



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

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Complete List of Authors:	Zhang, Junhui; Sichuan University, West China School of Public Health; Luzhou Medical College, School of Public Health Yin, Fei; Sichuan University, West China School of Public Health Zhang, Tao; Sichuan University, West China School of Public Health Yang, Chao; Luzhou Medical College, School of Public Health Zhang, Xingyu; Sichuan University, West China School of Public Health Feng, Zijian; Chinese Center for Disease Control and Prevention, Li, Xiaosong; Sichuan University, West China School of Public Health
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6 **Spatial analysis on human brucellosis incidence in**  
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8 **mainland China: 2004-2010**

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11 Junhui Zhang,<sup>1,2#</sup> Fei Yin,<sup>1#</sup> Tao Zhang,<sup>1</sup> Chao Yang,<sup>2</sup> Xingyu Zhang,<sup>1</sup> Zijian  
12  
13 Feng,<sup>3</sup> Xiaosong Li<sup>1\*</sup>

14  
15  
16 1 West China School of Public Health, Sichuan University, Chengdu 610041, PR  
17  
18 China

19  
20  
21 2 School of Public Health, Luzhou Medical College, Luzhou 646000, PR China

22  
23 3 Chinese Center for Disease Control and Prevention, Beijing 102206, PR China

24  
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28  
29 \*Correspondence to: Professor Xiaosong Li, Department of Medical Statistics,  
30  
31 West China School of Public Health, Sichuan University, No.17 Section 3, South  
32  
33 Renmin Road, Chengdu 610041, PR China. Tel: +86 18608021962

34  
35  
36 Email address: lixiaosong1019@163.com

37  
38  
39 # These authors contributed equally to this work

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43 **ABSTRACT**

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46 **Objectives:** China has experienced a sharply increasing rate of human  
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48 brucellosis in recent years. Effective spatial monitoring of human brucellosis  
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50 incidence is very important for successful implementation of control and  
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52 prevention programs. The purpose of this paper is to apply exploratory spatial  
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54 data analysis (ESDA) methods and the empirical Bayes (EB) smoothing  
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4 technique to monitor county-level incidence rates for human brucellosis in  
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6 mainland China from 2004 to 2010 by examining spatial patterns.  
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9 **Methods:** ESDA methods were used to characterize spatial patterns of EB  
10  
11 smoothed incidence rates for human brucellosis using county-level data  
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13 obtained from the China Information System for Disease Control and Prevention  
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15 (CISDCP) in mainland China from 2004 to 2010.  
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19 **Results:** EB smoothed incidence rates for human brucellosis were spatially  
20  
21 dependent during 2004-2010. The local Moran test identified one significant  
22  
23 northern cluster of high human brucellosis risk (all P-values <0.01), which  
24  
25 persisted during the seven-year study period. High-risk counties were centered  
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27 in Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei,  
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29 Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia  
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31 Autonomous Region where animal husbandry had developed. The number of  
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33 high-risk counties increased from 25 in 2004 to 54 in 2010.  
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39 **Conclusions:** ESDA methods and the EB smoothing technique can assist  
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41 public health officials in identifying high-risk areas. Allocating more resources to  
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43 high-risk areas could more effectively reduce human brucellosis incidence.  
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47 **Keywords:** *Human brucellosis, exploratory spatial data analysis, empirical*  
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49 *Bayes smoothing, spatial autocorrelation, cluster detection*  
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52 **Word Count:** 2747  
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## 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

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4 cluster areas with low false-positive rates especially performing well on  
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6 outlier detection had a better chance of being detected.  
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9 ■ The number of reported cases of human brucellosis obtained from the  
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11 CISDCP system might be only part of the actual incidence of human  
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13 brucellosis across the country as human brucellosis is often underreported  
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15 or misdiagnosed.  
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19 ■ Our analyses are based on county-level data. Smaller spatial units might  
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21 provide more location-specific information that can inform the design and  
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23 implementation stages of public health programs.  
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## 25 26 **INTRODUCTION**

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28 Brucellosis, caused by *Brucella* species, is a zoonotic disease recognized as an  
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30 emerging and re-emerging threat to public and veterinary health.[1] The disease  
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32 is transmitted to humans by direct/indirect contact with infected animals or  
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34 through the consumption of contaminated foods.[2-4] People with occupational  
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36 exposure are at highest risk for brucellosis, in particular those performing  
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38 husbandry activities, butchering, and livestock trading.[5 6] Worldwide economic  
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40 losses due to brucellosis are extensive not only in animal production but also in  
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42 public health.[1] Although brucellosis has been eradicated from many  
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44 industrialized countries, new foci of disease continually appear, particularly in  
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46 parts of Asia.[7]  
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50 Brucellosis is classified as one of the Class II national notifiable diseases by the  
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52 Centers for Disease Control and Prevention (CDC) and as a key disease in  
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4 Class II as described by the Implement Detailed Rules of the By-law  
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6 on Disease Prevention and Control of Livestock and Poultry in mainland  
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8 China.[8] The disease was first reported in China in 1905.[8] Human brucellosis  
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10 incidence was quite severe before 1980s in the country, later decreased and  
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12 remained at a low level. From 1995 to 2001, the incidence of human brucellosis  
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14 increased rapidly, and spread more than 10 provinces.[8] In recent years, With  
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16 the rapid development of China's animal husbandry, human brucellosis  
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18 incidence had increased sharply.[9] Nationwide surveillance data indicated that  
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20 the total incidence rate of human brucellosis in mainland China increased from  
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22 0.92 cases per 100,000 people in 2004 to 2.62 cases per 100,000 people in  
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24 2010.[10] Currently, human brucellosis is considered an important public health  
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26 problem in mainland China.[11]

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29 The incidence rates of human brucellosis are not distributed evenly across  
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31 regions in China.[10] Awareness of the spatial patterns of human brucellosis is  
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33 quite beneficial for the prevention and control of the disease. Exploratory spatial  
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35 data analysis (ESDA) methods are emerging useful approaches to achieve this  
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37 understanding.[12] ESDA is a set of techniques used to describe and visualize  
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39 spatial distributions, identify atypical locations or spatial outliers, discover  
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41 patterns of spatial association, clusters or hot spots, and suggest spatial regimes  
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43 or other forms of spatial heterogeneity.[12 13] The methods can be applied by  
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45 health officials to monitor spatial variations in disease rates, which can assist  
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47 health officials in designing more location-specific control and prevention  
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3 programs who take into account global and local spatial influences.[14]  
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6 Measures of spatial autocorrelation are at the core of ESDA methods.[13] ESDA  
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9 methods and the empirical Bayes (EB) smoothing technique are commonly  
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11 combined to characterize spatial epidemiology of diseases.[14-17] The EB  
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13 smoothing technique is used to reduce random variation and to provide greater  
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15 stability of rates mainly in small areas associated with small populations.[16]  
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18 The primary purpose of this paper is to apply ESDA methods and the EB  
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20 smoothing technique to monitor county-level incidence rates for human  
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22 brucellosis in mainland China from 2004 to 2010 by examining spatial patterns.  
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24 We also identified the potential presence of clusters of the disease in mainland  
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26 China, thus to provide spatial guidance for future research.  
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## 30 31 **METHODS**

### 32 33 **Data source**

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35 Human brucellosis cases including 2872 counties in mainland China from 2004  
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37 to 2010 were collected through the Internet-based disease-reporting system  
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39 (China Information System for Disease Control and Prevention, CISDCP), which  
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41 was established in 2004 and was more integrated, effective, and reliable than  
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43 the previous case-reporting system.[18 19] In this paper, the incidence rates of  
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45 human brucellosis in fact referred to the reported incidence rates. We used  
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47 seven-year reported human brucellosis cases to provide a stable measure of  
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49 disease incidence rate by time and location at the county level.[20] In order to  
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51 conduct a geographic information system (GIS) -based analysis of the spatial  
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4 distribution of human brucellosis, the county-level polygon map at a 1:1,000,000  
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6 scale was obtained.[20] Demographic information based on the 2000 census  
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8 was acquired from the National Bureau of Statistics of China. All human  
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10 brucellosis cases were geocoded and matched to the county-level layers of the  
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12 polygons by administrative code using the software Mapinfo7.0.[20]  
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### 15 16 **EB smoothing technique**

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18 When raw rates derived from different counties across the whole study area are  
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20 applied to estimate the underlying disease risk, differences in population size  
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22 result in variance instability and spurious outliers. This is because the rates  
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24 observed in areas with small populations may be highly unstable in that the  
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26 addition or deletion of one or two cases can cause drastic changes in the  
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28 observed values. Therefore, raw rates may not fully represent the relative  
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30 magnitude of the underlying risks if compared with other counties with high  
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32 population base. To overcome this problem, the EB smoothing technique  
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34 proposed by Clayton and Kaldor[16] was applied to our brucellosis data. This  
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36 method adjusts raw rates by incorporating data from other neighbouring spatial  
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38 units.[21] Essentially, raw rates get 'shrunk' towards an overall mean which is an  
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40 inverse function of the variance. Application of EB smoothed incidence rate not  
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42 only provides better visualization compared to raw rate but also serves to find  
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44 true outliers.[22]  
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### 53 54 **Spatial autocorrelation analysis**

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56 We performed spatial autocorrelation analysis in GeoDa0.9.5-i software.[23]  
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4 Both global and local Moran's I statistics were calculated. The global Moran's I  
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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

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4 EB smoothed incidence rates for human brucellosis over 100 cases per 100, 000  
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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	Xilin Gol	Sunitezuo Banner	1209.60	31.16	<0.001	1
2	Mongolia	League	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.

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4 Figure 1 presented a percentile map of annual EB smoothed incidence rates for  
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6 human brucellosis in mainland China by county from 2004 to 2010. The figure  
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8 gives an indication of spatial associations: counties with similar colour shades  
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10 tended to be near each other. Outlier counties with extreme values were  
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12 highlighted (both high as well as low). Six legend categories were created,  
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14 corresponding to < 1%, 1% to <10%, 10% to <50%, 50% to <90%, 90% to <99%  
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16 and >99%. There were 29 counties at the high end.  
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21 The global Moran's I value of annual EB smoothed incidence rates for human  
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23 brucellosis in mainland China by county from 2004 to 2010 was 0.5803 ( $Z=$   
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25 8.3660,  $P=0.0025$ ), statistically significant at the 0.01 level.  
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29 We also calculated the local Moran's I and gave a LISA cluster map of annual  
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31 EB smoothed incidence rates for human brucellosis in mainland China by county  
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33 from 2004 to 2010. LISA cluster map showed those counties with a significant  
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35 local Moran statistic classified by type of spatial correlation: bright red for the  
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37 high-high association, bright blue for low-low, light blue for low-high, and light red  
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39 for high-low (Figure 2). The high-high and low-low locations suggest clustering of  
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41 similar values, whereas the high-low and low-high locations indicate spatial  
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43 outliers, whereas the high-low and low-high locations indicate spatial  
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45 outliers.  
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49 The Local Moran's I method of annual EB smoothed incidence rates for human  
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51 brucellosis showed major clustered areas of high human brucellosis risk located  
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53 in northern China. High-risk counties were centered in Inner Mongolia (40  
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55 counties, 72.3%), Hebei (7 counties, 12.7%), Shanxi (5 counties, 9.1%),  
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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  $I$

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

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6 The number of high-risk counties in Inner Mongolia Autonomous Region was the  
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8 largest one, increased from 22 in 2004 to 46 in 2010. Among the 101 counties in  
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10 Inner Mongolia Autonomous Region, the number of EB smoothed incidence  
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12 rates over 100 cases per 100,000 people increased from 8 in 2004 to 29 in 2010.  
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14 The most notable change was that the EB smoothed incidence rate in Sunitezuo  
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16 Banner increased from 373.7 in 2004 to 2,482.1 in 2009, but then decreased to  
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18 1,443.0 cases per 100,000 people in 2010.  
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22 In Hebei Province, the number of high-risk counties kept an upward trend, rising  
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24 from 1 in 2004 to 3 in 2010. The most noteworthy change was that the EB  
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26 smoothed incidence rate in Wei County increased from 9.70 to 79.40 cases per  
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28 100,000 people between 2004 and 2010.  
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32 The number of high-risk counties in Shanxi Province increased from zero in  
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34 2004 to 2 in 2010. The most notable change was that the EB smoothed  
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36 incidence rate in Xinrong District increased from 0.9 to 88.1 cases per 100,000  
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38 people between 2004 and 2010.  
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42 In Jilin Province, the number of high-risk counties increased from zero in 2004 to  
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44 3 in 2010. The most notable change was that the EB smoothed incidence rate in  
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46 Tongyu County increased from zero to 155.6 cases per 100,000 people between  
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48 2004 and 2010.  
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52 In Heilongjiang Province, the number of high-risk counties decreased from 2 to 0  
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54 between 2004 and 2010. Meris Daur District had the highest EB smoothed  
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4 incidence rates of human brucellosis in the province, at more than 130 cases per  
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6 100,000 people per year between 2004 and 2010. The most notable change was  
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8 that the EB smoothed incidence rate in Zhaozhou County increased from 1.3 to  
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10 74.2 cases per 100,000 people between 2004 and 2010.  
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## 16 **DISCUSSION**

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18 In this paper, ESDA methods were used to explore spatial patterns of EB  
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20 smoothed incidence rates for human brucellosis at the county level in mainland  
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22 China from 2004 to 2010. We found that the occurrence of human brucellosis  
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24 persisted throughout many areas of the country and was spatially dependent  
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26 during the seven-year study period. Since human brucellosis is not a contagious  
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28 disease, spatial clusters of human brucellosis are most likely a result of animal  
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30 processing, shared food sources, more intensive agricultural production zones,  
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32 or similar socio-cultural practices.[17 28] Further researches are needed to  
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34 determine whether China's human brucellosis clusters are associated with  
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36 specific natural and/or social environmental characteristics. During the period  
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38 2004-2010, the areas with serious epidemics of human brucellosis persisted in  
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40 Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei,  
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42 Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia  
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44 Autonomous Region where animal husbandry had developed, all of which were  
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46 epidemic regions before the 1980s. This spatial pattern may be related to the  
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48 trans-boundary transfer of animal brucellosis in the region of Inner Mongolia  
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4 from the neighboring hyper-endemic Mongolia, which had been described as the  
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6 country with the second highest incidence worldwide.[7 29] In addition, the  
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8 leading risk factors for the high incidence rate of human brucellosis were the  
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10 increase in animal feeding, lack of immunization and animal quarantine, and  
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12 frequent trading.[9 29]

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15 Several intervention strategies had been suggested to reduce the incidence of  
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17 human brucellosis, such as increasing local knowledge of proper food handling  
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19 techniques of dairy products including pasteurization, decreasing occupational  
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21 exposures, quarantining, separating and eliminating of infected animals with  
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23 brucellosis, establishing surveillance point of brucellosis and its network, and  
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25 vaccination programs aimed at reducing the prevalence of disease in livestock.[8  
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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



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4 EB smoothing technique to smooth the human brucellosis incidence rates.  
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6 Therefore, random variability was reduced and greater stability of incidence  
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8 rates was provided mainly in small counties. Second, LISA has a better chance  
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10 of detecting true cluster areas with low false-positive rates especially performing  
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12 well on outlier detection.[32] In addition, our paper provides changes in human  
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14 brucellosis incidence rates from 2004 to 2010. This is the first study, to the best  
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16 of our knowledge, which has applied both ESDA methods and the EB smoothing  
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18 technique to analyze spatial patterns of incidence rates for human brucellosis at  
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20 the county level in mainland China. We believe that conclusions based on the  
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22 combinations of the two methods provide reliable results.  
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28 Our study is not without limitations. First of all, the number of reported cases of  
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30 human brucellosis obtained from the CISDCP system might be only part of the  
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32 actual incidence of human brucellosis across the country as human brucellosis  
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34 is often underreported or misdiagnosed.[29] True human brucellosis rates might  
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36 be much higher than reported. Nevertheless, the data used in this paper are still  
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38 able to reflect the current trend in human brucellosis incidence in mainland  
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40 China. Secondly, our analyses are based on county-level data. Smaller spatial  
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42 units might provide more location-specific information that can inform the design  
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44 and implementation stages of public health programs.[14] The methods  
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46 employed in this paper can be applied to finer geographic units (e.g. postal units).  
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48 Finer geographic units to identify clusters within counties with higher burdens of  
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50 human brucellosis would be focused on in further research.  
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4 In conclusion, our study offered a good understanding of the spatial patterns of  
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6 human brucellosis incidence in mainland China, and might contribute to  
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8 determine allocating resources to high risk areas in order to reduce human  
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10 brucellosis incidence. With the assistance of the spatial framework provided by  
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12 our study, China's human brucellosis control programs could be focused on  
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14 locations where they will have the greatest influence.  
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21 **Contributors** JZ designed the research, collected data, drafted the manuscript,  
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23 analysed the data and interpreted the results. FY designed the research,  
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25 collected data, interpreted the results critically reviewed and edited the  
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27 manuscript. TZ, CY, XZ interpreted the results critically reviewed and edited the  
28  
29 manuscript. XL designed the research, interpreted the results, critically reviewed  
30  
31 and edited the manuscript and funding, and supervised. ZH offered research  
32  
33 data and edited the manuscript. All authors read and approved the final  
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35 manuscript.  
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48  
49 data collection and analysis, decision to publish, or preparation of the  
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51 manuscript.  
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55 **Competing interests** None.  
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6 **Data sharing statement** No additional data are available.  
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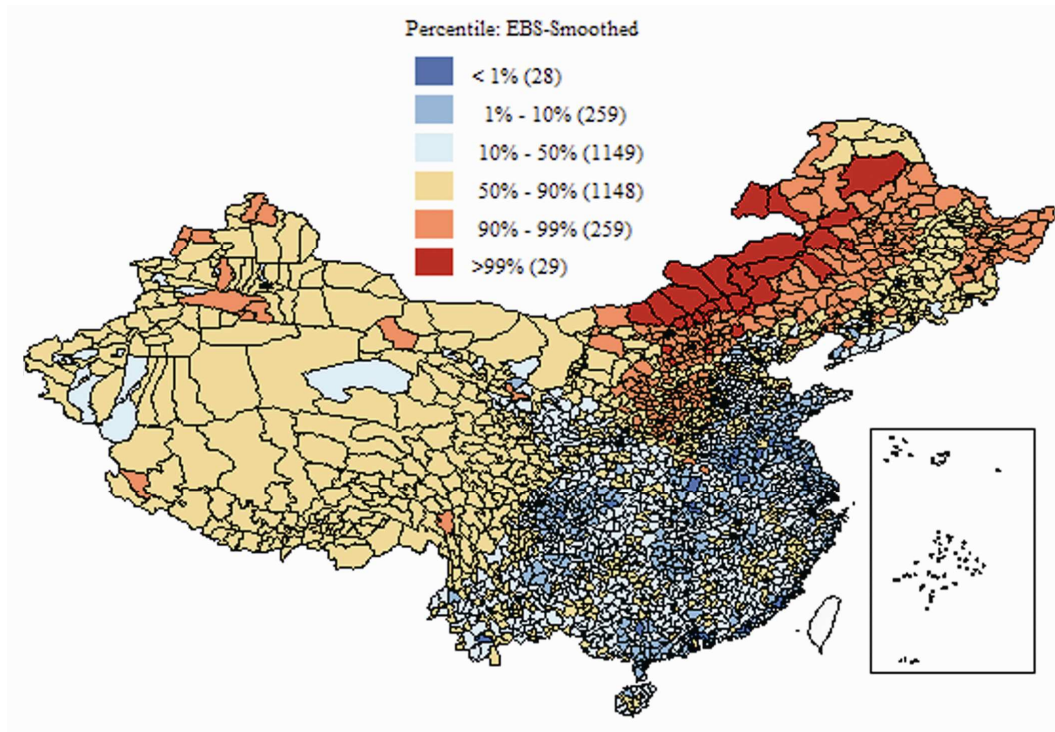


Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

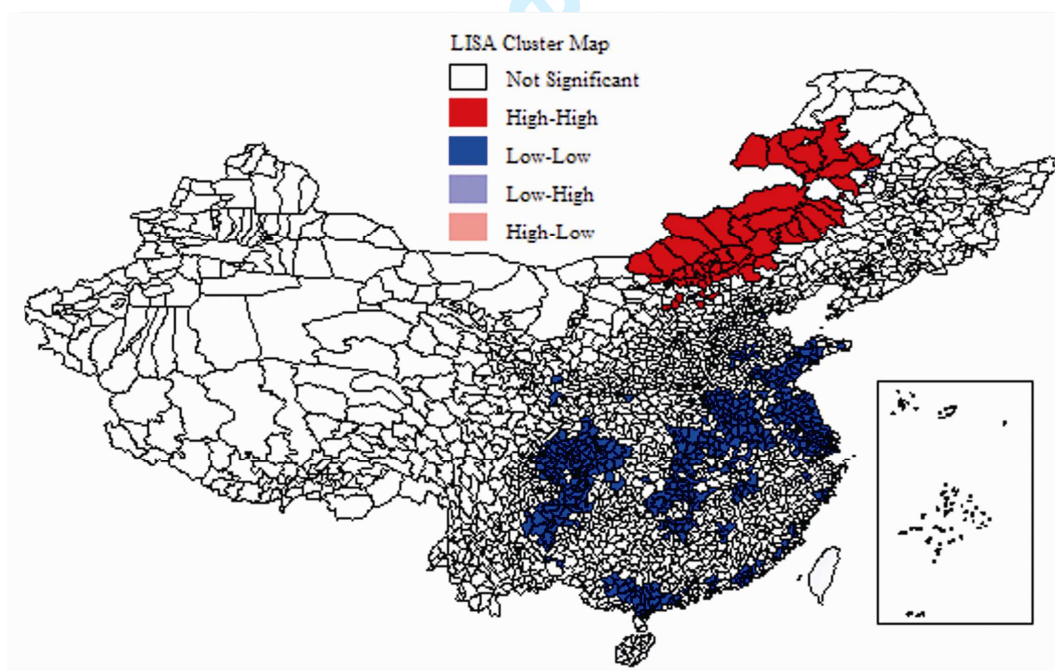


Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

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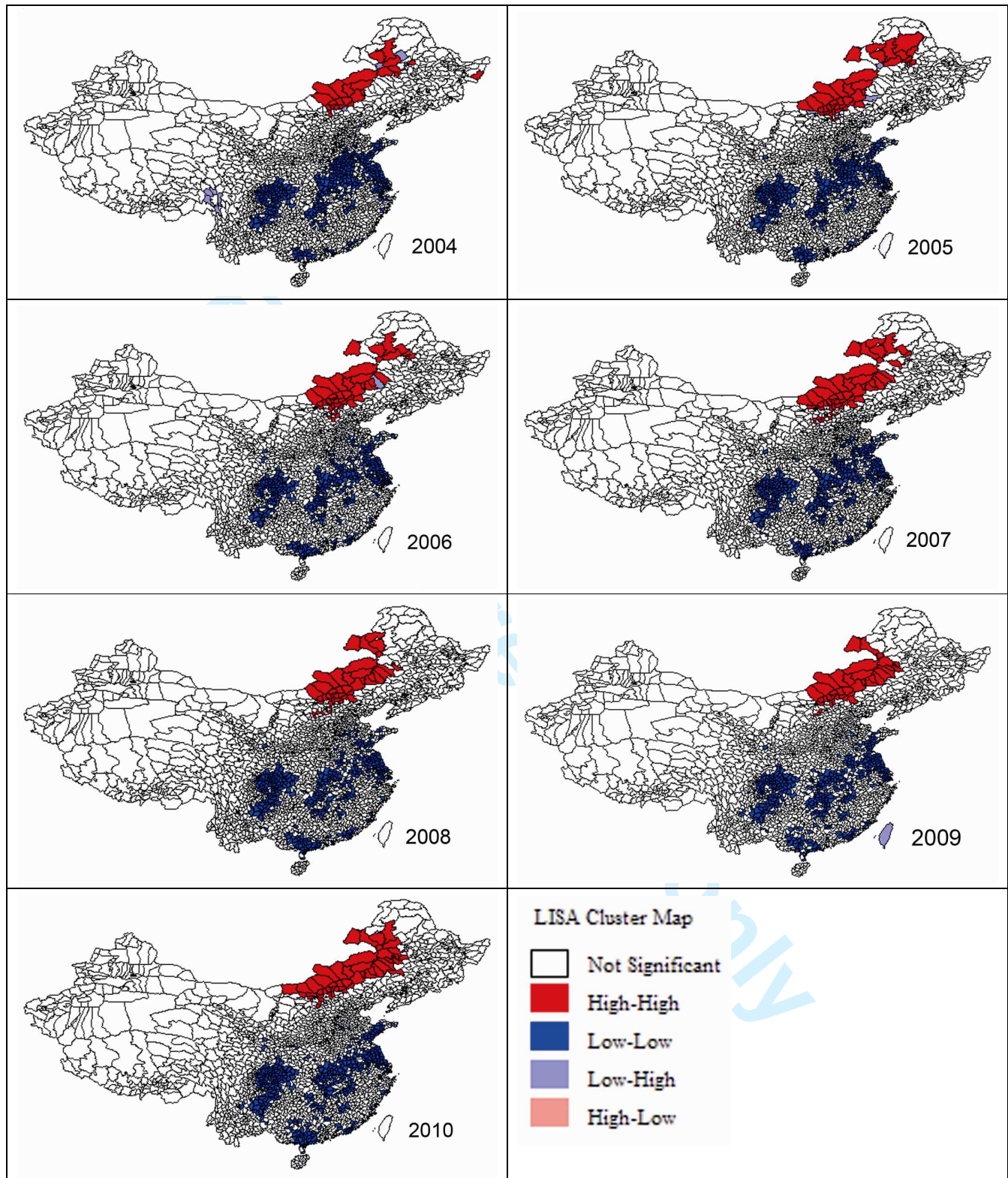
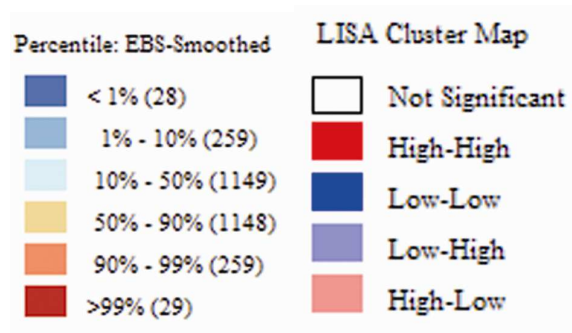


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010

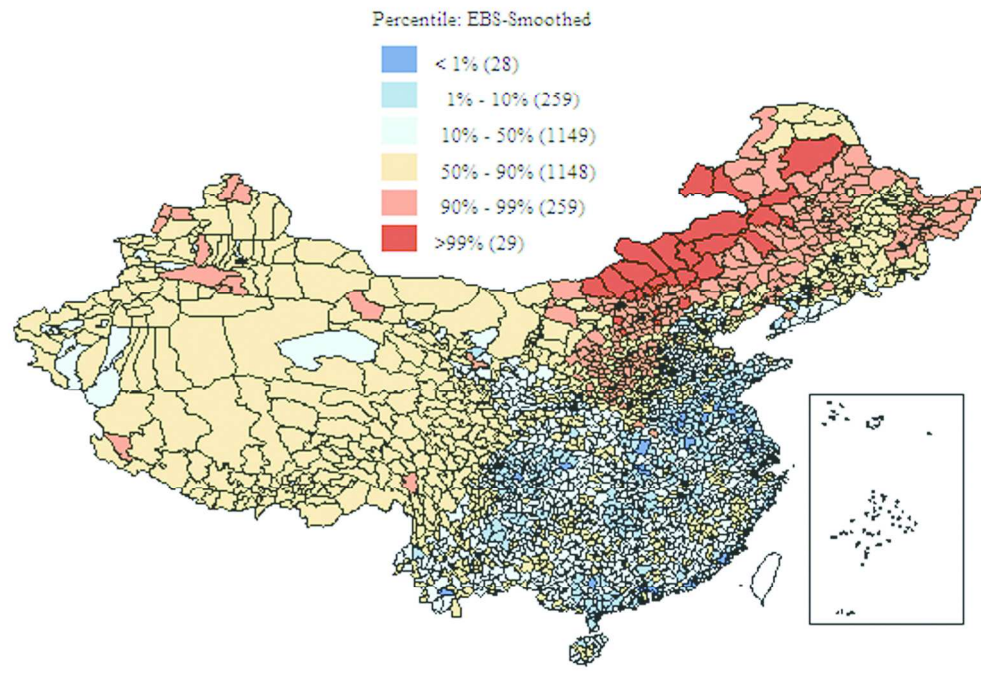


## Figure legends



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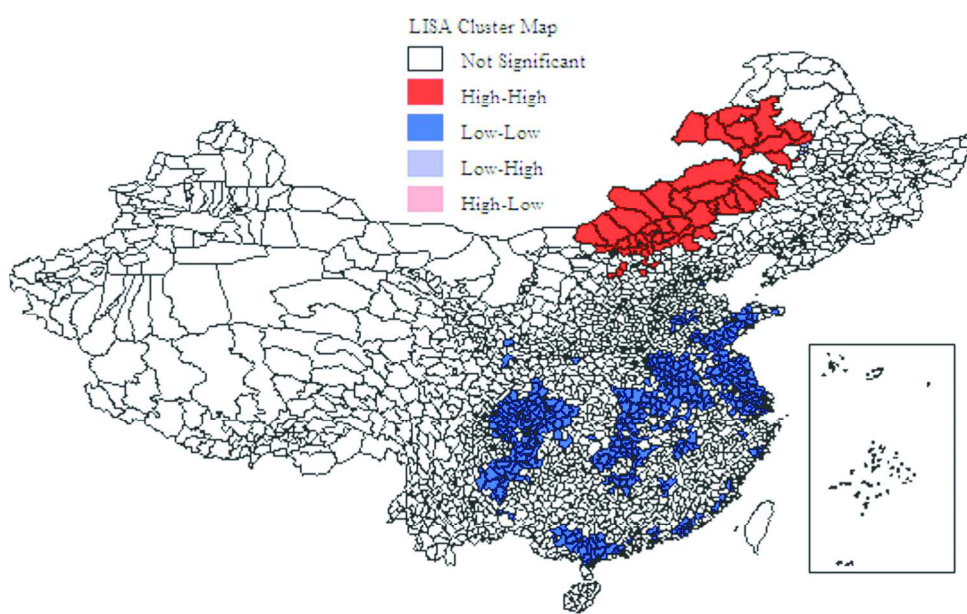
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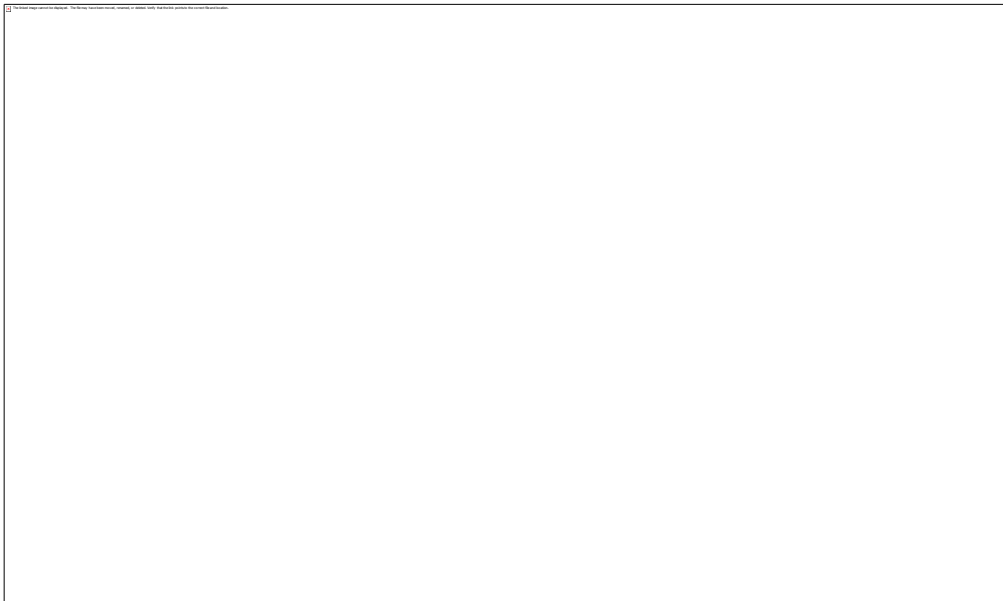
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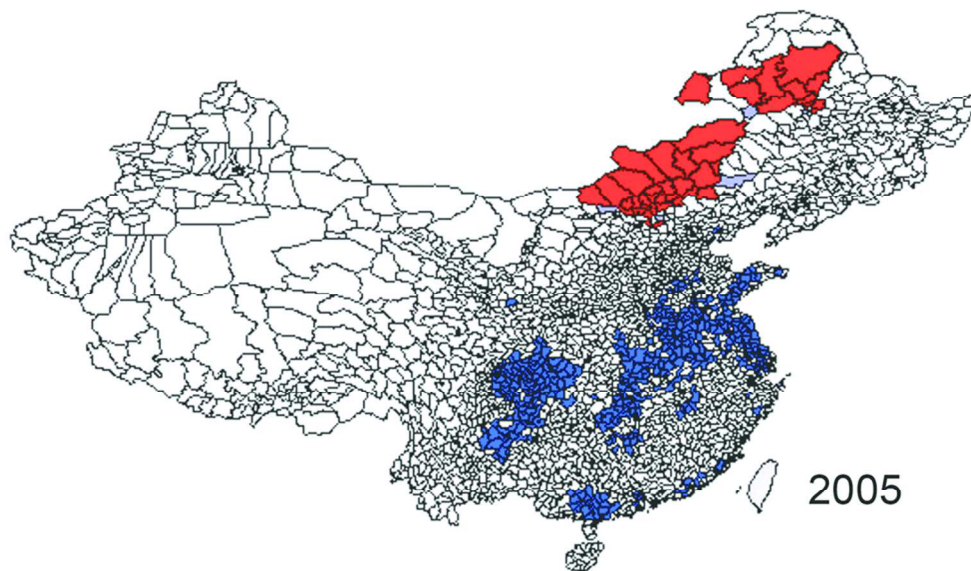
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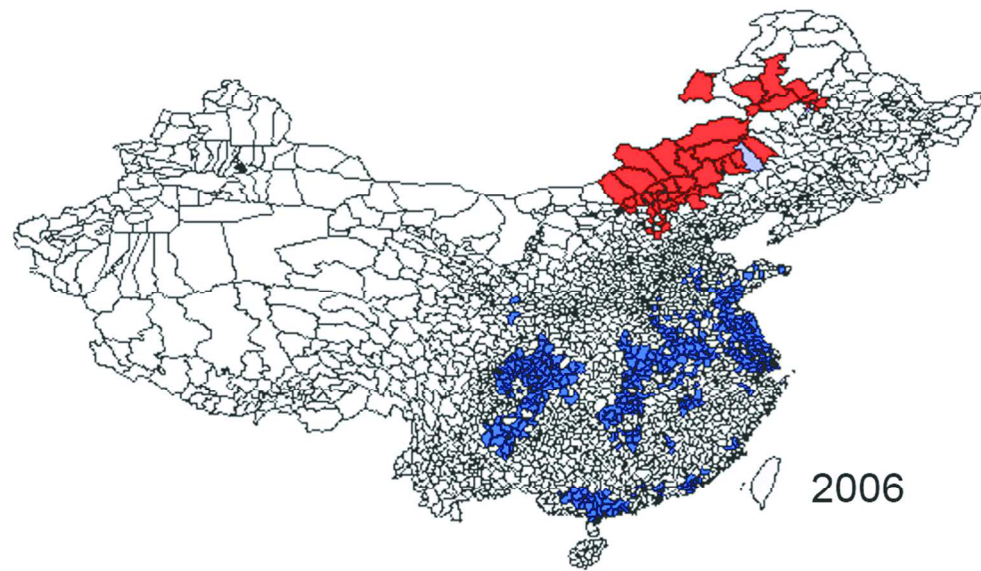


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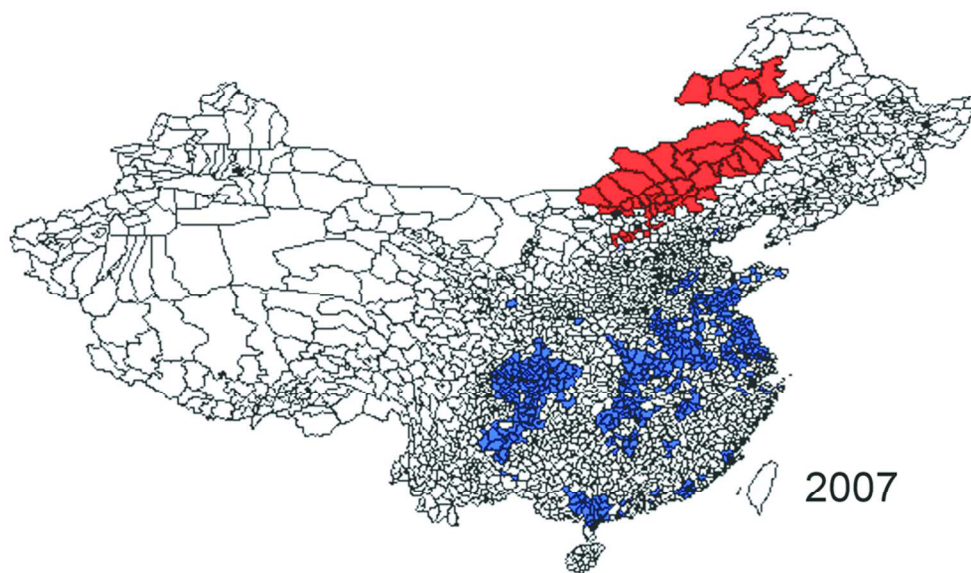
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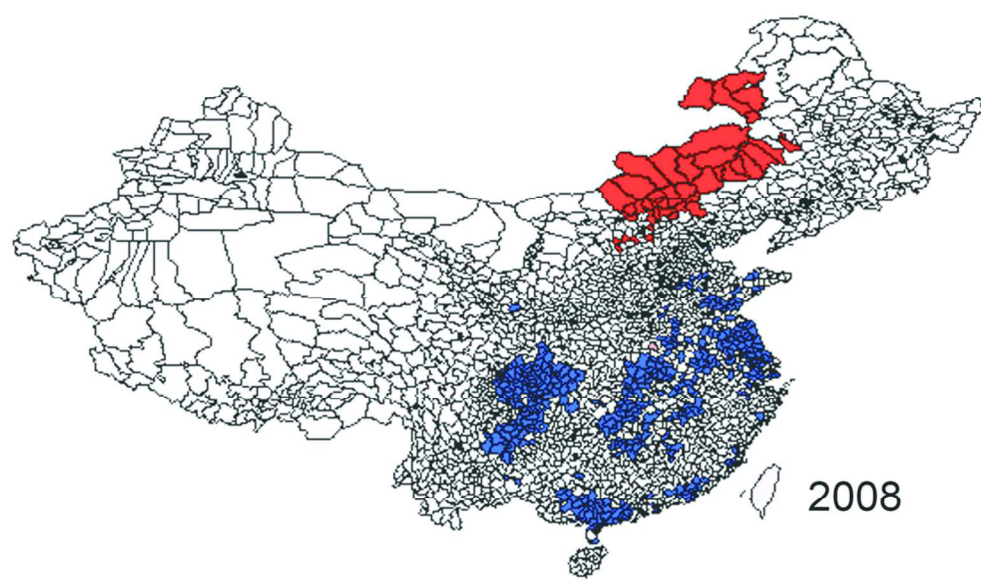


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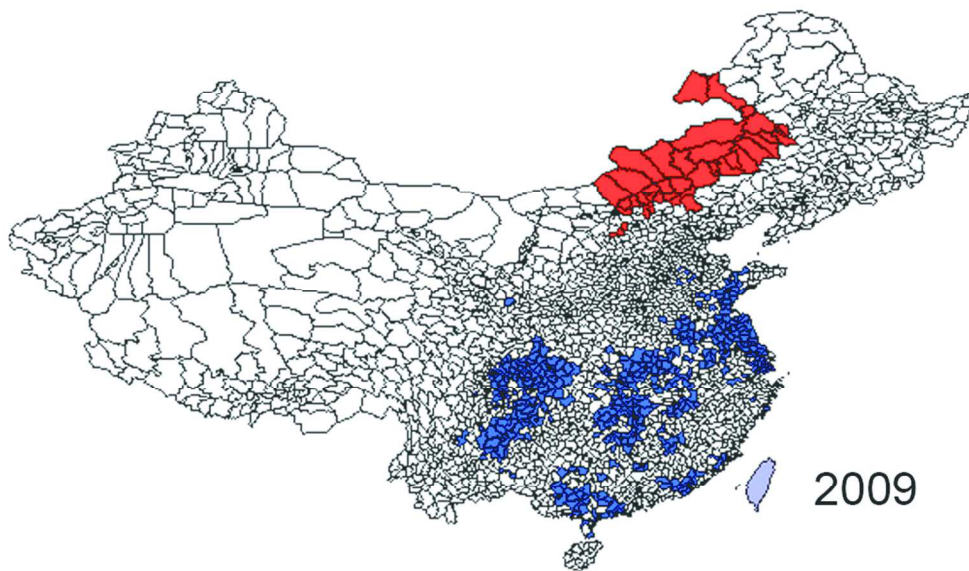
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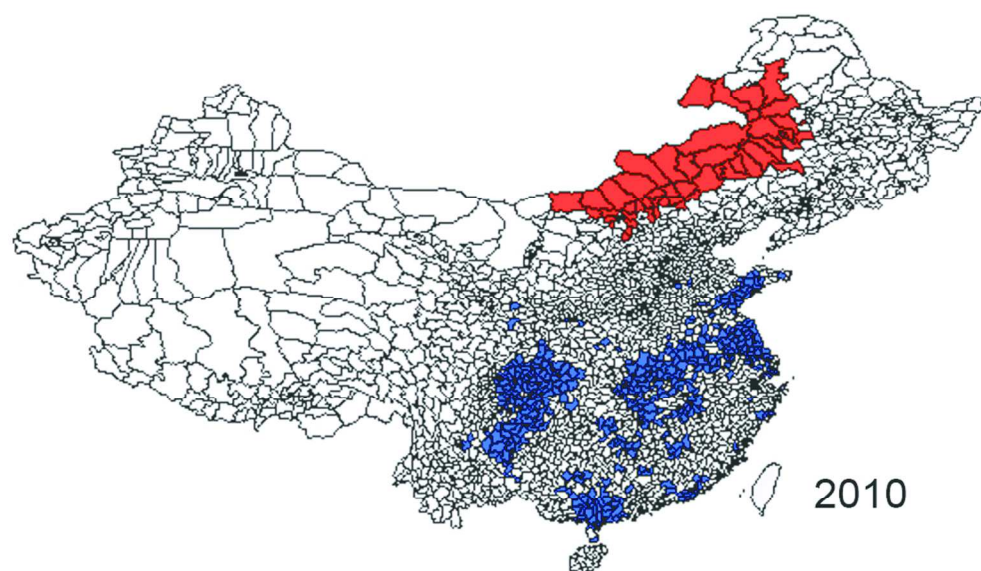


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**Spatial analysis on human brucellosis incidence in mainland  
China: 2004-2010**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-004470.R1
Article Type:	Research
Date Submitted by the Author:	15-Feb-2014
Complete List of Authors:	Zhang, Junhui; Sichuan University, West China School of Public Health; Luzhou Medical College, School of Public Health Yin, Fei; Sichuan University, West China School of Public Health Zhang, Tao; Sichuan University, West China School of Public Health Yang, Chao; Luzhou Medical College, School of Public Health Zhang, Xingyu; Sichuan University, West China School of Public Health Feng, Zijian; Chinese Center for Disease Control and Prevention, Li, Xiaosong; Sichuan University, West China School of Public Health
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Public health, Infectious diseases
Keywords:	Human brucellosis, exploratory spatial data analysis, empirical Bayes smoothing, spatial autocorrelation, cluster detection

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**Article type: research paper**

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

Junhui Zhang,<sup>1,2#</sup> Fei Yin,<sup>1#</sup> Tao Zhang,<sup>1</sup> Chao Yang,<sup>2</sup> Xingyu Zhang,<sup>1</sup> Zijian

Feng,<sup>3</sup> Xiaosong Li<sup>1\*</sup>

1 West China School of Public Health, Sichuan University, Chengdu 610041, PR  
China

2 School of Public Health, Luzhou Medical College, Luzhou 646000, PR China

3 Chinese Center for Disease Control and Prevention, Beijing 102206, PR China

\*Correspondence to: Professor Xiaosong Li, Department of Medical Statistics,  
West China School of Public Health, Sichuan University, No.17 Section 3, South  
Renmin Road, Chengdu 610041, PR China. Tel: +86 18608021962

Email address: lixiaosong1019@163.com

# These authors contributed equally to this work

## 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

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4 losses caused by brucellosis are extensive not only in animal production but also  
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6 in public health.[1] Although brucellosis has been eradicated from many  
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8 industrialized countries, new foci of disease continually appear, particularly in  
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10 parts of Asia.[7]

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13 Brucellosis is classified as one of the Class II national notifiable diseases by the  
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15 Centers for Disease Control and Prevention (CDC) and as a key disease in  
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17 Class II by the Implement Detailed Rules of the By-law  
18  
19 on Disease Prevention and Control of Livestock and Poultry in mainland  
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21 China.[8] The disease was first reported in China in 1905.[8] Human brucellosis  
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23 incidence was quite severe before 1980s in the country, later decreased and  
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25 remained at a low level. From 1995 to 2001, the incidence of human brucellosis  
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27 increased rapidly, and spread more than 10 provinces.[8] In recent years, With  
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29 the rapid development of China's animal husbandry, human brucellosis  
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31 incidence had increased sharply.[9] Nationwide surveillance data indicated that  
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33 the total incidence rate of human brucellosis in mainland China increased from  
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35 0.92 cases per 100,000 people in 2004 to 2.62 cases per 100,000 people in  
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37 2010.[10] Currently, human brucellosis is considered an important public health  
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39 problem in mainland China.[11]

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42 The incidence rates of human brucellosis are not distributed evenly across  
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44 regions in China.[10] Awareness of the spatial patterns of human brucellosis is  
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46 quite beneficial for the prevention and control of the disease. Exploratory spatial  
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48 data analysis (ESDA) methods are emerging useful approaches to achieve this  
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4 understanding.[12] ESDA is a set of techniques used to describe and visualize  
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6 spatial distributions, identify atypical locations or spatial outliers, discover  
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8 patterns of spatial association, clusters or hot spots, and suggest spatial regimes  
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10 or other forms of spatial heterogeneity.[12 13] The methods can be applied by  
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12 health officials to monitor spatial variations in disease rates, which can assist  
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14 health officials in designing more location-specific control and prevention  
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16 programs by taking into account global and local spatial influences.[14]  
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18 Measures of spatial autocorrelation are at the core of ESDA methods.[13] ESDA  
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20 methods and the empirical Bayes (EB) smoothing technique are commonly  
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22 combined to characterize spatial epidemiology of diseases.[14-17] The EB  
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24 smoothing technique is used to reduce random variation and to provide greater  
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26 stability of rates mainly in small areas associated with small populations.[16]  
27  
28 The primary purpose of this paper is to apply ESDA methods and the EB  
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30 smoothing technique to monitor county-level incidence rates for human  
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32 brucellosis in mainland China from 2004 to 2010 by examining spatial patterns.  
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34 We also identified the potential presence of clusters of the disease in mainland  
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36 China, thus to provide spatial guidance for future research.  
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## 46 **METHODS**

### 47 **Data source**

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49 Human brucellosis cases including 2872 counties in mainland China from 2004  
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51 to 2010 were collected through the Internet-based disease-reporting system  
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53 (China Information System for Disease Control and Prevention, CISDCP), which  
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3 was established in 2004 and was more integrated, effective, and reliable than  
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6 the previous case-reporting system.[18 19] In mainland China, human  
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9 brucellosis is a reportable disease. Suspected or confirmed cases must be  
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11 reported to local and provincial Centers for Disease Control and Prevention  
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13 (CDC) and then to Chinese CDC (CCDC). To meet case definitions, disease in  
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15 persons must be accompanied by clinical signs and must be confirmed by  
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17 serologic tests or isolation in accordance with the case definition of the World  
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19 Health Organization.[20]  
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23 In this paper, the incidence rates of human brucellosis in fact referred to the  
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25 reported incidence rates. In order to conduct a geographic information system  
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27 (GIS) -based analysis of the spatial distribution of human brucellosis, the  
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29 county-level polygon map at a 1:1,000,000 scale was obtained.[21]  
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33 Demographic information from 2004 to 2010 was acquired from the National  
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35 Bureau of Statistics of China. All human brucellosis cases were geocoded and  
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37 matched to the county-level layers of the polygons by administrative code using  
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39 the software Mapinfo7.0.[21]  
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#### 42 43 **EB smoothing technique**

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

### 25 26 **Spatial autocorrelation analysis**

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28 We performed spatial autocorrelation analysis in GeoDa0.9.5-i software.[24]  
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30 Both global and local Moran's I statistics were calculated. The global Moran's I  
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32 statistic was estimated to assess the evidence of global spatial autocorrelation  
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34 (clustering) of incidence rates over the study region.[25] Anselin's local Moran's I  
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36 (LISA) statistic indicates the location of local clusters and spatial outliers.[26]  
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38 Spatial autocorrelation statistics for human brucellosis incidence rates were  
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40 calculated based on the assumption of constant variance. The assumption might  
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42 be violated when incidence rates at the county level varied greatly across the  
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44 whole study region.[27] The EB smoothing technique was performed to adjust  
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46 for this violation. The standardized first-order contiguity Queen neighbours were  
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48 used as the criteria for identifying neighbors in this paper. A significant test was  
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50 performed through the permutation test, and a reference distribution was  
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4 generated under an assumption that the incidence was randomly distributed. In  
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6 order to obtain more robust results, the number of permutation test was set to  
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8 9999. Since multiple comparisons increased the chances of identifying  
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10 overlapping clusters, the significance level was set at 0.01. Based on these  
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12 permutations and threshold, we have plotted values on a map to display the  
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14 location of human brucellosis clusters in mainland China.[28]  
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## 18 **RESULTS**

### 19 **Annualized average of human brucellosis from 2004 to 2010**

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21 A total of 164,752 human brucellosis cases were reported in mainland China  
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23 from 2004 to 2010. Annual EB smoothed incidence rates for human brucellosis  
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25 from 2004 to 2010. Annual EB smoothed incidence rates for human brucellosis  
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27 for all 2872 counties were calculated. Table 1 presents annual EB smoothed  
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29 incidence rates for human brucellosis over 100 cases per 100, 000 people in 28  
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31 counties, which accounted for 34.41% of all cases in the country during the  
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33 study period. Inner Mongolia Autonomous Region had the highest number of 23,  
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35 centered in Xilin Gol League, Ulanqab League, Hulunbeier City, Xing'an League,  
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37 Baotou City, Chifeng City, Hohhot City, and Tongliao City.  
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41 Summary statistics for the annual EB smoothed incidence rates for all counties  
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43 were calculated. The mean and standard deviation were 4.64 and 38.66,  
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45 respectively, per 100,000 people. The statistic for outliers was the computed  
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47 z-value, which was the difference between the observed and expected mean of  
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49 the annual EB smoothed incidence rates standardized by the standard deviation.  
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51 Thus, it had a mean of zero and a standard deviation of 1. Sunitezuo Banner in  
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4 Xilin Gol League in Inner Mongolia had the highest annual EB smoothed  
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6 incidence rate of 1209.60, with 31.16 standard deviations from the mean. All 28  
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8 counties were at least 2.59 standard deviations from the mean, as shown in  
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11 Table 1.  
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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	Xilin Gol	Sunitezuo Banner	1209.60	31.16	<0.001	1
2	Mongolia	League	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	Siziwang Banner	257.90	6.55	<0.001	7
12		League	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.

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4 Figure 1 presented a percentile map of annual EB smoothed incidence rates for  
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6 human brucellosis in mainland China by county from 2004 to 2010. The figure  
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8 gives an indication of spatial associations: counties with similar colour shades  
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10 tended to be near each other. Outlier counties with extreme values were  
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12 highlighted (both high as well as low). Six legend categories were created,  
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14 corresponding to < 1%, 1% to <10%, 10% to <50%, 50% to <90%, 90% to <99%  
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16 and >99%. There were 29 counties at the high end.  
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21 The global Moran's I value of annual EB smoothed incidence rates for human  
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23 brucellosis in mainland China by county from 2004 to 2010 was 0.5803 (Z=  
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25 8.3660, P=0.0025), statistically significant at the 0.01 level.  
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29 We also calculated the local Moran's I and gave a LISA cluster map of annual  
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31 EB smoothed incidence rates for human brucellosis in mainland China by county  
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33 from 2004 to 2010. LISA cluster map showed those counties with a significant  
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35 local Moran statistic classified by type of spatial correlation: bright red for the  
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37 high-high association, bright blue for low-low, light blue for low-high, and light red  
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39 for high-low (Figure 2). The high-high and low-low locations suggest clustering of  
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41 similar values, whereas the high-low and low-high locations indicate spatial  
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43 outliers, whereas the high-low and low-high locations indicate spatial  
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45 outliers.  
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49 The Local Moran's I method of annual EB smoothed incidence rates for human  
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51 brucellosis showed major high-risk clustered areas of human brucellosis located  
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53 in northern China. High-risk counties were centered in Inner Mongolia (40  
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55 counties, 72.3%), Hebei (7 counties, 12.7%), Shanxi (5 counties, 9.1%),  
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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  $I$



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

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6 The number of high-risk counties in Inner Mongolia Autonomous Region was the  
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8 largest one, increased from 22 in 2004 to 46 in 2010. Among the 101 counties in  
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10 Inner Mongolia Autonomous Region, the number of EB smoothed incidence  
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12 rates over 100 cases per 100,000 people increased from 8 in 2004 to 29 in 2010.  
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14 The most notable change was that the EB smoothed incidence rate in Sunitezuo  
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16 Banner increased from 373.7 in 2004 to 2,482.1 in 2009, but then decreased to  
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18 1,443.0 cases per 100,000 people in 2010.  
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22 In Hebei Province, the number of high-risk counties kept an upward trend, rising  
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24 from 1 in 2004 to 3 in 2010. The most noteworthy change was that the EB  
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26 smoothed incidence rate in Wei County increased from 9.70 to 79.40 cases per  
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28 100,000 people between 2004 and 2010.  
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32 The number of high-risk counties in Shanxi Province increased from zero in  
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34 2004 to 2 in 2010. The most notable change was that the EB smoothed  
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36 incidence rate in Xinrong District increased from 0.9 to 88.1 cases per 100,000  
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38 people between 2004 and 2010.  
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42 In Jilin Province, the number of high-risk counties increased from zero in 2004 to  
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44 3 in 2010. The most notable change was that the EB smoothed incidence rate in  
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46 Tongyu County increased from zero to 155.6 cases per 100,000 people between  
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48 2004 and 2010.  
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52 In Heilongjiang Province, the number of high-risk counties decreased from 2 to 0  
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54 between 2004 and 2010. Meris Daur District had the highest EB smoothed  
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4 incidence rates of human brucellosis in the province, at more than 130 cases per  
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6 100,000 people per year between 2004 and 2010. The most notable change was  
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8 that the EB smoothed incidence rate in Zhaozhou County increased from 1.3 to  
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11 74.2 cases per 100,000 people between 2004 and 2010.  
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## 16 **DISCUSSION**

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18 In this paper, ESDA methods were used to explore spatial patterns of EB  
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20 smoothed incidence rates for human brucellosis at the county level in mainland  
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22 China from 2004 to 2010. We found that the occurrence of human brucellosis  
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24 persisted throughout many areas of the country and was spatially dependent  
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26 during the seven-year study period. Since human brucellosis is not a contagious  
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28 disease, spatial clusters of human brucellosis are most likely a result of animal  
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30 processing, shared food sources, more intensive agricultural production zones,  
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32 or similar socio-cultural practices.[17 29] Further researches are needed to  
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34 determine whether human brucellosis clusters in China are associated with  
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36 specific natural and/or social environmental characteristics. During the period  
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38 2004-2010, the areas with serious epidemics of human brucellosis persisted in  
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40 Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei,  
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42 Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia  
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44 Autonomous Region where animal husbandry had developed, all of which were  
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46 epidemic regions before the 1980s. This spatial pattern may be related to the  
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48 trans-boundary transfer of animal brucellosis in the region of Inner Mongolia  
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4 from the neighboring hyper-endemic Mongolia, which had been described as the  
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6 country with the second highest incidence worldwide.[7 30] In addition, the  
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8 leading risk factors for the high incidence rate of human brucellosis were the  
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10 increase in animal feeding, lack of immunization and animal quarantine, and  
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12 frequent trading.[9 30]

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15 Several intervention strategies had been suggested to reduce the incidence of  
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17 human brucellosis, such as increasing local knowledge of proper food handling  
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19 techniques of dairy products including pasteurization, decreasing occupational  
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21 exposures, quarantining, separating and eliminating of infected animals with  
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23 brucellosis, establishing surveillance point of brucellosis and its network, and  
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25 vaccination programs aimed at reducing the prevalence of disease in livestock.[8  
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31 31] However, Zhang[9] suggested that the most effective means of human  
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33 brucellosis control were the comprehensive measures of universal immunization  
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35 in livestock without quarantine in epidemic regions, which had been proved  
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37 effective measures.  
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41 Previous study analyzed cluster identification of the annualized raw incidence  
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43 rates of county-level human brucellosis in China by using SaTScan and ArcGIS  
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45 software.[32] Our work is very different from the previous study. Firstly,  
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47 we used the EB smoothing technique to smooth the human brucellosis incidence  
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49 rates. Therefore, random variability was reduced and greater stability of  
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51 incidence rates was provided mainly in small counties. Secondly, although  
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56 both the previous study and our work analyzed county-level human  
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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

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4 able to reflect the current trend in human brucellosis incidence in mainland  
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6 China. Secondly, cross-organizational collaboration (between public health,  
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8 clinics, and hospitals) has been very efficient within the healthcare system.  
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10 However, information-sharing between healthcare organizations and non-health  
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12 departments, such as the government's agriculture department, has not been  
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14 extensive. Currently, animal and human health disease surveillance databases  
15  
16 are not linked. Additionally, we can't obtain the data of animal brucellosis  
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18 because of confidentiality restrictions. [18] Therefore, we didn't analyze the  
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20 density of livestock compare with the distribution of human cases. Furthermore,  
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22 our analyses are based on county-level data. Smaller spatial units might provide  
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24 more location-specific information about the design and implementation stages  
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26 of public health programs.[14] The methods employed in this paper can be  
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28 applied to finer geographic units (e.g. postal units). Finer geographic units to  
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30 identify clusters within counties with higher burdens of human brucellosis would  
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32 be focused on in further research.  
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41 In conclusion, our study offered a good understanding of the spatial patterns of  
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43 human brucellosis incidence in mainland China, and might contribute to  
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45 determine allocating resources to high risk areas in order to reduce human  
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47 brucellosis incidence. With the assistance of the spatial framework provided by  
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49 our study, China's human brucellosis control programs could be focused on  
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51 locations where they will have the greatest influence.  
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12 data collection and analysis, decision to publish, or preparation of the  
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14 manuscript.  
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18 **Contributors** JZ designed the research, collected data, drafted the manuscript,  
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20 analysed the data and interpreted the results. FY designed the research,  
21  
22 collected data, interpreted the results critically reviewed and edited the  
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24 manuscript. TZ, CY, XZ interpreted the results critically reviewed and edited the  
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26 manuscript. XL designed the research, interpreted the results, critically reviewed  
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28 and edited the manuscript and funding, and supervised. ZH offered research  
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30 data and edited the manuscript. All authors read and approved the final  
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32 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

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4 **Article type: research paper**

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6 **Spatial analysis on human brucellosis incidence in**  
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8 **mainland China: 2004-2010**  
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11 Junhui Zhang,<sup>1,2#</sup> Fei Yin,<sup>1#</sup> Tao Zhang,<sup>1</sup> Chao Yang,<sup>2</sup> Xingyu Zhang,<sup>1</sup> Zijian  
12  
13 Feng,<sup>3</sup> Xiaosong Li<sup>1\*</sup>  
14

15  
16 1 West China School of Public Health, Sichuan University, Chengdu 610041, PR  
17  
18 China  
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20  
21 2 School of Public Health, Luzhou Medical College, Luzhou 646000, PR China  
22

23  
24 3 Chinese Center for Disease Control and Prevention, Beijing 102206, PR China  
25

26  
27  
28  
29 \*Correspondence to: Professor Xiaosong Li, Department of Medical Statistics,  
30  
31 West China School of Public Health, Sichuan University, No.17 Section 3, South  
32  
33 Renmin Road, Chengdu 610041, PR China. Tel: +86 18608021962  
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35  
36 Email address: lixiaosong1019@163.com  
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39 # These authors contributed equally to this work  
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44 **ABSTRACT**  
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46 **Objectives:** China has experienced a sharply increasing rate of human  
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48 brucellosis in recent years. Effective spatial monitoring of human brucellosis  
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50 incidence is very important for successful implementation of control and  
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52 prevention programs. The purpose of this paper is to apply exploratory spatial  
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54 data analysis (ESDA) methods and the empirical Bayes (EB) smoothing  
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4 technique to monitor county-level incidence rates for human brucellosis in  
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6 mainland China from 2004 to 2010 by examining spatial patterns.  
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9 **Methods:** ESDA methods were used to characterize spatial patterns of EB  
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11 smoothed incidence rates for human brucellosis based on county-level data  
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13 obtained from the China Information System for Disease Control and Prevention  
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15 (CISDCP) in mainland China from 2004 to 2010.  
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18 **Results:** EB smoothed incidence rates for human brucellosis were spatially  
19  
20 dependent during 2004-2010. The local Moran test identified significantly  
21  
22 high-risk clusters of human brucellosis (all P-values <0.01), which persisted  
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24 during the seven-year study period. High-risk counties were centered in Inner  
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26 Mongolia Autonomous Region and other Northern provinces (i.e., Hebei, Shanxi,  
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28 Jilin and Heilongjiang provinces) around the border with Inner Mongolia  
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30 Autonomous Region where animal husbandry was highly developed. The  
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32 number of high-risk counties increased from 25 in 2004 to 54 in 2010.  
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39 **Conclusions:** ESDA methods and the EB smoothing technique can assist  
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41 public health officials in identifying high-risk areas. Allocating more resources to  
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43 high-risk areas is an effective way to reduce human brucellosis incidence.  
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47 **Keywords:** *Human brucellosis, exploratory spatial data analysis, empirical*  
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49 *Bayes smoothing, spatial autocorrelation, cluster detection*  
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52 **Word Count:** 3208  
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## 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

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4 cluster areas with low false-positive rates especially performing well on  
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6 outlier detection had a better chance of being detected.  
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9 ■ The number of reported cases of human brucellosis obtained from the  
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11 CISDCP system might be only part of the actual incidence of human  
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13 brucellosis across the country as human brucellosis is often underreported  
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15 or misdiagnosed.  
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19 ■ Our analyses are based on county-level data. Smaller spatial units might  
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21 provide more location-specific information **about** the design and  
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23 implementation stages of public health programs.  
24

## 25 26 INTRODUCTION

27  
28 Brucellosis, caused by *Brucella* species, is a zoonotic disease recognized as an  
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30 emerging and re-emerging threat to public and veterinary health.[1] The disease  
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32 is transmitted to humans by direct/indirect contact with infected animals or  
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34 through the consumption of contaminated foods.[2-4] People with occupational  
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36 exposure are at highest risk for brucellosis, in particular those performing  
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38 husbandry activities, butchering, and livestock trading.[5 6] Worldwide economic  
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40 losses **caused by** brucellosis are extensive not only in animal production but also  
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42 in public health.[1] Although brucellosis has been eradicated from many  
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44 industrialized countries, new foci of disease continually appear, particularly in  
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46 parts of Asia.[7]  
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50 Brucellosis is classified as one of the Class II national notifiable diseases by the  
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52 Centers for Disease Control and Prevention (CDC) and **as a key disease in**  
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4 **Class II** by the Implement Detailed Rules of the By-law

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6 on Disease Prevention and Control of Livestock and Poultry in mainland  
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8 China.[8] The disease was first reported in China in 1905.[8] Human brucellosis  
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10 incidence was quite severe before 1980s in the country, later decreased and  
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12 remained at a low level. From 1995 to 2001, the incidence of human brucellosis  
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14 increased rapidly, and spread more than 10 provinces.[8] In recent years, With  
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16 the rapid development of China's animal husbandry, human brucellosis  
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18 incidence had increased sharply.[9] Nationwide surveillance data indicated that  
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20 the total incidence rate of human brucellosis in mainland China increased from  
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22 0.92 cases per 100,000 people in 2004 to 2.62 cases per 100,000 people in  
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24 2010.[10] Currently, human brucellosis is considered an important public health  
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26 problem in mainland China.[11]

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29 The incidence rates of human brucellosis are not distributed evenly across  
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31 regions in China.[10] Awareness of the spatial patterns of human brucellosis is  
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33 quite beneficial for the prevention and control of the disease. Exploratory spatial  
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35 data analysis (ESDA) methods are emerging useful approaches to achieve this  
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37 understanding.[12] ESDA is a set of techniques used to describe and visualize  
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39 spatial distributions, identify atypical locations or spatial outliers, discover  
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41 patterns of spatial association, clusters or hot spots, and suggest spatial regimes  
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43 or other forms of spatial heterogeneity.[12 13] The methods can be applied by  
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45 health officials to monitor spatial variations in disease rates, which can assist  
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47 health officials in designing more location-specific control and prevention  
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3 programs **by taking** into account global and local spatial influences.[14]  
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6 Measures of spatial autocorrelation are at the core of ESDA methods.[13] ESDA  
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8 methods and the empirical Bayes (EB) smoothing technique are commonly  
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10 combined to characterize spatial epidemiology of diseases.[14-17] The EB  
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12 smoothing technique is used to reduce random variation and to provide greater  
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14 stability of rates mainly in small areas associated with small populations.[16]  
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17 The primary purpose of this paper is to apply ESDA methods and the EB  
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19 smoothing technique to monitor county-level incidence rates for human  
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21 brucellosis in mainland China from 2004 to 2010 by examining spatial patterns.  
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24 We also identified the potential presence of clusters of the disease in mainland  
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27 China, thus to provide spatial guidance for future research.  
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## 30 31 **METHODS**

### 32 33 **Data source**

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36 Human brucellosis cases including 2872 counties in mainland China from 2004  
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38 to 2010 were collected through the Internet-based disease-reporting system  
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40 (China Information System for Disease Control and Prevention, CISDCP), which  
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42 was established in 2004 and was more integrated, effective, and reliable than  
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44 the previous case-reporting system.[18 19] **In mainland China, human**  
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46 **brucellosis is a reportable disease. Suspected or confirmed cases must be**  
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48 **reported to local and provincial Centers for Disease Control and Prevention**  
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50 **(CDC) and then to Chinese CDC (CCDC). To meet case definitions, disease in**  
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52 **persons must be accompanied by clinical signs and must be confirmed by**  
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4 serologic tests or isolation in accordance with the case definition of the World  
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6 Health Organization.[20]  
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9 In this paper, the incidence rates of human brucellosis in fact referred to the  
10 reported incidence rates. In order to conduct a geographic information system  
11 (GIS) -based analysis of the spatial distribution of human brucellosis, the  
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13 county-level polygon map at a 1:1,000,000 scale was obtained.[21]  
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17 Demographic information from 2004 to 2010 was acquired from the National  
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19 Bureau of Statistics of China. All human brucellosis cases were geocoded and  
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21 matched to the county-level layers of the polygons by administrative code using  
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23 the software Mapinfo7.0.[21]  
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### 28 **EB smoothing technique**

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

11 We performed spatial autocorrelation analysis in GeoDa0.9.5-i software.[24]  
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13 Both global and local Moran's I statistics were calculated. The global Moran's I  
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15 statistic was estimated to assess the evidence of global spatial autocorrelation  
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17 (clustering) of incidence rates over the study region.[25] Anselin's local Moran's I  
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19 (LISA) statistic indicates the location of local clusters and spatial outliers.[26]  
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21 Spatial autocorrelation statistics for human brucellosis incidence rates were  
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23 calculated based on the assumption of constant variance. The assumption might  
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25 be violated when incidence rates at the county level varied greatly across the  
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27 whole study region.[27] The EB smoothing technique was performed to adjust  
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29 for this violation. The standardized first-order contiguity Queen neighbours were  
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31 used as the criteria for identifying neighbors in this paper. A significant test was  
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33 performed through the permutation test, and a reference distribution was  
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35 generated under an assumption that the incidence was randomly distributed. In  
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37 order to obtain more robust results, the number of permutation test was set to  
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39 9999. Since multiple comparisons increased the chances of identifying  
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41 overlapping clusters, the significance level was set at 0.01. Based on these  
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43 permutations and threshold, we have plotted values on a map to display the  
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45 location of human brucellosis clusters in mainland China.[28]  
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## 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	Xilin Gol	Sunitezuo Banner	1209.60	31.16	<0.001	1
2	Mongolia	League	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	Siziwang Banner	257.90	6.55	<0.001	7
12		League	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.

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4 Figure 1 presented a percentile map of annual EB smoothed incidence rates for  
5  
6 human brucellosis in mainland China by county from 2004 to 2010. The figure  
7  
8 gives an indication of spatial associations: counties with similar colour shades  
9  
10 tended to be near each other. Outlier counties with extreme values were  
11  
12 highlighted (both high as well as low). Six legend categories were created,  
13  
14 corresponding to < 1%, 1% to <10%, 10% to <50%, 50% to <90%, 90% to <99%  
15  
16 and >99%. There were 29 counties at the high end.  
17  
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21 The global Moran's I value of annual EB smoothed incidence rates for human  
22  
23 brucellosis in mainland China by county from 2004 to 2010 was 0.5803 ( $Z=$   
24  
25 8.3660,  $P=0.0025$ ), statistically significant at the 0.01 level.  
26  
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29 We also calculated the local Moran's I and gave a LISA cluster map of annual  
30  
31 EB smoothed incidence rates for human brucellosis in mainland China by county  
32  
33 from 2004 to 2010. LISA cluster map showed those counties with a significant  
34  
35 local Moran statistic classified by type of spatial correlation: bright red for the  
36  
37 high-high association, bright blue for low-low, light blue for low-high, and light red  
38  
39 for high-low (Figure 2). The high-high and low-low locations suggest clustering of  
40  
41 similar values, whereas the high-low and low-high locations indicate spatial  
42  
43 outliers, whereas the high-low and low-high locations indicate spatial  
44  
45 outliers.  
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49 The Local Moran's I method of annual EB smoothed incidence rates for human  
50  
51 brucellosis showed **major high-risk clustered areas of human brucellosis** located  
52  
53 in northern China. High-risk counties were centered in Inner Mongolia (40  
54  
55 counties, 72.3%), Hebei (7 counties, 12.7%), Shanxi (5 counties, 9.1%),  
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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  $I$

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

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6 The number of high-risk counties in Inner Mongolia Autonomous Region was the  
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8 largest one, increased from 22 in 2004 to 46 in 2010. Among the 101 counties in  
9  
10 Inner Mongolia Autonomous Region, the number of EB smoothed incidence  
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12 rates over 100 cases per 100,000 people increased from 8 in 2004 to 29 in 2010.  
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14 The most notable change was that the EB smoothed incidence rate in Sunitezuo  
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16 Banner increased from 373.7 in 2004 to 2,482.1 in 2009, but then decreased to  
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18 1,443.0 cases per 100,000 people in 2010.  
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21  
22 In Hebei Province, the number of high-risk counties kept an upward trend, rising  
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24 from 1 in 2004 to 3 in 2010. The most noteworthy change was that the EB  
25  
26 smoothed incidence rate in Wei County increased from 9.70 to 79.40 cases per  
27  
28 100,000 people between 2004 and 2010.  
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32 The number of high-risk counties in Shanxi Province increased from zero in  
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34 2004 to 2 in 2010. The most notable change was that the EB smoothed  
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36 incidence rate in Xinrong District increased from 0.9 to 88.1 cases per 100,000  
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38 people between 2004 and 2010.  
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41  
42 In Jilin Province, the number of high-risk counties increased from zero in 2004 to  
43  
44 3 in 2010. The most notable change was that the EB smoothed incidence rate in  
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46 Tongyu County increased from zero to 155.6 cases per 100,000 people between  
47  
48 2004 and 2010.  
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51  
52 In Heilongjiang Province, the number of high-risk counties decreased from 2 to 0  
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54 between 2004 and 2010. Meris Daur District had the highest EB smoothed  
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4 incidence rates of human brucellosis in the province, at more than 130 cases per  
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6 100,000 people per year between 2004 and 2010. The most notable change was  
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8 that the EB smoothed incidence rate in Zhaozhou County increased from 1.3 to  
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10 74.2 cases per 100,000 people between 2004 and 2010.  
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14 <<Insert figure 3 here>>  
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## 16 **DISCUSSION**

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18 In this paper, ESDA methods were used to explore spatial patterns of EB  
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20 smoothed incidence rates for human brucellosis at the county level in mainland  
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22 China from 2004 to 2010. We found that the occurrence of human brucellosis  
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24 persisted throughout many areas of the country and was spatially dependent  
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26 during the seven-year study period. Since human brucellosis is not a contagious  
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28 disease, spatial clusters of human brucellosis are most likely a result of animal  
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30 processing, shared food sources, more intensive agricultural production zones,  
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32 or similar socio-cultural practices.[17 29] Further researches are needed to  
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34 determine whether **human brucellosis clusters in China** are associated with  
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36 specific natural and/or social environmental characteristics. During the period  
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38 2004-2010, the areas with serious epidemics of human brucellosis persisted in  
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40 Inner Mongolia Autonomous Region and other Northern provinces (i.e., Hebei,  
41  
42 Shanxi, Jilin and Heilongjiang provinces) around the border with Inner Mongolia  
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44 Autonomous Region where animal husbandry had developed, all of which were  
45  
46 epidemic regions before the 1980s. This spatial pattern may be related to the  
47  
48 trans-boundary transfer of animal brucellosis in the region of Inner Mongolia  
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4 from the neighboring hyper-endemic Mongolia, which had been described as the  
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6 country with the second highest incidence worldwide.[7 30] In addition, the  
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8 leading risk factors for the high incidence rate of human brucellosis were the  
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10 increase in animal feeding, lack of immunization and animal quarantine, and  
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12 frequent trading.[9 30]

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15 Several intervention strategies had been suggested to reduce the incidence of  
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17 human brucellosis, such as increasing local knowledge of proper food handling  
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19 techniques of dairy products including pasteurization, decreasing occupational  
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21 exposures, quarantining, separating and eliminating of infected animals with  
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23 brucellosis, establishing surveillance point of brucellosis and its network, and  
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25 vaccination programs aimed at reducing the prevalence of disease in livestock.[8  
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31 31] However, Zhang[9] suggested that the most effective means of human  
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33 brucellosis control were the comprehensive measures of universal immunization  
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35 in livestock without quarantine in epidemic regions, **which had been proved**  
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37 **effective measures.**  
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41 Previous study analyzed cluster identification of the annualized raw incidence  
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43 rates of county-level human brucellosis in China by using SaTScan and ArcGIS  
44  
45 software.[32] **Our work is very different from the previous study.** Firstly,  
46  
47 we used the EB smoothing technique to smooth the human brucellosis incidence  
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49 rates. Therefore, random variability was reduced and greater stability of  
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51 incidence rates was provided mainly in small counties. **Secondly, although**  
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53 **both the previous study and our work analyzed county-level human**  
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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

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4 able to reflect the current trend in human brucellosis incidence in mainland  
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6 China. Secondly, cross-organizational collaboration (between public health,  
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8 clinics, and hospitals) has been very efficient within the healthcare system.  
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10 However, information-sharing between healthcare organizations and non-health  
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12 departments, such as the government's agriculture department, has not been  
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14 extensive. Currently, animal and human health disease surveillance databases  
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16 are not linked. Additionally, we can't obtain the data of animal brucellosis  
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18 because of confidentiality restrictions. [18] Therefore, we didn't analyze the  
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20 density of livestock compare with the distribution of human cases. Furthermore,  
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22 our analyses are based on county-level data. Smaller spatial units might provide  
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24 more location-specific information about the design and implementation stages  
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26 of public health programs.[14] The methods employed in this paper can be  
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28 applied to finer geographic units (e.g. postal units). Finer geographic units to  
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30 identify clusters within counties with higher burdens of human brucellosis would  
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32 be focused on in further research.  
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41 In conclusion, our study offered a good understanding of the spatial patterns of  
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43 human brucellosis incidence in mainland China, and might contribute to  
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45 determine allocating resources to high risk areas in order to reduce human  
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47 brucellosis incidence. With the assistance of the spatial framework provided by  
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49 our study, China's human brucellosis control programs could be focused on  
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51 locations where they will have the greatest influence.  
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4 **Contributors** JZ designed the research, collected data, drafted the manuscript,  
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6 analysed the data and interpreted the results. FY designed the research,  
7  
8 collected data, interpreted the results critically reviewed and edited the  
9  
10 manuscript. TZ, CY, XZ interpreted the results critically reviewed and edited the  
11  
12 manuscript. XL designed the research, interpreted the results, critically reviewed  
13  
14 and edited the manuscript and funding, and supervised. ZH offered research  
15  
16 data and edited the manuscript. All authors read and approved the final  
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18 manuscript.  
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23  
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25  
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32 data collection and analysis, decision to publish, or preparation of the  
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34 manuscript.  
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40  
41 **Provenance and peer review** Not commissioned; externally peer reviewed.

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44 **Data sharing statement** No additional data are available.

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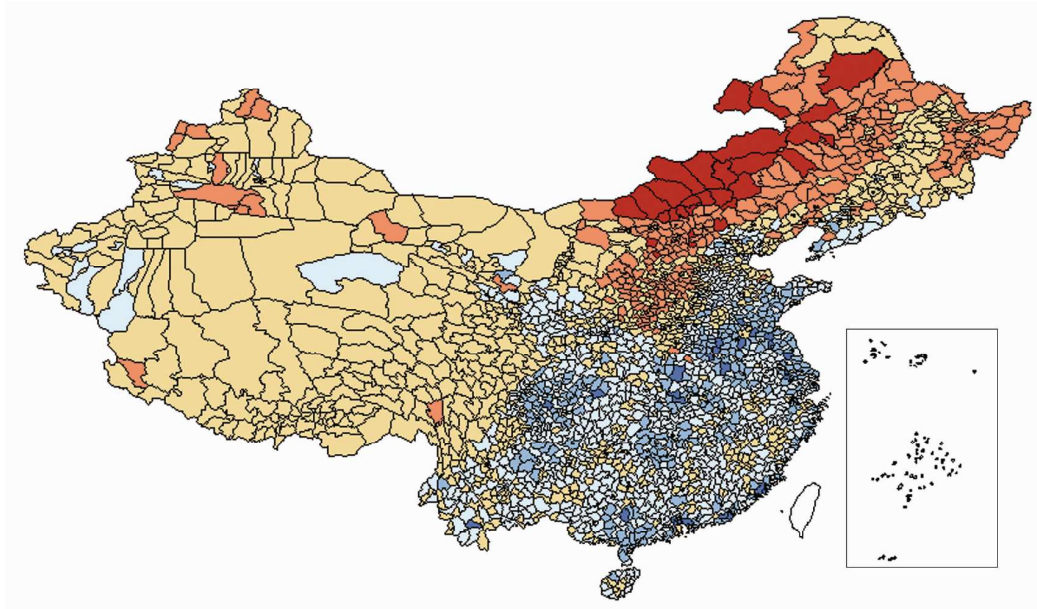


Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

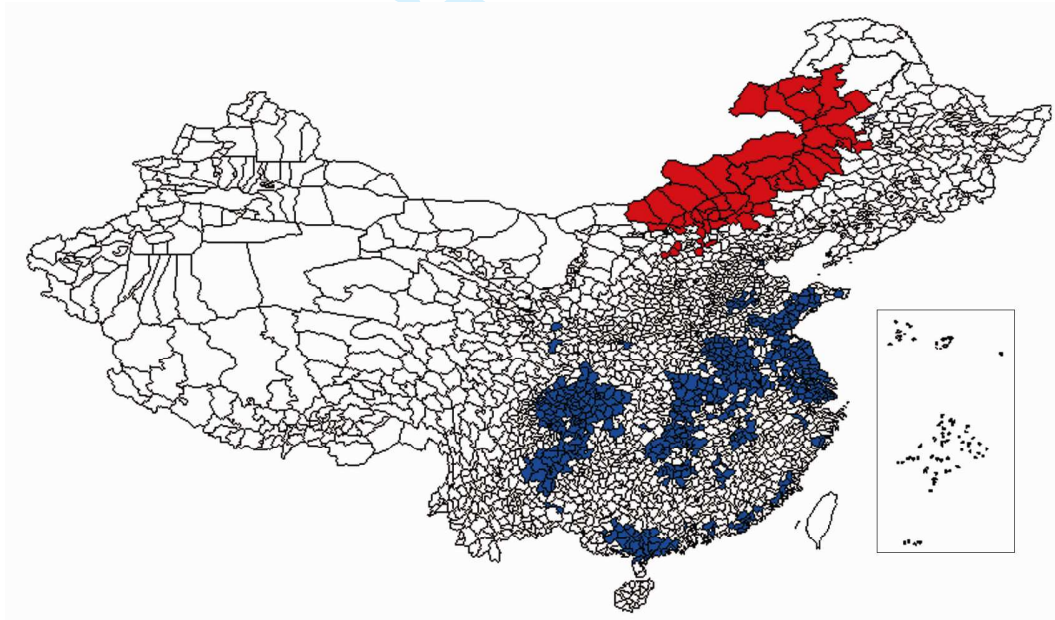


Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010

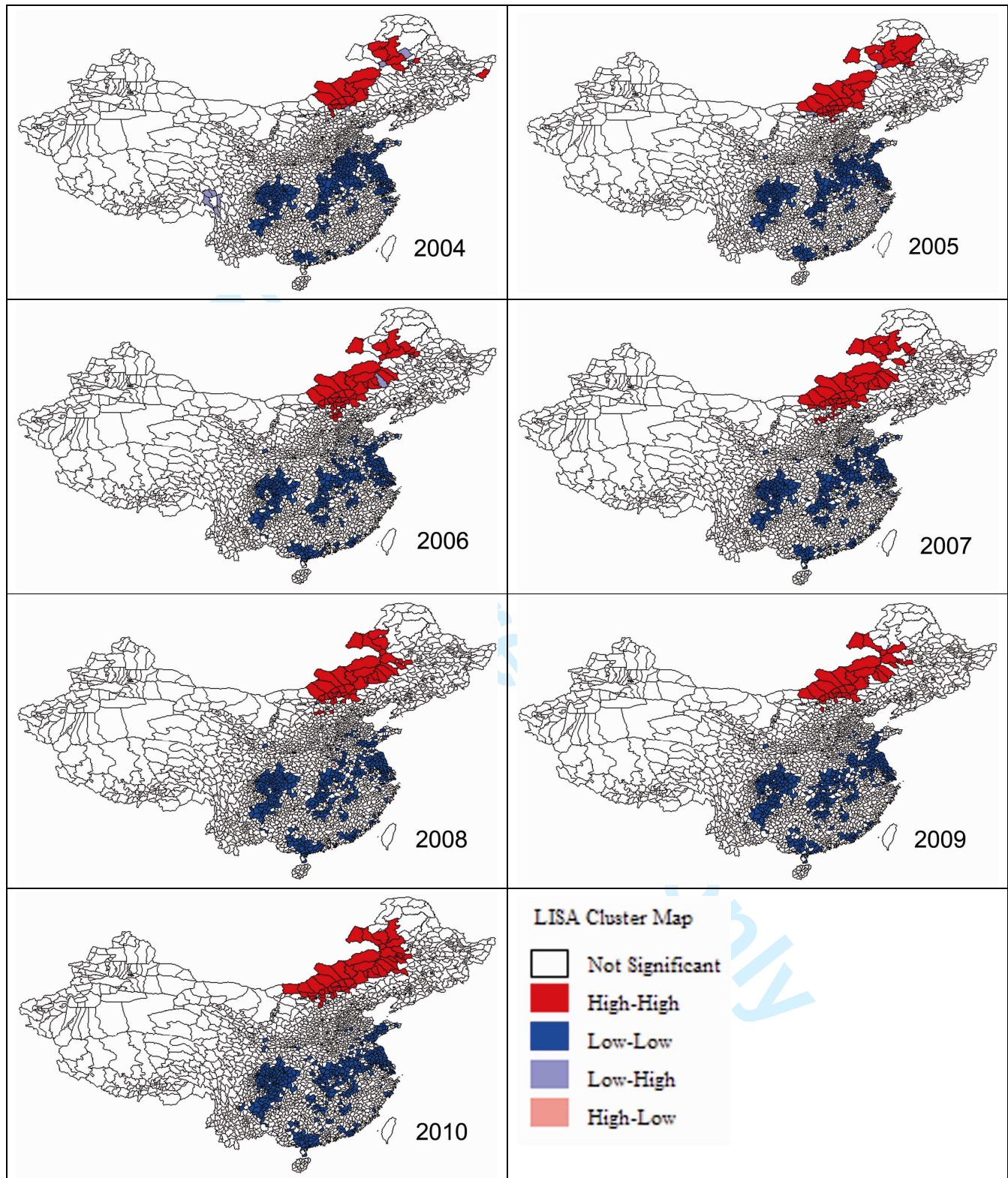


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010

## Figure legends

### Percentile: EBS-Smoothed

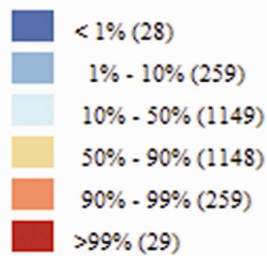


Figure legend 1 (for Figure 1)

### LISA Cluster Map

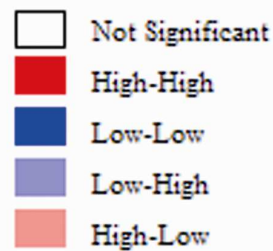


Figure legend 2 (for Figure 2 and Figure 3)

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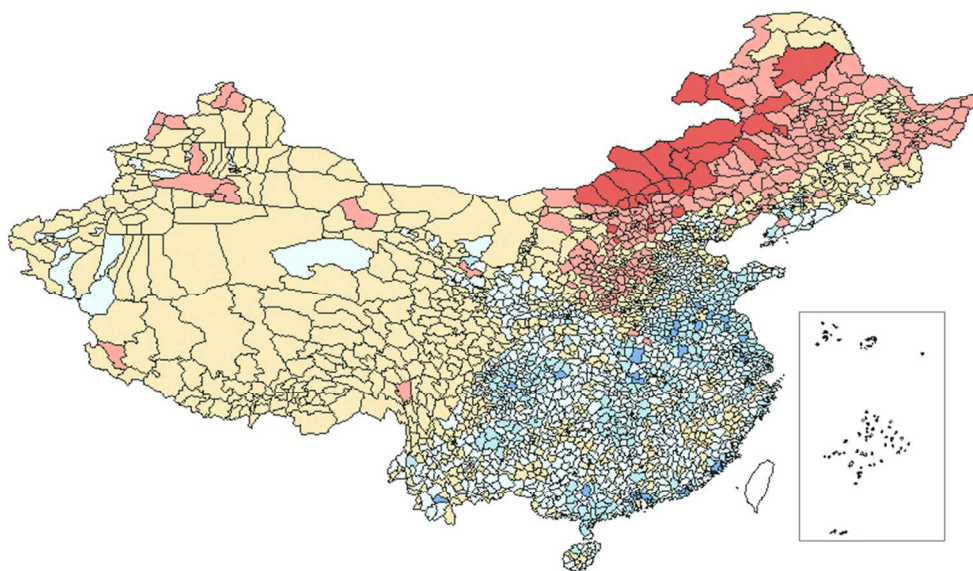


Figure 1 Percentile map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010  
102x60mm (300 x 300 DPI)

review only

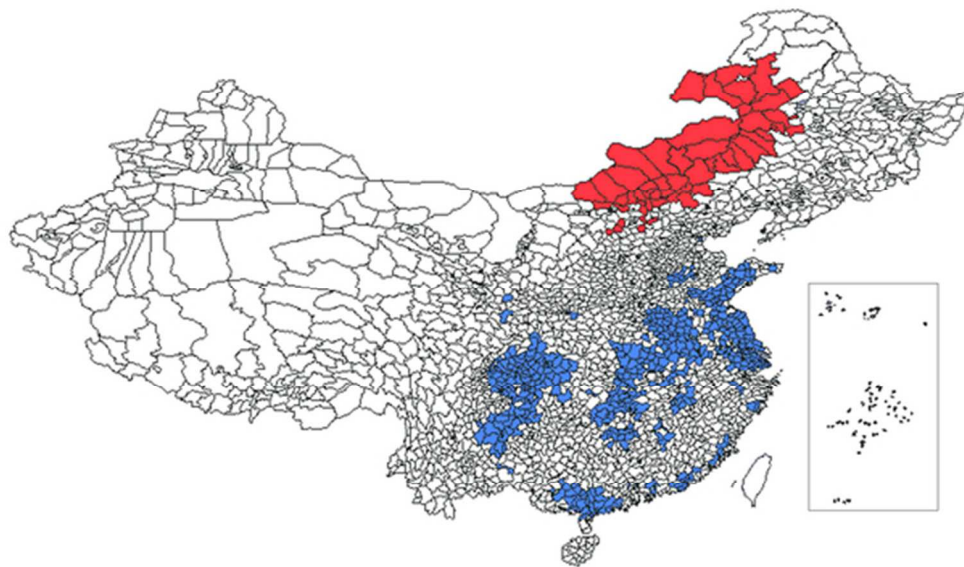


Figure 2 LISA cluster map of annual EB smoothed incidence rates for human brucellosis in mainland China by county, 2004-2010  
52x30mm (300 x 300 DPI)

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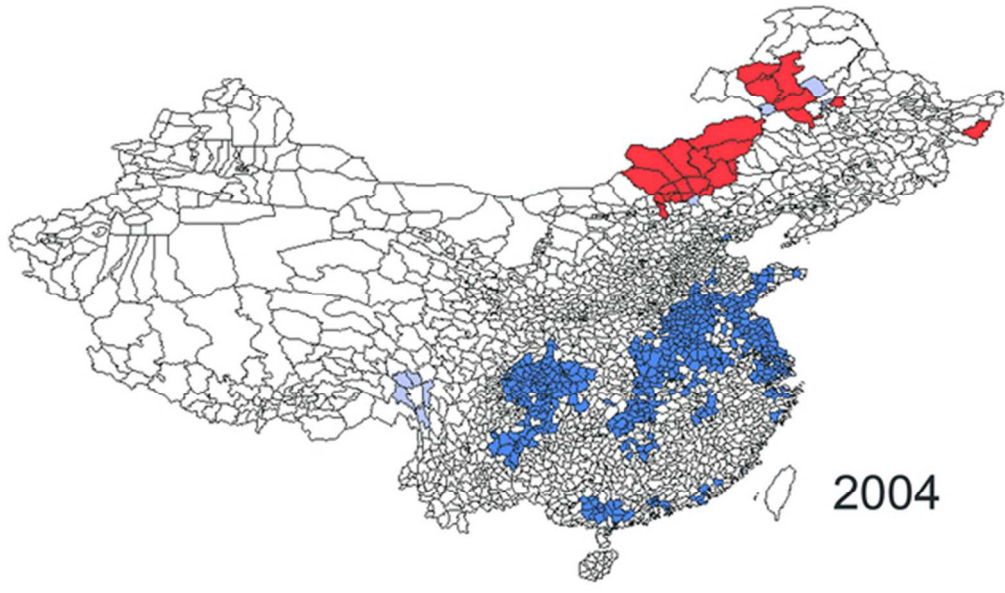


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
53x31mm (300 x 300 DPI)

Review only

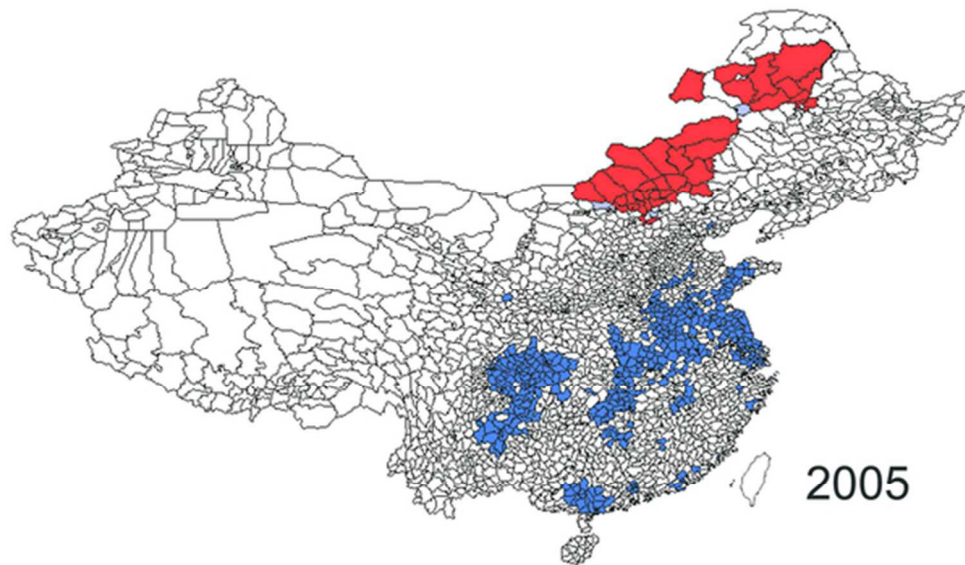


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
52x30mm (300 x 300 DPI)

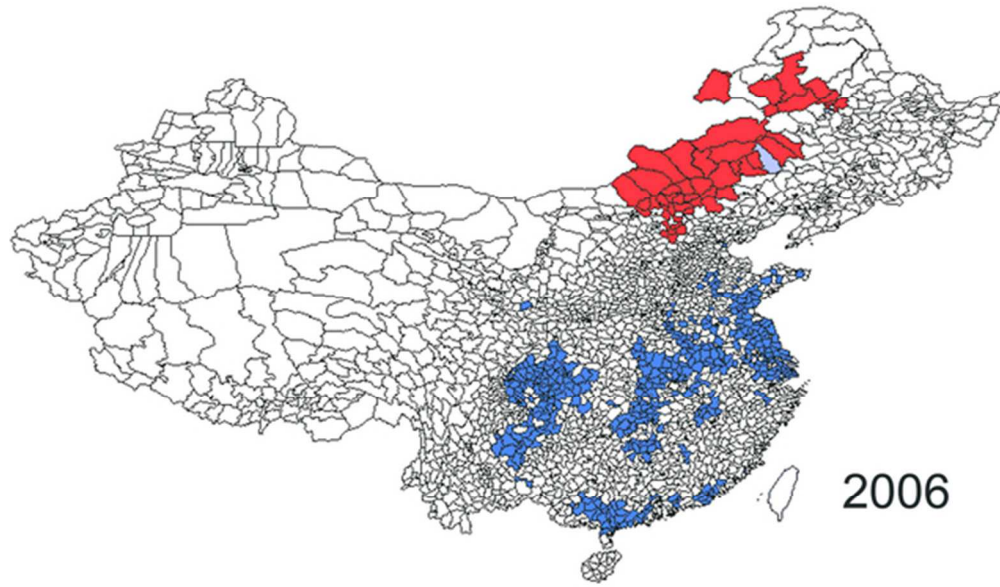


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
53x32mm (300 x 300 DPI)

review only



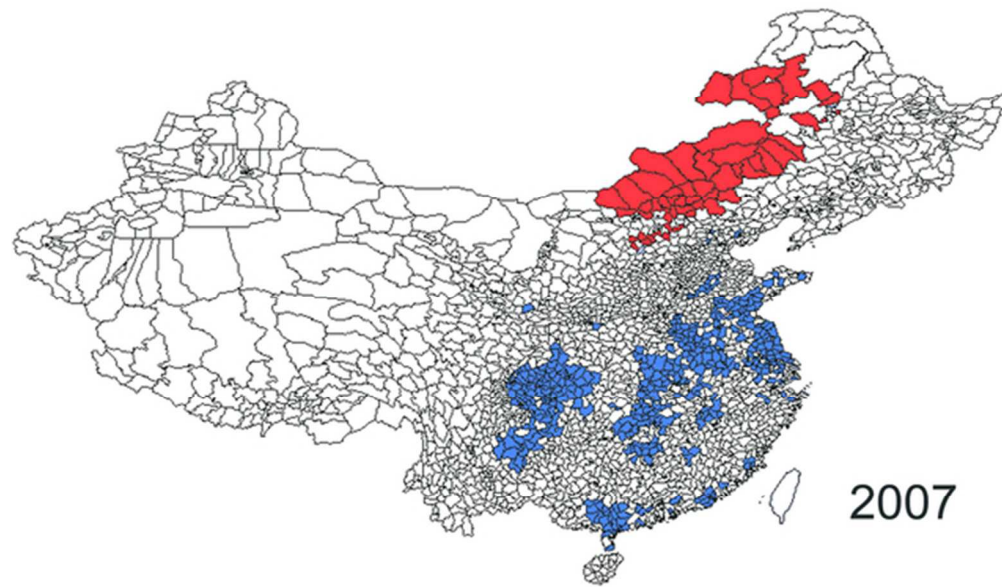


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
53x32mm (300 x 300 DPI)

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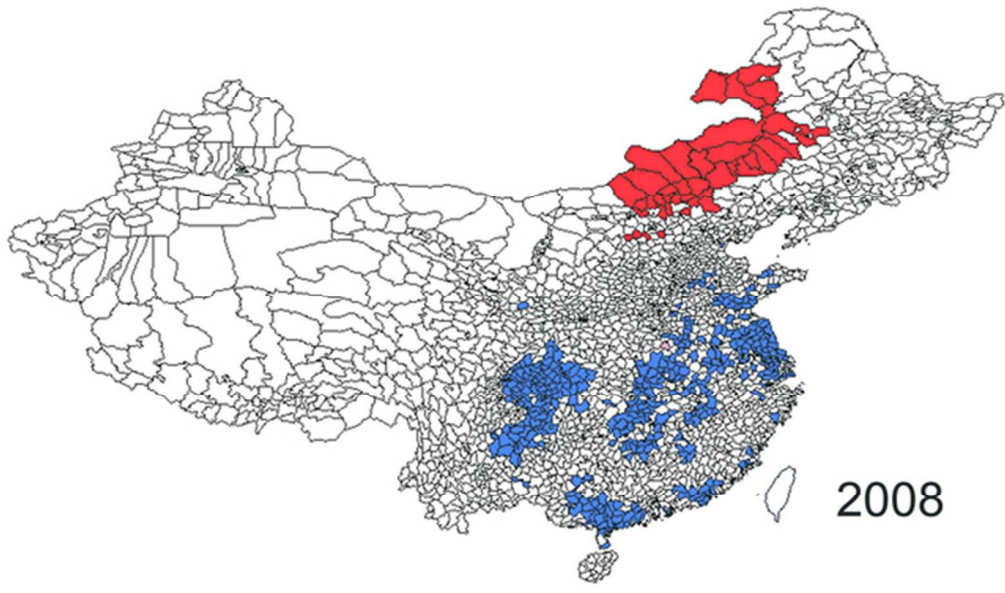


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
53x32mm (300 x 300 DPI)

review only

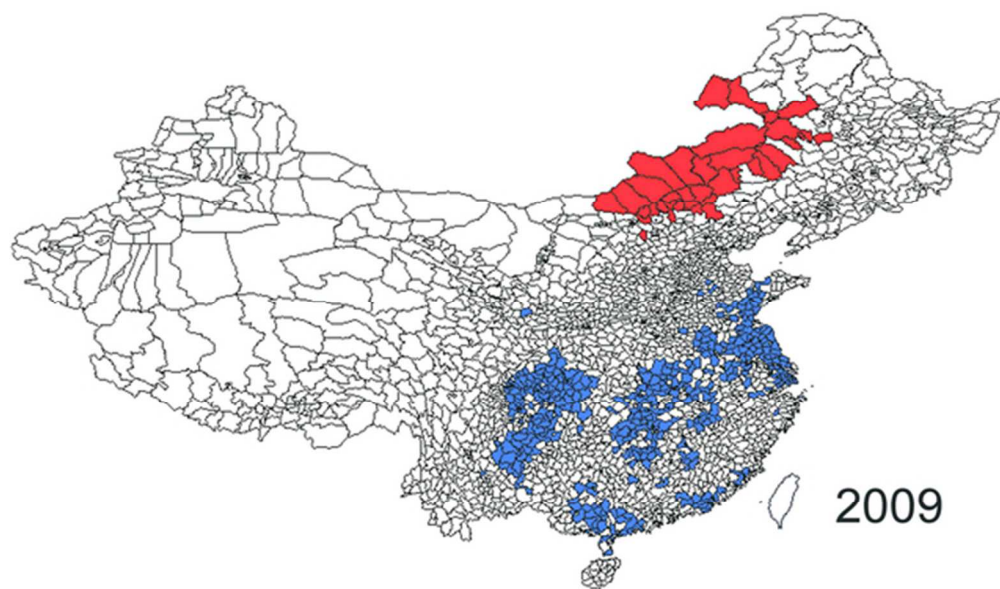


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
54x32mm (300 x 300 DPI)

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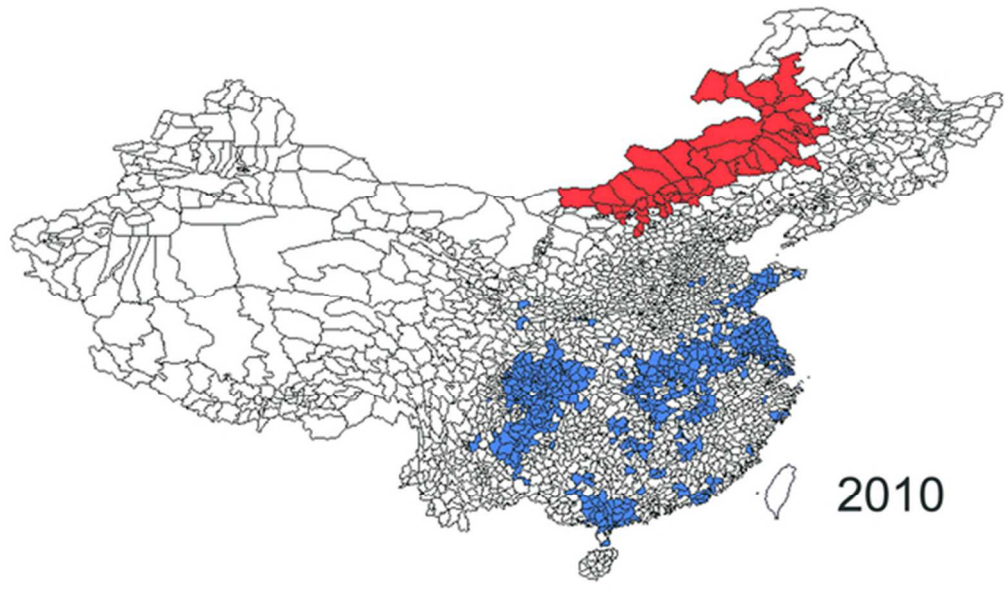


Figure 3 LISA cluster maps of EB smoothed incidence rates for human brucellosis in mainland China by county (per year), 2004-2010  
53x32mm (300 x 300 DPI)

review only