Spatial analysis on human brucellosis incidence in mainland China: 2004-2010

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Spatial analysis on human brucellosis incidence in mainland China: 2004-2010

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ABSTRACT

Objectives: China has experienced a sharply increasing rate of human brucellosis in recent years. Effective spatial monitoring of human brucellosis incidence is very important for successful implementation of control and prevention programs. The purpose of this paper is to apply exploratory spatial data analysis (ESDA) methods and the empirical Bayes (EB) smoothing technique to monitor county-level incidence rates for human brucellosis in mainland China from 2004 to 2010 by examining spatial patterns.

Methods: ESDA methods were used to characterize spatial patterns of EB smoothed incidence rates for human brucellosis using county-level data obtained from the China Information System for Disease Control and Prevention (CISDCP) in mainland China from 2004 to 2010.

Results: EB smoothed incidence rates for human brucellosis were spatially dependent during 2004-2010. The local Moran test identified one significant northern cluster of high human brucellosis risk (all P-values <0.01), which persisted during the seven-year study period. High-risk counties were centered in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia Autonomous Region where animal husbandry had developed. The number of high-risk counties increased from 25 in 2004 to 54 in 2010.

Conclusions: ESDA methods and the EB smoothing technique can assist public health officials in identifying high-risk areas. Allocating more resources to high-risk areas could more effectively reduce human brucellosis incidence.

Keywords: *Human brucellosis, exploratory spatial data analysis, empirical Bayes smoothing, spatial autocorrelation, cluster detection*

Word Count: 2747

ARTICLE SUMMARY

Article focus

- The incidence rates of human brucellosis are not distributed evenly across regions in China. Awareness of the spatial patterns of human brucellosis is quite beneficial for the prevention and control of the disease.
- ESDA methods and the empirical Bayes smoothing technique are commonly combined to characterize spatial epidemiology of diseases.

Key messages

- EB smoothed incidence rates for human brucellosis were spatially dependent during 2004-2010. The local Moran test identified one significant northern cluster of high human brucellosis risk, which persisted during the seven-year study period.
- High-risk counties were centered in Inner Mongolia Autonomous Region and other Northern provinces around the border with Inner Mongolia Autonomous Region where animal husbandry had developed.
- ESDA methods and the EB smoothing technique can assist public health officials in identifying high-risk areas.

Strengths and limitations of this study

- ESDA methods and the EB smoothing technique were used to analyze spatial patterns of incidence rates for human brucellosis at the county level in mainland China. Therefore, random variability was reduced and greater stability of incidence rates was provided mainly in small counties and true cluster areas with low false-positive rates especially performing well on outlier detection had a better chance of being detected.

- The number of reported cases of human brucellosis obtained from the CISDCP system might be only part of the actual incidence of human brucellosis across the country as human brucellosis is often underreported or misdiagnosed.
- Our analyses are based on county-level data. Smaller spatial units might provide more location-specific information that can inform the design and implementation stages of public health programs.

INTRODUCTION

Brucellosis, caused by Brucella species, is a zoonotic disease recognized as an emerging and re-emerging threat to public and veterinary health.[1] The disease is transmitted to humans by direct/indirect contact with infected animals or through the consumption of contaminated foods.[2-4] People with occupational exposure are at highest risk for brucellosis, in particular those performing husbandry activities, butchering, and livestock trading.[5 6] Worldwide economic losses due to brucellosis are extensive not only in animal production but also in public health.[1] Although brucellosis has been eradicated from many industrialized countries, new foci of disease continually appear, particularly in parts of Asia.[7]

Brucellosis is classified as one of the Class II national notifiable diseases by the Centers for Disease Control and Prevention (CDC) and as a key disease in

Class II as described by the Implement Detailed Rules of the By-law on Disease Prevention and Control of Livestock and Poultry in mainland China.[8] The disease was first reported in China in 1905.[8] Human brucellosis incidence was quite severe before 1980s in the country, later decreased and remained at a low level. From 1995 to 2001, the incidence of human brucellosis increased rapidly, and spread more than 10 provinces.[8] In recent years, With the rapid development of China's animal husbandry, human brucellosis incidence had increased sharply.[9] Nationwide surveillance data indicated that the total incidence rate of human brucellosis in mainland China increased from 0.92 cases per 100,000 people in 2004 to 2.62 cases per 100,000 people in 2010.[10] Currently, human brucellosis is considered an important public health problem in mainland China.[11]

The incidence rates of human brucellosis are not distributed evenly across regions in China.[10] Awareness of the spatial patterns of human brucellosis is quite beneficial for the prevention and control of the disease. Exploratory spatial data analysis (ESDA) methods are emerging useful approaches to achieve this understanding.[12] ESDA is a set of techniques used to describe and visualize spatial distributions, identify atypical locations or spatial outliers, discover patterns of spatial association, clusters or hot spots, and suggest spatial regimes or other forms of spatial heterogeneity.[12 13] The methods can be applied by health officials to monitor spatial variations in disease rates, which can assist health officials in designing more location-specific control and prevention programs who take into account global and local spatial influences.[14] Measures of spatial autocorrelation are at the core of ESDA methods.[13] ESDA methods and the empirical Bayes (EB) smoothing technique are commonly combined to characterize spatial epidemiology of diseases.[14-17] The EB smoothing technique is used to reduce random variation and to provide greater stability of rates mainly in small areas associated with small populations.[16] The primary purpose of this paper is to apply ESDA methods and the EB smoothing technique to monitor county-level incidence rates for human brucellosis in mainland China from 2004 to 2010 by examining spatial patterns. We also identified the potential presence of clusters of the disease in mainland China, thus to provide spatial guidance for future research.

METHODS

Data source

Human brucellosis cases including 2872 counties in mainland China from 2004 to 2010 were collected through the Internet-based disease-reporting system (China Information System for Disease Control and Prevention, CISDCP), which was established in 2004 and was more integrated, effective, and reliable than the previous case-reporting system.[18 19] In this paper, the incidence rates of human brucellosis in fact referred to the reported incidence rates. We used seven-year reported human brucellosis cases to provide a stable measure of disease incidence rate by time and location at the county level.[20] In order to conduct a geographic information system (GIS) -based analysis of the spatial distribution of human brucellosis, the county-level polygon map at a 1:1,000,000 scale was obtained.[20] Demographic information based on the 2000 census was acquired from the National Bureau of Statistics of China. All human brucellosis cases were geocoded and matched to the county-level layers of the polygons by administrative code using the software Mapinfo7.0.[20]

EB smoothing technique

When raw rates derived from different counties across the whole study area are applied to estimate the underlying disease risk, differences in population size result in variance instability and spurious outliers. This is because the rates observed in areas with small populations may be highly unstable in that the addition or deletion of one or two cases can cause drastic changes in the observed values. Therefore, raw rates may not fully represent the relative magnitude of the underlying risks if compared with other counties with high population base. To overcome this problem, the EB smoothing technique proposed by Clayton and Kaldor[16] was applied to our brucellosis data. This method adjusts raw rates by incorporating data from other neighbouring spatial units.[21] Essentially, raw rates get 'shrunk' towards an overall mean which is an inverse function of the variance. Application of EB smoothed incidence rate not only provides better visualization compared to raw rate but also serves to find true outliers.[22]

Spatial autocorrelation analysis

We performed spatial autocorrelation analysis in GeoDa0.9.5-i software.[23]

Both global and local Moran's I statistics were calculated. The global Moran's I statistic was estimated to assess the evidence of global spatial autocorrelation (clustering) of incidence rates over the study region.[24] Anselin's local Moran's I (LISA) statistic indicates the location of local clusters and spatial outliers.[25] Spatial autocorrelation statistics for human brucellosis incidence rates were calculated based on the assumption of constant variance. The assumption might be violated when incidence rates at the county level varied greatly across the whole study region.[26] The EB smoothing technique was performed to adjust for this violation. The standardized first-order contiguity Queen neighbors were used as the criteria for identifying neighbors in this paper. A significant test was performed through the permutation test, and a reference distribution was generated under an assumption that the incidence was randomly distributed. In order to obtain more robust results, the number of permutation test was set to 9999. Since multiple comparisons increased the chances of identifying overlapping clusters, the significance level was set at 0.01. Based on these permutations and threshold, we have plotted values on a map to display the location of human brucellosis clusters in mainland China.[27]

RESULTS

Annualized average of human brucellosis from 2004 to 2010

A total of 164,752 human brucellosis cases were reported in mainland China from 2004 to 2010. Annual EB smoothed incidence rates for human brucellosis for all 2872 counties were calculated. Table 1 presents 28 counties with annual

EB smoothed incidence rates for human brucellosis over 100 cases per 100, 000 people, which accounted for 34.41% of all cases in the country during the study period. Inner Mongolia Autonomous Region had the highest number of 23, centered in Xilin Gol League, Ulanqab League, Hulunbeier City, Xing'an League, Baotou City, Chifeng City, Hohhot City, and Tongliao City.

Summary statistics for the annual EB smoothed incidence rates for all counties were calculated. The mean and standard deviation were 4.64 and 38.66, respectively, per 100,000 people. The statistic for outliers was the computed z-value, which was the difference between the observed and expected mean of the annual EB smoothed incidence rates standardized by the standard deviation. Thus, it had a mean of zero and a standard deviation of 1. Sunitezuo Banner in Xilin Gol League in Inner Mongolia had the highest annual EB smoothed incidence rate of 1209.60, with 31.16 standard deviations from the mean. All 28 counties were at least 2.59 standard deviations from the mean, as shown in Table 1.

Table 1 Counties with annual EB smoothed incidence rates of human brucellosis over 100 per 100, 000 in mainland China, 2004–2010

No.	Province	City	County	Rate*	Z-value	P-value	Rank
1	Inner Mongolia	Xilin Gol League	Sunitezuo Banner	1209.60	31.16	<0.001	1
2			Abag Banner	1004.10	25.85	<0.001	2
3			Bordered Yellow Banner	826.90	21.27	<0.001	3
4			Plain Blue Banner	364.40	9.30	<0.001	4
5			Zhenxianghuang Banner	303.70	7.73	<0.001	5
6			Sunite Right Banner	294.60	7.50	<0.001	6
7			west ujimqin banner	243.50	6.18	<0.001	9
8			Xilinhot City	236.80	6.00	<0.001	10
9			East Ujumqin Banner	219.00	5.54	<0.001	11
10			Duolun County	176.70	4.45	<0.001	15
11		Ulanqab League	Siziwang Banner	257.90	6.55	<0.001	7
12			Huade County	179.00	4.51	<0.001	14
13			Qahar Right Wing Rear Banner	163.90	4.12	<0.001	16
14			Shangdu County	142.40	3.56	<0.001	20
15			Chahar Right Middle Banner	128.80	3.21	<0.002	23
16		Hulunbeier City	New Barhu Right Banner	255.10	6.48	<0.001	8
17			New Barhu Left Banner	203.40	5.14	<0.001	13
18			Zhalantun City	144.20	3.61	<0.001	19
19		Xing'an League	Horqin Right Wing Front Banner	146.00	3.66	<0.001	18
20		Baotou City	Daerhanmaomingan Union Banner	129.80	3.24	<0.002	22
21		Chifeng City	Keshiketeng Banner	126.50	3.15	<0.002	24
22		Hohhot City	Qingshuihe County	123.90	3.08	<0.005	25
23		Tongliao City	Jarud Banner	104.90	2.59	<0.010	28
24	Shanxi	Datong City	Tianzhen County	162.30	4.08	<0.001	17
25			Guangling County	136.50	3.41	<0.001	21
26		Xinzhou City	Shengchi County	107.70	2.67	<0.010	27
27	Heilongjiang	Qiqihar City	Meris Daur District	208.10	5.26	<0.001	12
28	Hebei	Zhangjiakou City	Chicheng County	117.60	2.92	<0.005	26

Rate*: These are annual EB smoothed incidence rates for human brucellosis.

Figure 1 presented a percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010. The figure gives an indication of spatial associations: counties with similar colour shades tended to be near each other. Outlier counties with extreme values were highlighted (both high as well as low). Six legend categories were created, corresponding to < 1%, 1% to <10%, 10% to <50%, 50% to <90%, 90% to <99% and >99%. There were 29 counties at the high end.

The global Moran's I value of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010 was 0.5803 (Z= 8.3660, P=0.0025), statistically significant at the 0.01 level.

We also calculated the local Moran's I and gave a LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010. LISA cluster map showed those counties with a significant local Moran statistic classified by type of spatial correlation: bright red for the high-high association, bright blue for low-low, light blue for low-high, and light red for high-low (Figure 2). The high-high and low-low locations suggest clustering of similar values, whereas the high-low and low-high locations indicate spatial outliers.

The Local Moran's I method of annual EB smoothed incidence rates for human brucellosis showed major clustered areas of high human brucellosis risk located in northern China. High-risk counties were centered in Inner Mongolia (40 counties, 72.3%), Hebei (7 counties, 12.7%), Shanxi (5 counties, 9.1%),

Heilongjiang (2 counties, 3.6%) and Jilin provinces (1 county, 1.8%) and included a total of 55 counties. These provinces accounted for 90.88% of the reported cases. EB smoothed incidence rates for these counties ranged from 7.70 to 1209.60 cases per 100,000 people.

<<Insert figure 1 here>>

<<Insert figure 2 here>>

Changes in human brucellosis incidence rates from 2004 to 2010

The value of Global Moran's I of EB smoothed incidence rates increased from 0.2460 to 0.6179 during 2004-2010, indicating that the spatial distribution of human brucellosis had become more uneven (that is, the clustering of high and low values is becoming more prominent) (Table 2). The formal test of spatial dependence was statistically significant at the 0.01 level, implying that distribution of human brucellosis was spatially dependent in mainland China.

Table 2 Global spatial autocorrelation analyses for EB smoothed incidence rates for human brucellosis in mainland China (per year), 2004–2010

Year	Moran's *I*	*Z*-score	*P* value
2004	0.2460	4.7733	0.0087
2005	0.4734	9.0229	0.0012
2006	0.4662	7.6853	0.0026
2007	0.5063	7.3102	0.0042
2008	0.5594	8.4932	0.0025
2009	0.5509	8.3389	0.0020
2010	0.6179	11.1187	0.0002

The clustered areas varied during the seven-year study period (Figure 3). The number of high-risk counties—that is, those counties included in clustered areas of high human brucellosis risk identified by the local Moran's I

method—increased from 25 in 2004 to 54 in 2010.

The number of high-risk counties in Inner Mongolia Autonomous Region was the largest one, increased from 22 in 2004 to 46 in 2010. Among the 101 counties in Inner Mongolia Autonomous Region, the number of EB smoothed incidence rates over 100 cases per 100,000 people increased from 8 in 2004 to 29 in 2010. The most notable change was that the EB smoothed incidence rate in Sunitezuo Banner increased from 373.7 in 2004 to 2,482.1 in 2009, but then decreased to 1,443.0 cases per 100,000 people in 2010.

In Hebei Province, the number of high-risk counties kept an upward trend, rising from 1 in 2004 to 3 in 2010. The most noteworthy change was that the EB smoothed incidence rate in Wei County increased from 9.70 to 79.40 cases per 100,000 people between 2004 and 2010.

The number of high-risk counties in Shanxi Province increased from zero in 2004 to 2 in 2010. The most notable change was that the EB smoothed incidence rate in Xinrong District increased from 0.9 to 88.1 cases per 100,000 people between 2004 and 2010.

In Jilin Province, the number of high-risk counties increased from zero in 2004 to 3 in 2010. The most notable change was that the EB smoothed incidence rate in Tongyu County increased from zero to 155.6 cases per 100,000 people between 2004 and 2010.

In Heilongjiang Province, the number of high-risk counties decreased from 2 to 0 between 2004 and 2010. Meris Daur District had the highest EB smoothed

incidence rates of human brucellosis in the province, at more than 130 cases per 100,000 people per year between 2004 and 2010. The most notable change was that the EB smoothed incidence rate in Zhaozhou County increased from 1.3 to 74.2 cases per 100,000 people between 2004 and 2010.

<<Insert figure 3 here>>

DISCUSSION

In this paper, ESDA methods were used to explore spatial patterns of EB smoothed incidence rates for human brucellosis at the county level in mainland China from 2004 to 2010. We found that the occurrence of human brucellosis persisted throughout many areas of the country and was spatially dependent during the seven-year study period. Since human brucellosis is not a contagious disease, spatial clusters of human brucellosis are most likely a result of animal processing, shared food sources, more intensive agricultural production zones, or similar socio-cultural practices.[17 28] Further researches are needed to determine whether China's human brucellosis clusters are associated with specific natural and/or social environmental characteristics. During the period 2004-2010, the areas with serious epidemics of human brucellosis persisted in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia Autonomous Region where animal husbandry had developed, all of which were epidemic regions before the 1980s. This spatial pattern may be related to the trans-boundary transfer of animal brucellosis in the region of Inner Mongolia

from the neighboring hyper-endemic Mongolia, which had been described as the country with the second highest incidence worldwide.[7 29] In addition, the leading risk factors for the high incidence rate of human brucellosis were the increase in animal feeding, lack of immunization and animal quarantine, and frequent trading.[9 29]

Several intervention strategies had been suggested to reduce the incidence of human brucellosis, such as increasing local knowledge of proper food handling techniques of dairy products including pasteurization, decreasing occupational exposures, quarantining, separating and eliminating of infected animals with brucellosis, establishing surveillance point of brucellosis and its network, and vaccination programs aimed at reducing the prevalence of disease in livestock.[8 30] However, Zhang[9] suggested that the most effective means of human brucellosis control were the comprehensive measures of universal immunization in livestock without quarantine in epidemic regions, which had been proved effective measures before.

Previous study analyzed cluster identification of the annualized raw incidence rates of county-level human brucellosis in China by using SaTScan and ArcGIS software.[31] We identified similar clustered areas, though the previous study identified more high-risk counties than our study. This may be the results from different clustering methodologies[32] and different significance levels. In our study, more high-risk counties will be identified if a significance level of 0.05 was used. Our study differs from previous study in several ways. First, we used the

EB smoothing technique to smooth the human brucellosis incidence rates. Therefore, random variability was reduced and greater stability of incidence rates was provided mainly in small counties. Second, LISA has a better chance of detecting true cluster areas with low false-positive rates especially performing well on outlier detection.[32] In addition, our paper provides changes in human brucellosis incidence rates from 2004 to 2010. This is the first study, to the best of our knowledge, which has applied both ESDA methods and the EB smoothing technique to analyze spatial patterns of incidence rates for human brucellosis at the county level in mainland China. We believe that conclusions based on the combinations of the two methods provide reliable results.

Our study is not without limitations. First of all, the number of reported cases of human brucellosis obtained from the CISDCP system might be only part of the actual incidence of human brucellosis across the country as human brucellosis is often underreported or misdiagnosed.[29] True human brucellosis rates might be much higher than reported. Nevertheless, the data used in this paper are still able to reflect the current trend in human brucellosis incidence in mainland China. Secondly, our analyses are based on county-level data. Smaller spatial units might provide more location-specific information that can inform the design and implementation stages of public health programs.[14] The methods employed in this paper can be applied to finer geographic units (e.g. postal units). Finer geographic units to identify clusters within counties with higher burdens of human brucellosis would be focused on in further research.

In conclusion, our study offered a good understanding of the spatial patterns of human brucellosis incidence in mainland China, and might contribute to determine allocating resources to high risk areas in order to reduce human brucellosis incidence. With the assistance of the spatial framework provided by our study, China's human brucellosis control programs could be focused on locations where they will have the greatest influence.

Contributors JZ designed the research, collected data, drafted the manuscript, analysed the data and interpreted the results. FY designed the research, collected data, interpreted the results critically reviewed and edited the manuscript. TZ, CY, XZ interpreted the results critically reviewed and edited the manuscript. XL designed the research, interpreted the results, critically reviewed and edited the manuscript and funding, and supervised. ZH offered research data and edited the manuscript. All authors read and approved the final manuscript.

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Competing interests None.

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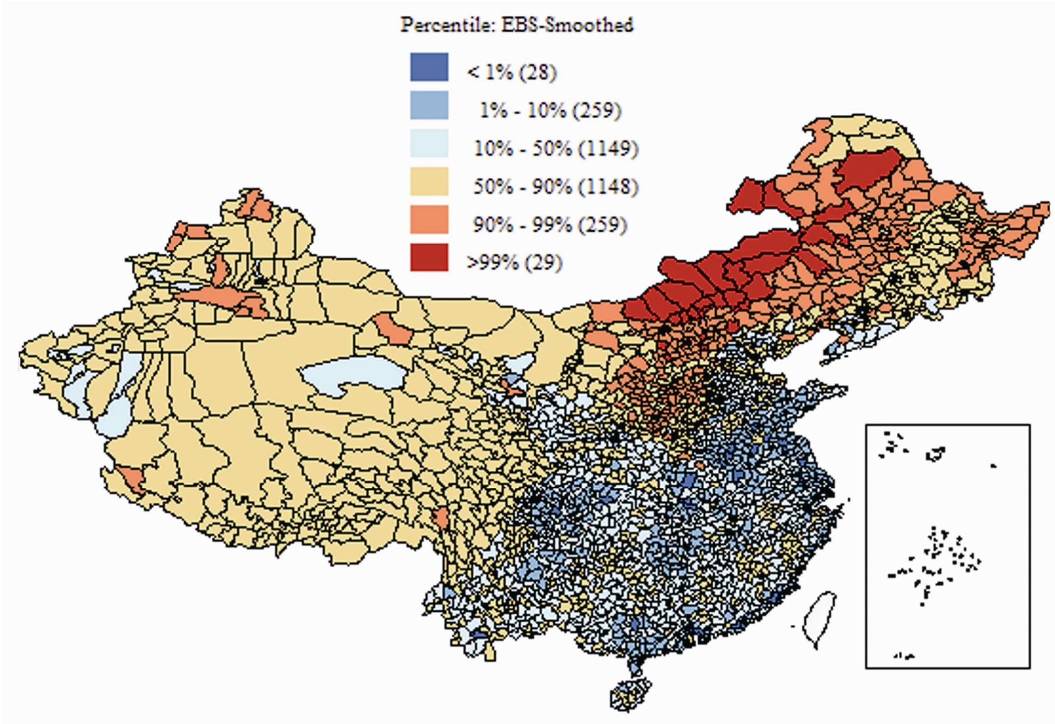


Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

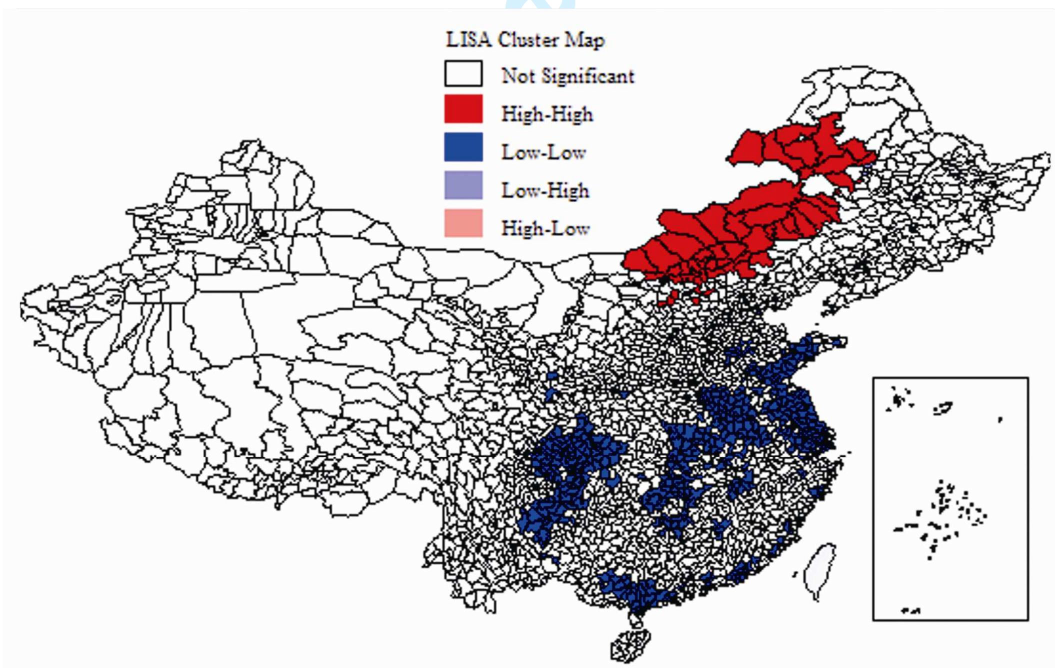


Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

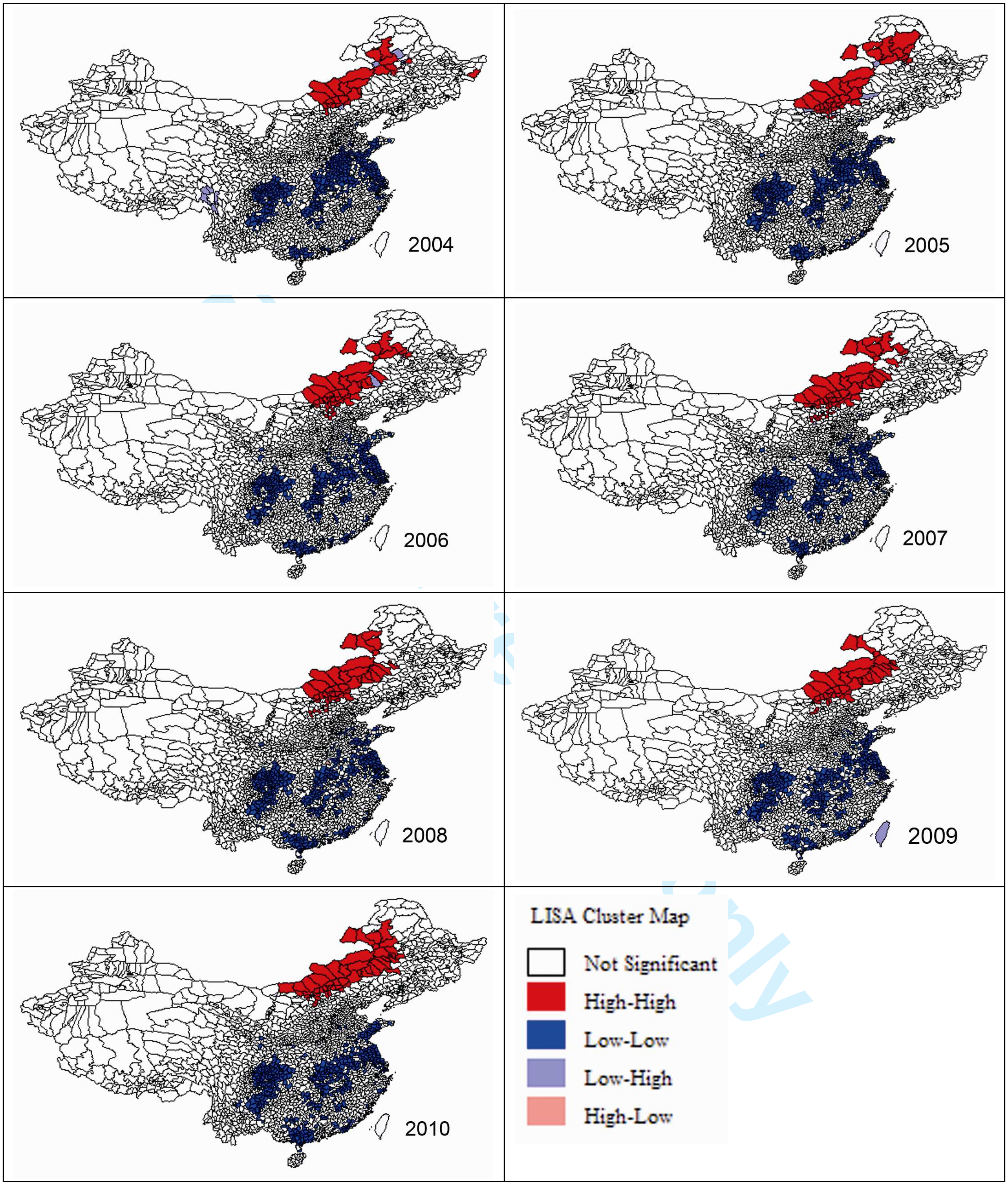
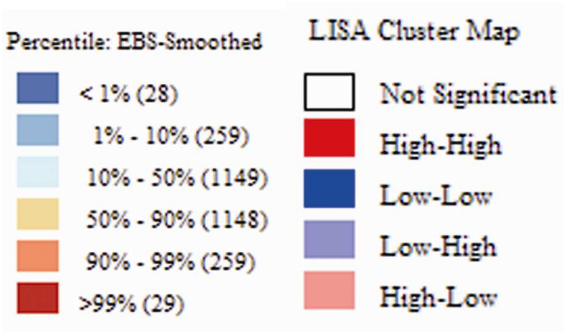
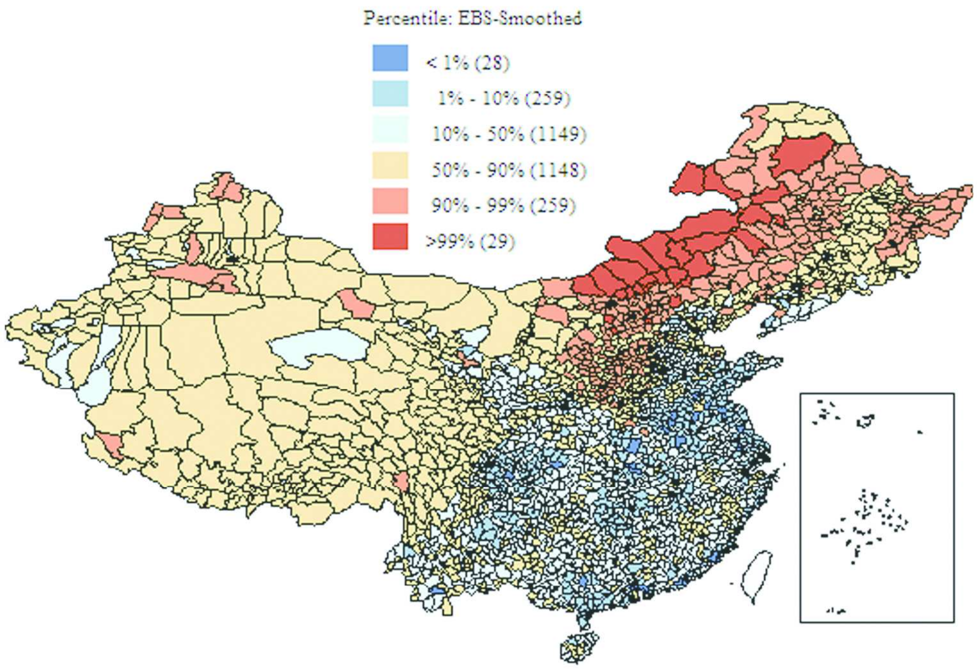


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010

Figure legends





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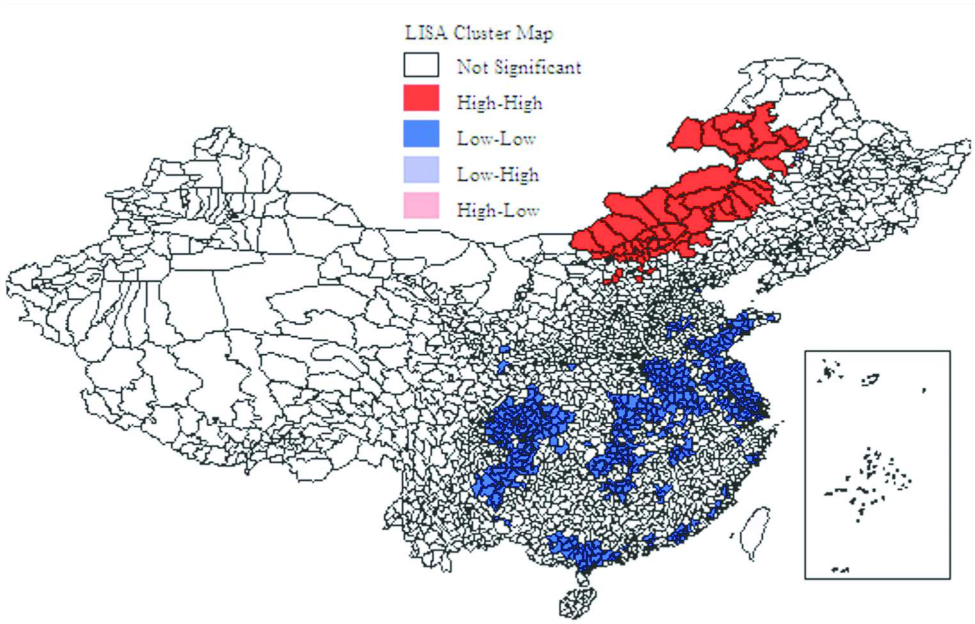

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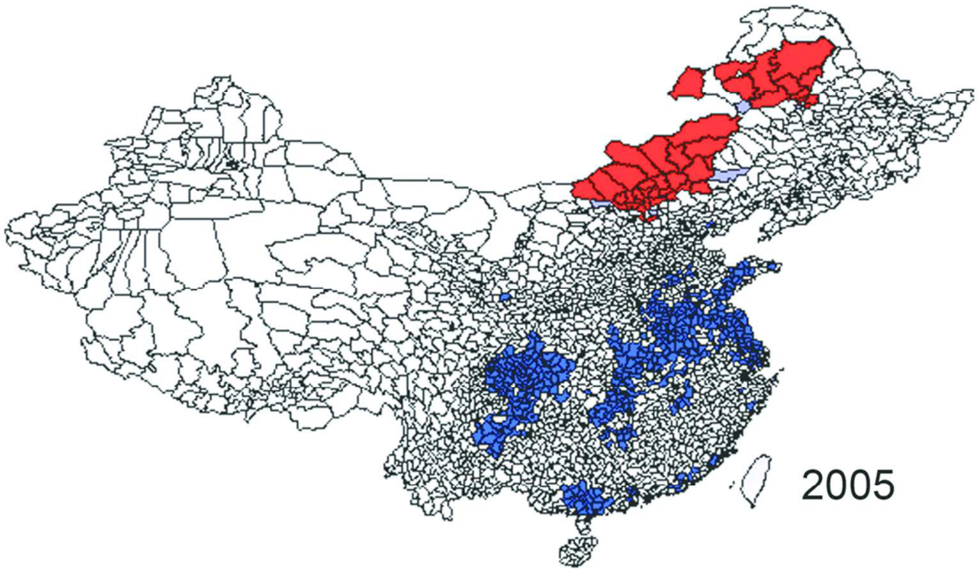

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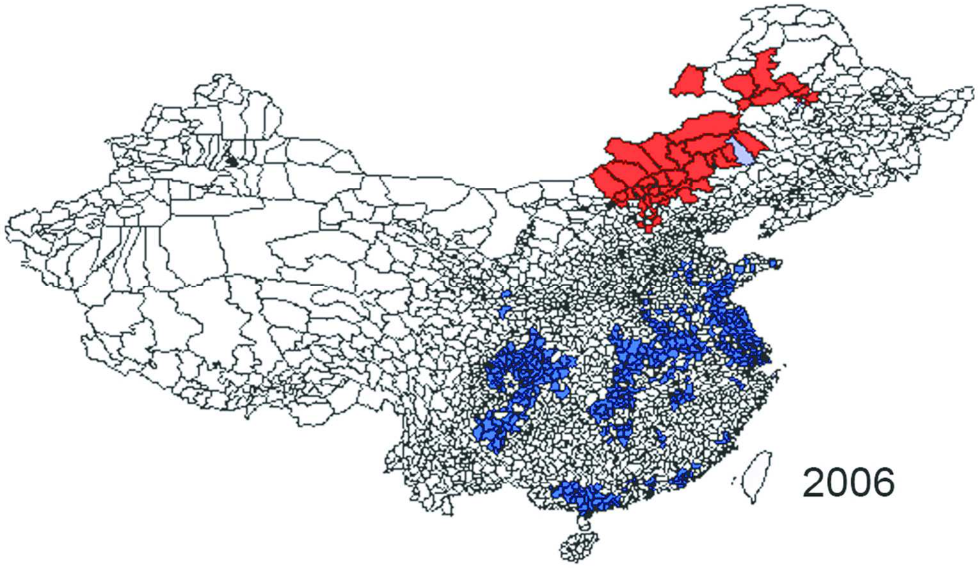

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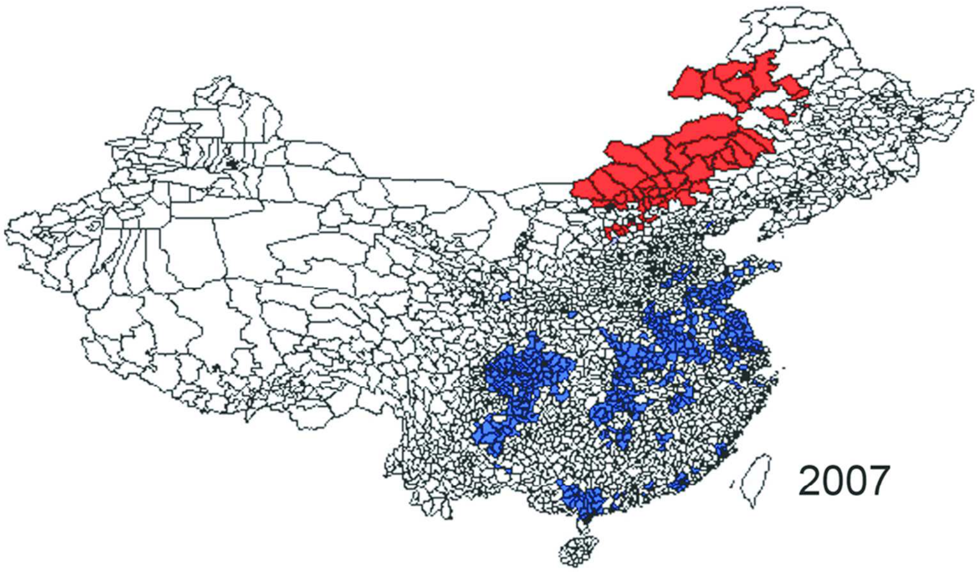

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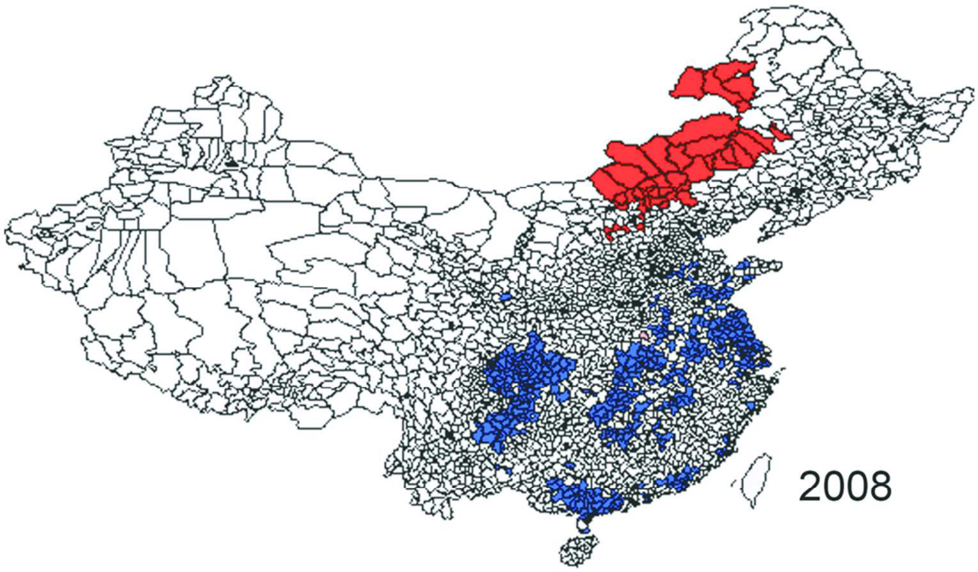

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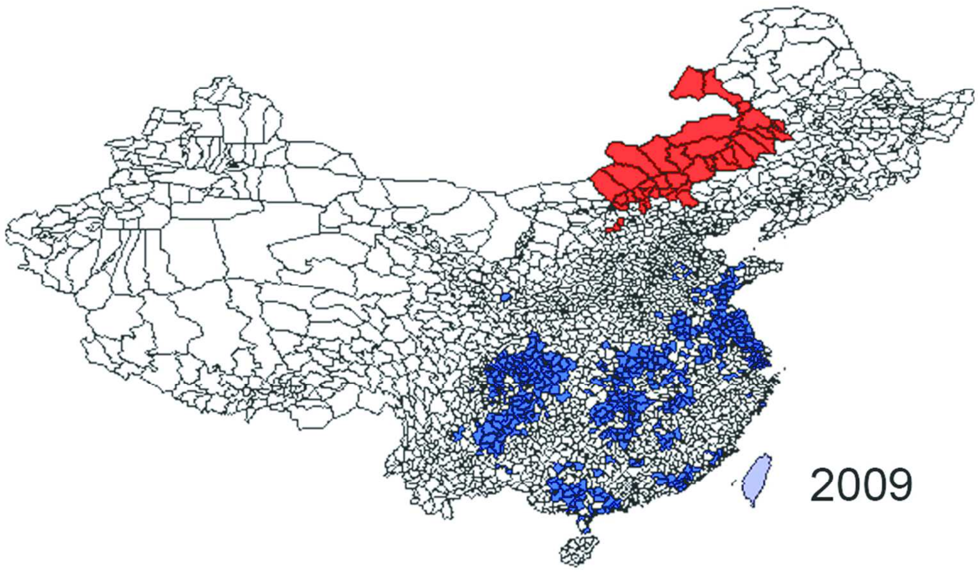

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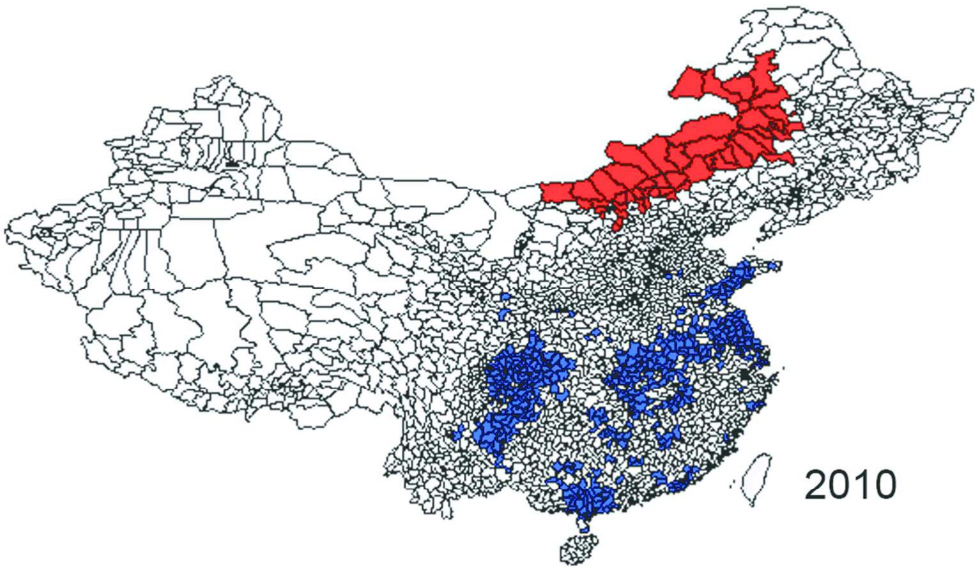

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Spatial analysis on human brucellosis incidence in mainland China: 2004-2010

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Spatial analysis on human brucellosis incidence in mainland China: 2004-2010

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ABSTRACT

Objectives: China has experienced a sharply increasing rate of human brucellosis in recent years. Effective spatial monitoring of human brucellosis incidence is very important for successful implementation of control and prevention programs. The purpose of this paper is to apply exploratory spatial data analysis (ESDA) methods and the empirical Bayes (EB) smoothing technique to monitor county-level incidence rates for human brucellosis in mainland China from 2004 to 2010 by examining spatial patterns.

Methods: ESDA methods were used to characterize spatial patterns of EB smoothed incidence rates for human brucellosis based on county-level data obtained from the China Information System for Disease Control and Prevention (CISDCP) in mainland China from 2004 to 2010.

Results: EB smoothed incidence rates for human brucellosis were spatially dependent during 2004-2010. The local Moran test identified significantly high-risk clusters of human brucellosis (all P-values <0.01), which persisted during the seven-year study period. High-risk counties were centered in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia Autonomous Region where animal husbandry was highly developed. The number of high-risk counties increased from 25 in 2004 to 54 in 2010.

Conclusions: ESDA methods and the EB smoothing technique can assist public health officials in identifying high-risk areas. Allocating more resources to

high-risk areas is an effective way to reduce human brucellosis incidence.

Keywords: *Human brucellosis, exploratory spatial data analysis, empirical Bayes smoothing, spatial autocorrelation, cluster detection*

Word Count: 3208

ARTICLE SUMMARY

Article focus

- The incidence rates of human brucellosis are not distributed evenly across regions in China. Awareness of the spatial patterns of human brucellosis is quite beneficial for the prevention and control of the disease.
- ESDA methods and the empirical Bayes smoothing technique are commonly combined to characterize spatial epidemiology of diseases.

Key messages

- EB smoothed incidence rates for human brucellosis were spatially dependent during 2004-2010. The local Moran test identified significantly high-risk clusters of human brucellosis, which persisted during the seven-year study period.
- High-risk counties were centered in Inner Mongolia Autonomous Region and other Northern provinces around the border with Inner Mongolia Autonomous Region where animal husbandry was highly developed.
- ESDA methods and the EB smoothing technique can assist public health

officials in identifying high-risk areas.

Strengths and limitations of this study

- ESDA methods and the EB smoothing technique were used to analyze spatial patterns of incidence rates for human brucellosis at the county level in mainland China. Therefore, random variability was reduced, and greater stability of incidence rates was provided mainly in small counties and true cluster areas with low false-positive rates especially performing well on outlier detection had a better chance of being detected.
- The number of reported cases of human brucellosis obtained from the CISDCP system might be only part of the actual incidence of human brucellosis across the country as human brucellosis is often underreported or misdiagnosed.
- Our analyses are based on county-level data. Smaller spatial units might provide more location-specific information about the design and implementation stages of public health programs.

INTRODUCTION

Brucellosis, caused by Brucella species, is a zoonotic disease recognized as an emerging and re-emerging threat to public and veterinary health.[1] The disease is transmitted to humans by direct/indirect contact with infected animals or through the consumption of contaminated foods.[2-4] People with occupational exposure are at highest risk for brucellosis, in particular those performing husbandry activities, butchering, and livestock trading.[5 6] Worldwide economic losses caused by brucellosis are extensive not only in animal production but also in public health.[1] Although brucellosis has been eradicated from many industrialized countries, new foci of disease continually appear, particularly in parts of Asia.[7]

Brucellosis is classified as one of the Class II national notifiable diseases by the Centers for Disease Control and Prevention (CDC) and as a key disease in Class II by the Implement Detailed Rules of the By-law on Disease Prevention and Control of Livestock and Poultry in mainland China.[8] The disease was first reported in China in 1905.[8] Human brucellosis incidence was quite severe before 1980s in the country, later decreased and remained at a low level. From 1995 to 2001, the incidence of human brucellosis increased rapidly, and spread more than 10 provinces.[8] In recent years, With the rapid development of China's animal husbandry, human brucellosis incidence had increased sharply.[9] Nationwide surveillance data indicated that the total incidence rate of human brucellosis in mainland China increased from 0.92 cases per 100,000 people in 2004 to 2.62 cases per 100,000 people in 2010.[10] Currently, human brucellosis is considered an important public health problem in mainland China.[11]

The incidence rates of human brucellosis are not distributed evenly across regions in China.[10] Awareness of the spatial patterns of human brucellosis is quite beneficial for the prevention and control of the disease. Exploratory spatial data analysis (ESDA) methods are emerging useful approaches to achieve this understanding.[12] ESDA is a set of techniques used to describe and visualize spatial distributions, identify atypical locations or spatial outliers, discover patterns of spatial association, clusters or hot spots, and suggest spatial regimes or other forms of spatial heterogeneity.[12 13] The methods can be applied by health officials to monitor spatial variations in disease rates, which can assist health officials in designing more location-specific control and prevention programs by taking into account global and local spatial influences.[14] Measures of spatial autocorrelation are at the core of ESDA methods.[13] ESDA methods and the empirical Bayes (EB) smoothing technique are commonly combined to characterize spatial epidemiology of diseases.[14-17] The EB smoothing technique is used to reduce random variation and to provide greater stability of rates mainly in small areas associated with small populations.[16] The primary purpose of this paper is to apply ESDA methods and the EB smoothing technique to monitor county-level incidence rates for human brucellosis in mainland China from 2004 to 2010 by examining spatial patterns. We also identified the potential presence of clusters of the disease in mainland China, thus to provide spatial guidance for future research.

METHODS

Data source

Human brucellosis cases including 2872 counties in mainland China from 2004 to 2010 were collected through the Internet-based disease-reporting system (China Information System for Disease Control and Prevention, CISDCP), which was established in 2004 and was more integrated, effective, and reliable than the previous case-reporting system.[18 19] In mainland China, human brucellosis is a reportable disease. Suspected or confirmed cases must be reported to local and provincial Centers for Disease Control and Prevention (CDC) and then to Chinese CDC (CCDC). To meet case definitions, disease in persons must be accompanied by clinical signs and must be confirmed by serologic tests or isolation in accordance with the case definition of the World Health Organization.[20]

In this paper, the incidence rates of human brucellosis in fact referred to the reported incidence rates. In order to conduct a geographic information system (GIS) -based analysis of the spatial distribution of human brucellosis, the county-level polygon map at a 1:1,000,000 scale was obtained.[21] Demographic information from 2004 to 2010 was acquired from the National Bureau of Statistics of China. All human brucellosis cases were geocoded and matched to the county-level layers of the polygons by administrative code using the software Mapinfo7.0.[21]

EB smoothing technique

When raw rates derived from different counties across the whole study area are applied to estimate the underlying disease risk, differences in population size result in variance instability and spurious outliers. This is because the rates observed in areas with small populations may be highly unstable in that the addition or deletion of one or two cases can cause drastic changes in the observed values. Therefore, raw rates may not fully represent the relative magnitude of the underlying risks if compared with other counties with high population base. To overcome this problem, the EB smoothing technique proposed by Clayton and Kaldor[16] was applied to our brucellosis data. This method adjusts raw rates by incorporating data from other neighbouring spatial units.[22] Essentially, raw rates get 'shrunk' towards an overall mean which is an inverse function of the variance. Application of EB smoothed incidence rate not only provides better visualization compared with raw rate but also serves to find true outliers.[23]

Spatial autocorrelation analysis

We performed spatial autocorrelation analysis in GeoDa0.9.5-i software.[24] Both global and local Moran's I statistics were calculated. The global Moran's I statistic was estimated to assess the evidence of global spatial autocorrelation (clustering) of incidence rates over the study region.[25] Anselin's local Moran's I (LISA) statistic indicates the location of local clusters and spatial outliers.[26] Spatial autocorrelation statistics for human brucellosis incidence rates were calculated based on the assumption of constant variance. The assumption might be violated when incidence rates at the county level varied greatly across the whole study region.[27] The EB smoothing technique was performed to adjust for this violation. The standardized first-order contiguity Queen neighbours were used as the criteria for identifying neighbors in this paper. A significant test was performed through the permutation test, and a reference distribution was generated under an assumption that the incidence was randomly distributed. In order to obtain more robust results, the number of permutation test was set to 9999. Since multiple comparisons increased the chances of identifying overlapping clusters, the significance level was set at 0.01. Based on these permutations and threshold, we have plotted values on a map to display the location of human brucellosis clusters in mainland China.[28]

RESULTS

Annualized average of human brucellosis from 2004 to 2010

A total of 164,752 human brucellosis cases were reported in mainland China from 2004 to 2010. Annual EB smoothed incidence rates for human brucellosis for all 2872 counties were calculated. Table 1 presents annual EB smoothed incidence rates for human brucellosis over 100 cases per 100, 000 people in 28 counties, which accounted for 34.41% of all cases in the country during the study period. Inner Mongolia Autonomous Region had the highest number of 23, centered in Xilin Gol League, Ulanqab League, Hulunbeier City, Xing'an League, Baotou City, Chifeng City, Hohhot City, and Tongliao City.

Summary statistics for the annual EB smoothed incidence rates for all counties were calculated. The mean and standard deviation were 4.64 and 38.66, respectively, per 100,000 people. The statistic for outliers was the computed z-value, which was the difference between the observed and expected mean of the annual EB smoothed incidence rates standardized by the standard deviation. Thus, it had a mean of zero and a standard deviation of 1. Sunitezuo Banner in

Xilin Gol League in Inner Mongolia had the highest annual EB smoothed incidence rate of 1209.60, with 31.16 standard deviations from the mean. All 28 counties were at least 2.59 standard deviations from the mean, as shown in Table 1.

Table 1 Counties with annual EB smoothed incidence rates of human brucellosis over 100 per 100, 000 in mainland China, 2004–2010

No.	*Province*	*City*	*County*	*Rate**	*Z-value*	*P-value*	**Rank**
1	Inner Mongolia	Xilin Gol League	Sunitezuo Banner	1209.60	31.16	<0.001	1
2			Abag Banner	1004.10	25.85	<0.001	2
3			Bordered Yellow Banner	826.90	21.27	<0.001	3
4			Plain Blue Banner	364.40	9.30	<0.001	4
5			Zhenxianghuang Banner	303.70	7.73	<0.001	5
6			Sunite Right Banner	294.60	7.50	<0.001	6
7			west ujimqin banner	243.50	6.18	<0.001	9
8			Xilinhot City	236.80	6.00	<0.001	10
9			East Ujumqin Banner	219.00	5.54	<0.001	11
10			Duolun County	176.70	4.45	<0.001	15
11		Ulanqab League	Siziwang Banner	257.90	6.55	<0.001	7
12			Huade County	179.00	4.51	<0.001	14
13			Qahar Right Wing Rear Banner	163.90	4.12	<0.001	16
14			Shangdu County	142.40	3.56	<0.001	20
15			Chahar Right Middle Banner	128.80	3.21	<0.002	23
16		Hulunbeier City	New Barhu Right Banner	255.10	6.48	<0.001	8
17			New Barhu Left Banner	203.40	5.14	<0.001	13
18			Zhalantun City	144.20	3.61	<0.001	19
19		Xing'an League	Horqin Right Wing Front Banner	146.00	3.66	<0.001	18
20		Baotou City	Daerhanmaomingan Union Banner	129.80	3.24	<0.002	22
21		Chifeng City	Keshiketeng Banner	126.50	3.15	<0.002	24
22		Hohhot City	Qingshuihe County	123.90	3.08	<0.005	25
23		Tongliao City	Jarud Banner	104.90	2.59	<0.010	28
24	Shanxi	Datong City	Tianzhen County	162.30	4.08	<0.001	17
25			Guangling County	136.50	3.41	<0.001	21
26		Xinzhou City	Shengchi County	107.70	2.67	<0.010	27
27	Heilongjiang	Qiqihar City	Meris Daur District	208.10	5.26	<0.001	12
28	Hebei	Zhangjiakou City	Chicheng County	117.60	2.92	<0.005	26

Rate*: These are annual EB smoothed incidence rates for human brucellosis.

Figure 1 presented a percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010. The figure gives an indication of spatial associations: counties with similar colour shades tended to be near each other. Outlier counties with extreme values were highlighted (both high as well as low). Six legend categories were created, corresponding to < 1%, 1% to <10%, 10% to <50%, 50% to <90%, 90% to <99% and >99%. There were 29 counties at the high end.

The global Moran's I value of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010 was 0.5803 (Z= 8.3660, P=0.0025), statistically significant at the 0.01 level.

We also calculated the local Moran's I and gave a LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010. LISA cluster map showed those counties with a significant local Moran statistic classified by type of spatial correlation: bright red for the high-high association, bright blue for low-low, light blue for low-high, and light red for high-low (Figure 2). The high-high and low-low locations suggest clustering of similar values, whereas the high-low and low-high locations indicate spatial outliers.

The Local Moran's I method of annual EB smoothed incidence rates for human brucellosis showed major high-risk clustered areas of human brucellosis located in northern China. High-risk counties were centered in Inner Mongolia (40 counties, 72.3%), Hebei (7 counties, 12.7%), Shanxi (5 counties, 9.1%),

Heilongjiang (2 counties, 3.6%) and Jilin provinces (1 county, 1.8%) and included a total of 55 counties. These provinces accounted for 90.88% of the reported cases. EB smoothed incidence rates for these counties ranged from 7.70 to 1209.60 cases per 100,000 people.

<<Insert figure 1 here>>

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Changes in human brucellosis incidence rates from 2004 to 2010

The value of Global Moran's I of EB smoothed incidence rates increased from 0.2460 to 0.6179 during 2004-2010, indicating that the spatial distribution of human brucellosis had become more uneven (that is, the clustering of high and low values is becoming more prominent) (Table 2). The formal test of spatial dependence was statistically significant at the 0.01 level, implying that distribution of human brucellosis was spatially dependent in mainland China.

Table 2 Global spatial autocorrelation analyses for EB smoothed incidence rates for human brucellosis in mainland China (per year), 2004–2010

Year	Moran's *I*	*Z*-score	*P* value
2004	0.2460	4.7733	0.0087
2005	0.4734	9.0229	0.0012
2006	0.4662	7.6853	0.0026
2007	0.5063	7.3102	0.0042
2008	0.5594	8.4932	0.0025
2009	0.5509	8.3389	0.0020
2010	0.6179	11.1187	0.0002

The clustered areas varied during the seven-year study period (Figure 3). The number of high-risk counties—that is, those counties included in clustered areas of high human brucellosis risk identified by the local Moran's I

method—increased from 25 in 2004 to 54 in 2010.

The number of high-risk counties in Inner Mongolia Autonomous Region was the largest one, increased from 22 in 2004 to 46 in 2010. Among the 101 counties in Inner Mongolia Autonomous Region, the number of EB smoothed incidence rates over 100 cases per 100,000 people increased from 8 in 2004 to 29 in 2010. The most notable change was that the EB smoothed incidence rate in Sunitezuo Banner increased from 373.7 in 2004 to 2,482.1 in 2009, but then decreased to 1,443.0 cases per 100,000 people in 2010.

In Hebei Province, the number of high-risk counties kept an upward trend, rising from 1 in 2004 to 3 in 2010. The most noteworthy change was that the EB smoothed incidence rate in Wei County increased from 9.70 to 79.40 cases per 100,000 people between 2004 and 2010.

The number of high-risk counties in Shanxi Province increased from zero in 2004 to 2 in 2010. The most notable change was that the EB smoothed incidence rate in Xinrong District increased from 0.9 to 88.1 cases per 100,000 people between 2004 and 2010.

In Jilin Province, the number of high-risk counties increased from zero in 2004 to 3 in 2010. The most notable change was that the EB smoothed incidence rate in Tongyu County increased from zero to 155.6 cases per 100,000 people between 2004 and 2010.

In Heilongjiang Province, the number of high-risk counties decreased from 2 to 0 between 2004 and 2010. Meris Daur District had the highest EB smoothed

incidence rates of human brucellosis in the province, at more than 130 cases per 100,000 people per year between 2004 and 2010. The most notable change was that the EB smoothed incidence rate in Zhaozhou County increased from 1.3 to 74.2 cases per 100,000 people between 2004 and 2010.

<<Insert figure 3 here>>

DISCUSSION

In this paper, ESDA methods were used to explore spatial patterns of EB smoothed incidence rates for human brucellosis at the county level in mainland China from 2004 to 2010. We found that the occurrence of human brucellosis persisted throughout many areas of the country and was spatially dependent during the seven-year study period. Since human brucellosis is not a contagious disease, spatial clusters of human brucellosis are most likely a result of animal processing, shared food sources, more intensive agricultural production zones, or similar socio-cultural practices.[17 29] Further researches are needed to determine whether human brucellosis clusters in China are associated with specific natural and/or social environmental characteristics. During the period 2004-2010, the areas with serious epidemics of human brucellosis persisted in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia Autonomous Region where animal husbandry had developed, all of which were epidemic regions before the 1980s. This spatial pattern may be related to the trans-boundary transfer of animal brucellosis in the region of Inner Mongolia

from the neighboring hyper-endemic Mongolia, which had been described as the country with the second highest incidence worldwide.[7 30] In addition, the leading risk factors for the high incidence rate of human brucellosis were the increase in animal feeding, lack of immunization and animal quarantine, and frequent trading.[9 30]

Several intervention strategies had been suggested to reduce the incidence of human brucellosis, such as increasing local knowledge of proper food handling techniques of dairy products including pasteurization, decreasing occupational exposures, quarantining, separating and eliminating of infected animals with brucellosis, establishing surveillance point of brucellosis and its network, and vaccination programs aimed at reducing the prevalence of disease in livestock.[8 31] However, Zhang[9] suggested that the most effective means of human brucellosis control were the comprehensive measures of universal immunization in livestock without quarantine in epidemic regions, which had been proved effective measures.

Previous study analyzed cluster identification of the annualized raw incidence rates of county-level human brucellosis in China by using SaTScan and ArcGIS software.[32] Our work is very different from the previous study. Firstly, we used the EB smoothing technique to smooth the human brucellosis incidence rates. Therefore, random variability was reduced and greater stability of incidence rates was provided mainly in small counties. Secondly, although both the previous study and our work analyzed county-level human brucellosis cases in mainland China from 2004 to 2010, the previous study performed cluster detection by using a seven-year average human brucellosis cases which merely reflected the average spatial aggregation. In this paper, we performed the cluster detection year by year by using the annual human brucellosis cases from 2004 to 2010 which fully reflected the year-by-year changes in spatial pattern of human brucellosis incidence rates from 2004 to 2010. Thirdly, compared with the spatial scan statistic, LISA has a better chance of detecting true cluster areas with low false-positive rates especially performing well on outlier detection.[33] This is the first study, to the best of our knowledge, which has applied both ESDA methods and the EB smoothing technique to analyze spatial patterns of incidence rates for human brucellosis at the county level in mainland China. We believe that conclusions on the basis of the combinations of the two methods provide reliable results. The results of these two methods differed slightly and complemented each other. In addition, the previous study is just a letter, the results of which is very simple and rough and provided very limited information.

Our study is not without limitations. First of all, the number of reported cases of human brucellosis obtained from the CISDCP system might be only part of the actual incidence of human brucellosis across the country as human brucellosis is often underreported or misdiagnosed.[30] True human brucellosis rates might be much higher than reported. Nevertheless, the data used in this paper are still able to reflect the current trend in human brucellosis incidence in mainland China. Secondly, cross-organizational collaboration (between public health, clinics, and hospitals) has been very efficient within the healthcare system. However, information-sharing between healthcare organizations and non-health departments, such as the government's agriculture department, has not been extensive. Currently, animal and human health disease surveillance databases are not linked. Additionally, we can't obtain the data of animal brucellosis because of confidentiality restrictions. [18] Therefore, we didn't analyze the density of livestock compare with the distribution of human cases. Furthermore, our analyses are based on county-level data. Smaller spatial units might provide more location-specific information about the design and implementation stages of public health programs.[14] The methods employed in this paper can be applied to finer geographic units (e.g. postal units). Finer geographic units to identify clusters within counties with higher burdens of human brucellosis would be focused on in further research.

In conclusion, our study offered a good understanding of the spatial patterns of human brucellosis incidence in mainland China, and might contribute to determine allocating resources to high risk areas in order to reduce human brucellosis incidence. With the assistance of the spatial framework provided by our study, China's human brucellosis control programs could be focused on locations where they will have the greatest influence.

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Contributors JZ designed the research, collected data, drafted the manuscript, analysed the data and interpreted the results. FY designed the research, collected data, interpreted the results critically reviewed and edited the manuscript. TZ, CY, XZ interpreted the results critically reviewed and edited the manuscript. XL designed the research, interpreted the results, critically reviewed and edited the manuscript and funding, and supervised. ZH offered research data and edited the manuscript. All authors read and approved the final manuscript.

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Figure legends

Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010

Article type: research paper

Spatial analysis on human brucellosis incidence in mainland China: 2004-2010

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ABSTRACT

Objectives: China has experienced a sharply increasing rate of human brucellosis in recent years. Effective spatial monitoring of human brucellosis incidence is very important for successful implementation of control and prevention programs. The purpose of this paper is to apply exploratory spatial data analysis (ESDA) methods and the empirical Bayes (EB) smoothing technique to monitor county-level incidence rates for human brucellosis in mainland China from 2004 to 2010 by examining spatial patterns.

Methods: ESDA methods were used to characterize spatial patterns of EB smoothed incidence rates for human brucellosis based on county-level data obtained from the China Information System for Disease Control and Prevention (CISDCP) in mainland China from 2004 to 2010.

Results: EB smoothed incidence rates for human brucellosis were spatially dependent during 2004-2010. The local Moran test identified significantly high-risk clusters of human brucellosis (all P-values <0.01), which persisted during the seven-year study period. High-risk counties were centered in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia Autonomous Region where animal husbandry was highly developed. The number of high-risk counties increased from 25 in 2004 to 54 in 2010.

Conclusions: ESDA methods and the EB smoothing technique can assist public health officials in identifying high-risk areas. Allocating more resources to high-risk areas is an effective way to reduce human brucellosis incidence.

Keywords: *Human brucellosis, exploratory spatial data analysis, empirical Bayes smoothing, spatial autocorrelation, cluster detection*

Word Count: 3208

ARTICLE SUMMARY

Article focus

- The incidence rates of human brucellosis are not distributed evenly across regions in China. Awareness of the spatial patterns of human brucellosis is quite beneficial for the prevention and control of the disease.
- ESDA methods and the empirical Bayes smoothing technique are commonly combined to characterize spatial epidemiology of diseases.

Key messages

- EB smoothed incidence rates for human brucellosis were spatially dependent during 2004-2010. The local Moran test identified significantly high-risk clusters of human brucellosis, which persisted during the seven-year study period.
- High-risk counties were centered in Inner Mongolia Autonomous Region and other Northern provinces around the border with Inner Mongolia Autonomous Region where animal husbandry was highly developed.
- ESDA methods and the EB smoothing technique can assist public health officials in identifying high-risk areas.

Strengths and limitations of this study

- ESDA methods and the EB smoothing technique were used to analyze spatial patterns of incidence rates for human brucellosis at the county level in mainland China. Therefore, random variability was reduced, and greater stability of incidence rates was provided mainly in small counties and true cluster areas with low false-positive rates especially performing well on outlier detection had a better chance of being detected.

- The number of reported cases of human brucellosis obtained from the CISDCP system might be only part of the actual incidence of human brucellosis across the country as human brucellosis is often underreported or misdiagnosed.
- Our analyses are based on county-level data. Smaller spatial units might provide more location-specific information about the design and implementation stages of public health programs.

INTRODUCTION

Brucellosis, caused by Brucella species, is a zoonotic disease recognized as an emerging and re-emerging threat to public and veterinary health.[1] The disease is transmitted to humans by direct/indirect contact with infected animals or through the consumption of contaminated foods.[2-4] People with occupational exposure are at highest risk for brucellosis, in particular those performing husbandry activities, butchering, and livestock trading.[5 6] Worldwide economic losses caused by brucellosis are extensive not only in animal production but also in public health.[1] Although brucellosis has been eradicated from many industrialized countries, new foci of disease continually appear, particularly in parts of Asia.[7]

Brucellosis is classified as one of the Class II national notifiable diseases by the Centers for Disease Control and Prevention (CDC) and as a key disease in

Class II by the Implement Detailed Rules of the By-law on Disease Prevention and Control of Livestock and Poultry in mainland China.[8] The disease was first reported in China in 1905.[8] Human brucellosis incidence was quite severe before 1980s in the country, later decreased and remained at a low level. From 1995 to 2001, the incidence of human brucellosis increased rapidly, and spread more than 10 provinces.[8] In recent years, With the rapid development of China's animal husbandry, human brucellosis incidence had increased sharply.[9] Nationwide surveillance data indicated that the total incidence rate of human brucellosis in mainland China increased from 0.92 cases per 100,000 people in 2004 to 2.62 cases per 100,000 people in 2010.[10] Currently, human brucellosis is considered an important public health problem in mainland China.[11]

The incidence rates of human brucellosis are not distributed evenly across regions in China.[10] Awareness of the spatial patterns of human brucellosis is quite beneficial for the prevention and control of the disease. Exploratory spatial data analysis (ESDA) methods are emerging useful approaches to achieve this understanding.[12] ESDA is a set of techniques used to describe and visualize spatial distributions, identify atypical locations or spatial outliers, discover patterns of spatial association, clusters or hot spots, and suggest spatial regimes or other forms of spatial heterogeneity.[12 13] The methods can be applied by health officials to monitor spatial variations in disease rates, which can assist health officials in designing more location-specific control and prevention programs by taking into account global and local spatial influences.[14] Measures of spatial autocorrelation are at the core of ESDA methods.[13] ESDA methods and the empirical Bayes (EB) smoothing technique are commonly combined to characterize spatial epidemiology of diseases.[14-17] The EB smoothing technique is used to reduce random variation and to provide greater stability of rates mainly in small areas associated with small populations.[16] The primary purpose of this paper is to apply ESDA methods and the EB smoothing technique to monitor county-level incidence rates for human brucellosis in mainland China from 2004 to 2010 by examining spatial patterns. We also identified the potential presence of clusters of the disease in mainland China, thus to provide spatial guidance for future research.

METHODS

Data source

Human brucellosis cases including 2872 counties in mainland China from 2004 to 2010 were collected through the Internet-based disease-reporting system (China Information System for Disease Control and Prevention, CISDCP), which was established in 2004 and was more integrated, effective, and reliable than the previous case-reporting system.[18 19] In mainland China, human brucellosis is a reportable disease. Suspected or confirmed cases must be reported to local and provincial Centers for Disease Control and Prevention (CDC) and then to Chinese CDC (CCDC). To meet case definitions, disease in persons must be accompanied by clinical signs and must be confirmed by serologic tests or isolation in accordance with the case definition of the World Health Organization.[20]

In this paper, the incidence rates of human brucellosis in fact referred to the reported incidence rates. In order to conduct a geographic information system (GIS) -based analysis of the spatial distribution of human brucellosis, the county-level polygon map at a 1:1,000,000 scale was obtained.[21] Demographic information from 2004 to 2010 was acquired from the National Bureau of Statistics of China. All human brucellosis cases were geocoded and matched to the county-level layers of the polygons by administrative code using the software Mapinfo7.0.[21]

EB smoothing technique

When raw rates derived from different counties across the whole study area are applied to estimate the underlying disease risk, differences in population size result in variance instability and spurious outliers. This is because the rates observed in areas with small populations may be highly unstable in that the addition or deletion of one or two cases can cause drastic changes in the observed values. Therefore, raw rates may not fully represent the relative magnitude of the underlying risks if compared with other counties with high population base. To overcome this problem, the EB smoothing technique proposed by Clayton and Kaldor[16] was applied to our brucellosis data. This method adjusts raw rates by incorporating data from other neighbouring spatial units.[22] Essentially, raw rates get 'shrunk' towards an overall mean which is an inverse function of the variance. Application of EB smoothed incidence rate not only provides better visualization compared with raw rate but also serves to find true outliers.[23]

Spatial autocorrelation analysis

We performed spatial autocorrelation analysis in GeoDa0.9.5-i software.[24] Both global and local Moran's I statistics were calculated. The global Moran's I statistic was estimated to assess the evidence of global spatial autocorrelation (clustering) of incidence rates over the study region.[25] Anselin's local Moran's I (LISA) statistic indicates the location of local clusters and spatial outliers.[26] Spatial autocorrelation statistics for human brucellosis incidence rates were calculated based on the assumption of constant variance. The assumption might be violated when incidence rates at the county level varied greatly across the whole study region.[27] The EB smoothing technique was performed to adjust for this violation. The standardized first-order contiguity Queen neighbours were used as the criteria for identifying neighbors in this paper. A significant test was performed through the permutation test, and a reference distribution was generated under an assumption that the incidence was randomly distributed. In order to obtain more robust results, the number of permutation test was set to 9999. Since multiple comparisons increased the chances of identifying overlapping clusters, the significance level was set at 0.01. Based on these permutations and threshold, we have plotted values on a map to display the location of human brucellosis clusters in mainland China.[28]

RESULTS

Annualized average of human brucellosis from 2004 to 2010

A total of 164,752 human brucellosis cases were reported in mainland China from 2004 to 2010. Annual EB smoothed incidence rates for human brucellosis for all 2872 counties were calculated. Table 1 presents annual EB smoothed incidence rates for human brucellosis over 100 cases per 100, 000 people in 28 counties, which accounted for 34.41% of all cases in the country during the study period. Inner Mongolia Autonomous Region had the highest number of 23, centered in Xilin Gol League, Ulanqab League, Hulunbeier City, Xing'an League, Baotou City, Chifeng City, Hohhot City, and Tongliao City.

Summary statistics for the annual EB smoothed incidence rates for all counties were calculated. The mean and standard deviation were 4.64 and 38.66, respectively, per 100,000 people. The statistic for outliers was the computed z-value, which was the difference between the observed and expected mean of the annual EB smoothed incidence rates standardized by the standard deviation. Thus, it had a mean of zero and a standard deviation of 1. Sunitezuo Banner in Xilin Gol League in Inner Mongolia had the highest annual EB smoothed incidence rate of 1209.60, with 31.16 standard deviations from the mean. All 28 counties were at least 2.59 standard deviations from the mean, as shown in Table 1.

Table 1 Counties with annual EB smoothed incidence rates of human brucellosis over 100 per 100, 000 in mainland China, 2004–2010

No.	*Province*	*City*	*County*	*Rate**	*Z-value*	*P-value*	**Rank**
1	Inner Mongolia	Xilin Gol League	Sunitezuo Banner	1209.60	31.16	<0.001	1
2			Abag Banner	1004.10	25.85	<0.001	2
3			Bordered Yellow Banner	826.90	21.27	<0.001	3
4			Plain Blue Banner	364.40	9.30	<0.001	4
5			Zhenxianghuang Banner	303.70	7.73	<0.001	5
6			Sunite Right Banner	294.60	7.50	<0.001	6
7			west ujimqin banner	243.50	6.18	<0.001	9
8			Xilinhot City	236.80	6.00	<0.001	10
9			East Ujumqin Banner	219.00	5.54	<0.001	11
10			Duolun County	176.70	4.45	<0.001	15
11		Ulanqab League	Siziwang Banner	257.90	6.55	<0.001	7
12			Huade County	179.00	4.51	<0.001	14
13			Qahar Right Wing Rear Banner	163.90	4.12	<0.001	16
14			Shangdu County	142.40	3.56	<0.001	20
15			Chahar Right Middle Banner	128.80	3.21	<0.002	23
16		Hulunbeier City	New Barhu Right Banner	255.10	6.48	<0.001	8
17			New Barhu Left Banner	203.40	5.14	<0.001	13
18			Zhalantun City	144.20	3.61	<0.001	19
19		Xing'an League	Horqin Right Wing Front Banner	146.00	3.66	<0.001	18
20		Baotou City	Daerhanmaomingan Union Banner	129.80	3.24	<0.002	22
21		Chifeng City	Keshiketeng Banner	126.50	3.15	<0.002	24
22		Hohhot City	Qingshuihe County	123.90	3.08	<0.005	25
23		Tongliao City	Jarud Banner	104.90	2.59	<0.010	28
24	Shanxi	Datong City	Tianzhen County	162.30	4.08	<0.001	17
25			Guangling County	136.50	3.41	<0.001	21
26		Xinzhou City	Shengchi County	107.70	2.67	<0.010	27
27	Heilongjiang	Qiqihar City	Meris Daur District	208.10	5.26	<0.001	12
28	Hebei	Zhangjiakou City	Chicheng County	117.60	2.92	<0.005	26

Rate*: These are annual EB smoothed incidence rates for human brucellosis.

Figure 1 presented a percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010. The figure gives an indication of spatial associations: counties with similar colour shades tended to be near each other. Outlier counties with extreme values were highlighted (both high as well as low). Six legend categories were created, corresponding to < 1%, 1% to <10%, 10% to <50%, 50% to <90%, 90% to <99% and >99%. There were 29 counties at the high end.

The global Moran's I value of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010 was 0.5803 (Z= 8.3660, P=0.0025), statistically significant at the 0.01 level.

We also calculated the local Moran's I and gave a LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county from 2004 to 2010. LISA cluster map showed those counties with a significant local Moran statistic classified by type of spatial correlation: bright red for the high-high association, bright blue for low-low, light blue for low-high, and light red for high-low (Figure 2). The high-high and low-low locations suggest clustering of similar values, whereas the high-low and low-high locations indicate spatial outliers.

The Local Moran's I method of annual EB smoothed incidence rates for human brucellosis showed major high-risk clustered areas of human brucellosis located in northern China. High-risk counties were centered in Inner Mongolia (40 counties, 72.3%), Hebei (7 counties, 12.7%), Shanxi (5 counties, 9.1%),

Heilongjiang (2 counties, 3.6%) and Jilin provinces (1 county, 1.8%) and included a total of 55 counties. These provinces accounted for 90.88% of the reported cases. EB smoothed incidence rates for these counties ranged from 7.70 to 1209.60 cases per 100,000 people.

<<Insert figure 1 here>>

<<Insert figure 2 here>>

Changes in human brucellosis incidence rates from 2004 to 2010

The value of Global Moran's I of EB smoothed incidence rates increased from 0.2460 to 0.6179 during 2004-2010, indicating that the spatial distribution of human brucellosis had become more uneven (that is, the clustering of high and low values is becoming more prominent) (Table 2). The formal test of spatial dependence was statistically significant at the 0.01 level, implying that distribution of human brucellosis was spatially dependent in mainland China.

Table 2 Global spatial autocorrelation analyses for EB smoothed incidence rates for human brucellosis in mainland China (per year), 2004–2010

Year	Moran's *I*	*Z*-score	*P* value
2004	0.2460	4.7733	0.0087
2005	0.4734	9.0229	0.0012
2006	0.4662	7.6853	0.0026
2007	0.5063	7.3102	0.0042
2008	0.5594	8.4932	0.0025
2009	0.5509	8.3389	0.0020
2010	0.6179	11.1187	0.0002

The clustered areas varied during the seven-year study period (Figure 3). The number of high-risk counties—that is, those counties included in clustered areas of high human brucellosis risk identified by the local Moran's I

method—increased from 25 in 2004 to 54 in 2010.

The number of high-risk counties in Inner Mongolia Autonomous Region was the largest one, increased from 22 in 2004 to 46 in 2010. Among the 101 counties in Inner Mongolia Autonomous Region, the number of EB smoothed incidence rates over 100 cases per 100,000 people increased from 8 in 2004 to 29 in 2010. The most notable change was that the EB smoothed incidence rate in Sunitezuo Banner increased from 373.7 in 2004 to 2,482.1 in 2009, but then decreased to 1,443.0 cases per 100,000 people in 2010.

In Hebei Province, the number of high-risk counties kept an upward trend, rising from 1 in 2004 to 3 in 2010. The most noteworthy change was that the EB smoothed incidence rate in Wei County increased from 9.70 to 79.40 cases per 100,000 people between 2004 and 2010.

The number of high-risk counties in Shanxi Province increased from zero in 2004 to 2 in 2010. The most notable change was that the EB smoothed incidence rate in Xinrong District increased from 0.9 to 88.1 cases per 100,000 people between 2004 and 2010.

In Jilin Province, the number of high-risk counties increased from zero in 2004 to 3 in 2010. The most notable change was that the EB smoothed incidence rate in Tongyu County increased from zero to 155.6 cases per 100,000 people between 2004 and 2010.

In Heilongjiang Province, the number of high-risk counties decreased from 2 to 0 between 2004 and 2010. Meris Daur District had the highest EB smoothed

incidence rates of human brucellosis in the province, at more than 130 cases per 100,000 people per year between 2004 and 2010. The most notable change was that the EB smoothed incidence rate in Zhaozhou County increased from 1.3 to 74.2 cases per 100,000 people between 2004 and 2010.

<<Insert figure 3 here>>

DISCUSSION

In this paper, ESDA methods were used to explore spatial patterns of EB smoothed incidence rates for human brucellosis at the county level in mainland China from 2004 to 2010. We found that the occurrence of human brucellosis persisted throughout many areas of the country and was spatially dependent during the seven-year study period. Since human brucellosis is not a contagious disease, spatial clusters of human brucellosis are most likely a result of animal processing, shared food sources, more intensive agricultural production zones, or similar socio-cultural practices.[17 29] Further researches are needed to determine whether human brucellosis clusters in China are associated with specific natural and/or social environmental characteristics. During the period 2004-2010, the areas with serious epidemics of human brucellosis persisted in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia Autonomous Region where animal husbandry had developed, all of which were epidemic regions before the 1980s. This spatial pattern may be related to the trans-boundary transfer of animal brucellosis in the region of Inner Mongolia

from the neighboring hyper-endemic Mongolia, which had been described as the country with the second highest incidence worldwide.[7 30] In addition, the leading risk factors for the high incidence rate of human brucellosis were the increase in animal feeding, lack of immunization and animal quarantine, and frequent trading.[9 30]

Several intervention strategies had been suggested to reduce the incidence of human brucellosis, such as increasing local knowledge of proper food handling techniques of dairy products including pasteurization, decreasing occupational exposures, quarantining, separating and eliminating of infected animals with brucellosis, establishing surveillance point of brucellosis and its network, and vaccination programs aimed at reducing the prevalence of disease in livestock.[8 31] However, Zhang[9] suggested that the most effective means of human brucellosis control were the comprehensive measures of universal immunization in livestock without quarantine in epidemic regions, which had been proved effective measures.

Previous study analyzed cluster identification of the annualized raw incidence rates of county-level human brucellosis in China by using SaTScan and ArcGIS software.[32] Our work is very different from the previous study. Firstly, we used the EB smoothing technique to smooth the human brucellosis incidence rates. Therefore, random variability was reduced and greater stability of incidence rates was provided mainly in small counties. Secondly, although both the previous study and our work analyzed county-level human brucellosis cases in mainland China from 2004 to 2010, the previous study performed cluster detection by using a seven-year average human brucellosis cases which merely reflected the average spatial aggregation. In this paper, we performed the cluster detection year by year by using the annual human brucellosis cases from 2004 to 2010 which fully reflected the year-by-year changes in spatial pattern of human brucellosis incidence rates from 2004 to 2010. Thirdly, compared with the spatial scan statistic, LISA has a better chance of detecting true cluster areas with low false-positive rates especially performing well on outlier detection.[33] This is the first study, to the best of our knowledge, which has applied both ESDA methods and the EB smoothing technique to analyze spatial patterns of incidence rates for human brucellosis at the county level in mainland China. We believe that conclusions on the basis of the combinations of the two methods provide reliable results. The results of these two methods differed slightly and complemented each other. In addition, the previous study is just a letter, the results of which is very simple and rough and provided very limited information.

Our study is not without limitations. First of all, the number of reported cases of human brucellosis obtained from the CISDCP system might be only part of the actual incidence of human brucellosis across the country as human brucellosis is often underreported or misdiagnosed.[30] True human brucellosis rates might be much higher than reported. Nevertheless, the data used in this paper are still able to reflect the current trend in human brucellosis incidence in mainland China. Secondly, cross-organizational collaboration (between public health, clinics, and hospitals) has been very efficient within the healthcare system. However, information-sharing between healthcare organizations and non-health departments, such as the government's agriculture department, has not been extensive. Currently, animal and human health disease surveillance databases are not linked. Additionally, we can't obtain the data of animal brucellosis because of confidentiality restrictions. [18] Therefore, we didn't analyze the density of livestock compare with the distribution of human cases. Furthermore, our analyses are based on county-level data. Smaller spatial units might provide more location-specific information about the design and implementation stages of public health programs.[14] The methods employed in this paper can be applied to finer geographic units (e.g. postal units). Finer geographic units to identify clusters within counties with higher burdens of human brucellosis would be focused on in further research.

In conclusion, our study offered a good understanding of the spatial patterns of human brucellosis incidence in mainland China, and might contribute to determine allocating resources to high risk areas in order to reduce human brucellosis incidence. With the assistance of the spatial framework provided by our study, China's human brucellosis control programs could be focused on locations where they will have the greatest influence.

Contributors JZ designed the research, collected data, drafted the manuscript, analysed the data and interpreted the results. FY designed the research, collected data, interpreted the results critically reviewed and edited the manuscript. TZ, CY, XZ interpreted the results critically reviewed and edited the manuscript. XL designed the research, interpreted the results, critically reviewed and edited the manuscript and funding, and supervised. ZH offered research data and edited the manuscript. All authors read and approved the final manuscript.

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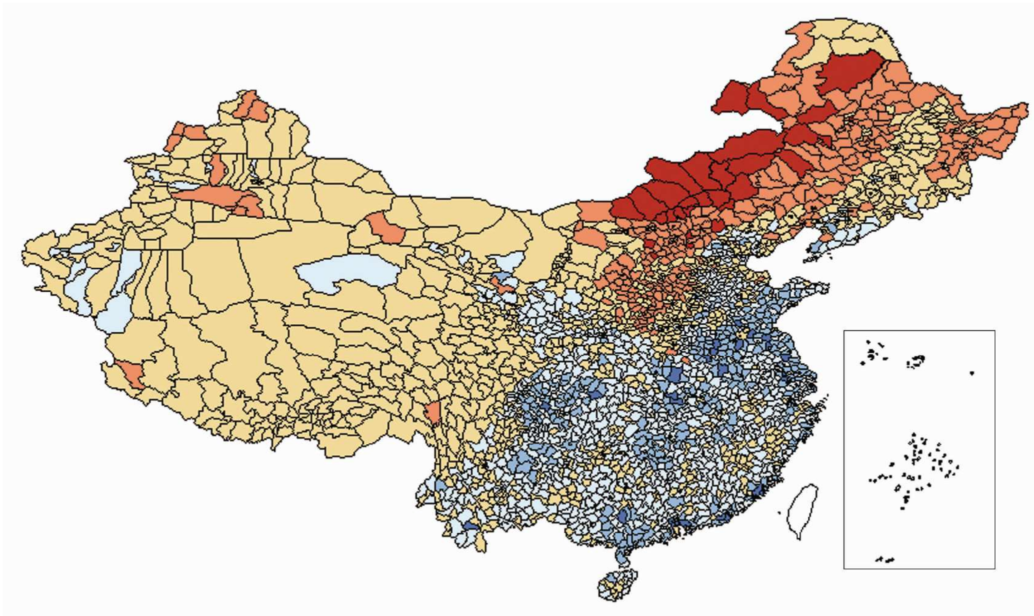

Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

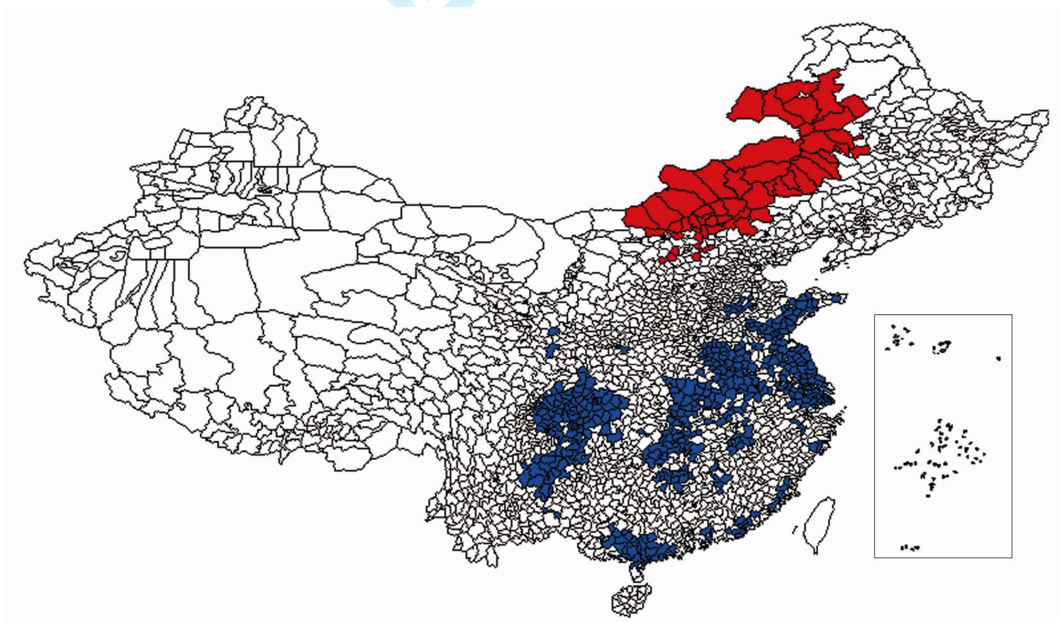

Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

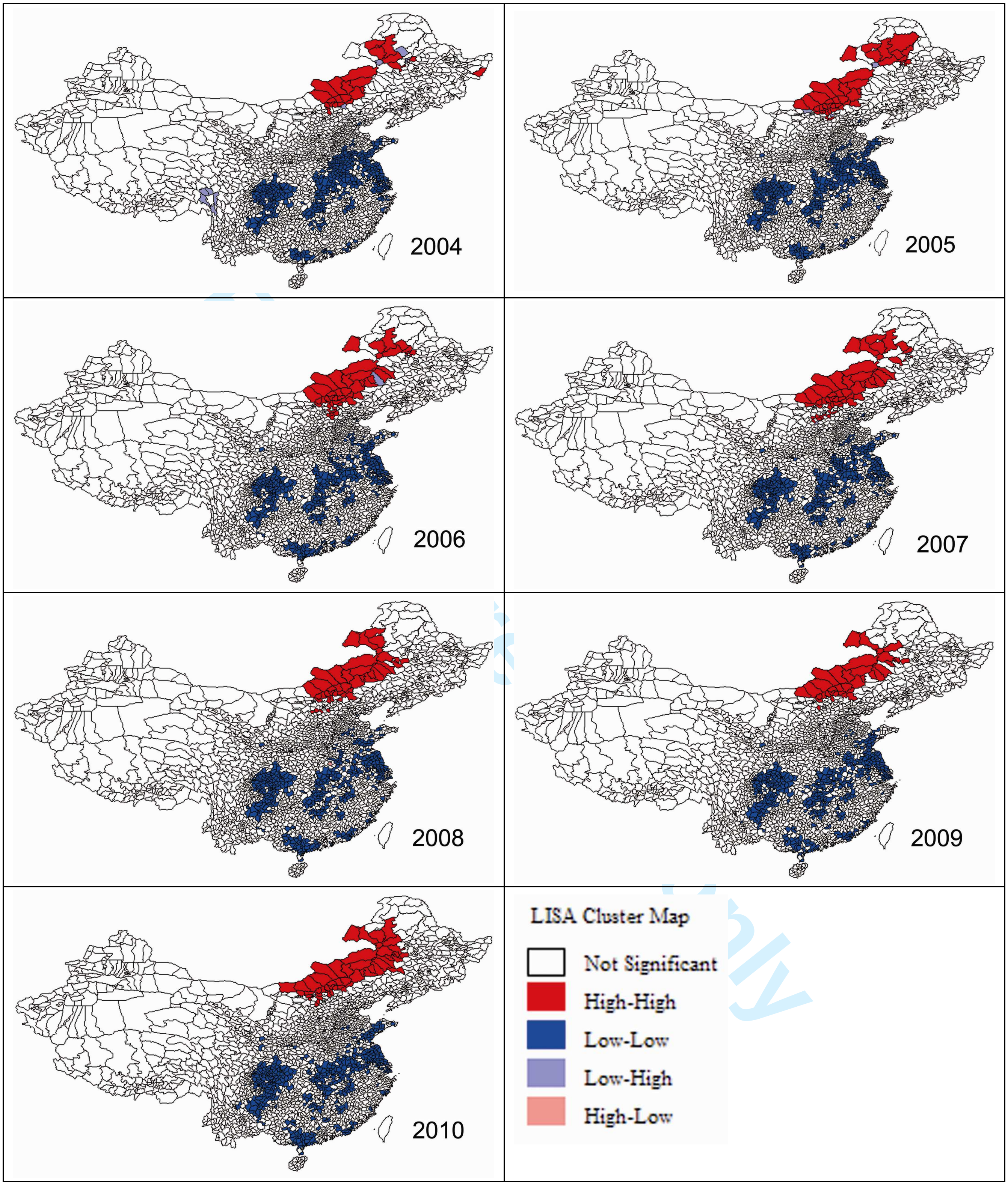

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010

Figure legends

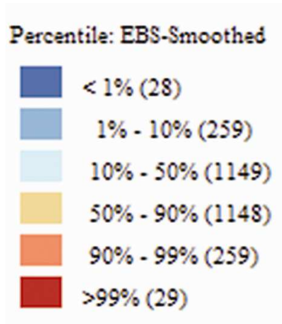

Figure legend 1 (for Figure 1)

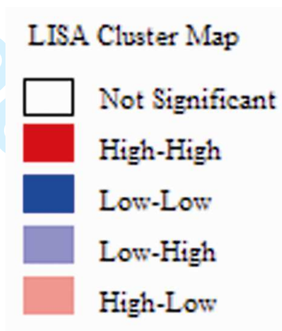

Figure legend 2 (for Figure 2 and Figure 3)

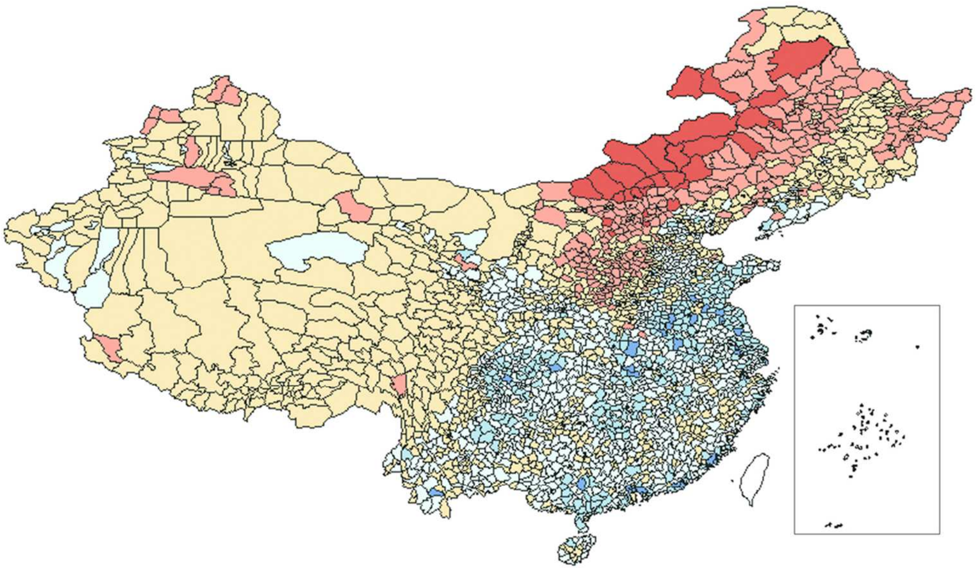

Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010
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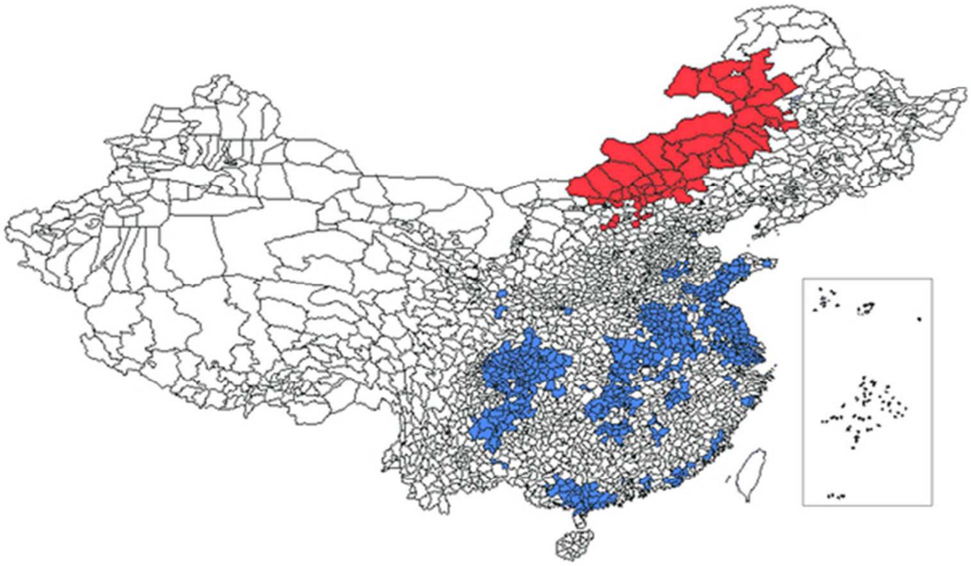

Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010
52x30mm (300 x 300 DPI)

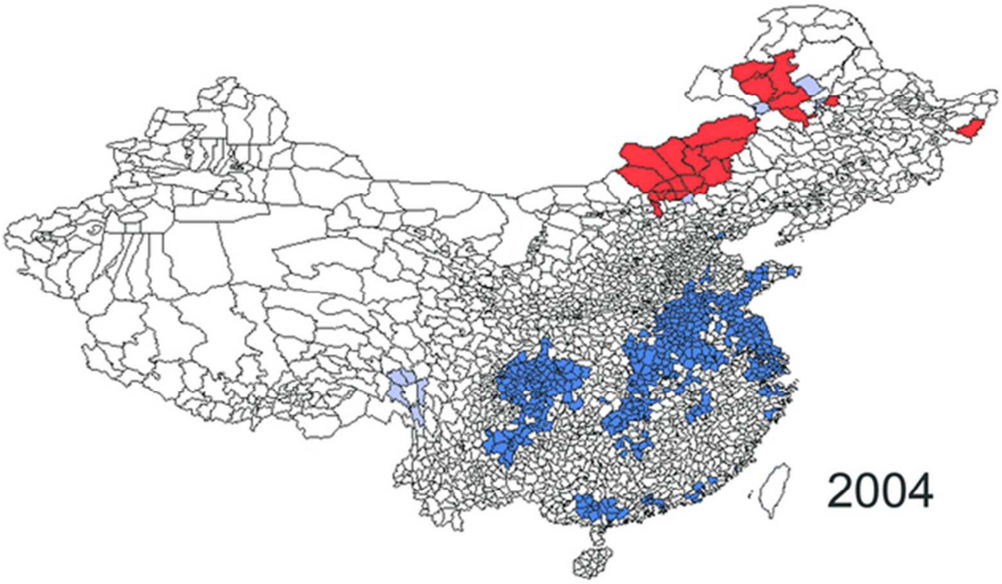

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
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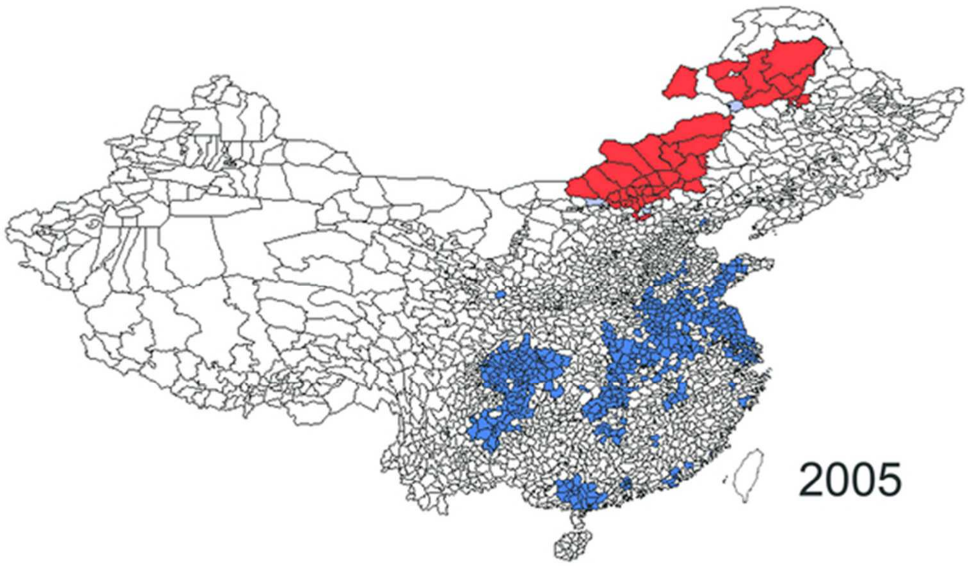

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
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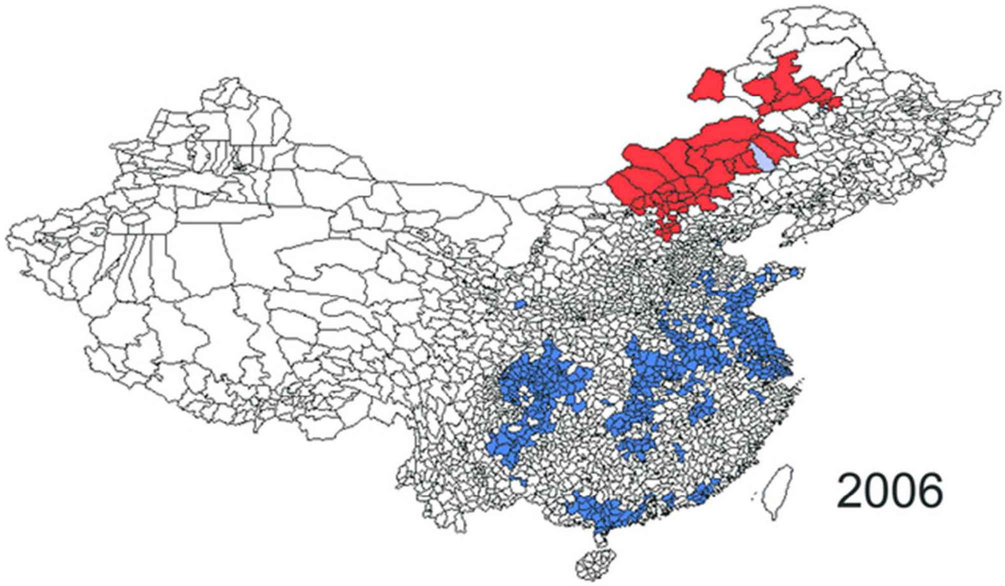

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
53x32mm (300 x 300 DPI)

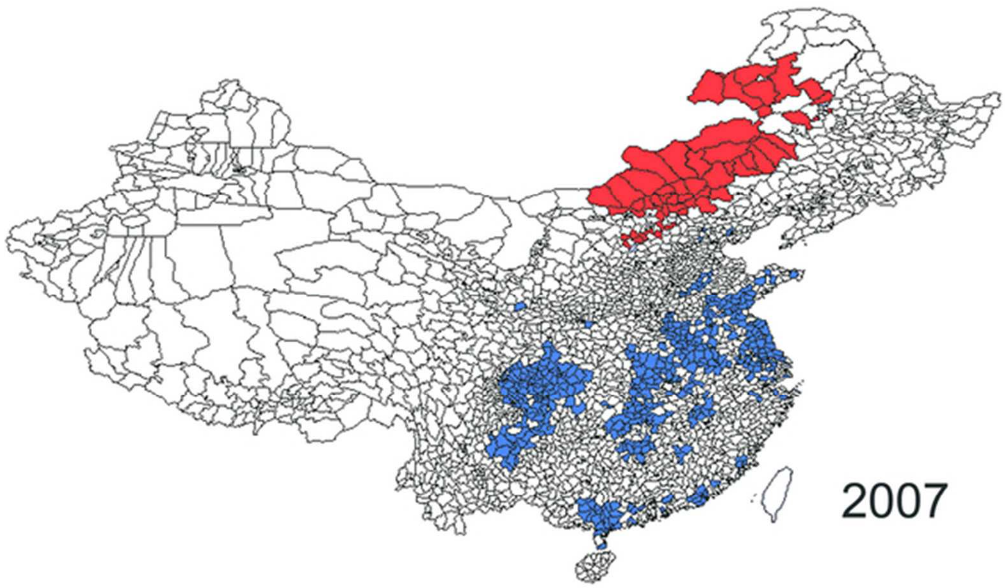

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
53x32mm (300 x 300 DPI)

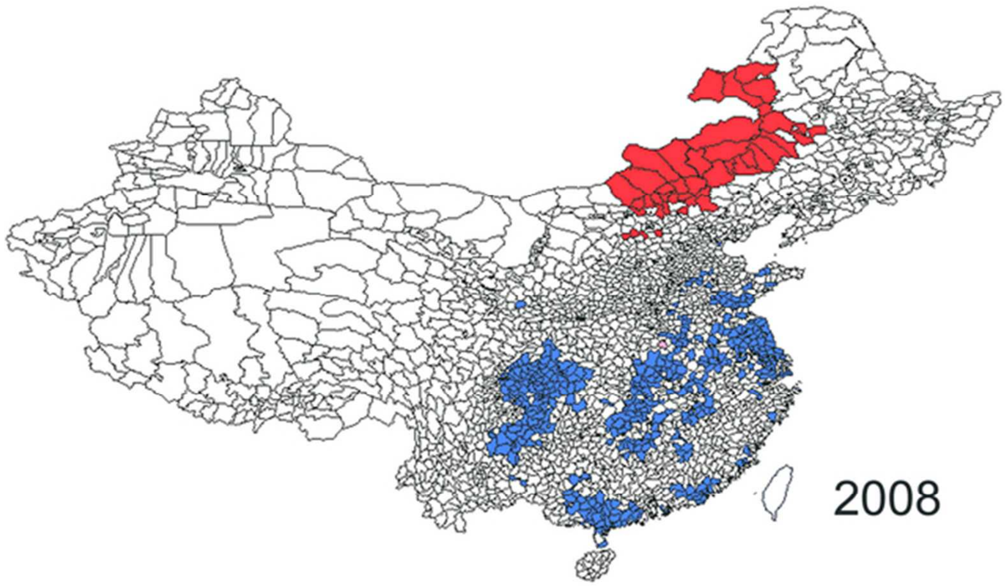

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
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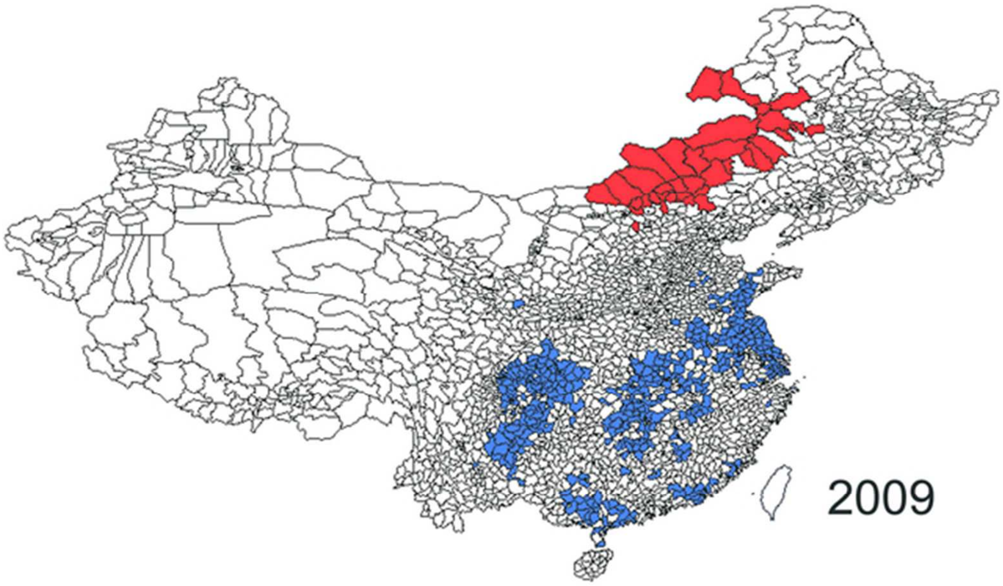

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
54x32mm (300 x 300 DPI)

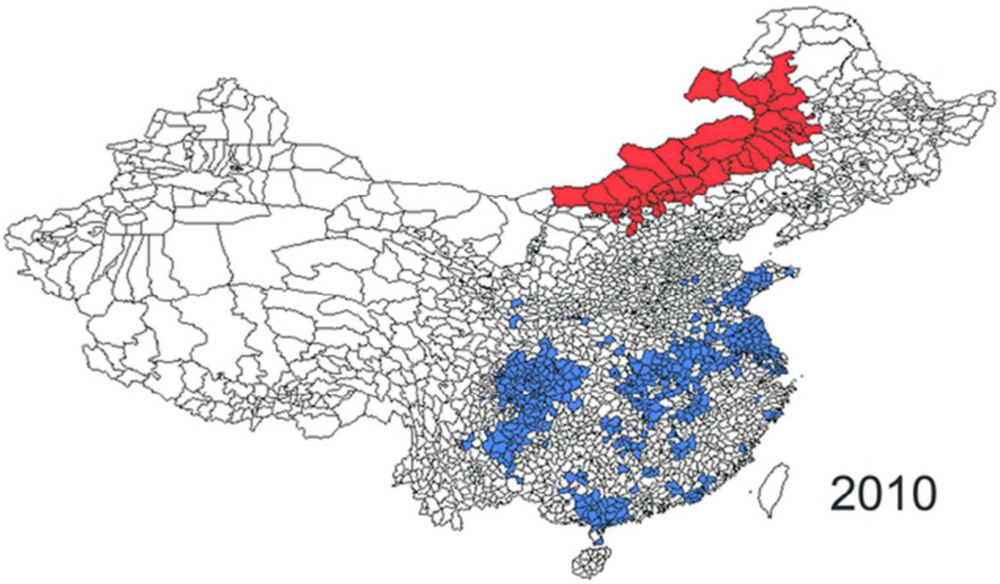

Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010
53x32mm (300 x 300 DPI)