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Spatiotemporal analysis of pertussis in Hunan Province, China, 2009–2019

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ABSTRACT

Objectives This study aims to explore the spatial and spatiotemporal distribution of pertussis in Hunan Province, and provide a scientific basis for targeting preventive measures in areas with a high incidence of pertussis.

Design In this retrospective spatial and spatiotemporal (ecological) study, the surveillance and population data of Hunan Province from 2009 to 2019 were analysed. The ArcGIS V.10.3 software was used for spatial autocorrelation analysis and visual display, and SaTScan V.9.6 software was used for statistical analysis of spatiotemporal scan data.

Settings Confirmed and suspected pertussis cases with current addresses in Hunan Province and onset dates between 1 January 2009 and 31 December 2019 were included in the study.

Participants The study used aggregated data, including 6796 confirmed and suspected pertussis cases.

Results The seasonal peak occurred between March and September, and scattered children were at high risk. The global Moran's I was between 0.107 and 0.341 ($p<0.05$), which indicated that the incidence of pertussis in Hunan had a positive spatial autocorrelation. The results of local indicators of spatial autocorrelation analysis showed that the hot spots were mainly distributed in the northeast region of Hunan Province. Moreover, both purely space and spatiotemporal scans showed that the central and northeastern parts were the most likely cluster areas with an epidemic period between March and October in 2018 and 2019.

Conclusion The distribution of the pertussis epidemic in Hunan Province from 2009 to 2019 shows spatiotemporal clustering. The clustering areas of the pertussis epidemic were concentrated in the central and northeastern parts of Hunan Province between March and October 2018 and 2019. In areas with low pertussis incidence, the strengthening of the monitoring system may reduce underreporting. In areas with high pertussis incidence where we could study whether the genes of endemic pertussis strains are mutated and differ from vaccine strains.

INTRODUCTION

Pertussis is an acute respiratory infectious disease caused by *Bordetella pertussis* infection. In the past, pertussis was an important cause of childhood morbidity and death worldwide, especially among children who were either unvaccinated or partially vaccinated with a pertussis-related vaccine.[1] In China, the earliest description of

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to explore the spatial clusters and spatiotemporal distribution of pertussis in Hunan Province.
⇒ The data for this study were retrieved from the Chinese Information System for Disease Control and Prevention, which stores all pertussis data reported by medical institutions at all levels since 2004.
⇒ Our study verified that spatial analysis and spatiotemporal analysis were feasible to explore the hot spots and spatiotemporal clusters of pertussis and, at the same time, provided a reference for the prevention and control of pertussis epidemics in Hunan Province.
⇒ The validity of the assumed parametric data distributions in scan statistics should be considered in real applications and non-parametric statistical methods.
⇒ The influence of laboratory testing ability, pertussis vaccination rate, patient characteristics and doctors' training was not deeply explored in this study.

pertussis can be traced back to the Sui Dynasty, approximately 1500 years ago. In the book 'Theory of Pathogeny and Phenology' by Yuan-fang Cao, the disease was described a paediatric disease similar to whooping cough, which was later simplified as 'pertussis'.[2] Moreover, pertussis outbreaks occurred in Persia in the 15th century and in Paris in the 16th century.[3] Hence, pertussis has affected humans for at least hundreds of years.

In 1906, Dr Jules Bordet and colleagues isolated *B. pertussis* in Paris and confirmed that this bacterium was the aetiological agent of pertussis. This achievement paved the way for the production of the pertussis vaccine, which greatly contributed to the control of pertussis outbreaks. With the widespread implementation of pertussis vaccine immunisation, the incidence of this disease has decreased significantly.[4 5] However, in the past two decades, outbreaks of pertussis have been reported in many areas worldwide,[6–9] and large-scale outbreaks of pertussis (termed as 'pertussis recurrence') have also been reported in Shandong, Taiwan, and other regions in China.[10 11]

In the past, most studies about pertussis mainly focused on the analysis of epidemiological characteristics, and only a few focused on the spatial cluster or spatiotemporal distribution characteristics.[12 13] Zhang *et al*[10 14 15] explored the hot spots and spatiotemporal clusters of pertussis in Shandong (China), Iran and Denver (Colorado) using geographical information systems, and verified the feasibility of related spatiotemporal analysis methods to explore pertussis clusters. However, the characteristics of pertussis outbreaks differ by region. Therefore, the incidence of pertussis in different regions needs to be analysed separately.

An outbreak of pertussis also occurred in Hunan Province in recent years, with the incidence rate rising from 0.088/100 000 in 2009 to 6.184/100 000 in 2019. To understand the spatial cluster and spatiotemporal distribution characteristics of pertussis in Hunan Province, the surveillance data of pertussis in Hunan Province from 2009 to 2019 were collected. This is the first study to perform spatial and spatiotemporal analysis for pertussis clusters in this region. This study aimed to provide certain references for developing targeted measures for pertussis prevention and control measures in Hunan Province.

METHODS
Study area
In this study, the data of Hunan Province (108°47'~114°15'E, 24°38'~30°08'N) were analysed. This region has a horseshoe-shaped landform surrounded by mountains on three sides and an open area to the north, with a subtropical monsoon climate. At the end of 2019, Hunan Province covered 211 800 km^2 comprising a resident population of 69.1838 million with a population density of 326.65 people per km^2 in 14 administrative cities and 122 counties or urban districts. All these areas were included in this study (figure 1).

Data collection
The surveillance data of pertussis from 2009 to 2019 and the population data of Hunan Province were provided by the Chinese Information System for Disease Control and Prevention, which stores all pertussis data reported by medical institutions at all levels since 2004, and its use in research has been authorised by the Hunan Provincial Center for Disease Control and Prevention. All clinically and laboratory-confirmed pertussis cases and suspected pertussis cases currently residing in Hunan Province and an onset date between 1 January 2009 and 31 December 2019 were included in the study. We used the 'Detailed Diagnostic Criteria of Pertussis' (WS274-2007) and the 'Recommendations for Diagnosis and Treatment of Pertussis in Chinese Children'.

The collected information included the case number, county administrative code, date of onset, date of diagnosis, sex, age, occupation, current address and other characteristics. Vector maps of China and Hunan Province
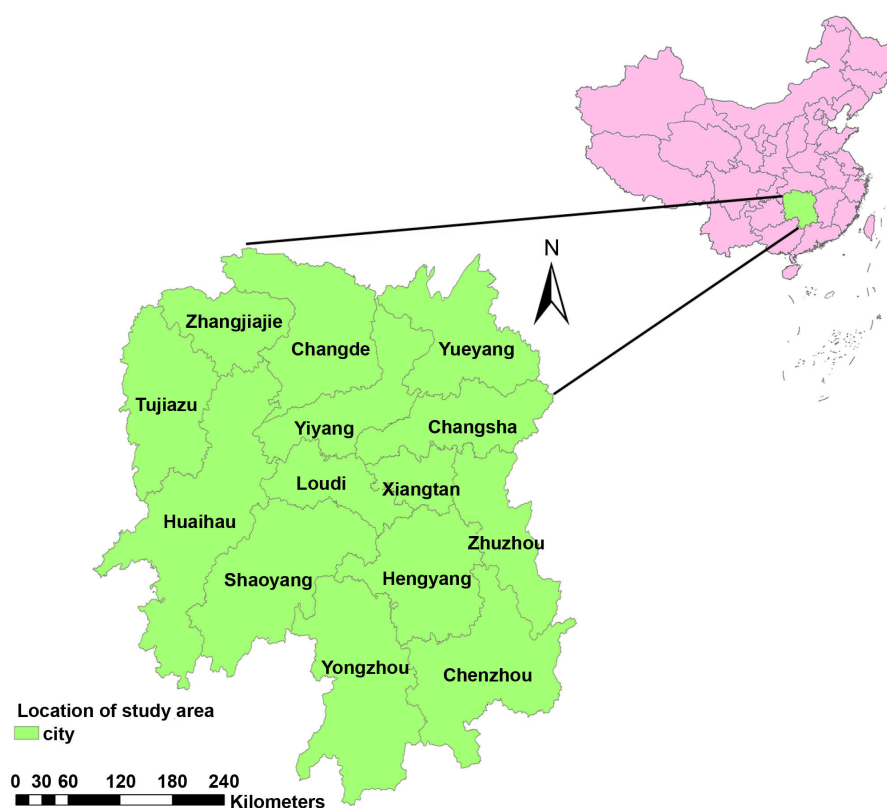
Figure 1 Geolocation of Hunan Province in China. This map was created using the ArcGIS software V.10.3 (ESRI, Redlands, California, USA).

were provided by the National Basic Geographic Information System.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Statistical analysis

Descriptive and geographical analysis

Descriptive statistical analysis was performed to describe the epidemiological characteristics of pertussis in Hunan Province from 2009 to 2019. To examine characteristics of Chinese patients with pertussis by age, the included cases were divided into the following age groups: <1 year, 1–<2 years, 2–<3 years, 3–<4 years, 4–<5 years, 5–9 years and ≥10 years old.[16] The annual incidence of pertussis in each county was calculated, and the ArcGIS V.10.3 software was used to draw thematic maps of the data. The incidence of pertussis was represented by the value of the colour; darkly coloured areas were correlated with a higher incidence of pertussis.

Spatial autocorrelation analysis

We performed global and local spatial autocorrelation analyses, which are often used to detect the spatial correlation of a variable. Moran's I was used for global autocorrelation analysis to determine the presence or absence of spatial clustering of pertussis in Hunan Province. Moran's I generally ranges from −1 to +1. It can be tested according to its Z-score and p value to determine whether to reject the null hypothesis that the incidence of pertussis was randomly distributed in space.[17] A positive value of Moran's I indicates a positive spatial autocorrelation in the incidence of pertussis in Hunan Province, and a negative value indicates a negative spatial autocorrelation. A value of 0 indicates a random spatial distribution of pertussis and that there was no spatial autocorrelation.

The local indicators of the spatial autocorrelation map were used to assess the local cluster of pertussis incidence in Hunan Province. The LISA map was divided into four spatial cluster patterns, namely high-high, low-low, high-low and low-high.[18 19] High-high patterns indicated that areas with a high incidence of pertussis were surrounded by areas with a high incidence of pertussis. Low-low patterns indicated that areas with a low incidence of pertussis were surrounded by areas with a low incidence of pertussis. High-low patterns indicated that areas with a high incidence of pertussis were surrounded by areas with a low incidence of pertussis, and low-high patterns indicated that areas with a low incidence of pertussis were surrounded by areas with a high incidence of pertussis.

Scan statistics

In this study, the scan statistics proposed by Kulldorff were used to detect the clusters of pertussis in Hunan Province purely in space and in specific space-time.[20 21] According to the data distribution type of this study, the discrete Poisson model was selected for calculation. The month of the report for pertussis cases in each county and the projected total population for each county each year were used to construct the Poisson model. Three tests were prepared for use in SaTScan V.9.6 software as follows: a case file representing the month of the report for pertussis cases in each county from January 2009 to December 2019; a coordinate file representing the geographical coordinates of each county; and a population file representing the projected total population for each county each year from January 2009 to December 2019. Purely spatial cluster analysis did not consider time, and an operator with a circular scanning window was applied to find possible spatial clusters in the map. The scanning unit was 122 counties or urban districts in Hunan Province. Spatiotemporal cluster analysis was performed using time and space dimensions. The scan window was a cylinder whose bottom represented the geographical location, whereas the height of the cylinder represented the clustering time.[22] The scanning unit of space was 122 counties or urban districts in Hunan Province, while time was measured in months from January 2009 to December 2019. Studies have shown that when the scan window radius is less than 30%, the results are highly accurate and stable.[23 24] In this study, the maximum spatial cluster radius was set to 10%–30% of the total population, and the maximum temporal cluster radius was set to 50% of the study period in the time window according to previous research experience.[25] The results of the space radius and time radius setting with larger log-likelihood ratio (LLR) and relative risk (RR) values were selected as the final result. The LLR was calculated by the Monte Carlo stochastic method to determine the cluster. The scan window with the largest LLR value was the most likely cluster, and the rest of the scan windows with p<0.05 were the clusters at other levels according to the LLR value. The number of Monte Carlo simulations was set to the default value of 999, and the p value was obtained through the Monte Carlo hypothesis test. A smaller p value indicated a higher possibility of clustering in the area.[26]

Statistical software

SaTScan V.9.6 software was used for spatiotemporal scan analysis. ArcGIS V.10.3 software was used for spatial autocorrelation analysis, mapping and visualisation. The statistically significant level was set at 0.05.

RESULTS

Epidemiological characteristics

From 2009 to 2019, 6796 pertussis cases were reported in Hunan Province with no deaths (average annual incidence of 0.899/100 000). The characteristics of pertussis cases in Hunan Province from 2009 to 2019 are shown in table 1. The male-to-female ratio was 1.14:1, including 3617 females and 3179 males. The age group of ≤1 year old accounted for the largest proportion (60.83%).

Table 1 Demographic characteristics of patients with pertussis in Hunan Province, China, 2009–2019

Variables	Case number	Percentage
Sex		
Male	3617	53.22
Female	3179	46.78
Age (years)		
≤1	4134	60.83
1–<2	1144	16.83
2–<3	406	5.97
3–<4	289	4.25
4–<5	279	4.11
5–9	461	6.78
≥10	83	1.22
Occupation		
Scattered children	6104	89.82
Nursery children	432	6.36
Students	224	3.30
Other	36	0.53
Seasons		
Spring	1059	15.58
Summer	2072	30.49
Autumn	2673	39.33
Winter	992	14.60
Total	6796	100

The mainly affected population was scattered children (89.82%). Pertussis mainly occurred in summer and autumn, accounting for 69.82% (n=4745) of all reported cases. From 2009 to 2017, the incidence of pertussis in Hunan Province remained at a low level, and an outbreak of pertussis began to occur in 2018. The incidence rose from 0.088/100 000 in 2009 to 2.895/100 000 in 2018 and continued to rise significantly to 6.184/100 000 in 2019 (online supplemental figure 1).

Incidence maps
The annual incidence of pertussis from 2009 to 2019 at the county level in Hunan Province is shown in online supplemental figure 2. From 2009 to 2016, the incidence of pertussis in all Hunan Province counties remained at a low level, with an average annual incidence of 0.077/100 000. The areas with a relatively high incidence were Ziyang District and Heshan District in Yiyang City, which was located in the northeast of Hunan Province. In 2017, areas with a high incidence of pertussis began to expand from the northeast to the southwest of Hunan Province. An outbreak of pertussis began to occur in 2018. Almost all counties showed different degrees of incidence, and the incidence rate increased significantly compared with before 2018. Meanwhile, the geographical distribution became more diverse. The areas with the top 10 incidents

were Louxing District (15.724/100 000), Tongdao Dong Autonomous County (14.232/100 000), Beihu District (13.113/100 000), Suxian District (12.688/100 000), Hanshou County (8.551/100 000), Zhengxiang District (7.813/100 000), Shigu District (7.623/100 000), Longshan County (7.508/100 000), Jishou City (7.478/100 000) and Heshan District (7.441/100 000). The incidence of pertussis continued to rise significantly in 2019. Tongdao Dong Autonomous County (32.047/100 000), Longshan County (26.634/100 000), Louxing District (23.068/100 000) and Heshan District (22.784/100 000) remained as areas with high incidence of pertussis.

Spatial autocorrelation analysis
The results of global spatial autocorrelation analysis of pertussis incidence in Hunan Province from 2009 to 2019 are shown in online supplemental table 1. The Moran's I of each year was bigger than 0. Except for 2013, 2014 and 2016, the global spatial autocorrelation analysis of the pertussis incidence showed a significant global correlation (p<0.05) (online supplemental table 1). According to the yearly LISA cluster maps of the incidence of pertussis, 49 high-high clusters, 25 low-low clusters, 47 low-high clusters and 41 high-high clusters were detected by local autocorrelation analysis from 2009 to 2019. The high-high clustering areas were relatively concentrated. Except for 2013, the high-high clustering from 2009 to 2019 mainly occurred in Taojiang County, Heshan District and Ziyang District, Yiyang City (figure 2).

Purely spatial cluster analysis
Purely spatial scanning statistical data were used to detect the pertussis clusters in Hunan Province from 2009 to 2019. A total of seven possible spatial clusters were detected (listed in online supplemental table 2). The most likely clusters are mainly located in the central and northeastern parts of Hunan Province, including Tianxin District, Yuhua District, Louxing District and Heshan District (radius=73.75 km, LLR=207.00, RR=1.74, p<0.001). Other possible clusters were located in the western and southern areas of Hunan Province (figure 3). Purely spatial cluster analysis showed that pertussis cases were not randomly distributed in space from 2009 to 2019.

Spatiotemporal cluster analysis
Spatiotemporal scanning statistics were used to detect the spatiotemporal clusters of pertussis. The four possible pertussis spatiotemporal clusters discovered in Hunan Province from 2009 to 2019 are shown in online supplemental table 3 and figure 4. The most likely clusters were located in the central and northeastern parts of Hunan Province, including 26 counties, which included Tianxin District, Yuhua District, Louxing District and Heshan District, from March 2019 to September 2019. The secondary cluster (n=1), the second secondary cluster (n=1) and the third secondary cluster (n=2) were located in the northwest, central, and southeastern areas
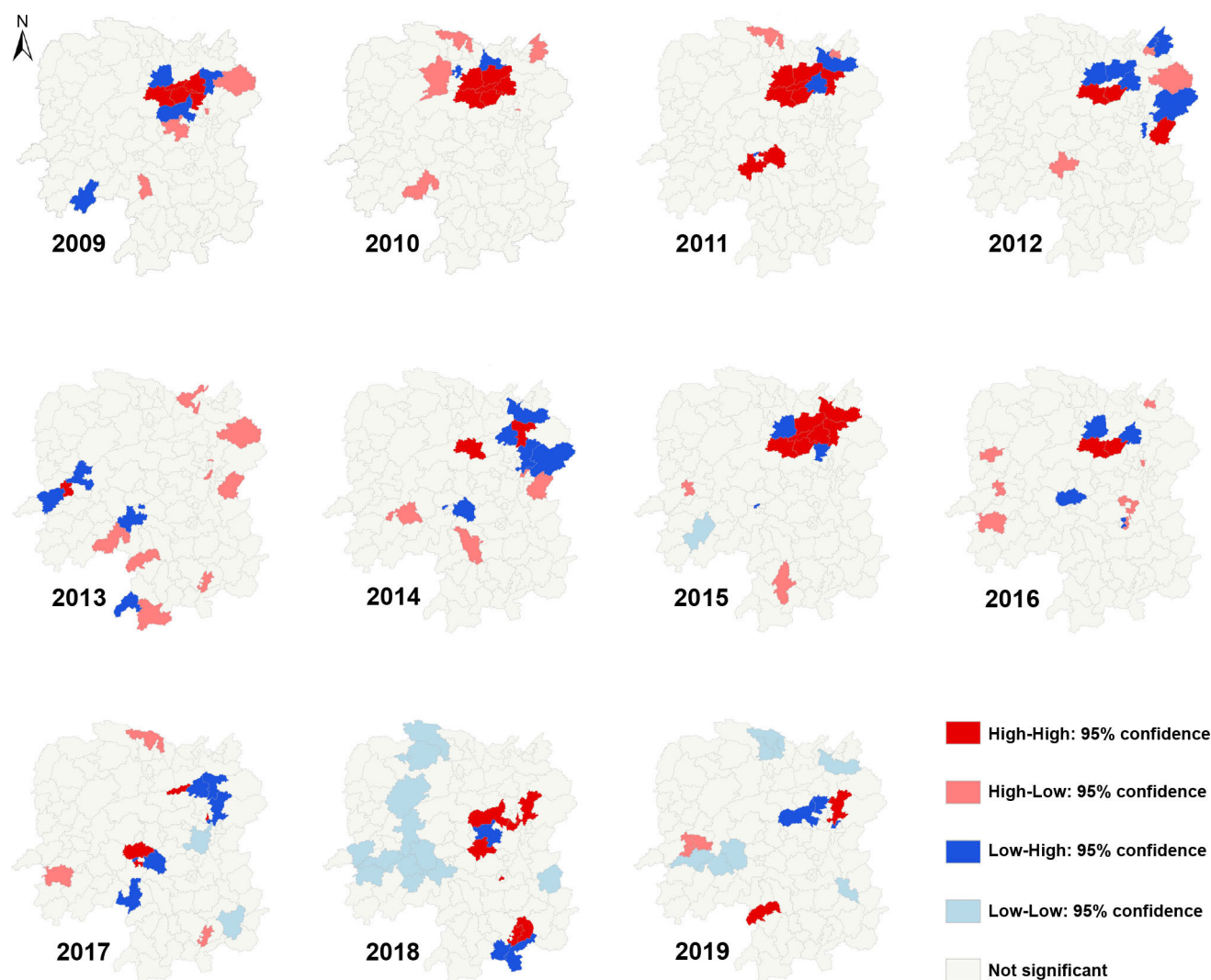
Figure 2 Yearly local indicators of spatial association cluster maps of pertussis incidence at the county level in Hunan Province, China, 2009–2019.

from March 2019 to October 2019, from April 2019 to September 2019, and from April 2018 to August 2019, respectively. In combination, 2018–2019 was the period with the highest incidence of pertussis, and the clustering time was from March to October.

DISCUSSION

This study investigated the epidemiological characteristics of pertussis and county-level spatial and spatiotemporal clusters in Hunan Province from 2009 to 2019. The results of the study verified the feasibility of spatial and spatiotemporal analysis methods in exploring the hot spots and spatiotemporal clusters of pertussis in Hunan and also provided health policymakers with reference data to develop measures for the prevention and control of epidemics.
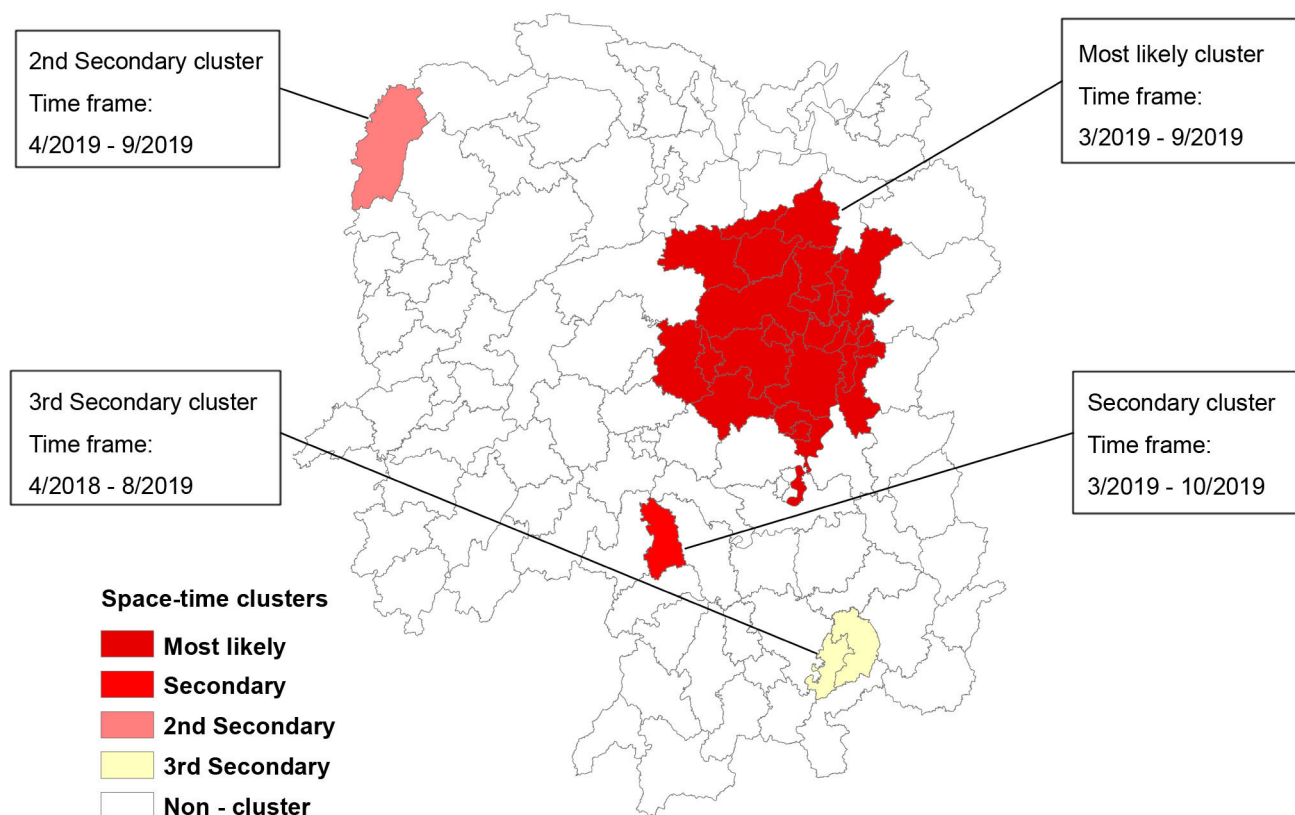
The incidence of pertussis in Hunan Province showed a downward trend from 2009 to 2013 and began to rise slowly in 2014, which was basically consistent with the trend of reported pertussis cases in China.[16 27] In 2018

and 2019, the incidence of pertussis in Hunan Province was much higher than in previous years. This increase in incidence may be related to the fact that Hunan Province began to replace diphtheria, tetanus and whole-cell pertussis vaccine (DTwP) with diphtheria, tetanus and acellular pertussis vaccine (DTaP) in 2009. According to the research results of Tartof *et al*, the immune protection time of DTaP is shorter than that of DTwP.[28] Another explanation could be that the 'recurrence of pertussis' in many world regions may have alerted clinicians to increase the clinical use of pertussis PCR.[29–31] The actual reasons remain to be studied.

Infants aged ≤1 year old accounted for 60.83% of the total cases. A study conducted in Italy also showed that infants aged <1 year had the highest frequency and rate of hospitalisation for pertussis.[32] Ning *et al* also pointed out that in China, approximately 70% of infants <1 year old have not reached the age of DTaP vaccination or have not completed basic immunisation.[16] The reported cases were mainly scattered children, and no increase in the
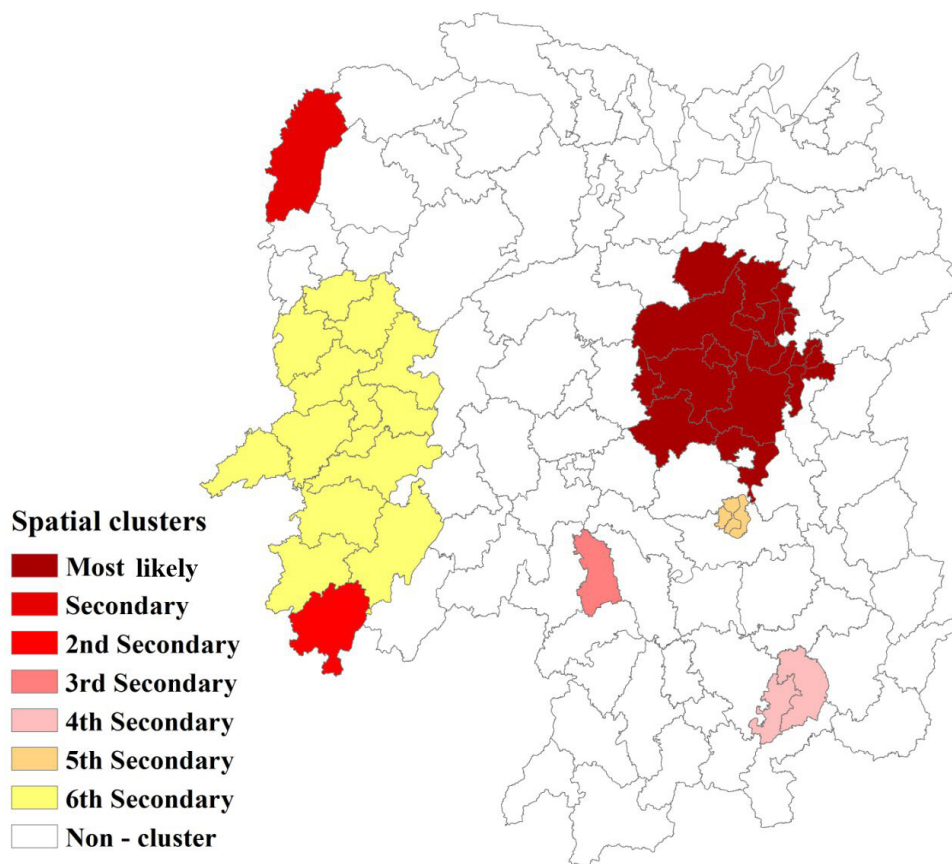
Figure 3 Spatial clusters of pertussis at the county level in Hunan Province, China, 2009–2019.

Figure 4 Spatiotemporal clusters of pertussis at the county level in Hunan Province, China, 2009–2019.

incidence of pertussis was observed in older children, adults and older subjects. This finding might be explained by the relatively better immune function in older age groups, insignificant symptoms after infection, and misdiagnosis or missed diagnosis. The highest number of cases occurred in summer and autumn (69.82%), but there may be differences in the time of high pertussis incidence in different areas. For example, autumn was the season with the highest incidence of pertussis in Guizhou Province,[33] while in Shenzhen, the highest incidence was noted in the summer,[34] indicating that the occurrence and spread of pertussis may be related to geographical and meteorological factors. Furthermore, research by Wang *et al* showed that monthly temperature, precipitation, air pressure and wind speed play an important role in the transmission of pertussis.[30]

The areas with the highest incidence of pertussis in Hunan Province were Changsha, Yiyang, Loudi and Xiangxi Tujia, and Miao Autonomous Prefecture. As the provincial capital, Changsha City has a large population density and frequent movement of people, making it prone to infectious disease outbreaks. The economic development level of Yiyang, Loudi and Xiangxi Tujia, and Miao Autonomous Prefecture is relatively low, and some counties and districts have relatively poor sanitary conditions, insufficient immunisation coverage, etc, which might be the reasons for the high incidence.

This study showed that since the outbreak of pertussis in 2018, its incidence increased significantly, and the geographical distribution became more diversified. Moreover, the incidence of pertussis in Hunan Province was not randomly distributed in space but had a certain spatial clustering. Forty-nine high-high clusters were detected in the LISA maps. These clusters were mainly located in Taojiang County, Heshan District and Ziyang District in Yiyang, northeastern Hunan Province, indicating that those areas were hot spots for pertussis. The most likely clusters determined by the purely spatial analysis were mainly located in Tianxin District, Yuhua District, Louxing District and Heshan District in the central and northeastern areas of Hunan Province. The results were similar but not equal to those of the local spatial autocorrelation analysis, and the analysis variables obtained by the two methods were different, which might have contributed to the differences. The years of the highest incidence of pertussis determined by spatiotemporal cluster analysis were 2018 and 2019, and the clustering time was from March to October. The most likely clusters were also located in the central and northeastern parts of Hunan Province, and the cluster time was from March to September 2019. High incidence and spatiotemporal clusters of pertussis in some areas have been reported in both developed and developing countries. For example, a study conducted in Iran by Alimohamadi *et al* suggested that the northern areas of that country have a high pertussis incidence and that the distribution of pertussis has a spatial pattern.[14] Similar results were obtained by Wi

et al in Olmsted County, Minnesota and by Munro *et al* in Lancashire and South Wales.[12 13]

Some limitations of this study should be acknowledged. First, the pertussis surveillance data were passive, and most of them were clinically diagnosed cases, with only 21.74% of cases having a laboratory-confirmed diagnosis. Therefore, the incidence of pertussis in Hunan Province was very likely underestimated. Second, due to the lack of relevant data, such as vaccination and environmental factors, we were unable to study the potential influence of coverage rate and identify the suitable population for the immunisation. Moreover, we could not perform a more sophisticated analysis of the potential factors related to the spatiotemporal distribution of pertussis and pertussis occurrence counts, such as community-level variables, environmental factors, population characteristics, the laboratory tests for pertussis diagnosis, the pertussis-related training of the clinical doctor and vaccination rates. Therefore, further research is necessary to identify relevant risk factors and determine local precise control measures. Third, scanning statistical analysis requires various model assumptions for the variation and distribution of spatiotemporal data. In practical applications, the assumed parameter data distribution is sometimes invalid. This is a limitation of spatial scan statistics. Some non-parametric statistical methods should be considered when detecting disease clusters in spatiotemporal data. Finally, spatiotemporal scans are useful for exploring spatial aggregation and highlighting areas of highest risk for a more accurate analysis, but it is worth noting that ecological bias is inevitable in any ecological study.

In summary, the distribution of pertussis epidemics in Hunan Province was temporary and spatially clustered. Pertussis epidemics mainly clustered in the central and northeastern regions of Hunan Province, and the cluster time was from March to October. The distribution of pertussis epidemic prevention and sanitation resources should be adjusted in combination with the temporal and spatial distribution characteristics of pertussis, and key epidemic prevention scopes should be divided accordingly to take targeted preventive measures.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics Committee of Hunan Provincial Center for Disease Control and Prevention waived the requirement of obtaining ethical approval due to the retrospective nature of the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study were available from the Chinese Information System for Disease Control and Prevention but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the Hunan Provincial Center for Disease Control and Prevention.

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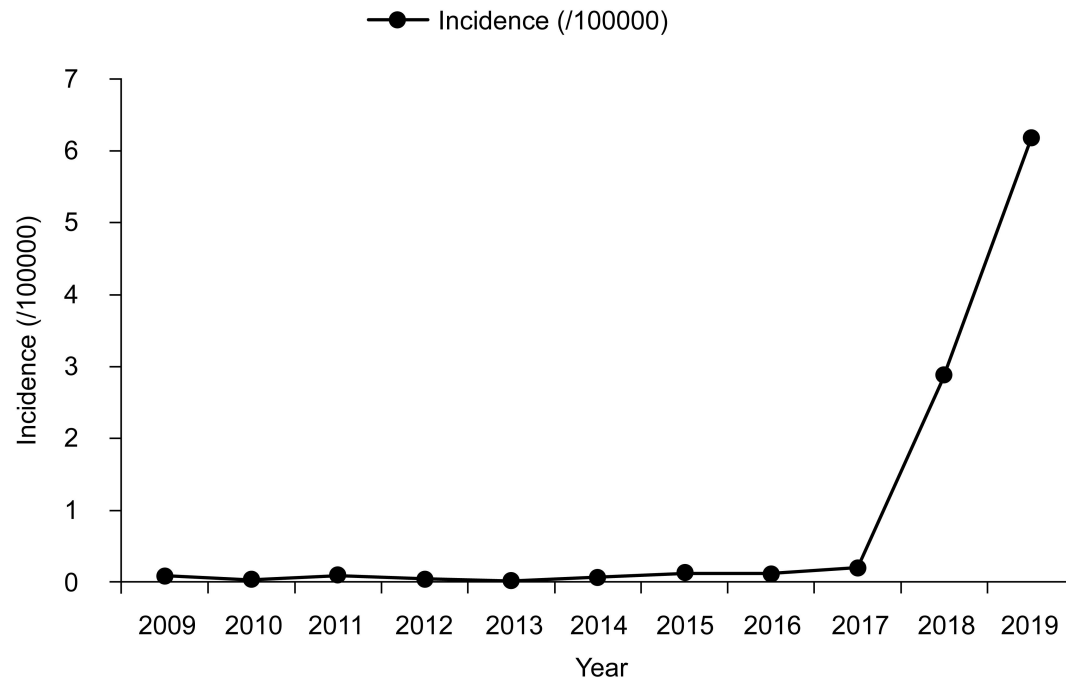
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SUPPLEMENTARY MATERIAL

Supplementary Figure 1. Annual incidence rate of pertussis in Hunan Province, China, 2009–2019.
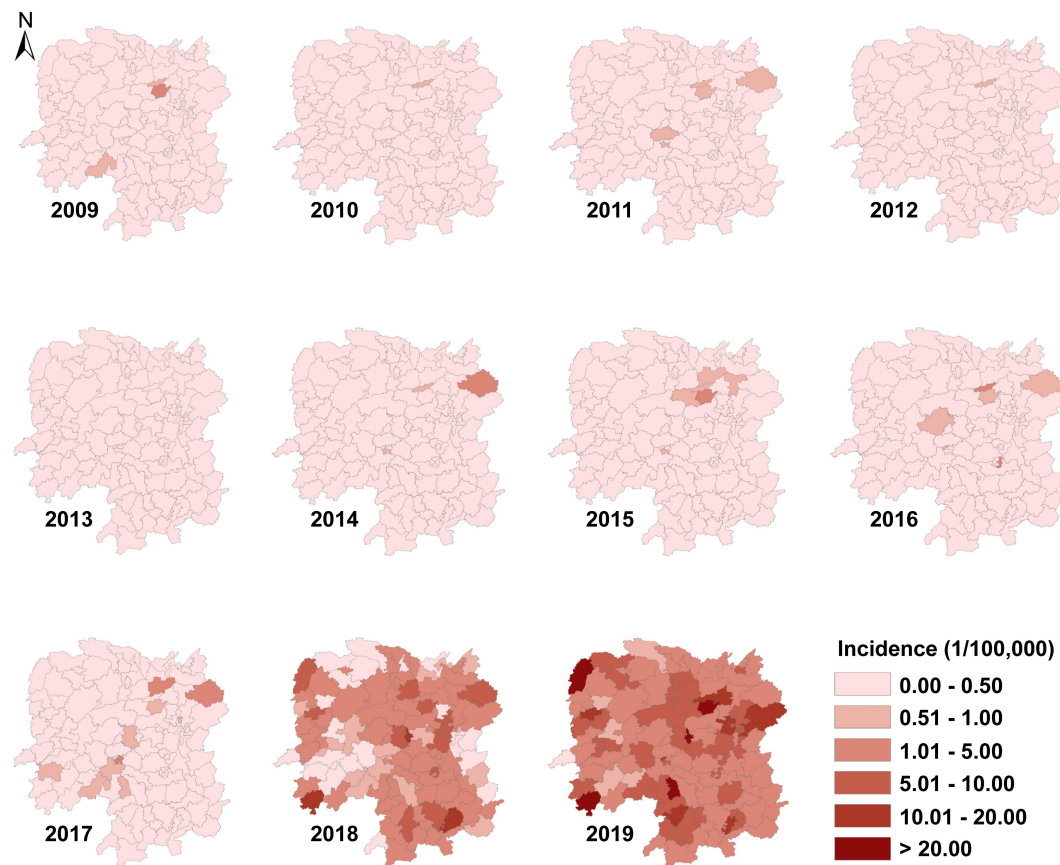
Supplementary Figure 2. Annual incidence of pertussis at county level in Hunan Province, China, 2009–2019.

Supplementary Table 1. Global spatial autocorrelation analysis of pertussis incidence in

Hunan Province, China, 2009–2019.

Year	Moran's I	Z-Score	P-Value
2009	0.189	3.928	<0.001
2010	0.341	7.021	<0.001
2011	0.207	4.134	<0.001
2012	0.122	2.860	0.004
2013	0.013	0.401	0.688
2014	0.058	1.317	0.188
2015	0.302	5.931	<0.001
2016	0.016	0.501	0.617
2017	0.128	2.571	0.010
2018	0.198	3.866	<0.001
2019	0.107	2.169	0.030

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Supplementary Table 2. The clusters of pertussis cases detected by using the purely

spatial scan statistics

Cluster type	Counties (n)	Radius (km)	Observed cases	Expected cases	*LLR*	*RR*	*P*
Most likely	20	73.75	2,151	1,431.45	207.00	1.74	<0.001
Secondary	1	0	167	47.23	92.23	3.60	<0.001
2nd Secondary	1	0	98	17.42	89.16	5.69	<0.001
3rd Secondary	1	0	173	59.20	72.68	2.97	<0.001
4th Secondary	2	24.93	212	90.80	59.66	2.38	<0.001
5th Secondary	4	12.63	151	96.28	13.46	1.58	<0.001
6th Secondary	13	102.83	318	245.60	10.16	1.31	0.003

LLR, larger log likelihood ratio; RR, relative risk

Supplementary Table 3. Clusters of pertussis cases detected by spatial-temporal scan

statistics

Cluster type	Time frame	Radius (km)	Cluster areas (n)	Observed	Expected	*LLR*	*RR*	*P*
Most likely	2019/03-2019/09	91.45	26	1422	531.76	574.97	3.12	<0.001
Secondary	2019/03-2019/10	0	1	129	20.32	130.60	6.45	<0.001
2nd Secondary	2019/04-2019/09	0	1	100	13.79	112.48	7.35	<0.001
3rd Secondary	2018/04/-2019/08	24.93	2	190	69.54	71.59	2.78	<0.001

LLR, larger log likelihood ratio; RR, relative risk