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Research paper

Antibody seroprevalence in the epicenter Wuhan, Hubei, and six selected provinces after containment of the first epidemic wave of COVID-19 in China

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ABSTRACT

Background: China implemented containment measures to stop SARS-CoV-2 transmission in response to the COVID-19 epidemic. After the first epidemic wave, we conducted population-based serological surveys to determine extent of infection, risk factors for infection, and neutralization antibody levels to assess the real infections in the random sampled population.

Methods: We used a multistage, stratified cluster random sampling strategy to conduct serological surveys in three areas - Wuhan, Hubei Province outside Wuhan, and six provinces selected on COVID-19 incidence and containment strategy. Participants were consenting individuals >1 year old who resided in the survey area >14 days during the epidemic. Provinces screened sera for SARS-CoV-2-specific IgM, IgG, and total antibody by two lateral flow immunoassays and one magnetic chemiluminescence enzyme immunoassay; positive samples were verified by micro-neutralization assay.

Findings: We enrolled 34,857 participants (overall response rate, 92%); 427 were positive by micro-neutralization assay. Wuhan had the highest weighted seroprevalence (4•43%, 95% confidence interval [95%CI]=3•48%-5•62%), followed by Hubei-ex-Wuhan (0•44%, 95%CI=0•26%-0•76%), and the other

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provinces (<0•1%). Living in Wuhan (adjusted odds ratio aOR=13•70, 95%CI= 7•91–23•75), contact with COVID-19 patients (aOR=7•35, 95%CI=5•05–10•69), and age over 40 (aOR=1•36, 95%CI=1•07–1•72) were significantly associated with SARS-CoV-2 infection. Among seropositives, 101 (24%) reported symptoms and had higher geometric mean neutralizing antibody titers than among the 326 (76%) without symptoms (30±2•4 vs 15±2•1, p<0•001).

Interpretation: The low overall extent of infection and steep gradient of seropositivity from Wuhan to the outer provinces provide evidence supporting the success of containment of the first wave of COVID-19 in China. SARS-CoV-2 infection was largely asymptomatic, emphasizing the importance of active case finding and physical distancing. Virtually the entire population of China remains susceptible to SARS-CoV-2; vaccination will be needed for long-term protection.

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Research in context

Evidence before this study

Accurately measuring the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in populations can help increase knowledge about immunity, transmission, response strategies, surveillance, and eventually vaccination of COVID-19. We searched PubMed for peer-reviewed articles on September 28, 2020, with no limitations of start date or language, using the terms, "COVID-19″, "SARS-CoV-2″, "antibody", "seroprevalence", and "seroepidemiology". Most serosurveys used convenience samples in hospital settings or were conducted among selected populations such as health care workers, blood donors, factory workers, or local community residents, limiting their ability to provide unbiased population seroprevalence estimates. Few studies were conducted immediately following containment of a COVID-19 epidemic, limiting comparability of containment by country or region.

Added value of this study

Between two and three weeks after the end of the first-wave of COVID-19 in China, we conducted population-based serological surveys to estimate prevalence of SARS-CoV-2-specific neutralizing antibodies (NAbs) among representative samples totaling 34,857 participants. We surveyed three areas – Wuhan City, Hubei-ex-Wuhan, and six provinces selected on the basis of containment strategy and COVID-19 incidence to ensure inclusion of the highest incidence provinces. Resulting seroprevalence estimates were: Wuhan, 4•43%; Hubei-ex-Wuhan, 0•44%; and the six other provinces, <0•1%. Seroprevalence was highly correlated with reported COVID-19 incidence. Most subjects with serologic evidence of infections were asymptomatic (76%). To our knowledge, this is the first nationally representative estimate of SARS-CoV-2 seroprevalence in China.

Implications of all the available evidence

The low overall seroprevalence, the steep gradient of seropositivity from Wuhan to Hubei-ex-Wuhan to the other provinces, and the high correlation with COVID-19 incidence provide evidence supporting the impact of China's centrally-coordinated, locally-implemented, "whole-of-government, whole-of-society" effort to contain the coronavirus. The low seroprevalence shows that the first wave of COVID-19 infected a relatively small number of individuals in China, leaving virtually the entire population susceptible to SARS-CoV-2 infection. That most infections were asymptomatic supports the importance of contact tracing strategies to stop transmission. Long-term protection of the population and the economy will necessitate using COVID-19 vaccination strategies to safely immunize populations and enable selective lifting of non-pharmaceutical interventions that are currently maintaining elimination of SARS-CoV-2 transmission. Prevention and control of COVID-19 will be a long-term effort, requiring considerable domestic work and effective global collaboration.

Introduction

In late December 2019, a cluster of patients with severe pneumonia of unknown etiology (PUE) was reported. A new coronavirus, now called SARS-CoV-2, was discovered in the PUE patients' bronchoaveolar lavage fluids (BALF), identified, and sequenced, and was reported to the World Health Organization (WHO) [1–3]. SARS-CoV-2 is highly contagious, and its human disease, COVID-19, causes significant morbidity and mortality [4]. WHO declared COVID-19 as a pandemic on March 11, 2020, and by the end of November, there have been over 62 million cases and 1.4 million deaths reported worldwide [5].

China took unprecedented stringent measures in response to COVID-19, managing it as a Category A disease (the highest level) with a centrally-coordinated, locally-implemented, "whole-of-government, whole-of-society" effort to contain the virus geographically and stop its transmission. Active case finding and isolation, contact tracing and management were implemented throughout China, and physical distancing measures were implemented in varying degrees depending on local transmission risk [6,7]. Lockdown travel restrictions were implemented for Wuhan City on January 23. After an epidemic surge of two months, the incidence of COVID-19 declined. By the end of March, 81,554 confirmed COVID-19 cases had been reported throughout China - 50,007 from Wuhan [8]. After confirming lack of local transmission, the Chinese government lifted Wuhan travel restrictions on April 8, 2020.

The end of the first wave of the COVID-19 epidemic in the first country affected by the pandemic provides an opportunity to assess the extent of infection of the population following a managed epidemic wave. COVID-19 surveillance and reporting in China mainly relies on polymerase chain reaction (PCR)–based testing of symptomatic individuals and close contacts of the infected persons. However, extent of infection can only be determined by population-based serological surveys, as asymptomatic infections are invisible to symptom-based surveillance, and individuals not seeking medical care would be unlikely to be identified and reported [9]. Serological surveys can assess cumulative incidence of subclinical and clinical infections and population had immunity profiles.

We report results of serological surveys in three geographic areas in China to determine extent of infections and degree of remaining susceptibility, spectra of illness, and risk factors for infections following the first wave of COVID-19 in China.

Methods

Study design and participants

Between April 10 to 18, we conducted independent surveys in three areas: Wuhan (population 11•1 million), Hubei-excluding-Wuhan (48•1 million), and six other provinces or municipalities (Beijing, Shanghai, Guangdong, Jiangsu, Sichuan, and Liaoning; total population 366•7 million). The six selected provinces or municipalities were chosen to reflect the "Four Lines" containment strategy in China [6,7] – Wuhan and Hubei to prevent exportation of cases, Beijing to prevent importation of cases, Hubei's neighboring provinces to slow spread, and all of China to prevent exportation (appendix pp 17–18). Selected provinces for study included those with the highest incidences of COVID-19 in China.

Eligible participants were over one year old who lived in the surveyed areas for at least 14 days during the epidemic period (December 2019 to March 2020). We used a multi-stage, stratified cluster, random sampling method to select participants. Within provinces, counties were selected randomly based on the reported incidence of COVID-19; within counties, communities were selected using a probability-proportion-to-size sampling method; within communities, households were selected systematically from lists of households; and all age-eligible (greater than 1 year old) members of selected households were invited to participate (appendix pp 2–4, and pp 11–14). Target sample sizes were 10,000 blood samples for each survey, with at least 1500 in each of five age groups (1–9 years, 10–19, 20–39, 40–59, and 60+). Target sample sizes were based on an expected prevalence of 0•5%−2%, with one-third increases to account for survey design and non-response. The 95% confidence intervals (CIs) for the prevalence estimates in each age group would be 0•2–1•0 with a 0•5% prevalence and 1•4–2•8 with a 2•0% prevalence.

The study was approved by the Institutional Review Board of Chinese Center for Disease Control and Prevention (approval no. 202,001). Participation was voluntary; participants gave written informed consent prior to enrolling in the study.

Procedures

We administered structured questionnaires in face-to-face interviews (appendix pp 21–24) and obtained information on demographics; perceived symptoms (fever, cough, shortness-of-breath); whether the participants recalled being diagnosed with COVID-19 between December 2019 and March 2020; and risk factors for infection, including travelling to or living in a high risk area, contact with individuals with fever or respiratory illness, and contact with a confirmed COVID-19 case. Refusals and reasons for refusal were recorded.

Qualified nurses obtained five mL blood samples (three mL for children under five) using Chinese Center for Disease Control and Prevention (China CDC) guidelines [10,11]. Samples were delivered to local CDC laboratories for pre-processing; sera were transferred to provincial laboratories and stored at −40 °C. Provincial laboratories screened samples for SARS-CoV-2-specific IgG, IgM, and total antibody. All reactive samples and 20 randomly selected non-reactive samples from each province and Wuhan were sent for confirmatory testing for neutralizing antibodies (NAb) at the National Institute for Viral Disease Control and Prevention (NIVDC), China CDC. During transfers, specimens were packed and transported in accordance with UN2814 transportation requirements.

China CDC developed a database for survey and laboratory results. Local CDC staff entered survey data and verified self-reported COVID-19 infection by matching individual-identifying data with records of confirmed COVID-19 cases in the national COVID-19 registry (appendix p 6). Laboratory staff entered serology results. Provincial and national CDC staff checked for missing data and logical errors.

Screening and confirmatory testing

Provincial laboratories used three commercially-available serological test kits in parallel - two lateral flow immunoassays (LFA) (Wondfo SARS-CoV-2 antibody test and Innovita 2019-nCoV antibody test for detection of SARS-CoV-2 specific IgM, IgG, and total antibody), and one magnetic chemiluminescence enzyme immunoassay (MCLIA) (Bioscience 2019-nCoV IgM and IgG antibody test) (appendix pp 6–9). The diagnostic accuracy of the three screening assays were evaluated in previous studies [12,13]. Sensitivities were 76%, 44%−58%, and 57%−71% respectively; and for specificity 100%, 98%−100%, and 100%, respectively. All kits were approved by the National Medical Products Administration [14]. One or more positive results was considered reactive.

Micro-neutralization (MN) assays were used to confirm presence of SARS-CoV-2-specific neutralizing antibody (NAb). All reactive sera were tested by MN assays. Two sets of serum samples from healthy individuals were used to validate the MN test - one set of archived historical serum samples ($n = 100$, from 13–65 year-olds) obtained in a 2013 national measles serological survey, and one set of contemporary serum samples ($n = 82$, from 1–81-year-olds) obtained from counties that reported no COVID-19 cases and whose adjacent counties reported no cases) (appendix pp 9–10, and 19). The cut-off threshold of MN tests was determined by the two healthy controls by calculating the geometric mean titer (GMT) of NAb plus 3 standard deviation. NT tests were conducted in a biosafety level 3 confinement facility (BSL-3) at NIVDC as per national guidelines [10,11].

Statistical analysis

The survey's primary outcome was seropositivity, defined as a neutralizing antibody titer in excess of the cut-off threshold for MN tests of greater than or equal to four. Seroprevalence was defined as the number of seropositives divided by the number of participants screened in the study, weighted to account for the complex sample procedures, non-response and post-stratification distribution of age and sex (appendix pp 4–6). We represented NAb as geometric mean titers (GMTs) ± standard deviations, imputing one for titers less than four, and 192 for values >128. Using a mixed-effects logistic regression model adjusting for nested levels of clustering at the community and county levels to account for correlation of data within levels (i.e. random effects), we explored risk factors predicting SARS-CoV-2-specific NAb positivity, including sex, age group, occupation, underlying medical condition, living in Wuhan, travelling to Wuhan, travelling aboard, contacting with COVID-19 patients, and contacting with febrile patients or patients with respiratory illnesses (i.e. fixed effects). Analyses were conducted in SAS version 9•4 M6 (SAS Institute, Cary, NC, USA), and R version 3•4•3 (R Foundation for Statistical Computing, Vienna, Austria) using "lme4" and "survey" packages.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Investigators and authors confirm their independence from funders and sponsors.

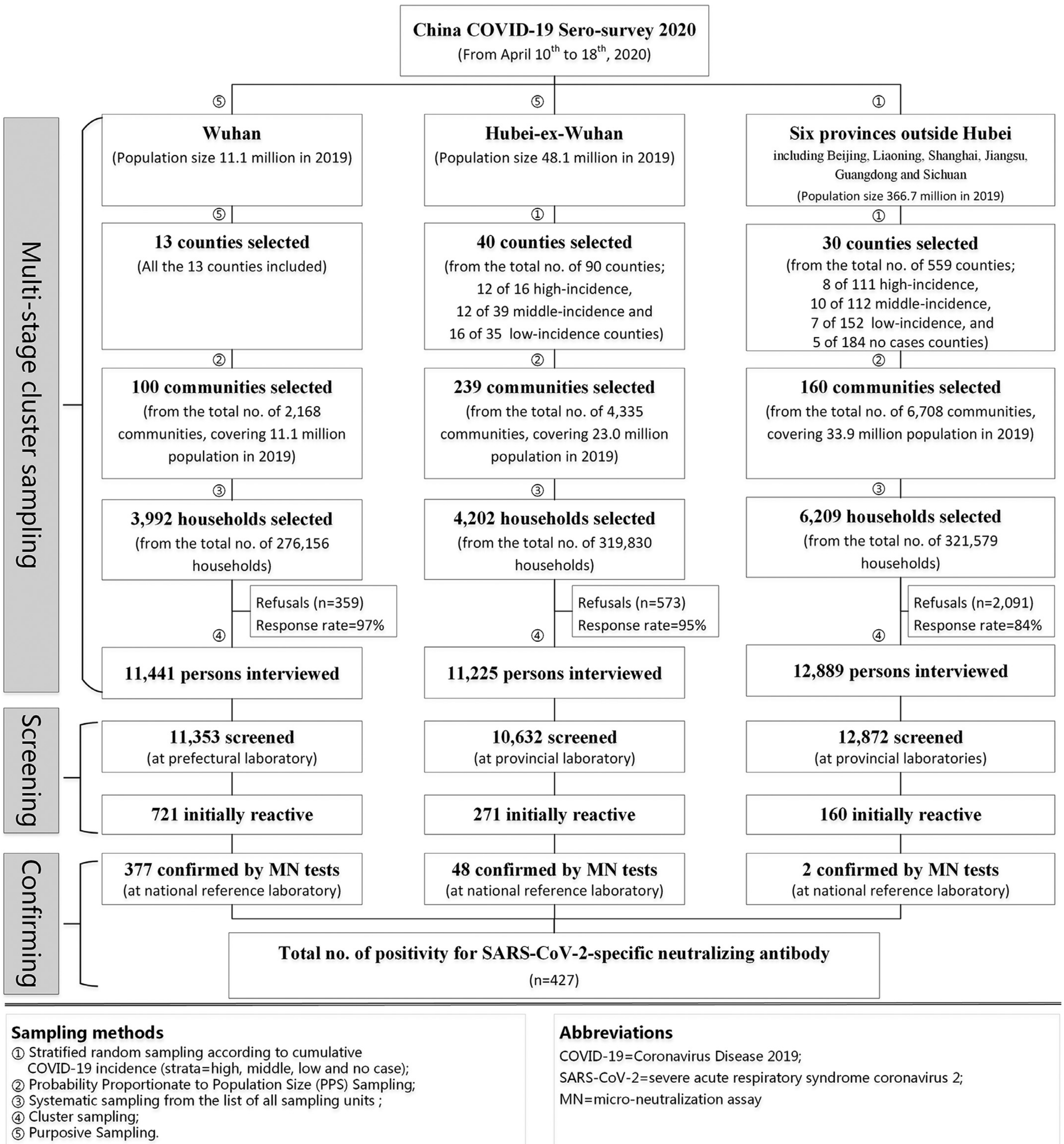

Fig. 1. Sample frames and study flow chart.

Results

Participants

A total of 34,857 participants completed the study: 11,353 from Wuhan, 10,632 from Hubei-ex-Wuhan, and 12,872 from the six other provinces (Fig. 1). The overall response rate was 92%, ranging from 84% in a non-Hubei province to 97% in Wuhan. Among respondents, 51% were female and 49% were male; the mean age was 40 years (interquartile range, 26–56). The age distributions of enrolled participants were similar to those of the represented populations, but with Wuhan and Hubei-ex-Wuhan enrolling relatively fewer persons 20–39 years old (appendix p 15).

Seroprevalence of SARS-CoV-2-specific neutralizing antibodies

We identified 1152 subjects with reactive antibodies; 427 were confirmed positive by MN tests (161 randomly-selected non-reactive sera all tested negative). Table 1 shows seroprevalence by survey, demographic characteristics, travel history, and con-

Table 1
Prevalence of SARS-CoV-2-specific neutralizing antibody positivity in China, 2020, by region.

	Wuhan				Hubei outside of Wuhan				Six other provinces outside Hubei			
	No. seropositivity	No. respondents	Weighted prevalence(%)	*p value*	No. seropositivity	No. respondents	Weighted prevalence(%)	*p value*	No. seropositivity	No. respondents	Weighted prevalence(%)	*p value*
Subtotals	377	11,353	4•43 (3•48–5•62)		48	10,632	0•44 (0•26–0•76)		2	12,872	0•009 (0•002–0•046)	
Gender				0•003				0•272				0•226
Female	226	5754	5•17 (4•11–6•48)		27	5394	0•48 (0•26–0•87)		0	6747	NA	
Male	151	5599	3•64 (2•65–4•97)		21	5238	0•40 (0•24–0•68)		2	6125	NA	
Age in years				0•003				0•052				0•351
1–9 years	18	978	2•44 (1•46–4•04)		4	1117	0•16 (0•04–0•62)		0	1169	NA	
10–19 years	20	1023	3•10 (1•76–5•40)		8	1145	1•17 (0•45–3•00)		0	1220	NA	
20–39 years	103	3348	3•96 (2•86–5•46)		12	2611	0•45 (0•21–0•97)		0	3742	NA	
40–59 years	154	4017	5•29 (4•02–6•94)		17	3529	0•34 (0•16–0•74)		2	4001	NA	
60+ years	82	1987	5•10 (3•37–7•64)		7	2230	0•39 (0•12–1•24)		0	2740	NA	
Occupation				0•001				0•218				1
others	209	7759	3•67 (2•93–4•59)		36	8962	0•34 (0•19–0•60)		2	9412	NA	
community workers	28	934	3•82 (2•39–6•06)		0	221	NA		0	620	NA	
service sector workers	30	861	4•08 (2•23–7•34)		5	607	1•31 (0•49–3•47)		0	786	NA	
retired people	104	1705	7•18 (4•58–11•08)		6	731	1•34 (0•46–3•83)		0	1733	NA	
clinicians	6	94	9•90 (4•07–22•13)		1	111	1•37 (0•22–8•08)		0	321	NA	
Underlying medical conditions*				0•859				0•872				0•255
no	298	9376	4•41 (3•49–5•55)		38	8904	0•45 (0•28–0•71)		1	11,110	NA	
yes	56	1512	4•56 (2•92–7•04)		4	1344	0•40 (0•10–1•64)		1	1762	NA	
Living in Wuhan				NA				<0•001				1
no	0	0	NA		36	10,080	0•33 (0•17–0•63)		2	12,800	NA	
yes	377	11,353	4•43 (3•48–5•62)		12	552	2•13 (1•11–4•06)		0	72	NA	
Travelling to Wuhan				NA				0•146				1
no	NA	NA	NA		45	10,387	0•42 (0•24–0•75)		2	12,839	NA	
yes	NA	NA	NA		3	245	1•10 (0•33–3•54)		0	33	NA	

(*continued on next page*)

Table 1 (*continued*)

	Wuhan				Hubei outside of Wuhan				Six other provinces outside Hubei			
	No. seropositivity	No. respondents	Weighted prevalence(%)	*p value*	No. seropositivity	No. respondents	Weighted prevalence(%)	*p value*	No. seropositivity	No. respondents	Weighted prevalence(%)	*p value*
Living in Hubei outside of Wuhan				0•055				NA				1
no	371	10,954	4•54 (3•57–5•76)		0	0	NA		2	12,579	NA	
yes	6	399	1•25 (0•42–3•66)		48	10,632	0•44 (0•26–0•76)		0	293	NA	
Travelling to Hubei, excluding Wuhan				0•227				NA				1
no	371	11,152	4•46 (3•53–5•63)		NA	NA	NA		2	12,826	NA	
yes	6	201	2•64 (0•99–6•86)		NA	NA	NA		0	46	NA	
Travelling aboard				0•107				<0•001				1
no	375	11,318	4•40 (3•47–5•57)		47	10,623	0•43 (0•25–0•74)		2	12,782	NA	
yes	2	35	9•73 (3•54–24•04)		1	9	19•29 (5•02–51•93)		0	90	NA	
Contact with COVID-19 patients				<0•001				<0•001				1
no	332	11,076	3•99 (3•23–4•91)		38	10,577	0•29 (0•16–0•51)		2	12,853	NA	
yes	45	277	18•95 (10•5–31•79)		10	55	30•73 (17•67–43•8)		0	19	NA	
Contact with febrile patients or patients with respiratory illness				<0•001				<0•001				1
no	307	10,760	3•76 (3•04–4•64)		41	10,432	0•40 (0•22–0•72)		2	12,690	NA	
yes	70	593	14•96 (8•44–2513)		7	200	3•44 (1•1–10•22)		0	182	NA	

Note: * Sums of values may not equal totals due to missing data. NA=data were not available. *P value* was calculated by using Rao-Scott Chi-Square tests and 95%CI based on Wilson confidence limits.

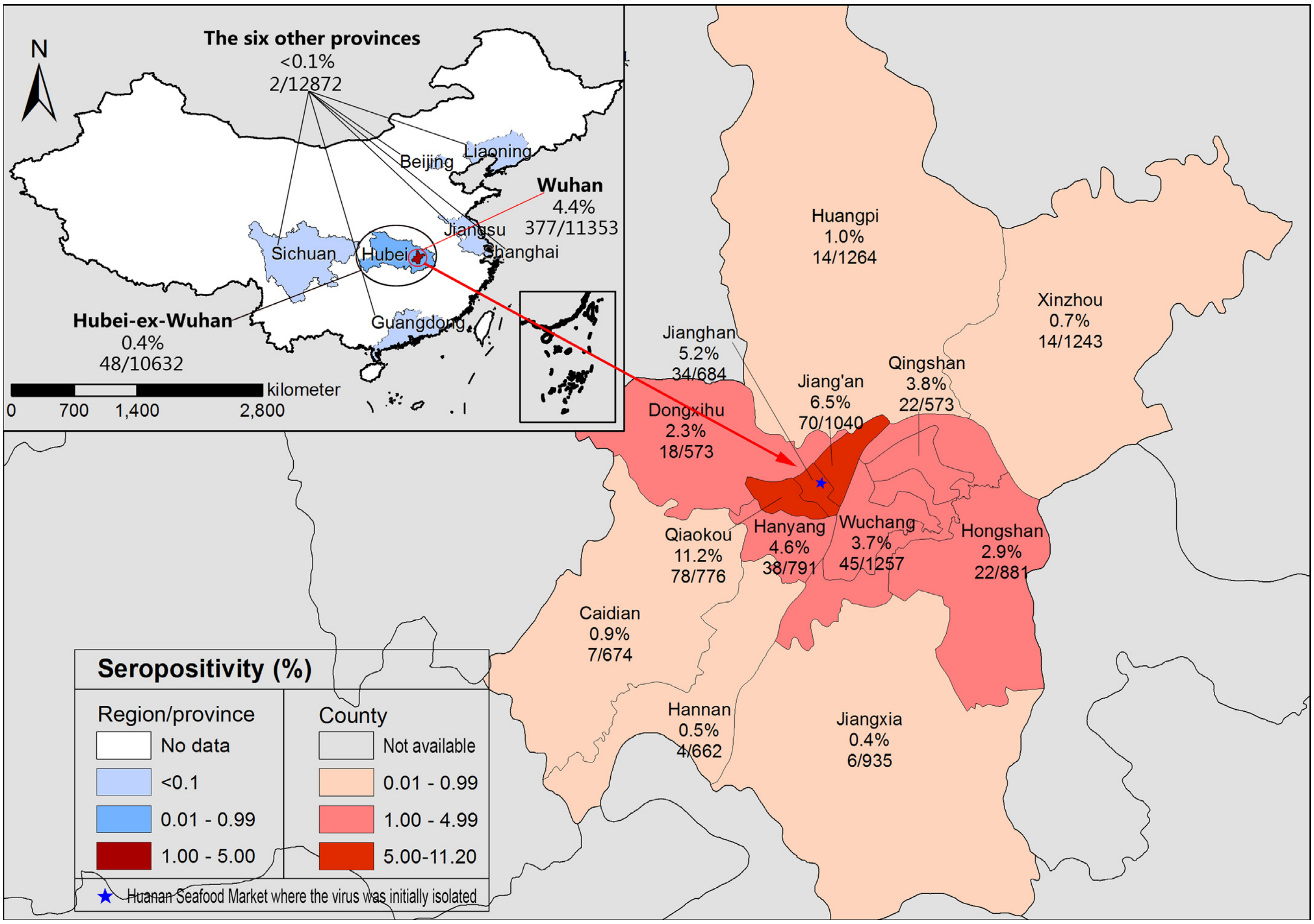

Fig. 2. Seroprevalence of SARS-CoV-2 neutralizing antibodies in China, April 2020, by county.

tact with ill individuals. Wuhan had the highest weighted seroprevalence at 4•43% (95% CI=3•48%–5•62%), followed by Hubei-ex-Wuhan (0•44%, 95% CI=0•26%–0•76%) and the six other provinces (<0•1%, 2/12,872). A gradient of decreasing seropositivity was observed in regions encircling Qiaokou District of Wuhan (Fig. 2) and was correlated with the reported cumulative incidence of COVID-19 in the counties (r = 0•917; p<0•001) (appendix p 20).

Symptoms and self-recalled diagnosis of COVID-19

Table 2 shows subject-perceived symptoms by age, sex, and seropositivity status. Between December 2019 and March 2020, 1228 subjects (3•5%) reported having had symptoms of illness. Participants in Wuhan more frequently reported illness (4•8% vs. 3•0% in Hubei-ex-Wuhan and 2•8% in the other provinces, p<0•001).

Among the 427 seropositive participants, 101 (23•7%) reported either fever, cough, or shortness of breath between December 2019 and the time of survey. NAb GMTs were 33±2•1 among diagnosed COVID-19 cases and 30±2•4 among those who reported an illness (n = 101) - all significantly higher than GMTs of the 326 seropositive participants who reported no symptoms during study period (GMT=15±2•1, p<0•001) (Fig. 3).

Factors predicting seropositivity

In multivariable mixed-effects logistic regression models adjusted for two nested levels of clustering at the community and county levels, living in Wuhan (adjusted Odds Ratio [aOR]=13•70, 95% CI=7•91–23•75), contact with COVID-19 patients (aOR=7•35, 95% CI=5•05–10•69) and age over 40 years (aOR=1•36, 95% CI=1•07–1•72) were significantly associated with SARS-CoV-2 positivity. There was no significant difference in seropositivity by presence or absence of underlying medical conditions (appendix p 16).

Discussion

Our serological surveys showed that one month after containment of the first wave of COVID-19 in China, SARS-CoV-2 seroprevalence was 4•4% in Wuhan City, 0•4% in Hubei-ex-Wuhan, and <0•1% in six additional provinces in China that had been selected based on COVID-19 incidence and control strategy. Extrapolation of these results implies that after the first wave of COVID-19 in China, approximately 500,000 people in Wuhan City, 210,000 people in Hubei-ex-Wuhan, and 120,000 people in provinces outside Hubei had antibodies to SARS-CoV-2 and therefore had been infected. Estimated seropositivity was highly correlated with reported COVID-19 incidence. The low seroprevalence shows that the infected population in the first wave of COVID-19 was relatively small in China, leaving virtually the entire population susceptible to SARS-CoV-2 infection.

The steep gradient of seroprevalence, with Wuhan at the peak, Hubei with low seroprevalence, and the outer provinces with nearly unmeasurable seroprevalences, provides evidence supporting success of the containment strategy and travel restrictions at stopping transmission. That transmission was stopped despite most infections being asymptomatic supports case iden-

Table 2
Self-perceived symptoms during December 2019 and March 2020, by region, sex, age group, and seropositivity.

	With symptoms (%)*	*p value*
Regions		<0•001
Wuhan	548/11,353 (4•8)	
Hubei-ex-Wuhan	320/10,632 (3•0)	
Six provinces outside Hubei	360/12,872 (2•8)	
Gender		1•00
Female	630/17,895 (3•5)	
Male	598/16,962 (3•5)	
Age in years		<0•001
1–9 years	152/3264 (4•7)	
10–19 years	77/3388 (2•3)	
20–39 years	439/9701 (4•5)	
40–59 years	349/11,547 (3•0)	
60+ years	211/6957 (3•0)	
Underlying medical conditions		<0•001
yes	220/4618 (4•8)	
no	920/29,390 (3•1)	
SARS-CoV-2-specific neutralizing antibody positive		<0•001
yes	101/427 (23•7)	
no	1127/34,430 (3•3)	

Note: Self-perceived symptoms included fever, cough, and shortness of breath.

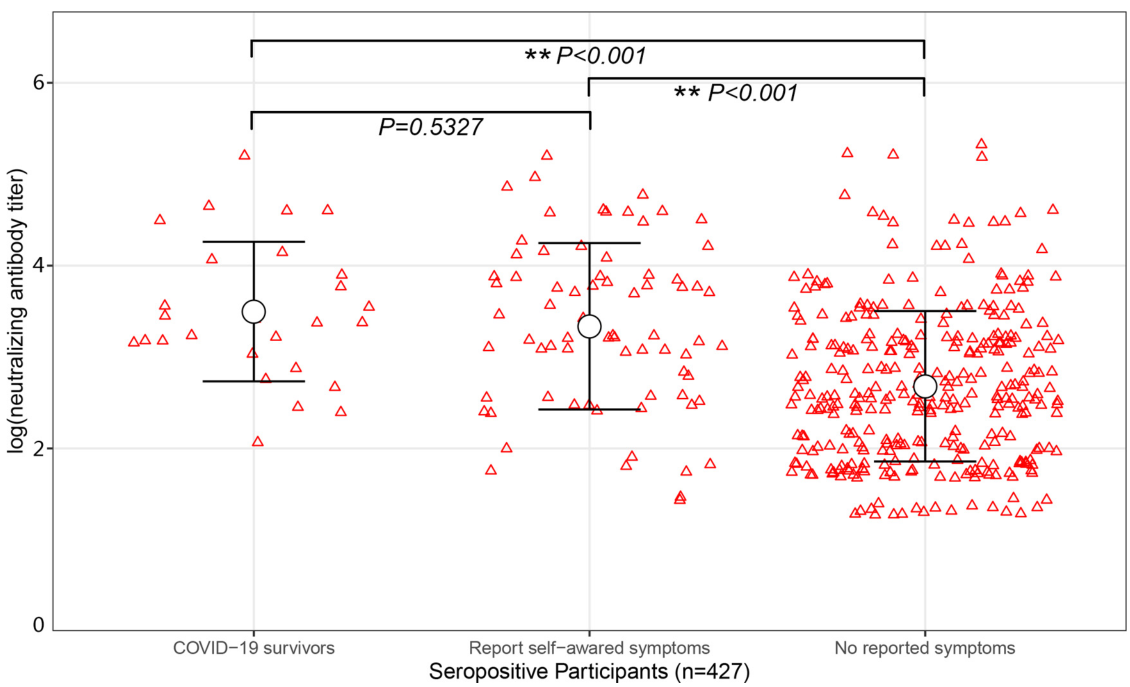

Fig. 3. SARS-CoV-2-specific neutralizing antibodies distribution among 427 seropositive participants, by illness presentation.

tification/isolation and quarantine of close contacts as a core containment strategy [6]. Our estimate of 4•4% SARS-CoV-2 seroprevalence in Wuhan is similar to an estimate of 4% seroprevalence among 452 Hong Kong residents evacuated from Hubei (80% from Wuhan) [15]. Wu and colleagues found 10% seroprevalence in patients in a hospital in Wuhan [16], similar to the peak district-level seoprevalence we found. Although our study did not provide a unified national estimate of SARS-CoV-2 seroprevalence, our estimates can contribute to the growing global seroprevalence data including Switzerland's (11%) and Spain's (3.7%–6.2%) recent national estimates [17–19].

SARS-CoV-2 infected people of all ages, but adults more than children, similar to other studies [17,18]. Having an underlying medical condition was not related to seropositivity, even though underlying medical conditions are known to be risk factors for COVID-19 and severity of illness [20]. We found that people with underlying medical conditions were slightly more likely to have symptoms. Contact with the COVID-19 case had the strongest association with infection – seven times higher than among those recalling no contact.

Three quarters of seropositive individuals perceived no COVID-19 symptoms. The finding that most infections were asymptomatic is different from previous estimates of 10% to 30% asymptomatic infection rates [21,22], but similar to an estimate from a cruise ship outbreak (67% asymptomatic) [23], and with an outbreak in a homeless shelter (87% asymptomatic) [24]. In a skilled nursing home, 57% of residents with SARS-CoV-2 infection were asymptomatic [25]. The high proportion of asymptomatic infections implies a lower infection-fatality rate than some estimates [20,26].

Strengths of our study relate to the survey and laboratory methods. The surveys were representative and had large sample sizes with good response rates. The timing of the survey assessed extent of infection after containment of the first national epidemic wave. The laboratory testing strategy was sensitive and specific, and was similar to the strategy suggested by Perera and colleagues [27], using sensitive screening tests and sensitive and specific verification with micro-neutralization assays in a *BSL-3* laboratory that used a low threshold of positivity (NAb $\geq$ 4) to avoid underestimating seropositivity.

Limitations to our study included that seven of mainland China's 31 provinces were assessed, rather than all provinces. Since these provinces were selected based on reported COVID-19 incidence and prevention strategy and included the highest incidence provinces, and since county-level COVID-19 incidence was highly correlated with seroprevalence, we believe that the results of the six provinces provide an upper limit of seroprevalence for all of mainland China outside of Hubei. A second limitation is that respondents were asked about symptoms that may have occurred several months earlier, resulting in recall bias. Although the risk of infection was not related to presence of medical conditions, our study did not have sufficient statistical power to evaluate risk for specific medical conditions, such as immunodeficiency syndromes. Third, since we included only fever, cough, and shortness-of-breath in our definition of symptomatic, subjects with other symptoms associated with COVID-19 (e.g., fatigue, headache, myalgia, sore throat, coryza, diarrhea, loss of smell, and loss of taste) would be considered asymptomatic if they had only non-queried symptoms. This would result in an overestimation of the proportion of asymptomatic infections. Finally, our finding that the oldest age group did not have the highest risk of infection, and that medical conditions were unrelated to infection risk is subject to survivor bias.

Our study has implications for prevention and control of COVID-19. The low population seroprevalence and its steep gradient from Wuhan on out, combined with COVID-19 surveillance, indicate that containment was successful, and provide a measure of confidence that future waves can be stopped [7,28]. That the strongest risk factor for infection was contact with individuals with COVID-19 supports isolation of infected individuals and tracing and quarantine of close contacts to interrupt virus transmission [6].

Disease surveillance will continue to be critically important and should be intensified. We found that asymptomatic SARS-CoV-2 infections were prominent in the spectrum of illness caused by SARS-CoV-2, and even though asymptomatic infections may not transmit well, they can transmit and must be considered in containment and surveillance strategies. If one estimates the number of infections in the first epidemic wave based on our serological survey, it is apparent that most infections were not detected, showing the need for developing innovative ways to conduct surveillance for asymptomatic and mild infections.

Most important, the finding of low seroprevalence implies that the population of China has virtually no immunity to SARS-CoV-2 and is vulnerable to future waves of COVID-19. As evidenced, mainland China has had to contain four importation caused local transmission outbreaks since April – Jilin (43 COVID-19 cases, May 8–24), Beijing (335 cases, June 12–July 6), Dalian (93 cases, July 23-August 6), and Xinjiang (828 cases, July 17–August 16) [29–33].

Maintaining low or no virus transmission has a very high health and socioeconomic value, but maintaining virus elimination with only non-pharmaceutical interventions (NPIs) has a high socioeconomic cost and is unsustainable in the long-term. Vaccines will almost certainly be approved for use that can augment outbreak containment strategies with outbreak response immunization, helping ensure outbreaks are controlled and stopped. As market-authorized vaccine supplies increase, population risk and susceptibility can be replaced by vaccine-induced herd immunity in an ethically, epidemiologically, and logically sound sequence of vaccination efforts. Domestic vaccine supply will need to be balanced with vaccine exports, as COVID-19 vaccines are a global public good.

Additional knowledge is needed. The nature of immunity to SARS-CoV-2 is incompletely understood and reliable immunologic correlates of protection have not been identified. Duration of infection- and vaccine-induced herd immunity and the risk of reinfection are unknown [34]. As vaccine is introduced and direct protection increases, evaluation and modeling will be needed to determine which, if any, NPIs should remain and under what circumstances. Prevention and control of COVID-19 will be a long-term effort, requiring considerable domestic work and global collaboration.

Contributors

ZL and GFG had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZL, HL, YQ, ZA, LL, HS, and WX designed and concepted the study. JS, LW, QG, NX, JL, BZ, XS, MW, XW, WY, WG, TS, and XY collated and collected data. JL, YL, JY, and ZP analyzed the data. ZL, NM, ZZ, YQ, JY, and LR wrote the first draft. LL, HS, NH, ZF, XG, and GFG interpreted the findings and commented on and revised drafts of the manuscript. GFG, ZL, LL, HS, NH, WY, XW, and TS received funding. GFG and ZF supervised the study. All authors contributed to reviewing, revising, and approving the final manuscript. ZL, XG, NM, HL, YQ, NH, ZZ and JY contributed equally to this work.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Data sharing

Data will become publicly available upon request from the corresponding author.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100094.

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