Epidemiol. Infect. (2015), **143**, 2451–2458. © Cambridge University Press 2014
doi:10.1017/S0950268814003598

Epidemic characteristics and spatio-temporal patterns of scrub typhus during 2006–2013 in Tai'an, Northern China

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Received 3 September 2014; Final revision 14 November 2014; Accepted 30 November 2014; first published online 29 December 2014

SUMMARY

Tai'an, a famous cultural tourist district, is a new endemic foci of scrub typhus in northern China. Frequent reports of travel-acquired cases and absence of effective vaccine indicated a significant health problem of scrub typhus in Tai'an. Thus, descriptive epidemiological methods and spatial-temporal scan statistics were used to describe the epidemic characteristics and detect the significant clusters of the high incidence of scrub typhus at the town level in Tai'an. Results of descriptive epidemiological analysis showed a total of 490 cases were reported in Tai'an with the annual average incidence ranging from 0·48 to 2·27/100 000 during 2006–2013. Females, the elderly and farmers are the high-risk groups. Monthly changes of scrub typhus cases indicated an obvious epidemic period in autumn. Spatial-temporal distribution analysis, showed significant clusters of high incidence mainly located in eastern and northern Tai'an. Our study suggests that more effective, targeted measures for local residents should be implemented in the eastern and northern areas of Tai'an in autumn. Meanwhile, it may prove beneficial for health policy makers to advise travellers to take preventive measures in order to minimize the risk of infection of scrub typhus in Tai'an.

Key words: Cluster analysis, epidemic characteristics, scrub typhus.

INTRODUCTION

Scrub typhus is an acute infectious disease caused by *Orientia tsutsugamushi* (*Ot*), which is transmitted to humans by infected larval trombiculid mites (chiggers). It is characterized by high fever, eschar or skin ulcer, enlarged lymph glands and rashes [1, 2]. Some patients may suffer with severe complications, including pneumonia, encephalitis, multi-organ failure or even death [3–6]. Scrub typhus is widely prevalent in the 'tsutsugamushi triangle', north to northern Japan and eastern Russia, south to northern Australia and west to Pakistan and Afghanistan. It has been estimated that about 1 billion people are at risk for scrub typhus, and almost 1 million scrub typhus cases occur annually [7].

In China, scrub typhus was known to occur mainly in southern regions before 1985. It has emerged and expanded rapidly in northern China since an outbreak in Shandong Province in 1986 [8, 9]. Tai'an, a new epidemic foci of scrub typhus, has gradually become one of the most seriously affected area for the disease in northern China since an outbreak in 2000 [10, 11].

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Fig. 1. Location of the study area, Tai'an district, Shandong Province, China.

A recent study identified the genetic diversity of *Ot* in Tai'an district [12] where the infection rate of *Ot* in rodents (the major host of chiggers) was 5·88% [13]. These factors might affect the severity and incidence of scrub typhus in Tai'an. Moreover, as a famous tourist attraction, Tai'an receives millions of visitors every year, this large number of tourists may increase the probability of scrub typhus infection. Moreover, with frequent reports of travel-acquired cases and absence of effective vaccine [7, 14–16], a better understanding of the spatial-temporal distribution patterns of scrub typhus in order to identify high-risk areas is imperative.

Thus, we explored the epidemic characteristics and spatial-temporal patterns of scrub typhus in Tai'an during 2006–2013 to detect high-risk groups and clustering areas, in order to provide information for the local health department to implement targeted surveillance and a control policy; moreover, this study will have important implications for the design of preventive measures for travellers.

MATERIAL AND METHODS

Study area

Tai'an is located in the central part of Shandong province (latitude 35° 38′ to 36° 28′ N, longitude 116° 02′ to 117° 59′ E) (Fig. 1). It includes 86 towns belonging to six counties with a population of about 5·53 million and has a temperate, semi-humid monsoonal climate. Tai'an has a variety of landscape types including mountains, hills, plains and lakes.

Data source

Surveillance data on reported scrub typhus cases from 2006 to 2013, including information about sex, age, residential address, occupation and onset date of symptoms were obtained from the Shandong Disease Reporting Information System (SDRIS). The diagnostic criteria for scrub typhus were based on epidemiological exposure history, clinical manifestations, and laboratory tests such as the Weil–Felix test. Confirmed cases were clinical cases with a positive result by indirect immunofluorescence antibody assay (IFA) or nested polymerase chain reaction (PCR) test targeting the 56-kDa type-specific antigen gene of *Ot* [2, 17].

METHODS

Demographic distribution analysis

The demographic distribution characteristics including age, sex and occupation distribution of scrub typhus cases from 2006 to 2013 in Tai'an were analysed according to surveillance data using χ^2 test and Kruskal–Wallis H signed-rank test with SPSS v. 16.0 (SPSS Inc., USA), $P < 0{\cdot}05$ was considered statistically significant.

Spatial autocorrelation analysis

To investigate global spatial autocorrelation of scrub typhus incidence at the town level, we used the spatial autocorrelation statistic (Moran's I) of GeoDa0.9.5-i, a freely available spatial statistics software package (https://geodacenter.asu.edu/). Monte Carlo randomization was employed to assess the significance of Moran's I and the number of permutation tests was set to 999. Z score ($\geqslant 1{\cdot}96$) indicated that scrub typhus incidence was not distributed randomly and cases were likely to cluster at the town level.

Spatial and spatial-temporal cluster analysis

We explored spatial and spatial-temporal distribution of scrub typhus based on the town-level polygon map

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Table 1. *Demographic characteristics of scrub typhus cases in Tai'an, 2006–2013*

	2006	2007	2008	2009	2010	2011	2012	2013	Total	Test statistic	*P* value
Sex										$\chi^2 = 16{\cdot}16$	0·024
Male	15	18	29	27	18	24	49	18	198		
Female	20	9	24	51	31	43	75	39	292		
Age group, yr										$H = 10{\cdot}47$	0·164
<10	1	0	4	4	3	2	6	2	22		
10–19	1	0	1	3	0	2	2	0	9		
20–29	0	2	2	3	0	3	4	2	16		
30–39	6	4	6	6	6	6	14	2	50		
40–49	6	6	9	20	15	16	24	8	104		
50–59	12	7	10	13	15	19	37	18	131		
60–69	5	6	14	20	7	14	22	16	104		
⩾70	4	2	7	9	3	5	15	9	54		
Occupation										$\chi^2 = 30{\cdot}47$	0·341
Farmers	29	22	39	69	40	61	105	46	411		
Workers	3	2	2	2	4	2	5	5	25		
Pupils	1	0	2	3	0	3	4	0	13		
Preschoolers	1	0	4	3	3	1	4	2	18		
Others	1	3	6	1	2	0	6	4	23		

of Tai'an at a scale of 1:100 000, on which all scrub typhus cases were geocoded to latitude and longitude coordinates and matched to the point layers. Demographic information of each town was obtained from the Tai'an Statistical Yearbook and ArcGIS 9.3 software (ESRI Inc., USA) was used for making quantitative thematic maps.

SaTScan v. 9.1.1 (http://www.satscan.org/) was applied to identify spatial and spatial-temopal potential clusters of scrub typhus. According to the town-level scrub typhus cases, demographic data and geographical data, a retrospective spatial cluster analysis for higher incidence based on Possion model was used [18]. The spatial scan statistic is defined by a circular (or elliptic) window which is in turn centred on each geographical area throughout the study area. The space–time scan statistic imposes a cylindrical window with a circular (or elliptic) geographical base and with height corresponding to time. Clusters were scanned by the variable-sized circular (or elliptic) or cylindrical moving window. The circular window was choosen for the analysis in our study. Monte Carlo simulation was used to test the null hypothesis assumed that the relative risk (RR) of scrub typhus was the same within the window compared to outside [19]. Meanwhile, SaTScan reported the most likely clusters comprised the one with the maximum likelihood, and secondary clusters in the same way as for the most likely cluster [20]. In this study, we set 50% of the total population at risk as the maximum spatial cluster size and 50% of the total population at risk as the maximum temporal cluster size to find possible sub-clusters. We set 999 as the number of Monte Carlo replications, and $P < 0{\cdot}05$ was considered statistically significant for clusters.

RESULTS

Descriptive analysis of scrub typhus in Tai'an

A total of 490 cases were reported in Tai'an from 2006 to 2013 with the annual average incidence ranging from 0·48/100 000 in 2007 to 2·27/100 000 in 2012. Of these, 198 cases (40·4%) were males and 292 cases (59·6%) were females. The annualized average incidence of females was significantly higher than that of males ($\chi^2 = 20{\cdot}41$, $P < 0{\cdot}001$) and distribution of cases by sex changed significantly ($\chi^2 = 16{\cdot}16$, $P = 0{\cdot}024$) during 2006–2013. We found there was no significant change in distribution of cases by age group (<10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, ⩾70 years) during the 8-year study period ($H = 10{\cdot}47$, $P = 0{\cdot}164$), and patients aged >50 years accounted for 59·0% of cases. Regarding occupation, 83·9% of scrub typhus patients were farmers. Workers (5·1%), preschoolers (3·7%) and pupils (2·7%) were also present (Table 1). The monthly changes of scrub typhus cases showed an obvious epidemic period from October to November, with a peak in October (Fig. 2).

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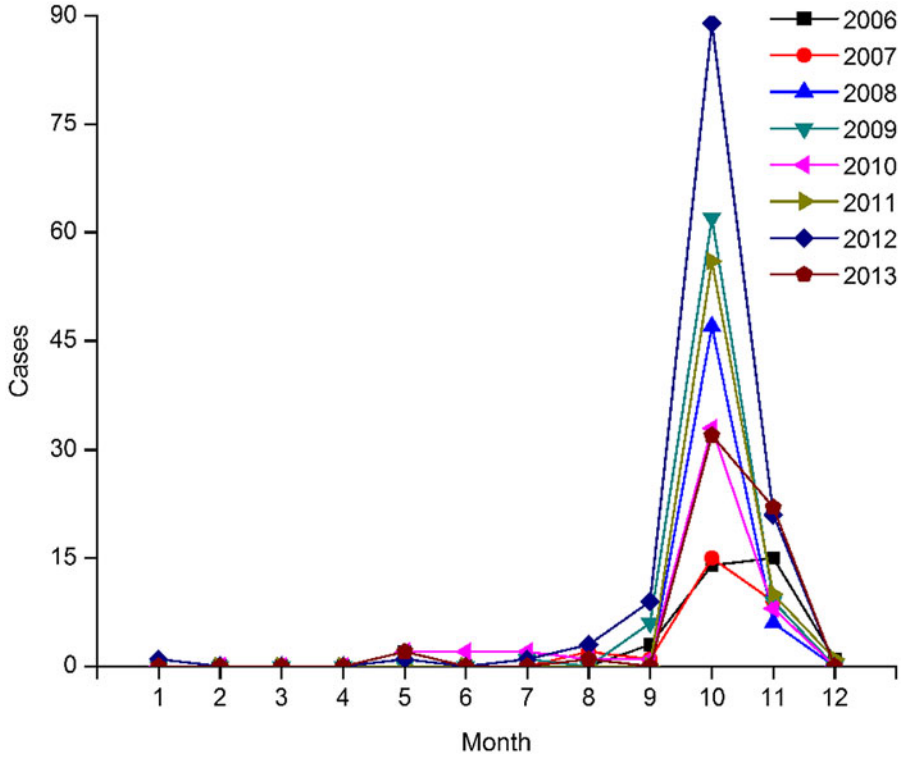

Fig. 2. Monthly distribution of scrub typhus cases in Tai'an, 2006–2013.

Spatial autocorrelation of scrub typhus in Tai'an

Moran's scatter plot and the significance assessment by permutation test of spatial autocorrelation for annualized average incidence of scrub typhus in Tai'an is presented in Figure 3. The value of global Moran's *I* statistic (0·4776) is shown in Figure 3*a*, and the number of permutations (999) and *Z* scores (7·4137) are shown in Figure 3*b*. Spatial autocorrelation analysis for annual incidence of scrub typhus in Tai'an from 2006 to 2013 showed that Moran's *I* statistic was significant from 2008 to 2013 at a significance level of 0·05, while it was not significant in 2006 and 2007 (Table 2).

Purely spatial analysis

Scrub typhus cases in Tai'an during 2006–2013 showed non-random distribution in space. The significant clusters of high incidence per year are listed in Table 3 and illustrated graphically in Figure 4. It was apparent that the locations of these clusters changed little by year. The most likely clusters were in the northern (2006) and eastern (2008–2013) regions of Tai'an, the size of the clusters expanded in 2008, 2011 and 2013. Secondary clusters were detected in eastern (2006) and northern (2012, 2013) Tai'an.

Spatial-temporal analysis

Table 4 and Figure 5 show statistically significant spatial-temporal clusters for high incidence of scrub typhus in Tai'an from 2006 to 2013 detected by the space–time scan statistic based on a Poisson model. It is noticeable that scrub typhus was not distributed randomly in space–time. One most likely statistically significant cluster was identified in the eastern region of Tai'an from September 2009 to November 2012 (RR = 20·67, $P < 0·001$), with 166 observed cases compared to 11·83 expected cases. One statistically significant secondary cluster was located in the area encompassing 42 towns around Mount Tai, with 35 observed cases compared to 2·52 expected cases in October 2012 (RR = 14·85, $P < 0·001$). It can be seen that scrub typhus endemic areas have expanded from the initial eastern parts of Tai'an in 2009 to the northern parts by 2012.

DISCUSSION

In this study, we describ the epidemic characteristics of scrub typhus cases reported in Tai'an district, northern China from 2006 to 2013. Our study found that the annualized average incidence of females was

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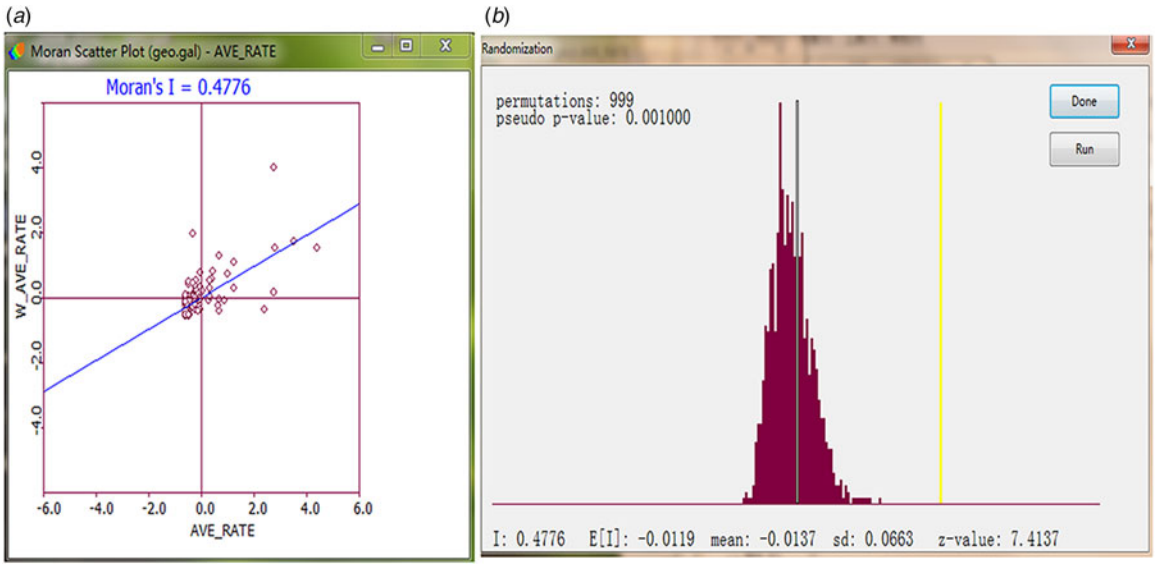

Fig. 3. Global spatial autocorrelation analysis for annual average incidence of scrub typhus in Tai'an from 2006 to 2013. (*a*) Moran's scatter plot for annualized average incidence of scrub typhus. (*b*) Histogram for significance assessment of Moran's *I*.

Table 2. *Spatial autocorrelation analysis for annualized incidence of scrub typhus in Tai'an, 2006–2013*

Year	Moran's *I*	Z *score*	*P* value
2006	0·0 116	0·4 806	0·1 710
2007	0·0 471	0·9 775	0·1 570
2008	0·1 909	2·8 610	0·0 080
2009	0·2 881	4·4 647	0·0 020
2010	0·4 631	6·7 514	0·0 010
2011	0·4 546	7·2 634	0·0 010
2012	0·3 499	5·7 917	0·0 010
2013	0·1 924	7·4 137	0·0 010

significantly higher than that of males in Tai'an (χ^2 = 20·41, $P < 0·01$), which means that women were more susceptible to scrub typhus than men in this area. Farmers and the elderly (people aged >50 years) are high-risk groups, which is consistent with previous studies [21, 22]. It is possible that the changing demographics of rural areas means that most younger males move to the cities for work leaving the elderly age group to engage in agriculture activities.

SaTScan was used to test whether a disease is randomly distributed, to detect the statistically significant clusters over space or space–time, to find risk factors, and to detect or predict disease outbreaks [20]. This method is being widely used in many diseases, including haemorrhagic fever with renal syndrome [23, 24], tuberculosis [25], cancer [26] and scrub typhus [27, 28], etc.

Our study found scrub typhus incidence had a positive spatial autocorrelation at the town level in Tai'an from 2008 to 2013. Cases detected by scan statistic analysis were non-randomly distributed and clustered in space and space–time. Purely spatial analysis found that the significant clusters (including most likely and secondary clusters) were located mainly in the eastern and northern regions of Tai'an, the location of clusters for high incidence changed little by year, while the size of clusters expanded in 2008, 2011 and 2013. Hills and mountains make up the main landform of eastern and northern Tai'an. The bushes and grassland vegetation of these areas provide an advantageous habitat for rodents, as well as for chigger mites [29–31]. Meanwhile, the growth of the rural population and increasing outdoor activities during harvest time may also contribute to the incidence of scrub typhus in these areas. Moreover, Xintai and Daiyue are both adjacent to Laiwu, the hyperendemic district of scrub typhus in Shandong Province, which may contribute to significant clusters of high incidence of scrub typhus. Thus, policy makers should give more attention to these regions.

Spatial-temporal analysis detected one most likely cluster for a high occurrence of scrub typhus in eastern Tai'an from September 2009 to November 2012, and one secondary cluster at the area around Mount Tai, including 42 towns belong to three regions (Taishan, Daiyue, Feicheng) in October 2012. The seasonal characteristic pattern of scrub typhus shown by our

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Table 3. *SaTScan statistics for spatial cluster with significant higher incidence in Tai'an, 2006–2013*

Year	Cluster type	Town numbers	Observed cases	Expected cases	Relative risk	*P* value
2006	Most likely	4	9	1·02	11·58	<0·001
	Secondary	4	13	2·74	6·96	<0·001
2007	Most likely	15	12	4·42	4·08	0·1 100
2008	Most likely	17	32	11·42	5·55	<0·001
2009	Most likely	6	44	8·36	10·78	<0·001
2010	Most likely	4	32	3·82	22·28	<0·001
2011	Most likely	18	48	15·22	8·59	<0·001
2012	Most likely	6	74	13·29	12·33	<0·001
	Secondary	1	8	0·95	8·96	0·0 015
2013	Most likely	17	38	12·29	7·28	<0·001
	Secondary	1	8	0·43	21·51	<0·001

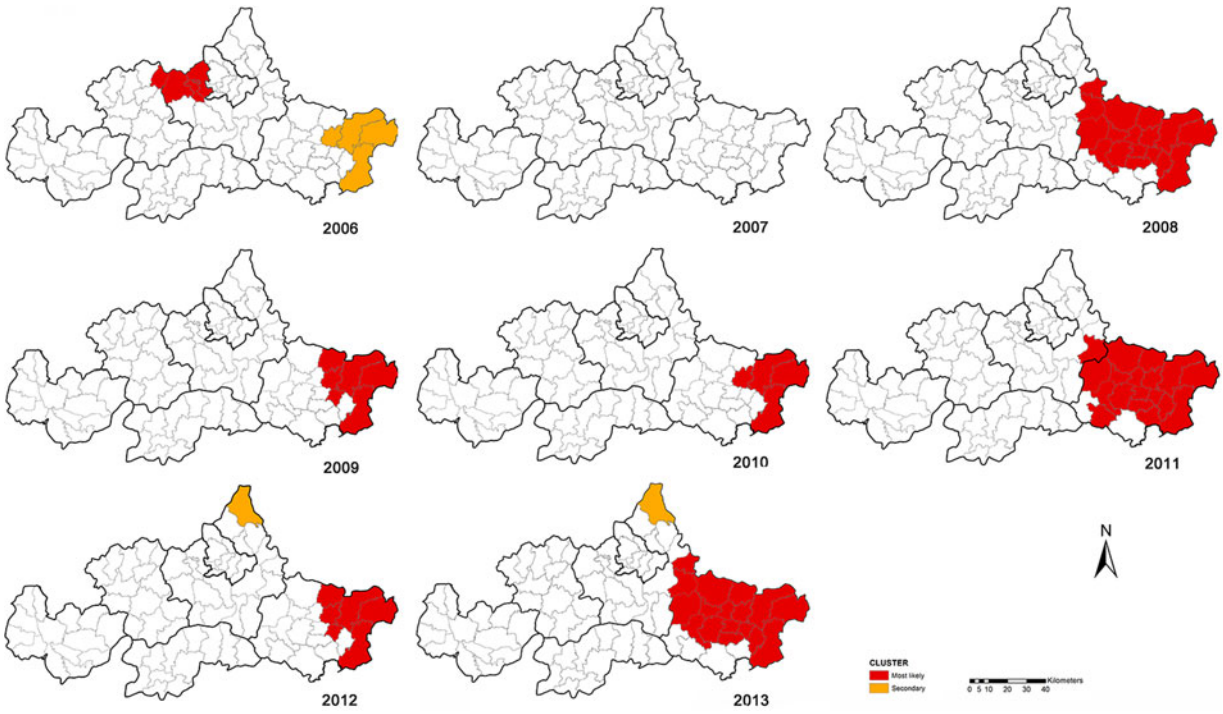

Fig. 4. Spatial clusters with significant higher incidence in Tai'an, 2006–2013.

study may be associated with the following factors. First, *Leptotrombidium scutellare*, the dominant transmission vector of scrub typhus in Shandong Province, was present from September to November with a peak in November [32]. Second, *Apodemus agrarius* was the main reservoir host in the field and its density fluctuation was consistent with the seasonal distribution of scrub typhus cases [33]. Third, the infection rate of *Ot* in rodents in Tai'an was high (5·88%) [13]. Fourth, poor living conditions in rural areas and increasing outdoor activities during harvest time enhanced the risk for local people to come into contact with the transmission vector [34]. The above factors may contribute to the high infection rate of scrub typhus during autumn.

Scrub typhus is a travel-associated disease and more than 20 travel-acquired cases have been reported since 1988 throughout the world [15], which indicates a significant health problem for popular tourist attractions. Tai'an is a famous tourist district which attracts millions of visitors; however, it is also a new epidemic foci of scrub typhus, which may increase the risk of tourists becoming infected. Thus, our study, which detected high-risk areas and time periods, will assist

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Table 4. *SaTScan statistics for space–time clusters with significant higher incidence in Tai'an, 2006–2013*

Cluster type	Time frame	Town numbers	Observed cases	Expected cases	Relative risk	*P* value
Most likely	1 Sept. 2009 to 30 Nov. 2012	4	166	11·83	20·67	<0·001
Secondary	1 Oct. 2012 to 31 Oct. 2012	42	35	2·52	14·85	<0·001

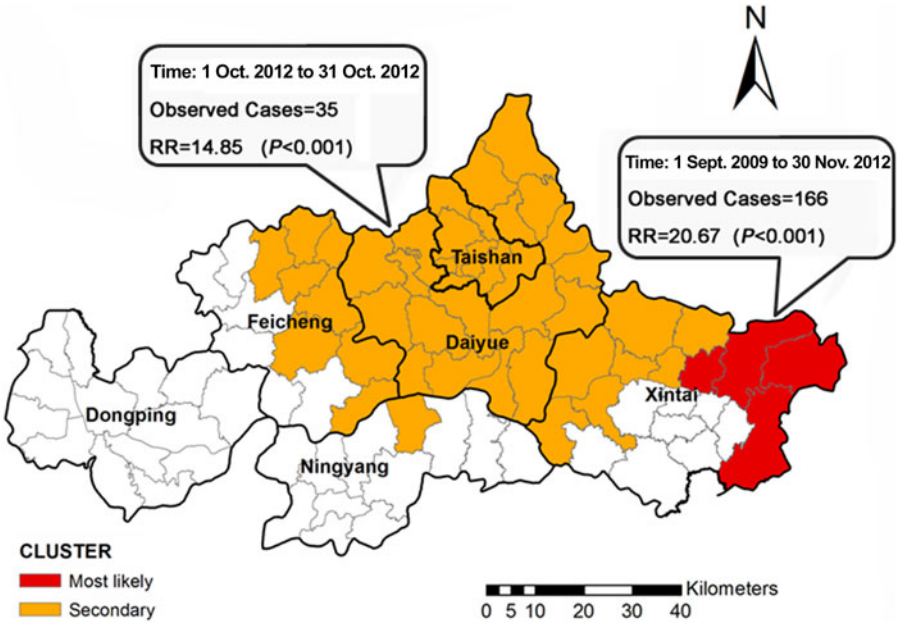

Fig. 5. Spatial-temporal clusters for high incidence of scrub typhus in Tai'an, 2006–2013. RR, Relative risk.

tourists in understanding the epidemic status of scrub typhus in Tai'an and help in taking preventive measures, such as choosing a non-epidemic season to visit, avoiding jungle areas with an abundance of chiggers, and wearing protective clothing, etc.

Our study had some limitations. First, cluster detection was based on the circular or cylindrical scan window, while the actual shapes of clusters were not all like that. Second, many factors related to incidence of scrub typhus were not considered, and future research should take environmental and socioeconomic factors into account.

In conclusion, our study described the epidemic characteristics, and identified spatio-temporal high-risk clusters of scrub typhus in Tai'an during 2006–2013. Our findings may help health authorities to implement efficient, targeted scrub typhus control measures for local residents, as well as for travellers.

ACKNOWLEDGEMENTS

The work was supported by a grant from the National Natural Science Foundation of China (No. 81 273 133).

DECLARATION OF INTEREST

None.

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