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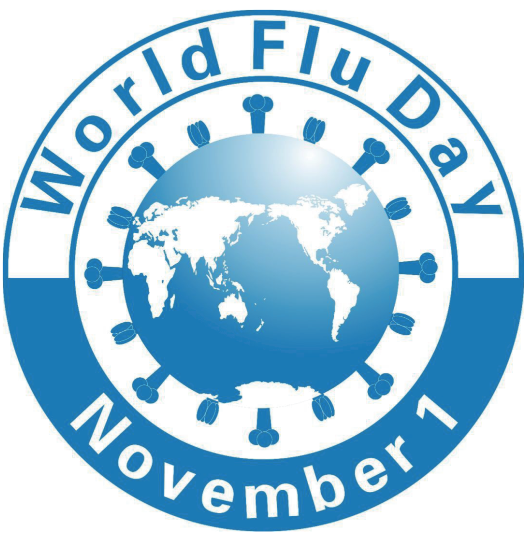

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Preplanned Studies

Inadequate Nutrition and Associated Factors in Children Aged 6 to 24 Months — 4 Counties, Liangshan Yi Autonomous Prefecture, China, 2018

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Summary

What is already known about this topic?

Symptoms of malnutrition including anemia, stunting, wasting, and being underweight among children remained one of the major public health problems in poorer areas in China. More research is needed to guide interventions to improve nutrition and health among children in low-income regions.

What is added by this report?

The prevalences of anemia, stunting, wasting, and being underweight were 51.9%, 25.6%, 14.6%, and 9.5%, respectively, among children aged 6 to 24 months in the poorest areas of Liangshan. Associated factors were gender, age, education level and occupation of mother, breastfeeding, and caregiver knowledge.

What are the implications for public health practice?

Improving caregiver knowledge of nutrition and child feeding practices is crucial to address malnutrition among children. These findings can help more precisely understand the child health needs in poorer areas in order to develop effective interventions. They also provide evidence-based information to formulate child health promotion strategies in other countries with similar situations.

Child malnutrition is an important public health challenge worldwide. The World Health Organization (WHO) reports that globally around 45% of under five deaths are linked to malnutrition (*1*). Optimal nutrition for children aged 6 to 24 months has a long-lasting impact on individuals and families (*1*). China has made great progress in achieving better nutrition among children overall, but some lower-income areas require more effort to improve child nutrition (*2*). Since July 2017, China's National Health Commission cooperated with the Bill & Melinda Gates Foundation to implement the "Child Nutrition and Health Program" in the poorest areas of Liangshan Yi Autonomous Prefecture, a provincial-level administrative division. In 2018, a baseline study was conducted to assess the nutritional status and associated factors among children aged 6 to 24 months in order to provide evidence-based information for further interventions. The prevalences of anemia, stunting, wasting, and being underweight were 51.9%, 25.6%, 14.6%, and 9.5%, respectively. Caregiver's knowledge was one of the significantly associated factors of child malnutrition. More effective approaches are required to deliver child health information efficiently to caregivers.

Health poverty alleviation programs have been launched as part of a national strategy to accelerate the development of impoverished areas towards building a more prosperous society by 2020. Liangshan has been covered by one of the government-funded health poverty alleviation programs that distributed soybean powder-based and iron-rich food supplements, also known as Ying Yang Bao (YYB), free to children aged 6 to 24 months since 2012 (*3*). YYB packages were recommended to be consumed at no less than four bags (12 g per bag) per week in order to decrease the prevalence of anemia. In close cooperation with the "Child Nutrition and Health Program", these programs aim to improve child nutrition and health in the poorest areas of Liangshan.

The baseline study used a stratified multiple-stage random sampling. First, 9 towns were randomly selected from the 4 lowest-income counties (Zhaojue, Yuexi, Meigu, and Butuo county) implementing "Child Nutrition and Health Program". Second, 3 villages were randomly selected from each of 9 towns. Third, using the child registration sheets from each village, children aged 6 to 24 months were divided into 3 age groups as 6 to 11 months, 12 to 17 months, and 18 to 24 months. Overall, 30% of the children were randomly selected from each age group, and 1,300 children aged 6 to 24 months were selected. Informed consent was obtained from a total of 1,244 caregivers. From April to July 2018, children and their caregivers were invited to village health stations for physical measurements and face-to-face interviews performed by trained health workers.

Weight was measured in kilograms (kg) and to the nearest 0.05 kg; height was measured in centimeters (cm) and to the nearest 0.1 cm. Portable hemoglobin analyzers (URIT-12) were used to collect blood sample and to assess hemoglobin concentrations. According to WHO recommendations, stunting was defined at length-for-age z-score of more than 2 standard deviations (SD) below the median of reference population; being underweight was defined as weight-for-age z-score more than 2 SD below the median of reference population; anemia was diagnosed at hemoglobin levels <110 g/L. Adjustments to the measured hemoglobin concentrations had been made based on the altitude and adjusted cut-offs have been described elsewhere (*4*). According to the Technical Specification of Child Health Examine Services, wasting was defined as weight-for-length z-score more than 2 SD below the median of reference population. Caregivers were interviewed about personal information, YYB consumption, breastfeeding practices, and complementary feeding. Questions related to nutrition and child feeding practice were asked to assess caregivers' knowledge.

Chi-square analysis was performed to determine the differences in the prevalence of anemia, stunting, wasting, and being underweight across genders and age groups. Logistic regression analysis was performed to assess the association of factors. Statistical significance was defined as $p<0.05$, and SPSS software (version 23.0; IBM) was used to conduct all analyses.

Among 1,244 children aged 6 to 24 months, there was no significant difference in child's gender across age groups ($\chi^2=3.590$, $p=0.166$). The primary caregiver was the mother for 93.9% of children (Table 1), and 95.3% of the mothers were identified as being of the Yi ethnic group. Over 90% had completed up to primary education, and 61.3% were housewives.

The prevalence of anemia was 51.9%, which was significantly higher among girls (55.6%) than boys (48.3%) ($\chi^2=7.078$, $p<0.05$) (Table 2). With a decrease in age, the prevalence among children aged 6 to 11 months was the highest at 60.4% ($\chi^2=24.116$, $p<0.05$). The prevalence of stunting, wasting, and being underweight were 25.6%, 14.6% and 9.5%, respectively. No statistically significant differences were found between genders. The prevalence of being underweight was significantly highest among children aged 18 to 24 months ($\chi^2=8.425$, $p<0.05$).

TABLE 1. Demographic characteristics of children aged 6 to 24 months and their caregivers.

Demographic characteristic	Total (n=1,244)	
	No.	Percentage (%)
Gender		
Male	627	50.4
Female	617	49.6
Age (Month)		
6-11	454	36.5
12-17	387	31.1
18-24	403	32.4
Primary caregiver		
Mother	1,144	93.9
Father	17	1.4
Grandparents	57	4.7
Mother's ethnic group		
Yi	1,060	95.3
Han	50	4.5
Zang	2	0.2
Mother's education level		
Up to primary school	1,020	91.6
Middle school	64	5.7
High school and above	30	2.7
Mother's occupation		
Housewife	682	61.3
Public institution staff	27	2.4
Farmer	385	34.6
Others	19	1.7

Overall, 83.5% of caregivers knew YYB was beneficial to child health, and 73.4% of children had no less than four bags of YYB in previous one week. An estimated 96.2% of children had been breastfed, 23.7% of caregivers believed complementary foods should be added at 3 months of age, and 26.0% believed at 6 months of age. Most caregivers (54.6%) were aware of the most suitable complementary foods to be added first, and 28.5% of caregivers knew of iron-rich foods and 47.8% knew that anemia was related to iron deficiency.

The result of logistic regression analysis showed that gender, age, mother's education level and occupation, whether child had been breastfed, whether had been breastfed continuously after 6 months of age, whether the caregiver believed "complementary foods should be added at 6 months of age", "grain puree is the most suitable complementary food to be added first", "iron-rich foods include animal blood and red meat," and

TABLE 2. Prevalence of anemia, stunting, wasting, and being underweight across genders and age groups.

Item	Total (n)	Anemia (n, %)	Stunting (n, %)	Underweight (n, %)	Wasting (n, %)
Gender					
Male	627	303 (48.3)	166 (26.5)	64 (10.2)	87 (13.9)
Female	617	343 (55.6)	153 (24.8)	54 (8.8)	95 (15.4)
χ^2		7.078	0.414	0.766	0.617
p value		0.008	0.520	0.381	0.432
Age (Month)					
6−11	454	274 (60.4)	104 (22.9)	39 (8.6)	72 (15.9)
12−17	387	197 (50.9)	99 (25.6)	27 (7.0)	58 (15.0)
18−24	403	175 (43.4)	116 (28.8)	52 (12.9)	52 (12.9)
χ^2		24.116	3.660	8.425	1.756
p value		0.000	0.160	0.015	0.416
Total	1,244	646 (51.9)	319 (25.6)	118 (9.5)	182 (14.6)

"anemia is related to iron deficiency" were factors associated with anemia, stunting, wasting, and being underweight (Table 3).

DISCUSSION

This study reports two major findings: 1) child malnutrition remains as a major public health issue in Liangshan with relatively higher prevalences of anemia, stunting, wasting, and being underweight; and 2) the associated factors of child malnutrition were gender, age, mother's education level and occupation, breastfeeding, and caregiver's knowledge.

Compared with other low-income areas in western China, the prevalence of anemia among children aged 6 to 24 months in the 4 counties of Liangshan in 2018 was lower than that of Qinghai Province (67.8%, 2012) and Guizhou Province (57.6%, 2013), but higher than that of Chongqing Municipality(51.7%, 2013) (*2*,*5*–*6*). The highest prevalence occurred during 6 to 11 months of age and then decreased with age. This result was consistent with a study conducted in 5 provinces in western China (*2*). The key period to start transitioning from breatfeading to family foods was from 6 months of age onwards (*6*). Inadequate complementary feeding might result in a higher risk of developing anemia among children after 6 months of age (*6*).

The prevalence of stunting and being underweight were 25.6% and 9.5%, respectively, which was lower than that among children under 3 years of age in poor areas in Sichuan Province in 2001 (25.9% and 15.9%, respectively) (*7*). However, the National Nutrition and Health Monitoring system reported in 2013 that the average prevalence of stunting and being underweight among children under 5 years of age in poor rural China were 19.0% and 5.1%, respectively (*8*). Studies reported a low diversity and frequency of child feeding in western China, which might contribute to a higher prevalence of stunting and anemia (*2*,*5*). Our results indicated that stunting, wasting, and being underweight shared same influencing factors, and preventive interventions such as promotion of and support for better breastfeeding and complementary feeding might have positive impacts on all of these conditions (*9*).

This study showed that over 70% of children had consumed YYB, but YYB could not replace high quality complementary food and was not enough independently to improve child nutrition. Our study found caregiver's knowledge of child feeding practices was one of the significant associated factors of child malnutrition, and health education was proven to be positively associated with better breastfeeding and complementary feeding (*10*). Health education has been integrated into child health services at different levels in China and has provided an effective platform to deliver child health information to caregivers. However, the percentage of caregivers knowing key information related to nutrition was still low in our study, ranging from 26.0% to 54.6%. This indicated that there were still gaps between senders (health workers) and recipients (caregivers) during the dissemination of health information. Context-based and need-oriented educational activities are needed to fill these gaps and adequately inform caregivers. Also, follow-ups are required to ensure that key information is understood by caregivers.

TABLE 3. Factors associated with anemia, stunting, wasting, and being underweight among children aged 6 to 24 months.

Associated factors	OR (95% CI)	*p* value
Anemia		
Age	0.80 (0.67−0.96)	0.015
Mother's education level	0.78 (0.65−0.92)	0.004
Caregiver believes complementary foods should be added at 3 months of age	1.87 (1.35−2.60)	<0.001
Caregiver knows grain puree is the most suitable complementary food to be added first	2.34 (1.77−3.09)	<0.001
Has been breastfed continuously after 6 months of age	0.66 (0.49−0.89)	0.007
Stunting		
Gender	0.69 (0.51−0.94)	0.019
Age	1.53 (1.24−1.88)	<0.001
Mother's education level	0.52 (0.39−0.68)	<0.001
Mother's occupation	0.93 (0.87−0.99)	0.046
Caregiver believes complementary foods should be added at 3 months of age	1.98 (1.40−2.80)	<0.001
Caregiver knows that iron−rich foods include animal blood and red meet	0.41 (0.28−0.59)	<0.001
Caregiver knows anemia is related to iron deficiency	0.48 (0.34−0.67)	<0.001
Has been breastfed	2.69 (1.26−5.75)	0.010
Has been breastfed continuously after 6 months of age	0.52 (0.35−0.74)	<0.001
Being Underweight		
Age	1.45 (1.09−1.92)	0.010
Mother's occupation	0.86 (0.77−0.96)	0.005
Caregiver believes complementary foods should be added at 3 months of age	1.85 (1.18−2.91)	0.008
Caregiver knows that iron−rich foods include animal blood and red meet	0.39 (0.23−0.67)	0.001
Has been breastfed continuously after 6 months of age	0.42 (0.25−0.70)	0.001
Wasting		
Mother's occupation	0.89 (0.83−0.96)	0.003
Caregiver believes complementary foods should be added at 6 months of age	1.60 (1.10−2.33)	0.014
Caregiver knows that iron−rich foods include animal blood and red meet	1.46 (1.03−2.07)	0.034

This study was subjected to some limitations. First, self-reported information on YYB consumption, practices of breastfeeding, and complementary feeding might have been subjected to recall and social desirability biases, which might affect the accuracy of the information provided. Second, other variables such as dietary patterns, illnesses, and sanitation might affect child nutritional status but were not assessed in this study.

China has launched the health poverty alleviation programs as part of the national strategy. Improving child health plays an important role and contributes to lifelong health. Despite the limitations, results of this study might help understand child health needs in Liangshan in order to develop precise interventions. These findings also provide evidence-based information to formulate child health promotion strategies in other countries with similar situations.

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Preplanned Studies

Short-Term Exposure to Ambient Ozone and Outpatient Visits for Respiratory Diseases — 5 Cities, China, 2013−2015

Yue Niu[1]; Cong Liu[1]; Renjie Chen[1,#]; Haidong Kan[1]

Summary

What is already known about this topic?

Few studies have elucidated the relationships between ambient ozone and respiratory morbidity, especially in developing countries.

What is added by this report?

This study involved 5 cities in China with a wide variation in ozone concentrations and therefore could add credible evidence for the associations between short-term ozone exposure and increased respiratory morbidity.

What are the implications for public health practice?

The results could be used to better assess disease burden of short-term exposure to ozone and further guide policymaking for reducing ozone air pollution and improving public health.

Few studies have elucidated the associations between short-term exposure to ozone and respiratory morbidity, especially in developing countries. We designed this time series study (from 2013 to 2015) in 5 cities in China to investigate the relationships between ambient ozone concentrations and respiratory outpatient visits. Health data were obtained from 9 hospitals and exposure data were collected from fixed-site monitoring stations. Generalized additive models were used to analyze hospital-specific associations and then a random-effect meta-analysis was used to pool them. The average concentrations of ambient ozone for each city ranged from 40.89 μg/m^3 to 75.56 μg/m^3, and the daily mean counts of respiratory outpatient visits varied by hospital from 37 to 2,191. In the present study, we observed positive associations between ozone exposure and respiratory outpatient visits, and the associations remained robust in sensitivity analyses. For a 10 μg/m^3 increase in ozone concentration (lag 03 days), there was a 0.91% (95% CI: 0.34%, 1.47%) increase in the count of outpatient visits for respiratory diseases. Furthermore, the significant associations occurred earlier and became slightly stronger during warm periods. This study suggested a significant and lagged association between short-term exposure to ozone and increased respiratory morbidity.

We conducted this time series study in the cities and municipalities of Shanghai, Zhoushan, Guangzhou, Wuhan, and Xi’an, which are located in different geographic regions with a wide diversity in ozone concentrations. The study period was from January 1, 2013 to December 31, 2015. Data on outpatient visits were obtained from 9 hospitals with 1 to 2 hospitals from each city, including tertiary and secondary hospitals to capture a more representative sample of patients. The hospitals were selected according to data accessibility. Outpatient visits for respiratory diseases were diagnosed and classified according the 10th International Classification of Diseases (ICD-10: J00-J99), and the daily counts were subsequently extracted by experienced physicians. The study was restricted to resident populations. Exposure data on the 5 criterial air pollutants and weather conditions were obtained from the National Urban Air Quality Real-time Publishing Platform and the China Meteorological Data Service Center, respectively. Daily concentrations of each air pollutant were averaged from all available measurements from fixed-site monitoring stations by city.

We applied a two-stage analytic strategy. In the first stage, we estimated hospital-specific associations using generalized additive models with quasi-Poisson regression. Several covariates were *a prior* added into the model (*1*) and details are provided in the supplementary material (available http://weekly.chinacdc.cn/). According to the results from a previous study (*2*), a moving average of the current and previous 3 days (lag 03 d) exposure was used for the main model. In the second stage, we pooled hospital-specific estimates using a random-effect meta-analysis. To illustrate the pooled association between ozone and respiratory outpatient visits, we plotted an exposure–response (E-R) curve via the same approach as done in a previous study (*3*). We further conducted a stratified analysis by season (warm season, from May through October; cool season, from November through April). To examine the robustness of the main models, we performed 2 sensitivity analyses and details are provided in the supplementary material (available in http://weekly.chinacdc.cn/). All statistical analyses were conducted in R software (version 3.6.1, R Foundation for Statistical Computing, Austria) using the "*mgcv*" and "*rmeta*" packages. Effect estimates were presented as percentage changes and their 95% confidence intervals (CIs) in the count of respiratory outpatient visits that were associated with a 10 μg/m^3 increase in ozone concentration. A two-sided p<0.05 was considered statistically significant.

Table 1 summarizes the descriptive statistics on ozone concentrations and counts of respiratory outpatient visits. The mean concentrations of ambient ozone ranged from 40.89 ± 23.95 μg/m^3 in Xi'an to 75.56 ± 24.61 μg/m^3 in Zhoushan. The average daily counts of outpatient visits varied substantially by hospital from 37 ± 13 in Hanyang Hospital of Wuhan to 2,191 ± 523 in Xinhua Hospital of Shanghai.

Figure 1 shows the lag pattern of the associations between ozone and outpatient visits for respiratory diseases. For the single-day lags, the significant association occurred at a lag of 1 day, became the strongest at a lag of 2 days, and then was attenuated over longer lag periods. When exposure was lagged over multiple days, the association became the strongest during the 0–3 days lag period. For this lag period, a 10 μg/m^3 increase in ozone concentration was associated with a 0.91% (95% CI: 0.34%, 1.47%) increase in the count of outpatient visits for respiratory diseases. The estimates of hospital-specific associations between ozone and outpatient visits are available in the supplementary material (Supplementary Figure S1, available in http://weekly.chinacdc.cn/). Figure 1 also depicts the associations by season. In warm seasons, the association was significant in the present day of exposure and could last for 3 days, whereas the association in cool seasons became significant at a lag of 2 days. For multiple-day lags, the associations in warm seasons were slightly stronger than that in cool seasons. The pooled relationship between ozone and respiratory outpatient visits had no obvious changes after adjusting other air pollutants or altering the degrees of freedom of the smooth functions for time trend and weather conditions (Supplementary Table S1, available in http://weekly.chinacdc.cn/).

Figure 2 illustrates the E-R curve for the association of ozone exposure (lag 03 days) with respiratory outpatient visits. Specifically, the curve increases slowly at low concentrations (<50 μg/m^3) and moderately at 50 μg/m^3 to 100 μg/m^3, levels off at 100 μg/m^3 to 120 μg/m^3, and raises rapidly when concentrations were >120 μg/m^3.

TABLE 1. Summary statistics on ambient ozone concentrations in 5 cities and the count of outpatient visits for respiratory diseases in 9 hospitals from 2013 to 2015.

City/Hospital	Mean	SD	Min	P25	Median	P75	Max
Ozone							
Shanghai *	70.22	28.69	9.97	48.68	71.37	89.95	176.23
Zhoushan *	75.56	24.61	4.83	58.18	75.47	92.00	156.88
Guangzhou	46.99	24.32	4.81	27.98	43.27	61.77	147.44
Wuhan	59.38	29.85	7.27	35.27	57.34	79.69	166.25
Xi'an	40.89	23.95	6.70	20.82	35.73	57.25	128.19
Outpatient visit							
Hospital 1 (Shanghai) *	2,191	523	696	1,878	2,186	2,503	3,872
Hospital 2 (Zhoushan) *	412	81	110	360	411	464	678
Hospital 3 (Zhoushan) *	296	82	90	238	296	350	573
Hospital 4 (Guangzhou)	945	330	35	721	991	1,165	2,006
Hospital 5 (Guangzhou)	198	105	1	108	209	275	522
Hospital 6 (Wuhan)	43	17	0	33	43	52	147
Hospital 7 (Wuhan)	37	13	4	28	35	44	96
Hospital 8 (Xi'an)	488	188	44	382	529	621	894
Hospital 9 (Xi'an)	419	127	31	332	424	509	742

Abbreviations: SD=standard deviation; Min=minimum; Max=maximum; P25=25th percentile; P75=75th percentile.

* Data were from January 1, 2014 to December 31, 2015.

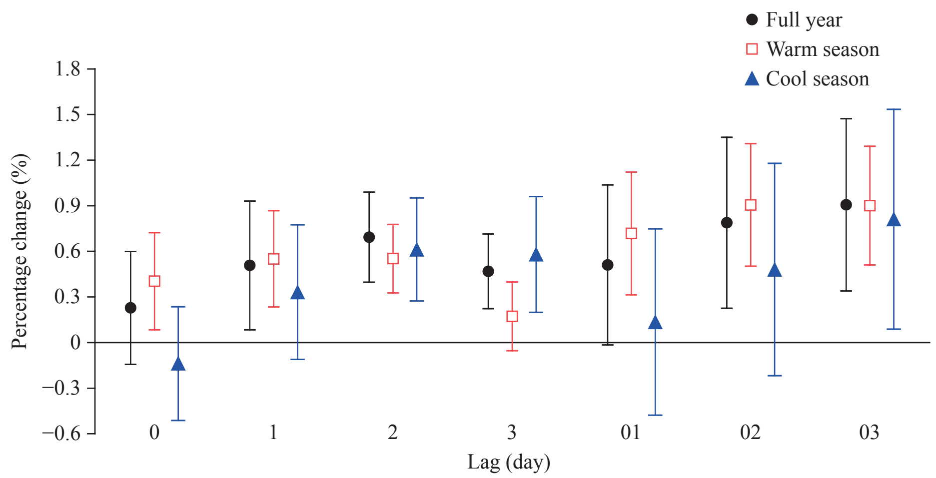

FIGURE 1. Percentage changes in the daily count of outpatient visits for respiratory diseases per 10- μg/m³ increase in ambient ozone concentration over different single-day and multiple-day lag periods. Warm season refers to the period from May through October and cool season refers to the period from November through April.

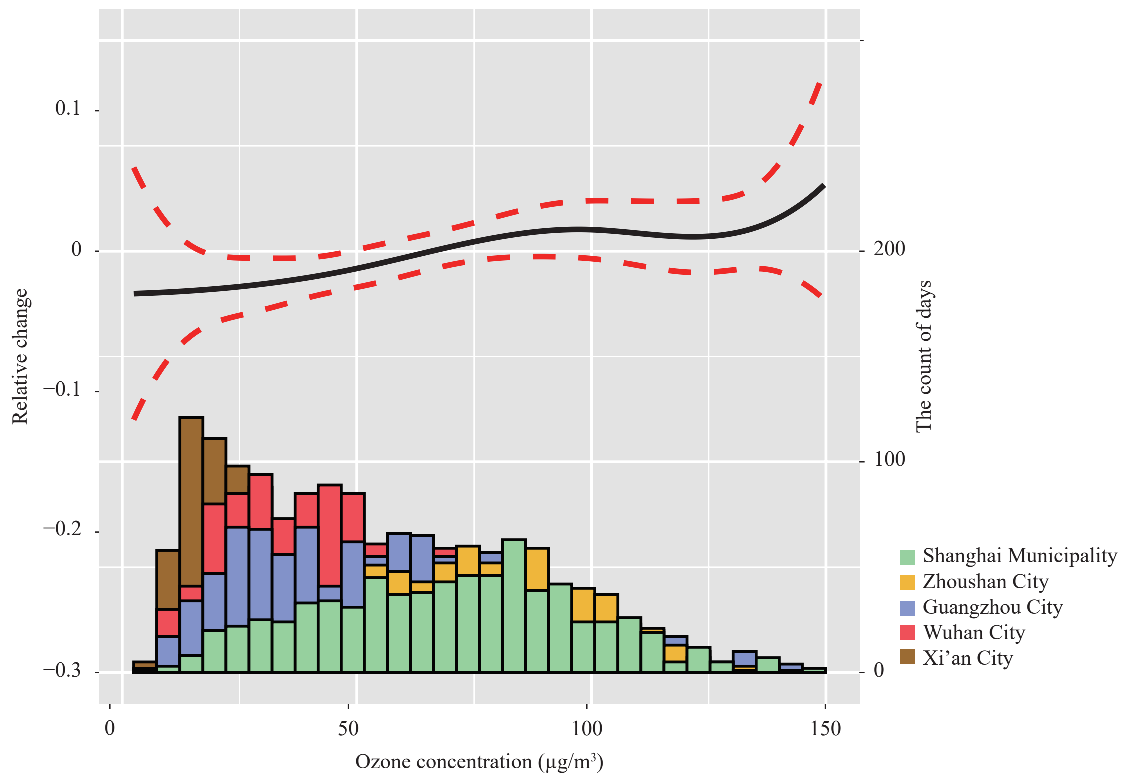

FIGURE 2. Exposure-response curve for the association of ozone concentrations (lag 03 days) with outpatient visits for respiratory diseases and distributions of daily mean ozone concentrations by cities. The left Y-axis can be interpreted as the log-relative change from the mean effect of ozone on outpatient visits. The solid line represents the mean estimate, and the dashed lines represent 95% confidence intervals. The height of each bar in the histogram represents the number of days in each bin of ozone concentration.

DISCUSSION

We conducted a time series study in 5 cities in China to investigate the relationships between ozone exposure and respiratory morbidity. In this study, we found a significantly positive association between ambient ozone concentrations and outpatient visits for respiratory diseases. The pooled effect occurred earlier and were slightly stronger during warm periods. The E-R curve showed the strongest effects of ozone on respiratory outpatient visits at concentrations >120 μg/m^3.

Our results suggested a significant association between short-term ozone exposure and increased respiratory morbidity. This finding was consistent with a number of previous epidemiological studies. For instance, a meta-analysis demonstrated that a 10-ppb increase in ozone concentration was associated with a 0.80% (95% CI: 0.19%–1.41%) increase in emergency department visits for respiratory diseases (*4*). A multi-site study in the US observed a 0.8% (95% CI: 0.6%–1.0%) increase in respiratory emergency department visits in relation to a 10-ppb increase in ozone concentration (*5*). Such positive associations were also found in Japan (*6*). For cause-specific respiratory morbidity, the associations between ozone exposure and increased hospital admission for pneumonia and chronic obstructive pulmonary disease have been reported previously (*1*,*7*). However, inconsistently, some studies did not find that ozone exposure could cause elevated risks for respiratory morbidity (*8*), which may result from differences in study population and ozone levels. The results of our study also suggested that there were relatively weaker relationships between ozone exposure and respiratory morbidity in cities with lower levels of ozone air pollution.

Furthermore, we found that the lag pattern of the associations was somewhat different between warm and cool seasons, and the magnitude of associations was slightly greater in warm seasons, suggesting a potential modification effect of ambient temperature on ozone-related respiratory morbidity. This finding was similar with many previous studies that found a significant interaction effect between temperature and ozone on health outcomes (*9*). Higher ozone concentrations and more outdoor activities on warm days may lead to higher ozone exposure and reduce exposure misclassification. This would consequently add more credibility to the results. The modification effect of temperature may be indicated by the E-R curve that slope is relatively small at low concentrations and becomes the largest when concentrations are >120 μg/m^3.

This study was subject to at least three limitations. First, exposure misclassification was inevitable because we used fixed-site monitoring measurements as population exposure, and diagnosis misclassification was possible because cases were extracted according to ICD-10 codes from the database. Second, study areas and hospitals included in the study were selected according to data accessibility, which may lead to selection bias. Therefore, further studies conducted on a larger scale are warranted to confirm our results. Third, we cannot recognize susceptible populations to ozone exposure in this study because demographic data (such as age, sex, and education levels) were unavailable.

In summary, our findings provided relatively creditable evidence for the associations between ozone exposure and increased respiratory morbidity. The results could be used to better assess disease burden of short-term exposure to ozone and further guide policymaking to reduce ozone air pollution and improve public health.

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Supplementary Material

Statistical model

We used generalized additive models with quasi-Poisson regression to analyze the associations between ozone concentrations and respiratory outpatient visits. Several covariates were added into the models, including: (1) natural cubic spline regression to control time trend with 7 degrees of freedom (dfs) per year; (2) an indicator variable for day of the week; (3) a binary dummy variable for holidays; and (4) natural cubic spline regression to control ambient temperature and relative humidity with 3 dfs for both.

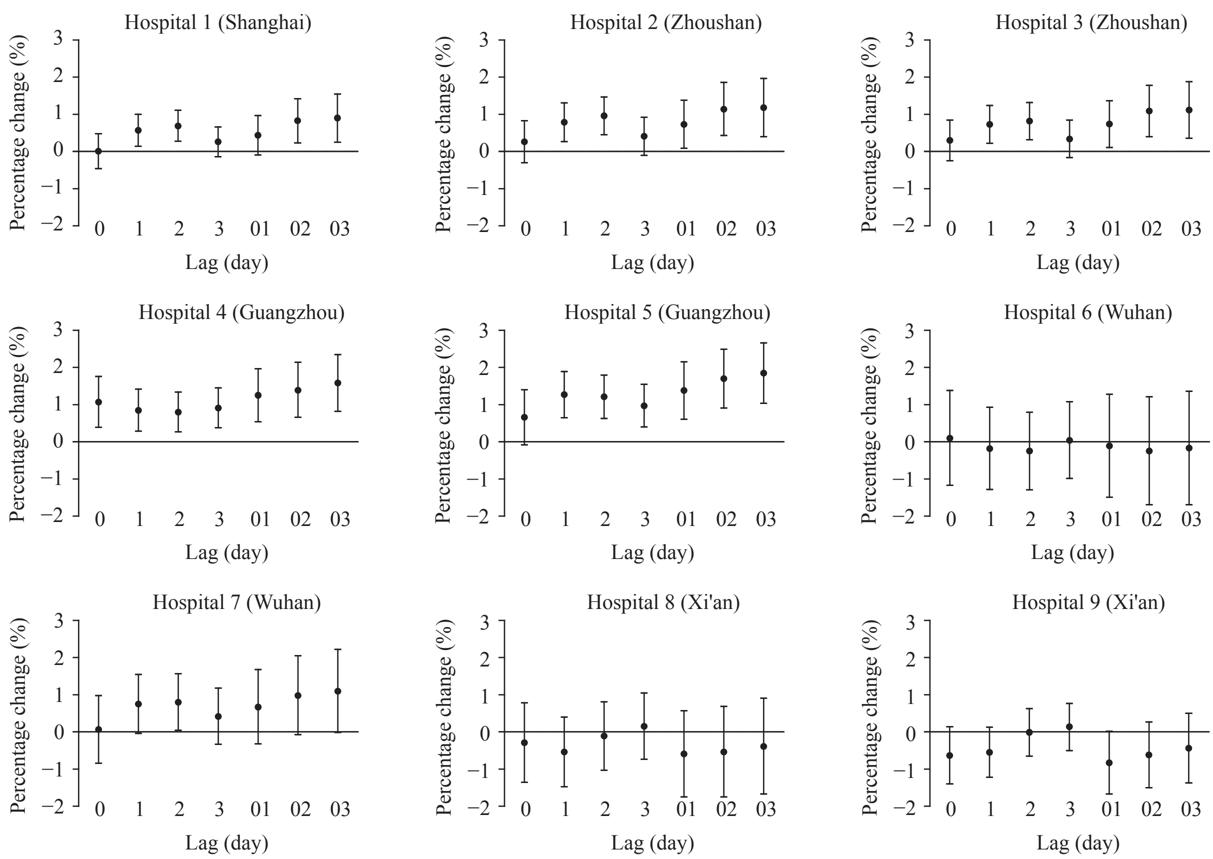
Sensitivity analyses

To examine the robustness of the main model, we performed 2 sensitivity analyses. First, we adjusted fine particulate matter, sulfur dioxide, nitrogen dioxide, and carbon monoxide individually in the main model. Second, we assessed alternative dfs of the smooth functions for time trend (dfs=6 or 8), ambient temperature (dfs=6), and relative humidity (dfs=6).

We applied a Z-test to examine the difference between the adjusted models and the main model.

$$Z = \frac{(\beta 1 - \beta 2)}{\sqrt{Se_1^2 + Se_2^2}} \tag{1}$$

where β 1 and β 2 refer to the coefficient of outpatient visits associated with one unit change in ozone concentration in the main model and adjusted model, respectively; Se_1 and Se_2 refer to their standard errors, respectively; Z refer to Z test score for pairwise comparison. A *p*-value <0.05 was considered statistically significant.



SUPPLEMENTARY FIGURE S1. Hospital-specific percentage changes in the count of outpatient visits for respiratory diseases per 10-μg/m³ increase in ozone concentration over different single-day and multiple-day lag periods.

SUPPLEMENTARY TABLE S1. Summary estimates of sensitivity analyses for the associations between ozone concentrations (lag 03 days) and outpatient visits for respiratory diseases

Item	Percentage Change (95% CI)	*p*-value*
Main Model		
Single-pollutant, df_{time}=7, df_{temp}=3, df_{rh}=3	0.91% (0.34%–1.47%)	–
Two-pollutant Model		
Main Model + $PM_{2.5}$	0.67% (0.27%–1.07%)	0.502
Main Model + SO_2	0.80% (0.40%–1.21%)	0.776
Main Model + NO_2	0.72% (0.38%–1.06%)	0.574
Main Model + CO	0.80% (0.37%–1.22%)	0.763
Alternative Degrees of Freedom		
Single-pollutant, df_{time}=6, df_{temp}=3, df_{rh}=3	0.70% (0.15%–1.26%)	0.615
Single-pollutant, df_{time}=8, df_{temp}=3, df_{rh}=3	0.77% (0.37%–1.18%)	0.706
Single-pollutant, df_{time}=7, df_{temp}=6, df_{rh}=3	0.77% (0.24%–1.29%)	0.723
Single-pollutant, df_{time}=7, df_{temp}=3, df_{rh}=6	0.89% (0.41%–1.37%)	0.967
Single-pollutant, df_{time}=7, df_{temp}=6, df_{rh}=6	0.81% (0.29%–1.33%)	0.805

* *p* values for difference between estimates from the adjusted models and the main model.

Abbreviations: CI=confidence interval; $PM_{2.5}$=fine particulate matter; SO_2=sulfur dioxide; NO_2=nitrogen dioxide; CO=carbon monoxide; df_{time}=degree of freedom for time trend; df_{temp}=degree of freedom for ambient temperature; df_{rh}=degree of freedom for ambient relative humidity.

Notes from the Field

The First Case of Asymptomatic Infection of COVID-19 — Kashgar Prefecture, Xinjiang Uygur Autonomous Region, China, October, 2020

Ji Wang[1,&]; Jun Zhao[2,&]; Xiang Zhao[1]; Zhenguo Gao[2]; Yang Song[1]; Xin Ma[2]; Kai Nie[1]; Aimin Xu[3]; Mahemuti[2]; Ling Zhang[2]; Wenbo Xu[1,#]; Yan Cui[2,#]

On October 24, 2020, a 17-year-old female was detected as having an asymptomatic infection of coronavirus disease 2019 (COVID-19) during a regular nucleic acid test in Kashgar Prefecture, Xinjiang Uygur Autonomous Region. She was then transferred to a local designated hospital for medical observation. The patient lived in Shufu County of Kashgar Prefecture and worked in a local garment factory. On the afternoon of October 24 after she was diagnosed as positive, a total of 831 persons in the garment factory were tested and the results were all negative. Afterwards, 16 close contacts and 406 of close contacts of close contacts were also tested, and 137 were positive and had asymptomatic infections.

On October 26, genome sequencing was performed at Xinjiang CDC using the Ion S5 (Thermo Fisher) and MinION (Oxford Nanopore) platform guided by experts of China CDC. Compared with the sequence of the Wuhan reference strain (NC_045512) (*1*), the whole genome sequence of the first asymptomatic infection of COVID-19 case had 23 nucleotide site mutations. Among them, 6 nucleotide mutation sites (C241T, C3037T, C14408T, A23403G, C18877T, G25563T) were characteristic of the European branch of the European family of the L genotype II.3 (Figure 1). The virus sequence had 3 additional nucleotide mutation sites (C2113T, C7765T, C17690T). The above 9 nucleotide mutation sites belong to the branch of B.1.9.

In addition, the virus sequence had 14 unique nucleotide mutation sites (T433C, C1415T, G8653T, C9891T, A13483G, G13920T, G16852T, G17658T, G17686T, T23978C, C25460T, G25912T, G26426T, C28887T), which were not retrieved from the published global new coronavirus genome database and no sequence with more than two of these nucleotide mutation sites was retrieved. This suggested that these 14 mutation sites were characteristic of the asymptomatic infection case. The sequencing results showed that the genotype of the first asymptomatic infection case was different from that which had affected China and was not the spread from the reemergent cases in Xinjiang in July (*2*). The source of the virus was not a new "spillover" from the host or intermediate host.

The source of the COVID-19 virus has not yet been determined, and further investigation and large-scale nucleic acid testing are still being conducted.

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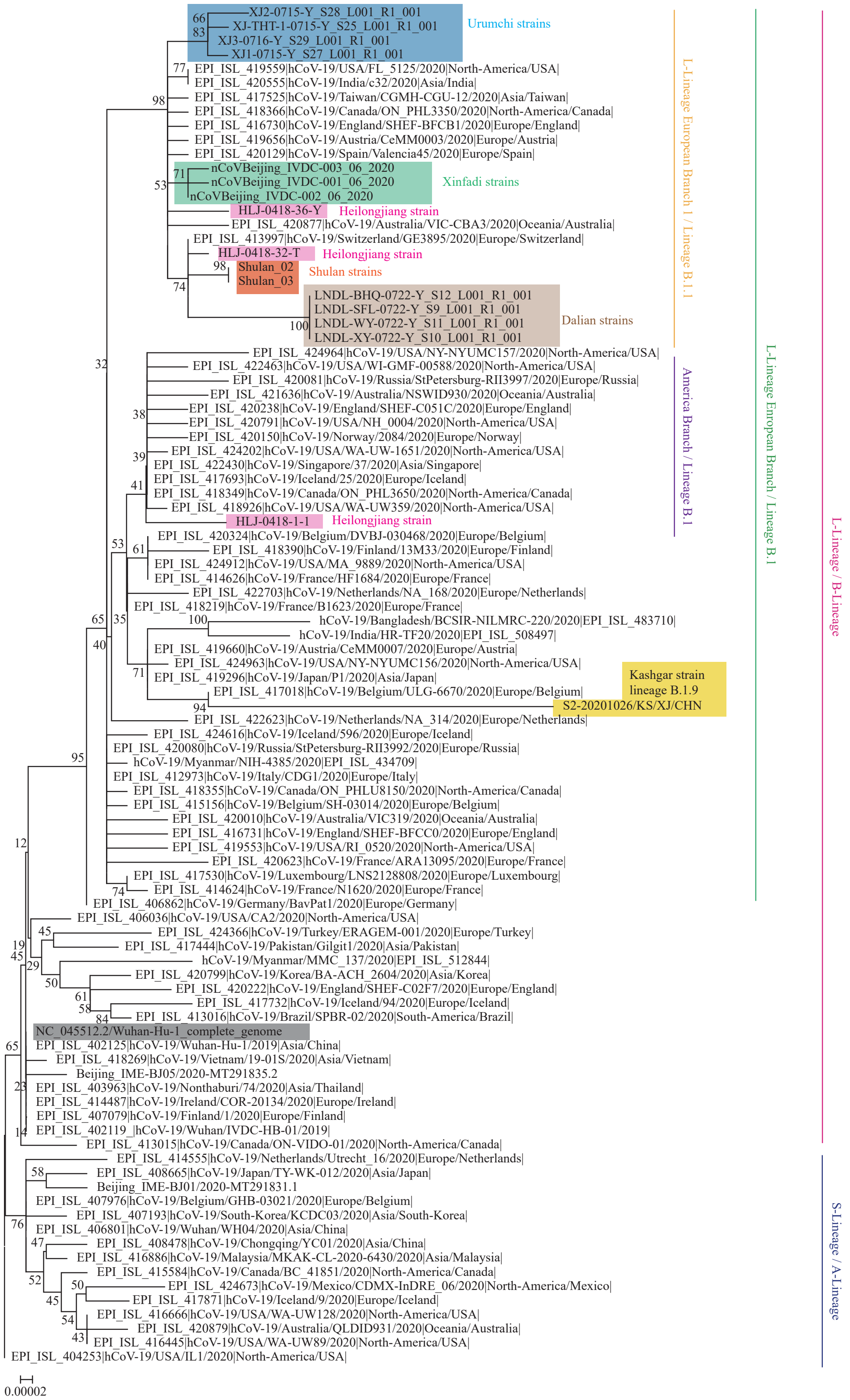

FIGURE 1. Phylogenetic tree based on the full-length genome sequences of the COVID-19 virus. The strains associated with specific outbreaks are as follows: Kashgar Prefecture (yellow); Urumchi (blue); Wuhan City in December 2019 (gray); Beijing Municipality Xinfadi Wholesale Market (green); northeastern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

Perspectives

Cooperation Between Japan's NIID and China CDC in Japan's COVID-19 Response

Takaji Wakita[1,#]

Emerging infectious diseases such as avian influenza and coronavirus disease 2019 (COVID-19) are important issues for health security in every country. Furthermore, since no country borders exist for these emerging infectious pathogens, international cooperation is indispensable to reduce disease transmission. For this reason, the National Institute of Infectious Diseases, Japan (NIID) reached an agreement with China CDC on a cooperative framework for infectious disease research and signed a memorandum of understanding in August 2006. Based on this memorandum, the NIID has further deepened cooperation between the two organizations and has been promoting research cooperation and the exchange of human resources for infectious disease control.

The NIID and China CDC have a history of information sharing and research cooperation between individual researchers and laboratories. In particular, the NIID provided considerable support to China for the World Health Organization (WHO) polio eradication program. Based on this relationship, the NIID has been organizing to deepen the cooperative relationship with China CDC, which is the core to infectious disease research and response in China. Furthermore, in April 2006, a similar memorandum of cooperation was signed with the Korea Centers for Disease Control and Prevention [now the Korea Disease Control and Prevention Agency (KDCA)]. Based on the cooperative relationship between these three countries, attempts are being made to strengthen cooperation in infectious disease control in East Asia. Since 2006, the Japan-China-Korea Forum on Communicable Disease Control and Prevention has been held with the NIID, China CDC, and KDCA. In this forum, information is exchanged on emerging infectious diseases including new strains of influenza and severe fever with thrombocytopenia syndrome, as well as core activities such as surveillance and field epidemiology training programs.

The present COVID-19 pandemic offers a stark reminder of the importance of preparedness for emerging and reemerging infectious diseases as the world continues to struggle with COVID-19. At the end of 2019, cases of pneumonia of unknown cause (PUE) were reported in Wuhan, China. Initially, there were reports of an outbreak that occurred among people in relation to the Huanan Seafood Wholesale Market in Wuhan, and the epidemic then began to spread worldwide. On January 10, 2020, the viral genome sequence of COVID-19 virus was reported, and the NIID immediately started to develop a viral genome polymerase chain reaction (PCR) test. On January 15, the first domestic case of COVID-19 was confirmed in Japan. A patient with pneumonia stayed in Wuhan and was reported to the WHO based on International Health Regulations (*1*).

On January 30, the WHO Emergency Committee declared COVID-19 a Public Health Emergency of International Concern (*2*). After that, the *Diamond Princess* cruise ship, which arrived at Yokohama Port on February 3, was quarantined for 2 weeks starting from February 5. In total, 712 of 3,711 crew members and passengers tested positive for COVID-19 (331 of whom were asymptomatic pathogen carriers), and 13 deaths were confirmed. All passengers were subsequently required to self-quarantine at home for an additional 14 days after disembarking, and as a result, the infection did not spread from the cruise ship to Japan (*3–5*).

Due to its spread and severity, on March 11, the WHO declared the COVID-19 outbreak a global pandemic. In Japan, the number of imported cases from foreign countries increased from the beginning of March, and the number of cases without a clear infectious source continued to increase in the middle of March. Furthermore, in late March, the number of infection clusters were increasing rapidly, mainly in urban areas, and a sharp increase of newly infected cases was seen. In response to this situation, on March 10, the Japan Cabinet made the decision to revise in part and activate the Act on Special Measures for Pandemic Influenza and New Infectious Diseases Preparedness and Response to include and stipulate COVID-19. On March 28, "Basic Action Policies for

Countermeasures Against the Novel Coronavirus Disease" were announced, and it was considered important to reduce the number of infected cases and maintain the medical care provision system and social functions. Avoiding the "Three Cs" (i.e., closed spaces with poor ventilation, crowds, and close-contact settings) and containing outbreaks and clusters through active epidemiological studies were therefore promoted.

On April 7, due to the rapid increase in new cases and the tight medical care provision system, a state of emergency was declared for 7 prefectures in Japan. Citizens of these prefectures were told to reduce contact by 80% and to refrain from going out and traveling across prefectural borders, telework was promoted, and some businesses were shut down. The state of emergency was expanded to all prefectures on April 16. As the epidemic spread from March to April, the day with the highest number of newly reported cases in the National Epidemiological Surveillance of Infectious Disease system was April 9, but the most frequent date of symptom onset was April 1. It was therefore considered that the number of infected cases rose sharply from mid-March, peaked in early April, and then decreased and began to flatten in mid-May. The state of emergency was gradually lifted from May 14 to 25, when it was officially lifted in all prefectures (*6*). After easing restrictions against going out and using facilities, the level of socioeconomic activity gradually increased, and on June 19, the restriction on traveling across prefectural borders was completely lifted nationwide. However, since mid-June, the number of new cases started to increase again, mainly among those aged in their 20s and 30s and in large urban areas and their surrounding vicinities (*7*).

Since June, the spread of infection among young people has been remarkable, especially in connection with restaurants with entertainment venues in the Shinjuku area. However, as the number of infected cases increases among the younger population, the number of middle-aged and older people who are at high risk of becoming severely infected is also increasing. As of July 22, 18 severely ill patients required ventilator support in Tokyo, and this number has been rising.

After the state of emergency was lifted, Japan's major countermeasures against COVID-19 included basic individual infection prevention (e.g., wearing masks, hand hygiene, social distancing), avoiding the "Three Cs", and cluster surveillance in active epidemiological surveys with a focus on securing an effective medical care provision system. However, after lifting the restrictions on going out, doing business, and traveling, the number of infected cases surged again. The risk of infection is considered to be high in situations in which a person talks in a loud voice or exhales in a "Three Cs" setting. Cluster infections originating from facilities such as pubs and daytime karaoke bars were detected. In addition, infections often spread to medical institutions and welfare facilities for the aged. At present, balance is needed between socioeconomics and infection control to substantially reduce the risk of infection in places and industries where such risk is considered high. In addition, older people at high risk of severe disease and other generations with whom they may come into contact also need to take extra steps to reduce the risk of infection.

Currently, non-pharmaceutical interventions are the main focus, but the rapid development of vaccines and therapeutic agents is needed before a fundamental solution for COVID-19 is possible. In addition, although the seasonality of the pandemic remains unclear, an urgent response is needed during influenza season. It is therefore necessary to combine wisdom from the fields of clinical medicine, infectious diseases, public health, and virology. In that sense, cooperation between the NIID, China CDC, and KDCA is the most important factor.

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Profiles

Guang Zeng, China CDC's Former Chief Expert of Epidemiology

Peter Hao[1,&]; Nankun Liu[1,&]; Jingjing Xi[1,#]; Feng Tan[1,#]

Guang Zeng was born in Beijing in 1946 and completed his undergraduate studies in the Medical Department of Hebei Medical University in 1970. Zeng then completed a master's degree in epidemiology from Peking Medical College in 1982. Zeng served as a researcher and PhD supervisor as China CDC's Chief Expert of Epidemiology (2000–2019); a counselor of the Beijing Municipal Government (2007–present); the seventh chair of the Public Health Branch of the Chinese Medical Association; the founder and honorary consultant of the Chinese Field Epidemiology Training Program (CFETP); a member of the Public Health Emergencies Expert Group of the National Health Commission (NHC) of the People's Republic of China.

The CFETP, which Zeng founded in 2001, has blossomed across the country and has trained almost 500 talented students with practical capabilities to serve as the backbone for central and local CDCs. Hundreds of CFETP graduates played an important role on the frontlines in the prevention and treatment of coronavirus disease 2019 (COVID-19) pandemic.

When the severe acute respiratory syndrome (SARS) epidemic occurred in 2003, Zeng was hired as a consultant to the joint headquarters of the capital to lead a team to investigate the Peking University People's Hospital, which was the most severely infected hospital. He put forward the proposal to close the hospital and transfer SARS patients to the outer suburbs, which was then immediately adopted and implemented by the government to establish the Beijing Xiaotangshan Hospital within seven days. On April 28, 2003, he was invited by the Ministry of Health (now known as the NHC) to give a lecture on the scientific prevention and treatment measures for SARS to the Political Bureau of the CPC Central Committee. His public health measures proposed mainly around isolation were adopted by the Party Central Committee.

On January 18, 2020, Zeng was selected as a member of the high-level expert group on the prevention and treatment of COVID-19 from the NHC and was dispatched to Wuhan to carry out investigations. On the morning of January 20, he stated to the leaders of the State Council of the People's Republic of China that the Spring Festival transport season had begun and that it was necessary to learn historical lessons from the 1967 Spring Festival transport season that led to the outbreak of meningitis across the country. At the press conference of the NHC that afternoon, on behalf of the expert group, he called for "people from Wuhan not to leave and for people from other places not to go in."

In recent years, Zeng led his team to investigate other major public health emergencies including the suspected case of "sudden death of unknown cause in Yunnan" that lasted for more than 20 years and the "methotrexate drug damage" incident that affected 12 provincial-level administrative divisions (PLADs) including Shanghai Municipality and Beijing Municipality. He dedicated himself to eliminating potential health risks that seriously threatened people's health.

He is the winner of special government allowances from the State Council and has won the National May 1 Labor Day Medal, the Science and the Technological Achievement Award from the Ministry of Health, the National Family Planning Commission, and the Chinese Preventive Medicine Association.

Zeng has been conducting research on the theory and practice of public health for a long time and proposed new concepts such as the "five public" attributes and "zero-level prevention" of public health. He has edited the *Modern Epidemiology Methods and Application*, *Modern Epidemiology*, *New Thinking of Chinese Public Health and Health*, and *Chinese Public Health Theory*, etc.

Though retired, Zeng's role as an epidemiologist contributed significantly to the protection of China's public health, the research and development of modern epidemiological methods, and insurance of public safety.

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