private and small enterprises have exceeded that of the large state-owned companies after 2013. This is probably due to the rapid development of small and medium-sized enterprises in recent years. Moreover, the production equipment and occupational health conditions in small and medium-sized enterprises are not as good as those of large state-owned enterprises. Therefore, it makes the occurrence of CBP increased and scattered. The supervision and management of small and medium-sized enterprises need to be strengthened.

In the past 15 year, the production and use of benzene was mainly in manufacturing, which accounts for one-third of all industries in China (GB/T 4754–2017). We further analyzed the manufacturing sub-industry and found that most industries with CBP were general and special equipment manufacturing, as well as chemical raw materials and chemical products manufacturing. Studies reported that the median benzene exposure level for general equipment manufacturing was 4.32 mg/m^3 (range: 0.03–244.51 mg/m^3) and was 3.52 mg/m^3 (range: 0.79–8.30 mg/m^3) for chemical raw materials and chemical products manufacturing during 1983–2014 (*7*). Though these exposure levels were lower than the 6 mg/m^3 required by the PC-TWA in China, there was no significant decrease in the average number of new cases from 2005 to 2019 compared to 1996–2003, suggesting that the occupational exposure limit of benzene at 6 mg/m^3 may need to be reconsidered. Furthermore, in high-income countries like the United States, benzene exposure levels are well below this occupational exposure limit (3.25 mg/m^3), so CBP cases were relatively rare (*8*). There was an average of only 10 CBP cases per year among 240,000 occupational benzene-exposed workers in the United States (*9*). By comparison, 186 of the 342,212 workers exposed to benzene in 5 PLADs in China in 2017 suffered from CBP.

During 1979–1981, CBP patients mainly occurred in spray paint workers (34.1%), painters (20.8%), and shoemakers (12%) (*4*). Less than 1% of shoemakers had CBP cases in the 6 PLADs by 2019. The number of CBP cases in computer and electronic product manufacturing began to increase, while the leather, fur, feather products, and shoe manufacturers were no longer the main industry for CBP (Table 2). Differing from China, the International Agency for Research on Cancer report states that synthetic rubber, paint, and ink manufacturing and painting are important sub-industries within manufacturing with serious CBP hazards. It can be seen that the distribution of industries associated with CBP in China is still quite different from that in other countries.

This study was subject to at least some limitations. First, this study included more than 50% of total CBP patients in China among 6 PLADs, but the descriptive statistics on the distribution of these cases may not be comprehensive, which could lead to an imprecise estimation of the distribution. Further investigation could include more patients and other PLADs. Second, the number of reported CBP cases was lower than the actual number of cases due to the lack of obvious clinical symptoms in CBP patients and the lack of full coverage of workers by physical examination, which may have led to an underestimation of the extent of CBP cases.

All enterprises and industries can benefit from a comprehensive approach to CBP prevention. A hierarchy of controls needs to be fully implemented. First, elimination and substitution: using non-toxic and low toxic substances instead of toxic or high toxic substances is the first choice to reduce exposure to toxic hazards. Second, engineering controls: strengthening ventilation and other engineering controls to bring the concentration of benzene in the workplace within the occupational exposure limit. Third, administrative controls: decreasing occupational benzene exposure limits to a safer concentration. Fourth, personal protective equipment (PPE): proper use of PPE to protect benzene workers. Other community-based strategies include strengthening economic supports, health education, and early finding, diagnosis, and treatment.

Acknowledgment: Guangdong Provincial Key Laboratory of Occupational Disease Prevention and Treatment staff.

Conflicts of Interest: No conflicts of interest were reported.

Funding: The study was funded by the Project of Occupational Health Risk Assessment and National Occupational Health Standard Formulation of National Institute of Occupational Health and Poison Control (Project No.: 131031109000150003).

doi: 10.46234/ccdcw2020.243

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Submitted: October 19, 2020; Accepted: November 18, 2020

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Methods and Applications

A Case Study of Applying Metagenomic Sequencing in Precise Epidemiology for the COVID-19 Pandemic — Sichuan Province, China, 2020

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ABSTRACT

Introduction: Determining the transmission chain of a virus in its incipient stages is extremely time consuming in traditional approaches that rely mainly on case incidence and interview-based contact data. With the development of high-throughput sequencing technology, genome-based epidemiology approach is showing promise in detecting viral transmission. However, there is still insufficient evidence for the relationship between the viral genetic variations and real viral transmission.

Methods: To explore the possible relationship between transmission chains and viral genetic variations, we combined both epidemiological data and viral genomes of COVID-19 virus collected from Sichuan Province. A phylogenetic approach was used to infer the transmission chain, which was then compared to the transmission chain that came from epidemiological data.

Results: We found that the putative transmission chains were highly concordant to the true transmission chains from epidemiological data, suggesting a strong correlation between viral genetic variations and the viral transmission chain.

Discussion: Our results showed advantages of viral genomic sequencing in tracking and perceiving pathogen transmission, which allowed for potential improvements in the design and implementation of population-level public health interventions.

INTRODUCTION

It is crucial to understand the evolution and transmission of a virus in its incipient pandemic, especially the transmission chains, which can help to design effective strategies for disease control and prevention (*1*). However, it is time consuming and costly to ascertain transmission chains traditionally, in which the process largely relies on case incidence data and interview-based contact tracing (*2*). A recent study on the epidemiology of coronavirus disease 2019 (COVID-19) in Guangdong Province, China found the transmissions from epidemiological data were congruent with the phylogenetic cluster patterns that inferred from single nucleotide variations (SNVs) of COVID-19 virus genomes (*3*), suggesting the possibility to infer transmission chains from viral genomes. To investigate possible correlations between transmission chains and viral genetic variations, we combined both epidemiological data and viral genomes of COVID-19 virus collected from Sichuan Province. We found the putative transmission chains are highly concordant to the true transmission chains from epidemiological data. Given to the low cost and convenience of sequencing viral genomes, this approach showing promise to assist disease control and prevention during viral pandemic.

METHODS

Clinical and Epidemiological Data

A total of 44 samples were collected from 44 patients, who tested positive with COVID-19 infection by real-time reverse transcription polymerase chain reaction (RT-PCR). These samples can be further divided from two different batches. Batch 1 includes 29 local patient samples in Sichuan Province collected in early February, whereas batch 2 includes samples from 14 asymptomatic imported COVID-19 patients in mid-March, all returning to China from Egypt. The clinical and epidemiological data were originally collected by multiple hospitals in Sichuan Province and centralized by Sichuan Provincial CDC.

Metagenomic Sequencing

An untargeted metagenomic sequencing approach was used to detect and acquire the COVID-19 virus genomic sequences. RNA-based metagenomic sequencing libraries were prepared according to the manufacturer's protocol of KAPA Stranded RNA-Seq Library Preparation Kit (Illumina Platforms). Metagenomic sequencing was performed on Illumina Novaseq 6000 sequencing platform that hosted by HitGen Inc.

Data Analysis

Raw reads were further processed by Trim Galore (V0.6.4_dev) for adaptors removal and quality control. Clean reads were mapped to the reference genome of COVID-19 virus (NCBI reference sequence: NC_045512.2) using Bowtie2 (V2.4.1, University of Maryland). Variants were called using LoFreq (V2, Genome Institute of Singapore) with default parameters and filtered to only keep SNVs belong to primary strain (SNVs with allele frequencies ≥0.5) for each individual. To make sure the multiple sequence alignments were in the length, consensus sequences for these individuals were reconstructed from the filtered VCF files using the *consensus* function incorporated in BCFtools (V1.9, Wellcome Sanger Institute).

Multiple sequence alignment was performed using MAFFT (V7.4, Osaka University). Following alignment, we used maximum likelihood (ML) tree, neighbor-joining (NJ) tree, and Bayesian coalescent tree to explore the phylogenetic structure of these COVID-19 virus strains. FastTree (V2.1.10, Lawrence Berkeley National Laboratory) and BEAST (V2, The University of Auckland) were used to construct the ML tree and Bayesian coalescent tree, respectively. The NJ tree was built using the *ape* (V5.3) package in R (V 3.6.1, R Foundation). The ML and NJ tree were visualized using FigTree (V1.4.4, University of Edinburgh). The Bayesian coalescent trees were visualized using DensiTree (V2.2.6, The University of Auckland).

RESULTS

The genome coverage of COVID-19 virus from 29 local patients' samples are all above 98%, with average sequencing depth ranging from 23 to more than 11,400. For 14 imported patients, only nCoVTS0414-6 sample has 90.13% virus genome coverage with an average sequencing depth of 6.07. The rest of the samples have more than 98% genome coverage with average depths from 15 to 13,241.

A total of 6 transmission chains were found among batch 1 COVID-19 samples according to the

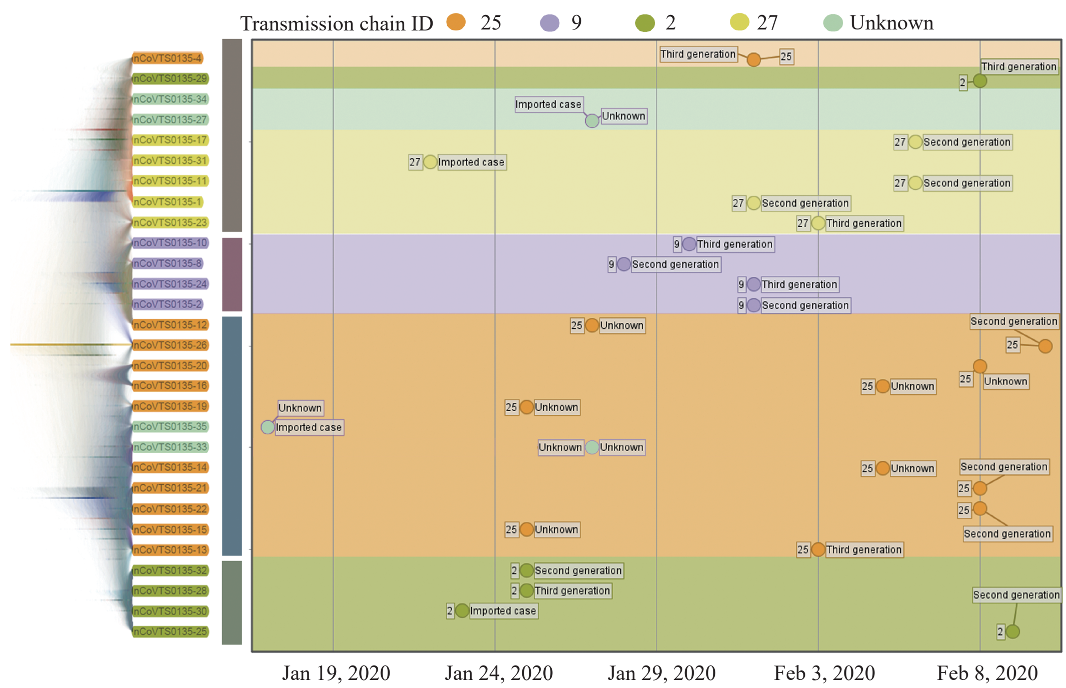

FIGURE 1. Phylogenetic relationship of COVID-19 virus strains and the transmission chains from 29 samples. Each dot in the figure represents a patient sample. The onset date of each patient was plotted on the x-axis. The y-axis of these samples were organized based on the position from the Bayesian coalescent tree result. The transmission chain and the generation of the sample in the chain were labelled on the left and right side of each dot, respectively. It was evident that the preliminary transmission chains could be constructed by combining the onset date and the phylogenetic relationship of the COVID-19 virus strains even with limited epidemiological information.

epidemiological data. Surprisingly, we found COVID-19 virus strains that belong to the same transmission chain were tightly clustered on Bayesian coalescent tree (Figure 1), in spite of sporadic dispersions. Notably, even though COVID-19 virus strains from the same transmission chain were clustered together, we found difficulty distinguishing the introduced case from the other COVID-19 cases within each transmission chain. Collectively, using the heterogeneous data apart from Guangdong Province, we showed the phylogenetic results from genomic data were highly concordant to the transmission chain from epidemiological data.

To explore the optimal phylogenetic methods for this study, we also compared the topologies of Bayesian coalescent tree with ML tree and NJ tree (Figure 2). We found the clustering pattern between Bayesian coalescent tree and ML tree were similar to each other and were highly concordant to the transmission chains reconstructed from epidemiological data. However, the clustering pattern of the NJ tree was distinct from the Bayesian coalescent tree and the ML tree, as well as the reconstructed transmission chains. Our results indicated that the NJ tree was incapable of correlating the genomic variations with the transmission chain as accurately as the Bayesian coalescent tree and the ML tree.

Among positive COVID-19 cases, a considerable proportion were asymptomatic (*4*), which brought significant challenges to epidemic prevention and control because of the difficulty of getting transmission information from the epidemiological data (*5*). Mutations accumulated in the virus genome during host-to-host transmission could potentially provide more information for transmission chain construction (*6*). To verify this hypothesis, we conducted phylogenetic analysis using 14 asymptomatic COVID-19 cases. Interestingly, we found that clustering patterns of 14 asymptomatic cases on the Bayesian coalescent tree were highly correlated with travel history of patients (Figure 3A). Among which, patients with COVID-19 virus strains clustered into clade A and clade B had European travel history, while

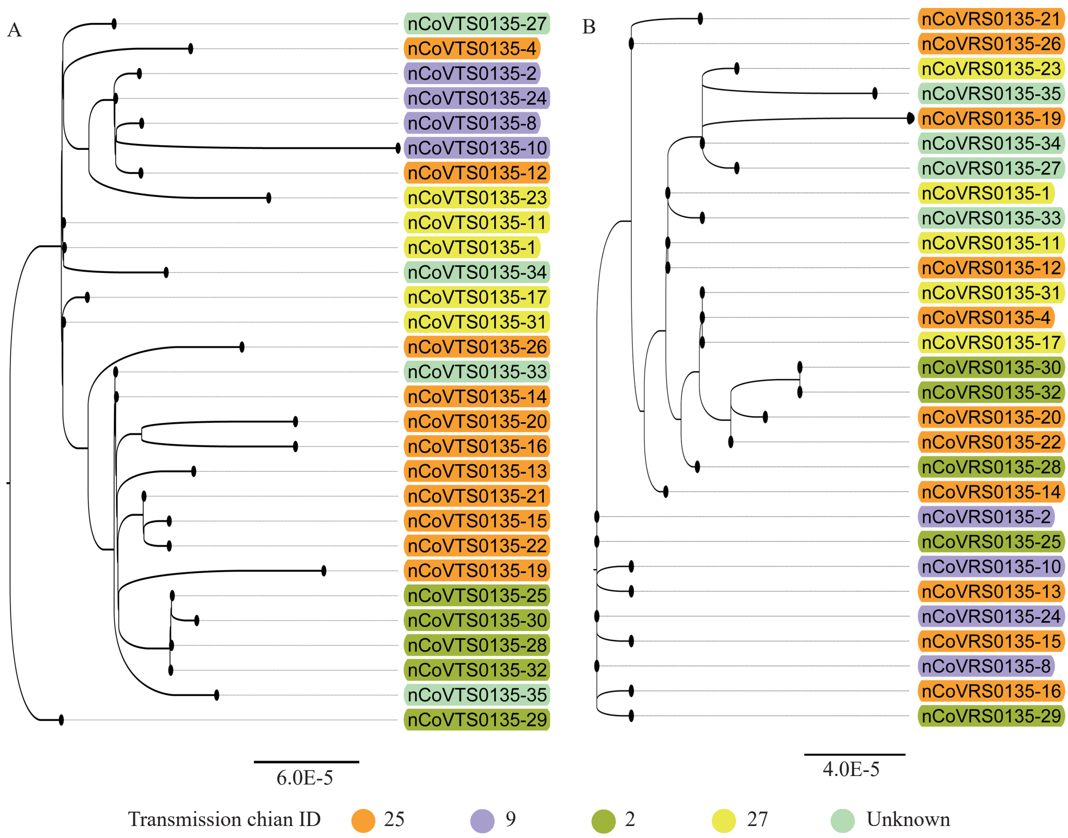

FIGURE 2. The phylogenetic analyses showed distinct structures between maximum likelihood (ML) tree and neighbor-joining (NJ) tree. (A) The phylogenetic tree was constructed using maximum likelihood method. (B) The phylogenetic tree was constructed using neighbor-joining method.

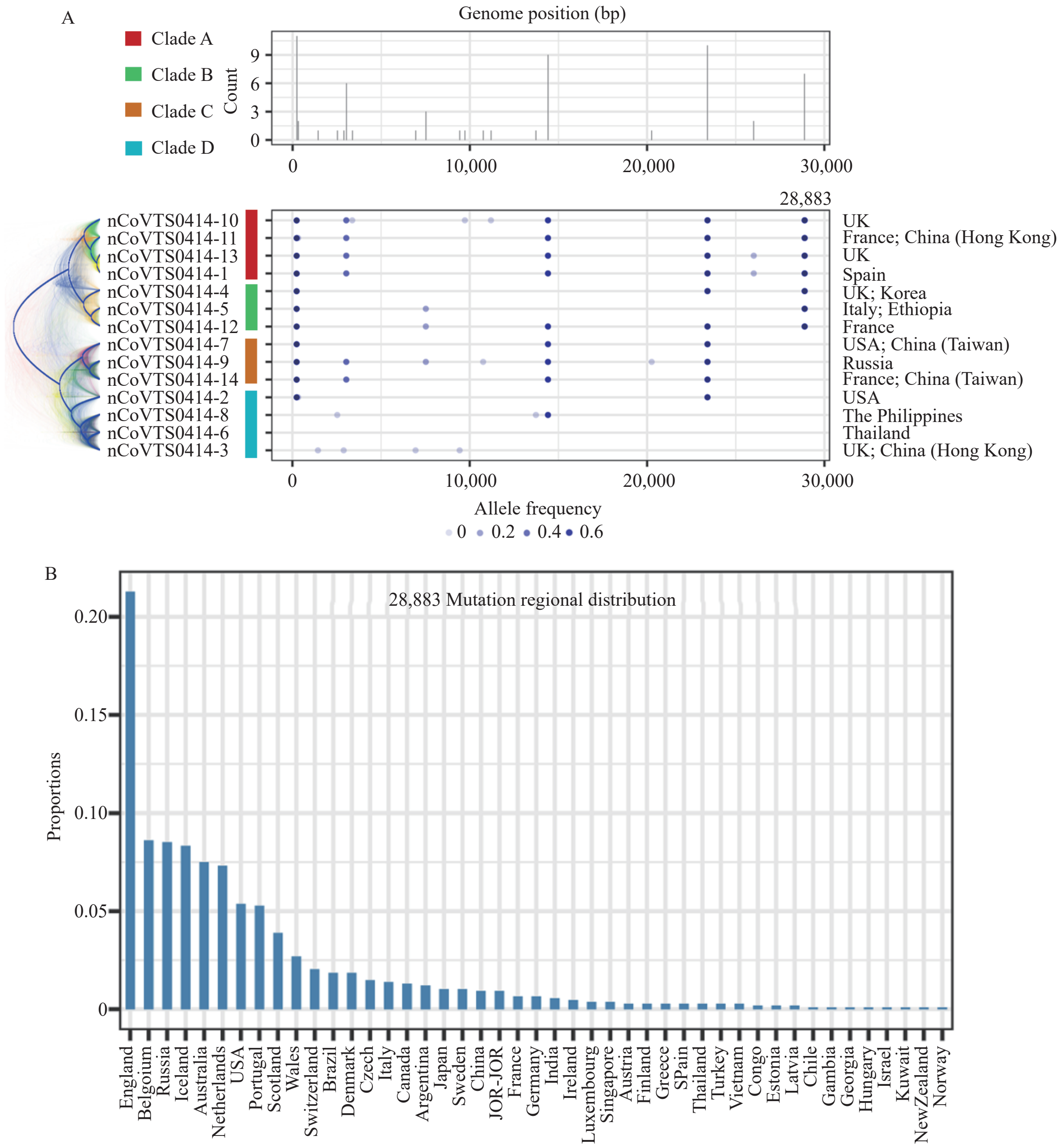

FIGURE 3. Phylogenetic analyses on 14 asymptomatic cases revealed high correlation between travel history and viral phylogenies. (A) The distribution of COVID-19 virus variations among 14 asymptomatic COVID-19 cases and the variations underlie phylogenetic structure. The left panel showed the Bayesian coalescent tree, and the right panel showed the variations in each COVID-19 virus strain. (B) The bar plot shows the regional distribution of G28883C mutation.

those who clustered into clade C and clade D had Pacific Rim travel history. Moreover, we found the clustering pattern was largely affected by the G28883C mutation, which is a missense variant that lead to a p.204G>R change on QHD43423.2 (Figure 3A). We further found this mutation had a much higher frequency in European COVID-19 cases compared to other regions (Figure 3B), indicating COVID-19 virus strains carrying this mutation might have originated in Europe. Taken together, our results suggested that the Bayesian coalescent method can be helpful in inferring the transmission relationship of asymptomatic COVID-19 cases.

DISCUSSION

Targeted interventions have been proven to be an effective way for constraining timing, size, and duration of the epidemic of COVID-19, especially in the early phases of an outbreak (*3*,*7*). However, the design of targeted interventions depends on rapid recognizing of an outbreak, which are rarely achieved by traditional approaches through clinical and epidemiological data, especially for asymptomatic infections. Fortunately, with the development of high-throughput sequencing, using pathogen genomes to understand pathogen transmission appears to be possible. In this study, we explored the possibility of inferring transmission chains from genomic sequences using epidemiological data of COVID-19 virus in Sichuan Province. We found that the transmission relationships inferred from genomic variations of COVID-19 virus were highly concordant to the transmission chains that were reconstructed from clinical and epidemiological data. This finding is consistent with the epidemiological study of COVID-19 virus in Guangdong Province (*3*) and the epidemiology study of Zika virus in the United States (*8*). However, we were not able to get similar phylogenetic structures among the Bayesian coalescent tree, the ML tree, and the NJ tree. This difference might be caused by the low genetic diversity among COVID-19 virus strains in our study due to regional sampling. As the Bayesian coalescent method is based on aggregate numbers of mutations, which is more robust compared to other methods when there are limited variations within populations (*9*).

Asymptomatic cases are difficult to recognize without nucleic acid amplification tests. Thus, it is nearly impossible to reconstruct the transmission chains for asymptomatic cases due to their limited clinical and epidemiological data. Using the genomic epidemiology approach in this study, we inferred the transmission relationships among 14 asymptomatic cases and found their phylogenetic relationships were highly correlated with each patient's travel history. Our results suggested advantages of genomic epidemiology in surveying the spread of asymptomatic cases.

This study was still subject to some limitations. Despite the positive results, this study was still limited by regional sampling. As mentioned by a previous study, underdamping of regions with high incidence can bias phylogenetic analyses (*3*). Nevertheless, our results showed advantages in the speed and granularity of viral genomic sequencing in tracking and perceiving pathogen transmission, which allowed for potential improvements in the design and implementation of population-level public health interventions.

Acknowledgments: Sichuan Science and Technology Program (nos. 2020FYS0015 and 2020FYS0017); and the National Natural Science Foundation of China (no. 82041033).

doi: 10.46234/ccdcw2020.244

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Submitted: July 17, 2020; Accepted: September 27, 2020

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Policy Notes

Interpretation of the Protocol for Prevention and Control of COVID-19 in China (Edition 7)

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INTRODUCTION

After coronavirus disease 2019 (COVID-19), previously known as pneumonia of unknown etiology (PUE) and 2019 novel coronavirus (2019-nCoV), was first discovered in Wuhan City, Hubei Province, the Chinese government took measures to stop the spread of the epidemic nationwide and interrupted local transmission in China (*1–2*). Although there have been several localized outbreaks that were caused by overseas importation of the virus — including Heilongjiang, Jilin, Beijing, Liaoning, and other provincial-level administrative divisions (PLADs) — these outbreaks have been stopped within two to four weeks and were limited in scope to less than ten cases or a few hundred cases for each event. With the COVID-19 pandemic still uncontrolled globally, the threat of importing the virus continues unabated and still threatens China's population, virtually all of which is susceptible.

Non-pharmaceutical measures that effectively contained COVID-19 and stopped outbreaks due to importation were described in previous editions of the National Health Commission's (NHC) Protocol for Prevention and Control of COVID-19. The NHC and external experts cooperated to update this Protocol to a seventh edition to ensure effective responses to outbreaks and to a possible epidemic of COVID-19 this autumn and winter and to include experiences gained domestically, globally, and through research. This article described the primary content and key updates in the Protocol, including surveillance, multi-method monitoring, early warnings, and close contact tracing and management and discusses the scientific rationale for revisions of the protocol.

EPIDEMIOLOGICAL CHARACTERISTICS

Respiratory droplets and close contact are still considered the primary routes of COVID-19 transmission, but the new edition indicates that contact with virus-contaminated products can also cause infection (*3*). COVID-19 virus is sensitive to heat, but remains viable at low temperatures and can survive for an indeterminate period of time in low temperature environments, especially, as has been seen, in frozen foods and packaging. Investigations of the Beijing, Dalian, and Qingdao outbreaks showed that contaminated imported frozen foods were sources of the outbreak viruses. Edition 7 notifies localities of the need to monitor low-temperature environments for COVID-19, especially in frozen foods, to prevent similar epidemics.

CASE SURVEILLANCE

At present, COVID-19 transmission has essentially been disrupted in China (*4*), and strengthening case surveillance and early detection of COVID-19 is the top priority of the current control and prevention strategies. The revised protocol clearly requires strengthening of case surveillance in medical institutions, communities, schools, etc., to further increase the sensitivity of case detection.

In medical institutions, Edition 7 expands the nucleic acid testing requirements. Patients with respiratory symptoms like fever and dry cough who have an epidemiological history should undergo nucleic acid testing. However, patients without an epidemiological history who have respiratory symptoms like fever and dry cough, have engaged in cold chain food processing or sales, or have been at a farmers market, institutions for the elderly or disabled, a hospital, a detention center, a nursing home, or a school should undergo nucleic acid testing for the COVID-19. In addition to the relatively recently-discovered transmission potential from contaminated frozen foods, many COVID-19 outbreaks have occurred in crowded and enclosed places, such as welfare institutions, places of detention, nursing homes, and schools. Therefore, routine nucleic acid testing of patients from these locations is conducive to early detection of COVID-19 and outbreak prevention.

For communities, management staff must monitor the health of key populations, including individuals discharged from hospitals or quarantine, close contacts of quarantined individuals, and people entering China who completed quarantine. Experience from the initial containment effort in China showed that 10% to 12% of patients with COVID-19 tested positive after discharge. Although transmission from positive-testing, discharged patients has not been observed in China, some people who entered China tested positive after being released from isolation. To ensure discovery of sources of infection as much as possible, Edition 7 requires health monitoring of people returning to communities from high-risk settings such as quarantine or a COVID-19 hospital.

CLUSTERS

Presence of a cluster of cases is used as an indicator for categorizing geographic areas by risk — low, medium, and high. County and district sizes vary greatly in China, with populations ranging from tens of thousands to millions of people. For precise control and prevention measures that reasonably categorize medium- and high-risk areas, Edition 7 modifies the definition of a cluster to be "5 or more cases found within a small area such as a school, residential community, factory, village, or medical institution within a 14-day period." This is a change from Edition 6 (*5*), which used a cutoff of two or more cases within 14 days. The new cluster definition increases the threshold for taking strict prevention and control measures. For example, if 2 cases were seen in a family in a county with millions of people, the Edition 6 definition would impact everyone in the county, whereas Edition 7 would not.

MONITORING OF COLD-CHAIN FOOD PRODUCTS

Outbreaks of COVID-19 have been documented among workers who process and handle frozen seafood domestically and overseas. China Customs has found multiple instances of COVID-19 nucleic acid positive samples from the outer packaging of frozen seafood and meat and from the outer packaging of frozen food sold in farmers markets. To address this importation risk, Edition 7 strengthens monitoring of cold-chain food products, farmers markets, and related business and their personnel. The purpose of this strengthening is to refine risk assessment of COVID-19 transmission, to improve environmental sanitation conditions for the production, processing, and trading of these products, and to improve everyday use of recommended protective measures.

MULTI-METHOD MONITORING

Edition 7 has a new section on multi-method monitoring and early warning. Relevant agencies are required to conduct fever monitoring in transportation and public service locations including airports, railway stations and wharfs, and shopping malls; kindergartens and schools must conduct absenteeism and symptom monitoring; pharmacies will monitor the designated drug sales; farmers markets and medical institutions will conduct environmental and personnel monitoring; and cold-chain food businesses will monitor their environment and personnel, as described above. Monitoring data will be collected in health department monitoring and early warning information platforms. Timely and comprehensive analyses of these data reflect risk of local epidemics and will help detect COVID-19 cases and asymptomatic infections, contaminated food, and coronavirus mutations as early as possible. Accurate assessment and the timely release of early warning information will better inform society and improve response times.

CLOSE CONTACTS MANAGEMENT

The seventh edition updates management of close contacts. Edition 6 did not require close contacts with no symptom to undergo nucleic acid testing during quarantine, but Edition 7 requires 3 nucleic acid tests during quarantine of close contacts. The first nucleic acid test is to be done within a day of starting centralized quarantine and medical observation, and the second test is done with a 1-day interval following the first. The third test is on the last day of the 14-day quarantine. The first two closely-spaced nucleic acid tests increase sensitivity for early detection of infected individuals to prevent transmission and provide timely treatment. Quarantine experience to date has found that many close contacts test positive or are ill at the beginning of quarantine and that some patients have longer incubation periods, sometimes more than 14 days. The timing of the third nucleic acid test is to reduce the likelihood of discharging an infected individual.

Edition 7 defines a new risk group — close contacts of close contacts (i.e., secondary contacts). Secondary contacts are to be identified through tracing and then managed for 14 days of centralized quarantine. This new requirement is based on several observations. Close contact tracing has been able to identify less than 40% of all cases, and over 60% of cases were not brought into quarantined management in time. During investigation of the Beijing and Jilin COVID-19 outbreaks, we found that there were instances in which there were lengthy times between onset, detection, and isolated management — sometime more than 10 days. In such circumstances, close contacts may have been infected and been transmitting virus to their close contacts. The rationale for defining this new risk group is to find as many sources of infection as possible to stop the outbreak as rapidly as possible. Identification of secondary contacts, therefore, should identify more individuals at risk of infection.

TRAVELERS INTO CHINA

Edition 6, released in March 2020, did not specify management of travelers coming into China. At the time of Edition 6 being released, imported cases were not a significant proportion of cases. Starting in April, the NHC began to require people entering China from other countries to be quarantined for 14 days at the point of entry. Currently, the global pandemic is still severe but with the containment of COVID-19 in China, work and production have resumed and the number of people entering China has increased. Edition 7 adjusts management of travelers entering China to “7+7” and “2+1” strategies: “7+7” strategy means that people entering China have a required centralized quarantine and medical observation at the point of entry for 7 days, and individuals with a negative nucleic acid test can continue quarantine at home for 7 more days; “2+1” means that the entering traveler will undergo nucleic acid testing at the port of entry and again on the Day 7 of centralized quarantine. After two negative nucleic acid tests, the individual can quarantine at home and be tested again on Day 7–the last day of home quarantine. The use of the “7+7” and “2+1” methods for quarantine can accommodate more people and make quarantine more palatable, promoting the reopening of international flights and land borders. Thus far, there has been no documented transmission in areas adopting these two strategies.

EPIDEMIC RESPONSE

Edition 7 clarifies the scope and timing of prevention and control measures based on results of risk assessments. In medium-risk areas, the scope of prevention and control areas is delimited by school classes, building units, factory workshops, offices, and families as the smallest units. In high-risk areas, schools, buildings, factories, workplaces, and villages are the smallest units to delimit the scope of prevention and control areas. Edition 7 also clarifies specific measures to be taken in areas having different risk assessments. These adjustments are used to promote precise scientific prevention and control measures to minimize the impact of the measures on social and economic development and normal life for residents.

MENTAL HEALTH SERVICES

Mental health services are new inclusions in Edition 7. The COVID-19 pandemic is said to be a once-in-a-century public health emergency (*6*). The pandemic’s severity and complexity have caused great social and psychological impacts on community residents, especially patients, quarantined people and their families, front-line disease prevention and control workers, and the elderly. Social and psychological stress leads to additional problems and adverse outcomes. Edition 7 requires relevant departments to jointly form psychological counseling and social work service teams that provide psychological counseling and assistance for key groups, including patients, people in quarantine, front-line workers, and the elderly. Services include psychological assistance hotlines, online psychological service platforms, and onsite counseling, all intended to promote physical and psychological recovery, a return to normal life and work, and social stability.

DISCUSSION

Edition 7 of the Protocol is based on the current domestic and international epidemic situations, new understandings of COVID-19, and the overall strategy of timely detection, rapid response, precise management, and interruption of transmission. It emphasizes strengthening case surveillance and multi-method monitoring, including sampling and testing of cold-chain food products and at-risk cold-chain workers, with the objective of detecting all possible sources of infection in time and increasing overall surveillance sensitivity. Edition 7 revises the definition of a cluster, streamlines delineation of control and prevention areas, and carefully relaxes management of persons entering China — changes made to reduce the impact on the normal social lives of residents and promote socioeconomic development while maintaining highly effective prevention and control of COVID-19.

As the science on COVID-19 advances at home and abroad, the epidemic situation in China evolves, and vaccines, diagnostics, and drugs are developed, the NHC's Protocol for Prevention and Control of COVID-19 will be updated to always provide the best possible technical support for achieving China's prevention and control targets.

Funding: This work was supported by China Ministry of Science and Technology (grant no. 2018ZX10713001), National Natural Science Foundation of China (No. 91846302).

doi: 10.46234/ccdcw2020.245

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Submitted: November 13, 2020; Accepted: November 18, 2020

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Healthy China

Focus and Progress of the Occupational Health Initiative

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Summary

China's rapid socioeconomic development has led to the coexistence of traditional and modern occupational hazards, and workers are facing increasingly serious risks of physical and mental health issues.

Combined with the Healthy China strategy acting as the innovative force in advancing China's public health, a series of national action plans has been implemented providing comprehensive strategies for protecting worker's benefits and strengthening occupational disease prevention by integrating the sources of government, employers, workers, and other stakeholders. This article interprets the objectives, strategies, and features of the Occupational Health Protection Campaign and the Action Plan for the Prevention and Control of Pneumoconiosis as two national programs for promoting occupational health and the Healthy Enterprises initiative as a great practice in integrating national theories of workplace health promotion and the World Health Organization's concepts of the healthy workplace model.

It concludes that all occupational health progress achieved in the Healthy China Initiative contributes to defending health and well-being of occupational populations and promoting the sustainable development of the economy and society in China.

China has the largest working population in the world with about 776 million workers in 2018, and most of them spend half of their life cycles working (*1*). As a rapidly developing country, the remarkable socioeconomic changes during the last 30 years have posed increasing risk of occupational hazards. According to a series of national occupational disease reports, annual new cases of occupational diseases rose steadily from 12,511 in 2003 to 31,789 in 2016 (*2*), and over 975,000 cases of occupational disease have been reported cumulatively by the end of 2018, of which 90% were pneumoconiosis (about 873,000 cases) (*3*). However, the actual burden of occupational diseases in China was likely to have been underestimated due to low rates of occupational health examinations. In addition, the transformation and upgrading of the economy and technology have led to work-related mental illness and musculoskeletal disorders resulting from psychosocial and ergonomic factors, which pose great challenges in protecting worker health. The Chinese government has always prioritized occupational disease control and prevention as the National Health Commission and other agencies have introduced 11 regulations and more than 700 standards on occupational health and has issued a five-year plan (2016–2020) on the control and prevention of occupational diseases including pneumoconiosis. In 2019, a series of national action plans has been implemented to prevent and control occupational diseases and to protect worker's health.

OCCUPATIONAL HEALTH PROTECTION CAMPAIGN (OHPC)

To ensure full implementation of the Healthy China 2030 blueprint, the State Council has released Opinions of the State Council on Implementing the Healthy China Initiative in July 2019 with new paradigm shifts from treating diseases to providing full-lifecycle health services (*4*). With emphasis on disease prevention and health promotion, an action plan from 2019 to 2030 was unveiled to "intervene in health influencing factors, protect full-life-cycle health, and prevent and control major diseases." Consisting of 15 special campaigns, it specified the objectives and tasks of each campaign and the responsibilities of different sectors in the campaigns. As one of these campaigns, the OHPC focuses on protecting occupational health and the wellbeing of almost 776 million workers in China and proposed medium to long-term action plans to provide comprehensive occupational health services from 2019 to 2030 (*5*).

OHPC strategies are embodied at three levels including employees, employers, and government. Strategies for employees include promoting healthy working styles; fostering occupational health awareness; increasing consciousness of occupational laws and regulations; strengthening personal protection at work; improving emergency response capabilities;

enhancing chronic and non-communicable disease prevention and control; protecting employees who work at desks or maintain forward sitting positions for a long periods (such as white-collar workers); protecting employees who stand for long periods while working (such as teachers, traffic police, doctors, and nurses); and protecting employees who keep fixed positions at work (such as drivers).

For employers, the strategies focused on the following: establishing an accountability system for occupational disease control and prevention, especially primary-responsibility legal bodies for enterprises; strengthening the source control of occupational hazards, specifically construction enterprises or institutions that should fulfill the responsibility of controlling, preventing, and eliminating occupational hazards; building clean, hygienic, green, comfortable, and pleasing working environments; implementing protection measures for workers' health (such as work-break exercise and smoke-free programs); and establishing overall management strategies for employment including labor contracts, work-related injury insurance, occupational hazard reporting, routine surveillance, occupational diagnosis, health insurance for workers, etc.

Supported by joint efforts of 10 ministries and commissions, the OHPC has also developed strategies for government including the following: reviewing relevant laws and policies including the Code of Prevention and Control of Occupational Disease and other relevant rules and regulations; developing and promoting innovative technology, facilities and materials to protect workers' health; improving occupational disease prevention and control systems; enhancing the regulatory and supervisory system of occupational health; strengthening supervision of occupational disease prevention on labor dispatch units, especially starting with rural migrant workers; improving reporting of occupational hazards by establishing a united and efficient data management mechanism of law enforcement and supervision; and incorporating the Healthy Enterprises as a priority into the Healthy Cities program, as well as enriching the scope of occupational health with an emphasis on job stress, musculoskeletal disorders, and other emerging occupational exposures.

Complemented by the National Plan on Occupational Disease Prevention and Control Program (2016–2020), the OHPC proposed 3 major outcome indices as listed in Table 1. In addition, it also included several other advocated indices and the awareness of work-related hazards and protection knowledge, health management, and comprehensive strategies such as advancing technology and adjusting schedules to protect employees from monotonous, repetitive, and stressful work conditions.

The transformation of economic growth in China from a high-speed mode to a high-quality mode with constant changes in industrialization, urbanization, population aging, occupational disease spectrum, ecological environment, and lifestyle has led to new occupational health problems. Pneumoconiosis, chemical poisoning, occupational hearing loss, and radiation sickness resulting from traditional occupational hazards pose a serious threat to workers' health. Meanwhile, teachers, traffic police, healthcare workers, and other key populations highlighted by OHPC are facing increasing work-related exposures. Although these disorders were not legally included in the Classification and Categorization of Occupational Diseases, certain diseases such as cervical spondylosis and work-related stress have become increasingly common among office employees (*2*). In the progress of the Healthy China 2030 initiative, resolving this situation is necessary through designing political strategies and guidelines to protect key occupational populations. This campaign advocates to strengthen the promotion and training for knowledge of occupational disease prevention and prevent both occupational diseases and other work-related diseases at this stage. Employers are encouraged to improve technique and working systems to prevent fatigue and other related disorders and take integrated measures to reduce job stress and other negative health effects.

TABLE 1. Major outcome indices by the Occupational Health Protection Campaign.

Indices	Targeted data	
	2020	2020
Coverage of industrial injury insurance	Steadily improved; Baseline: 236 million in 2018	Achieved legally full coverage
New pneumoconiosis cases among workers with exposure to dust ≤ 5 years accounted for all reported cases per year (%)	Significantly declined	Continuously declined
Rates of occupational health inspection and coverage of diagnostic service	≥80%	≥90%

Protecting occupational health is an important basis for improving people's health, wellbeing, and quality of life. By prioritizing the people's health, the National Health Commission is cooperating closely with other agencies to accelerate the switch from hazard control and disease treatment to workers' health by holding workplaces accountable for preventing, treating, and controlling diseases and promoting health protection knowledge. Dedicated to comprehensive health protection for workers, related departments, government, and society at all levels should fulfill their responsibilities and enhance coordination to ensure the achievement of Healthy China Initiative 2030 goals.

ACTION PLAN FOR THE PREVENTION AND CONTROL OF PNEUMOCONIOSIS

Among all occupational diseases in China, pneumoconiosis—a chronic and irreversible lung disease caused by inhaling coal or silicon dust—is the most prevalent as it makes up more than 90% of all work-related illnesses. As the world's largest coal producer, China actually increased its coal production from 1.02 billion tons in 1990 to 3.68 billion tons in 2018 (*6*). Often under poor, unsafe working conditions, coal workers in China are subject to long-term exposure to respirable coal mine dust, leading to pneumoconiosis. An Action Plan for the Prevention and Control of Pneumoconiosis has been issued on behalf of the National Health Commission jointly with other nine government departments such as the National Healthcare Security Administration and the Ministry of Human Resources and Social Security (*7*). As another key national program, it is a vital part of the OHPC that aims to control the widespread exposure to different types of dust and the high prevalence of pneumoconiosis by vowing to fulfill the targets in the plan by the end of 2020.

Focusing on pneumoconiosis prevention, the action plan proposes five major tasks including special management of dust hazards, treatment of pneumoconiosis patients, regulatory enforcement of occupational health, employer responsibility, and improving technical capacity for prevention and control. The remarkable progress will be made in the rectification and control of dust hazards in industries such as coal mining, non-coal mining, metallurgy, and construction materials. According to the action plan, a nationwide survey investigating threats of dust poisoning covering these key industries and health conditions of reported pneumoconiosis patients will be completed. It pledges that by the end of 2020, authorities must grasp the dust hazards of related employers and the employer's reporting of the health status of occupational pneumoconiosis patients to supervisors. It also establishes a goal that work-related injury insurance should cover more than 80% of employees working in these industries. The action plan emphasizes the necessity of treating pneumoconiosis patients and calls for delivering multiple forms of assistance to workers with lung disease including basic medical insurance, insurance plans for critical diseases, and other medical and legal assistance.

HEALTHY ENTERPRISES

The World Health Organization (WHO) defined a healthy city as "one that is continually developing those public policies and creating those physical and social environments which enable its people to mutually support each other in carrying out all functions of life and achieving their full potential (*8*)." The National Patriotic Health Campaign Committee of China has defined a healthy city as an upgraded version of a hygienic city and specified that constructing healthy cells (healthy schools, institutions/enterprises, and communities) as one of the key tasks (*9*). Because the occupational population is in a complicated situation with multiple disease threats and various risk factors, guiding the enterprises to effectively fulfill their responsibility is highly important to protecting worker health. To further implement the Code of Occupational Disease Prevention, Healthy China 2030 and other requirements of the Healthy City movement, the National Patriotic Health Campaign Committee and other seven government departments jointly issued the Notice on Promoting Healthy Enterprises and tentative Guidelines on the Construction of Healthy Enterprises in November of 2019 (*10*).

The Healthy Enterprise initiative aims to achieve the coordinated development of enterprises and human health through constant optimization of enterprise management systems, effective improvement of enterprise environments, promotion of health management and service quality, and cultivation of corporate health culture and satisfaction of employees' health demands. Through the priority construction of "healthy cells" (Figure 1), Healthy Enterprises is a starting point with great practices integrating national theories of workplace health promotion and concepts of healthy cities according to the WHO (*11*). Based on

FIGURE 1. Structure relationship of Healthy Enterprises, Healthy City and Healthy China

the healthy workplace model published by the WHO, the guidelines standardize four major areas which are improving management systems, building a healthy work environment, providing health management and services, and creating a healthy culture. With emphasis on statutory liabilities and obligations of enterprises in protecting worker's health, the construction of Healthy Enterprises engages employers and employees jointly to build a healthy, safe, harmonious, and sustainable working environment.

CONCLUSION

Through strengthening coordination among relevant departments, the government is focusing on monitoring and executing laws and regulations, improving the insurance system to protect vulnerable working populations, providing occupational health knowledge to the public, etc. Directing actions towards promoting occupational health as Healthy China has guided direct actions to promote occupational health and has made significant progress with efforts to defend the health and wellbeing of working populations and promote the sustainable development of the economy and society in China.

doi: 10.46234/ccdcw2020.232

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Submitted: April 15, 2020; Accepted: September 23, 2020

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Notes from the Field

A Case of COVID-19 Detected in a Cargo Worker at Pudong Airport — Shanghai Municipality, China, November 8, 2020

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On November 8, 2020, a 51-year-old male went to the fever clinic of Shanghai Pudong New Area People's Hospital for diagnosis and treatment of symptoms and was tested for coronavirus disease 2019 (COVID-19). In the early hours of November 9, the municipal and district-level CDCs determined his nucleic acid test results were positive, and after consultation with experts, comprehensive clinical examination, and inspection of imaging results, the COVID-19 diagnosis was confirmed.

The patient was from nearby Anhui Province, lived in Yingqian Village of Zhuqiao Township of Pudong District's New Area in Shanghai Municipality, and worked in the cargo station of the Shanghai Pudong Airport West Division. By the evening of November 9, 28 close contacts were traced in the city and were placed under medical isolation and observation; all 28 contacts had negative nucleic acid test results. By November 10, an additional 8,717 persons were traced to the initial patient, and their test results were all negative. In addition, 374 samples were taken from work-related environments, and the test results were all negative. The venues where the initial patient worked or spent extensive time had been closed for disinfection. The source of the virus is still being investigated, but due to the lack of an apparent transmission chain, the initial suspicion is transmission by materials rather than person to person.

On November 10, the sample of the initial COVID-19 patient in Shanghai was sequenced using Ion GeneStudio S5. Compared to the Wuhan reference sequence (EPI_ISL_402119) (*1*), 10 nucleotide mutation sites were detected in this Shanghai strain. Furthermore, 4 mutation sites (C241T, C3037T, C14408T, A23403G) were single nucleotide polymorphisms (SNPs) that defined the L-lineage European branch with no SNPs of other sub-lineages detected. Another mutation site (A20268G) was detected as characteristic of Pangolin lineage B.1.5 (*2*), which was the European lineage associated with several strains that likely originated in Spain and transmitted globally. In addition, the Shanghai strain had 5 other unique nucleotide mutation sites (C10537T, A17861G, C25708T, T27242C, C28854T), and no sequence with more than 2 of these sites could be retrieved (Figure 1). Data from GISAID and Genbank showed that strains with the most shared mutation sites (7 SNPs) as the Shanghai strain were several that were detected in July in Mexico, but these strains had their own unique mutations not shared by the Shanghai strain.

Recent emerging strains spreading worldwide had roughly 15 SNPs when compared with the Wuhan reference strain, suggesting that the Shanghai strain had a lower number of mutation sites. This may indicate that the virus may have been transmitting undetected through contamination of products that may have occurred months ago and retained its infectivity. Continued monitoring of environmental contamination with COVID-19 is recommended to reduce the impact of related outbreaks.

Fuyang City of Anhui Province reported a confirmed case of COVID-19 on November 10 in a close contact of the initial patient in Shanghai. This close contact was also engaged in airport cargo handling at Shanghai Pudong Airport, and the gene sequencing results indicated that this strain was highly homologous to the Shanghai strain, suggesting direct transmission.

doi: 10.46234/ccdcw2020.246

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Submitted: November 17, 2020; Accepted: November 18, 2020

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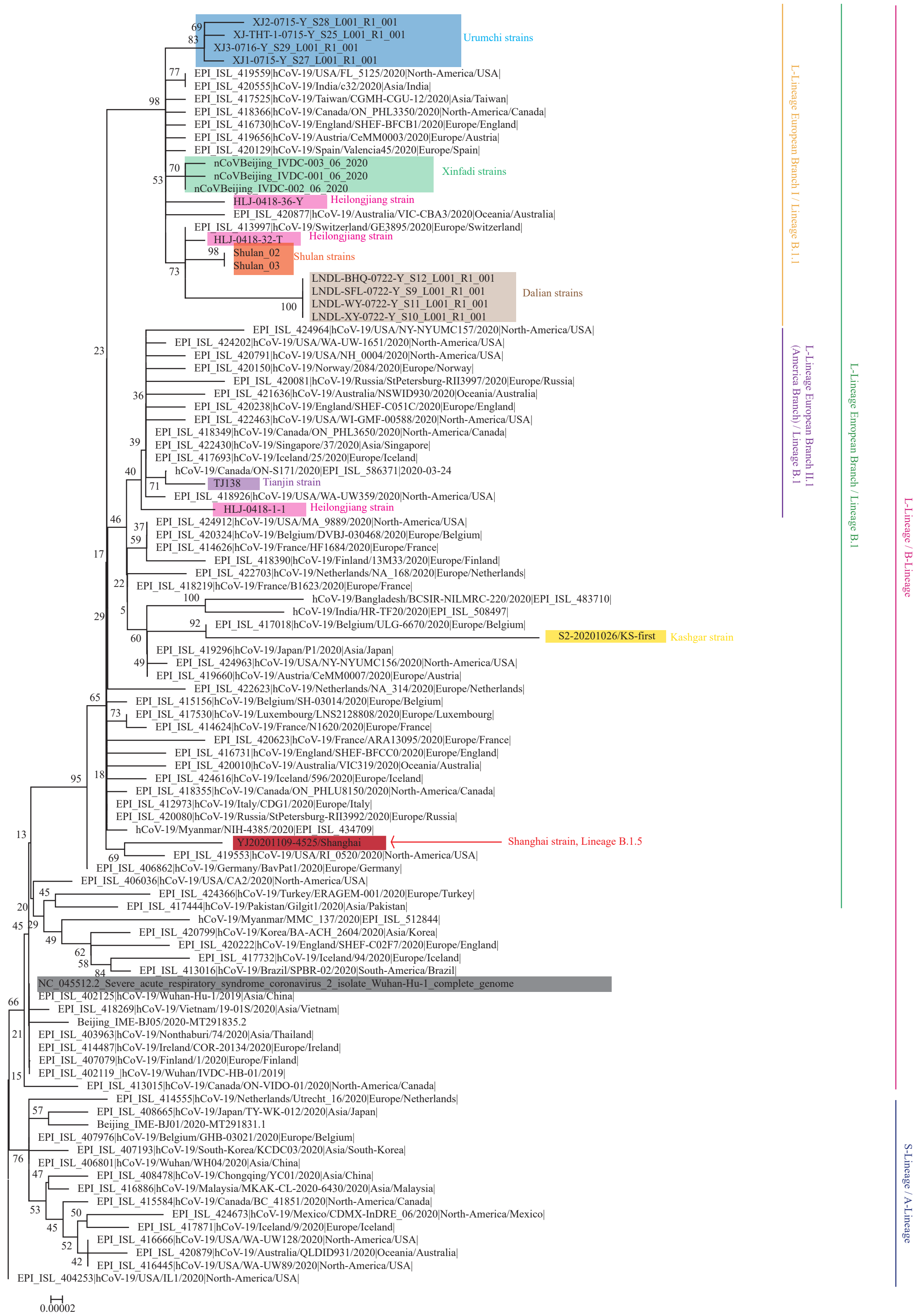

FIGURE 1. Phylogenetic tree based on the full-length genome sequences of the COVID-19 virus. The strains associated with specific outbreaks are as follows: Shanghai Municipality (red); Tianjin Municipality (purple); Kashgar Prefecture (yellow); Urumchi (blue); Beijing Municipality Xinfadi Wholesale Market (green); northeastern China including Shulan and Heilongjiang Province related to imported cases (orange and pink, respectively); Dalian City (brown) and Wuhan City in December 2019 (dark gray); The S(A)- or L(B)-lineage and sublineages of the COVID-19 virus were marked and colored on the right.

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

CCDC weekly

Vol. 2 No. 47 Nov. 20, 2020

Responsible Authority

National Health Commission of the People's Republic of China

Sponsor

Chinese Center for Disease Control and Prevention

Editing and Publishing

China CDC Weekly Editorial Office

No.155 Changbai Road, Changping District, Beijing, China

Tel: 86-10-63150501, 63150701

Email: weekly@chinacdc.cn

CSSN

ISSN 2096-7071

CN 10-1629/R1