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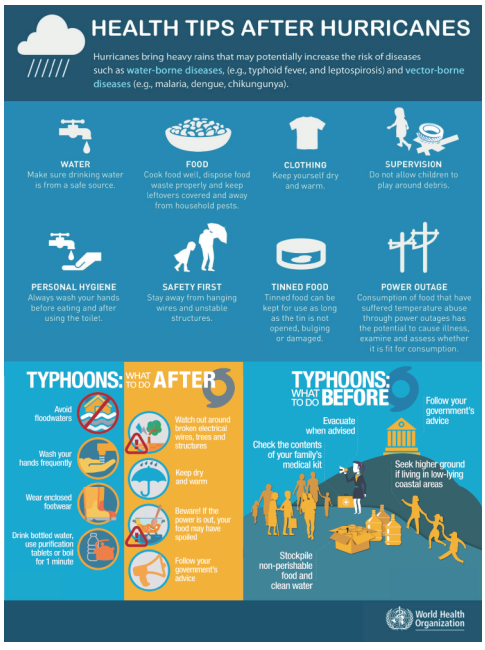

Preplanned Studies

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Cover Image: adapted from the World Health Organization, https://www.who.int/health-topics/tropical-cyclones#tab=tab_1.

Preplanned Studies

Increased Mortality Risks from a Spectrum of Causes of Tropical Cyclone Exposure — China, 2013–2018

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Summary

What is already known about this topic?

Tropical cyclone (TC) has a substantial and adverse impact on non-accidental mortality. However, whether heterogeneity exists when examining deaths from sub-causes and how TC impacts non-accidental mortality in the short term remain unclear.

What is added by this report?

This study found substantial associations at lag 0 between TC exposure and circulatory and respiratory mortality. TC exposures were associated with increased risks for several mortality sub-causes at lag 0 day, including ischemic heart disease, myocardial infarction, cardiac arrest, cerebrovascular disease, stroke, chronic obstructive pulmonary disease, and Parkinson's disease.

What are the implications for public health practice?

This finding suggests an urgent need to expand the public health focus of natural disaster management to include non-accidental mortality and sub-causes.

Tropical cyclone (TC) is significantly and adversely associated with both accidental and non-accidental mortality (*1*–*2*). Additionally, accidental deaths from drowning, physical trauma, and electrocution during TCs have been well characterized in epidemiologic studies. However, whether heterogeneity exists in TC-associated risk for non-accidental mortality sub-causes remains unclear. Recognizing non-accidental mortality sub-causes susceptible to TCs is essential for devising mitigation. While the longer-term effect of TCs on non-accidental mortality, such as circulatory mortality, has been recognized (*2*), little is known about the short-term non-accidental mortality risk of TCs.

TC's complex features generally stimulate cascading responses affecting non-accidental disease mortality (*3*). There is evidence that TC could substantially increase the risk of non-accidental mortality. The associated risks could result from several pathways; for example, TC can cause problems in accessing medical care (*3*), can damage infrastructure including public transportation and utility systems, and can increase exposure to other hazards like extreme heat.

We examined short-term associations of TC with mortality outcomes in China. China's relatively high daily mortality enables the statistical analysis of rare health outcomes (*4*). Specifically, we aimed to 1) quantify TC-associated mortality risk and identify sensitive sub-causes; 2) recognize vulnerable sub-population and regions.

From the China Mortality Surveillance System of the National Center for Chronic and Noncommunicable Disease Control and Prevention, China CDC, we obtained mortality data, including residents' daily mortality for 280 Chinese counties from 1 January 2013 to 31 December 2018 (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). The International Classification of Diseases classified mortality data, 10th Revision (ICD–10), including all-cause (A00–Z99), non-accidental (A00–R99), accidental (V00–X56), circulatory (I00–I99), and respiratory diseases (J00–J99). We also included mortality data due to 18 sub-causes (Supplementary Table S1, available in https://weekly.chinacdc.cn/).

We obtained TCs data from the Tropical Cyclone Information Center of the China Meteorological Administration. For each TC event, we classified a county as exposed if the storm's central track came within 60 km of the county's geographic center (Supplementary Figure S2, available in https://weekly.chinacdc.cn/). Meteorological data were collected from the European Centre for Medium-Range Weather Forecasts.

A case-crossover study design was used to examine the county-level association between TCs and mortality. Each exposed day was matched to five unexposed days by county. We considered TC-associated risk up to six following days (*1*). Using the matched multi-county data, we fit generalized linear mixed-effect models (GLMMs) with a Poisson distribution to estimate TC-associated mortality risk (expressed as rate ratio, *RR*), adjusting for potential

confounders. An unconstrained distributed lag function was used for the TC exposure variable. A county-specific random intercept was included.

We performed stratified analyses by sex, age, and the subset of counties by TC exposure frequency. We conducted sensitivity analyses to investigate the model's robustness. All the statistical analyses were completed using R (Version 3.6.1, The R Foundation for Statistical Computing). More details are provided in the Supplementary Materials.

China was hit by forty-six TCs during 2013–2018 (Figure 1). 153 out of 280 counties were exposed to at least one TC and were analyzed. Southeast coastal areas were frequently affected (Figure 1). The total counts of all-cause mortality were 4,147 and 20,062 on TC-exposed days and selected five reference days, respectively (Table 1).

Compared with reference days, TC-associated *RR*s for all-cause and non-accidental mortality were 1.07 [95% confidence interval (*CI*): 1.03–1.10] and 1.08 (95% *CI*: 1.04–1.11) at lag 0 day (the exposure day), respectively. Although accidental mortality did not increase on the TC-exposed day, it did by the third day following exposure (*RR*=1.18, 95% *CI*: 1.06–1.30). We found significant associations at lag 0 between TC exposure and circulatory mortality (*RR*=1.12, 95% *CI*: 1.06–1.18) and respiratory mortality (1.12, 95% *CI*: 1.01–1.23) (Supplementary Table S2, Supplementary Figure S3, available in https://weekly.chinacdc.cn/). Effect estimates from sensitivity analyses were consistent with the primary ones (Supplementary Table S3, available in https://weekly.chinacdc.cn/).

TC was associated with increased risks for several mortality sub-causes at lag 0 day, including ischemic heart disease, myocardial infarction (MI), cardiac arrest, cerebrovascular disease, stroke, chronic obstructive pulmonary disease (COPD), and Parkinson's disease; for example, MI mortality risk increased by 15% (Figure 2). The estimated *RR*s remained elevated for mortality due to cardiac arrest, cerebrovascular disease, and stroke in the subsequent 2–3 days. We also observed appreciable lagged effects

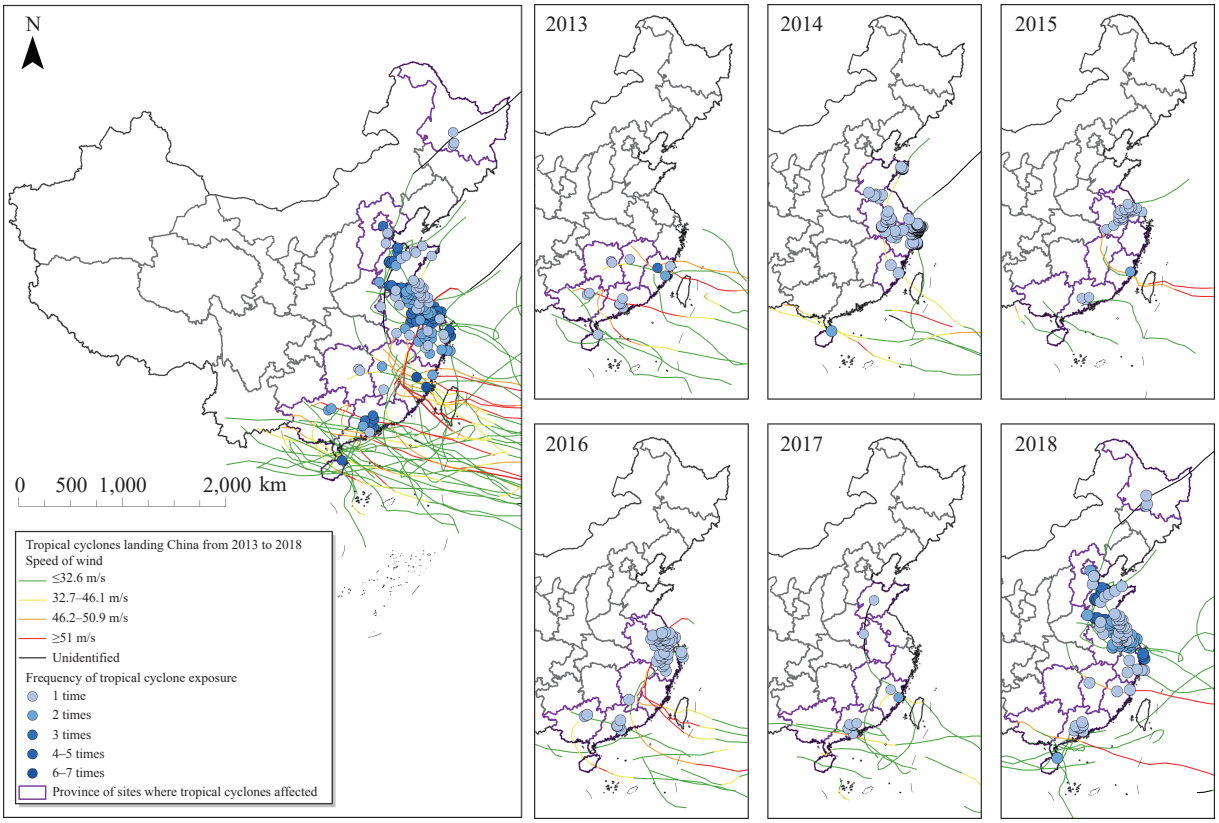

FIGURE 1. Spatial distribution of 153 eastern Chinese counties (blue circles) that were exposed to at least one tropical cyclone over the study period (2013–2018).
Note: Curves show the tracks of the 46 tropical cyclones that made landfall on China continent in this period; color of storm tracks denotes the maximum wind speed. Color of the circle in each county indicates the frequency of tropical cyclone exposures during the study period.

TABLE 1. Summary statistics of daily mortality on tropical cyclone exposure days and reference days (exposure：reference= 1：5) in 153 Chinese counties (2013–2018).

Variable	Exposure days (*N*=336)				Reference days (*N*=1,680)			
	Total	Mean±SD	Median (P25, P75)	Maximum	Total	Mean±SD	Median (P25, P75)	Maximum
All-cause	4,147	12.3±7.9	10 (7, 17)	48	20,062	11.9±7.6	10 (6, 16)	43
Cause-specific								
Non-accidental	3,844	11.4±7.3	10 (6, 15)	40	18,472	11.0±7.0	10 (6, 15)	39
Accidental	303	0.9±1.2	1 (0, 1)	8	1,590	1.0±1.2	1 (0, 1)	7
Circulatory disease	1,648	4.9±3.9	4 (2, 7)	26	7,557	4.5±3.4	4 (2, 6)	24
Respiratory disease	449	1.3±1.5	1 (0, 2)	8	2,323	1.4±1.5	1 (0, 2)	8
Sex								
Male	2,405	7.2±4.9	6 (4, 10)	28	11,471	6.8±4.6	6 (3, 10)	28
Female	1,742	5.2±3.7	4 (2, 7)	20	8,591	5.1±3.8	4 (2, 7)	23
Age (years)								
0–64	964	2.9±2.4	2 (1, 4)	17	4,826	2.9±2.3	2 (1, 4)	14
65–74	802	2.4±2.1	2 (1, 3)	11	3,907	2.3±2.0	2 (1, 3)	12
>75	2,381	7.1±5.0	6 (3, 10)	24	11,329	6.7±4.8	6 (3, 9)	29

Note: *N*=the number of TC exposure days.

for lower respiratory infection, asthma,influenza, and pneumonia (Figure 2).

Males had a higher TC-associated risk for accidental and circulatory mortality than females but lower for respiratory mortality (Supplementary Figure S4, available in https://weekly.chinacdc.cn/). The difference in risk estimates by sex was not statistically significant. Residents aged 65–74 years presented a significantly lower respiratory mortality risk than those younger than 65 and older than 74 years. We observed a higher cardiorespiratory mortality risk in counties that experienced ≥3 TC events than in those experiencing 1–2 events and lower accidental mortality risks, though the difference was not significant (Supplementary Figure S4).

DISCUSSION

To the best of our knowledge, this is the first multi-center, multi-event study examining the short-term associations of TCs with many mortality outcomes in China. Among residents in 153 Chinese counties during 2013–2018, TCs were associated with elevated risks for several non-accidental mortality, especially circulatory and respiratory sub-causes. TCs were also associated with renal failure and Parkinson's disease mortality. Our findings suggest an urgent need to expand the public health focus of natural disaster management to include non-accidental mortality outcomes.

Two similar Chinese studies existed but on a much smaller scale. One study reported a *RR* of 1.05 (95% *CI:* 0.96–1.16) for circulatory mortality associated with TCs in Guangzhou (2008–2011) (*5*). The other indicated elevated mortality risk during the two years following Typhoon Morakot (2009) in Taiwan (*6*). These reported longer-term TC-associated mortality risks were consistent with western studies (*2*). However, TC-associated circulatory mortality risk was much more substantial in the short term, with a 12% increase on the TC-exposed day in this study and a 1.2% increase in the following month from a previous study (*2*). Our findings complement the limited knowledge by providing evidence of TC's short-term circulatory mortality risk, focusing on a time scale relevant to rapid public health response.

Mortality due to several circulatory diseases markedly increased in association with TC. TC immediately impacted cardiac arrest and MI mortality. It is known that TC may have a longer-term effect on MI; for example, 30-day MI mortality increased by 31% during Hurricane Sandy in New Jersey (*7*). We found MI mortality increased by 15% on TC-exposed days, suggesting a short-term risk of TC. Psychological stress after TC exposure may help explain the elevated risk associated with TC. TC occurrences typically generate psychological stress for affected individuals, provoking physiological responses. Among these responses, the hypothalamic-pituitary-adrenocortical and autonomic nervous system responses primarily

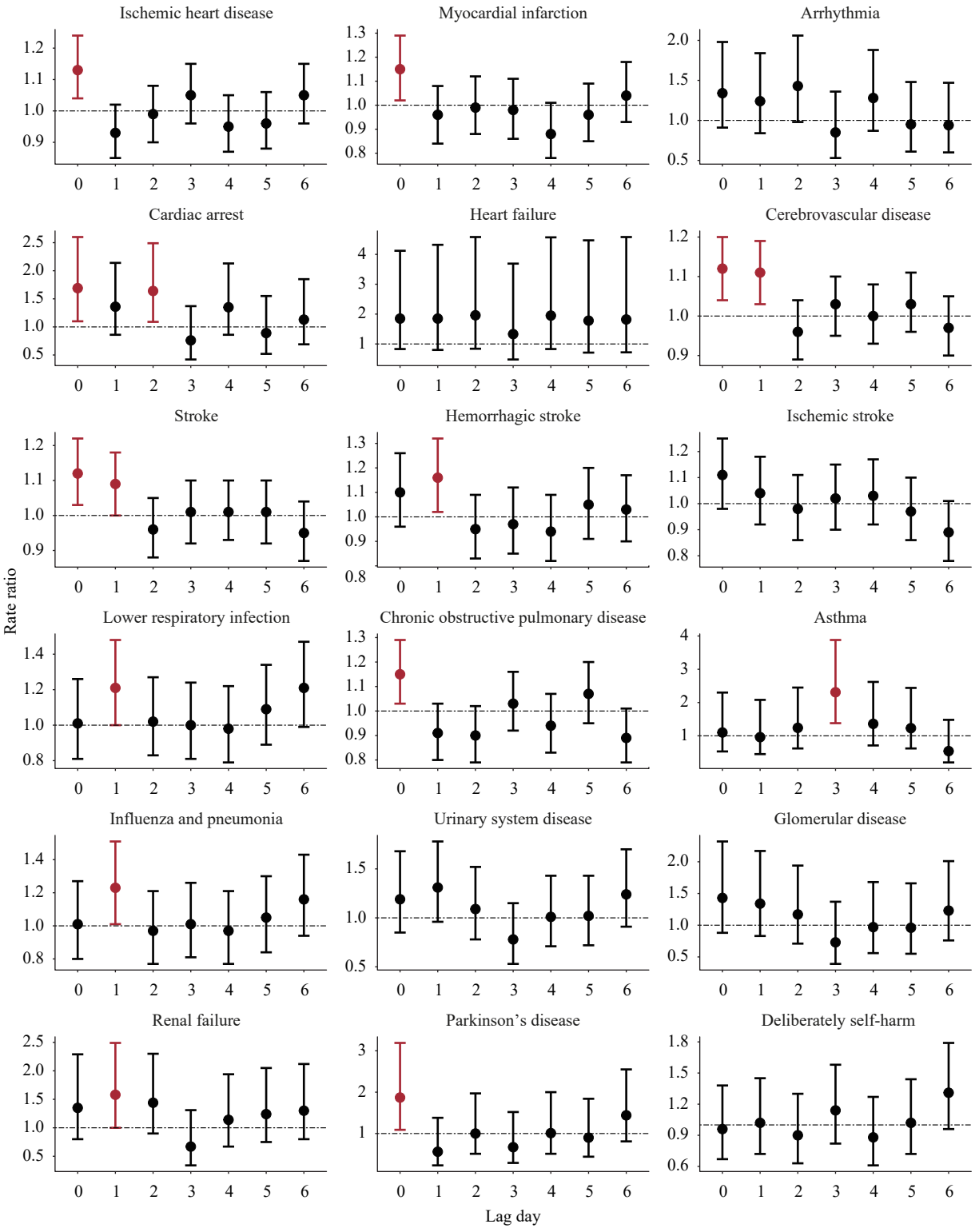

FIGURE 2. Lag-specific rate ratio of sub-cause mortality associated with tropical cyclone exposure, on average across all exposed counties.

contribute to cardiovascular disease development (*8*). Stress may also trigger stroke, a possible explanation of TC-associated increased risk of cerebrovascular disease and stroke mortality (*9*). Our findings suggest an urgent need to expand the public health focus of TC management to include circulatory sub-causes.

Accidental deaths (like drowning and being hit by falling tree limbs) often occur during TC (*10*). We

only observed increased accidental mortality risk at lag day 3 (*RR*=1.18). During TCs, fatal injuries or drowning often occur in heavily impacted areas where strong winds and severe rainfalls may block roads and damage communications. Therefore, the rescue teams might not arrive in time, and the deceased had to be determined a few days later. It may also be possible that it took several days to find and identify all accidental deaths caused by TCs. Furthermore, though insignificant, TC-associated accidental mortality risk was higher in males than females, which is consistent with previous findings. For example, the ratio of males to females was 1.87/1.00 among victims of Hurricane Sandy. Occupation type by sex might be a reason for this result, as men dominate some jobs (like bus drivers and rescue team members) with higher health risks than others during TCs.

TC was also associated with an increased mortality risk due to lower respiratory infections, COPD, influenza and pneumonia, renal failure, and urinary system diseases. While the underlying mechanism is not adequately understood, TCs likely affect mortality through damaging infrastructure (*3*). First, TCs can damage transportation and communication infrastructure, which may impede people from seeking medical treatment. Beyond that, utilities and power outages play a crucial role in increasing the risk of death for patients relying on electrically powered medical technologies like ventilators and oxygen, especially for those at hospitals who are particularly vulnerable to the impact of power outage (*3*).

Parkinson's disease mortality significantly increased on TC days but not in the next few days. External shocks and movement difficulties may partly explain the elevated mortality risks. According to a previous study on TCs' effects on Parkinson's disease in American older adults, the hospitalization rate for Parkinson's disease increased in the week after TCs (*2*). It can be possible that patients with severe Parkinson's disease might be extremely fragile to the impacts of tropical cyclones and more likely to die than those who had less severe conditions and could be hospitalized in the following days.

Our study has some limitations. First, exposure misclassification may exist. Previous research has evaluated TC-associated health risks in America using a multi-hazard-based exposure assessment (*1*–*2*). Distance from a storm track effectively captured some signal of TC's health risk (*1*). Future research is needed to develop alternative methods of TC exposure assessment in China. Second, confounding residuals may be possible. We used a matched design by county; county-level confounding factors that were time-invariant could be controlled at the study design stage. However, some county-level confounders (such as socioeconomic characteristics) could be time-variant. So confounding residuals may exist in the results (*2*).

Our findings offer practical implications. Firstly, it is crucial to improve TC's early warning system, which should be able to alarm vulnerable individuals to take proper measures. The authorities should provide adequate medical resources for affected residents, especially people with TC-associated sensitive diseases. Also, the public should be well educated about TC's health risk.

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SUPPLEMENTARY MATERIAL

Tropical Cyclone (TC)

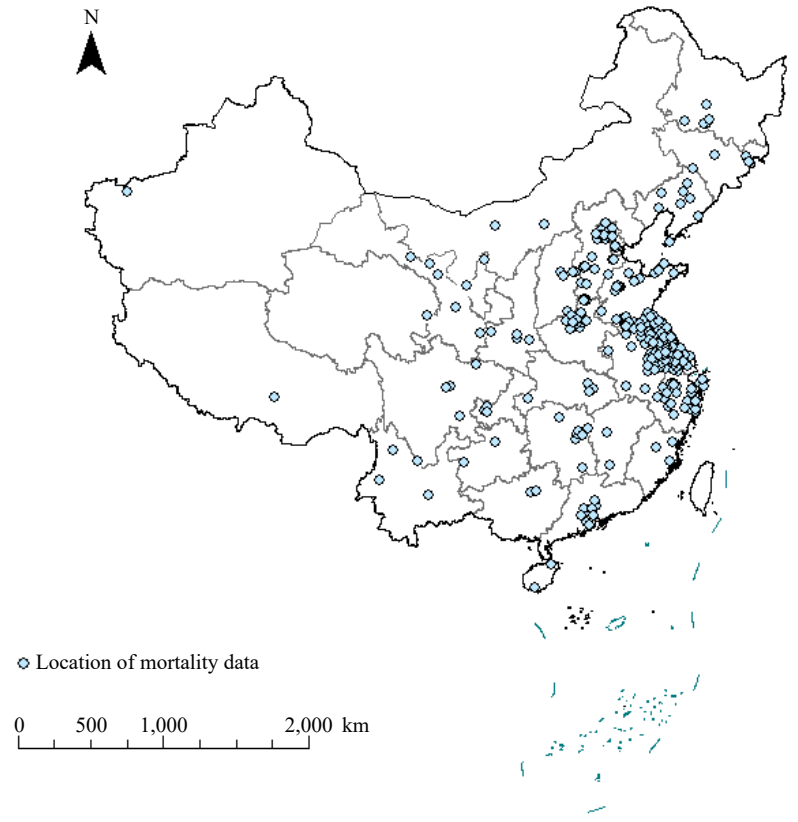
A tropical cyclone is an intense circular storm that originates over warm tropical oceans which often threatens human health and has devastating impacts on society (*1*).

Mortality Data

This study obtained mortality data from the China Mortality Surveillance System of the National Center for Chronic and Noncommunicable Disease Control and Prevention, China CDC. The data include daily mortality counts for residents living in 280 Chinese counties (locations shown in Supplementary Figure S1) from January 1, 2013 to December 31, 2018. The International Classification of Diseases classified mortality data, 10th Revision (ICD–10), including all-cause (ICD–10, A00–R99), non-accidental (ICD–10, A00–R99), accidental (ICD–10, V00–X56), circulatory (ICD–10, I00–I99), and respiratory (ICD–10, J00–J99). We also included mortality data due to 18 sub-causes in our analysis, with details in Supplementary Table S1. Residential population data was obtained from the Sixth National Census in 2010.

TC Data

TC exposure data was collected from the Tropical Cyclone Information Center of China Meteorological Administration (http://tcdata.typhoon.org.cn/). This database includes the track and maximum wind speed of TCs that made landfall in China. For each TC event during the study period, we classified a county as exposed if the storm's central track came within 60 km of the county's geographic center (*2*). When a county was assessed as exposed, the exposure date was determined as the date the storm came closest to that county.



SUPPLEMENTARY FIGURE S1. Locations of 280 counties with mortality data.

TC Exposure

For each tropical cyclone during the study period, we classified a county as exposed if the storm's central track came within 60 km of the county's geographic center. When a county was classified as exposed, the exposure date was determined as the date the storm came closest to that county. An example denoting the definition of tropical cyclone-exposed counties is shown in Supplementary Figure S2.

In Supplementary Figure S2, the curve shows the track of a tropical cyclone. Circles show five counties (i.e., sites 1, 2, 3, 4, 5) along the storm track. The lines connecting the circles and the curve show the distances between each county's geographic center and the tropical cyclone's track. The distances for sites 1, 3, 4, and 5 were less than 60 km; these sites were included in the data analysis. Site 2 was excluded from the data analysis, as the distance (70 km) was greater than 60 km.

Meteorological Data

Meteorological data (mean temperature and mean relative humidity data) were collected from the European Centre for Medium-Range Weather Forecasts (ECMWF, https://apps.ecmwf.int/datasets/). For each county, we

SUPPLEMENTARY TABLE S1. Descriptive analysis of cause-specific mortality on case and control days.

Disease (ICD code)	Case						Control					
	Mean	SD	q25	q50	q75	Max	Mean	SD	q25	q50	q75	Max
All (A00-Z99)	12.34	7.87	7	10	17	48	11.94	7.58	6	10	16	43
Non-accidental (A00-R99)	11.44	7.26	6	10	15	40	11.00	6.96	6	10	15	39
Accidental (V00-X58)	0.90	1.23	0	1	1	8	0.95	1.21	0	1	1	7
Circulatory (I00-I99)	4.90	3.87	2	4	7	26	4.50	3.39	2	4	6	24
Hypertensive heart disease (I10-I15)	0.35	0.83	0	0	0	10	0.38	0.75	0	0	1	6
Ischemic heart disease (I20-I25)	1.76	1.89	0	1	3	13	1.59	1.76	0	1	2	11
Myocardial infarction (I21-I23)	1.02	1.44	0	1	2	12	0.93	1.33	0	0	1	10
Arrhythmia (I44-I49)	0.08	0.30	0	0	0	2	0.06	0.24	0	0	0	2
Cardiac arrest (I46)	0.07	0.28	0	0	0	2	0.04	0.21	0	0	0	2
Heart failure (I50)	0.02	0.20	0	0	0	3	0.01	0.11	0	0	0	1
Cerebrovascular disease (I60-I69)	2.56	2.42	1	2	4	16	2.33	2.14	1	2	3	15
Stroke (I60-I64)	1.83	2.12	0	1	3	16	1.76	1.83	0	1	3	14
Hemorrhagic stroke (I60-I61)	0.73	1.11	0	0	1	7	0.75	1.00	0	0	1	8
Ischemic stroke (I63)	0.92	1.23	0	1	1	9	0.84	1.09	0	1	1	8
Respiratory (J00-J99)	1.34	1.52	0	1	2	8	1.38	1.51	0	1	2	8
Lower respiratory infection (J12-J18&J20-J22)	0.26	0.58	0	0	0	4	0.29	0.66	0	0	0	5
Chronic obstructive pulmonary disease (J41-J44)	0.98	1.37	0	1	1	8	0.98	1.32	0	1	1	7
Asthma (J45-J46)	0.02	0.15	0	0	0	1	0.03	0.19	0	0	0	2
Influenza and pneumonia (J09-J18)	0.23	0.52	0	0	0	3	0.27	0.61	0	0	0	5
Digestive (K00-K93)	0.24	0.55	0	0	0	4	0.21	0.47	0	0	0	2
Nervous (G00-G99)	0.19	0.48	0	0	0	3	0.20	0.49	0	0	0	5
Parkinson's disease (G20-G21)	0.05	0.21	0	0	0	1	0.02	0.15	0	0	0	1
Genitourinary (N00-N99)	0.12	0.35	0	0	0	2	0.11	0.34	0	0	0	3
Urinary system disease (N00-N39)	0.11	0.34	0	0	0	2	0.10	0.33	0	0	0	2
Glomerular disease (N00-N08)	0.05	0.23	0	0	0	1	0.05	0.22	0	0	0	2
Renal failure (N17-N19)	0.05	0.23	0	0	0	2	0.04	0.21	0	0	0	2
Deliberately self-harm (X60-X84)	0.10	0.31	0	0	0	2	0.10	0.34	0	0	0	2

Note: The ratio of case to control is 1 to 5. In the analysis, tropical events (case) and reference days (control) are 336 days and 1,680 days from 2013 to 2018, respectively. Minority of daily mortality for both case and control is 0.

aggregated the hourly data from ECMFW to generate a daily measure for our study period.

Statistical Model

We used a case-crossover study design to examine county-level associations between TC exposure and mortality risk. For counties exposed to at least one TC event, we matched each exposed day to five unexposed days randomly

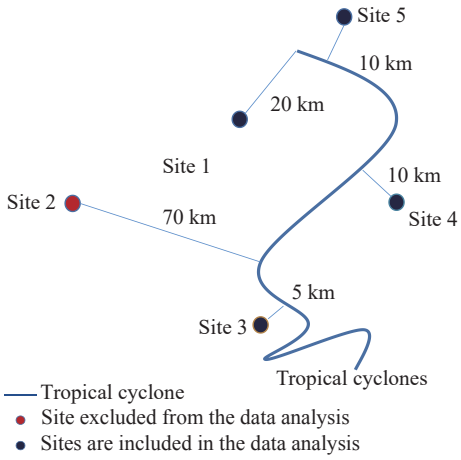
SUPPLEMENTARY TABLE S2. Numerical results from main model.

Cause of death	Rate ratio (95% confidence interval)						
	Lag 0 (Exposure day)	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6
All-cause	1.07 (1.03, 1.10)	1.01 (0.98, 1.05)	0.99 (0.96, 1.02)	1.02 (0.99, 1.05)	0.95 (0.92, 0.98)	1.03 (1.00, 1.07)	0.99 (0.96, 1.02)
Non-accidental	1.08 (1.04, 1.11)	1.02 (0.99, 1.06)	0.98 (0.95, 1.01)	1.01 (0.97, 1.04)	0.95 (0.92, 0.99)	1.03 (1.00, 1.07)	0.99 (0.96, 1.03)
Accidental	0.94 (0.83, 1.06)	0.95 (0.85, 1.07)	1.07 (0.96, 1.19)	1.18 (1.06, 1.3)	0.92 (0.82, 1.04)	1.06 (0.95, 1.18)	0.97 (0.87, 1.09)
Circulatory	1.12 (1.06, 1.18)	1.05 (0.99, 1.10)	0.98 (0.93, 1.04)	1.01 (0.96, 1.06)	0.99 (0.94, 1.04)	1.01 (0.96, 1.07)	1.00 (0.95, 1.05)
Respiratory	1.12 (1.01, 1.23)	0.98 (0.89, 1.09)	0.95 (0.86, 1.05)	1.05 (0.95, 1.16)	0.96 (0.86, 1.06)	1.06 (0.96, 1.17)	0.97 (0.87, 1.07)
Digestive	1.13 (0.90, 1.41)	1.03 (0.82, 1.30)	0.98 (0.78, 1.25)	1.06 (0.85, 1.34)	0.82 (0.64, 1.07)	0.98 (0.78, 1.25)	1.14 (0.91, 1.42)
Nervous	1.08 (0.83, 1.40)	0.87 (0.66, 1.15)	1.08 (0.84, 1.38)	0.86 (0.66, 1.14)	0.68 (0.5, 0.93)	0.95 (0.73, 1.24)	1.13 (0.89, 1.45)
Genitourinary	1.22 (0.88, 1.70)	1.28 (0.94, 1.74)	1.07 (0.77, 1.49)	0.77 (0.53, 1.14)	0.96 (0.68, 1.37)	1.06 (0.76, 1.48)	1.22 (0.90, 1.66)
Hypertensive heart disease	1.01 (0.84, 1.23)	1.11 (0.94, 1.33)	1.02 (0.85, 1.22)	0.79 (0.65, 0.97)	1.02 (0.85, 1.22)	0.98 (0.81, 1.18)	0.84 (0.69, 1.02)
Ischemic heart disease	1.13 (1.04, 1.24)	0.93 (0.85, 1.02)	0.99 (0.9, 1.08)	1.05 (0.96, 1.15)	0.95 (0.87, 1.05)	0.96 (0.88, 1.06)	1.05 (0.96, 1.15)
Myocardial infarction	1.15 (1.02, 1.29)	0.96 (0.84, 1.08)	0.99 (0.88, 1.12)	0.98 (0.86, 1.11)	0.88 (0.78, 1.01)	0.96 (0.85, 1.09)	1.04 (0.93, 1.18)
Arrhythmia	1.34 (0.91, 1.98)	1.24 (0.84, 1.84)	1.43 (0.98, 2.06)	0.85 (0.53, 1.36)	1.28 (0.87, 1.88)	0.95 (0.61, 1.48)	0.94 (0.60, 1.47)
Cardiac arrest	1.69 (1.10, 2.60)	1.36 (0.86, 2.14)	1.64 (1.09, 2.49)	0.76 (0.42, 1.37)	1.35 (0.86, 2.13)	0.89 (0.52, 1.55)	1.13 (0.69, 1.85)
Heart failure	1.85 (0.83, 4.12)	1.85 (0.80, 4.32)	1.96 (0.84, 4.58)	1.33 (0.48, 3.69)	1.95 (0.83, 4.57)	1.78 (0.71, 4.47)	1.82 (0.72, 4.58)
Cerebrovascular disease	1.12 (1.04, 1.20)	1.11 (1.03, 1.19)	0.96 (0.89, 1.04)	1.03 (0.95, 1.10)	1.00 (0.93, 1.08)	1.03 (0.96, 1.11)	0.97 (0.90, 1.05)
Stroke	1.12 (1.03, 1.22)	1.09 (1.00, 1.18)	0.96 (0.88, 1.05)	1.01 (0.92, 1.10)	1.01 (0.93, 1.10)	1.01 (0.92, 1.10)	0.95 (0.87, 1.04)
Hemorrhagic stroke	1.1 (0.96, 1.26)	1.16 (1.02, 1.32)	0.95 (0.83, 1.09)	0.97 (0.85, 1.12)	0.94 (0.82, 1.09)	1.05 (0.91, 1.20)	1.03 (0.90, 1.17)
Ischemic stroke	1.11 (0.98, 1.25)	1.04 (0.92, 1.18)	0.98 (0.86, 1.11)	1.02 (0.90, 1.15)	1.03 (0.92, 1.17)	0.97 (0.86, 1.10)	0.89 (0.78, 1.01)
Lower respiratory infection	1.01 (0.81, 1.26)	1.21 (1.00, 1.48)	1.02 (0.83, 1.27)	1.00 (0.81, 1.24)	0.98 (0.79, 1.22)	1.09 (0.89, 1.34)	1.21 (0.99, 1.47)
Chronic obstructive pulmonary disease (COPD)	1.15 (1.03, 1.29)	0.91 (0.80, 1.03)	0.90 (0.79, 1.02)	1.03 (0.92, 1.16)	0.94 (0.83, 1.07)	1.07 (0.95, 1.20)	0.89 (0.79, 1.01)
Asthma	1.10 (0.53, 2.30)	0.96 (0.45, 2.08)	1.24 (0.62, 2.45)	2.31 (1.38, 3.88)	1.36 (0.71, 2.62)	1.23 (0.62, 2.44)	0.54 (0.20, 1.48)
Influenza and pneumonia	1.01 (0.80, 1.27)	1.23 (1.01, 1.51)	0.97 (0.77, 1.21)	1.01 (0.81, 1.26)	0.97 (0.77, 1.21)	1.05 (0.84, 1.30)	1.16 (0.94, 1.43)
Parkinson's disease	1.87 (1.09, 3.19)	0.56 (0.23, 1.38)	1.00 (0.51, 1.97)	0.67 (0.29, 1.52)	1.01 (0.51, 2.00)	0.90 (0.44, 1.84)	1.44 (0.81, 2.55)
Urinary system disease	1.19 (0.85, 1.68)	1.31 (0.96, 1.78)	1.09 (0.78, 1.52)	0.78 (0.53, 1.15)	1.01 (0.71, 1.43)	1.02 (0.72, 1.43)	1.24 (0.91, 1.70)
Glomerular disease	1.43 (0.88, 2.32)	1.34 (0.83, 2.17)	1.17 (0.71, 1.94)	0.73 (0.39, 1.37)	0.97 (0.56, 1.68)	0.96 (0.55, 1.66)	1.23 (0.76, 2.01)
Renal failure	1.35 (0.80, 2.29)	1.58 (1.00, 2.49)	1.44 (0.90, 2.30)	0.67 (0.34, 1.31)	1.14 (0.67, 1.94)	1.24 (0.75, 2.05)	1.30 (0.80, 2.12)
Deliberately self-harm	0.96 (0.67, 1.38)	1.02 (0.72, 1.45)	0.90 (0.63, 1.30)	1.14 (0.82, 1.58)	0.88 (0.61, 1.27)	1.02 (0.72, 1.44)	1.31 (0.96, 1.79)

SUPPLEMENTARY TABLE S3. Results from sensitive analysis.

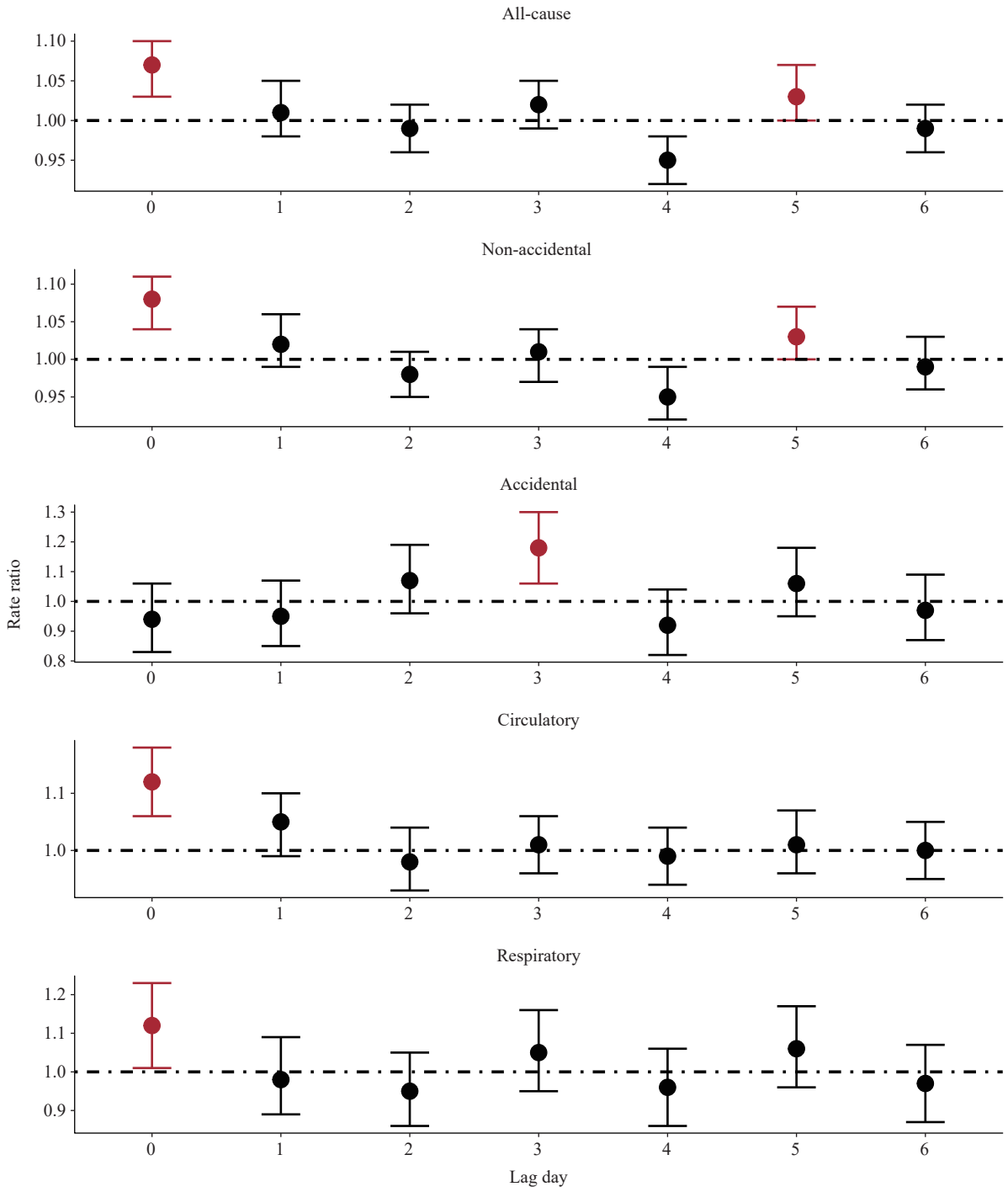
Model	Cause of death	Rate ratio (95% confidence interval)						
		Lag 0 (Exposure day)	Lag 1	Lag 2	Lag 3	Lag 4	Lag 5	Lag 6
Model 1 (3 reference periods)	All-cause	1.07 (1.04, 1.11)	1.02 (0.99, 1.05)	0.99 (0.96, 1.03)	1.03 (0.99, 1.06)	0.96 (0.93, 0.99)	1.04 (1.01, 1.07)	1.00 (0.97, 1.03)
	Non-accidental	1.09 (1.05, 1.13)	1.03 (0.99, 1.07)	0.99 (0.95, 1.02)	1.01 (0.98, 1.05)	0.96 (0.93, 1.00)	1.04 (1.00, 1.08)	1.00 (0.97, 1.04)
	Accidental	0.90 (0.79, 1.01)	0.93 (0.83, 1.05)	1.05 (0.94, 1.17)	1.15 (1.04, 1.28)	0.90 (0.8, 1.02)	1.04 (0.93, 1.16)	0.96 (0.85, 1.07)
	Circulatory disease	1.14 (1.08, 1.20)	1.06 (1.00, 1.12)	0.99 (0.94, 1.05)	1.02 (0.97, 1.08)	1.00 (0.95, 1.06)	1.02 (0.97, 1.08)	1.01 (0.96, 1.07)
	Respiratory disease	1.13 (1.02, 1.24)	0.99 (0.89, 1.09)	0.95 (0.86, 1.05)	1.05 (0.95, 1.16)	0.96 (0.86, 1.06)	1.06 (0.96, 1.18)	0.97 (0.87, 1.08)
Model 2 (6 reference periods)	All-cause	1.06 (1.03, 1.10)	1.02 (0.98, 1.05)	0.99 (0.96, 1.02)	1.02 (0.99, 1.06)	0.95 (0.92, 0.99)	1.04 (1.00, 1.07)	1.00 (0.96, 1.03)
	Non-accidental	1.08 (1.04, 1.11)	1.02 (0.99, 1.06)	0.99 (0.95, 1.02)	1.01 (0.98, 1.05)	0.96 (0.93, 0.99)	1.04 (1.00, 1.07)	1.00 (0.97, 1.03)
	Accidental	0.90 (0.80, 1.02)	0.94 (0.83, 1.05)	1.05 (0.95, 1.17)	1.16 (1.04, 1.28)	0.91 (0.81, 1.02)	1.04 (0.94, 1.16)	0.96 (0.86, 1.07)
	Circulatory disease	1.13 (1.08, 1.19)	1.06 (1.01, 1.12)	1.00 (0.94, 1.05)	1.02 (0.97, 1.08)	1.00 (0.95, 1.06)	1.02 (0.97, 1.08)	1.01 (0.96, 1.07)
	Respiratory disease	1.11 (1.01, 1.22)	0.97 (0.88, 1.08)	0.94 (0.85, 1.04)	1.04 (0.94, 1.15)	0.95 (0.85, 1.05)	1.05 (0.95, 1.16)	0.96 (0.87, 1.06)
Model 3 (GLM with county)	All-cause	1.08 (1.03, 1.13)	1.02 (0.98, 1.07)	0.99 (0.95, 1.04)	1.03 (0.98, 1.08)	0.96 (0.92, 1.01)	1.04 (1.00, 1.10)	1.01 (0.96, 1.06)
	Non-accidental	1.09 (1.04, 1.15)	1.03 (0.98, 1.08)	0.98 (0.94, 1.03)	1.01 (0.96, 1.06)	0.97 (0.92, 1.02)	1.04 (0.99, 1.10)	1.01 (0.96, 1.06)
	Accidental	0.92 (0.81, 1.05)	0.95 (0.84, 1.08)	1.08 (0.96, 1.22)	1.19 (1.06, 1.33)	0.91 (0.80, 1.04)	1.06 (0.94, 1.20)	0.98 (0.86, 1.11)
	Circulatory disease	1.16 (1.09, 1.24)	1.06 (0.99, 1.13)	0.98 (0.91, 1.05)	1.01 (0.95, 1.08)	1.01 (0.94, 1.08)	1.02 (0.95, 1.09)	1.00 (0.94, 1.07)
	Respiratory disease	1.13 (1.01, 1.26)	1.01 (0.90, 1.14)	0.97 (0.86, 1.1)	1.07 (0.95, 1.20)	0.99 (0.88, 1.11)	1.10 (0.98, 1.23)	1.01 (0.90, 1.14)

Notes: Model 1 and Model 2 have the same specifications as the main model, using three and six reference periods, respectively; Model 3 is a generalized linear model (GLM) to control year, population, temperature, relative humidity, and a fixed effect of county (rather than the random effect of county used in the main model).



SUPPLEMENTARY FIGURE S2. An example showing the definition of tropical cyclone exposed counties.

selected from a candidate pool of days which were: 1) in the same county; 2) in a different year; 3) the same day of the year as the TC exposure day; and 4) not within a seven-day window of another TC exposure day. Since TCs typically occur in seasons when ambient temperature is high, we also excluded as potential controls days with daily maximum temperature exceeding 35 ℃ (the threshold of defining a high temperature day based on China Meteorological Administration) to reduce possible confounding from extreme heat. We considered TC-associated risk up to six days following the TC exposure day (in full, a seven-day period we refer to as the "exposure period").

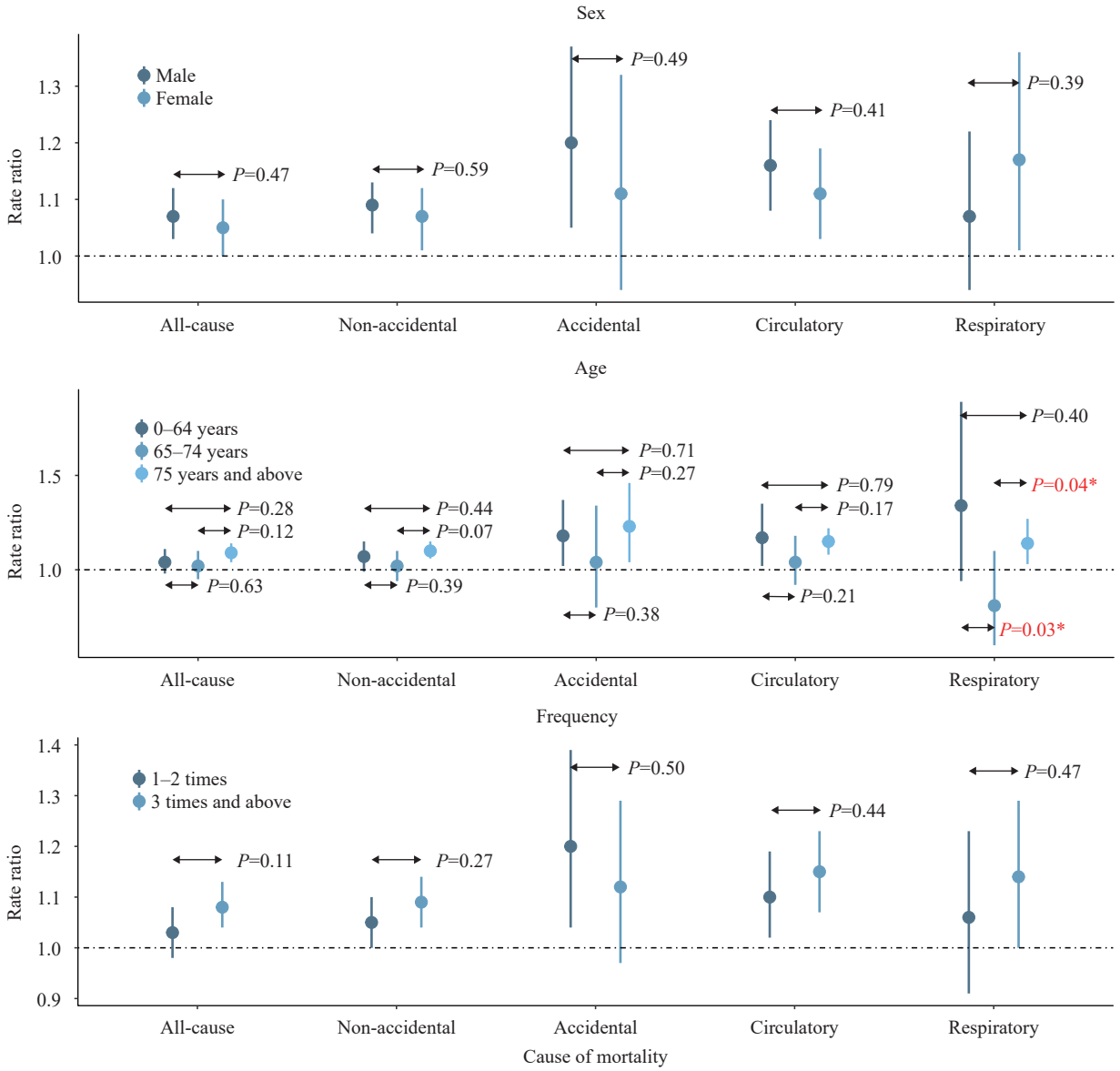


SUPPLEMENTARY FIGURE S3. Lag-specific rate ratio for all-cause and broad cause mortality associated with tropical cyclone exposure, on average across tropical cyclone-exposed counties.

Following an approach that we previously developed, with the matched multi-county data, we fit generalized linear mixed-effect models (GLMMs) with a Poisson distribution to estimate the mortality risk associated with TC exposure. We fit the model separately for each mortality outcome. We adjusted for potential confounding effects due to long-term time trend and weather conditions. The model equation for the GLMMs is:

$$\log\left[\mathrm{E}\left(\mathrm{Y}_{\mathrm{t}}^{\mathrm{c}}\right)\right] = \log\left(\mathrm{P}^{\mathrm{c}}\right) + \alpha + \alpha^{\mathrm{c}} + \sum_{\mathrm{l}=0}^{6}\beta_{\mathrm{l}}\chi_{\mathrm{t}+\mathrm{l}}^{\mathrm{c}} + \gamma\mathrm{Year}_{\mathrm{t}}^{\mathrm{c}} + \delta_{1}\mathrm{T}_{\mathrm{t}}^{\mathrm{c}} + \delta_{2}\mathrm{Rh}_{\mathrm{t}}^{\mathrm{c}} \quad (1)$$

where $\mathrm{Y}_{\mathrm{t}}^{\mathrm{c}}$ is the daily mortality count for county c on day t; P^{c} is the total residential population of county c based



SUPPLEMENTARY FIGURE S4. Rate ratio (*RR*) of mortality associated with tropical cyclone exposure stratified by sex, age, and tropical cyclones' frequency in the county over the study period. *RR*s were estimated at lag 3 for accidental mortality and lag 0 for other mortality outcomes.

on the 2010 census data, which is included as an offset term; α is the model intercept; α^{c} is a random intercept for county c, included to account for within-county correlations; $\sum_{l=0}^{6}\beta_l\chi_{t+l}^{c}$ is unconstrained distributed lag function for TC exposure χ. β_l is a vector of length 7 of coefficients from day t to lag day l; χ_{t+l}^{c} is an indicator variable denoting whether a given day at lag day l from day t is within TC exposure or within the matched reference period in county c; Year_t^c is year for day t for county c to control for a linear long-term trend in mortality rates over study years; γ is the linear coefficients for year; T_t^c is the daily mean temperature for county c on day t; δ_1 is the coefficient for mean temperature; Rh_t^c is the daily average relative humidity for county c on day t; δ_2 is the coefficient for relative humidity. We calculated rate ratio (*RR*) of tropical cyclone exposure on mortality outcomes at each lag day based on the estimated β_l.

Stratified Analysis

We performed secondary analyses by fitting the same model for 1) the population stratified by sex (male and female) and age (≤64, 65–74, and ≥75 years old); and 2) TC exposure frequency (counties experienced 1–2 TC

events and ≥3 events) during our study period (*3*). The Z test was used to compare the two effect estimates derived from subgroup analysis:

$$Z = \frac{\beta_1 - \beta_2}{\sqrt{SE_1^2 + SE_2^2}} \quad (2)$$

Where β_1 and β_2 were coefficient estimates from subgroups (e.g., males and females); SE_1 and SE_2 were the corresponding standard error for coefficients. *P* values for the Z test were reported and shown with the results.

Sensitivity Analysis

We conducted sensitivity analyses to investigate the robustness of our results. First, instead of selecting five reference periods for each exposed period, we tested using three and six referent periods. Second, to account for potential confounding effects due to spatial variation, we replaced the random effect for county with a fixed effect by including an indicator variable of county in a generalized linear model. All the statistical analyses were completed using R (Version 3.6.1, The Foundation for Statistical Computing). Several R packages were used in statistical analyses, including "dlnm", "dplyr", "MASS", "purrr", "lme4" and "splines".

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Preplanned Studies

Immunogenicity and Safety of Homologous Booster Doses of CoronaVac COVID-19 Vaccine in Elderly Individuals Aged 60 Years and Older: A Dosing Interval Study — Yunnan Province, China, 2021–2022

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Summary

What is already known about this topic?

Neutralization levels induced by inactivated vaccines rapidly wane after primary immunization, and a homologous booster can recall specific immune memory, resulting in a remarkable increase in antibody concentration. The optimal interval between primary and booster doses has yet to be determined.

What is added by this report?

Booster doses given at three months or more after the two-dose regimen of the CoronaVac COVID-19 vaccine in elderly individuals aged 60 years and older triggered good immune responses. The geometric mean titers of neutralizing antibody on Day 14 after the booster doses increased by 13.3–26.2 fold of baseline levels, reaching 105.45–193.59 in groups with different intervals (e.g., 3, 4, 5, and 6 months).

What are the implications for public health practice?

A 4- to 5-month interval between receiving the primary and booster series of CoronaVac could be an alternative to the 6-month interval in order to promote vaccine-induced immunity in elderly individuals. The findings support the optimization of booster immunization strategies.

Vaccination has been proven to be highly effective in reducing the burden of coronavirus disease 2019 (COVID-19) in the context of emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants based on real-world evidence (*1*–*2*). With the efforts of the whole of Chinese society, vaccine coverage of primary immunization has reached 90% (*3*). As neutralization antibody levels rapidly decline after primary immunization (*4*), especially for vulnerable populations, determining the optimal interval between primary and booster series is an urgent step in promoting vaccine-induced population immunity. To explore the immunogenicity, immune persistence, and safety of homologous booster doses of CoronaVac administered at 3-month, 4-month, 5-month, and 6-month intervals in elderly individuals aged 60 years and older, we conducted a single-center, open-label trial in Yongde County, Yunnan Province. We found that booster doses given at three months or more after the two-dose regimen of CoronaVac in elderly individuals aged 60 years and older could trigger good immune responses, especially at four to six months. This would be conducive to optimizing intervals for the booster vaccination strategy.

In this single-center, open-label clinical trial conducted in Yongde County, Yunnan Province, China, participants aged 60 years and over who had received two doses of CoronaVac three to six months prior were recruited. The detailed inclusion and exclusion criteria are listed in Supplementary Table S1 (available in https://weekly.chinacdc.cn/). Eligible participants were assigned to four groups according to the time elapsed after their two-dose immunization, namely, the 3-month, 4-month, 5-month, and 6-month interval groups. All participants provided written informed consent prior to enrollment. The study protocol and informed consent were approved by the Ethics Committee of Yunnan CDC (#2021-14). This trial was registered with ClinicalTrials.gov, NCT05398926.

Blood samples were collected from participants before booster administration and on Days 14, 28, and 180 after booster doses to assess immunogenicity. Neutralizing antibody levels against live SARS-CoV-2 (virus strain SARS-CoV-2/human/CHN/CN1/2020, GenBank accession number MT407649.1) were quantified using a previously described micro cytopathogenic effect assay (*5*–*6*). Titers lower than the limit of detection (1∶4) were treated as half the limit of

detection. Participants were observed for 30 minutes after vaccine administration in case of any immediate reactions. Solicited local and systemic adverse events within 7 days, unsolicited adverse events within 28 days, and serious adverse events within 6 months were collected after booster doses. All adverse events were graded according to China National Medical Products Administration guidelines and coded by the Medical Dictionary for Regulatory Activities (MedDRA 25.0) System Organ Class. The causal relationships between adverse events and vaccination were assessed by the investigators and an expert committee organized by CDC.

The primary outcomes included geometric mean titers (GMTs) of neutralizing antibodies against live SARS-CoV-2 on Day 14, Day 28, and Day 180, as well as any vaccine-related adverse events within 28 days after booster doses. The incidence of solicited adverse events within 7 days and serious adverse events reported during the 6-month follow-up were evaluated as secondary safety endpoints. Post hoc analysis assessed fold increases in antibody levels before administration to Day 14 and fold decreases from Day 14 to Day 180 after booster doses in each group. The immunogenic outcomes were evaluated in the per-protocol set, comprising participants who completed their assigned vaccination and had available blood samples at prespecified time points. Participants who received booster doses were included in the safety analysis.

We used the Pearson χ^2 test or Fisher's exact test for categorical outcomes and the Clopper-Pearson method for corresponding 95% confidence intervals (*CI*s). GMTs and corresponding 95% *CI*s were calculated on the basis of the standard normal distribution of the log-transformed antibody titers. Fold increases/decreases in antibody levels were calculated as the geometric mean of the ratios of paired sera at two visits. Analysis of variance (ANOVA) with log-transformation was used to test the differences between groups and between follow-up times. Comparisons were performed between groups or by group *t* tests with log-transformation. Bonferroni correction was performed as a post hoc test if variance was significant. Subgroup analyses of immunogenicity were conducted by sex and self-reported comorbidity status. Hypothesis testing was two-sided, and a *P* value <0.05 was considered to indicate statistical significance. We used R (version 4.2.1; R Core Team, Vienna, Austria) for all analyses.

Between December 6 and 24, 2021, a total of 400 participants were enrolled in the study and allocated to four groups according to the interval between their second and booster doses; 101, 99, 100, and 100 participants were allocated to the 3-month, 4-month, 5-month, and 6-month groups, respectively (Supplementary Figure S1, available in https://weekly.chinacdc.cn/). The median age of the participants was 65 [interquartile range (IQR), 63–68] years, and the distribution was balanced among groups. Of the 400 participants, 198 (50%) were male, and 312 (78%) were ethnically Han. Hypertension was the most common comorbidity, present in 102 (26%) participants. The demographic characteristics are detailed in Table 1.

The GMTs of neutralizing antibodies before administration of booster doses were 8.06 (95% *CI*: 6.68–9.72) in the 3-month group, 7.98 (95% *CI*: 6.56–9.70) in the 4-month group, 7.40 (95% *CI*: 6.13–8.94) in the 5-month group, and 5.26 (95% *CI*: 4.43–6.25) in the 6-month group, which were significantly different between the 3-month and 6-month (*P*=0.012), and 4-month and 6-month groups (*P*=0.008), respectively. Remarkable increases in GMTs were observed in all groups on Day 14 after the boosters, reaching 105.45 (95% *CI*: 86.14–129.08), 187.31 (95% *CI*: 152.99–229.33), 193.59 (95% *CI*: 151.84–246.82), and 135.52 (95% *CI*: 111.32–164.99) in the four groups (*P*<0.0001), respectively. Only the antibody levels in the 4-month and 5-month groups significantly exceeded those in the 3-month group (both *P*<0.0001) and there were no significant differences in neutralizing antibody levels between the other three groups and the 6-month group (*P*=0.57, 0.20, 0.11), which was the recommended minimum interval between primary and booster regimens in China before December 2022. No significant differences in fold increases were observed among the four groups. A declining tendency in GMT values was observed in all groups from Day 14 to Day 28 after the booster doses. GMTs by six months after the boosters were highest in the 5-month group (15.45, 95% *CI*: 12.23–19.52), followed by the 4-month group (10.24, 95% *CI*: 8.51–12.32), the 6-month group (9.82, 95% *CI*: 8.03–12.01), and the 3-month group (7.21, 95% *CI*: 6.05–8.58) (Table 2 and Figure 1). The fold decreases from Day 14 to Day 180 after booster doses were similar among the four groups (Table 2). When compared between follow-up times, there was no significant difference between baseline and Day 180, or between Day 14 and Day 28 in all groups, except the 4-month group, in which the GMT on Day 14 was significantly different from Day 28 after the booster

TABLE 1. Baseline demographic characteristics of participants who received booster doses of CoronaVac COVID-19 vaccine.

Characteristics	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)
Sex					
Male	43 (43%)	49 (49%)	54 (54%)	52 (52%)	198 (50%)
Female	58 (57%)	50 (51%)	46 (46%)	48 (48%)	202 (50%)
Age group (years)					
60–70	74 (73%)	87 (88%)	81 (81%)	85 (85%)	327 (82%)
70–80	26 (26%)	11 (11%)	19 (19%)	15 (15%)	71 (18%)
80+	1 (1%)	1 (1%)	0 (0%)	0 (0%)	2 (1%)
BMI (kg/m^2, IQR)	22.58 (20.86, 24.77)	23.71 (21.00, 25.98)	22.82 (20.83, 24.91)	22.44 (20.67, 24.15)	22.80 (20.83, 24.98)
Ethnicity					
Han	72 (71%)	76 (77%)	68 (68%)	96 (96%)	312 (78%)
Others	29 (29%)	23 (23%)	32 (32%)	4 (4%)	88 (22%)
Comorbidity					
At least one	40 (40%)	42 (42%)	36 (36%)	24 (24%)	142 (36%)
Hypertension	32 (32%)	29 (29%)	28 (28%)	13 (13%)	102 (26%)
Diabetes	6 (6%)	7 (7%)	5 (5%)	2 (2%)	20 (5%)
Cerebral infarction	1 (1%)	9 (9%)	5 (5%)	4 (4%)	19 (5%)
Coronary heart disease	4 (4%)	3 (3%)	3 (3%)	0 (0%)	10 (3%)
Hyperthyroidism	0 (0%)	1 (1%)	1 (1%)	1 (1%)	3 (1%)
Others	6 (6%)	6 (6%)	3 (3%)	12 (12%)	27 (7%)
Interval between 3rd and 2nd doses (days, IQR)	110.00 (98.00, 117.00)	132.00 (131.00, 132.00)	166.00 (163.00, 168.00)	185.00 (185.00, 185.00)	153.50 (117.00, 172.75)

Note: Data are presented as the median (IQR, interquartile range) or number (percentage). Continuous variables were compared using the Kruskal–Wallis H-test. Categorical variables were compared using the chi-square test or Fisher's exact test.
Abbreviation: BMI=body mass index.

TABLE 2. GMTs of neutralizing antibodies in different interval groups at different time points.

Time points	3-month group	4-month group	5-month group	6-month group	*P* value*
Baseline (Pre-booster)					
No. of participants	*n*=101	*n*=99	*n*=100	*n*=100	
GMT (95% *CI*)	8.06 (6.68, 9.72)	7.98 (6.56, 9.70)	7.40 (6.13, 8.94)	5.26 (4.43, 6.25)	0.0036
Day 14 after dose 3					
No. of participants	*n*=101	*n*=98	*n*=98	*n*=99	
GMT (95% *CI*)	105.45 (86.14, 129.08)	187.31 (152.99, 229.33)	193.59 (151.84, 246.82)	135.52 (111.32, 164.99)	<0.0001
Fold increases *vs.* baseline (95% *CI*)	13.26 (10.55, 16.67)	23.09 (18.31, 29.11)	25.82 (19.53, 34.14)	26.22 (20.82, 33.01)	0.17
Day 28 after dose 3					
No. of participants	*n*=97	*n*=97	*n*=96	*n*=92	
GMT (95% *CI*)	90.57 (73.53, 111.54)	138.81 (113.26, 170.11)	169.01 (132.97, 214.82)	123.64 (100.93, 151.46)	0.0006
Day 180 after dose 3					
No. of participants	*n*=87	*n*=85	n=91	*n*=94	
GMT (95% *CI*)	7.21 (6.05, 8.58)	10.24 (8.51, 12.32)	15.45 (12.23, 19.52)	9.82 (8.03, 12.01)	<0.0001
Fold decreases *vs.* Day 14 (95% *CI*)	14.99 (12.62, 17.79)	17.72 (14.51, 21.64)	12.29 (9.97, 15.16)	14.26 (11.85, 17.15)	0.60

Note: GMT was calculated based on log-transformed data.
Abbreviation: GMTs=geometric mean titers; *CI*=confidence interval; ANOVA=analysis of variance.
* ANOVA with log-transformation (GMT) was used to detect differences among the four groups. Differences between groups were assessed by *t* test on log-transformed data.

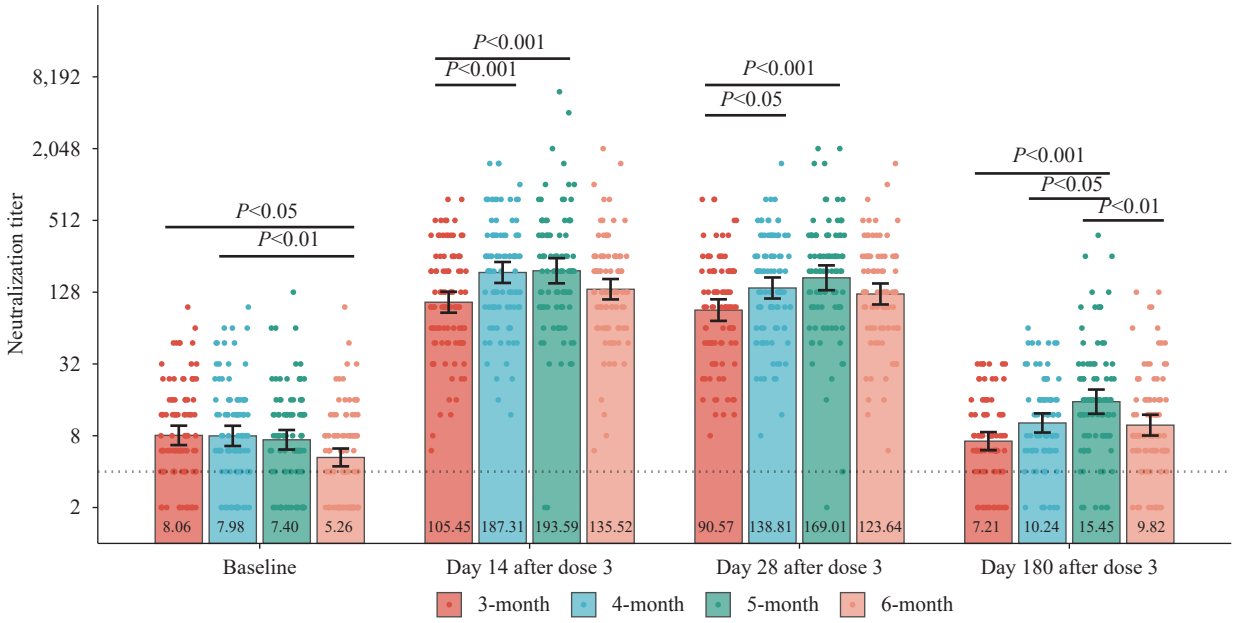

FIGURE 1. Neutralizing antibody levels to live SARS-CoV-2 before and after the booster vaccination in different interval groups.
Note: Numbers at the bottom of the bars are GMTs, and error bars indicate 95% *CI*s. Dots are reciprocal neutralizing antibody titers for individuals in the per-protocol population. Numbers above the short horizontal lines are *P* values for comparisons among the 3-month group, 4-month group, 5-month group, and 6-month group using ANOVA with log-transformation. Bonferroni correction was performed as a post hoc test if the variance was significant. Only *P* values indicating significant differences are marked. The dotted horizontal line represents the limit of detection (1∶4). Titers lower than the limit of detection are presented as half of that.
Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; GMTs=geometric mean titers; *CI*s=confidence intervals; ANOVA=analysis of variance.

doses. In subgroup analyses, no significant differences in neutralizing antibodies were found between sex groups and comorbidity status (Supplementary Figures S2 and S3, available in https://weekly.chinacdc.cn/).

Solicited adverse events within 7 days were graded as mild (Grade 1) or moderate (Grade 2) in all groups (Supplementary Table S2, available in http://weekly.chinacdc.cn/). The proportions of participants who experienced vaccine-related adverse events within 28 days after the booster dose were 9% in the 3-month group, 8% in the 4-month group, 14% in the 5-month group, and 4% in the 6-month group, with no significant difference among groups (*P*=0.10; Supplementary Table S3, available in http://weekly.chinacdc.cn/). During the six-month follow-up period after booster doses, no vaccine-related serious adverse events were recorded (Supplementary Table S4, available in http://weekly.chinacdc.cn/).

DISCUSSION

Our study found that neutralization antibody levels continued to decline at three months post vaccination with a two-dose regimen of CoronaVac in elderly individuals aged 60 years and older, were sustained through months three to five, and exhibited an obvious reduction at six months. Waning of antibody levels in infection-naive individuals around a one- to three-month period after the second dose administration has been identified in most COVID-19 vaccines (*7*), which is associated with reduced protection, especially against emerging variants due to immune escape (*8*). The significantly lower antibody level in the 6-month group than other groups could prove that it would be preferable to provide the booster doses no more than six months after primary immunization to avoid the increasing risk of infection among elderly individuals.

None of the participants experienced natural infections before or during the study period, and there were no local outbreaks in Yunnan Province. Booster doses of inactivated vaccines given at three to six months after primary immunization could recall specific immune memory and rebound neutralization antibody levels in elderly individuals. Antibody titers in the 5-month group were numerically higher than those in the other three groups over the six-month follow-up

after booster doses, but there was no significant difference between the 4-month, 5-month, and 6-month groups on Day 14 and 28 after the booster doses. Prolonged intervals between doses could facilitate the affinity maturation of memory B cells (*9*) and several studies indicated that longer intervals before the booster dose elicited better neutralizing antibody levels (*10*–*11*), which was consistent with relatively poor immune responses in the 3-month group in our study. Our results showed that a 4- to 5-month interval between receiving the primary and booster series of CoronaVac would be an alternative choice to the 6-month interval to promote vaccine-induced immunity for elderly individuals.

On Day 180 after the first booster doses, GMTs declined to nearly undetectable levels. Previous follow-up studies (*6*,*12*) also reported a decreasing tendency after the first booster doses, suggesting that a second booster should be administered in a timely manner to provide extra protection against waning of protective antibodies. Real-world studies have reported the relative effectiveness of the second booster, indicating additional protection compared to the first booster (*13*–*14*).

This study has several limitations. First, we did not assess T-cell responses and neutralization tests in vitro against emerging variants of concern, particularly Omicron and its subvariants. Second, the proportion of participants aged 80 years or older and those with severe comorbidities was too small to determine immunogenicity for this older age group and high-risk population. Third, we did not assess the neutralizing antibody level between 28 and 180 days after booster doses to quantify the specific waning pattern.

In summary, homologous inactivated boosters after the two-dose regimen showed good immunogenicity and safety profiles in elderly individuals aged 60 years and older. Since November 29, 2022, the recommended minimum interval between the primary and booster series of COVID-19 vaccines in China has been shortened to three months for elderly individuals aged 60 years and older. Our results also imply that a 4- to 5-month interval between receiving the primary and booster series of CoronaVac could be an alternative choice to the 6-month interval to promote vaccine-induced immunity for elderly individuals. Further studies with more follow-up visits are needed to better understand immunogenicity after the first booster immunization and to help optimize the second booster immunization strategy. Real-world studies on the severity of infection and booster-dose effectiveness should be conducted.

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Conflicts of interest: HJ.Y. has received research funding from Sanofi Pasteur, GlaxoSmithKline, Yichang HEC Changjiang Pharmaceutical Company, Shanghai Roche Pharmaceutical Company and Sinovac Biotech Ltd. X.M., TT.Z. and G.Z. are employees of Sinovac Biotech and Y.H. is an employee of Sinovac Life Sciences. The remaining authors declare no competing interests.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Inclusion and exclusion criteria.

Criteria
Inclusion criteria
(1) People aged 60 years and older;
(2) Able to provide legal proof of identity;
(3) People who have received prime immunization by two doses of CoronaVac 21 to 35 days apart 3 to 6 months earlier;
(4) Able to understand and sign the Informed Consent Form voluntarily, willing to comply with the research plan and complete the study.
Exclusion criteria
(1) History of laboratory-confirmed SARS-CoV-2 infection;
(2) Having received SARS-CoV-2 vaccines other than CoronaVac, or having been boosted after prime immunization of CoronaVac;
(3) History of serious adverse reactions to vaccines or vaccine components, such as urticaria, dyspnea, and angioneuroedema;
(4) Subjects with autoimmune diseases or immune deficiency/immune inhibition;
(5) Subjects with severe chronic diseases, such as severe cardiovascular diseases, hypertension, diabetes, liver and kidney diseases, and malignant tumors that cannot be controlled by drugs;
(6) Subjects with severe nervous system disorders (epilepsy, convulsions or tic) or mental diseases;
(7) Having received the immunosuppressive therapy, cytotoxic therapy or inhaled corticosteroids therapy (excluding corticosteroid spray therapy for allergic rhinitis, and topical corticosteroid therapy for acute non-concurrent dermatitis) in the past 6 months, or are scheduled to receive these treatments during the study period;
(8) Subjects who have received blood products within 3 months before vaccination with the test vaccine, or are scheduled to receive these treatments during the study period;
(9) Subjects who have received other study drugs within 30 days before vaccination with the test vaccine;
(10) Subjects who have received live attenuated vaccines within 14 days before vaccination with the test vaccine, or who have received subunit or inactivated vaccines within 7 days before vaccination with the test vaccine;
(11) Subjects having an attack of various acute or chronic diseases within 7 days;
(12) Subjects with axillary temperature >37.0 ℃ at the time of vaccination;
(13) Subjects who are not suitable for participating in this clinical trial according to the investigator.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

SUPPLEMENTARY TABLE S2. Solicited adverse events within 7 days after administration of booster doses.

Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	*P* value*
Total	11	7	16	4	
Any local reaction	2 (2%)	1 (1%)	4 (4%)	0	0.22
Vaccination site pain	0	1 (1%)	2 (2%)	0	0.62
Vaccination site swelling	1 (1%)	0	1 (1%)	0	1.00
Vaccination site pruritus	1 (1%)	0	1 (1%)	0	1.00
Any systemic reaction	9 (9%)	6 (6%)	12 (12%)	4 (4%)	0.10
Fever	2 (2%)	1 (1%)	2 (2%)	1 (1%)	1.00
Acute allergic reaction	1 (1%)	0	0	0	1.00
Diarrhoea	1 (1%)	0	0	0	1.00
Vomiting	1 (1%)	0	0	0	1.00
Nausea	1 (1%)	1 (1%)	2 (2%)	0	0.90
Headache	2 (2%)	2 (2%)	3 (3%)	0	0.53
Cough	1 (1%)	2 (2%)	4 (4%)	3 (3%)	0.71
Fatigue	0	0	1 (1%)	0	1.00

Note: Data are *n* (%).
* *P* value was calculated by Fisher exact probability method and of the comparison of incidence rate among four groups.

SUPPLEMENTARY TABLE S3. Incidence of vaccine-related adverse events by system organ class and preferred term reported within 28 days after administration of booster doses.

Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)	*P* value*
No. of participants	9 (9%)	8 (8%)	14 (14%)	4 (4%)	35 (35%)	0.10
No. of events	12	9	16	4	41	
Cardiac disorders						
Arrhythmia	0	1 (1%)	0	0	1 (1%)	1.00
Gastrointestinal disorders						
Abdominal distension	0	0	1 (1%)	0	1 (1%)	1.00
Diarrhea	1 (1%)	0	0	0	1 (1%)	1.00
Nausea	1 (1%)	1 (1%)	2 (2%)	0	4 (4%)	0.90
Vomiting	1 (1%)	0	0	0	1 (1%)	1.00
General disorders and administration site conditions						
Fatigue	0	0	1 (1%)	0	1 (1%)	1.00
Pyrexia	2 (2%)	1 (1%)	2 (2%)	1 (1%)	6 (6%)	1.00
Vaccination site pain	0	1 (1%)	2 (2%)	0	3 (3%)	0.62
Vaccination site pruritus	1 (1%)	0	1 (1%)	0	2 (2%)	1.00
Vaccination site swelling	1 (1%)	0	1 (1%)	0	2 (2%)	1.00
Immune system disorders						
Hypersensitivity	1 (1%)	0	0	0	1 (1%)	1.00
Nervous system disorders						
Dizziness	1 (1%)	0	0	0	1 (1%)	1.00
Headache	2 (2%)	3 (3%)	2 (2%)	0	7 (7%)	0.53
Respiratory, thoracic and mediastinal disorders						
Cough	1 (1%)	2 (2%)	2 (2%)	2 (2%)	7 (7%)	1.00
Nasal obstruction	0	0	1 (1%)	0	1 (1%)	1.00
Rhinorrhea	0	0	1 (1%)	1 (1%)	2 (2%)	1.00

Note: Data are *n* (%).
* *P* value was calculated by Fisher exact probability method and of the comparison of incidence rate among four groups.

SUPPLEMENTARY TABLE S4. Serious adverse events by system organ class and preferred term reported during 6-month follow-up after administration of booster doses.

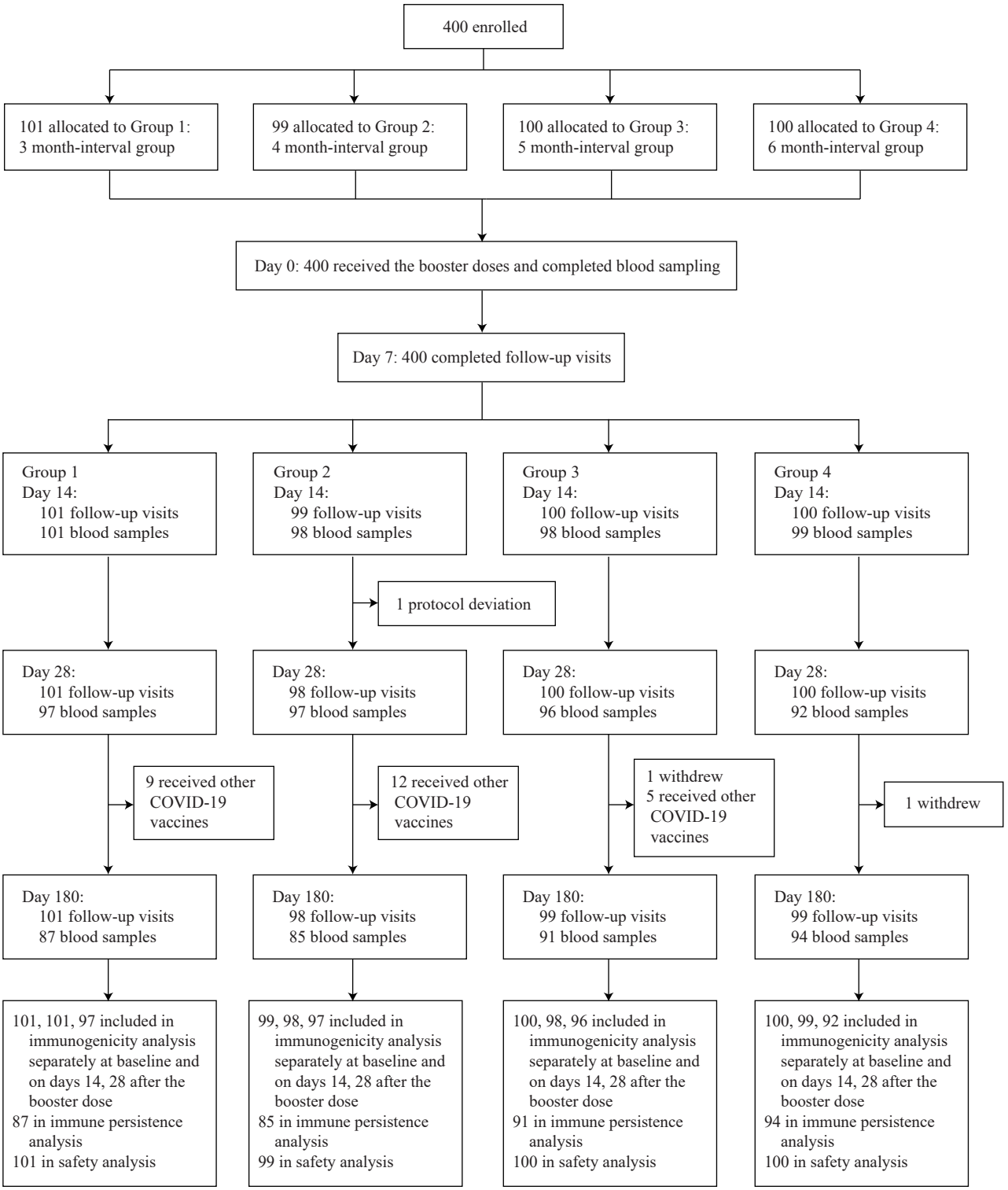
Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)	*P* value*
No. of participants	5 (5%)	4 (4%)	7 (7%)	6 (6%)	22 (22%)	0.88
No. of events	6	7	22	13	48	
Cardiac disorders						
Cardiac failure	0	0	1 (1%)	0	1 (1%)	1.00
Sinus tachycardia	0	0	1 (1%)	0	1 (1%)	1.00
Ear and labyrinth disorders						
Vertigo	0	1 (1%)	0	0	1 (1%)	1.00
Eye disorders						
Cataract	1 (1%)	0	1 (1%)	1 (1%)	3 (3%)	1.00
Gastrointestinal disorders						
Duodenal bulb deformity	0	0	0	1 (1%)	1 (1%)	1.00
Duodenitis	0	0	0	1 (1%)	1 (1%)	1.00
Gastritis	0	0	0	2 (2%)	2 (2%)	0.25
Oesophagitis	0	0	0	1 (1%)	1 (1%)	1.00

TABLE S4. (Continued)

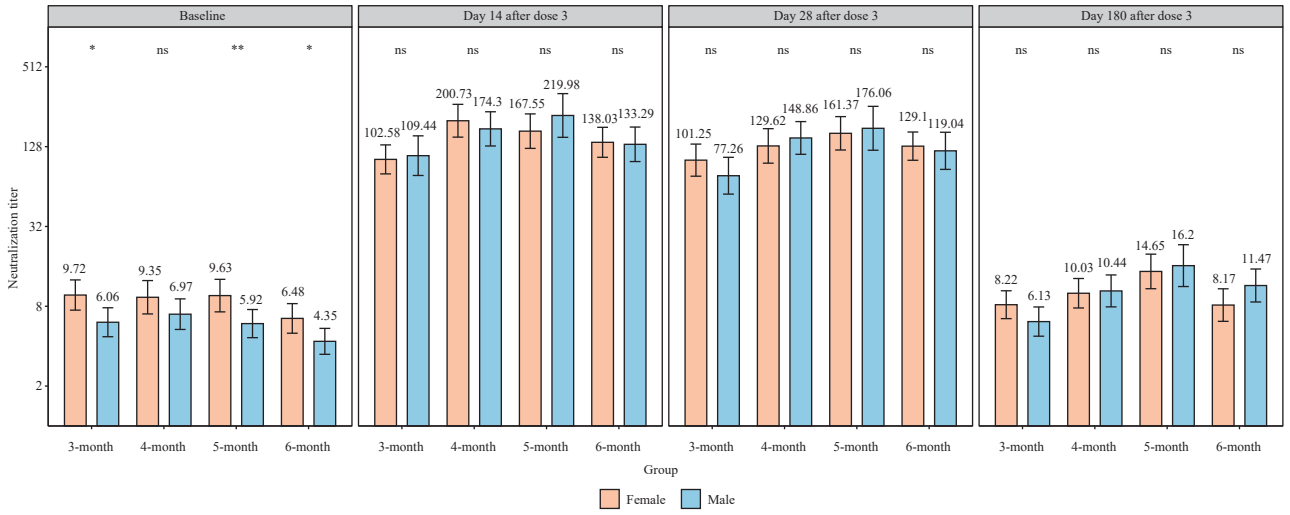
Adverse events (MedDRA 25.0)	3-month group (*n*=101)	4-month group (*n*=99)	5-month group (*n*=100)	6-month group (*n*=100)	Total (*N*=400)	*P* value*
Hepatobiliary disorders						
Cholecystitis	0	0	0	1 (1%)	1 (1%)	1.00
Cholecystitis chronic	0	0	1 (1%)	0	1 (1%)	1.00
Infections and infestations						
Bronchitis	0	0	1 (1%)	0	1 (1%)	1.00
Cervicitis	0	0	1 (1%)	0	1 (1%)	1.00
Herpes zoster	0	1 (1%)	0	0	1 (1%)	1.00
Infective exacerbation of bronchiectasis	1 (1%)	0	0	0	1 (1%)	1.00
Pneumonia	0	0	1 (1%)	1 (1%)	2 (2%)	1.00
Injury, poisoning and procedural complications						
Brain contusion	0	0	1 (1%)	0	1 (1%)	1.00
Fracture	1 (1%)	0	0	0	1 (1%)	1.00
Radius fracture	0	0	1 (1%)	0	1 (1%)	1.00
Skull fractured base	0	0	1 (1%)	0	1 (1%)	1.00
Musculoskeletal and connective tissue disorders						
Arthritis	0	1 (1%)	0	0	1 (1%)	1.00
Arthropathy	1 (1%)	1 (1%)	0	0	2 (1%)	1.00
Intervertebral disc protrusion	0	0	1 (1%)	1 (1%)	2 (2%)	1.00
Spinal osteoarthritis	0	1 (1%)	0	0	1 (1%)	1.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Cervix carcinoma	1 (1%)	0	0	0	1 (1%)	1.00
Gastric cancer	0	0	0	1 (1%)	1 (1%)	1.00
Lung neoplasm malignant	0	0	1 (1%)	0	1 (1%)	1.00
Metastases to lung	0	0	0	1 (1%)	1 (1%)	1.00
Pericardial effusion malignant	0	0	1 (1%)	0	1 (1%)	1.00
Nervous system disorders						
Cerebral infarction	1 (1%)	0	1 (1%)	1 (1%)	3 (3%)	1.00
Epilepsy	0	1 (1%)	0	0	1 (1%)	1.00
Lacunar infarction	0	0	1 (1%)	0	1 (1%)	1.00
Partial seizures with secondary generalization	0	1 (1%)	0	0	1 (1%)	1.00
Subarachnoid hemorrhage	0	0	1 (1%)	0	1 (1%)	1.00
Subdural effusion	0	0	1 (1%)	0	1 (1%)	1.00
Renal and urinary disorders						
Renal cyst	0	0	1 (1%)	0	1 (1%)	1.00
Respiratory, thoracic and mediastinal disorders						
Atelectasis	0	0	1 (1%)	0	1 (1%)	1.00
Bronchitis chronic	0	0	1 (1%)	0	1 (1%)	1.00
Pleural effusion	0	0	1 (1%)	0	1 (1%)	1.00
Pleurisy	0	0	1 (1%)	0	1 (1%)	1.00
Vascular disorders						
Venous thrombosis	0	0	0	1 (1%)	1 (1%)	1.00

Note: Data are *n* (%).

* *P* value was calculated by Fisher exact probability method and of the comparison of incidence rate among four groups.



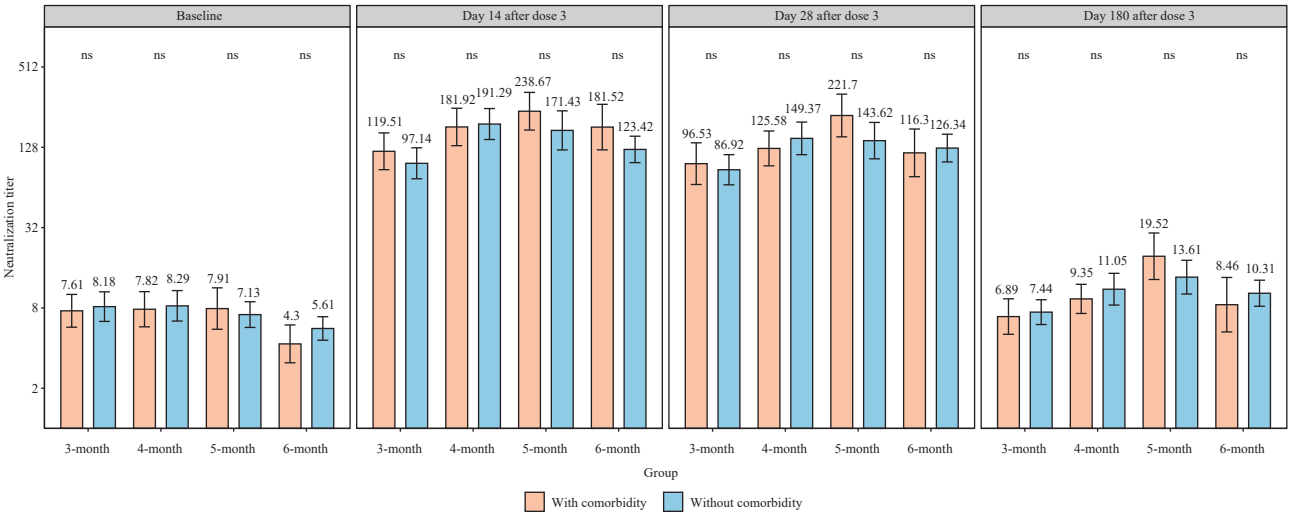
SUPPLEMENTARY FIGURE S1. Inclusion and follow-up in analyses of immunogenicity and safety of CoronaVac in elderly individuals aged 60 years and older.



SUPPLEMENTARY FIGURE S2. Geometric mean titers of neutralizing antibodies against live SARS-CoV-2 before and after booster vaccination stratified by sex groups.

Note: Numbers above the error bars are GMTs, and error bars indicate 95% *CI*s. Symbols at the top are *P* values for comparisons between subgroups using ANOVA with log-transformation. **, *, ns denote $P<0.01$, $P<0.05$, $P\geq0.05$, respectively.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; GMTs=geometric mean titers; *CI*s=confidence intervals; ANOVA=analysis of variance.



SUPPLEMENTARY FIGURE S3. Geometric mean titers of neutralizing antibodies against live SARS-CoV-2 before and after booster vaccination stratified by comorbidity status.

Note: Numbers above the error bars are GMTs, and error bars indicate 95% *CI*s. Symbols at the top are *P* values for comparisons between subgroups using ANOVA with log-transformation. ns denotes $P\geq0.05$.

Abbreviation: SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; GMTs=geometric mean titers; *CI*s=confidence intervals; ANOVA=analysis of variance.

Preplanned Studies

Temporal Trends of Clinical Characteristics and Treatments in People Living with HIV at the Initiation of Antiretroviral Therapy — Beijing Municipality, China, 2010–2020

Jinjuan Zhang[1,2,&]; Mengge Zhou[3,4,&]; Peicheng Wang[4]; Duoduo Wang[1,2]; Yuanqi Mi[5]; Jufen Liu[1,2,#]; Feng Cheng[4,#]

Summary

What is already known about this topic?

Antiretroviral therapy (ART) eligibility criteria and treatment regimens were updated in national guidelines. However, whether treatment was timely and followed guidelines was under-assessed.

What is added by this report?

Among 22,591 people living with human immunodeficiency virus (PLWH) who initiated ART in Beijing between 2010 and 2020, the time from diagnosis to initiating ART decreased, the clinical condition of PLWH improved, and ART regimens changed in accordance with guidelines.

What are the implications for public health practice?

Over the past decade, improvements in clinical status have been observed among PLWH; however, a proportion of PLWH remain who started ART late. Early linkage to human immunodeficiency virus (HIV) care should be further improved.

With the improvement in efficacy and reduction of side effects from antiretroviral therapy (ART), mounting evidence supports the early initiation of ART regardless of CD4 cell counts (*1*–*2*). In 2018, all people living with human immunodeficiency virus (PLWH) were recommended to receive ART in China (*3*–*4*). However, whether treatment is timely and following the updated guidelines has been under-assessed. Based on clinical data from Beijing Center for Disease Prevention and Control, the time from diagnosis to ART initiation, yearly proportion of CD4 cell counts, and ART regimens at initial treatment were analyzed among PLWH between 2010 and 2020. The median days from diagnosis of human immunodeficiency virus (HIV) to initiating ART decreased from 91 days in 2011 to 14 days from 2018 to 2020. The proportion of patients with CD4 ≤200 cells/mm^3 peaked at 67.1% in 2010 and then decreased with time, leveling off at approximately 25%–30% from 2017 onward. The proportion of PLWH taking a single-tablet regimen (EVG/c/FTC/TAF) significantly increased from 2.2% in 2019 to 18.3% in 2020. Although improvements have been observed in the clinical status of treatment-naïve PLWH in China in recent years, nearly one-third of PLWH still started ART late, indicating that health education should be strengthened for high-risk groups and early diagnosis should be promoted for them. For those who have been diagnosed with HIV infection, early linkage to HIV care for PLWH should be further improved.

Data used in the current study were from a surveillance system that collects clinical data of PLWH receiving ART with long-term follow-up care in the STD/AIDS Prevention and Treatment Institute, Beijing CDC in Beijing, China. Clinicians in four hospitals in Beijing designated for HIV treatment (Peking Union Medical College Hospital, Beijing You' an Hospital, Beijing Ditan Hospital, and 302 Military Hospital of China) reported data on the platform. All PLWH who were treatment-naïve and initiated therapy in one of the above hospitals between January 1, 2010 and December 31, 2020 were included in our analysis. A total of 23,714 HIV-infected adults who started ART in Beijing, China were enrolled in the current study. After excluding those without CD4 count measurement at HIV diagnosis (n=965) and those aged 18 years or younger (n=158), 22,591 remaining cases were included in this study.

The time from diagnosis to initiating ART was defined as the number of days between HIV-reactive screening results and the receipt of HIV treatment. Temporal trends of the time from diagnosis to ART were described by year. Further subgroup analysis was performed by stratified age groups (19–29 years, 30–44 years, 45–59 years, and 60 years or older), sex, and infection route [men who have sex with men (MSM), heterosexual sex, injection drug uses (IDU),

and other (blood transfusion, mother-to-child transfusion, and unknown)]. CD4 cell count was stratified into four groups, ≤200 cells/mm^3, 200–349 cells/mm^3, 350–499 cells/mm^3, and ≥500 cells/mm^3 according to the ART-eligible policy in the guidelines for China. CD4 threshold adjusted with guideline updating, "late ART initiation" was defined as the CD4 cell count <200 cells/mm^3, at WHO stage 3 or 4, or having a clinical AIDS diagnosis prior to ART initiation. The prescription for an ART regimen at the first visit was directly obtained from the database.

Continuous variables with a normal distribution were presented as mean (standard deviation) and differences between groups were compared using one-way analysis of variance (ANOVA). Continuous variables with a skewed distribution were presented as median [interquartile range (IQR)] and compared using the Kruskal–Wallis test. Categorical variables were presented as numbers (percentages) and compared using the chi-square test or Cochran-Armitage trend test. Two-tailed *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed with Stata version 16 (StataCorp LLC, College Station, Texas, USA).

Of the 22,591 PLWH within the current study, the median age was 31 years (IQR: 26–39 years), 95.5% were men, 68.2% were single, and 82.0% were MSM. The median CD4 count was 291.2 cells/mm^3 (IQR: 177.0–410.4). The median number of days from diagnosis to initial ART was 28 days (IQR: 13.0–103.0) (Supplementary Table S1, available in https://weekly.chinacdc.cn/).

The median days from diagnosis to initiating ART dramatically decreased from 91 (IQR: 33–471) days in 2011 to approximately 14 days from 2018 to 2020 (*P* for trend <0.001, Figure 1A). Trend analysis of this time interval by sex and age group showed a significant decline over time (Figure 1B and 1C, *P* for trend <0.001), especially in women (decreased by 94.1%, from 261.5 to 15.5 days) and PLWH aged 19 to 29 years (decreased by 89.6%, from 134 to 14 days). However, the median days from diagnosis to ART among PLWH who were IDU remained longer than that of other transmission routes, although without statistical significance, fluctuating between 127 and 992 days from 2010 to 2020, with a high of 780 days in 2020 (Figure 1D, *P*=0.333; *P* for trend 0.959). The proportion of PLWH with CD4 ≥500 cells/mm^3 was only 0.8% in 2010 but increased to 17% and stabilized from 2016 to 2020 (*P* for trend <0.001). On the contrary, the proportion of PLWH with CD4 ≤200 cells/mm^3 decreased from 67.1% in 2010 to ranging from 25% to 30% between 2016 and 2020 (Figure 2). The proportion of late ART initiation for PLWH declined from 52.5% in 2010 to 30.1% in 2020.

The most frequently used regimens of initial ART included EFV+3TC+TDF (76.0%), EFV+3TC+AZT (11.1%), LPV/r+3TC+TDF (3.0%), NVP+3TC+AZT (2.1%), and EVG/c/FTC/TAF (1.5%), accounting for 93.4% of all regimens from 2010 to 2020. Five of the most frequently used regimens for each year are shown in Figure 3. EFV+3TC+TDF was the predominantly used regimen, although its proportion declined from 2015. The proportion of EFV+3TC+AZT dropped from 43.6% in 2010 to only 1% in 2018. The use of NVP+3TC+AZT declined from 22.2% in 2010 to 0.3% in 2015. The use of EFV+3TC+d4T and NVP+3TC+d4T both decreased since 2010 (15.3% in 2010 to 1.0% in 2013; 14.7% in 2010 to 2.4% in 2012, respectively). However, the proportion of EVG/c/FTC/TAF significantly increased from 2.2% in 2019 to 18.3% in 2020.

DISCUSSION

Based on an 11-year surveillance study among PLWH in Beijing, China, we observed that the time from diagnosis to initiating ART has been substantially shortened, the condition of PLWH at the start of ART has been improved, and regularly prescribed ART regimens have constantly changed with the updated guidelines over the past decade.

Due to the concerted international effort to combat HIV, there has been a worldwide reduction in the time between HIV diagnosis and initiation of ART. In our study, we observed a significant decrease in the median days from HIV diagnosis to ART initiation for all PLWH, dropping from nearly 90 days in 2010 to 14 days in 2018, representing a reduction of 85%.Similarly, the time interval decreased from 660 days in 2013 to 15 days in 2019 in the African Cohort Study (AFRICOS) (*5*); from 418 days in 2011 to 77 days in 2015 in Australia (*6*), and from 69 days in 2005 to 6 days in 2018 according to the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) in the United States (*7*). Similar results were observed in Yunnan Province where the time from HIV diagnosis to ART initiation dropped from 1,776 days in 2004 to 27 days in 2016 (*8*). These results indicate an encouraging improvement in early ART initiation in China and

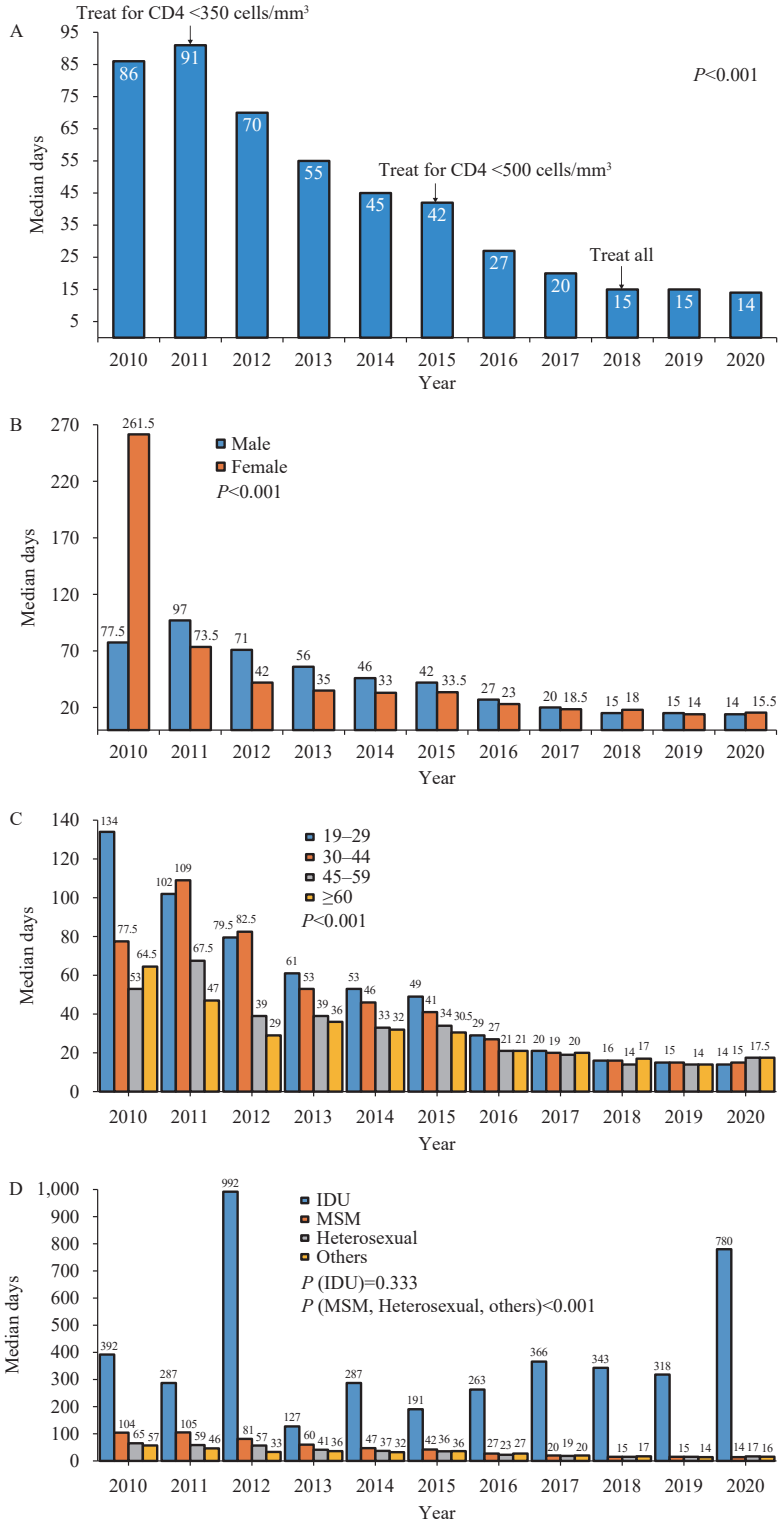


FIGURE 1. Median days from HIV diagnosis to initiating ART among PLWH in total sample and subgroups in Beijing, 2010–2020. (A) Median days from HIV diagnosis to initiating ART among PLWH in Beijing 2010–2020. (B) Median days from HIV diagnosis to initiating ART among PLWH in Beijing by sex, 2010–2020. (C) Median days from HIV diagnosis to initiating ART among PLWH in Beijing by age, 2010–2020. (D) Median days from HIV diagnosis to initiating ART among PLWH in Beijing by route of infection, 2010–2020.

Abbreviation: ART=antiretroviral therapy; HIV=human immunodeficiency virus; PLWH=people living with HIV; MSM=men who have sex with men; IDU=injection drug users.

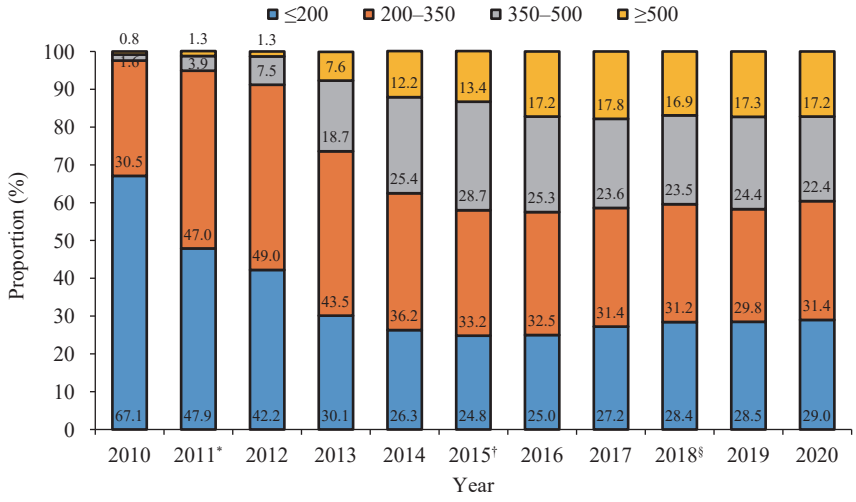


FIGURE 2. Proportion of CD4+ cell counts (stratified) among PLWH at initial treatment in Beijing, 2010–2020.
Abbreviation: PLWH=people living with human immunodeficiency virus.
* ART was recommended for PLWH whose CD4 <350 cells/mm^3 in the national guideline in 2011.
† ART was recommended for PLWH whose CD4 <500 cells/mm^3 in the national guideline in 2015.
§ ART was recommended for all PLWH regardless of CD4 cell counts in the national guideline in 2018.

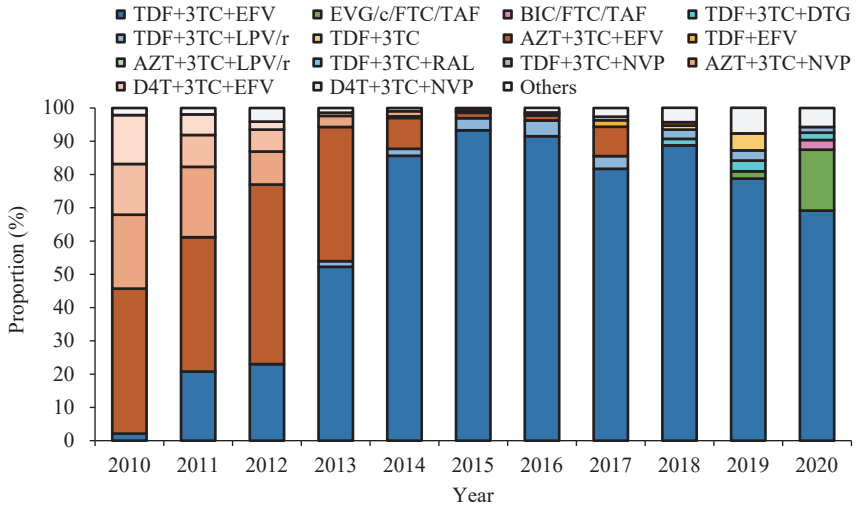


FIGURE 3. Trend of top five most commonly prescribed initial ART regimens for each year among PLWH in Beijing, 2010–2020.
Abbreviation: ART=antiretroviral therapy; PLWH=people living with human immunodeficiency virus.

worldwide with evolving clinical guidelines and supportive strategies.

However, the median number of days from diagnosis to ART still remained long in persons with intravenous drug use (PWID) in 2020, exceeding two years in Beijing, which was much longer than the 60 days reported in Yunnan in 2016 (*9*). Although PWID only accounted for a small proportion in this study, a large number of PWID may fear going to the hospital for ART due to criminalization and stigmatization of IDU. Therefore, it is necessary to take certain measures to identify this group of patients and provide them with targeted assistance, such as joint administration of ART and opioid substitution therapy.

In addition to shortening the median days from HIV diagnosis to ART initiation, we also found continuous improvement in the clinical status of HIV-infected individuals at initial treatment over the past 10 years. An increase in the proportion of PLWH with CD4 cell count >500 cells/mm^3 at ART initiation was observed from 2010 to 2020, from less than 1% in 2010 to more than 17% in 2020, which was higher than the 8.5% in 2014 and 14% in 2016–2019 reported in China's National Free Antiretroviral

Therapy Program. This may be owing to the treatment guideline being updated to adopt the strategy of "treat all" in China. China has made great progress in HIV control in recent decades, with the scaling up of HIV testing and treatment. However, it is remarkable that, in the era of "treat all", about one-third of PLWH still initiated ART late in 2020, which was much higher than the 21% in Canada in 2012 (*9*), indicating that health education should be strengthened for high-risk groups and early diagnosis should be promoted for them. For those who have been diagnosed with HIV infection, follow-up should be strengthened and early treatment should be urged.

EFV+3TC+TDF was the most commonly prescribed regimen during our study period, although its proportion declined from 2015, likely due to its status as the first-line recommended regimen in the national treatment guidelines since 2011. NVP+3TC+AZT declined and only accounted for 0.3% in 2015; this was the first-line recommended regimen in 2005 in China, but it became an alternative regimen in 2011 due to its hepatotoxicity (*10*).

Reducing the pill burden with the use of a single-tablet regimen (first recommended as the first-line regimen in the Chinese guideline in 2018) has been shown to improve adherence to ART. Consequently, the proportion of PLWH using single-tablet regimens significantly increased and accounted for nearly one-fifth in 2020, reflecting the influence of national guideline recommendations on clinical practice. To a certain extent, ART has become more effective and easier to take.

Our study has some limitations. First, the data were obtained during clinical care and were not primarily for research purposes; thus, some important variables, such as CD4 cell counts at HIV diagnosis, were not collected. Second, we included PLWH who were initiating ART, which may have missed undiagnosed and untreated PLWH; thus, the burden of HIV may have been underreported. Third, the HIV epidemic in China is diverse and complex. The data in this study were all collected from hospitals in Beijing; therefore, generalization of the research results is limited. In addition, as we did not have data on HIV collected in 2021 and 2022, we could not symmetrically evaluate the impact of the COVID-19 pandemic on HIV care in Beijing. Future studies will be conducted with more sufficient data.

In conclusion, notable improvements in clinical condition were observed in initial ART among HIV-infected adults in Beijing between 2010 and 2020, which may be attributed to the continuous evolution of national strategies. However, there was a substantial number of PLWH starting ART late, indicating that health education should be strengthened for high-risk groups and early diagnosis should be promoted for them. For those who have been diagnosed with HIV infection, early linkage to HIV care for PLWH should be further improved. In addition, although the time from diagnosis to treatment was shortened, it remained long in PWID. For public health practitioners, health education and intervention regarding HIV diagnosis and treatment should be further strengthened according to different characteristics in certain regions. Current ART treatment patterns highlight the high uptake of guideline-recommended ART regimens among treatment-naïve individuals initiating ART. It is foreseeable that the single-tablet regimen will be more widely used in PLWH.

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SUPPLEMENTARY TABLE S1. Baseline characteristics of study population, Beijing, 2010–2020.

Variable (*n*=22,591)	*N* (%)
Age, median (IQR), years	31 (26.0–39.0)
Men	21,563 (95.5)
Marital status	
Married or living with partner	5,591 (24.8)
Single	15,403 (68.2)
Widowed, divorced, or separated	1,340 (6.0)
Unknown	257 (1.1)
Routes of HIV transmission	
MSM	18,531 (82.0)
Heterosexual	2,245 (9.9)
IDU	160 (0.7)
Others*	1,655 (7.4)
Coinfections	
HBsAg positive†	966 (5.2)
Anti-HCV positive§	362 (2.0)
OIs	658 (2.9)
CD4 cell counts, median (IQR), cells/mm^3	291.2 (177.0–410.4)
CD8 cell counts, median (IQR), cells/mm^3	951 (656–1,329)
CD4/CD8 ratio	0.3 (0.2, 0.4)
Time from diagnosis to initial ART, median (IQR), days	28.0 (13.0–103.0)
WHO clinical stages at diagnosis	
Stage Ⅰ	17,471 (77.3)
Stage Ⅱ	2,517 (11.1)
Stage Ⅲ	1,229 (5.4)
Stage Ⅳ	1,374 (6.1)
Proportion of CD4 cell counts, cells/mm^3	
≤200	6,608 (29.3)
200–349	7,808 (34.6)
350–499	5,065 (22.4)
≥500	3,110 (13.8)
VL, median (IQR), $\log_{10}$ copies/mL	4.5 (3.9–5.0)
Year of ART initiation	
2010	374 (1.7)
2011	775 (3.4)
2012	1,199 (5.3)
2013	1,772 (7.8)
2014	2,475 (11.0)
2015	3,054 (13.5)
2016	3,231 (14.3)
2017	3,131 (13.9)
2018	2,804 (12.4)
2019	2,214 (9.8)
2020	1,562 (6.9)

Abbreviation: MSM=men who have sex with men; IDU=intravenous drug use; OIs=opportunistic infections; ART=antiretroviral therapy; IQR=interquartile range; VL=viral load.

* Including blood transfusion, mother-to-child transfusion and unknown.

† HBsAg, hepatitis B surface antigen, data of HBsAg were not available for 3,880 patients.

§ HCV, hepatitis C virus, data of anti-HCV were not available for 4,214 patients.

Preplanned Studies

Attitudes Regarding Influenza Vaccination Among Public Health Workers during COVID-19 Pandemic — China, September 2022

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Summary

What is already known about this topic?

Public health workers (PHWs) were listed as a priority group recommended for influenza vaccination during the coronavirus disease 2019 (COVID-19) pandemic. Understanding the drivers of influenza vaccine hesitancy among PHWs can promote influenza vaccination in the COVID-19 pandemic.

What is added by this report?

The study found that 10.7% of PHWs were hesitant to get an influenza vaccination. Drivers associated with vaccine hesitancy were assessed based on "3Cs model." The absence of a government or workplace requirement and concerns about vaccine safety were the biggest obstacles for PHWs to recommend influenza vaccination.

What are the implications for public health practice?

Interventions are needed to improve PHWs' influenza vaccine coverage to prevent the co-circulation of influenza and COVID-19.

Globally, influenza causes 3–5 million hospitalizations and 290,000–650,000 respiratory deaths each year (*1*). From February through August 2022, influenza activity was at its highest level compared to similar periods since the start of the coronavirus disease 2019 (COVID-19) pandemic globally (*2*). As the priority group recommended for influenza vaccination during the COVID-19 pandemic, healthcare workers (HCWs), including public health workers (PHWs), have a greater chance of contracting influenza viruses; this poses a greater risk of transmission (*3*). PHWs refer to those who are engaged in public health services and vaccination work in the Center for Disease Control and Prevention (CDC) system, community health service centers, or township health centers. Previous surveys have shown that willingness and influence factors of front-line staff involved in the work of influenza control are of higher concern (*4*–*5*). The research mainly focused on assessing PHWs' attitudes toward influenza vaccination in 2022–2023. Univariate analysis and multivariable logistic regression analysis were used to evaluate factors associated with vaccine hesitancy. A total of 3,127 PHWs were surveyed. 10.7% were hesitant about influenza vaccination in the coming season. Multivariate logistic regression analysis found that PHWs who did not receive an influenza vaccine between September 2021 and April 2022 [odds ratio (*OR*)=5.08, 95% confidence interval (*CI*): 3.54–7.29] and PHWs who believed vaccination had no importance for health (*OR*=21.32, 95% *CI*: 10.15–44.80) were more likely to hesitate to get vaccinated. The results suggest that effective measures should be taken to strengthen the willingness of PHWs to vaccinate against influenza. This reduces the burden of the COVID-19 responding and medical facilities.

From September 16 to 26, 2022, a link to the questionnaire for the survey was posted on *Listening to the Experts*, a learning and communication platform that authenticates real identity information of registered users and was used by professionals in the field of vaccination in China (*6*). PHWs could voluntarily participate in the survey and forward it to their colleagues, but each participant could only answer once. As of September 30, 2022, the *Listening to the Experts* platform has over 650,000 PHW users, covering 31 provincial-level administrative divisions (PLADs) in China. Data on respondents' sociodemographic characteristics, workplace interventions, knowledge of influenza vaccination, influenza vaccination history and attitudes towards recommending influenza vaccination were collected. The per capita gross domestic product (GDP) of each PLAD was obtained from the National Bureau of Statistics of China (*7*). Vaccine hesitancy refers to delay in acceptance or refusal of vaccination despite availability of vaccination services. According to the "3Cs model" of vaccine hesitancy (*8*), the impact of confidence, complacency, and convenience on

hesitancy to receive influenza vaccination was analyzed and concerns of PHWs in recommending influenza vaccination were presented. The study protocol and questionnaire were approved by the Chinese Academy of Medical Sciences and Peking Union Medical College (No. CAMS&PUMC-IEC-2022-019, on March 14, 2022).

Univariate analysis included frequency and ratio calculations and Pearson's chi-squared test for differences. Multivariate logistic regression was used to evaluate factors associated with intention to accept vaccination. ORs and 95% *CI*s were calculated. Alpha level was set at 0.05. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 26.0, SPSS Inc, Chicago, IL, USA.).

A total of 3,145 PHWs from 28 PLADs participated in the survey, with 18 incomplete questionnaires excluded. Among the 3,127 respondents in China, 823 (26.3%) work at CDC systems, and 2,304 (73.7%) were from community or township health service centers. Nearly half had an intermediate professional title or above and 10.7% (336) had influenza vaccine hesitancy. In the 2021–2022 influenza season, 52.5% respondents (1,643/3,127) were vaccinated against influenza, including 64.9% (1,067/1,643) vaccinated at a community or township health service center, 21.4% (352/1,643) vaccinated at a hospital, 12% (197/1,643) vaccinated at a CDC vaccination clinic, and 1.6% (27/1,643) vaccinated elsewhere.

Of the 336 respondents with vaccine hesitancy, 22.3% (75/336) worked at CDC systems and 77.7% (261/336) worked at community or township health service centers. The analysis results based on the "3Cs model" illustrated that 43.45% of the respondents believed complacency, 24.88% believed confidence, and 20.79% believed convenience had an impact on vaccine hesitancy. In terms of complacency, 43.3% (146/336) believed that influenza infection would not cause serious illness and it did not matter if they were not vaccinated (Table 1).

Of the 94.2% (2,945/3,127) of respondents who were willing to recommend influenza vaccines to others, no requirements at the government or workplace level for recommendation, fear of misinterpreting recommendation as having commercial interests, and potential adverse reactions were their primary concerns. Of the remaining respondents who were unwilling to recommend influenza vaccines, no requirements at the government or workplace level for recommendation and potential adverse reactions of influenza vaccines were their primary concerns (Table 2).

According to the results of univariate analysis,

TABLE 1. Reasons for influenza vaccine hesitancy among PHWs (Based on 3Cs model) in China, September 2022.

Variable	Very unacceptable (%)	Unacceptable (%)	Acceptable (%)	Highly acceptable (%)
Convenience				
High prices	37.8	21.1	27.4	13.7
Don't know when to vaccinate	66.1	12.8	14.0	7.1
No appropriate to take influenza vaccination	56.8	24.4	12.2	6.5
Vaccination place is inconvenient	69.3	12.8	9.5	8.3
Spend long time waiting for taking influenza vaccination	62.5	20.5	11.3	5.7
Don't know where to vaccinate	73.2	11.6	8.9	6.3
Influenza vaccination services are hard to make appointment	67.9	17.6	9.8	4.8
Confidence				
Being worried about adverse reactions	50.3	21.4	21.7	6.5
No influenza vaccination notification at workplace	56.0	16.4	14.3	13.4
Influenza vaccine is not effective	49.4	25.0	20.2	5.4
Having contraindications	56.0	19.6	16.1	8.3
Pregnant or lactating	67.0	14.6	10.1	8.3
Complacency				
Influenza will not cause severe illness	31.3	25.3	32.1	11.3

Abbreviation: PHWs=public health workers.

TABLE 2. Reasons for influenza vaccine recommendation among PHWs in China, September 2022.

Variable	Total (*n*, %)	Willing to recommend (*n*, %)
Worried about the misunderstanding of commercial interests by recipients	1,440 (46.1)	1,387 (47.1)
Worried about the adverse reactions of recipients	1,313 (42.0)	1,252 (42.5)
No recommendation on requirement by national authorities or at workplace	1,312 (42.0)	1,233 (41.9)
Pregnancy or have contraindications	1,123 (35.9)	1,068 (36.3)
Influenza won't cause severe illness and vaccination is unnecessary	1,065 (34.1)	1,004 (34.1)
Worried about the medical tangle caused by recommendation	927 (29.6)	886 (30.1)
Influenza vaccine is not effective	861 (27.5)	819 (27.8)
Due to self-unvaccinated and lack of influenza vaccine confidence	596 (19.1)	551 (18.7)
Influenza vaccination is inconvenient	354 (11.3)	336 (11.4)

Abbreviation: PHWs=public health workers.

vaccine hesitancy was high among PHWs who did not receive an influenza vaccine in the 2021–2022 season (19.7%), who reported the payment method was inconvenient (15.7%), who were not concerned about the risk of influenza in the 2022–2023 season (14.7%), and who believed influenza vaccination was not important to health (65.6%) (Table 3).

Multivariable logistic regression analysis was used to assess factors associated with influenza vaccine hesitancy among PHWs. Those who had no influenza infection history (*OR*=1.98, 95% *CI*: 1.21–3.24), who did not receive an influenza vaccine between September 2021 and April 2022 (*OR*=5.08, 95% *CI*: 3.54–7.29), who could not receive on-site vaccination at workplace (*OR*=1.50, 95% *CI*: 1.03–2.20), who were not concerned about the risk of influenza this year (*OR*=5.26, 95% *CI*: 1.09–25.41), who believed the health influence of influenza vaccine is not important at all (*OR*=21.32, 95% *CI*: 10.15–44.80), a little important (*OR*=4.21, 95% *CI*: 2.81–6.30) and moderately important (*OR*=2.50, 95% *CI*: 1.71–3.64) were more likely to have hesitation toward influenza vaccination (Table 3).

DISCUSSION

The study found that 10.7% of PHWs were hesitant to get vaccinated against influenza during the COVID-19 pandemic. 52.5% of PHWs were vaccinated in the 2021–2022 season, which was higher than the 35.4% among respiratory care practitioners in the same season and 11.6% among HCWs in the 2018–2019 season (*4*–*5*). Although the influenza vaccination coverage in this survey is fairly optimistic, the small proportion of influenza vaccination hesitancy among PHWs still needs attention. The most cost-effective way to prevent influenza and its complications is annual vaccination, especially during the COVID-19 pandemic. As a high-risk population, PHWs vaccination against influenza not only reduces the harm from associated diseases and the use of medical resources, but also promotes health information communication and public confidence in influenza vaccination. The study elucidated primary concerns or no mandatory government or workplace recommendations for vaccination and vaccine safety among PHWs. In the interest of self-protection, potential adverse reactions to vaccines affect PHW willingness to recommend vaccines (*9*).

The study also suggested that complacency remains the biggest driver to influenza vaccine hesitancy and has the greatest impact on the willingness of PHWs to get vaccinated. Among the 336 hesitant PHWs, those without influenza infection and vaccination history were more prone to vaccine hesitancy, and those who did not worry about getting influenza in the current season or did not believe getting an influenza vaccination was important were at higher risk. Since the COVID-19 outbreak, public health interventions such as mask-wearing and social distancing have reduced influenza activity significantly. However, the measures also led to a decline in existing immunity and increased susceptibility to influenza. An increasing trend of influenza activity was observed in the northern hemisphere, highlighting the need for close monitorization and preparation for the co-circulation of influenza viruses and severe acute respiratory syndrome coronavirus 2 (*10*). PHWs need to be fully aware of the severity of influenza and the necessity for influenza vaccination as well as extensively understand the burden of influenza disease and prevention and control strategies during the COVID-19 pandemic. This helps reduce hesitancy toward influenza vaccines.

TABLE 3. Univariate analysis and multivariable logistic regression analysis of influenza vaccine hesitancy among public health workers in China, September 2022 (ref: willing to vaccination).

Variable	Total (*n*, %)	Vaccination willingness (*n*, %)	Vaccine hesitancy (*n*, %)	Univariate analysis		Logistic regression analysis	
				χ^2	*P* for chi-square test	*OR* (95% *CI*)	*P*-value
PLAD by GDP per capita*							
Low GDP area	680 (21.7)	588 (86.5)	92 (13.5)	8.81	0.012	Ref	
Middle GDP area	1,413 (45.2)	1,262 (89.3)	151 (10.7)			0.85 (0.61–1.19)	0.346
High GDP area	1,034 (33.1)	941 (91.0)	93 (9.0)			0.61 (0.43–0.88)	0.008
Type of workplace							
Community health service centers/Township health centers	2,304 (73.7)	2,043 (88.7)	261 (11.3)	3.10	0.078	Ref	
Center for Disease Control and Prevention	823 (26.3)	748 (90.9)	75 (9.1)			0.86 (0.60–1.22)	0.392
Professional title							
None	347 (11.1)	296 (85.3)	51 (14.7)	8.88	0.031	Ref	
Junior	1,206 (38.6)	1,070 (88.7)	136 (11.3)			1.21 (0.78–1.86)	0.397
Middle	1,212 (38.8)	1,095 (90.3)	117 (9.7)			1.19 (0.76–1.87)	0.446
Senior	362 (11.6)	330 (91.2)	32 (8.8)			1.25 (0.70–2.23)	0.458
Chronic diseases history (Except for simple hypertension)							
Yes	153 (4.9)	133 (86.9)	20 (13.1)	3.37	0.185	Ref	
No	2,922 (93.4)	2,615 (89.5)	307 (10.5)			0.51 (0.28–0.94)	0.030
Unclear	52 (1.7)	43 (82.7)	9 (17.3)			0.72 (0.26–2.03)	0.538
Influenza infection history since September 2021							
Yes	424 (13.6)	400 (94.3)	24 (5.7)	13.26	0.001	Ref	
No	2,176 (69.6)	1,926 (88.5)	250 (11.5)			1.98 (1.21–3.24)	0.006
Unclear	527 (16.9)	465 (88.2)	62 (11.8)			1.98 (1.14–3.42)	0.015
Received influenza vaccine between September 2021 and April 2022							
Yes	1,643 (52.5)	1,600 (97.4)	43 (2.6)	238.48	<0.001	Ref	<0.001
No	1,484 (47.5)	1,191 (80.3)	293 (19.7)			5.08 (3.54–7.29)	
On-site vaccination at workplace							
Yes	2,650 (84.7)	2,400 (90.6)	250 (9.4)	31.60	<0.001	Ref	
No	403 (12.9)	332 (82.4)	71 (17.6)			1.50 (1.03–2.20)	0.037
Unclear	74 (2.4)	59 (79.7)	15 (20.3)			1.47 (0.71–3.07)	0.303
Ways of influenza vaccine payment							
Self-paid	2,333 (74.6)	2,047 (87.7)	286 (12.3)	43.49	<0.001	Ref	
Free	329 (10.5)	313 (95.1)	16 (4.9)			0.60 (0.31–1.17)	0.132
Employer paid	225 (7.2)	214 (95.1)	11 (4.9)			0.89 (0.43–1.87)	0.763
Medical insurance	208 (6.7)	188 (90.4)	20 (9.6)			0.63 (0.36–1.11)	0.111
Unclear	32 (1.0)	29 (90.6)	3 (9.4)			0.39 (0.10–1.58)	0.185
Convenience of payment method							
Very convenient	973 (31.1)	910 (93.5)	63 (6.5)	43.49	<0.001	Ref	
Moderately convenient	1,295 (41.4)	1,157 (89.3)	138 (10.7)			0.95 (0.66–1.39)	0.807
A little convenient	558 (17.8)	463 (83.0)	95 (17.0)			1.32 (0.86–2.01)	0.202
Not at all convenient	301 (9.6)	261 (86.7)	40 (13.3)			1.10 (0.65–1.86)	0.717

TABLE 3. (Continued)

Variable	Total (*n*, %)	Vaccination willingness (*n*, %)	Vaccine hesitancy (*n*, %)	Univariate analysis		Logistic regression analysis	
				χ^2	*P* for chi-square test	*OR* (95% *CI*)	*P*-value
Perceived risk of influenza this season							
Very concerned	132 (4.2)	130 (98.5)	2 (1.5)	41.06	<0.001	Ref	
Moderately concerned	243 (7.8)	230 (94.7)	13 (5.3)			2.53 (0.48–13.47)	0.276
A little concerned	1,590 (50.8)	1,440 (90.6)	150 (9.4)			3.11 (0.64–15.04)	0.158
Not at all concerned	1,162 (37.2)	991 (85.3)	171 (14.7)			5.26 (1.09–25.41)	0.039
Health influence of the influenza vaccine							
Very important	1,531 (49.0)	1,482 (96.8)	49 (3.2)	396.93	<0.001	Ref	
Moderately important	1,055 (33.7)	932 (88.3)	123 (11.7)			2.50 (1.71–3.64)	<0.001
A little important	480 (15.4)	356 (74.2)	124 (25.8)			4.21 (2.81–6.30)	<0.001
Not at all important	61 (2.0)	21 (34.4)	40 (65.6)			21.32 (10.15–44.80)	<0.001
Whether the trivalent or quadrivalent influenza vaccine affects willingness							
No	1,137 (36.4)	975 (85.8)	162 (14.2)	22.86	<0.001	Ref	
Yes	1,990 (63.6)	1,816 (91.3)	174 (8.7)			0.97 (0.72–1.31)	0.836
Whether the inactivated or live-attenuated vaccine influences willingness							
No	1,325 (42.4)	1,139 (86.0)	186 (14.0)	25.99	<0.001	Ref	
Yes	1,802 (57.6)	1,652 (91.7)	150 (8.3)			0.66 (0.49–0.89)	0.006
Workplace vaccination policy (free for all staff)							
Yes	810 (25.9)	766 (94.6)	44 (5.4)	34.16	<0.001	Ref	
No	2,038 (65.2)	1,788 (87.7)	250 (12.3)			0.88 (0.55–1.41)	0.602
Unclear	279 (8.9)	237 (84.9)	42 (15.1)			0.70 (0.39–1.28)	0.248
Expectation from colleagues toward influenza vaccination this season							
No	65 (2.1)	44 (67.7)	21 (32.3)	213.15	<0.001	Ref	
Yes	1,715 (54.8)	1,653 (96.4)	62 (3.6)			0.18 (0.09–0.37)	<0.001
Unclear	1,347 (43.1)	1,094 (81.2)	253 (18.8)			0.58 (0.28–1.19)	0.135
Attitudes toward influenza vaccine this season at your workplace							
Required	343 (11.0)	328 (95.6)	15 (4.4)	94.5	<0.001	Ref	
Encouraged	1,038 (33.2)	978 (94.2)	60 (5.8)			1.15 (0.59–2.25)	0.678
Neutrality	1,442 (46.1)	1,249 (86.6)	193 (13.4)			1.42 (0.73–2.74)	0.301
Unclear	304 (9.7)	236 (77.6)	68 (22.4)			1.57 (0.76–3.23)	0.219
How extensive do you consider your knowledge of the influenza vaccine							
Very confident	1,361 (43.5)	1,280 (94.0)	81 (6.0)	88.5	<0.001	Ref	
Moderately confident	1,181 (37.8)	1,044 (88.4)	137 (11.6)			1.22 (0.87–1.72)	0.252
A little confident	447 (14.3)	354 (79.2)	93 (20.8)			1.45 (0.98–2.16)	0.065
Not at all confident	138 (4.4)	113 (81.9)	25 (18.1)			1.66 (0.91–3.03)	0.101

Abbreviations: *OR*=adds ratio; *CI*=confidence interval.
* In terms of GDP per capita, provincial-level administrative divisions (PLADs) are divided into three levels: low, middle and high.
Low for Anhui, Qinghai, Jiangxi, Shanxi, Heilongjiang, Guangxi, Guizhou,Yunnan, Gansu;
Middle for Chongqing, Shaanxi, Liaoning, Jilin, Hunan, Hainan, Henan, Sichuan, Hebei;
High for Beijing, Shanghai, Tianjin, Jiangsu, Zhejiang, Fujian, Guangdong, Shandong, Inner Mongolia, Hubei.

Similar to other studies (*4*), the convenience of vaccination services is also an important factor for PHWs considering vaccination. Over the past year, many vaccination facilities have been used for

COVID-19 vaccination, affecting the accessibility of influenza vaccines. The influenza vaccination payment did not affect the will of PHWs from this study. Generally, the first concern of PHWs with the medical background was the safety and effectiveness of vaccines. Influenza vaccine payment did not directly impact their vaccination decisions and intentions.

This study has some limitations. First, in the interest of quick, simple and feasible survey results, the online questionnaire was a quantitative survey without individual interviews. The results of the study were influenced by the cooperative attitude of the participants. Second, individual indicators vary considerably, and further expansion of the sample size is recommended. Third, specific differences could not be analyzed as the matrix questionnaire was used for PHWs' intention to recommend influenza vaccine.

In conclusion, in the context of the potential co-circulation of influenza and COVID-19 in Winter 2022–2023, targeted interventions are needed among HCWs to improve influenza vaccination attitudes and behaviors, reduce the social hazards of influenza and protect the health of the population at large.

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