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Mapping the distribution of tick-borne encephalitis in mainland China

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ABSTRACT

Tick-borne encephalitis (TBE) has become an increasing public health threat in recent years, ranging from Europe, through far-eastern Russia to Japan and northern China. However, the neglect of its expansion and scarce analyses of the dynamics have made the overall disease burden and the risk distribution of the disease being unclear in mainland China. In this study, we described epidemiological characteristics of 2117 reported human TBE cases from 2006 to 2013 in mainland China. About 99% of the cases were reported in forest areas of northeastern China, and 93% of reported infections occurred during May–July. Cases were primarily male (67%), mostly in 30–59 years among all age-gender groups. Farmers (31.6%), domestic workers (20.1%) and forest workers (17.9%) accounted for the majority of the patients, and the proportions of patients from farmers and domestic workers were increasing in recent years. The epidemiological features of TBE differed slightly across the affected regions. The distribution and features of the disease in three main endemic areas of mainland China were also summarized. Using the Boosted Regression Trees (BRT) model, we found that the presence of TBE was significantly associated with a composite meteorological index, altitude, the coverage of broad-leaved forest, the coverage of mixed broadleaf-conifer forest, and the distribution of *Ixodes persulcatus* (*I. persulcatus*) ticks. The model-predicted probability of presence of human TBE cases in mainland China was mapped at the county level. The spatial distribution of human TBE in China was largely driven by the distributions of forests and *I. persulcatus* ticks, altitude, and climate. Enhanced surveillance and intervention for human TBE in the high-risk regions, particularly on the forest areas in north-eastern China, is necessary to prevent human infections.

1. Introduction

Tick-borne encephalitis (TBE), also called forest encephalitis in China, is a zoonotic disease caused by the TBE virus (TBEV), which mainly attacks the central nervous system of infected patients (Wu et al., 2013). TBEV belongs to the genus Flavivirus, family Flaviviridae, and consists of three subtypes, namely the European (TBEV-Eu), the Siberian (TBEV-Sib), and the Far Eastern (TBEV-FE) subtypes (Lindquist and Vapalahti, 2008; Pintér et al., 2013; Gritsun et al., 2003). The TBEV-FE subtype is endemic in northern China and mainly transmitted by *Ixodes persulcatus* (*I. persulcatus*) (Lindquist and Vapalahti, 2008; Lu et al., 2008). Human infections with the TBEV-FE are usually more severe than the other two subtypes, with more frequent encephalitis signs and with a higher fatality rate estimated as 5–35%, compared to 1–2% for TBEV-Eu and 6–8% for TBEV-Sib (Gritsun et al., 2003; Lu et al., 2008). The disease usually presents itself with flu-like symptoms, including fever, headache and vomiting. Some patients may develop severe neurological sequelae or even death (Weber, 2000; Kang et al., 2013). Despite the availability of effective vaccines, the disease is endemic in Europe, far-eastern Russia, Japan and northern China, and approximately 10,000–12,000 cases are reported annually (Kollaritsch et al., 2012).

In China, the first reporting of human TBE case dates back to 1943, and TBEV was first isolated from patients and ticks in 1952 (Gao et al.,

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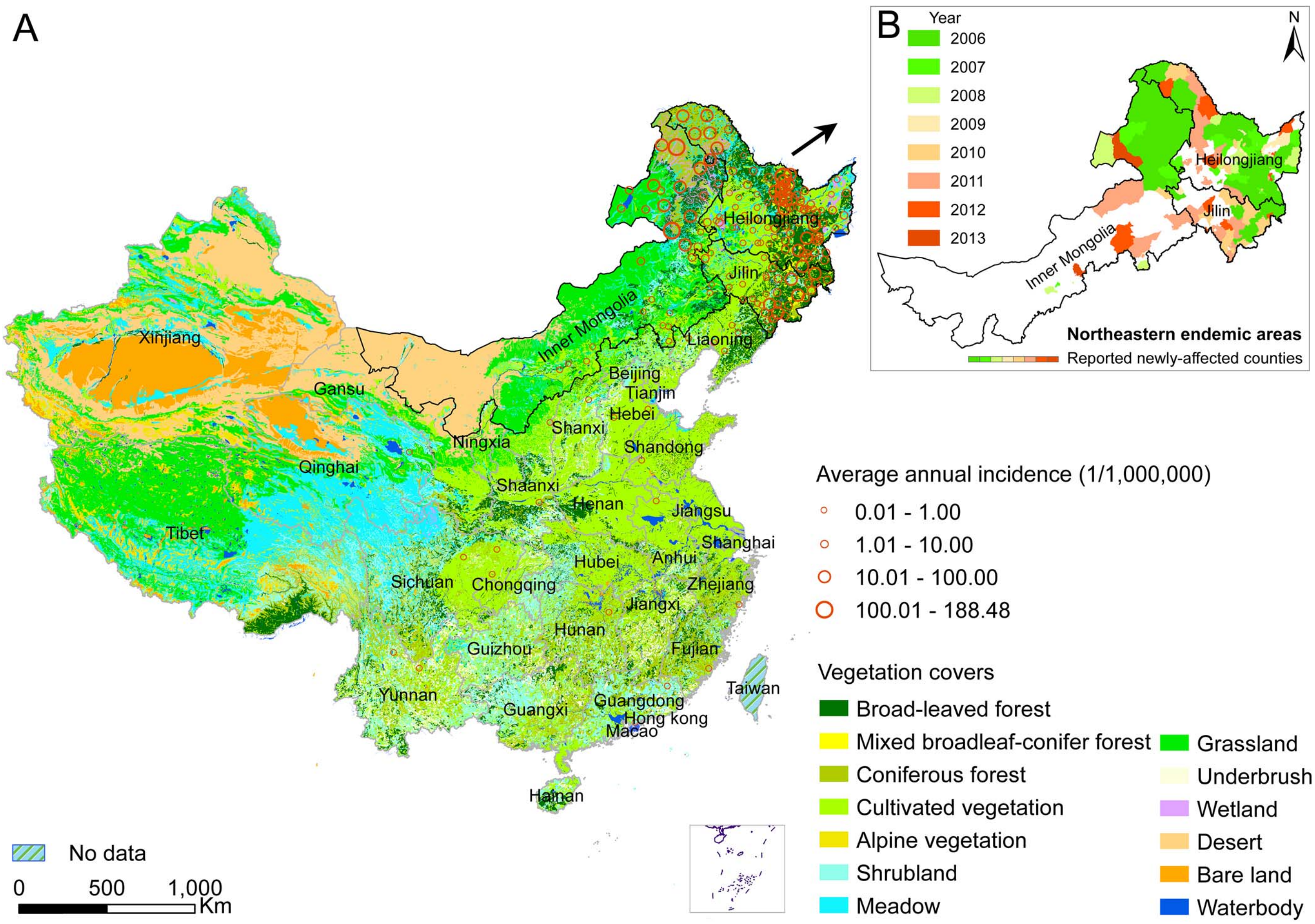

Fig. 1. Spatial distribution of human TBE cases and vegetation covers in mainland China, 2006–2013. (A) The red circles represent the average annual incidence of TBE at the county level between 2006 and 2013. (B) Newly-affected counties in the northeastern endemic areas are colored by the year of first reporting during the study period. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2010). The forest areas in northeastern China (Heilongjiang and Jilin provinces, and the northeastern Inner Mongolia Autonomous Region) have been regarded as the most typical and important endemic areas of TBEV (Lu et al., 2008). Additional endemic areas of TBEV have been identified in Xinjiang Autonomous Region and Yunnan Province during the last 60 years (Lu et al., 2008; Xie et al., 1991; Zhang et al., 2013; Bi et al., 1997; Gong et al., 2001; Yang et al., 1993). Because of the reduced morbidity in the 1980s, TBE has been removed from the list of notifiable diseases in China since 1990 (Lu et al., 2008). In recent years, the number of human TBE cases has increased notably, and TBEV has been detected in previously unaffected areas (Wu et al., 2013; Süss, 2008; Csángó et al., 2004; Stefanoff et al., 2013; Stjernberg et al., 2008; Petri et al., 2010), making the disease a growing public health threat. However, the role of ecological factors associated with this reemerging infectious disease remains unclear and needs to be further investigated. This study aimed to provide a comprehensive overview of TBE in China and to evaluate the underlying ecological risk factors for human TBEV infections at the county level.

2. Materials and methods

2.1. Ethics statement

The ethical approval of this study was determined by the National Health and Family Planning Commission, China, that the collection of data from TBE cases was part of continuing public health surveillance of an infectious disease and was exempt from institutional review board assessment.

2.2. Data collection and management

Although TBE is not a notifiable disease, clinical TBE cases diagnosed at medical institutions have been reported to the Chinese Information System for Diseases Control and Prevention (CISDCP) by the majority of provinces since 2002. In this study, Heilongjiang Province, Inner Mongolia Autonomous Region, Jilin Province, Liaoning Province, Hebei Province, and further 13 of the 31 provinces in mainland China were systematically studied. These data provide an opportunity for a systematic epidemiologic study of the disease in China during the last decade. We extracted eight-year data of human TBE cases from January 2006 to December 2013 in mainland China from CISDCP. The available information includes age, gender, occupations, date of onset, date of admission and zone code at township level for individual case. All the data of cases used in this study were anonymized and the identity of any individual case cannot be uncovered. There is no international standard for TBE diagnosis (Lu et al., 2008; Süss, 2008). According to the national guidelines, the diagnostic criteria for a clinically diagnosed TBE case is mainly based on the presence of clinical symptoms (such as acute fever, headache, vomiting and/or typical central nervous system symptoms) in connection with exposure in forests during spring or summer, or a tick bite history. A laboratory-confirmed TBE case is defined as a reported TBE case who is confirmed by laboratory serological tests (increased anti-TBEV IgG and IgM or ≥4-fold increase in specific antibody to TBEV between acute and convalescent serum samples) and, if necessary, PCR tests (a positive result for TBEV RNA by molecular detection) (The Ministry of Health of People's Republic of China, 2002).

To map the risk distribution of TBE in China, we collected from published literatures the information on natural foci of TBE where the TBEV was isolated from ticks, host animals or patients (search strategies were described in supplementary text). Meteorological data including monthly average temperature and relative humidity, and monthly accumulative rainfall and sunshine hours during 2006–2013 were obtained from the China Meteorological Data Sharing Service System (http://cdc.cma.gov.cn/index.jsp). Altitude data were obtained from the Shuttle Radar Topography Mission (SRTM) archives (http://www.srtm.csi.cigar.org). Raster-type data with a resolution of one kilometer on vegetation types were provided by the China National Forestry Bureau. Demographic data for each county were obtained from the China Bureau of Statistics from the Sixth National Census in 2010. In addition, we gathered the information of geographic distribution of the main vector *I. persulcatus* in China, as well as other tick species such as *Dermacentor silvarum* (*D. silvarum*), *Haemaphysalis concinna* (*H. concinna*), *Haemaphysalis japonica* (*H. japonica*), and *Ixodes ovatus* (*I. ovatus*) from the literature (search strategies were given in supplementary text). Finally, a total of 13 potential explanatory variables for the risk of human TBEV infections at the county level were extracted from these data using the ArcGIS 9.2 software (ESRI Inc., Redlands, CA, USA) (Supplemental Table 1).

2.3. Epidemiological overview

Each case was geo-referenced to create maps showing the spatial distribution of average annual incidences in mainland China, as well as the spatial dynamics of reported TBE cases in the northeastern endemic areas at the county level (Fig. 1). The temporal trend and seasonality were shown by plotting monthly numbers and annual incidence of cases for major epidemic provinces, including Inner Mongolia, Heilongjiang and Jilin as well as for the whole country (Fig. 2). The demographic distribution of the disease and its temporal changes were shown by plotting age- and gender-specific case numbers and occupational proportions over time (Fig. 3). We also compared the epidemiological features of TBE cases across most heavily affected provinces. To better understand the general ecological background of TBEV, we summarized the habitat conditions of the three main endemic areas in China: northeastern endemic areas (Inner Mongolia, Heilongjiang and Jilin), northwestern endemic areas (Xinjiang), and southwestern endemic areas (Yunnan).

2.4. Risk assessment

To assess the risk factors associated with the occurrence of human TBEV infections in China, a boosted regression trees (BRT) model coupled with the maximum entropy method was applied at the county level. BRT has been widely used for disease modeling because it performs well in the prediction of distributions of organisms while accounting for non-linear relationships and interactions between the risk and covariates (Elith et al., 2008; Fang et al., 2013; Cheong et al., 2014; Deribe et al., 2015). In our BRT model based on the full study period (2006–2013), all counties with either TBE cases or laboratory-confirmed natural foci were considered positive, and five times as many negative controls were selected randomly from the remaining counties. A total of 189 counties reported TBE cases. In addition, 12 counties in Xinjiang Autonomous Region and 2 counties in Yunnan Province have been reported to have laboratory-confirmed natural foci of TBEV and were thus included in the total of 203 positive counties. The positive and negative counties were used as the binary outcome variable in this analysis. As the meteorological variables (monthly average temperature and relative humidity, and monthly accumulative rainfall and sunshine hours during the study period) were found to be highly correlated with each other (correlation coefficients > 0.7, Supplemental Table 2), a principal component analysis (PCA) was performed to transform these data into low-dimensional uncorrelated variables (Ringnér, 2008; Upadhyayula et al., 2015; Salas et al., 2013). The first principal component accounted for 84.43% of the total meteorological variance, whereas the eigenvalues of other components were nearly zero (Supplemental Table 3). The influence of meteorological variables in the principal component was shown by the loadings (Supplemental Table 3). As a result, we selected the first component as the sole meteorological predictor (to which we refer as the composite meteorological index) in the following BRT analysis.

In this study, a tree complexity of five, a learning rate of 0.005, and a bag fraction of 75% were used to identify the optimal number of trees. The weight of each variable was estimated from the identified trees and served as an indicator of each variable's relative importance for predicting the risk of TBE. A bootstrapping procedure was employed to provide a robust estimation of model parameters. Specifically, we first generated 50 bootstrap data sets by randomly sampling 1015 control counties from the 2719 counties that had neither reported human TBE cases nor laboratory-confirmed natural foci of TBEV and combining the sampled controls with the 203 positive counties (1-to-5 case-control ratio). Second, each bootstrap data set was randomly split into a training dataset with 75% of data points and a test dataset with 25%. Third, a BRT model was built using the training set, and then the model was validated using the test set; receiver-operating characteristic (ROC) curves and area under the curve (AUC) were produced based on each BRT model to estimate the predictive power of that model. Finally, a risk distribution map of TBE was created based on the average predicted probabilities over all 50 bootstrap datasets (Fig. 4). All statistical analyses were performed using R software (version 3.1.1; R Development Core Team 2014), and package "gbm" version 2.0-8, package "dismo" version 0.8-11, package "ROCR" version 1.0–4, and package "pROC" version 1.5.4 were used in the analysis. In addition, we performed the prospective analysis using the data of 2011–2013 to verify the BRT model that was created by using the data of 2006–2010. As in the endemic season and area, not all the clinically diagnosed TBE cases were confirmed by laboratory test because of a shortness of resources and time, we also conducted a further analysis only including laboratory-confirmed TBE case in another BRT model which may provide further information for the dynamic of the disease.

3. Results

3.1. Epidemiological overview

A total of 2117 human TBE cases (including 1205 clinically diagnosed and 912 laboratory-confirmed cases) with 19 deaths were reported from January 2006 to December 2013, yielding a case fatality rate (CFR) of 0.9%. Cases were distributed in 189 counties of 17 provinces with the average annual incidence of 4.07 cases per 1,000,000 persons (range: 0.09–188.48 case per 1,000,000 persons). The majority of the cases (98.86%) were located in northeastern China, including the northeastern Inner Mongolia (40.15%, 850 cases), Heilongjiang (36.56%, 774 cases) and Jilin (22.15%, 469 cases) provinces. The rest (24 cases) including 14 clinically diagnosed and 10 laboratory-confirmed cases with 1 death were distributed sporadically in 14 provinces except areas from Inner Mongolia, Heilongjiang and Jilin (Fig. 1A). A spatial expansion of the disease towards southwest in recent years was observed in the northeastern endemic areas, especially in Inner Mongolia Autonomous Region and Jilin Province (Fig. 1B). The annual incidence of TBE increased substantially during 2009–2011 but fell back in 2012 and was flat in 2013 (Fig. 2A). The majority of cases (92.96%) occurred during May to July, and disease incidence usually peaked in June (Fig. 2A). Inner Mongolia experienced the sharpest increase in 2011 and decrease in 2012 (Fig. 2B). Heilongjiang followed a similar pattern with milder changes (Fig. 2C). However, there seemed to be a long-term increasing trend in Jilin (Fig. 2D).

Cases were primarily male (67%, Chi-square test, $P < 0.001$), and were mostly in their 30′s, 40′s and 50′s (Fig. 3A). The median age of

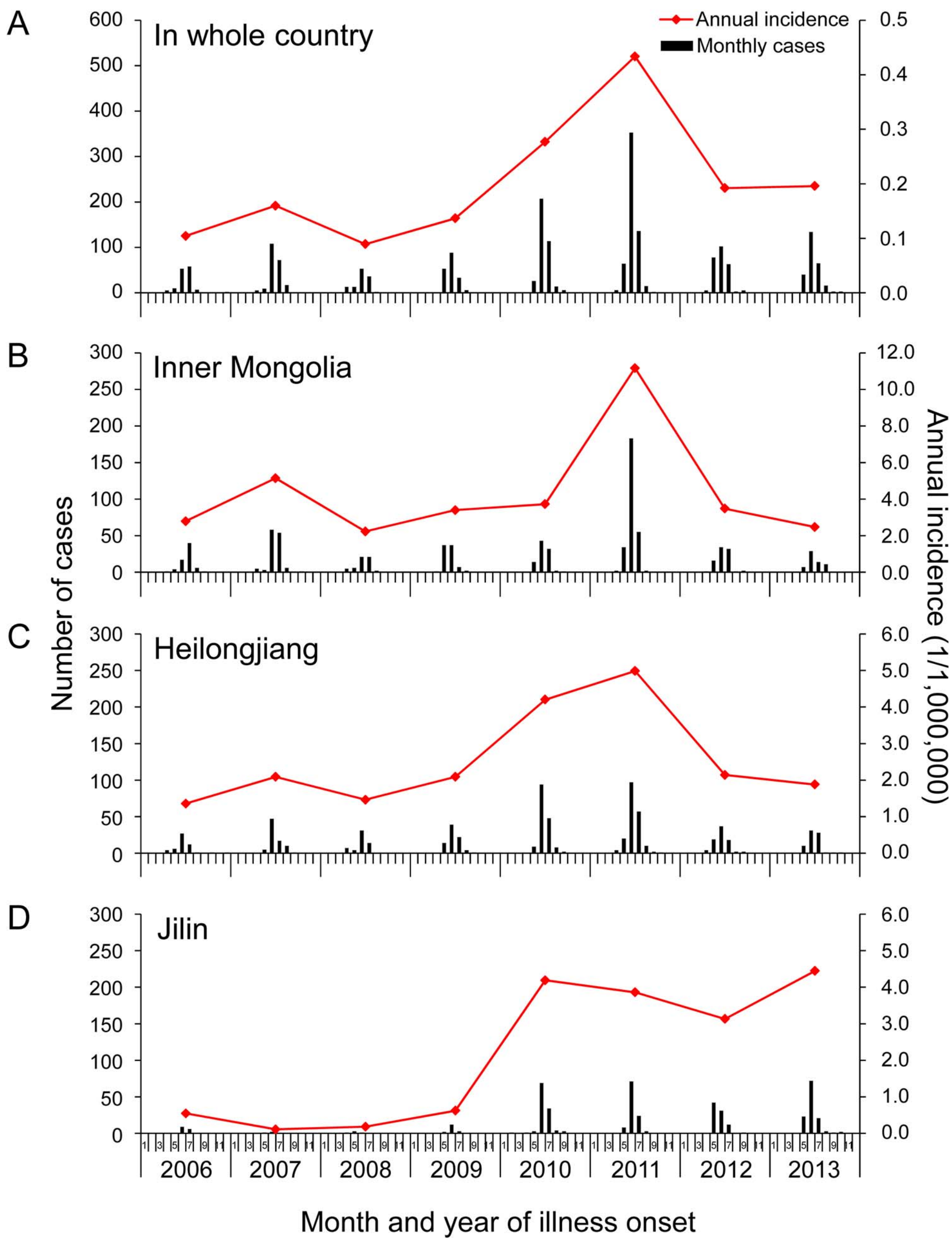

Fig. 2. Temporal distribution of the human TBE cases, 2006–2013. The bar charts represent the monthly number of cases, and the curve indicates the annual incidence of cases. (A) The whole country; (B) Inner Mongolia; (C) Heilongjiang; (D) Jilin.

female (46 years of age) was significantly older than that of male (42 years of age) (Wilcoxon rank-sum test, $P < 0.001$). Males in their 40′s and 50′s had the highest and quickest increase in the number of TBE cases during 2009–2011 (Fig. 3B and C). The majority of the patients were farmers (31.6%, 668 cases), followed by domestic workers (20.1%, 426 cases) and forest workers (17.9%, 380 cases). The epidemiological features of TBE differed slightly across the affected regions, especially between the northeastern endemic areas and the others (Table 1). Within the northeastern endemic areas, based on the proportion of affected counties among all counties, the disease was most widely distributed in Heilongjiang (75.0%), followed by Jilin (54.7%) and Inner Mongolia (30.4%). Gender and age distributions were similar among the three provinces. However, most cases in Heilongjiang and Jilin were farmers, whereas the majority of cases in Inner Mongolia were either domestic workers or forest workers (Table 1). In addition, the proportions of farmers and domestic workers among the reported cases were rising in recent years, while the proportion of forest workers was decreasing (Fig. 3D). The 24 sporadic cases in other regions had a younger median age (35 years) and a longer median time from onset to hospital admission as compared to those in the northeastern endemic areas (Table 1).

The habitat conditions of the three main endemic areas of TBEV in mainland China are summarized in Table 2. The northeastern endemic areas comprises of Daxing'an Mountains in Inner Mongolia (peak altitude over 1000 m), Xiaoxing'an Mountains in Heilongjiang (an average altitude of 500–800 m), and Changbai Mountains in Jilin (including Zhangguangcai Mountain, Laoye Mountain, Longgang Mountain, Tumen Mountain etc.). This region has a temperate continental monsoon climate, with mixed broadleaf-conifer forests as the dominant vegetation (Fig. 1A). Besides the primary vector *I. persulcatus*, TBEV can also be carried by *Dermacentor silvarum*, *Haemaphysalis concinna*, and *Haemaphysalis japonica* found in this region (Supplemental Fig. 1). In northwestern China, broad-leaved forests and mixed broadleaf-conifer forests on Tianshan Mountains and Altai Mountains in

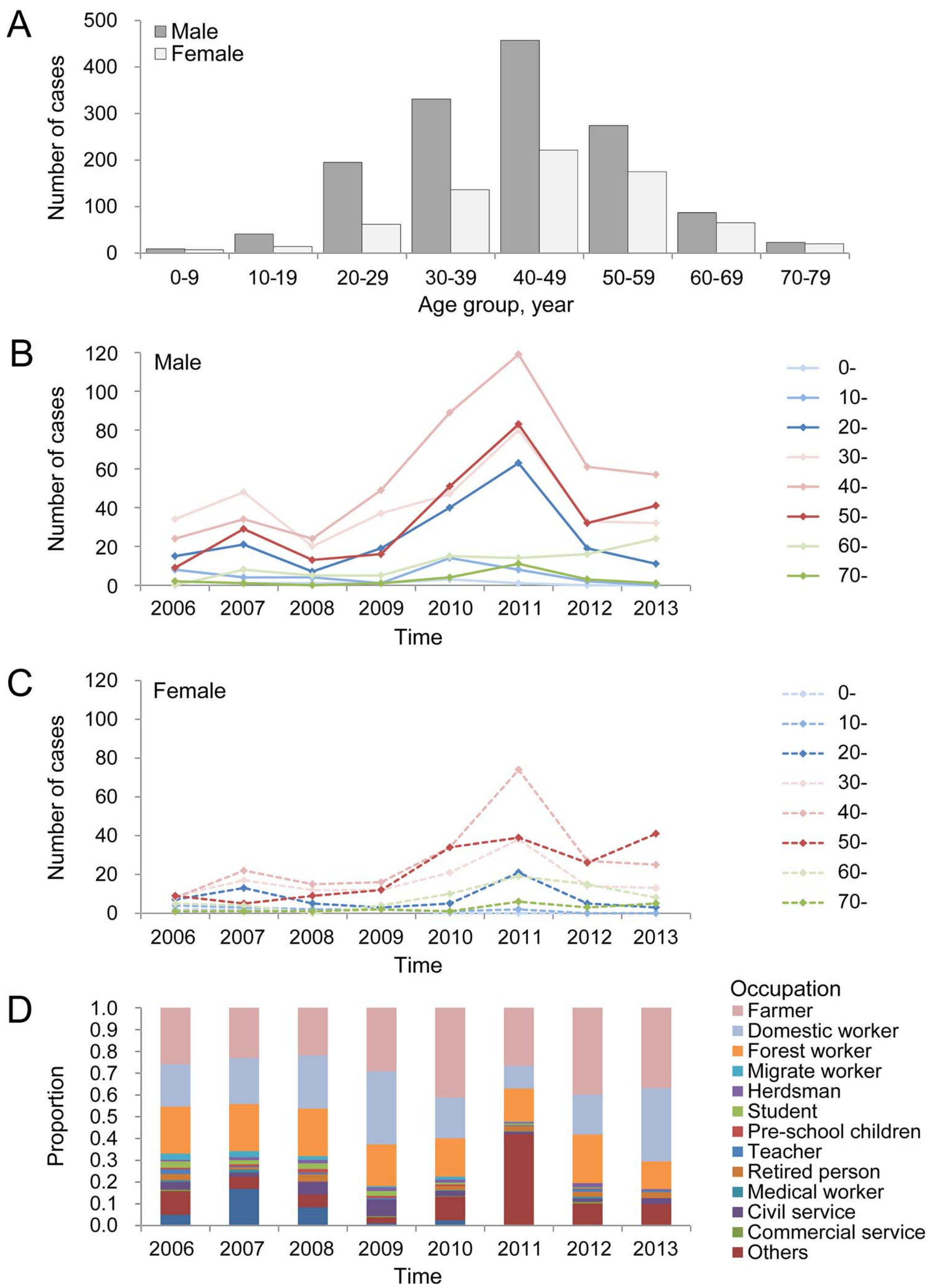

Fig. 3. The demographic distribution (age, gender and occupation) in human TBE cases in mainland China, 2006–2013. (A) Male and female case numbers by 10-year age group. (B) The temporal dynamics of male case numbers by age group. (C) The temporal dynamics of female case numbers by age group. (D) The proportions of human TBE cases by occupation from 2006 to 2013.

Xinjiang constitute another endemic area of the disease, nourished by a temperate continental climate. *I. persulcatus* is also the dominant tick species, along with *Dermacentor silvarum*, *Haemaphysalis concinna*, and *Dermacentor marginatus* in this area. In southwestern China, Gaoligong Mountains in Yunnan is an important endemic area, featuring a plateau monsoon climate. Different from the other two endemic areas, *Ixodes ovatus* is the dominant vector tick (Supplemental Fig. 1). The main reservoir hosts in these TBEV-endemic areas are rodents.

3.2. Risk assessment

Based on the BRT model, the occurrence of TBE was found to be significantly associated with the composite meteorological index, altitude, the coverage of broad-leaved forest, the coverage of mixed broadleaf-conifer forest, and the distribution of *I. persulcatus* ticks (Table 3), all with average BRT weights > 5.0%. Supplemental Fig. 2A showed the model-fitted marginal relationship between the risk of TBE and each of the important predictors. The risk for human TBEV infections was negatively associated with the composite meteorological index. According to the loadings of the meteorological variables on this index (Supplemental Table 3), higher risk was associated with lower average temperature, relative humidity, rainfall but with longer average sunshine hours over the study period (2006–2013). The effect of altitude seemed to be non-monotonic and segmental, with the highest risk at the altitude level of 400–600 m, followed by 1400–1700 m and 2000–3000 m. Increasing percentage coverage of broad-leaved forest elevated the predicted risk first and then plateaued at about 70% coverage. A similar pattern was seen for the percentage

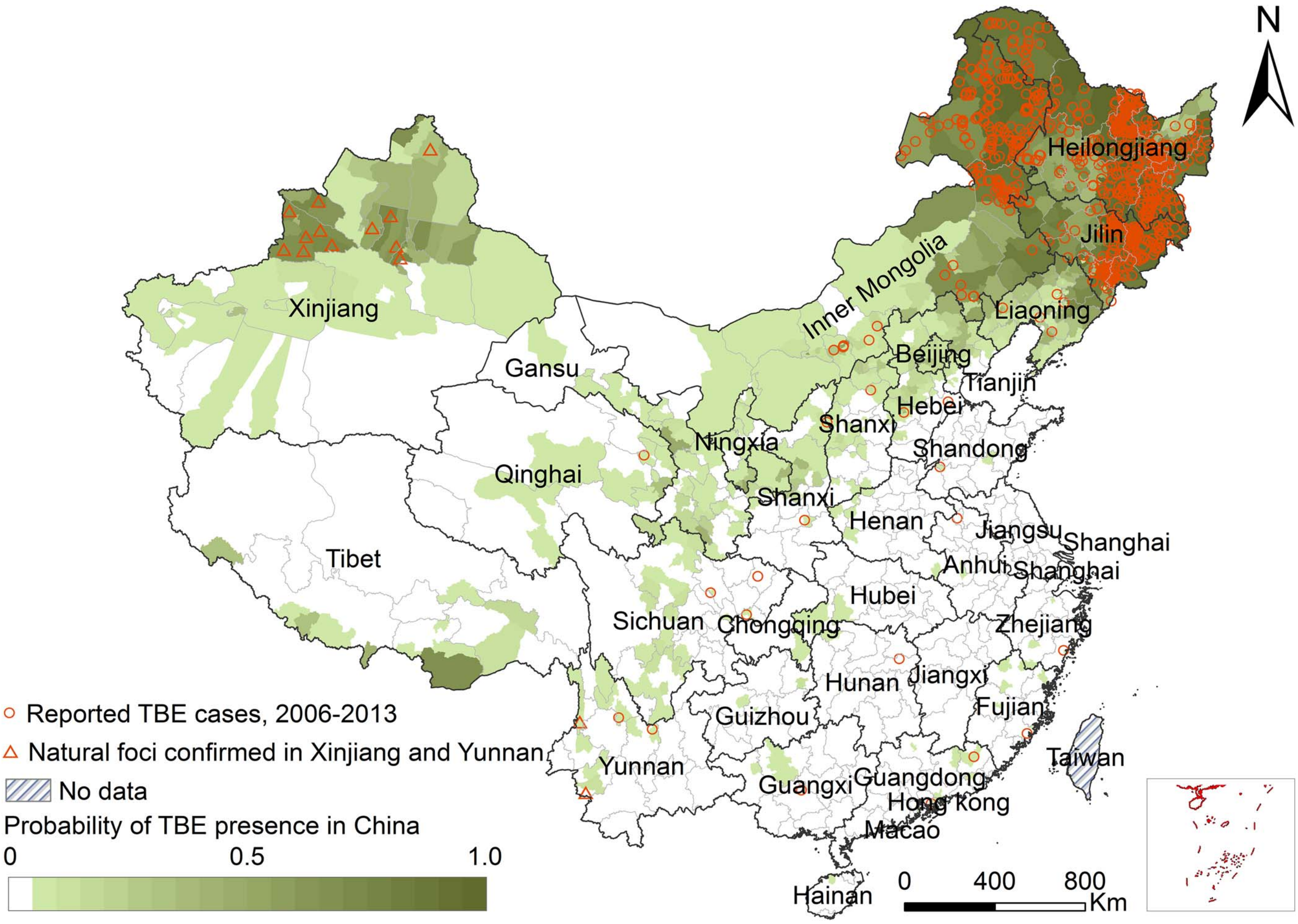

Fig. 4. The predicted risk distribution of TBE at the county level in mainland China. The different color grades represent the predicted risk of occurrence of human TBEV infections, red circles represent human TBE cases location between 2006 and 2013, and orange triangles represent confirmed endemic areas of TBEV at the county level in Xinjiang and Yunnan. The map was created in ArcGIS 9.2 software (ESRI Inc., Redlands, CA, USA). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1
Epidemiologic features of human TBE cases in the affected regions of China, 2006–2013.

Provinces/Autonomous regions	Inner Mongolia	Heilongjiang	Jilin	Others*
Total cases	850	774	469	24
Affected counties[a]	30.4%	75.0%	54.7%	1.45%
Male[b]	69.9%	64.3%	65.2%	79.2%
Age				
median (range)	42 (0.08–97)	44 (6–79)	47 (6–78)	35 (13–74)
mean (SD)	41.4 (12.6)	43.2 (12.9)	45.8 (12.9)	38.3 (15.7)
Occupation[c]				
Farmers	5.8%	44.1%	57.6%	33.3%
Domestic workers	24.6%	20.5%	11.7%	12.5%
Forest workers	28.2%	14.7%	4.7%	16.7%
Peak months (% among all cases)	May–July (93.9%)	May–July (91.2%)	May–July (95.7%)	May–July (62.5%)
Median time from onset to admission (range)	10 (0–71)	4 (0–64)	5 (0–80)	18 (0–200)

SD: standard deviation.
*All the other provinces in mainland China (excluding Inner Mongolia, Heilongjiang and Jilin) were included.
[a] The proportion of affected counties.
[b] The proportion of male patients.
[c] The distribution of occupation among TBE cases (only farmers, domestic workers and forest workers were listed).

coverage of mixed broadleaf-conifer forest, except that the plateau interval is wider, starting from below 5% coverage. As expected, risk of acquiring TBE was higher in the presence of *I. persulcatus* ticks, consistent with previous studies (Tokarevich et al., 2011; Bi et al., 1997). The model results were consistent with what was observed by overlapping TBE occurrences with thematic maps of these predictors (Supplemental Figs. 3 and 4).

The BRT model showed satisfactory predictive accuracy with an estimated AUC of 0.970 (95% confidence interval [CI]: 0.960–0.979). The AUC based on the training dataset (0.985, 95% CI: 0.980–0.991), was better than that based on the test dataset (0.939, 95% CI: 0.919–0.959) (Supplemental Fig. 2B). On the basis of the model-predicted probabilities averaged over 50 bootstrap datasets, a risk map overlaid with the observed TBE cases and laboratory-confirmed endemic areas of TBEV was created at the county level (Fig. 4). The high-risk areas were mainly distributed in northeastern China, including the northeastern Inner Mongolia, Heilongjiang, Jilin, and part of Liaoning Province, followed by the northern part of Xinjiang Autonomous Region in northwestern China. A few small high-risk areas were scattered along a belt extending from the Northeast towards the Southwest of China, covering parts of Beijing, Tianjin, Hebei, Shanxi, Ningxia, Shaanxi, Gansu, Qinghai, Sichuan, Guizhou, Yunnan and Tibet. The densely populated areas in central, eastern, southern and southeastern China showed almost no risk of TBE occurrence, although few travel-related cases were reported in those areas as well. We also performed a sensitivity analysis using the data from 2011 to 2013 to

Table 2
Distribution and features on the three main endemic areas of TBEV in mainland China.

Regions	Northeastern endemic areas	Northwestern endemic areas	Southwestern endemic areas
	Inner Mongolia (IM), Heilongjiang (HLJ), and Jilin (JL)	Xinjiang	Yunnan
No. of affected counties during 2006–2013	IM: 31 HLJ: 99 JL: 35	0	2
No. of population	IM: 24,706,291 HLJ: 38,313,991 JL: 27,452,815	21,815,815	45,966,766
Area (Km^2)	IM: 1,125,347 HLJ: 467,110 JL: 190,517	1,630,396	383,966
Altitude, median(range)	IM: 1097 m (165–1745 m) HLJ: 214 m (55–834 m) JL: 267 m (133–1092 m)	1231 m (288–4622 m)	1826 m (760–3640 m)
Climate feature	Temperate continental monsoon	Temperate continental	Tropical rainforest and plateau monsoon
Major natural foci	IM: Daxing'an Mountains HLJ: Xiaoxing'an Mountains JL: Changbai Mountains	Tianshan Mountains* Altai Mountains*	Gaoligong Mountains*
Primary vector ticks	*Ixodes persulcatus*	*Ixodes persulcatus*	*Ixodes ovatus*
Other ticks associated with TBEV	*Dermacentor silvarum Haemaphysalis concinna Haemaphysalis japonica*	*Dermacentor silvarum Haemaphysalis concinna* *Dermacentor marginatus*	
Main reservoir hosts	*Myodes rufocanus* *Myodes rutilus Eutamias sibiricus Apodemus agrarius*	*Apodemus sylvaticus Dryomys nitedula Marmota baibacina*	*Apodemus draca Niviventer confucianus Eothenomys eleusis*
Main landscape of natural foci	Mixed broadleaf-conifer forest	Mixed broadleaf-conifer forest; Broad-leaved forest	Broad-leaved forest; Mixed broadleaf-conifer forest

*The no. of cases was not reported in recent years.

Table 3
Summary of the weights (%) of predictor variables for the occurrence of human TBEV infections in the BRT model.

Variables	Boosted Regression Trees	
	Weight (mean)	Weight (SD)
Composite meteorological index[a]*	26.81	2.32
Altitude*	18.79	2.90
Percentage coverage of broad-leaved forest*	22.28	4.24
Percentage coverage of mixed broadleaf-conifer forest*	9.06	3.13
Percentage coverage of coniferous forest	2.06	0.80
Percentage coverage of cultivated	2.94	0.73
Percentage coverage of shrubland	3.70	0.75
Percentage coverage of grassland	2.03	0.77
Percentage coverage of underbrush	2.74	1.02
Ixodes persulcatus[b]*	9.59	3.05

SD: standard deviation.
*Variables whose mean of weight in the BRT model more than 5 were considered to be significantly contribute to the occurrence of human TBEV infections.
[a] Composite meteorological index is the score of the first principal component according to meteorological variables during 2006–2013.
[b] *Ixodes persulcatus* is a binary variable, whether the tick presence or absence in each county.

verify the BRT model, which is created by using the data from 2006 to 2010. The weights of predictor variables, the ROC curves and the AUC's were similar to our current model based on the full study period (the predictive accuracy with an estimated AUC value of 0.931, 95% CI: 0.905–0.956) (Supplemental Table 4 and Supplemental Fig. 5).

As there is no international standard for TBE diagnosis (Lu et al., 2008; Süss, 2008), the TBE patients were diagnosed according to the national guidelines of TBE prevention and treatment published by the National Health and Family Planning Commission of People's Republic of China (NHFPC) in this study. In the endemic season and area, not all the clinically diagnosed TBE cases were confirmed by laboratory test because of a shortness of resources. In this study, we have conducted a further analysis by only including a total number of 912 laboratory-confirmed TBE cases (accounting for more than 43% of the totally reported TBE cases). The spatial distribution of laboratory-confirmed TBE cases covered 66% reported TBE cases in our study (Supplemental Fig. 6). We also conducted further analysis with the laboratory-confirmed cases in another BRT model, which has indicated a small variation (Supplemental Table 5 and Supplemental Fig. 7. The occurrence of laboratory-confirmed cases were found to be associated with the composite meteorological index, altitude, the coverage of broad-leaved forest, and our model also demonstrated that the occurrence of laboratory-confirmed cases were associated with the coverage of mixed broadleaf-conifer forest, and the distribution of *I. persulcatus* ticks, with average BRT weights near 5.0% (Supplemental Table 5 and Supplemental Fig. 7).

4. Discussion

TBE is considered a potentially emerging neglected viral disease, particularly amongst the economically marginalized population in developing countries (Hotez et al., 2015). An increasing incidence of TBE was reported in recent years in China, paralleling the increasing disease burden in Russia and European countries such as Czech Republic, Estonia, Latvia, Lithuania, Slovakia, Slovenia, Sweden, Switzerland, and Germany (Wu et al., 2013; Kollaritsch et al., 2012; Süss, 2008; Petri et al., 2010). This wide scope of emergence and reemergence indicates that the disease is becoming an increasing threat to public health in Eurasia, and thus should not be neglected. Our study provides a complete overview of the epidemiological characteristics of TBE and features on endemic areas of TBEV in mainland China during the last decade, and is the first risk assessment of TBE occurrence in China. Northeastern China, especially the forestry areas in the northeastern Inner Mongolia Autonomous Region (Daxing'an Mountains), Heilongjiang Province (Xiaoxing'an Mountains) and Jilin Province (Changbai Mountains), were shown to be the epicenters of the TBE occurrence, accounting for more than 98% of all reported cases in the country, where approximately 13.0%–14.3%, 0.79%–6.45%, and 0–37.5% virus detection rate were reported from groups of adult *I. persulcatus* during epidemiological surveys of TBE virus in the three natural foci, respectively (Li et al., 1999; Wang et al., 1995; Yang et al., 2009; Liu et al., 1979). Another important epidemic area of TBE was surrounding Tianshan Mountains and Altai Mountains of the Xinjiang Autonomous Region, northwestern China, where a 36.8% (14.3%–47.7%) virus detection rate was reported from groups of adult *I. persulcatus* of seven sampling sites but the detection of human TBE patients has been nearly neglected (Xie et al., 1991; Lu et al., 2008). In southwestern China, the Gaoligong Mountains have been confirmed as a natural focus of TBEV, where TBE viruses have been isolated from adult *Ixodes ovatus* with about 8.3% virus detection rate from 12 groups of the tick, and also were isolated from rodents, insectivores, and TBE patients (Lu et al., 2008; Hou et al., 1991; Hou et al., 1992; Gong et al., 1992; Huang et al., 2001). Although neither TBE patients were reported, nor TBE viruses were isolated in the neighboring Tibet, there was serological evidence for infections of TBEV among residents of two prefectures (Ma et al., 1996, 1998), indicating the need for enhanced disease surveillance in the predictive risk areas in this study, although where no TBE patient has been reported up to now (Fig. 4).

Seasonality of human TBE cases is closely related to the seasonal peak of the vector ticks (Korenberg, 2000). In general, the peak in the reporting of human cases occurs 2 weeks following the peak in tick activity (Gao et al., 2010; Bi et al., 1997). In addition, the warming-up in the late spring and early summer (from May to July) is often associated with increasing outdoor activities, which in turn increases the likelihood of exposure to tick bites. The risk heterogeneity by age and gender could be explained by the fact that, in China, forestry industry and agriculture activities are usually undertaken by males in their work age (30–59 years old), who consequently have the highest risk of exposure to ticks (Li et al., 1999). The occupational distribution of the disease has changed significantly during the past decades in China, probably as a result of the changes in the occupations themselves in response to economic developments. The proportion of forestry workers has been declining, whereas there has been a growing proportion of farmers and domestic workers who are engaged in potherb-picking activities during spring and summer (Wu et al., 2013; Li et al., 1999). Compared to forestry workers, farmers and domestic workers are far less experienced in protecting themselves from tick bite and have a much lower coverage of TBEV vaccination, and are therefore subject to a higher risk of infections (Zheng et al., 2003).

The BRT model identified a few important predictors for human TBE occurrence, in particular the composite meteorological index and the distribution of *I. persulcatus* ticks. Meteorological factors such as temperature, relative humidity, rainfall and sunshine hours are known to influence the life cycle of ticks, viral replication and transmission, host animal behavior, and human outdoor exposure, which might further affect the seasonal pattern of tick-borne diseases (Gilbert et al., 2014; Jore et al., 2014; Subak, 2003; Estrada-Peña and de la Fuente, 2014; Fang et al., 2015). An increase in winter temperatures has been indicated to raise the risk of tick-borne disease dissemination due to the northward extension and increased abundance of *Ixodes ricinus* (Parola, 2004; Altizer et al., 2013; Harrus and Baneth, 2005). However, the link between climate changes and the spatial distributon of TBE needs further investigation. The primary vector of TBEV in China is *I. persulcatus*, which is mainly distributed in forest areas of northern China, including Liaoning, Jilin, Heilongjiang, Inner Mongolia, and Xinjiang (Gao et al., 2010). The areas with TBE are mostly consistent with the distribution of the main tick vectors (Gao et al., 2010). In the northeastern endemic areas, most cases occurred in forest areas at altitudes ranging from 400 to 600 m at which tick densities are relatively high. At that altitude, the mixed broadleaf-conifer forest and the broad-leaved forest are the dominant vegetation (Lu et al., 2008; Cai et al., 2012). The high risk of TBE occurrence also exists in the northwestern endemic areas where *I. persulcatus* is mainly distributed at altitudes 1400–1700 m, as well as in the southwestern endemic areas where altitudes between 2000 and 3000 m are covered by mixed broadleaf-conifer forests, a suitable habitat for the ticks (Bi et al., 1997).

In addition to northeastern China, Xinjiang, Yunnan and Tibet, we found a potential-risk belt connecting the northeastern and the southwestern endemic areas, covering a few densely populated regions such as Beijing, Shaanxi and Sichuan provinces where the environment could be suitable for the occurrence of TBE if the TBEV is imported. We recommend improvement in surveillance programs for TBE in these zones. The predictive risk map can help public health officials to locate areas in most need of control, vaccination and health education.

The incidence of TBE decreased in China during the 1980s, however, has been rising in recent years, as noted by disease control and prevention sectors and local hospitals. As a zoonosis, the "re-emergence" of the disease may have been associated with ecological, socioeconomic and climatic changes (Imhoff et al., 2015; Sumilo et al., 2008; Randolph, 2001; Lindgren and Gustafson, 2001). The vegetation covers in China have changed substantially over the years, as a result of the state-initiated "Greening" Program to regain forests and grasslands from former agricultural lands since the mid-1990s (Liu et al., 2008). Such changes might have partially shaped the temporal trend of the TBE occurrence, by altering the abundance of ticks, suitable ecological environment for survival or activity of wild and domestic hosts, virus circulation and people's contact with infected ticks in these regions. On the other hand, the few cases reported in low-risk zones could have traveled to endemic areas of the disease, as a result of increasing tour activities and economic development (Wu et al., 2013; Haditsch and Kunze, 2013).

A few limitations of this study are relevant to the interpretation of the results. First, TBE is not a notifiable disease in China, and under-reporting likely exists because of being neglected or misclassified by clinical physicians, especially in the predicted high-risk areas where none or only a few TBE cases were found. That would inevitably result in a bias in the risk evaluation of the disease in our ecological model, so we look forward to further systematic field work on a larger scale, which would make up for the deficiency of the present study because of different diagnostic criteria for TBE. Second, some potentially important determinants of the occurrence of human TBEV infections were not available, including but not limited to ticks density, the abundance of host animals, population immunity, and relevant data on the changes of the vegetation covers over the years in China. Finally, while the composite meteorological index was notable in the BRT model, we are unable to interpret clearly the effect of each meteorological variable included and seasonality of the disease, due to the sparseness of cases in most counties and the vast heterogeneity in meteorological conditions across the country.

In conclusion, our study provided the epidemiological overview on the spatiotemporal dynamics of reported TBE cases, as well as distribution and features on endemic areas of TBEV in China. The occurrence of TBE was significantly associated with the composite meteorological index, altitude, the coverage of broad-leaved forest, the coverage of mixed broadleaf-conifer forest, and the distribution of *Ixodes persulcatus*, and we first predicted the risk distribution for human TBEV infections in mainland China. Our findings not only promote the understanding and risk recognition of TBE in China, but can also help policy makers and health practitioners prioritize risk areas for control and prevention efforts.

Conflict of interests

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ttbdis.2017.04.009.

References

Altizer, S., Ostfeld, R.S., Johnson, P.T., Kutz, S., Harvell, C.D., 2013. Climate change and infectious diseases: from evidence to a predictive framework. Science 341, 514–519.
Bi, W.M., Deng, H.P., Bu, X.Y., 1997. Studies on the partition of natural foci of tick-borne encephalitis. J. Cap. Norm. Univ. 18, 100–107 (in Chinese).
Cai, H., Zhang, S., Yang, X., 2012. Forest dynamics and their phenological response to climate warming in the Khingan Mountains, Northeastern China. Int. J. Environ. Res. Public Health 9, 3943–3953.
Cheong, Y.L., Leitão, P.J., Lakes, T., 2014. Assessment of land use factors associated with dengue cases in Malaysia using Boosted Regression Trees. Spat. Spatiotemporal Epidemiol. 10, 75–84.
Csángó, P.A., Blakstad, E., Kirtz, G.C., Pedersen, J.E., Czettel, B., 2004. Tick-borne encephalitis in southern Norway. Emerg. Infect. Dis. 10, 533–534.
Deribe, K., Cano, J., Newport, M.J., Golding, N., Pullan, R.L., Sime, H., Gebretsadik, A., Assefa, A., Kebede, A., Hailu, A., Rebollo, M.P., Shafi, O., Bockarie, M.J., Aseffa, A., Hay, S.I., Reithinger, R., Enquselassie, F., Davey, G., Brooker, S.J., 2015. Mapping and modelling the geographical distribution and environmental limits of podoconiosis in Ethiopia. PLoS Negl. Trop. Dis. 9, e0003946.
Elith, J., Leathwick, J.R., Hastie, T., 2008. A working guide to boosted regression trees. J. Anim. Ecol. 77, 802–813.
Estrada-Peña, A., de la Fuente, J., 2014. The ecology of ticks and epidemiology of tick-borne viral diseases. Antiviral Res. 108, 104–128.
Fang, L.Q., Li, X.L., Liu, K., Li, Y.J., Yao, H.W., Liang, S., Yang, Y., Feng, Z.J., Gray, G.C., Cao, W.C., 2013. Mapping spread and risk of avian influenza A (H7N9) in China. Sci. Rep. 3, 2722.
Fang, L.Q., Liu, K., Li, X.L., Liang, S., Yang, Y., Yao, H.W., Sun, R.X., Sun, Y., Chen, W.J., Zuo, S.Q., Ma, M.J., Li, H., Jiang, J.F., Liu, W., Yang, X.F., Gray, G.C., Krause, P.J., Cao, W.C., 2015. Emerging tick-borne infections in mainland China: an increasing public health threat. Lancet Infect. Dis. 15, 1467–1479.
Gao, X., Nasci, R., Liang, G., 2010. The neglected arboviral infections in mainland China. PLoS Negl. Trop. Dis. 4, e624.
Gilbert, L., Aungier, J., Tomkins, J.L., 2014. Climate of origin affects tick (*Ixodes ricinus*) host-seeking behavior in response to temperature: implications for resilience to climate change? Ecol Evol. 4, 1186–1198.
Gritsun, T.S., Lashkevich, V.A., Gould, E.A., 2003. Tick-borne encephalitis. Antiviral Res. 57, 129–146.
Haditsch, M., Kunze, U., 2013. Tick-borne encephalitis: a disease neglected by travel medicine. Travel Med. Infect. Dis. 11, 295–300.
Harrus, S., Baneth, G., 2005. Drivers for the emergence and re-emergence of vector-borne protozoal and bacterial diseases. Int. J. Parasitol. 35, 1309–1318.
Hotez, P.J., Bottazzi, M.E., Strych, U., Chang, L.Y., Lim, Y.A., Goodenow, M., AbuBakar, S., 2015. Neglected tropical diseases among the Association of Southeast Asian Nations (ASEAN): overview and update. PLoS Negl. Trop. Dis. 9, e0003575.
Hou, Z.L., Zi, D.Y., Huang, W.L., Yu, Y.X., Wang, Z.W., Gong, Z.D., Liu, L.H., Lv, X.H., Lei, Y.M., Ji, Y.S., 1991. Two strains of viruses related to Russian spring summer encephalitis virus isolated from *Ixodes ovatus* in Yunnan. Chin. J. Virol. 7, 75–77 (in Chinese).
Hou, Z.L., Huang, W.L., Zi, D.Y., Gong, Z.D., Lei, Y.M., 1992. First isolation of Russian spring-summer encephalitis viruses from rodents and insectivora. Virol. Sin. 7, 397–403 (in Chinese).
Huang, W.L., Hou, Z.L., Zi, D.Y., Gong, Z.D., Lei, Y.M., Mi, Z.Q., Zhang, H.L., 2001. Investigation of the Russian spring-summer encephalitis virus in Yunnan Province. Chin. J. Prev. Vet. Med. 23, 231–233 (in Chinese).
Imhoff, M., Hagedorn, P., Schulze, Y., Hellenbrand, W., Pfeffer, M., Niedrig, M., 2015. Review: sentinels of tick-borne encephalitis risk. Ticks Tick Borne Dis. 6, 592–600.
Jore, S., Vanwambeke, S.O., Viljugrein, H., Isaksen, K., Kristoffersen, A.B., Woldehiwet, Z., Johansen, B., Brun, E., Brun-Hansen, H., Westermann, S., Larsen, I.L., Ytrehus, B., Hofshagen, M., 2014. Climate and environmental change drives *Ixodes ricinus* geographical expansion at the northern range margin. Parasit. Vectors 7, 11.
Kang, X., Li, Y., Wei, J., Zhang, Y., Bian, C., Wang, K., Wu, X., Hu, Y., Li, J., Yang, Y., 2013. Altitude of matrix metalloproteinase-9 level in cerebrospinal fluid of tick-borne encephalitis patients is associated with IgG extravassation and disease severity. PLoS One 8, e77427.
Kollaritsch, H., Paulke-Korinek, M., Holzmann, H., Hombach, J., Bjorvatn, B., Barrett, A., 2012. Vaccines and vaccination against tick-borne encephalitis. Expert Rev. Vaccines 11, 1103–1119.
Korenberg, E.I., 2000. Seasonal population dynamics of ixodes ticks and tick-borne encephalitis virus. Exp. Appl. Acarol. 24, 665–681.
Li, H., Wang, Q., Wang, J., Han, S.Z., 1999. The epidemiological study of tick-borne encephalitis in the forest areas in Daxing'an Mountains. Chin. J. Zoonoses. 15, 78 (in Chinese).
Lindgren, E., Gustafson, R., 2001. Tick-borne encephalitis in Sweden and climate change. Lancet 358, 16–18.
Lindquist, L., Vapalahti, O., 2008. Tick-borne encephalitis. Lancet 371, 1861–1871.
Liu, Y.G., Jiang, Y.T., Guo, C.S., Guan, B.P., 1979. Some epidemiological characters of tick-borne encephalitis natural foci in Jilin province. Acad. Mil. Med. Sci. 109–120 (in Chinese).
Liu, J.G., Li, S.X., Ouyang, Z.Y., Tam, C., Chen, X.D., 2008. Ecological and socioeconomic effects of China's policies for ecosystem services. Proc. Natl. Aacd. Sci. U. S. A. 105, 9477–9482.
Lu, Z., Bröker, M., Liang, G., 2008. Tick-borne encephalitis in mainland China. Vector Borne Zoonotic Dis. 8, 713–720.
Ma, S.J., Lu, D.M., Zhang, Y.Z., 1996. Seroepidemiologic study on natural epidemic diseases in Linzhi Tibet. Chin. J. Prev. Med. 30, 346 (in Chinese).
Ma, S.J., Lu, D.M., Zhang, Y.Z., 1998. Seroepidemiologic study on natural epidemic diseases in Chayu Tibet. Mod. Prev. Med. 25, 202–203 (in Chinese).
Parola, P., 2004. Tick-borne rickettsial diseases: emerging risks in Europe. Comp. Immunol. Microbiol. Infect. Dis. 27, 297–304.
Petri, E., Gniel, D., Zent, O., 2010. Tick-borne encephalitis (TBE) trends in epidemiology and current and future management. Travel Med. Infect. Dis. 8, 233–245.
Pintér, R., Madai, M., Vadkerti, E., Németh, V., Oldal, M., Kemenesi, G., Dallos, B., Gyuranecz, M., Kiss, G., Bányai, K., Jakab, F., 2013. Identification of tick-borne encephalitis virus in ticks collected in southeastern Hungary. Ticks Tick Borne Dis. 4, 427–431.
Randolph, S.E., 2001. The shifting landscape of tick-borne zoonoses: tick-borne encephalitis and Lyme borreliosis in Europe. Philos. Trans. R. Soc. Lond. B Biol. Sci. 356, 1045–1056.
Ringnér, M., 2008. What is principal component analysis? Nat. Biotechnol. 26, 303–304.
Süss, J., 2008. Tick-borne encephalitis in Europe and beyond-the epidemiological situation as of 2007. Euro Surveill. 13.
Salas, L.A., Cantor, K.P., Tardon, A., Serra, C., Carrato, A., Garcia-Closas, R., Rothman, N., Malats, N., Silverman, D., Kogevinas, M., Villanueva, C.M., 2013. Biological and statistical approaches for modeling exposure to specific trihalomethanes and bladder cancer risk. Am. J. Epidemiol. 178, 652–660.
Stefanoff, P., Zielicka-Hardy, A., Hlebowicz, M., Konior, R., Lipowski, D., Szenborn, L., Siennicka, J., Orlikova, H., enhanced surveillance working group, T.B.E., 2013. New endemic foci of tick-borne encephalitis (TBE) identified in districts where testing for TBE was not available before 2009 in Poland. Parasit. Vectors 6, 180.
Stjernberg, L., Holmkvist, K., Berglund, J., 2008. A newly detected tick-borne encephalitis (TBE) focus in south-east Sweden: a follow-up study of TBE virus (TBEV) seroprevalence. Scand. J. Infect. Dis. 40, 4–10.
Subak, S., 2003. Effects of climate on variability in lyme disease incidence in the northeastern United States. Am. J. Epidemiol. 157, 531–538.
Sumilo, D., Bormane, A., Asokliene, L., Vasilenko, V., Golovljova, I., Avsic-Zupanc, T., Hubalek, Z., Randolph, S.E., 2008. Socio-economic factors in the differential upsurge of tick-borne encephalitis in Central and Eastern Europe. Rev. Med. Virol. 18, 81–95.
The Ministry of Health ofPeople's Republic of China, 2002. Diagnostic Criteria of Occupational Forest Encephalitis. (in Chinese). http://www.moh.gov.cn/cmsresources/zwgkzt/wsbz/zybzdbz/zyb/zyb/088.pdf.
Tokarevich, N.K., Tronin, A.A., Blinova, O.V., Buzinov, R.V., Boltenkov, V.P., Yurasova, E.D., Nurse, J., 2011. The impact of climate change on the expansion of Ixodes persulcatus habitat and the incidence of tick-borne encephalitis in the north of European Russia. Glob. Health Action 4, 8448.
Upadhyayula, S.M., Mutheneni, S.R., Chenna, S., Parasaram, V., Kadiri, M.R., 2015. Climate drivers on malaria transmission in Arunachal Pradesh, India. PLoS One 10, e0119514.
Wang, S.Y., Li, Y.G., Ren, G.S., Yan, D.C., Wang, D.Y., Zhu, J.H., Liu, M.Z., Guo, S.J., 1995. The survey report of tick-borne encephalitis natural foci in Greater Khingan Mountains forest regions of Inner Mongolia. Endemic Dis. Bull. 10, 72–74 (in Chinese).
Weber, W., 2000. Germany halts tick-borne encephalitis vaccination. Lancet 356, 52.
Wu, X.B., Na, R.H., Wei, S.S., Zhu, J.S., Peng, H.J., 2013. Distribution of tick-borne diseases in China. Parasit. Vector. 6, 119.
Xie, X.C., Yu, X., Zhang, T.X., Jiang, G.Y., 1991. A survey report on the natural foci of tick-borne encephalitis in the mountainous areas of Tianshan and Altay Mountains in Xinjiang. Endemic Dis. Bull. 6, 109–114 (in Chinese).
Yang, L.P., Zhang, T.S., Yuan, X.P., Zi, D.Y., 1993. Two strains of tick-borne encephalitis virus isolated from Boophilus Microplus and Hipposideros Armiger in Yunnan province. Chin. J. Zoonoses 9, 22–23 (in Chinese).
Yang, L.W., Hou, Y., Shi, Y., Sun, X.F., Li, M., Wen, Z.Q., Yang, J., Fan, D.H., 2009. The preliminary study on tick-brone diseases at Heilongjiang Port. Chin. J. Front. Health Quar. 32, 354–362 (in Chinese).
Zhang, G.L., Liu, R., Sun, X., Zheng, Y., Liu, X.M., Zhao, M., Dang, R.L., Liu, S.K., Xia, J., Zheng, Z., Yang, Y.H., 2013. Investigation on the endemic foci of new emerged tick-borne encephalitis in Charles Hilary, Xinjiang. Chin. J. Epidemiol. 34, 438–442 (in Chinese).
Zheng, Y.C., Yang, X.K., Zhang, L.J., 2003. Study on the structure of tick-borne encephalitis patients. Chin. J. Zoonoses 19, 18 (in Chinese).