Am. J. Trop. Med. Hyg., 101(1), 2019, pp. 189–197
doi:10.4269/ajtmh.18-0958

Epidemiological Characteristics and Spatial Analysis of Tick-Borne Encephalitis in Jilin Province, China

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Abstract. Tick-borne encephalitis (TBE) is a viral infectious disease and has become a reemerging public health threat in recent years in northeastern China. However, no studies has characterized the epidemiologic features and explored the spatial dynamics and environmental factors of TBE cases in Jilin Province. In this study, we have described the epidemiological features of 846 reported human TBE cases from 2006 to 2016 in Jilin Province. There was an obvious single peak pattern of TBE cases from May to July in Jilin Province. More than 60% of TBE cases occurred in farmers, and the people in 50- to 59-year-old group had the high incidence of the disease. The results of Getis-Ord Gi* statistics demonstrated that the human TBE cases were more clustered in the northeastern border including Dunhua and Yanji cities and Antu and Wangqing counties, and southern areas including Huinan, Jingyu, Jiangyuan, and Liuhe counties in Jilin Province. We demonstrated that the temporal dynamics of TBE in Jilin was significantly associated with the dynamics of meteorological factors especially after 2009. The results from the auto-logistic regression analysis showed that the percentage coverage of forest, temperature, and autoregressive term were significantly associated with the occurrence of human TBE cases in Jilin Province. Our findings will provide a scientific evidence for the targeted prevention and control programs.

INTRODUCTION

Tick-borne encephalitis (TBE) is a viral infectious disease caused by TBE virus (TBEV), which mainly attacks the central nervous system.[1] Tick-borne encephalitis virus belongs to the genus *Flavivirus* of the family Flaviviridae and consists of five subtypes (the European subtype, the Siberian subtype, the Baikalian subtype, the Far Eastern subtype, and the Himalayan subtype).[2–5] The spectrum of clinical symptoms varies from subclinical infections to permanent neuropsychiatric consequences. The course of TBE is often asymptomatic. About 30% of TBE patients will exhibit a feverish flu-like disease. Ten to twenty percent of patients will have neurological disorders.[3,6] The most commonly reported neurological symptoms were upper limb paresis, lower limb paresis, sensation disorders, cranial nerve paresis, and cerebellar syndrome.[7–10] The clinical course and the probability of death or severe neurologic sequelae depended on the age of the TBE patients—the disease severity was increasing with age. Moreover, the clinical outcome may in part depend on the infecting TBEV subtype. The case fatality rate (CFR) in patients with TBEV-European or TBEV-Siberian was less than 1%,[7] whereas with the TBEV-Far Eastern, CFRs had been reported to be up to 30–40%.[2,7,11,12] Tick-borne encephalitis virus is transmitted by the bite of infected ticks and is maintained in the transmission cycle between the ticks and wild vertebrate hosts.[6,13] Tick-borne encephalitis can also be transmitted by contaminated milk. It mainly occurs in Europe, Far Eastern Russia, Japan, and northern China. Approximately 10,000–12,000 TBE cases are reported every year, and TBE is becoming a growing public health concern in these aforementioned endemic regions.[14]

Historically, TBE was first reported in mainland China in 1943 and TBEV was isolated from human TBE cases and ticks in 1952.[15] Previous studies have demonstrated that three main TBE foci, including foci in northeastern, northwestern, and southwestern, existed in mainland China. In China, more than 98% TBE cases were reported in the northeastern foci.[6,15] And, the woodlands in northeastern China have been recognized as the most important and typical endemic areas of TBEV.[15] In the northeastern China, TBEV is mainly transmitted by *Ixodes persulcatus* and the vertebrate reservoir hosts, such as the rodents (*Myodes rufocanus*, *Apodemus sylvaticus*, and *Eutamias sibiricus*), *Capreolus capreolus*, *Vulpes vulpes*, and *Sus scrofa*.[16,17]

Jilin Province is located in the northeastern China, and about one-third of the total reported human TBE cases in China occurred in this province. However, no study has characterized epidemiologic features and explored the spatial dynamics and environmental factors contributing to the distribution of TBE cases in Jilin Province. This information is very important to make informed decisions around the high-risk areas for disease and vector control and prevention. Thus, the objectives of this study are to describe the epidemiological features of human TBE cases, to detect the spatial hot spots for human TBE cases, and to identify the potential environmental factors contributing to the spatial distribution of TBE cases in Jilin Province.

MATERIALS AND METHODS

Study area. Jilin Province is located in the northeastern China between 121°38′–131°19′E and 40°50′–46°19′N (Figure 1). Jilin Province includes 1,002 administrative townships of 64 counties, with a total population of 27,533,000 and a total area of 187,400 km^2. Jilin Province has a continental

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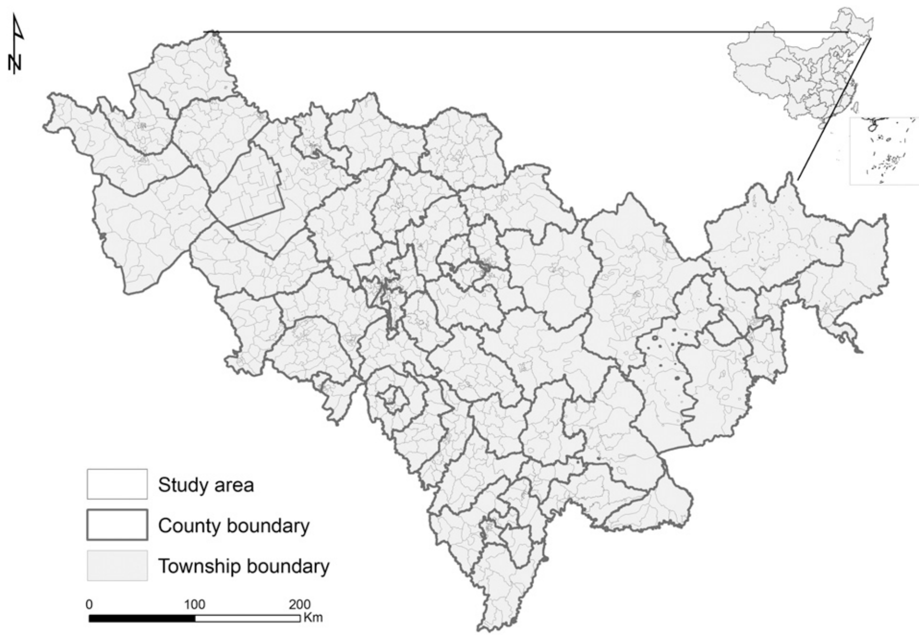

FIGURE 1. Spatial distribution of Jilin Province and its location in China.

monsoon climate, with short, warm summers and long, cold winters.

Data collection and management. Data on TBE cases from January 1, 2006, to December 31, 2016, were collected from the China Information System for Disease Control and Prevention from the Centre for Disease Control and Prevention of Jilin Province (Jilin CDC). The dataset includes age, gender, occupation, residential address, date of onset

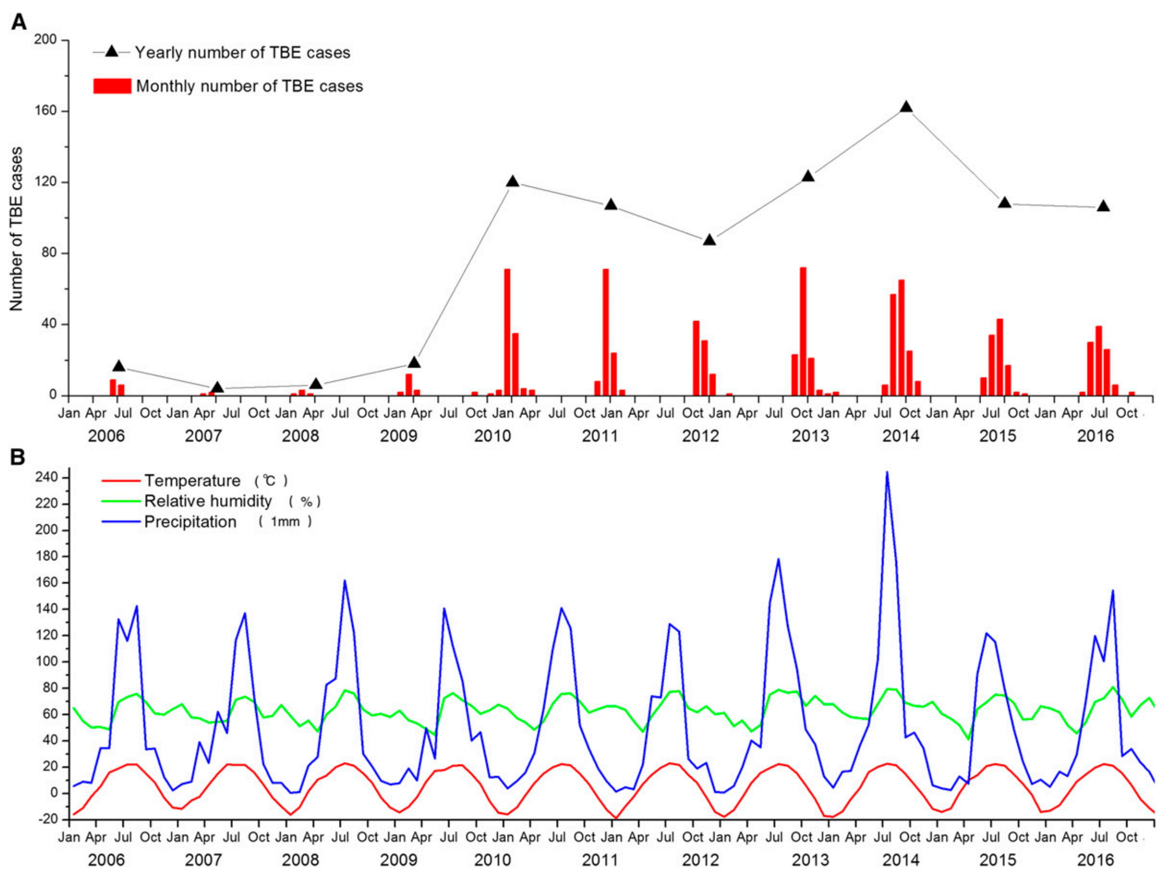

FIGURE 2. (**A**) Temporal distribution and monthly cumulative number of TBE case in Jilin Province. (**B**) Temporal dynamics of monthly temperature, relative humidity, and precipitation in Jilin Province. This figure appears in color at www.ajtmh.org.

of symptoms, laboratory diagnosis, and clinical outcome for each case. Digital township-level map of Jilin Province was obtained from the China Resource and Environment Data Cloud Platform (http://www.resdc.cn/). Demographic data for each township were obtained from the National Bureau of Statistics of China, including the population for age groups and the number of female and male. Meteorological variables, including temperature, relative humidity, and precipitation, were obtained from the China National Meteorological Information Center (http://data.cma.cn/). Land cover variables such as the percentage coverage of forest, shrub, grassland, irrigated cropland, rainfed cropland, and built-up land were provided by the China Resource and Environment Data Cloud Platform (http://www.resdc.cn/).

Analysis of spatial dynamics of TBE in Jilin Province. Each case was geocoded and linked to the map of Jilin Province at township level according to their residence addresses at the time of symptom onset using geographic information system technologies. To describe the epidemiological features of human TBE cases in Jilin during 2006 to 2016, the demographic, temporal, and spatial distributions were assessed. An epidemic curve was created by plotting the monthly cumulative number of TBE cases according to their onset of symptoms (Figure 2A). The temporal dynamics of meteorological variables, including monthly temperature, relative humidity, and precipitation, in Jilin were also plotted (Figure 2B). The cumulative number of TBE cases for each gender and the annual incidence among different age groups were calculated (Figure 3). The spatial distribution and dynamics of TBE cases from 2006 to 2016 were created by mapping the yearly cumulative TBE cases at the township level (Figure 4). Getis-Ord Gi* statistics were used to assess the positive spatial autocorrelation and detect hot spots in Jilin Province. A calculated value of Gi* > 1.96 indicated that township i and its neighboring townships had more TBE cases than other townships, which was defined as a TBE hot spot. And, the difference of TBE cases between hot spots and other townships is statistically significant.[15] The spatial distribution of TBE cases, annual incidence of TBE cases, and the spatial hot and cold spots of TBE cases in Jilin Province were mapped by using the ArcGIS software (version 10.1, ESRI, Redlands, CA) (Figure 5). The annual incidence of TBE in Jilin Province at the township level was mapped (Figure 6).

Analysis of the potential factors associated with TBE cases. The temporal dynamics of TBE and meteorological variables were examined by the Spearman correlation. To identify the potential ecological and meteorological factors contributing to the spatial distribution of TBE cases in Jilin Province, an auto-logistic regression model was built to explore the potential risk factors, including the density of human population and the percentage coverage of shrub, forest, grassland, irrigated cropland, built-up land, and rainfed cropland at the township level with the presence/absence of TBE infections. Meteorological variables that were included in the analysis were as follows: monthly temperature, relative humidity, and precipitation for the 3 months of the year when TBE was at its highest. To account for the effect of spatial autocorrelation in the response variables, an additional covariate (autoregressive term) was included in the model.[13] The odds ratios (ORs), their 95% CIs, and *P*-values were estimated using maximum likelihood methods. Univariate analysis was first performed to examine the effect of each variable separately in the auto-logistic regression analysis. Then, multivariate analysis was performed using variables with *P*-values < 0.1 from the univariate analysis as covariates. Continuous variables were presented as categorical results to allow inspection of the data and determine if assumptions regarding continuous variables were justified. If

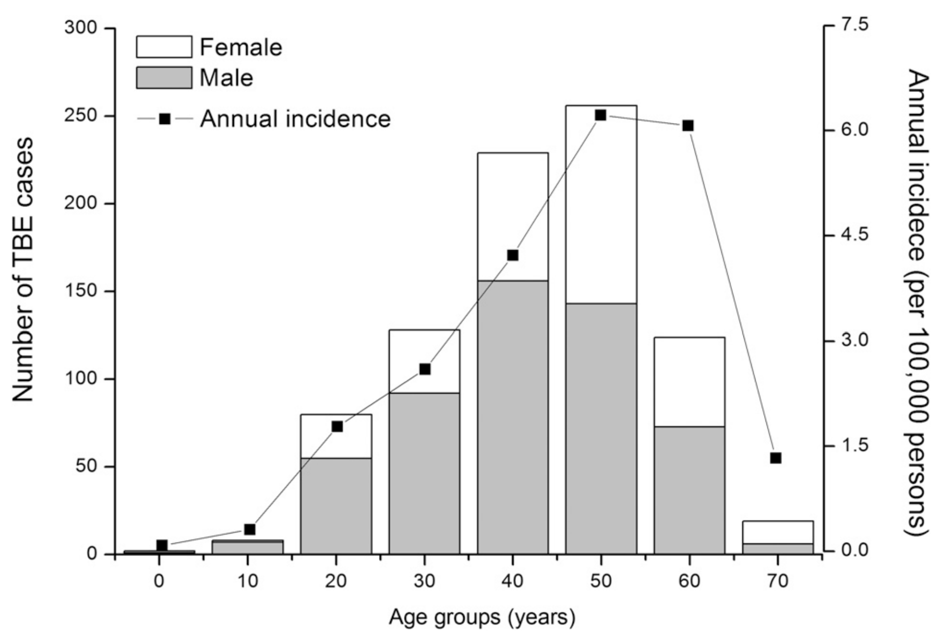

FIGURE 3. Age and gender distribution of TBE patients in Jilin Province, from 2006 to 2016. The black bar represents the number of male patients and the white bar represents the number of female patients over different age groups. The line represents the annual incidence over different age groups.

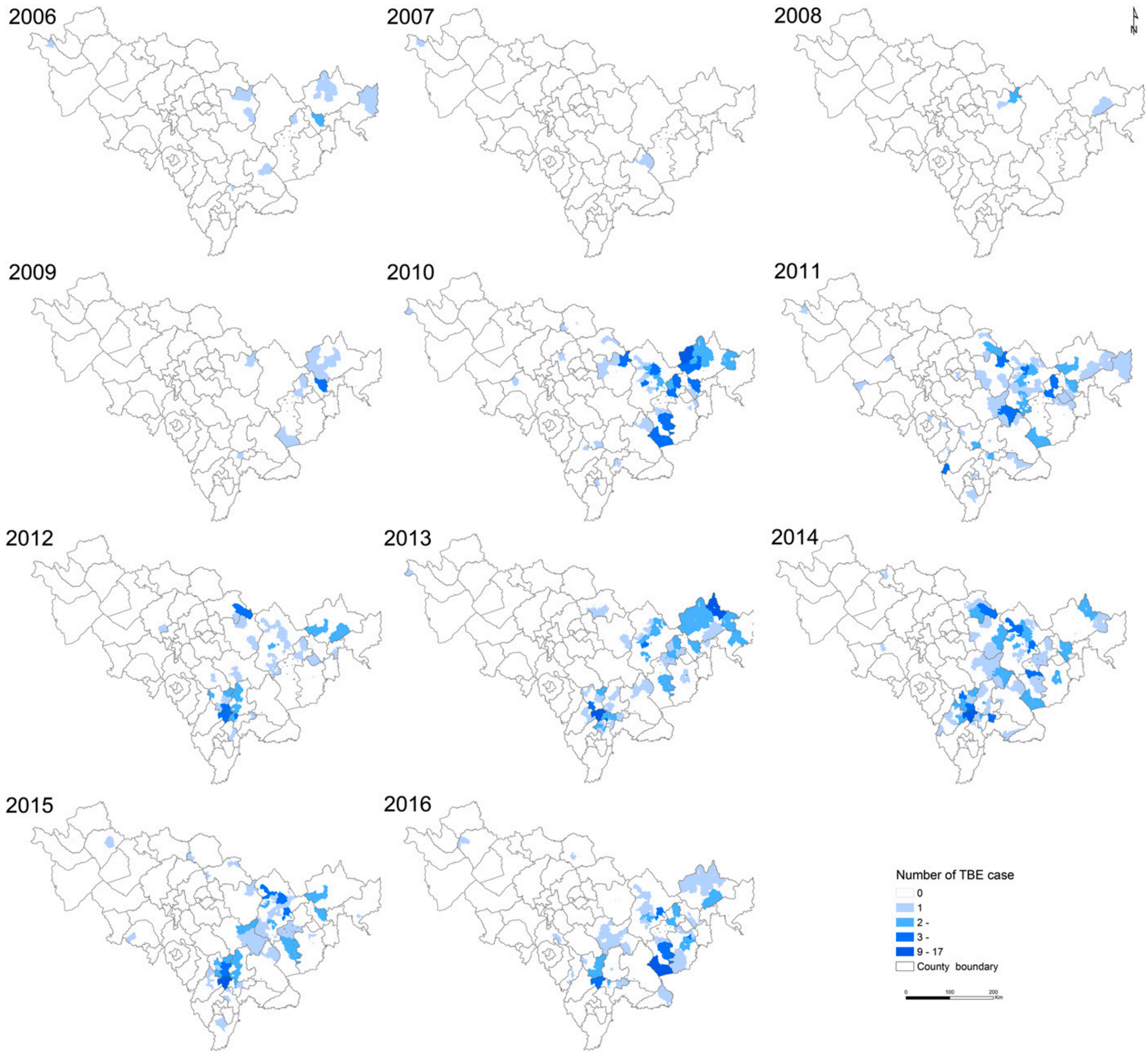

FIGURE 4. Spatial distribution of TBE cases in Jilin Province, from 2006 to 2016. This figure appears in color at www.ajtmh.org.

significant, nonlinear associations were found between the presences of TBE infections, they were incorporated into a polynomial regression analysis.[18] Statistical analyses were performed using the STATA software (Stata Corp LP, College Station, TX).

RESULTS

A total of 846 TBE cases were reported in Jilin Province from 2006 to 2016, and six cases were fatal. The number of TBE cases per year from 2006 to 2016 was 15, 3, 5, 17, 119, 106, 86, 122, 161, 107, and 105, respectively (Figure 2A, Table 1). From 2006 to 2009, the number of reported annual TBE cases in Jilin Province remained stable, with a sharp increase starting in 2010. This increase in the number of annual cases remained through 2016, peaking in 2014 with a total of 161 cases throughout the whole region. Overall, the annual TBE cases had an increasing trend in Jilin Province during the study period (Cochran–Armitage trend test, $z = 16.31$, $P < 0.001$). The number of TBE cases in Jilin Province increased in April each year, and peaked in June, then decreased in October. However, no human TBE cases were reported after October. The epidemic curve of human TBE cases showed an obvious seasonal pattern, with 93.1% (788/846) TBE cases occurring between May and July (Figure 2A). We also reported a significant association between temperature, relative humidity, and precipitation, and the monthly reported cases, and the Spearman correlations (rho) were 0.656 ($P < 0.001$), 0.258 ($P = 0.003$), and 0.639 ($P < 0.001$), respectively (Figure 2B). Especially, higher Spearman correlations (rho) were reported after 2009: 0.776 ($P < 0.001$), 0.294 ($P < 0.001$), and 0.734 ($P < 0.001$), respectively.

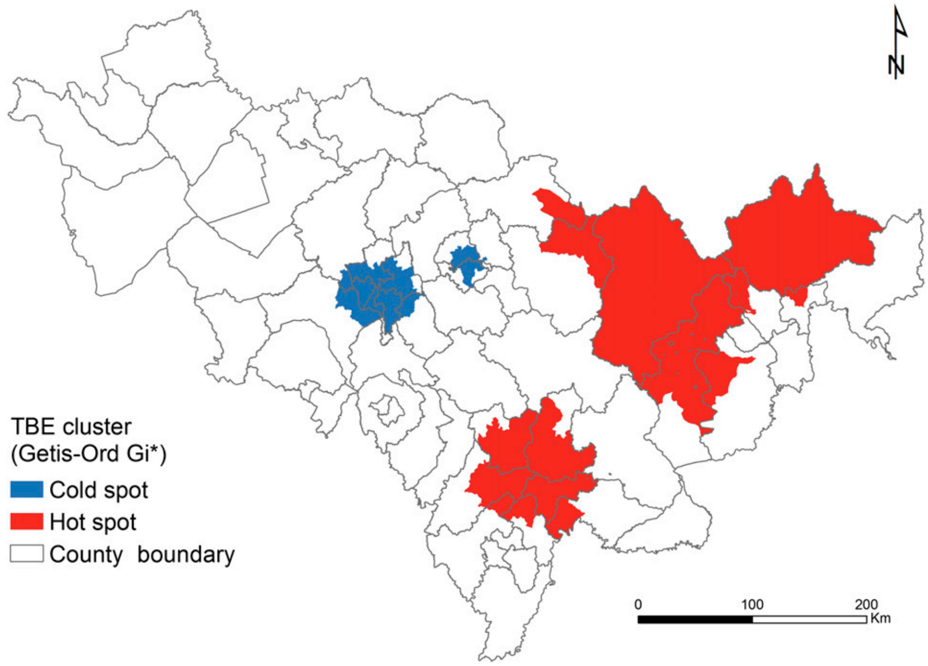

FIGURE 5. Spatial hot and cold spots of TBE cases in Jilin Province, from 2006 to 2016. This figure appears in color at www.ajtmh.org.

Five hundred thirty-three (63%) of the reported cases in Jilin Province were male. The TBE incidence in Jilin Province among males was significantly higher than that among females (χ^2 = 49.41, P < 0.001). People aged 30–39, 40–49, 50–59, and 60–69 years comprised 15.48%, 28.14%, 29.43%, and 14.54% of the whole cases, respectively. The mean age of male TBE patients (46 years) was significantly less than that of female TBE patients (50 years) (Wilcoxon rank-sum test, P < 0.001). Most TBE patients in Jilin Province were farmers (60.99%), followed by domestic workers (16.08%) and forest workers (4.6%). Figure 3 showed the annual incidence of TBE in different age groups increased with the increase in age, and people aged 50–59 years had the highest incidence compared with other age groups in Jilin Province (χ^2 = 433.86, P < 0.001).

As shown in Figure 4, before 2010, only sporadic cases were reported during 2006–2009. Since 2010, more TBE cases were reported and mainly occurred in the northeastern and southern parts of Jilin Province. Subsequently, TBE cases were continually observed in those and surrounding regions.

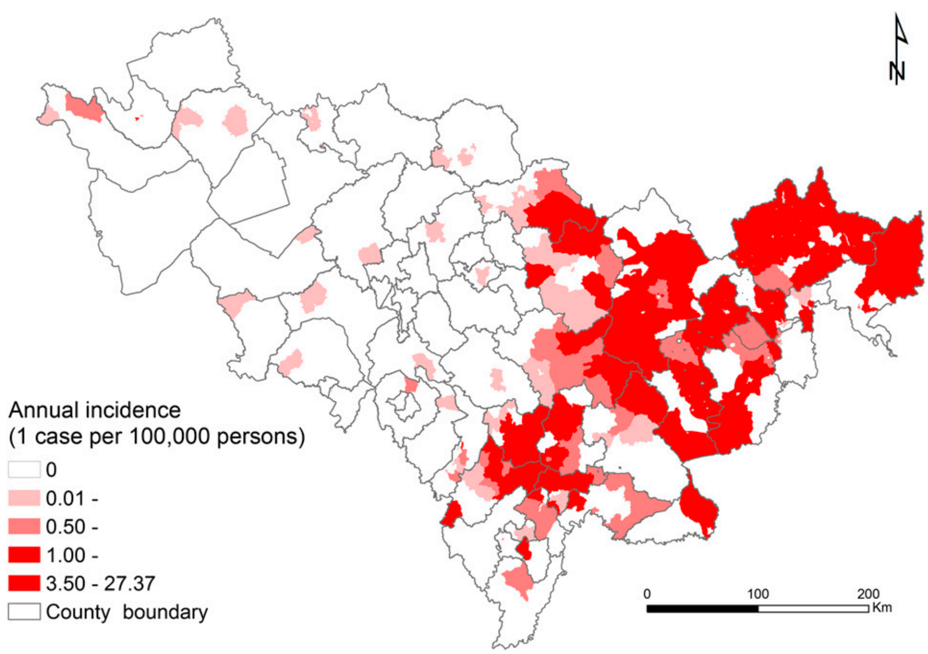

FIGURE 6. Annual incidence of TBE at the township level in Jilin Province, from 2006 to 2016. This figure appears in color at www.ajtmh.org.

TABLE 1
Summary of epidemiological characteristics of tick-borne encephalitis in Jilin Province, from 2006 to 2016

Characteristic	Total cases (n = 846)
Demographic characteristic	
Male, no. (%)	533 (63.0)
Age, mean ± SD (range)	47.3 ± 12.5 (6–79)
Farmers (%)	510 (60.3)
Temporal distribution	
2006	15
2007	3
2008	5
2009	17
2010	119
2011	106
2012	86
2013	122
2014	161
2015	107
2016	105
Epidemic peak, no. (%)	May to July, 788 (93.1)
Spatial distribution	
Affected townships, no. (%)	175 (17.5)

Tick-borne encephalitis cases were reported in only 45 townships of Jilin Province in 2010, and later, more than 50 townships were newly reported with TBE presence. Our hot spot analysis demonstrated that the human TBE cases were more clustered in the northeastern border including Dunhua and Yanji cities and Antu and Wangqing counties, and southern areas including Huinan, Jingyu, Jiangyuan, and Liuhe Counties in Jilin Province (Figure 5). Our hot spot analysis also demonstrated two cold spots for TBE dynamics in the center parts of Jilin Province (Figure 5).The whole TBE cases in Jilin Province occurred in 175 townships from 42 counties during 2006–2016, covering 33.2% of the total area of Jilin Province. The annual incidence of human TBE cases varied greatly at the township level, ranging from 0 to 27.37 per 100,000 persons (Figure 6). Of those 175 townships with TBE cases, there were nine townships with the annual incidence of more than 10.00 per 100,000 persons.

The results from the auto-logistic regression analysis showed that the TBE cases were significantly associated with the density of human population; the percentage coverage of forest, rainfed cropland, and built-up land; temperature; relative humidity; precipitation; and the autoregressive term in the univariate analysis (Table 2). In the multivariate analysis, the percentage coverage of forest, temperature, and the autoregressive term were found to be independent risk factors in the occurrence of TBE in Jilin Province (Table 2). The OR for percentage coverage of forest was 1.16 (95% CI: [1.08–1.25], $P < 0.001$), for temperature was 0.62 (95% CI: [0.45–0.86], $P = 0.003$), and for autoregressive term was 1.52 (95% CI: [1.35–1.70], $P < 0.001$), respectively.

DISCUSSION

In this study, we described the epidemiologic features of TBE and explored the potential risk factors influencing the distribution of TBE cases in Jilin Province from 2006 to 2016. Our study found the annual TBE cases had increased in Jilin Province during the study period, especially after 2010. This abrupt increase in TBE cases may result from improved laboratory diagnostic capabilities of local CDCs or hospitals. We also observed an obvious single peak pattern of TBE cases from May to July in Jilin Province. More than 60% TBE patients were farmers, and the people in the 50- to 59-year-old group had the highest incidence in this province. The percentage coverage of forest, temperature, and autoregressive term were significantly associated with the occurrence of human TBE cases in Jilin Province.

An obvious seasonal pattern of human TBE cases was observed in Jilin Province in our study, which was consistent with the previous studies.[15] In Jilin Province, *I. persulcatus* is the dominant tick species and the main vector of TBE, whereas some other tick species, such as *Haemaphysalis japonica douglasi*, *Haemaphysalis concinna*, and *Dermacentor silvarum*, have also been identified as vectors for TBE.[16] The seasonality of human TBE cases is closely associated with the activity peak of the ticks.[15,19] Human TBE cases may be confirmed after tick bites, with 2 weeks before the symptom onset.[15,20] After overwintering, the ticks in Jilin Province often become active and seek blood meals in early April each year. An activity peak is reached from May to June, which is in accordance with the seasonality of human TBE cases in Jilin Province. Another possible reason for the dynamic seasonality for TBE was the frequency of outdoor activities. In the late spring and early summer, the farmers went into the woods for recreation, which increased the exposure chances for ticks.

In China, TBE has been considered an occupational disease because most patients have been forest workers. However, the occupational distribution of TBE cases has changed significantly with increasing proportion of non-forestry workers during the past decades in China. In our study, 77.1% of the patients in Jilin Province were non-forest–working farmers and domestic workers who also entered the forest areas of TBE foci. The changes in the occupations of TBE patients may be resulting from the changes in the occupations themselves in response to economic developments.

The number of forestry workers kept declining. However, the number of farmers and domestic workers engaged in potherb-picking activities has been increasing.[21,22] The farmers and domestic workers have a weak awareness in protecting themselves from tick bites and have rarely been vaccinated; therefore, these individuals are at a higher risk of TBEV infections.[23]

Our results showed that the TBE cases have been rising during our study periods and the geographical distribution of TBE cases has expanded in Jilin Province. Our study demonstrated that the TBE cases were more clustered in the northeastern and southern areas in Jilin Province. As a tick-borne disease, the intensity and distribution of TBE may have been associated with the ecological, socioeconomic, and climate factors.[24–27] In our study, the percentage coverage of forest and temperature had been found to be associated with the TBE in Jilin Province. The vegetation covers in Jilin Province have changed substantially during the past decades, with the initiation of the programs to restore the former agricultural lands to the woodlands.[28] Such "Greening" programs might have partially caused the expansion of TBE cases in Jilin Province, by shaping the suitable ecological environment for survival or activity of the ticks and wild vertebrate hosts in this province. With the economic development, more and more people traveled to TBE-endemic areas in Jilin Province, thus increasing the numbers of TBE cases in this province.[21,29]

Table 2
Summary results of the auto-logistic regression models for spatial distribution of TBE in Jilin Province, from 2006 to 2016

Variables (unit)	No. of townships with TBE cases (95% CI)	Univariate analysis		Multivariate analysis	
		Crude odds ratio (95% CI)	*P*-value	Adjusted IRR (95% CI)	*P*-value
Density of human population (categorical, 1,000 persons per km^2)					
< 0.1	97 (81–113)	–	–	–	–
0.1	45 (33–57)	–	–	–	–
> 0.5	32 (22–42)	–	–	–	–
Density of human population (continuous, 1,000 persons per km^2)	–	0.94 (0.90–0.98)	0.002	–	–
Percentage coverage of forest (categorical, 10%)					
< 0.04	24 (15–33)	–	–	–	–
0.04	27 (17–37)	–	–	–	–
> 3	123 (106–140)	–	–	–	–
Percentage coverage of forest (continuous, 10%)	–	1.35 (1.28–1.42)	< 0.001	1.16 (1.08–1.25)	< 0.001
Percentage coverage of shrub (categorical, 10%)					
< 0.01	82 (65–99)	–	–	–	–
0.01	31 (22–40)	–	–	–	–
> 0.1	61 (48–74)				
Percentage coverage of shrub (10%) (continuous, 10%)	–	1.20 (0.82–1.75)	0.352	–	–
Quadratic percentage coverage of shrub (continuous)	–	0.92 (0.74–1.14)	0.451	–	–
Percentage coverage of grassland (categorical, 10%)					
< 0.01	53 (40–66)	–	–	–	–
0.01	101 (84–118)	–	–	–	–
> 0.5	20 (12–28)	–	–	–	–
Percentage coverage of grassland (continuous, 10%)	–	0.78 (0.56–1.08)	0.134	–	–
Quadratic percentage coverage of grassland (continuous)	–	0.79 (0.63–1.01)	0.061	–	–
Percentage coverage of irrigated cropland (categorical, 10%)					
< 0.001	55 (41–69)	–	–	–	–
0.001	77 (62–92)	–	–	–	–
> 1	42 (30–54)	–	–	–	–
Percentage coverage of irrigated cropland (continuous, 10%)	–	0.97 (0.85–1.10)	0.620	–	–
Quadratic percentage coverage of irrigated cropland (continuous)	–	0.98 (0.95–1.01)	0.213	–	–
Percentage coverage of rainfed cropland (categorical, 10%)					
< 2	88 (72–104)	–	–	–	–
2	63 (49–77)	–	–	–	–
> 5	23 (14–32)	–	–	–	–
Percentage coverage of rainfed cropland (continuous, 10%)	–	0.82 (0.77–0.87)	< 0.001	–	–
Percentage coverage of built-up land (categorical, 10%)					
< 0.25	91 (75–107)	–	–	–	–
0.25	48 (35–61)	–	–	–	–
> 0.9	35 (24–46)	–	–	–	–
Percentage coverage of built-up land (continuous, 10%)	–	0.87 (0.80–0.94)	< 0.001	–	–
Temperature* (categorical, 1°C)					
< 19.2	141 (123–159)	–	–	–	–
19.2	22 (13–31)	–	–	–	–
> 20.3	11 (5–17)	–	–	–	–
Temperature* (continuous, 2°C)	–	0.27 (0.22–0.34)	< 0.001	0.62 (0.45–0.86)	0.003
Relative humidity* (categorical, 10%)					
< 6.4	15 (8–22)	–	–	–	–
6.4	36 (25–47)	–	–	–	–
> 6.95	123 (106–140)	–	–	–	–
Relative humidity* (continuous, 5%)	–	4.12 (3.15–5.40)	< 0.001	–	–
Precipitation* (categorical, 1 mm)					
< 90	22 (13-31)	–	–	–	–
90	57 (43–71)	–	–	–	–
> 113	95 (79–111)	–	–	–	–
Precipitation* (continuous, 50 mm)	–	4.49 (2.74–7.34)	< 0.001	–	–
Autoregressive term	–	1.88 (1.68–2.11)	< 0.001	1.52 (1.35–1.70)	< 0.001

IRR = incidence rate ratio; TBE = tick-borne encephalitis.
* The meteorological variables that were included in the analysis were monthly temperature, relative humidity, and precipitation for the 3 months of the year when TBE was at its highest.

The results of our study should be interpreted in light of the studies' limitations: first, the TBE case data were collected from a passive surveillance system, and some TBE cases may be underreported because of their subclinical symptoms or misclassified by clinical physicians. Second, some data about the potential influencing factors of human TBE cases were not available in Jilin Province, such as ticks distribution and density, the distribution and abundance of host animals, population vaccination rate, and the dynamics of the land covers over the years. In addition to the natural environmental factors, many socioeconomic and climate factors may also affect the spatial distribution and seasonality of TBE.[30] In our study, we did not consider the impact of socioeconomic and medical factors on TBE, for example, the mode of agricultural and livestock production, medical and health conditions, population movement, personal habits of hygiene, and public health.

In conclusion, our results showed that the TBE cases in Jilin Province have increased and the geographic distribution of TBE appears to have expanded during recent years, indicating that TBE remains an important public health problem in Jilin Province. This is the first research on the spatiotemporal epidemiology of TBE in Jilin Province, which can provide scientific evidence for the targeted prevention and control programs. In addition, based on the hot spots identified in this study, we recommended that timely measures be taken in the high-risk areas in Jilin Province to increase health education and awareness of TBE, expand the vaccination rate, and continue surveillance of this disease.

Received December 2, 2018. Accepted for publication March 31, 2019.

Published online May 6, 2019.

Acknowledgments: The work was partly supported by grants from the National Mega Project for the Prevention and Control of Infectious Diseases (No. 2018ZX10713003), major projects in the 13th Five-Year Plan (No. AWS16J020), the Open Funding of State Key Laboratory of Pathogen and Biosecurity (SKLPBS1525), grant from State Key Laboratory of Resources and Environmental Information System, and grant from Aerospace System. We thank the medical staff for case reporting, laboratory testing, and field investigation.

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