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DOI: 10.1542/peds.2020-0702
Journal: *Pediatrics*
Citation: Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics.* 2020; doi: 10.1542/peds.2020-0702

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Pre-publication Release

Epidemiology of COVID-19 Among Children in China

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Short title: Epidemiology of COVID-19 among Children in China

Funding Source: This work was partially supported by the Science and Technology Commission of Shanghai Municipality (grant number: 18411951600)

Financial Disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose.

Conflict of Interest: The authors have indicated they have no potential conflicts of interest to disclose.

Abbreviations:

COVID-19: 2019 novel coronavirus disease
CDC: center for disease control and prevention
WHO: world health organization
PHEIC: public health emergency of international concern
ACE2: angiotensin converting enzyme II

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Table of Contents Summary

This study examined the epidemiological characteristics and transmission patterns of 2143 pediatric patients with COVID-19, using a retrospective analytical approach.

What's Known on This Subject

A growing number of studies have focused on 2019 novel coronavirus disease (COVID-19) since its outbreak, but few data are available on epidemiological features and transmission patterns of children with COVID-19.

What This Study Adds

Children at all ages were susceptible to COVID-19, but no significant gender difference was found. Clinical manifestations of pediatric patients were generally less severe than those of adults' patients. However, young children, particularly infants, were vulnerable to 2019-nCoV infection.

Contributors' Statement

Prof Tong conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript.

Ms Dong and Dr Mo carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Qi, Mr Hu and Profs Jiang and Jiang critically reviewed the manuscript for important intellectual content.

Prof Tong obtained the funding. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Abstract

OBJECTIVES: To identify the epidemiological characteristics and transmission patterns of pediatric patients with COVID-19 in China.

METHODS: Nationwide case series of 2143 pediatric patients with COVID-19 reported to the Chinese Center for Disease Control and Prevention from January 16 to February 8, 2020 were included. The epidemic curves were constructed by key dates of disease onset and case diagnosis. Onset-to-diagnosis curves were constructed by fitting a log-normal distribution to data on both onset and diagnosis dates.

RESULTS: There were 731 (34.1%) laboratory-confirmed cases and 1412 (65.9%) suspected cases. The median age of all patients was 7 years (interquartile range: 2-13), and 1213 cases (56.6%) were boys. Over 90% of all patients were asymptomatic, mild, or moderate cases. The median time from illness onset to diagnoses was 2 days (range: 0 to 42 days). There was a rapid increase of disease at the early stage of the epidemic and then there was a gradual and steady decrease. Disease rapidly spread from Hubei Province to surrounding provinces over time. More children were infected in Hubei province than any other province.

CONCLUSIONS: Children at all ages appeared susceptible to COVID-19, and there was no significant gender difference. Although clinical manifestations of children's COVID-19 cases were generally less severe than those of adults' patients, young children, particularly infants, were vulnerable to infection. The distribution of children's COVID-19 cases varied with time and space, and most of the cases concentrated in Hubei province and surrounding areas. Furthermore, this study provides strong evidence for human-to-human transmission.

Key words: 2019 coronavirus disease; acute respiratory disease; mortality; transmission

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In early December 2019, a number of pneumonia cases of unknown origins emerged in Wuhan, Hubei province, China.[1,2] Most of these patients reported exposure to the Huanan Seafood Wholesale Market selling many species of live animals. The disease has rapidly spread, domestically, to other parts of China, and globally, to many countries across 6 continents. On 3 January 2020, a novel member of enveloped RNA coronavirus was identified in samples of bronchoalveolar lavage fluid from a patient in Wuhan and subsequently confirmed as the cause of this disease by the Chinese Center for Disease Control and Prevention (China CDC).[3-5] On 7 January 2020, the World Health Organization (WHO) named it as the 2019 novel coronavirus (i.e., 2019-nCoV). On 11 February 2020, WHO named the illness associated with 2019-nCoV as the 2019 coronavirus disease (COVID-19).

Emergence of 2019-nCoV has attracted global attention, and WHO has declared the COVID-19 a public health emergency of international concern (PHEIC).[6] Since the outbreak of severe acute respiratory syndrome (SARS) in Guangdong, China, in 2003, WHO has declared 5 PHEICs: H1N1 (2009), polio (2014), Ebola in West Africa (2014), Zika (2016), and Ebola in the Democratic Republic of Congo (2019). Declaring a PHEIC is an urgent call, at the highest level, for the international community to launch a global coordinated effort to stop the outbreak, which requires strong public health response, high-level political commitment and sufficient funding. As of 2 March 2020, a total of 80174 COVID-19 cases in China and 8774 cases in 64 countries (and regions) have been confirmed.[7] Despite the worldwide spread, the epidemiological and clinical patterns of the COVID-19 remain largely unclear, particularly among children. In this study, we explored the epidemiological characteristics and transmission patterns of 2143 pediatric patients with COVID-19 in mainland China.

Methods

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Data Sources

We conducted a retrospective study on the epidemiological characteristics of 2143 pediatric patients with COVID-19. Children were defined as being less than 18 years old. The cases were initially diagnosed on the basis of clinical manifestations and exposure history.[8,9] Within the last 2 weeks, if a child exposed to a COVID-19 case, or lived in an epidemic area (*i.e.,* Hubei province) or community where COVID-19 case(s) were reported, or in a non-epidemic area where no COVID-19 case(s) were reported, s/he was defined as having high, medium or low risk, respectively, based on the possibility of contracting the disease. Suspected cases were identified if a child at high risk had two of the following conditions: 1) fever or respiratory symptoms or digestive symptoms (*e.g.*, vomiting, nausea and diarrhea) or fatigue; 2) laboratory test: white blood cell count is normal or decreased or with lymphocyte count or increased level of C-reactive protein; 3) abnormal chest X-ray imaging. For a child at medium or low risk, similar diagnostic criteria were applied after excluding influenza and other common respiratory infections. Suspected cases who met any one of the following criteria were defined as confirmed cases:

1. Nasal and pharyngeal swab specimens or blood samples tested positive for 2019-nCoV nucleic acid using real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay;
2. Genetic sequencing of respiratory tract or blood samples is highly homologous with 2019-nCoV.

The severity of COVID-19 was defined based on the clinical features, laboratory testing and chest X-ray imaging, including asymptomatic infection, mild, moderate, severe and critical cases. The diagnostic criteria were as follows: [8]

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1. Asymptomatic infection: without any clinical symptoms and signs and the chest imaging is normal, while the 2019-nCoV nucleic acid test is in a positive period.

2. Mild: symptoms of acute upper respiratory tract infection, including fever, fatigue, myalgia, cough, sore throat, runny nose, and sneezing. Physical examination shows congestion of the pharynx and no auscultory abnormalities. Some cases may have no fever, or have only digestive symptoms such as nausea, vomiting, abdominal pain and diarrhea.

3. Moderate: with pneumonia, frequent fever and cough, mostly dry cough, followed by productive cough , some may have wheezing, but no obvious hypoxemia such as shortness of breath, and lungs can hear sputum or dry snoring and / or wet snoring. Some cases may have no clinical signs and symptoms, but chest CT shows lung lesions, which are subclinical.

4. Severe: Early respiratory symptoms such as fever and cough, may be accompanied by gastrointestinal symptoms such as diarrhea. The disease usually progresses around 1 week, and dyspnea occurs, with central cyanosis. Oxygen saturation is less than 92%, with other hypoxia manifestations.

5. Critical: Children can quickly progress to acute respiratory distress syndrome (ARDS) or respiratory failure, and may also have shock, encephalopathy, myocardial injury or heart failure, coagulation dysfunction, and acute kidney injury. Organ dysfunction can be life threatening.

Both the laboratory-confirmed and suspected cases were included in the analysis. The datasets were extracted from the electronic master database at the Chinese Center for Disease Control and Prevention (China CDC). Data were entered into a computer and secured with a

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password at Shanghai Children's Medical Center. Cross-check and data cleaning was performed before the data analysis.

Statistical Analysis

We firstly described case characteristics, including age, sex, dates of disease onset and diagnosis, and location where the case was notified. Chi-square tests and Fisher's exact tests were used for categorical variables as appropriate and Mann-Whitney U test was used for comparing median values of non-normally distributed variables. The epidemic curves were constructed by key dates of disease onset, and case diagnosis. Due to the data unavailability (*i.e.*, no detailed exposure data), we were unable to estimate the incubation period. Onset-to-diagnosis curves were constructed by fitting a log-normal distribution to data on both onset and diagnosis dates. All analyses were conducted with the use of Statistical Product and Service Solutions (SPSS 22.0) software and distribution maps were plotted using ArcGIS version 10.2.

Ethics

Due to the nature of aggregated data and the ongoing public health response to control the outbreak, as well as the importance of sharing the research findings and bridging the knowledge gaps, an ethical approval was considered to be waived by institutional review board.

Results

By Feb 8, 2020, 2143 pediatric patients with COVID-19 were reported to China CDC (Table 1). Of them, 731 (34.1 %) patients were identified as laboratory-confirmed cases, and

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1412 (65.9 %) were suspected cases. The median age of all patients was 7 years (Interquartile range: 2-13). Among those patients, 1213 cases (56.6 %) were boys and there was no statistically significant difference in the number of pediatric patients between boys and girls. For the severity of patients (including both confirmed and suspected cases), 94 (4.4 %), 1091 (50.9 %) and 831 (38.8 %) patients were diagnosed as asymptomatic, mild or moderate cases, respectively, totally accounted for 94.1 % of all cases. About a half of patients were from Hubei province (984, 45.9 %), while 397 (18.5%) cases were from Anhui, Henan, Hunan, Jiangxi, Shanxi and Chongqing which border Hubei province.

Table 2 shows the severity of illness by age and it reveals that young children, particularly infants, were vulnerable to 2019-nCoV infection. The proportion of severe and critical cases was 10.6 %, 7.3%, 4.2%, 4.1% and 3.0% for the age group of <1, 1-5, 6-10, 11-15 and ≥16 years, respectively. Besides, a 14-year-old boy from Hubei province died on Feb 7, 2020.

In the temporal distribution, among the 2143 pediatric patients, there was a trend of the rapid increase of disease onset in the early stage of the epidemic, and then, a gradual and steady decrease (Fig 1). The total number of pediatric patients increased remarkably between mid-January and early February, peaked around Feb 1, and then declined since early February 2020. The number of diagnoses had been rising every day from January 20 when the first case was diagnosed. Similar trends of onset and diagnoses were found in confirmed (Fig 2 & Fig 3) and suspected cases (Supplementary Fig 1 & Fig 2). The earliest date of illness onset was Dec 26, 2019, while the earliest date of diagnoses was Jan 20, 2020. The median days from illness onset to diagnoses was 2 days (range: 0 to 42 days). Fig 4 shows that most cases were diagnosed in the 1st week after illness onset occurred.

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In the spatial distribution, there was a clear trend that disease rapidly spread from Hubei Province to surrounding provinces and cities over time. There were more children infected in the areas around Hubei province than areas farther away except for Heilongjiang Province (Fig 5).

Discussion

To the best of our knowledge, this is the first retrospective study on the epidemiological characteristics and transmission dynamics of children's COVID-19 in China. As most of these children were likely to expose themselves to family members and/or other children with COVID-19, it clearly indicates person-to-person transmission. Supportive evidence of such a transmission pathway has also been reported from studies on adult patients.[10-12] As of 8 February 2020, of the 2143 pediatric patients included in this study, only one child died and most cases were mild, with much fewer severe and critical cases (5.9%) than adult patients (18.5%).[13] It suggests that, compared with adult patients, clinical manifestations of children's COVID-19 may be less severe.

Coronaviruses are large, enveloped, positive strand RNA viruses that can be divided into 4 genera: alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans, which is called human coronaviruses (HCoVs).[14] Four HCoVs (HCoV 229E, NL63, OC43, and HKU1) are endemic globally and account for 10% to 30% of upper respiratory tract infections in adults.[15] Although HCoVs have long been regarded inconsequential pathogens due to their mild phenotypes in humans, in the early 21st century, two large-scale epidemics with alarming morbidity and mortality – *i.e.*, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), have changed that view.

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During December 2019-February 2020 (when the paper is writing), 2019-nCoV, another highly pathogenic HCoV, has caused tens of thousands of illnesses and over 2000 deaths.[16] The epidemic is ongoing and rapidly evolving, and the ultimate scope and impact of this event is still unclear.

Genomic analyses suggest that the 2019-nCoV may originally come from bats, because of the similarity of its genetic sequence to those of other known coronaviruses, but the pathogen was probably transmitted to humans by other animals which may serve as intermediate hosts, facilitating recombination and mutation events with expansion of genetic diversity.[3-5] On 7 February 2020, researchers in Guangzhou, China, identified the pangolin as one of the potential sources of 2019-nCoV on the basis of a genetic comparison of CoVs in the samples taken from the animals and from humans infected in the outbreak and other findings.[17,18] Genetic sequences of viruses isolated from the scaly animals are 99% similar to that of the circulating virus.

Why most of the children's COVID-19 cases were less severe than adults' cases is puzzling. This may be related to both exposure and host factors. Children were usually well cared for at home and might have relatively less opportunities to expose themselves to pathogens and/or sick patients. Angiotensin converting enzyme II (ACE2) was known as cell receptor for SARS-CoV.[19] 2019-nCoV has some amino acid homology to SARS-CoV and may be able to use ACE2 as a receptor. Recent evidence indicates that ACE2 is also likely the cell receptor of 2019-nCoV.[20,21] It is speculated that children were less sensitive to 2019-nCoV because the maturity and function (*e.g.*, binding ability) of ACE2 in children may be lower than that in adults.[22] Additionally, children often experience respiratory infections (*e.g.*, respiratory syncytial virus (RSV)) in winter, and may have higher levels of antibody against virus than adults. Furthermore,

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children's immune system is still developing, and may respond to pathogens differently to adults. However, we found that the proportion of severe and critical cases was 10.6%, 7.3%, 4.2%, 4.1% and 3.0% for the age group of <1, 1-5, 6-10, 11-15 and >15 years, respectively. These results suggest that young children, particularly infants, were vulnerable to 2019-nCoV infection. Therefore, the mechanisms for the difference in clinical manifestations between children and adults remain to be determined.

There were more severe and critical cases in the suspected than confirmed category in this study. However, it remains to be determined whether these severe and critical cases in the suspected group were caused by 2019-nCoV or other pathogens (e.g., RSV). It may become clearer as the epidemic is quickly unfolding.

We observed slightly more boys than girls (56.6% vs 43.4%) affected in the COVID-19 outbreak, which is similar to the two recent epidemiological studies.[13, 23] However, no significant gender difference was observed in this study. The median age of all children's COVID-19 cases was 7 years (Interquartile range: 11), but it ranged from 1 day to 18 years. It suggests that all ages at childhood were susceptible to 2019-nCoV.

Temporal distribution of children's COVID-19 cases shows that, in the early stage of the epidemic (*i.e.*, between Dec., 2019 and early Feb., 2020), there was a trend of the rapid increase of disease onset. Since early February 2020, the number of children's COVID-19 cases has been declining. It indicates that the disease control measures implemented by the government were effective, and it is likely that this epidemic will continue to decline, and finally stop in the near future unless sustained human-to-human transmissions occur. Most of the children's COVID-19 cases concentrated in Wuhan, but spread to other areas of Hubei province and further to other

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areas of China. It seems that the closer to Wuhan, the more cases in that area, which suggests that population mobility is an important factor for the spread of 2019-nCoV. Heilongjiang province is an exception, which may be because many visitors went there, including those from Wuhan, due to the Ice Sculpture Festival in Harbin, the provincial capital.

This study has several strengths. First, this is the first nationwide study, to date, with a major focus on the epidemiological characteristics and transmission dynamics of children's COVID-19 in China. It shows that, compared with the adults' cases, the severity of children's COVID-19 cases was milder, and the case fatality rate was much lower. [13, 23] Second, the large number of children's COVID-19 cases enabled us to conduct detailed stratified analyses on sex, age, and spatiotemporal distribution. Finally, we included both confirmed and suspected COVID-19 cases, and it may reveal a comprehensive picture of pediatric patients with COVID-19 in China.

This study also has a number of limitations. First, we were unable to assess clinical characteristics of children's COVID-19 as these data were unavailable at the time of analysis. As an important and urgent issue, clinical features of children's COVID-19 need to be analyzed in further research. It appeared to have more severe and critical cases in the suspected than confirmed group (Table 1), which suggests that some suspected cases might be caused by other respiratory infections (*e.g.*, RSV). Second, we did not have information on children's exposure history, and thus, the incubation period was not examined in this study. Finally, since the epidemic of COVID-19 is on-going and rapidly evolving, many children affected still remain hospitalized. To gain a better understanding of children's COVID-19, more detailed patient information, particularly clinical outcomes (*e.g.*, discharge, transferred to intensive care unit, or death), should be collected in future studies.

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Conclusions

Children at all ages were sensitive to COVID-19, and there was no significant gender difference. Clinical manifestations of children's COVID-19 cases were less severe than those of adults' patients. However, young children, particularly infants, were vulnerable to 2019-nCoV infection. The distribution of children's COVID-19 cases varied with time and space, and most of the cases concentrated in Wuhan and surrounding areas. Furthermore, the results of this study provide strong evidence for human-to-human transmission as children were unlikely to visit the Huanan Seafood Wholesale Market where the early adult patients were reported to obtain 2019-nCoV.

Acknowledgments

The authors are grateful to the support provided by Chinese Center for Disease Control and Prevention.

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Table 1 Characteristics of Children' COVID-19 Cases in China

Characteristics	All cases	Different Category		
		Confirmed	Suspected	*P* Value
Median age (Interquartile range)	7.00 (11.0)	10.00(11.0)	6.00(10.0)	<0.001
Age group				
<1	379(17.7)	86(11.8)	293(20.8)	
1-5	493(23.0)	137(18.7)	356(25.2)	
6-10	523(24.4)	171(23.4)	352(24.9)	<0.001
11-15	413(19.3)	180(24.6)	233(16.5)	
>15	335(15.6)	157(21.5)	178(12.6)	
Gender				
Boy	1213(56.6)	420(57.5)	793(56.2)	0.567
Girl	930(43.4)	311(42.5)	619(43.8)	
Severity of illness				
Asymptomatic	94(4.4)	94(12.9)	0(0.0)	
Mild	1091(50.9)	315(43.1)	776(54.9)	
Moderate	831(38.8)	300(41.0)	531(37.6)	
Severe	112(5.2)	18(2.5)	94(6.7)	<0.001
Critical	13(0.6)	3(0.4)	10(0.7)	
Missing	2(0.1)	1(0.1)	1(0.1)	
Days from symptom onset to diagnosis				
Median days (Interquartile range)	2(4.0)	3(4.0)	2(4.0)	<0.001
Range	0-42	0-42	0-36	
Province				
Hubei	984(45.9)	229(31.3)	755(53.5)	
Surrounding areas*	397(18.5)	155(21.2)	242(17.1)	<0.001
Others	762(35.6)	347(47.5)	415(29.4)	
Total	2143	731(34.1)	1412(65.9)	

Data are presented with median (Interquartile range) and n (%).
*Surrounding areas are the provinces and Municipality bordering Hubei, they are Anhui, Henan, Hunan, Jiangxi, Shaanxi and Chongqing.

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Table 2 Different Severity of Illness by Age Group

Age group*	Asymptomatic	Mild	Moderate	Severe	Critical	Total
<1	7(7.4)	205(18.8)	127(15.3)	33(29.5)	7(53.8)	379(17.7)
1-5	15(16.0)	245(22.5)	197(23.7)	34(30.4)	2(15.4)	493(23.0)
6-10	30(31.9)	278(25.5)	191(23.0)	22(19.6)	0(0)	521(24.3)
11-15	27(28.7)	199(18.2)	170(20.5)	14(12.5)	3(23.1)	413(19.3)
>15	15(16.0)	164(15.0)	146(17.5)	9(8.0)	1(7.7)	335(15.7)
Total	94	1091	831	112	13	2141(100)

Data were presented with number and percent (%);*Two cases had missing values.

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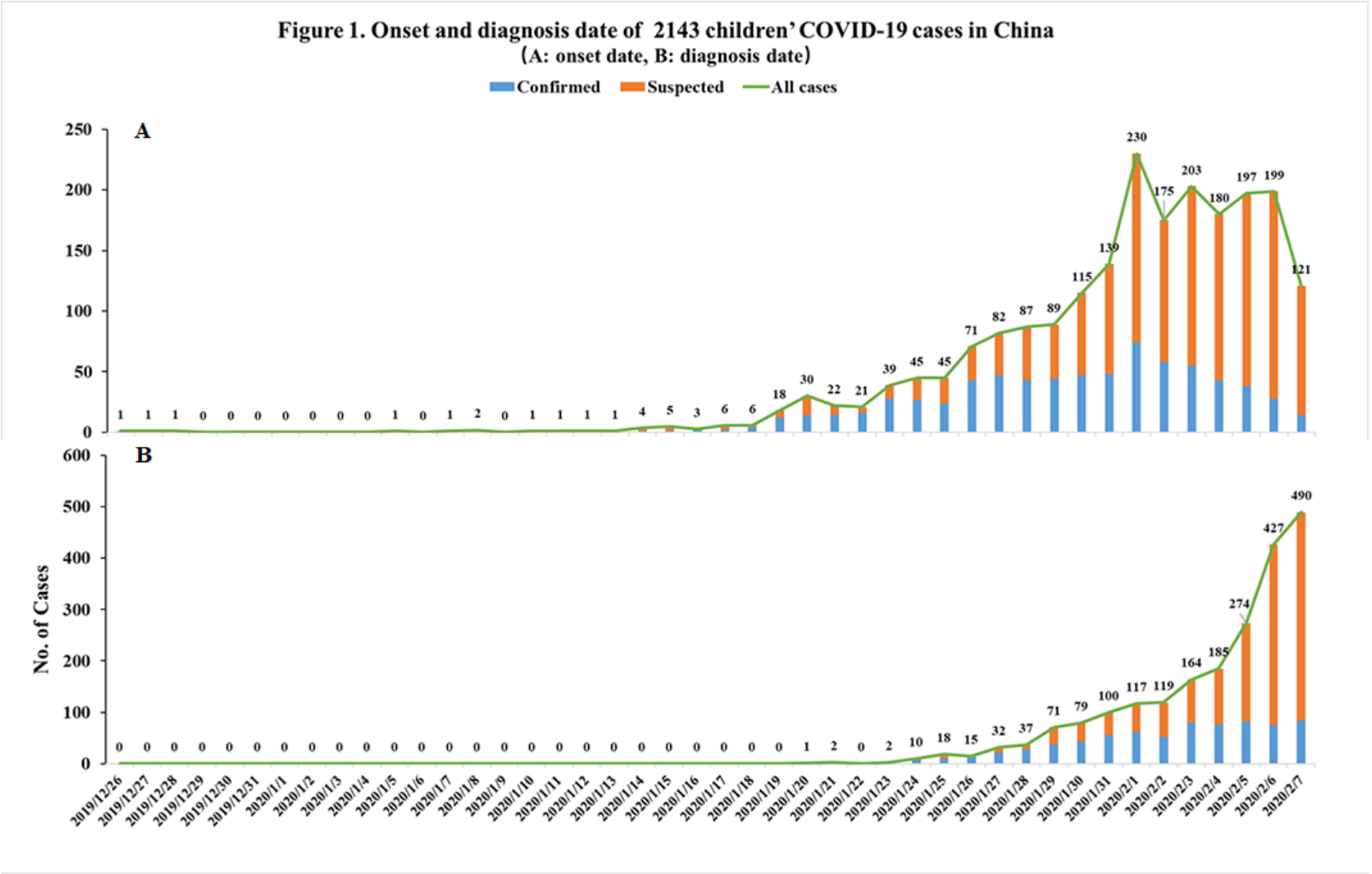

Fig 1 Onset and Diagnosis Date of 2143 children's COVID-19 Cases in China. A: onset date; B: diagnosis date

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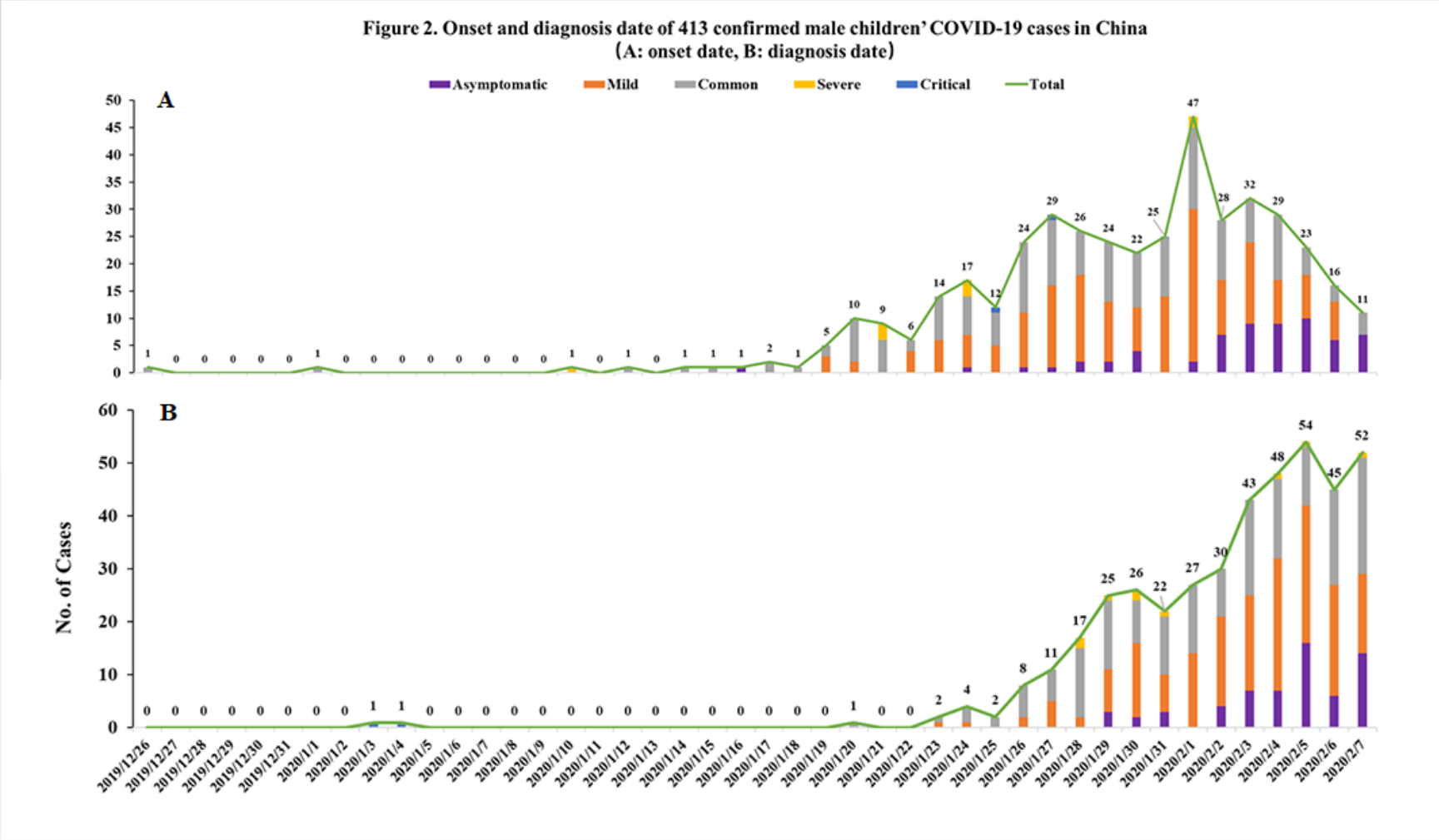

Fig 2 Onset and Diagnosis Date of 413 Confirmed Male Children's COVID-19 Cases in China. A: onset date; B: diagnosis date

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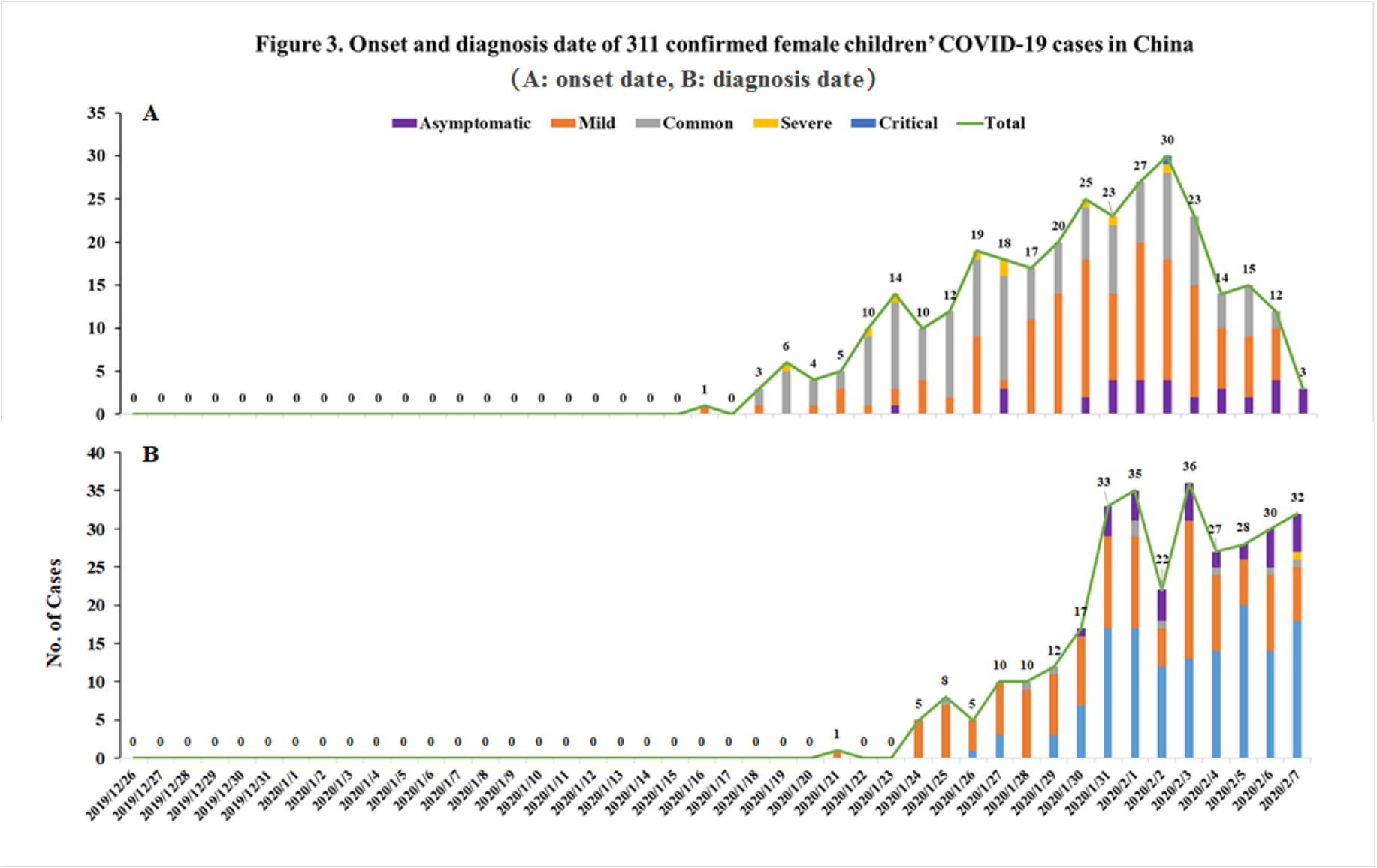

Fig 3 Onset and Diagnosis Date of 311 Confirmed Female Children's COVID-19 Cases in China. A: onset date; B: diagnosis date

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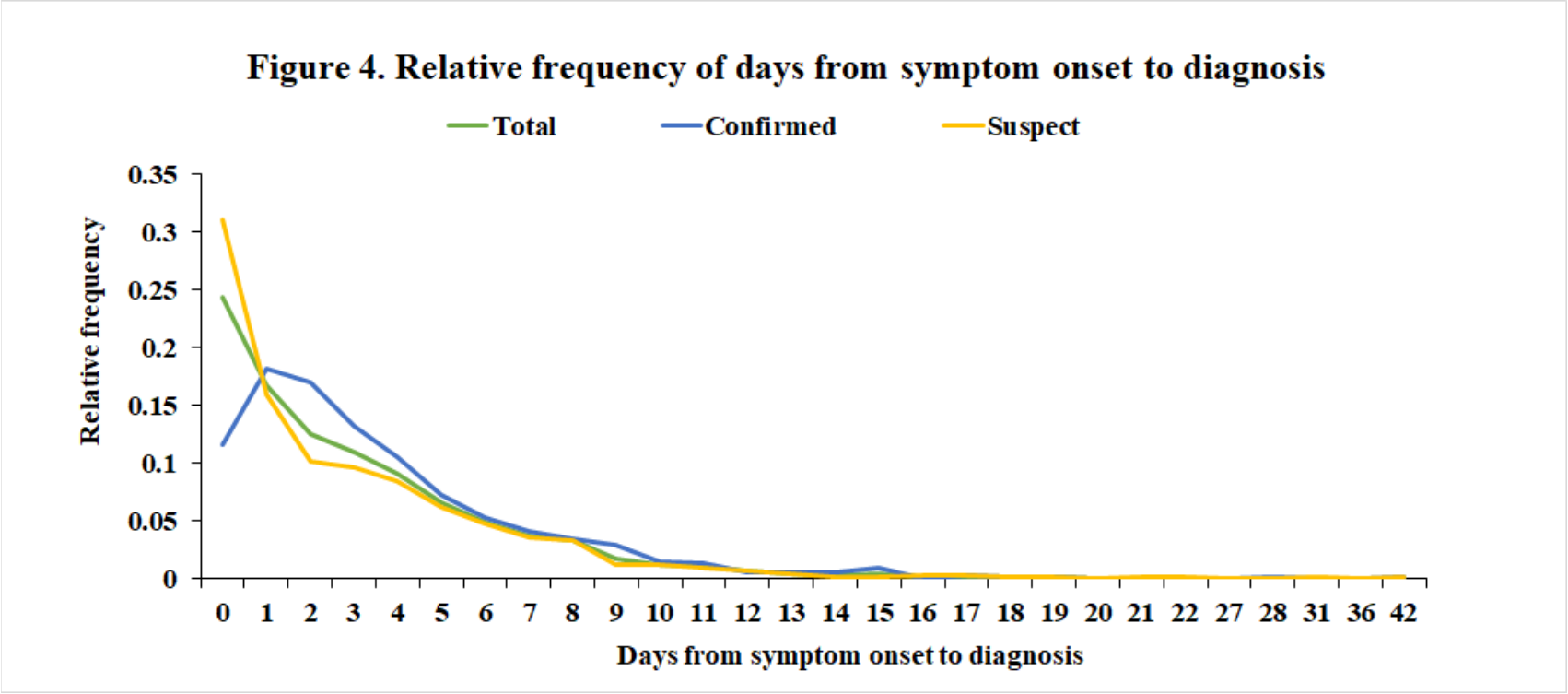

Fig 4 Relative Frequency of Days from Symptom Onset to Diagnosis.

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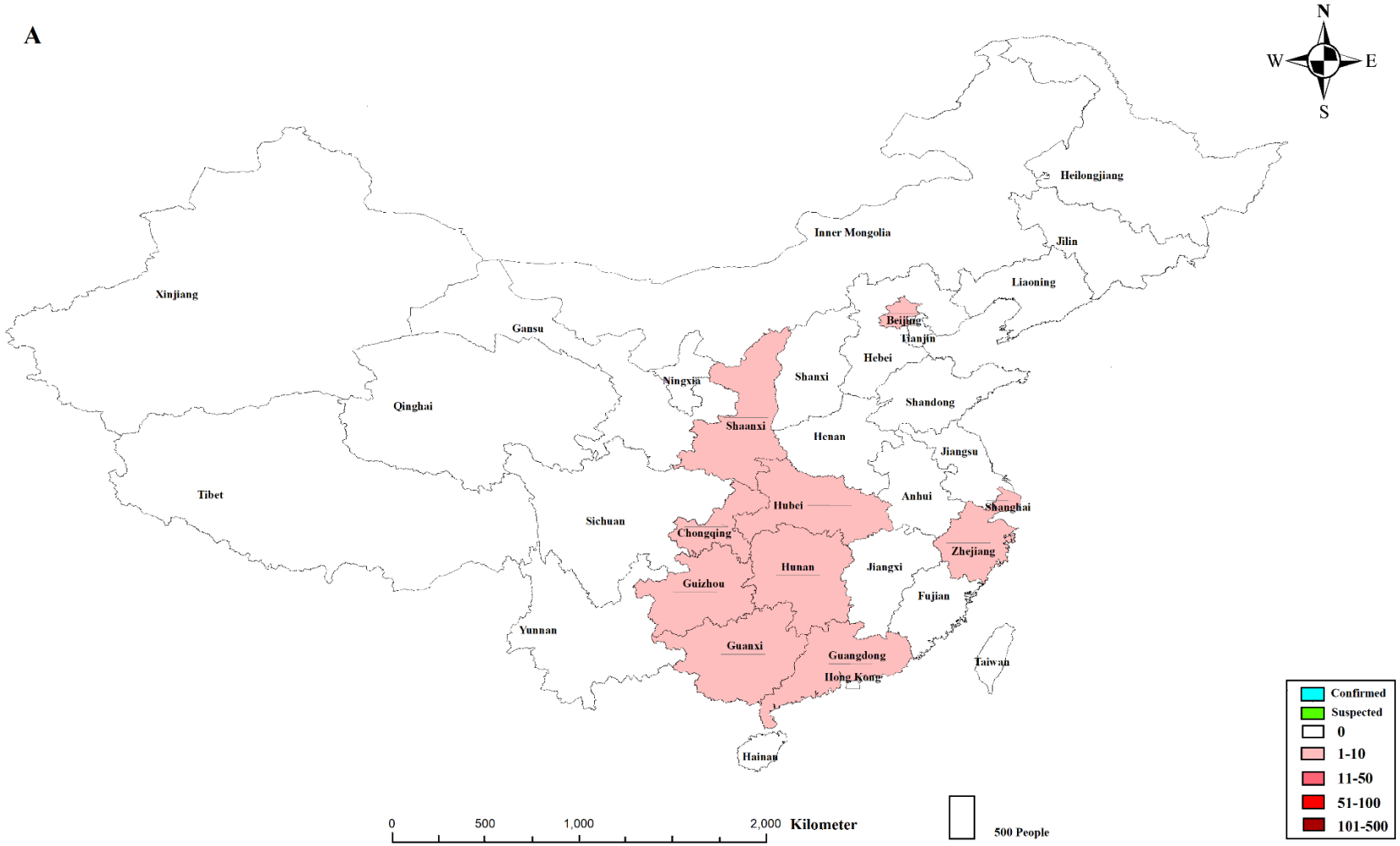
Fig 5 Spatial Distribution of Children's COVID-19 Cases Diagnosed in Different Time Periods. **A**, from Jan 20, 2020 to Jan 24, 2020; **B**, from Jan 25, 2020 to Jan 31, 2020; **C**, from Feb 1, 2020 to Feb 7, 2020; **D**, from Jan 20, 2020 to Feb 7, 2020.



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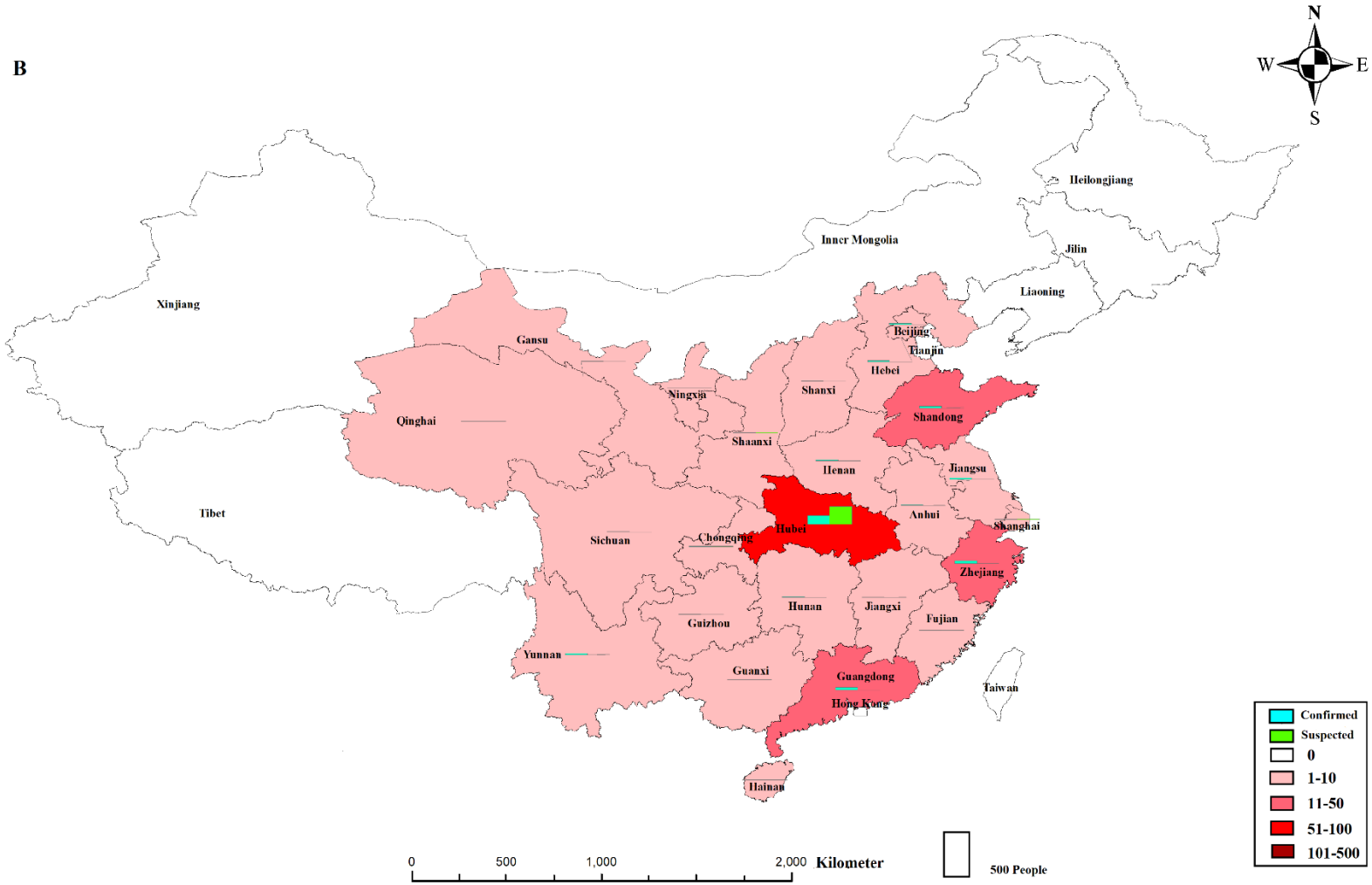

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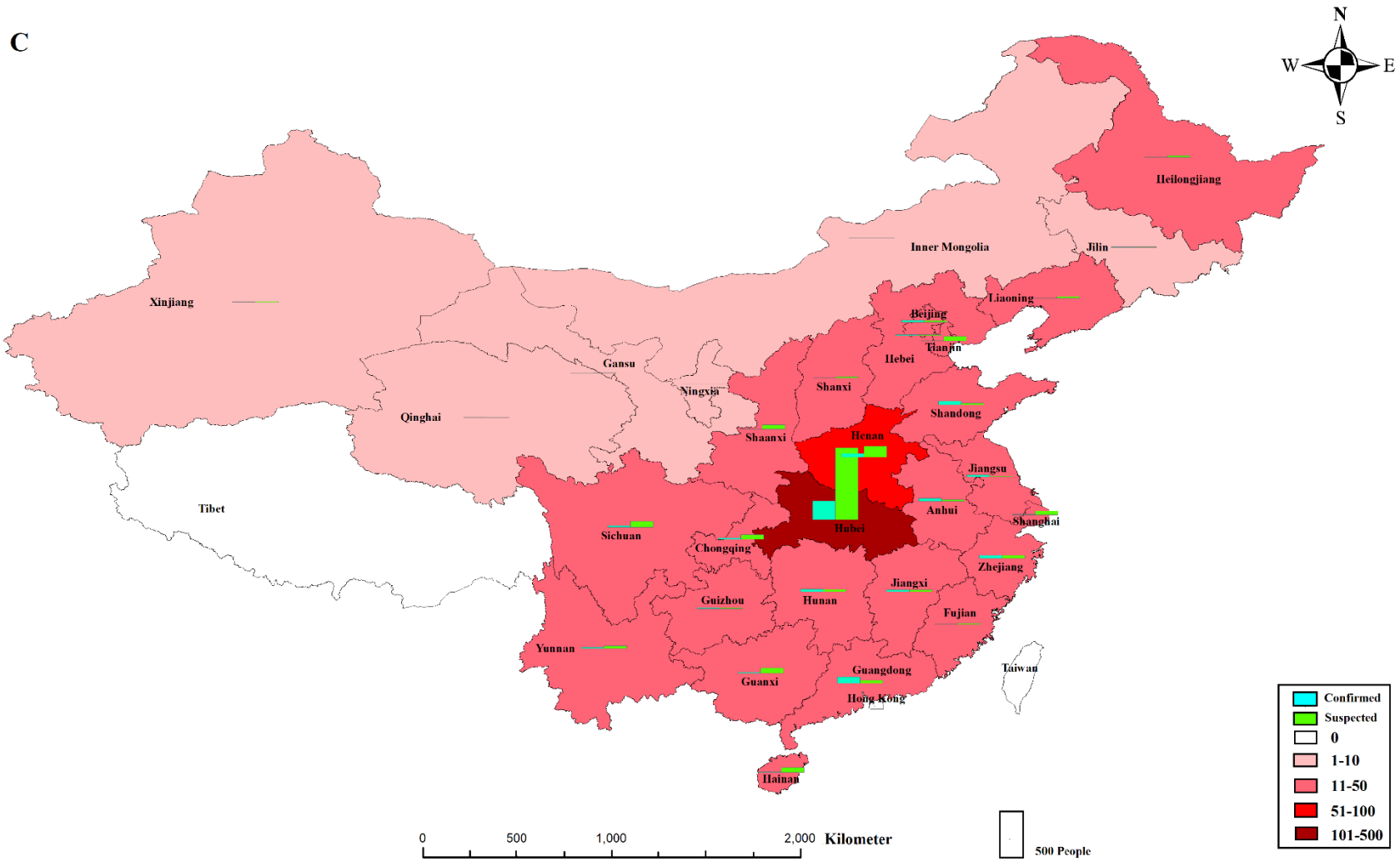

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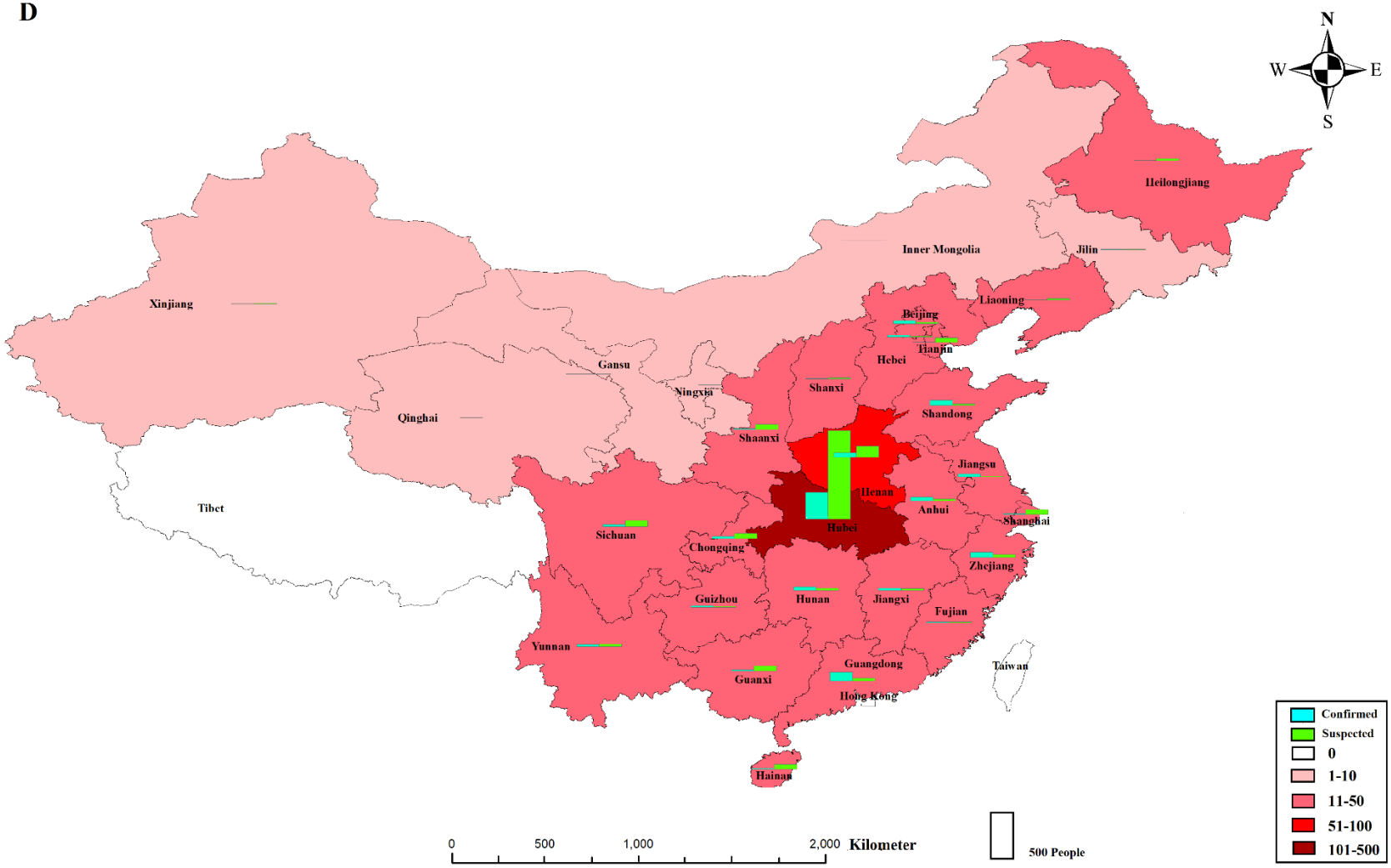

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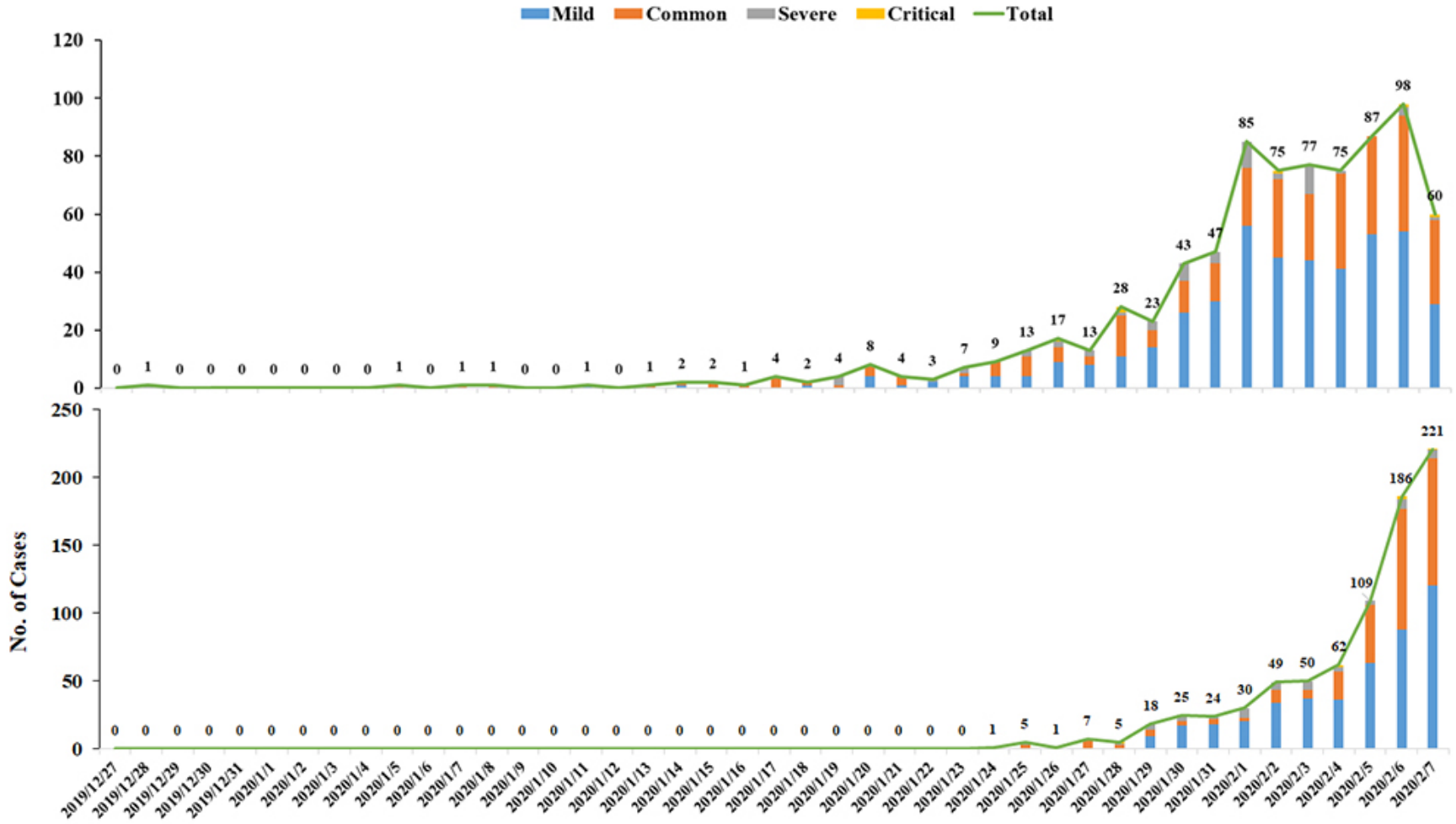
Supplementary figure 1. Onset and diagnosis date of 793 suspected male children' COVID-19 cases in China (A: onset date, B: diagnosis date)



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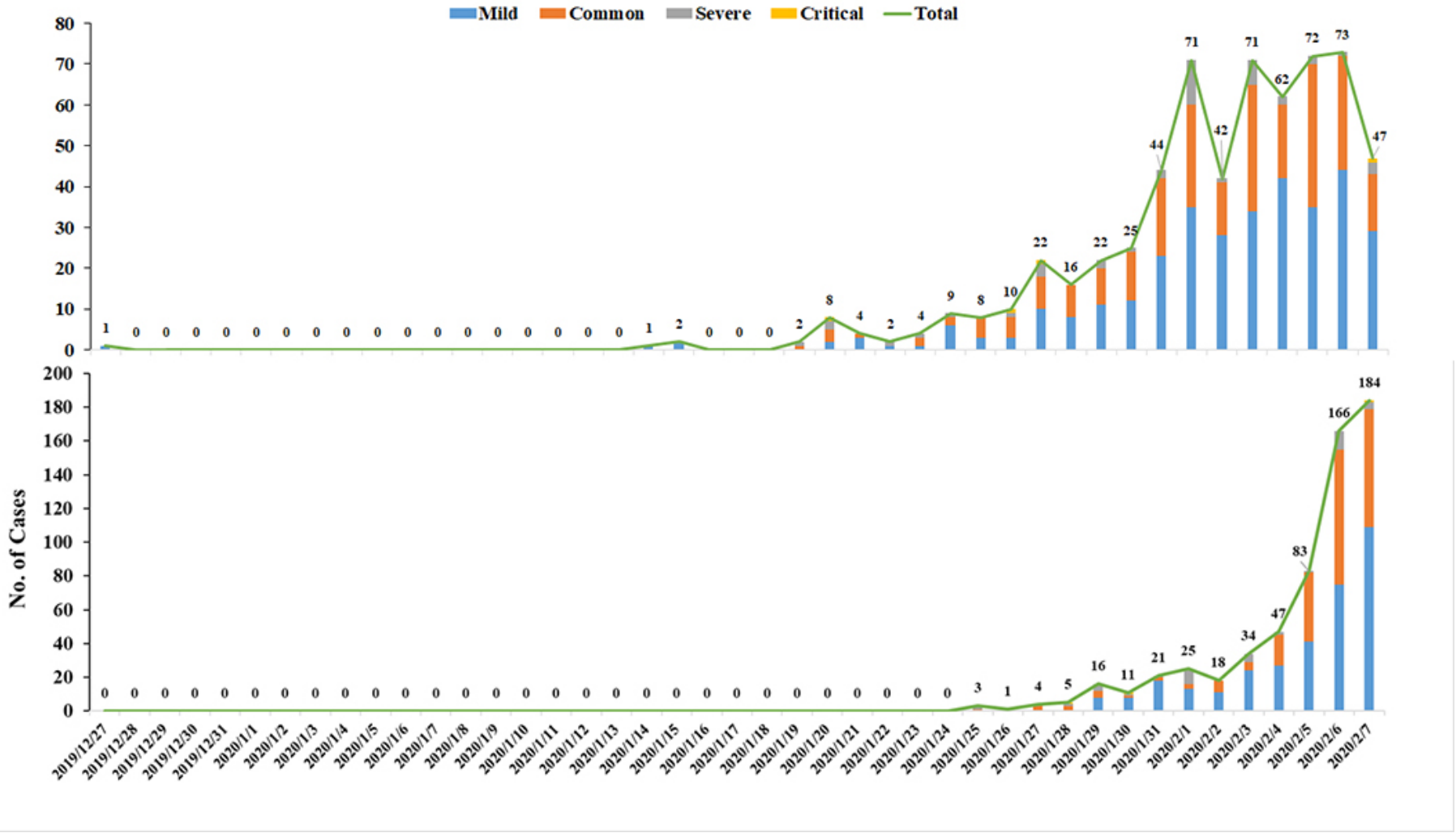
Supplementary figure 2.Onset and diagnosis date of 618 suspected female children' COVID-19 cases in China
(A: onset date, B: diagnosis date)



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