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RESEARCH

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The spatial-temporal distribution of hepatitis B virus infection in China,2006–2018

Liping Jiao[1], Tuo Shen[1*], Yingzi Han[1], Wen Liu[2], Wei Liu[1], Lin Dang[1], Mingmin Wei[1], Yunyun Yang[1], Jingjing Guo[1], Meirong Miao[1] and Xiangming Xu[1]

Abstract

Objectives Hepatitis B is a liver disease caused by Hepatitis B virus (HBV) infection and is highly prevalent in China. To better understand the epidemiological characteristics of hepatitis B in China and develop effective disease control strategies, we employed temporal and spatial statistical methods.

Methods We obtained HBV incidence data from the Public Health Science Data Center of the Chinese Center for Disease Control and Prevention for the years 2006 to 2018. Using Geographic Information System (GIS) and SaTScan scanning technology, we conducted spatial autocorrelation analysis and spatiotemporal scan analysis to create a map and visualize the distribution of hepatitis B incidence.

Results While hepatitis B incidence rebounded in 2011 and 2017, the overall incidence in China decreased.In the trend analysis by item, the incidence varies from high to low. The global spatial autocorrelation analysis revealed a clustered distribution, and the Moran index analysis of spatial autocorrelation within local regions identified five provinces as H-H clusters (hot spots), while one province was an L-L cluster (cold spot). Spatial scan analysis identified 11 significant spatial clusters.

Conclusions We found significant clustering in the spatial distribution of hepatitis B incidence and positive spatial correlation of hepatitis B incidence in China. We also identified high-risk times and regional clusters of hepatitis B incidence.

Keywords Geographic information system, Hepatitis B infection, Cluster, Time-spatial distribution, Spatial epidemiology, Moran's I

Background

Hepatitis B virus (HBV) infection is a major global public health challenge due to its high prevalence worldwide. HBV causes liver disease which can lead to serious complications such as fulminant hepatitis, cirrhosis, liver failure, hepatocellular carcinoma, and even death [1]. The virus can replicate indefinitely and infect liver cells, posing a significant risk to human health [2, 3]. Clinical manifestations of the disease include weakness, anorexia, nausea, abdominal distension, and pain in the liver area. Chronic liver disease, spider nodes, laminitis, splenomegaly, and abnormal or persistent liver function can

*Correspondence:
Tuo Shen
st2005shengke@163.com
[1]Laboratory Department, Weinan Center for Disease Control and Prevention, Weinan, Shaanxi, China
[2]Department of Biological Sciences, University of Alberta, Edmonton, Alberta, Canada

also accompany severe disease, which can be classified as mild, moderate, or severe depending on the clinical presentation.

HBV spreads through contact with blood and bodily fluids, and it is highly infectious, with the ability to survive for more than seven days in a stable external environment [4]. Chronic hepatitis B affects an estimated one in 12 people and the virus infects approximately 257 million people worldwide, with about 800,000 deaths annually due to cirrhosis and hepatocellular carcinoma [5]. HBV carriers are more likely to develop hepatocellular carcinoma (HCC) and end-stage liver disease, while patients with chronic hepatitis B (CHB) are more likely to develop cirrhosis and HCC, leading to approximately one million deaths each year [6, 7]. In 2016, the World Health Organization (WHO) set a goal to eliminate hepatitis B as a public health threat by 2030, aiming to reduce new cases of chronic infection by 95% and mortality by 65% [8].

Hepatitis B is the third communicable disease among cancers in China [9], with over 93 million people carrying the virus, of whom approximately 20 million have chronic hepatitis B [10]. HBV infection is responsible for 56% of hepatocellular carcinoma (HCC) [11], which is the major histologic type of primary liver cancer. More than half of the world's HCC incident and mortality occur in China [12], with an estimated annual number of cases and deaths from liver cancer for men and women being 360,000 and 350,000, respectively [13]. The Sustainable Development Goals (SDGs) prioritize combating hepatitis, waterborne diseases, and other infectious diseases, which are significant impediments to achieving the SDGs [14].

Serologic surveys conducted in 1979 and 1992 revealed that HBV was extremely common in China, with a hepatitis B surface antigen (HBsAg) prevalence of 10% [15]. The second national cross-sectional seroepidemiological hepatitis survey in China, conducted in 1992, revealed that the prevalence of hepatitis B surface antigen in people aged 1–59 years was 9.75%, indicating a large prevalence area for hepatitis B. According to the findings of this survey, an estimated 120 million Chinese people have HBsAg, 20 million have chronic viral hepatitis B, and nearly 300,000 die each year from HBV chronic infection [16].

Disease spread can vary significantly depending on time and location [17], making spatial and temporal distribution an important factor to consider when planning disease control measures for severe infectious disease outbreaks [18]. Epidemiological studies have shown that spatio-temporal analysis is critical for identifying trends in disease spread and determining the geographical distribution of infectious diseases [19]. To this end, researchers have utilized geographic information systems (GIS) to examine the spatio-temporal distribution of various infectious diseases, including H7N9 [18], cutaneous leishmaniasis [20], hepatitis B [21], and hepatitis C [22, 23].

This study utilised the spatial autocorrelation, spatial clustering, and spatiotemporal scanning functionalities of Geographic Information Systems (GIS) to gain a new perspective on the geographical distribution and temporal changes of hepatitis B in China. The spatio-temporal distribution of different types of hepatitis (A, B, C, E) in various regions of China has been examined in prior studies [23–29]. For instance, significant characteristics of spatio-temporal distribution in hepatitis incidence have been unveiled through the application of descriptive epidemiology, spatial autocorrelation analysis, and spatio-temporal scan statistics [24, 26, 28]. The INLA method was utilized to incorporate spatio-temporal models and reveal noteworthy features of spatio-temporal distribution in hepatitis B within Xinjiang [27]. Spatio-temporal epidemiological methods were employed to identify clustering patterns and dynamic changes in HCV genotype distribution in Shanghai. This indicates that the composition of different transmission routes for HCV infection is constantly evolving [23, 29]. Furthermore, a study investigated the spatio-temporal changes and spatial drivers influencing hepatitis-related mortality across 183 countries [25].

However, prior to this research, no systematic and comprehensive GIS study had been conducted to assess the incidence rate of hepatitis B in China. Therefore, our study fills this research gap by offering a new viewpoint for gaining deeper insights into the spatiotemporal distribution of hepatitis B in China.

This research collected data on the incidence rate of hepatitis B in China from 2006 to 2018. GIS technology was used for spatial autocorrelation analysis and spatiotemporal scanning analysis to examine the spatiotemporal distribution characteristics of hepatitis B across different provinces in China. Spatial autocorrelation analysis was used to identify hotspot areas for hepatitis B, while spatiotemporal scanning analysis revealed transmission trends and patterns at various times and locations. This research contributes to a deeper understanding of the geographical epidemiological characteristics of hepatitis B and provides a scientific foundation for developing targeted prevention and control strategies.

Materials and methods

Data collection of Hepatitis B

Data Collection for Hepatitis B: We collected data on hepatitis B infectious diseases from the Public Health Science Data Center [30], which is published by the Chinese Center for Disease Control and Prevention's Information System, for the period from 2006 to 2018. This database has been collecting hepatitis B data from all 31 provinces (excluding Hong Kong, Macau, and Taiwan) since 2005. The data includes case numbers, deaths, incidence, and mortality. All cases of hepatitis B infectious diseases were identified using the diagnostic criteria and management principles for notifiable infectious diseases of the National Health Commission of the People's Republic of China. We obtained the provincial population data from the China Statistical Yearbook of the China National Bureau of Statistics for the same period. To calculate the incidence of hepatitis B, we used the number of hepatitis B cases and the total population in each province as the numerator and denominator, respectively. We created a comprehensive spatial analysis database by linking and matching the hepatitis B incidence data with the national vector map (1:1,000,000) using the serial number in the attribute database.

Trend analysis of different project segments

We divided the analysis points into five categories: the number of provinces with incidence rates greater than 100/100,000 per year, the season, the age group, the geographical area, and the dynamics of hepatitis B case development, which we used to show the trend of hepatitis B changes from 2006 to 2018. We counted and plotted the incidence rate of hepatitis B for each year, as well as the number of provinces with incidence rates greater than 100/100,000 in the current year, to observe the trend over time. We used seasonal analysis to statistically analyze the hepatitis B incidence by dividing it into four seasons (spring, summer, autumn, and winter). We divided the population into four groups for age group analysis, based on the WHO age classification criteria: adolescents (0–19), youth (19–45), middle-aged (46–59), and the elderly (60+), and investigated the incidence of hepatitis B in each group. Geographic regional analysis was carried out by dividing China into seven regions: North China, South China, Central China, East China, Northwest China, Southwest China, and Northeast China, and analyzing the change in the hepatitis B incidence rate in each. We examined the dynamics of hepatitis B case development from 2006 to 2018 based on absolute growth, development rate, and growth rate. Finally, we subdivided each group into corresponding components for synthetic statistical analysis using Excel to observe overall incidence trends and dynamics from 2006 to 2018 [31–36].(Annual Absolute increment = Current period incidence cases — Previous period incidence cases; Cumulative absolute increment = Current period incidence cases — Base period incidence cases; Fixed-base development Speed = Current period incidence cases ÷ Base period incidence cases × 100%; Link-Relative development Speed = Current period incidence cases ÷ Base period incidence cases× 100%; Fixed-period increase Velocity = Fixed-base development Speed — 1; Link-Relative increase Velocity = Link-Relative development Speed — 1).

Spatial autocorrelation analysis

We calculated the annual incidence of hepatitis B in China from 2006 to 2018 using spatial autocorrelation analysis and geographic information system localization. To create a spatial weight matrix, we used the spatial conceptualization approach based on inverse distance, which takes into account the geographically adjacent relationships between China's province administrative regions. We employed ArcGIS 10.2 software to determine both the global and local Moran's I indices based on the specified weight matrix [37]. The global Moran's I assesses the overall spatial autocorrelation and spatial distribution of the research objects, while the local Moran's I describes the spatial autocorrelation and clustering areas in local areas. The global Moran's I shows the overall level of clustering and the distribution of hepatitis B, while the local Moran's I specifies the specific clustering regions and categories of hepatitis B, as well as the hotspot analysis of hepatitis B [38]. Moran's I statistic is a commonly used spatial autocorrelation statistic, with values ranging from −1 to 1. A value of $I > 0$ indicates positive correlation, and the higher the value, the stronger the correlation of the spatial distribution, that is, the more evident the phenomenon of spatial clustering. A value of $I < 0$ indicates negative correlation, and the lower the value, the weaker the correlation. When I tends to 0, this means that the spatial distribution exhibits a random distribution [39].

Spatial clustering analysis

Moran's I is typically assessed using the Z-score test statistics, where differences with $P < 0.05$ are considered statistically significant. Local Moran's I avoids the drawback of global spatial autocorrelation by analyzing the spatial autocorrelation of some of the features within a local area. We classified the local Moran's I clustering results into four categories: high-high, high-low, low-high, and low-low clustering. High-high clustering (HH) indicates that the high-incidence area is surrounded by other high-incidence areas and is a hotspot; high-low clustering (HL) indicates that the high-incidence area is surrounded by low-incidence areas; low-high clustering (LH) indicates that the low-incidence area is surrounded by high-incidence areas; and low-low clustering (LL) indicates that the low-incidence area is surrounded by other low-incidence areas. We identified spatial clusters of hepatitis B by detecting where high-prevalence areas bordered other high-prevalence areas (H-H) and where high-prevalence areas bordered low-prevalence areas (H-L).

This paper investigates the incidence of hepatitis B from 2006 to 2018 and analyzes the time trend of this infectious disease. Kulldorff spatial scanning statistical analysis software SaTScan 9.6 was used to perform clustering analysis [40, 41]. SaTScan calculates circular windows of varying sizes and locations to identify high-risk and low-risk areas for hepatitis B clusters in China. We analyze the log-likelihood ratio (LLR) of the inner and outer spatial unit attributes of different window regions and use Poisson distribution for statistical analysis. We then arrange the LLR values of scanned circular windows by size, with larger values indicating statistically significant differences, which suggests the regions contained in this window can identify the most important hepatitis B clusters. The method of arranging LLR values in order of size can identify different levels of clusters, ranging from important to unimportant, which are classified as first, second, third, and so on. In this paper, we use the Monte Carlo method for log-likelihood ratio testing, with 999 tests, a 1-year temporal clustering interval, and a significance level of 0.05. We set the maximum spatial cluster size for the high-risk population in this study at 50% [42].

We also use ArcGIS 10.2 software to visualize the spatial distribution of hepatitis B incidence in provincial areas of China from 2008 to 2018. We classify similar incidence rates and use the natural segmentation method in ArcMap to divide the hepatitis B incidence in each province in ArcGIS 10.2 software. We mark the incidence rate using the method of grade division, with a dark color system indicating a high incidence rate and a light color system indicating a low incidence rate.

Results

The distribution and temporal trends of HBV cases

Between 2006 and 2018, there was a gradual decrease in the reported annual incidence of hepatitis B in China. The number of provinces with incidence rates greater than 100/100,000 decreased from 13 in 2006 to a minimum of 7 between 2014 and 2016. There was a peak in the number of cases in 2009 and a trough in 2015. Although the incidence of hepatitis B rebounded in 2011 and 2017, the overall trend was downward.(Fig. 1B). The cumulative analysis of the number of hepatitis B cases nationwide found that, Guangdong Province had the highest number of reported hepatitis B cases (1,748,392 people), followed by Henan Province (1,459,351 people), Hubei Province (858,795 people), Hebei Province (725,426 people), and Sichuan Province (695,962 people)

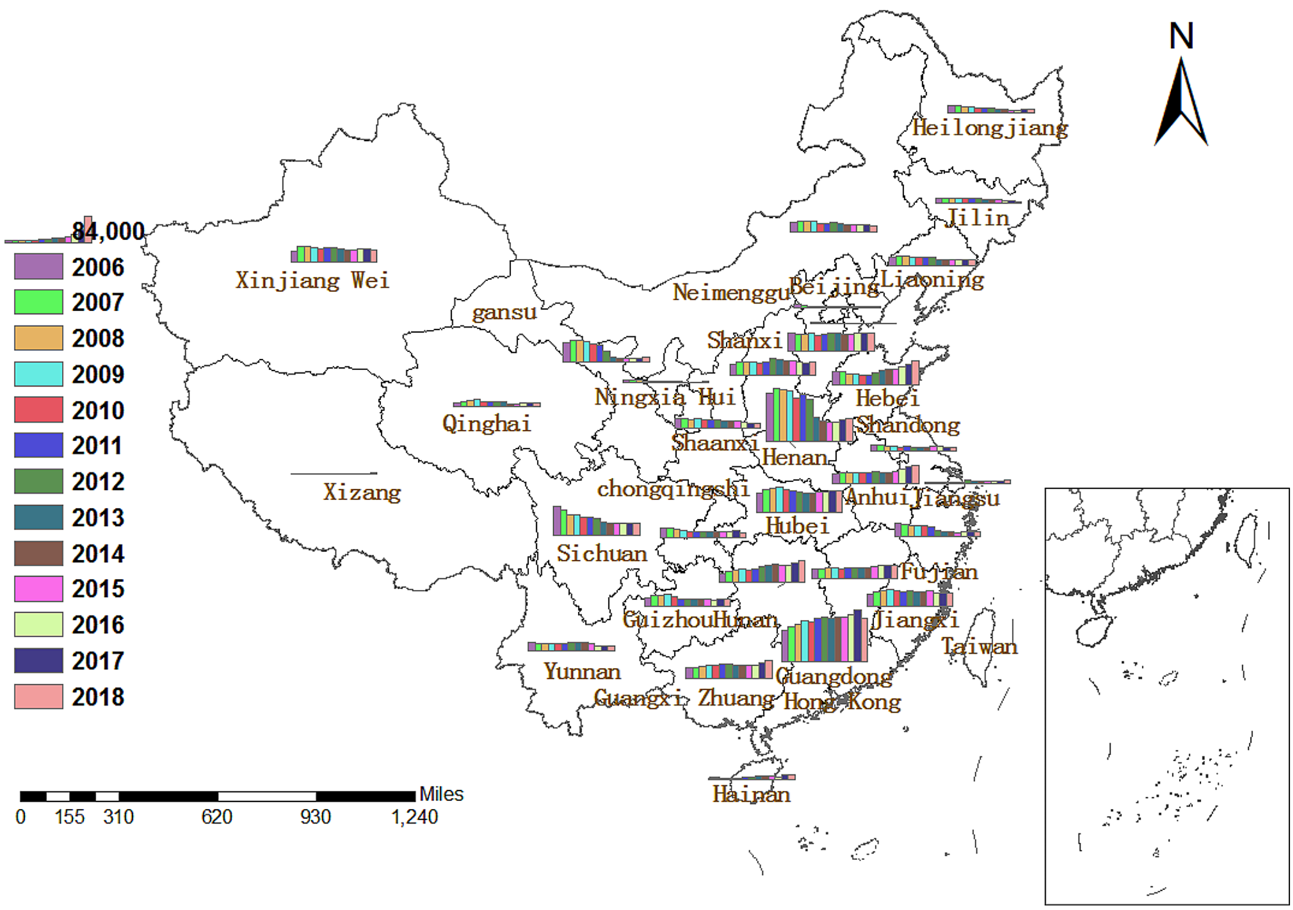

Fig. 1A Number of reported cases of hepatitis B by province, 2006–2018

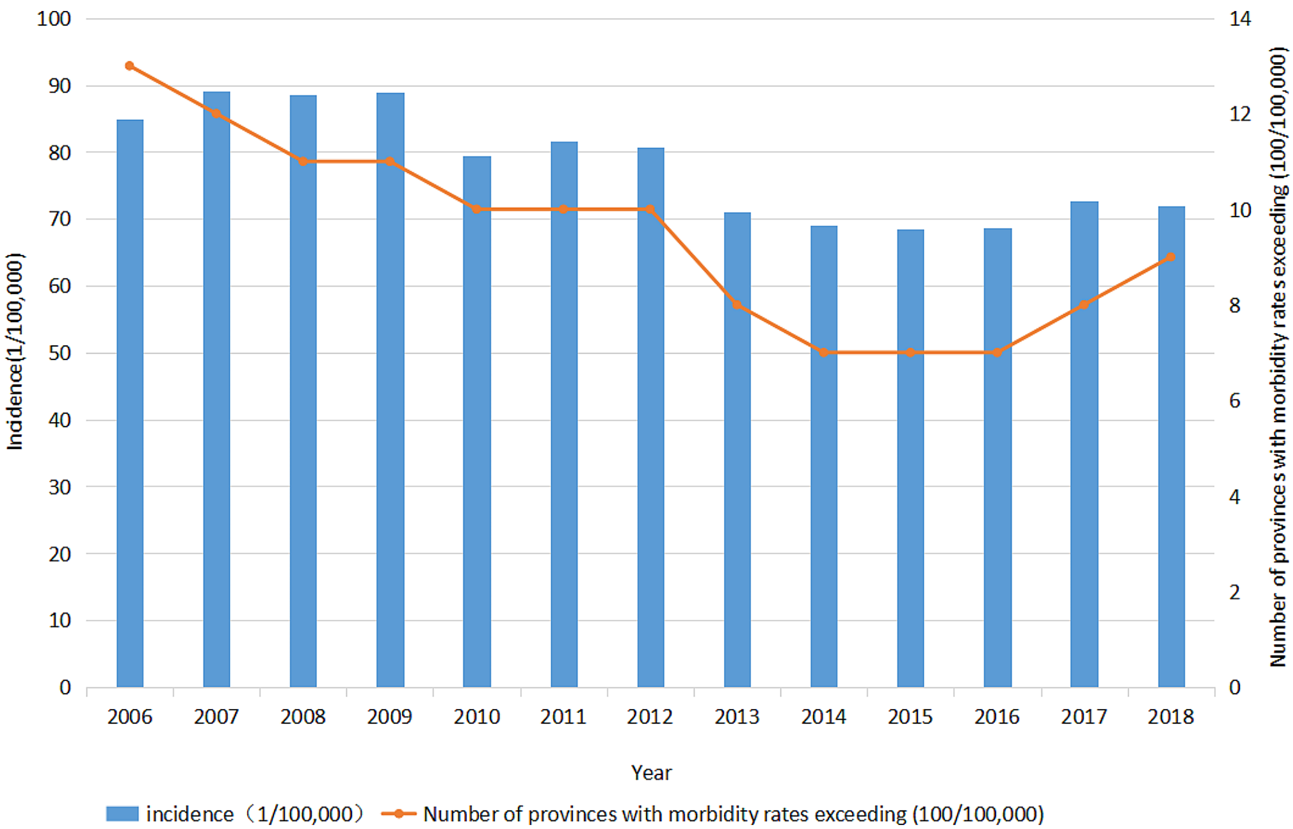

Fig. 1B Number of provinces with more than 100/100,000 hepatitis B prevalence and hepatitis B incidence rates per 100,000 habitants reported in China during 2006–2018 period. The plotted points correspond to incidence rates and the lines consist in short term trends

Table 1 2006–2018 developments in the number of hepatitis B cases

Year	Cases	Absolute increment		Speed of development(100%)		Velocity of increase(100%)	
		Cumulative increment	Annual increment	Fixed Base	Link-Relative	Fixed Base	Link-Relative
2006	1,109,130	-	-	-	-	-	-
2007	1,169,946	60,816	60,816	105.48	105.48	5.48	5.48
2008	1,169,569	60,439	-377	105.45	99.97	5.45	-0.03
2009	1,179,607	70,477	10,038	106.35	100.86	6.35	0.86
2010	1,060,582	-48,548	-119,025	95.62	89.91	-4.38	-10.09
2011	1,093,335	-15,795	32,753	98.58	103.09	-1.42	3.09
2012	1,087,086	-22,044	-6249	98.01	99.43	-1.99	-0.57
2013	962,974	-139,907	-124,112	86.82	88.58	-13.18	-11.42
2014	935,702	-54,403	-27,272	84.36	97.17	-15.64	-2.83
2015	934,215	-174,915	-1487	84.23	99.84	-15.77	-0.16
2016	942,268	-166,862	8053	84.96	100.86	-15.04	0.86
2017	1,001,952	-107,178	59,684	90.34	106.33	-9.66	6.33
2018	999,985	-109,145	-1967	90.16	99.80	-9.84	-0.20

(Fig. 1A). In 2006, there were 1,109,130 reported cases of hepatitis B in China, and in 2018, there were 999,985 reported cases, indicating a 10.91% decrease in the number of cases over a 13-year period. The average incidence rate was 73.07 cases per 100,000 population (Table 1). The overall development of reported cases of hepatitis B followed a downward trend, with the average rate of development was 99.14% and the average growth rate of -0.86% between 2006 and 2018. Although the growth rate fluctuated between years, ranging from − 11.42 to 6.33%, it remained generally downward.

From 2006 to 2018, spring was the season with the highest incidence of hepatitis B, except in 2006(Fig. 2A1). Except for 2006, summer is the second highest incidence of hepatitis B(Fig. 2A3).The lowest incidence occurred in the fall or winter, with the lowest incidence

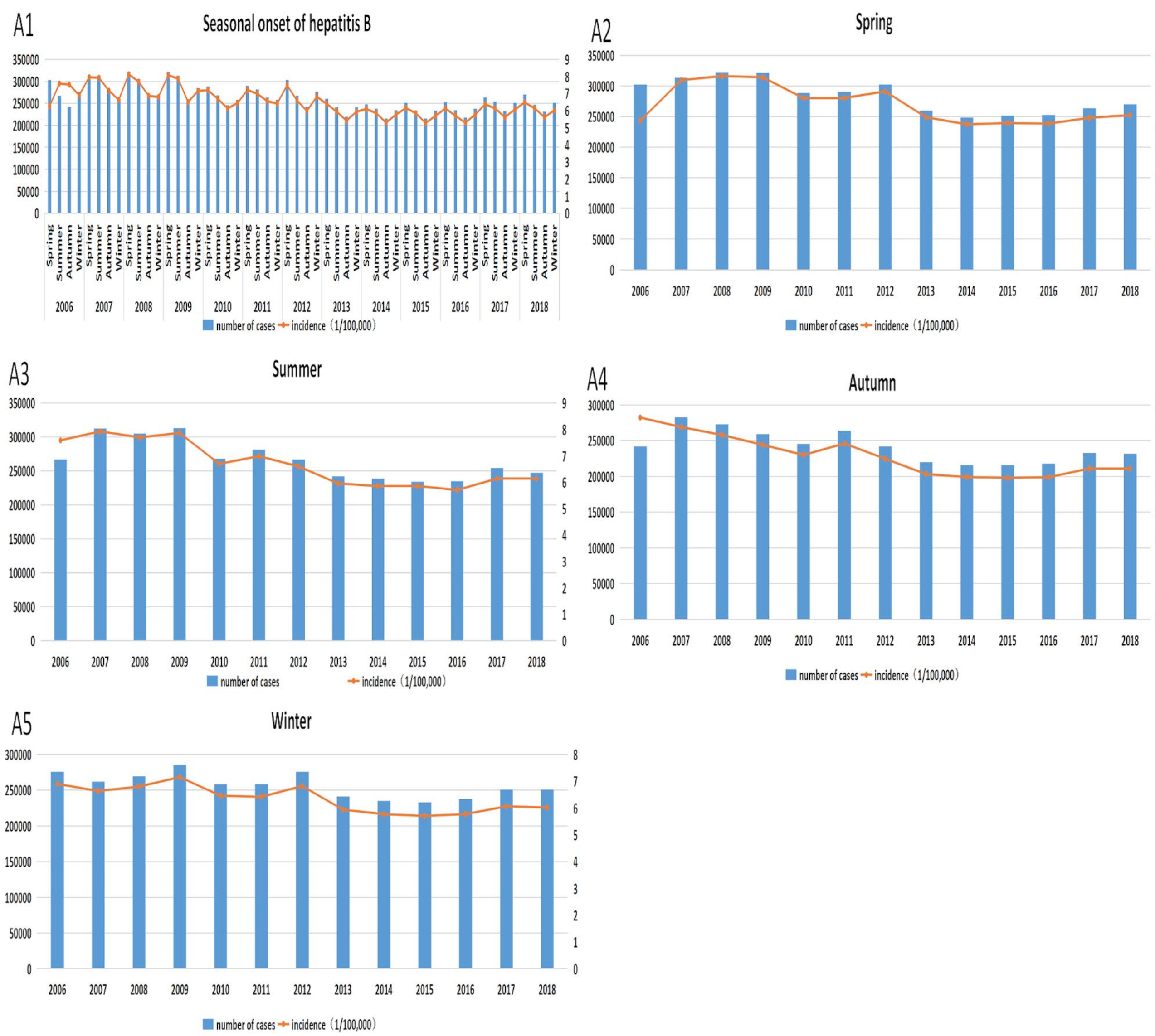

Fig. 2A Analysis of the incidence of hepatitis B by season from 2006 to 2018

in the fall of 2015 at 5.28/100,000 (Fig. 2A4). The lowest incidence of hepatitis B in winter is 5.70/100,000 in 2015(Fig. 2A5).The highest incidence in the spring was in 2008 at 8.13/100,000 (Fig. 2A2). The youth group had the highest incidence rate before 2011, while the midlife group had the highest incidence rate after 2011(Fig. 2B1). In 2018, the teenager group had the lowest incidence rate at 4.47/100,000 (Fig. 2B2), and the group of youth had the highest incidence rate in 2007 at 127.36/100,000 (Fig. 2B3). There was an overall increasing trend in the number of incidences in the midlife and senium groups, with the lowest incidence in these two groups at 2015, with 74.67/100,000 in the midlife group (Fig. 2B4) and 45.11/100,000 in the senium group (Fig. 2B5).Before 2013, Northwest China had the highest prevalence while South China had the highest prevalence after 2013 (Fig. 2C1). The regions with the lowest prevalence were East and Southwest China before 2012 and Northeast China after 2013 (Fig. 2C1). The highest incidence rate of 212.02/100,000 occurred in Northwest China in 2009, and the lowest rate of 33.11/100,000 people occurred in the Northeast in 2016 (Fig. 2C1).Overall, the incidence of hepatitis B in North China (Fig. 2C2), Central China (Fig. 2C4), Southwest China (Fig. 2C6),Northwest China (Fig. 2C7), and Northeast China (Fig. 2C8)showed an overall decreasing trend during 2006–2018, however, South China (Fig. 2C5) and East China (Fig. 2C3)showed an overall increasing trend.

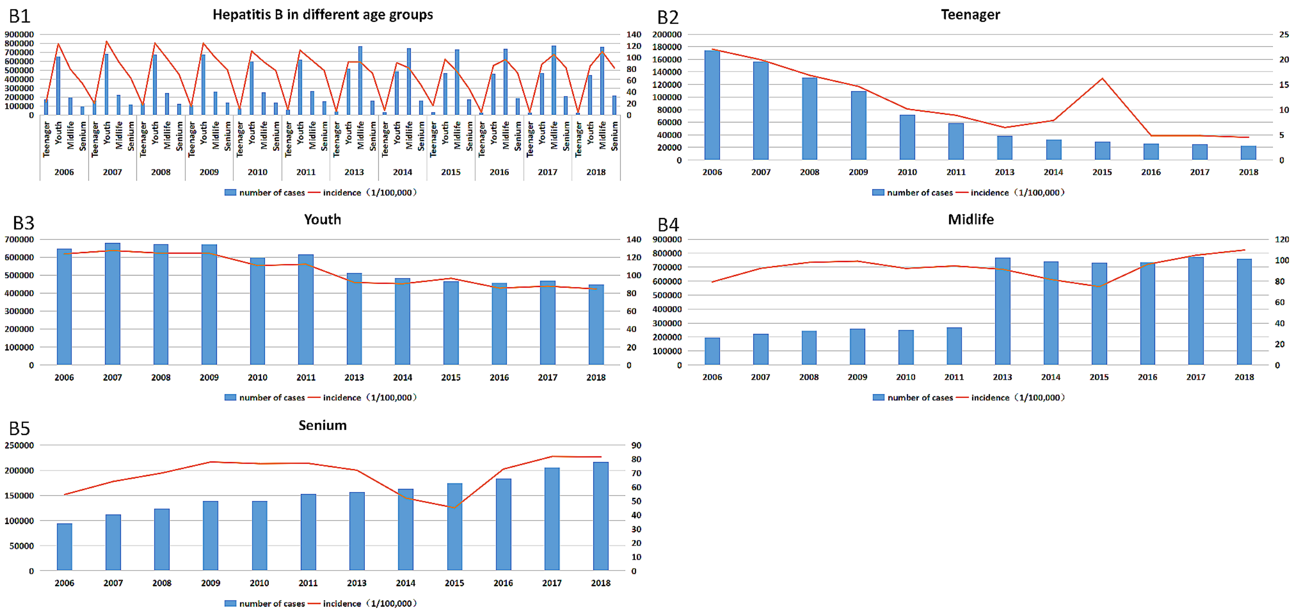

Fig. 2B Analysis of the incidence of hepatitis B by age group from 2006 to 2018

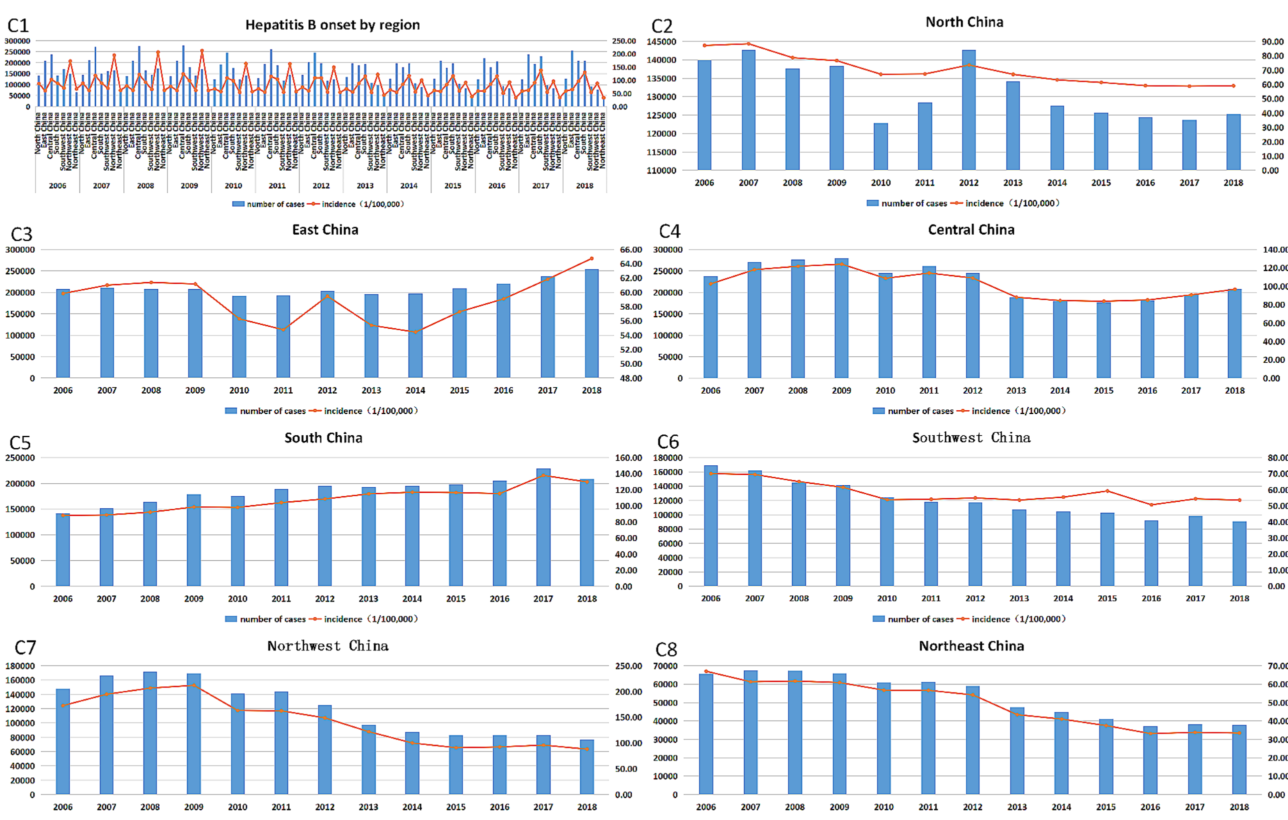

Fig. 2C Analysis of the incidence of hepatitis B by geographic region from 2006 to 2018

Spatial autocorrelation analysis

Based on the results of the global spatial autocorrelation analysis, the incidence of hepatitis B decreased from 84.824/100,000 in 2006 to 71.988/100,000 in 2018. Although the hepatitis B. incidence rate increased between 2011 and 2017, the overall incidence rate decreased. The Moran index ranged from 0.180 to 0.349 for the mean incidence of hepatitis B. This result showed that it was statistically significant in all years except for 2011 when $P > 0.05$, indicating a significant spatial correlation of hepatitis B cases. (Table 2)

The local spatial autocorrelation analysis revealed that the distribution of hepatitis B incidence in the study area exhibited a clear clustering phenomenon, indicating that it was not random. Figure 3 illustrates the incidence of hepatitis B in different provinces from 2006 to 2018, divided into six tiers based on the severity of the incidence. Different colors indicate varying degrees of incidence, with darker colors indicating higher incidence. For example, the highest hepatitis B incidence rate was 267.44/100,000 in 2007, and the grade range was divided into six tiers from 0.01 to 267.44, namely 0.01–42.75, 42.75–59.48, 59.48–82.46, 82.46–126.9, 126.90-177.96, and 177.96-267.44. During the 13-year period from 2006 to 2018, Qinghai, Xinjiang, Gansu, Guangdong, Fujian, and Shanxi had the highest incidence rates, while Jiangsu, Beijing, Tianjin, Shanghai, and Tibet had the lowest incidence rates (Fig. 3).

Spatial clustering analysis

Figure 4 depicts the spatial clustering map of hepatitis B. The Moran index was used to examine spatial autocorrelation within local regions. Between 2006 and 2018, five H-H clustering areas (hot spots) were identified, namely Xinjiang, Qinghai, Gansu, Ningxia, and Guangdong, but no hot spot clustering area was identified in 2014. Jiangsu is the L-L clustering area (cold spot) that was discovered in 2006, 2011, 2012, and 2014. Tibet was identified as an L-H cluster area for seven consecutive years from 2006 to 2012.

Spatio-temporal scan analysis

We employed spatio-temporal scanning analysis to investigate the likelihood of clusters, which were identified based on LLR values. The clusters were divided into the most probable cluster, sub-clusters 1 to 6, and cluster time. Between 2006 and 2018, the spatio-temporal scanning method detected 11 significant spatial clusters, including two most likely spatial clusters and eight sub-clusters. The results showed that Xinjiang and Henan were the most probable clusters with a time span of 2006–2011 and an RR value of 2.31 ($p < 0.001$). Gansu was the center of Sub-cluster 1, with a time span of 2006–2011 and an RR value of 2.97 ($p < 0.001$). Sub-cluster 2 was centered in Hubei and covered five provinces: Hubei, Shandong, Hunan, Fujian, and Guangdong. It had a time span of 2006–2011 and an RR value of 1.32 ($p < 0.001$). Sub-cluster 3 was centered in Shanxi, with a time span of 2010–2015 and an RR value of 1.68 ($p < 0.001$). Sub-cluster 4 was centered in Inner Mongolia, with a time span of 2006–2011 and an RR value of 1.61 ($p < 0.001$). Finally, Sub-cluster 5 was centered in Shaanxi, with a time span of 2006–2009 and had an RR value of 1.07 ($p < 0.001$) (Table 3; Fig. 5).

After conducting a spatial and temporal scan analysis of 31 provinces and autonomous regions in China, it was found that the most likely clusters in 2006–2011 were centered in Xinjiang and Henan provinces. Specifically, the most likely clusters were centered in Xinjiang 6 times with a cluster center at 23.73'N, 120.96'E and a cluster radius of 398.15 km. Within this range, the average annual incidence rate was 172.58/100,000. The most likely clusters in 2012 and 2017–2018 included eight provinces: Hunan, Hubei, Anhui, Fujian, Henan, Guangdong, Shandong, and Xinjiang. The most likely cluster was centered in Hunan three times with a cluster center located at 23.34'N, 113.36'E, and a cluster radius of 775.30 km. The average annual incidence within this range was 103.87/100,000. The most likely clusters from 2013 to 2016 were found in Guangdong and Hubei. The most likely cluster was centered in Guangdong four times with a cluster center at 19.18'N, 109.74'E and a cluster radius of 524.47 km. Within this range, the average annual incidence was 124.37/100,000. Typically, there are 8 to 12 clusters per year, with 1 to 8 provinces per cluster (Fig. 6A).The analysis classified Xinjiang, Gansu, and Qinghai as hotspot areas, areas with high disease incidence, while Jiangsu was classified as a coldspot area, an area with low disease incidence. The results of the local hotspot analysis revealed a total of four cold hotspot areas for the local autocorrelation of hepatitis B incidence nationwide (Fig. 6B).

Table 2 Incidence (cases/100,000) of Hepatitis B and its global spatial autocorrelation

Year	Incidence rate	Moran's I	Z	*P*-value
2006	84.824	0.254	2.432	0.015
2007	89.005	0.231	2.266	0.023
2008	88.517	0.237	2.314	0.021
2009	88.824	0.265	2.538	0.011
2010	79.460	0.232	2.265	0.024
2011	81.537	0.180	1.894	0.058
2012	80.683	0.273	2.686	0.007
2013	71.119	0.349	3.325	0.001
2014	69.047	0.298	2.939	0.003
2015	68.568	0.259	2.859	0.004
2016	68.739	0.329	3.251	0.001
2017	72.614	0.343	3.296	0.001
2018	71.988	0.328	3.145	0.002

Moran's I: Global Moran's I coefficient. ***Z***: Global Moran I statistics. ***P-value***: The *P*-value of the global Moran I statistics.

Discussion

Temporal and spatial epidemiological analysis has grown in importance over the years with the advancement of spatial statistics. However, few studies have conducted spatio-temporal analysis of hepatitis B samples. This study employs analytical techniques, such as ArcGIS

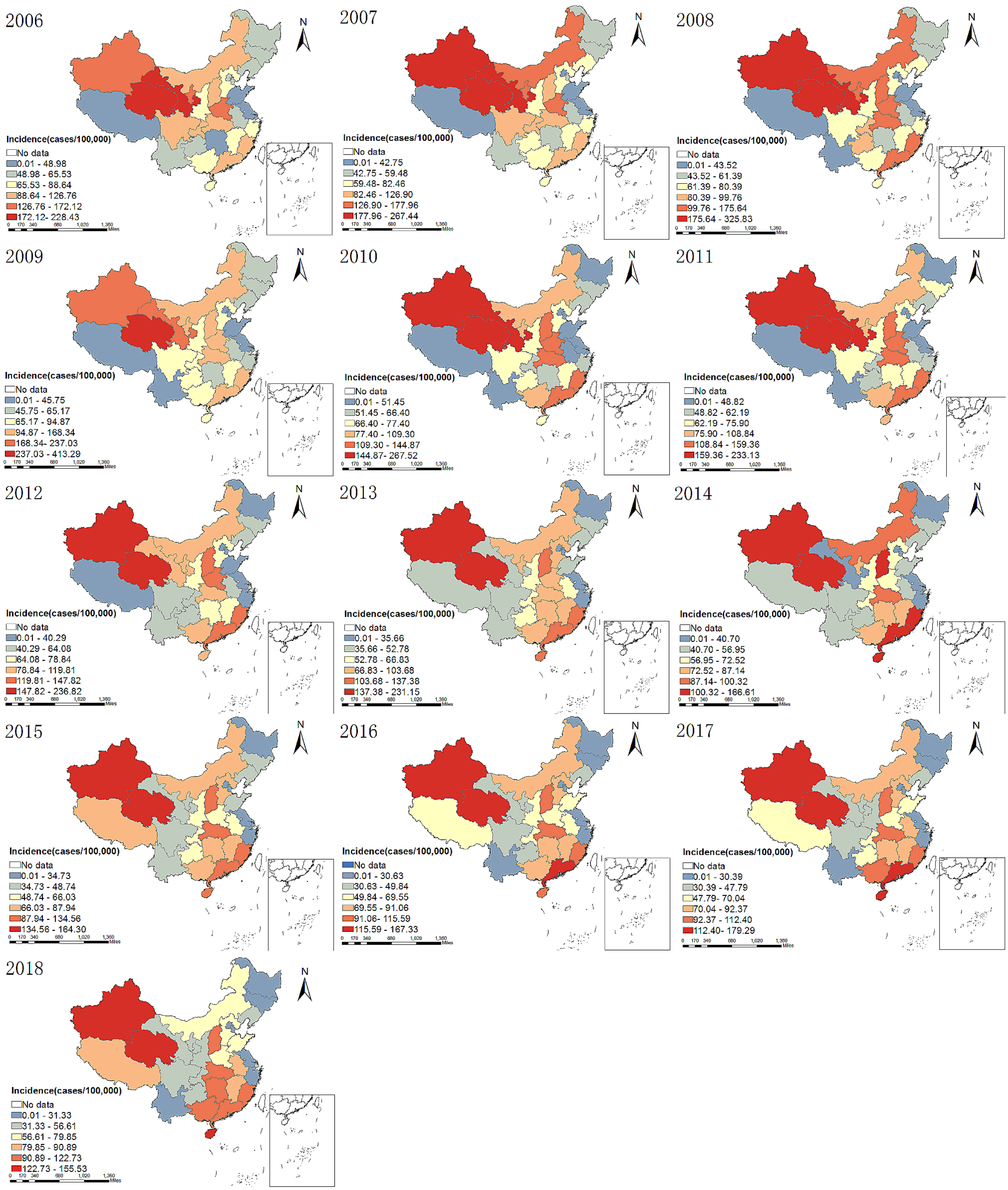

Fig. 3 Distribution of annual hepatitis B incidence rates in different provinces in China from 2006 to 2018

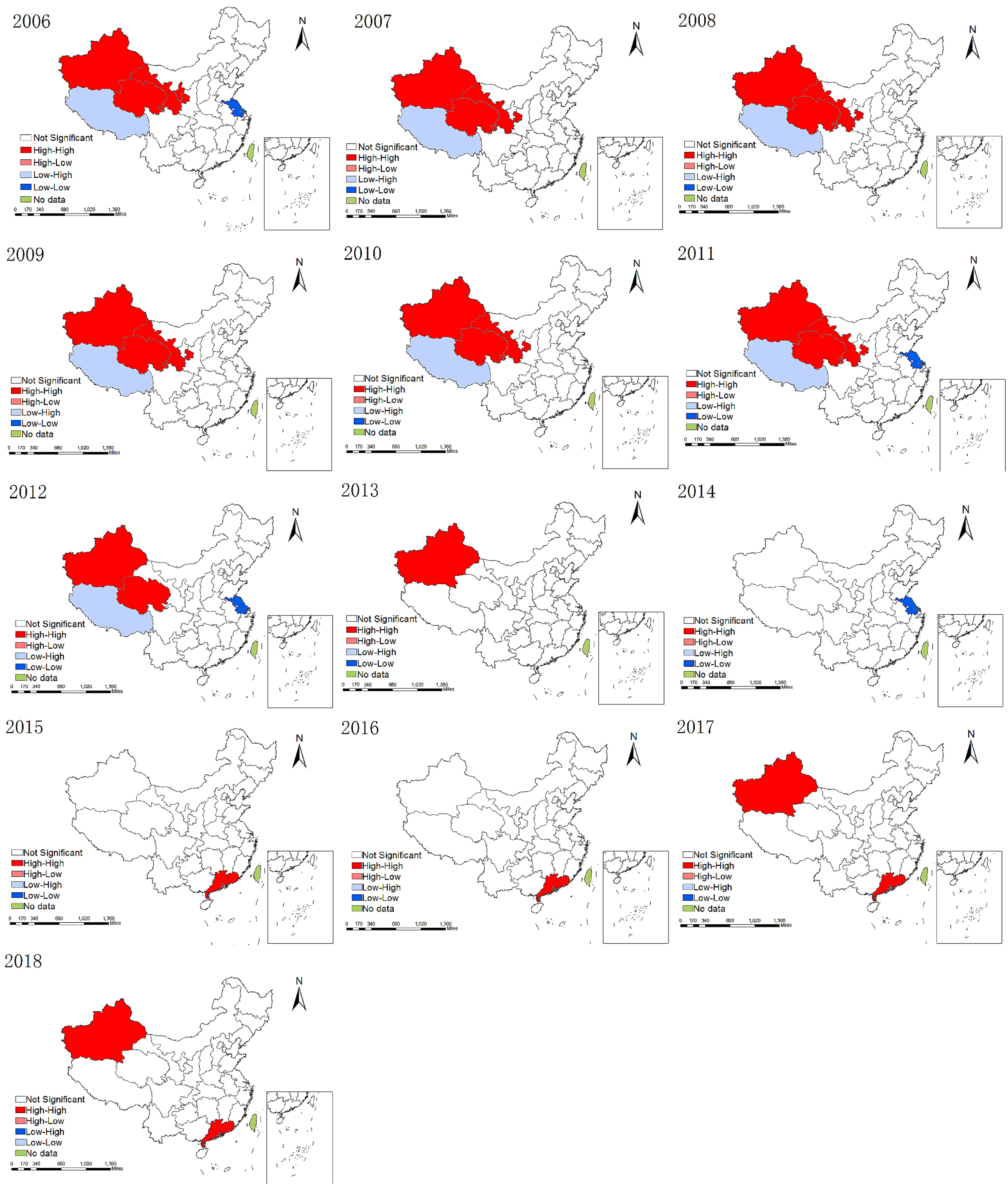

Fig. 4 Annual spatial clustering map for hepatitis B from 2006 to 2018

Table 3 HBV infection spatio temporal clusters with high rates identifed by SaTScan discrete Poisson method, China,2006–2018

Cluster	Coordinates	Radius(Km)	Location center	*N*	Time(Year)	Number of cases	Expected cases	Annual cases/100,000	RR	LLR	*P*-value
Most likely cluster	23.73 N,120.96 E	398.15 km	XINJIANG	2	2006–2011	1,191,516	542358.34	172.5	2.31	304982.30	< 0.001
Secondary cluster	39.49 N, 116.05 E	0	GANSU	1	2006–2011	358,734	122784.48	229.4	2.97	150737.74	< 0.001
2nd Secondary cluster	23.82 N, 108.77 E	524.47 km	HUBEI	5	2006–2011	2,209,084	1746686.26	99.3	1.32	65524.87	< 0.001
3rd Secondary cluster	37.25 N,106.15E	0	SHANXI	1	2010–2015	281,391	168655.26	131.0	1.68	31777.86	< 0.001
4th Secondary cluster	31.54 N, 88.63 E	0	NEIMENGGU	1	2006–2011	181,931	113812.96	125.5	1.61	17392.26	< 0.001
5th Secondary cluster	30.03 N,107.84 E	0	SHANNXI	1	2006–2009	125,870	117532.19	84.1	1.07	291.55	< 0.001

RR, Relative risk; LLR, Log likelihood ratio; N,the cluster number of province was identified by SaTScan

visual analysis and SatScan scanning statistics, to analyze the spatio-temporal epidemiology of hepatitis B incidence in 31 Chinese provinces from 2006 to 2018. The hepatitis B spatio-temporal analysis provides an understanding of the epidemiological characteristics of the distribution of hepatitis B infectious diseases in China, as well as a scientific basis and reference for effective hepatitis B prevention and treatment policies, as well as more in-depth research and analysis.

The study found that China is transitioning from being highly endemic to moderately endemic for hepatitis B. While the country's reported cases of hepatitis B are generally decreasing, there is an increasing trend of incidence in some provinces, possibly due to increased access to diagnosis and medical care, as well as improved ability to detect viral hepatitis. These factors could be potential determinants of the temporary trend of HBV infection.

In recent years, the Chinese government has implemented several measures to improve hepatitis B prevention and control. On the one hand, the risk of hepatitis B virus transmission through blood has been effectively reduced through improved regulation of blood-using institutions and blood collection processes, as well as increased supervision. On the other hand, the hepatitis B vaccination program has been widely implemented in China for the past 30 years, preventing many people from becoming infected with HBV [43].

The incidence of hepatitis B shows a clear seasonal pattern, with the highest incidence in spring (6.92/100,000) and the lowest in autumn and winter (6.22/100,000). This is consistent with Zhang's study [44]. Changes in extrinsic and intrinsic factors that come with the changing of seasons, such as stressful low temperatures and energy metabolism changes in winter, may suppress the immune system during the winter [45–49], leading to increased HBV replication. We suggest that the increase in HBV replication in winter may activate the immune system in some patients, which, coupled with the gradually increasing temperature and other factors in spring, results in the reactivation of chronic HBV infection, leading to chronic hepatitis B flares in the spring.

Before 2011, the majority of hepatitis B cases in China occurred in young people aged 20–45, but after 2011, the majority of cases were in the middle-aged population aged 46–59. This is due in part to a lack of public awareness of hepatitis B, a lack of health awareness among community hepatitis B-positive patients, and a lack of awareness of hepatitis B prevention among medical professionals [50]. However, the incidence of hepatitis B in the youth group has decreased since China's hepatitis B vaccine immunization strategy, which includes neonatal hepatitis B vaccination [51], a combined immunization strategy of mother-infant interruption [52], and the policy of "catch-up vaccination" for children under 15 years of age [53]. These measures have had significant prevention and control effects, as previous studies have shown [54, 55]. Due to increased vaccination rates, the incidence of hepatitis B in young people has gradually decreased. Prior to the implementation of the EPI, the highest incidence was in the youth group, which later changed to the peak middle-aged group several years later.

From 2006 to 2018, Guangdong Province, Henan Province, and Hubei Province had the highest number of reported hepatitis B cases. Meanwhile, Qinghai Province, Xinjiang Uygur Autonomous Region, and Gansu Province were identified as the top three provinces with the highest incidence rates. Although the number of hepatitis B cases in Guangdong Province was ten times higher

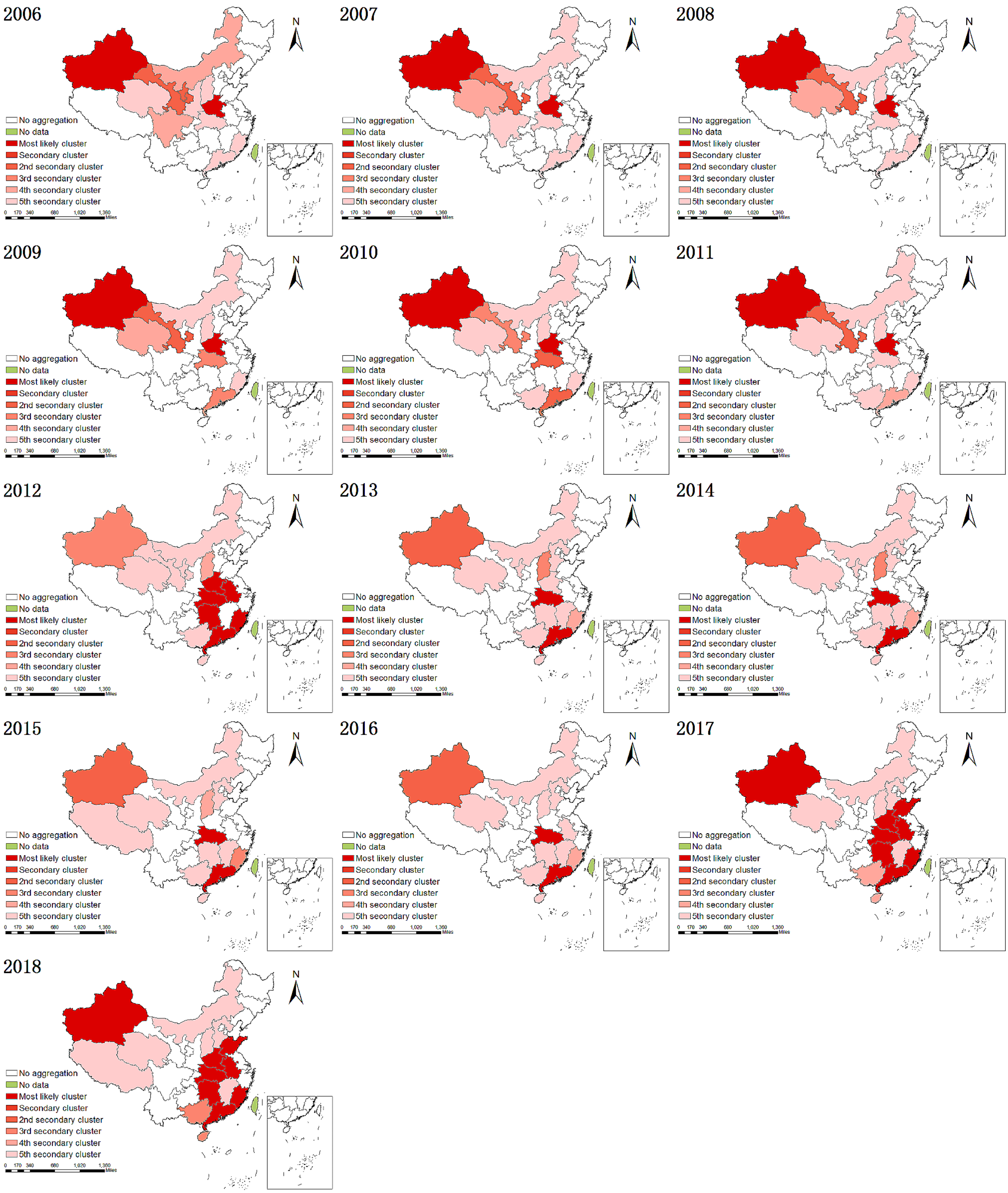

Fig. 5 Annual satscan cluster analysis of hepatitis B from 2006 to 2018

than in Qinghai Province, the incidence rate in Qinghai Province was 1.75 times higher than in Guangdong Province. Hepatitis B was primarily found in northwest China before 2013, but after that, the incidence rate of hepatitis B in southern China increased annually, as also reported by Song [56]. Regional factors, such as geographical conditions, slow economic development, a lack of medical resources, and low public awareness of infectious

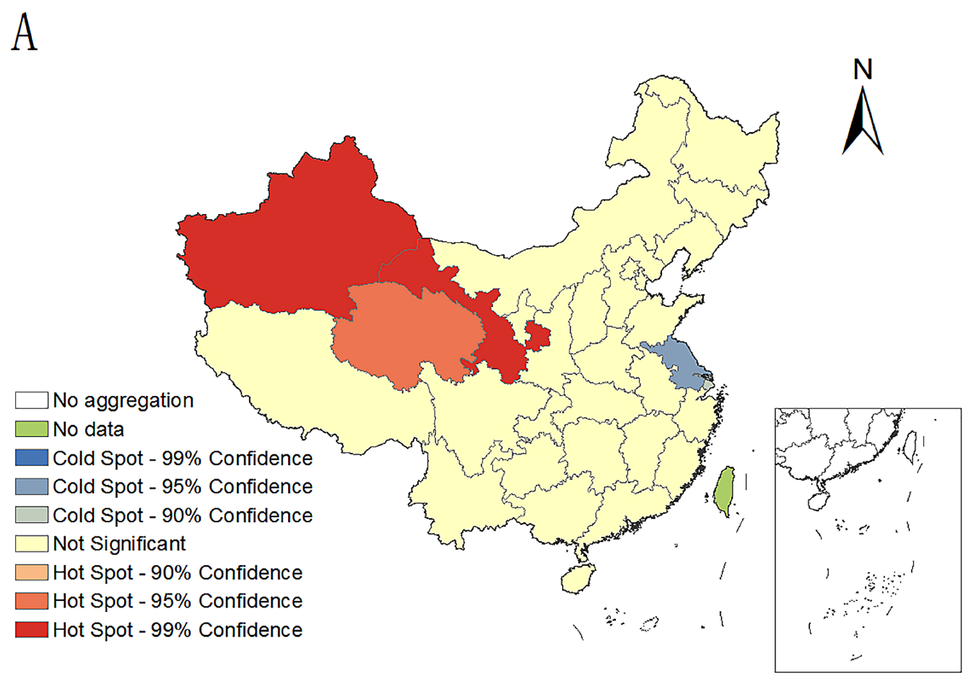

Fig. 6A Hepatitis B cold hotspot analysis between 2006 and 2018

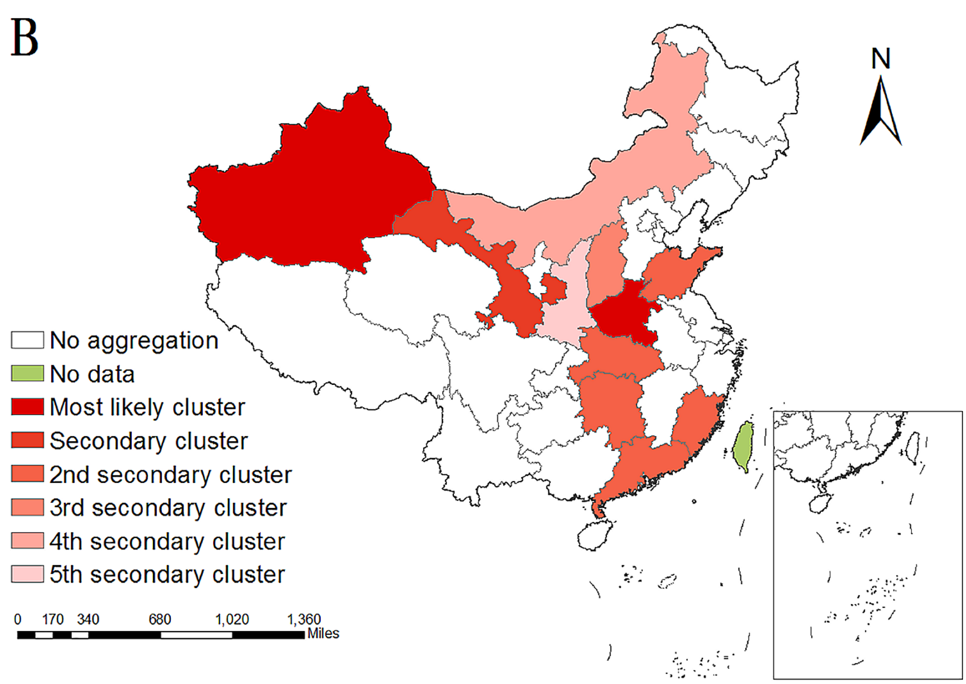

Fig. 6B Hepatitis B spatiotemporal clustering analysis between 2006 and 2018

diseases, are primarily responsible for the higher prevalence of hepatitis B in northwest China compared to the eastern region. China has better medical resources and health investment power in the eastern region than in the central and western regions, such as in the number of medical and health institutions, the number of health personnel, the number of beds in health institutions, equipment, health funding, etc [57].

The spatial distribution of hepatitis B was not random, with positive correlation and strong spatial aggregation in specific regions. Moran'S I values were all greater than 0 that indicated a significant spatial autocorrelation. The H-H clustering areas were primarily concentrated in five provinces, namely Xinjiang, Qinghai, Gansu, Ningxia, and Guangdong. This suggests that hepatitis B prevention and control measures should be strengthened in these areas. Jiangsu had the highest concentration of L-L clustering areas. According to the results of the local hot spot analysis, Xinjiang, Gansu, and Qinghai were classified as positive hot spots, while Jiangsu was identified as a cold spot region. The economic development, medical resources, customs and habits, and public awareness level were considered to be the primary reasons behind the variation in the incidence rates of hepatitis B in different regions. Since 2013, the hotspot of hepatitis B clusters shifted from northwest to south China, indicating a gradual decrease in hepatitis B incidence in the former region due to national policies. However, the recent increase in incidence in southern China can be attributed to the reduction in misreporting and underreporting of hepatitis B cases, low awareness rate of hepatitis B vaccination, and repeated reporting of infectious disease cards [58].

While spatial autocorrelation analysis can detect the presence of local aggregation around a region, spatio-temporal scan analysis is necessary to determine the size and extent of the aggregation [59]. The analysis of the spatial and temporal distribution of hepatitis B incidence revealed that before 2011, the provinces with high incidence were mainly concentrated in Xinjiang and Henan, particularly in Xinjiang, while after 2011, the provinces with high incidence were concentrated in Hunan, Guangdong, and Hubei, followed by Anhui, Fujian, Henan, Guangdong, Shandong, and Xinjiang. This suggests that the incidence of hepatitis B has gradually shifted from western regions to southern China. Over the years, Guangdong and Henan have had the highest number of hepatitis B cases in the country. The risk of clustering has remained high in the Xinjiang, Qinghai, and Henan regions, which may be associated with the persistence of high-risk factors in these regions. Hepatitis B prevalence in these areas is influenced by several factors, including poor living conditions, slow economic development, limited medical resources, and people's lifestyle habits. The increased incidence of hepatitis B in the south is due to increased mobility resulting from economic development and a lower rate of infectious disease underreporting. Consequently, the government should develop corresponding measures based on the current situation and actively intervene in areas prone to hepatitis B outbreaks to control hepatitis B cases promptly through early detection, early diagnosis, and early treatment.

For this research, all data on hepatitis B since the direct reporting of infectious diseases network in 2006 were collected. Firstly, the trend analysis of five aspects, such as the number of provinces with an annual incidence over 100/100,000, season, age group, geographical area, and the development dynamics of hepatitis B cases, was conducted. Secondly, spatial autocorrelation analysis was used to identify disease spatial aggregation at the survey area scale. Thirdly, local autocorrelation analysis and spatial clustering analysis were used to identify clustering hotspots and positive and negative "hotspot" areas. Finally, the time and extent of aggregation were ascertained using spatial and temporal scan analysis. Combining the above four methods and using a combined spatio-temporal approach, taking into account both the temporal dimension and the spatial-geographic dimension, coinciding with the infectious characteristics of the disease, and gradually deepening the analysis, the study results were made more systematic and complete. The spatio-temporal distribution characteristics and some triggering causes of hepatitis B cases nationwide from 2006 to 2018 were discovered, which are of great importance.

Although spatio-temporal scanning is a valuable tool for analyzing disease distribution and identifying high-risk areas [60], there are some limitations to our research. Ecological studies are subject to ecological bias [61], which is an inherent limitation. It is important to note that the data we used can only be used to investigate the spatial and temporal distribution of hepatitis B incidence at the provincial level, but not at the prefecture-level city or local town or district and county levels. Due to the large and imprecise study area, differences in the intensity and quality of hepatitis B disease reporting exist among provinces (municipalities directly under the Central Government and autonomous regions), as well as regional differences between provinces. Moreover, this research did not assess the potential environmental risk factors and demographic characteristics associated with the different spatial and temporal distributions of hepatitis B. Therefore, further research is necessary to identify geographic factors and develop targeted regional control measures. Follow-up studies at the county and township levels are necessary to develop different models for different regions, which can investigate the underlying causes of spatial autocorrelation and hepatitis B aggregation. This will provide a more comprehensive and targeted framework for developing hepatitis B prevention and control strategies in each province (municipality directly under the Central Government and autonomous region).

Conclusions

Our combined temporal and spatial analysis-revealed significant clustering of hepatitis B incidence across China. The global Moran's I index confirmed a positive spatial correlation, with high-incidence areas adjacent to other high-incidence areas and low-incidence areas adjacent to other low-incidence areas.The highest incidence rates were observed in Qinghai and Xinjiang, with increasing rates in Guangdong and Fujian over time. Northwest China showed the highest incidence rates, possibly due to local lifestyle and habits, economic development, medical conditions, and personal perceptions.To prevent and control the spread of infectious diseases like hepatitis B, it is critical for the government to closely monitor and implement effective interventions, including timely vaccination and locally appropriate preventive measures.

Abbreviations

GIS	Geographic information system
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
CHB	Chronic hepatitis B
WHO	World Health Organization
SDGs	Sustainable Development Goals
HBsAg	Hepatitis B surface antigen
EPI	Expanded Program on Immunization
HIV	Human Immunodeficiency Virus
PMTCT	Preventing mother-to-child transmission
Moran's	I Global Moran's I coefficient
RR	Relative risk
LLR	Log likelihood ratio

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Author contributions
LP J drafted and revised the manuscript, and analyzed the data. LP J, TS designed and implemented the research, and reviewed the manuscript. YZ H, WL1 and WL2 revised the manuscript.LD, MM W, YY Y, JJ G collected and managed the data.MM M, XM X provided the analytical tools for the study. All authors read and approved the final manuscript.

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Data availability
The datas that support the findings of this study are available from the Public Health Science Data Center Database (China CDC), but restrictions apply to the availability of these datas, which were not publicly available. Requests for access to these datas should be sent to the Public Health Science Data Center Database(China CDC). All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethical approval and consent to participate
The study was approved by the Ethical Committee of Weinan Center for Disease Prevention and Control.Because this study constituted public health surveillance rather than research in human beings, and was a retrospective analysis with no ethical issues.Therefore, our study was exempt from ethical review by the Ethics Committee of Weinan Center for Disease Control and Prevention. The datas provided did not have any individual patient details, so the requirement for informed consent was waived by the Ethical Committee of Weinan Center for Disease Prevention and Control.All methods were carried out in accordance with relevant guidelines and regulations.The original datas uesd in this study were obtained from "Public Health Science Data Center Database" with the approval by Public Health Science Data Center of China CDC.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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