RESEARCH PAPER

SPATIO-TEMPORAL HETEROGENEITY AND POTENTIAL DRIVERS OF HUMAN TICK-BORNE ENCEPHALITIS IN THE SOUTH OF RUSSIAN FAR EAST

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ABSTRACT. The south of the Russian Far East is distinguished by diversity of natural conditions for the presence of vectors and circulation of pathogens, primarily tick-borne infections. Despite the relatively low proportion of tick-borne encephalitis in the structure of tick-borne infections and the rather low incidence rate compared to other Russian regions, the disease here has epidemiological significance, which is associated with its severe course. Therefore, it is important to identify local areas of greatest epidemic manifestation of the disease and potential drivers influencing the spread of tick-borne encephalitis.

This study uses data on population incidence in the municipal districts of Khabarovsk Krai, Amur Oblast, Jewish Autonomous Oblast and Zabaikalsky Krai between 2000 and 2020. Based on Kulldorf spatial scanning statistics, a temporally stable cluster of virus circulation in the population in the southwest of Zabaikalsky Krai was identified, which existed during 2009-2018. Regression modeling using zero-inflated negative binomial regression based on a set of environmental and socio-economic predictors allowed to identify variables determining the probability of infection: the share of forest, the amount of precipitation in the warm period, population density, as well as variables reflecting population employment and socio-economic well-being.

Despite the fact that tick-borne encephalitis is a natural focal disease and may be characterized by natural periods of increased incidence, the influence of the social component can have a strong impact on the epidemiological manifestation. The identified spatio-temporal differences within the study region and potential drivers must be taken into account when developing a set of preventive measures.

KEYWORDS: SatScan, GeoDa, endemic areas, space-time clusters, modeling, GIS

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INTRODUCTION

Tick-borne infections are caused by pathogens that are transmitted through tick bites. These infections include a wide range of diseases, some of which can pose a serious threat to human health. Regarding the variety of environmental factors that contribute to the existence of vectors and the spread of infections, the south of the Russian Far East region is especially significant. The structure of incidence of natural focal diseases in the region is dominated by pathologies transmitted by ixodid ticks: tick-borne rickettsioses, primarily Siberian tick-borne typhus (STT), account for about 40% of all registered cases; 30% of the overall incidence structure are ixodid tick-borne borrelioses (TBB), while tick-borne encephalitis (TBE) accounts for 13%. Human granulocytic anaplasmosis (HGA) and human monocytic ehrlichiosis (HME) are less frequent (Malkhazova et al., 2023). Because a single tick can harbor more than one pathogenic agent, the population may be infected with more than one pathogen simultaneously, adding to the challenges of diagnosis and treatment. As the incidence of tick-borne diseases increases and the geographic areas in which they occur expand, healthcare providers are increasingly required to distinguish between the diverse and often overlapping clinical manifestations of these diseases.

In most regions in the southern part of the Russian Far East, the incidence of the three predominant tick-borne infections is observed annually, with the highest rates recorded in Primorsky and Khabarovsk krais. At the same time, there is a geographic heterogeneity in the spread of tick-borne infections in the region (Fig. 1). For example, in Zabaikalsky and Primorsky krais, the predominance of TBB in the morbidity structure is noticeable, while in Amur Oblast, Khabarovsk Krai, and Jewish Autonomous Oblast, STT is more frequent. Over the years, there is a discernible shift in the severity of morbidity manifestations, which is particularly noticeable in TBE.

Despite the low share of TBE in the structure of tick-borne infections and the rather low incidence rate in the south of the Far East compared to other regions of the country, the long-term average rate is 1.4 per 100 thousand population. This number approximately corresponds to the national average (1.34) and falls behind the most affected areas of the Urals and Southern Siberia (8-12 per 100 thousand population (On the state.., 2023). This indicates that the disease is of great epidemiological significance. TBE is caused by the TBE virus (TBEV) belonging to the genus *Flavivirus* of the family *Flaviviridae*, and consists of three main subtypes: European, Siberian, and Far Eastern TBEV (Ecker et al., 1999; Lindquist, Vapalahti, 2008). In the Far East, the infection is especially severe, with a large number of adverse outcomes, which is associated with the high virulence of the Far Eastern subtype virus (Andaev et al., 2021). Retrospective analysis revealed that TBE cases were recorded in the southern region of the Far East in the late 19th and early 20th centuries. Over the past 30 years, there have been significant fluctuations in the incidence rate (Leonova, 2020). The spread of the infection is confined to the south of the Far East within the range of the main vector, the tick *Ixodes persulcatus*, whose habitat belongs to taiga landscapes (Korenberg et al., 2013). In addition, *I. pavlovskyi* may play a role in the transmission of infection as well, but its significance has not been sufficiently studied (Chicherina et al., 2015). The TBE virus has also been isolated from ticks of the genus *Dermacentor, D. nuttalli*, and *D. silvarum*, which are native to open steppe and forest-steppe biotopes (Dampilova, Turanov, 2014; Shchuchinova et al., 2015; Kholodilov et al., 2019).

The aims of this study were to identify the geographical heterogeneity of TBE distribution within the endemic region and to define the main drivers that can be used in creating preventive strategies. In this study, we investigated spatio-temporal patterns as well as potential drivers of TBE using incidence data (2000–2020) from the south of Russian Far East. First, we identified areas with high and low clustering of TBE incidence within the region. Then we explored whether various environmental and social conditions, including climatic, landscape and socio-economic variables, can explain the spatial patterns of TBE.

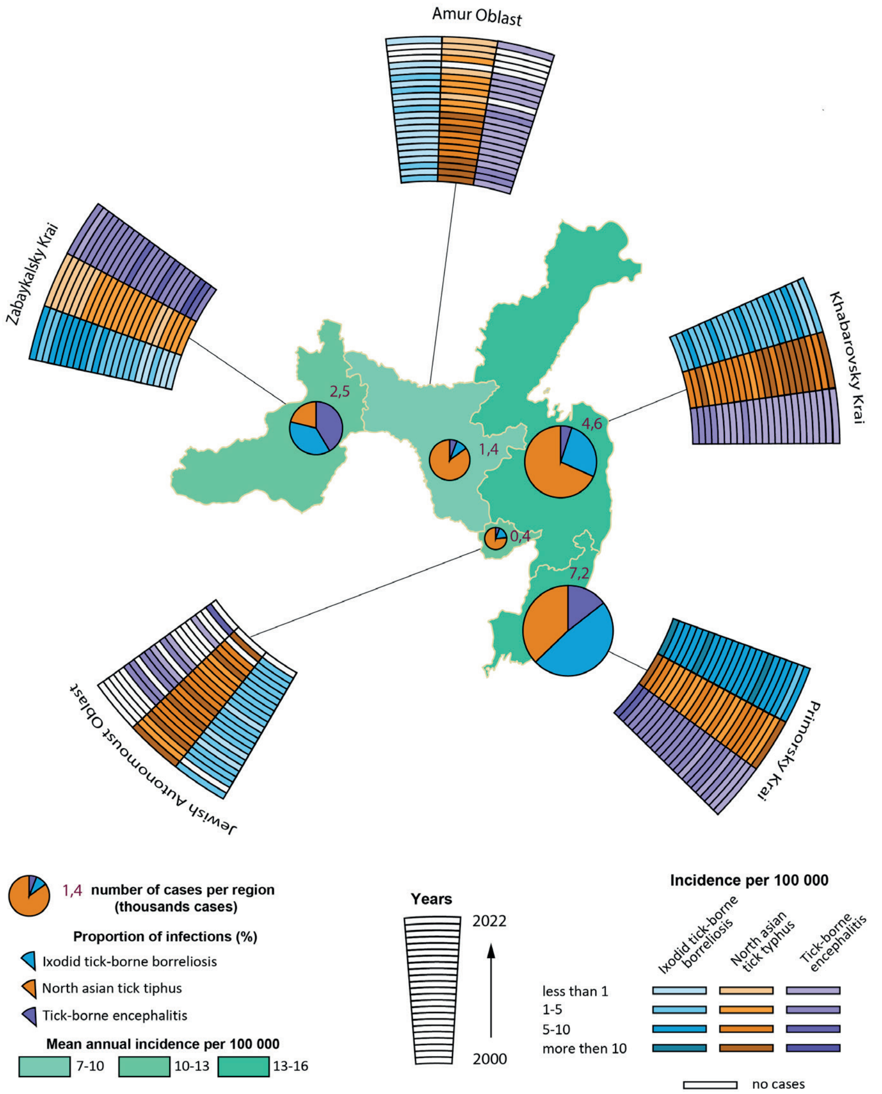

Fig. 1. Incidence of major tick-borne infections in the Russian Far East

Materials and methods

Study area

The study area includes four federal entities of the Russian Federation located in the south of the Far East: Zabaikalsky Krai, Khabarovsk Krai, Amur Oblast, and Jewish Autonomous Oblast. Three northern municipal districts of the Khabarovsk Krai (Okhotsky, Ayano-Maisky, and Tuguro-Chumikansky districts), extending beyond the ranges of ixodid ticks, were excluded from the analysis. The region under study is characterized by a variety of climatic and physical-geographical conditions. According to the Köppen-Geiger classification, most of the territory is influenced by warm humid continental climate (Dfb) and subarctic climate (Dfc), with the inclusion of a cold semi-arid climate (Bsk) in Zabaikalsky Krai, as well as hot humid continental climate (Dfa) in Jewish Autonomous Oblast (Beck et al., 2018). The territory is dominated by mountainous terrains. The relief of Zabaikalsky Krai presents itself in a form of elongated low and medium-high ridges, with the highest peak at 3067 m, while Amur Oblast is characterized by an alternation of medium-high and low ridges with plains, lowlands, and depressions. The vegetation is represented by taiga complexes of coniferous, coniferous-deciduous, and broad-leaved forests and forest steppe landscapes (National Atlas of Russia, vol. 2, 2007). This creates different habitat conditions for the tick population and functioning of the natural TBE foci. The socioeconomic conditions in the study region differ significantly, which could have an impact on the population's TBE circulation.

TBE data

Initial TBE incidence data were presented as absolute (annual number of cases) and relative (annual number of cases per 100,000 population) indicators aggregated by municipal units for the period from 2000 to 2020. A total of 85 municipal districts were included in the analysis. The data were officially sourced from the regional departments of the Federal Service for Supervision of Consumer Rights Protection and Human Welfare (Rospotrebnadzor).

Environmental and socio-economic data

Variables reflecting the effects of natural and socioeconomic conditions on the possible spread of tick-borne encephalitis are presented in Table 1. The choice of variables is determined by the environmental requirements of vectors, primarily climate, vegetation, and topography, as well as the peculiarities of the epidemiology of TBE and the possible influence of the socioeconomic component. Ixodid ticks are sensitive to humidity and temperature conditions (Burri et al., 2011, Tokarevich et al., 2017); therefore the distribution of natural foci of TBE is determined by the sum of temperatures for a period with a stable average daily temperature above 5 °C of at least 1600 °, with a moisture index varying from 0.15 to 0.60 and even slightly higher (Korenberg, Kovalevsky, 1985). Ixodid tick habitats are largely determined by forest structure (Daniel et al., 1998). Altitude can also potentially influence the distribution of various tick species (Kholodilov et al., 2019).

Information about natural conditions was obtained using a digital elevation model, ERA5 climate reanalysis data aggregated by month, and data on land use and surface temperature presented in the Google Earth Engine catalog (https://earthengine.google.com). After downloading the calculated variables (altitude, share of forest territories, precipitation in the warm period, land surface temperature for the warm period, and depth of snow cover) in raster format with the spatial resolution of the original datasets, the most represented pixel value was then recalculated to municipal units.

Human activity and behavior can significantly affect the spread of TBE. For example, the use of forest resources, changes in agriculture, or other types of anthropogenic activities may be reasons for the increase in the incidence of TBE (Kriz et al., 2004; Stefanoff et al., 2012; Panatto et al., 2022). These changes may be influenced by differences in broader socioeconomic circumstances (Randolf, 2008).

Data on socio-economic conditions (population density; share of people employed in agriculture, hunting, and forestry; fishing and fish farming; share of people employed in mining; share of the total area of residential premises equipped with sewerage; share of dilapidated housing; and density of paved roads) were obtained from open sources of the Federal State Statistics Service (Rosstat). The listed indicators characterize both the employment and living conditions, can generally reflect the socio-economic development of the municipality and the well-being of the population living in it, and indirectly influence the possibility of the spread of infection.

Data on natural and socio-economic conditions were limited to the period from 2016 to 2020. The primary processing and preparation of data for subsequent analysis were performed using the JavaScript Earth Engine API on the Google Earth Engine platform as well as the mapping service QGIS.

Spatio-temporal statistical analysis

Kulldorff spatial scan statistics implemented in SaTScan 9.6 software (Kulldorff, 2018) were used to identify possible spatio-temporal clusters of high TBE incidence in the study area during the period from 2000 to 2020. This approach is based on moving a cylindrical scanning window across the area of interest. The vertical dimension of the cylinder represents time. The radius and height of the cylinder varied from zero to 50% of the size of the study area and study period, respectively. Those cylinders within which there was a statistically significant excess of the observed number of cases over the expected number were then represented as spatio-temporal clusters. The expected number of cases was estimated based on the hypothesis of its Poisson distribution depending on the population in the municipal area using a discrete Poisson model (Kulldorff, 1997).

Spatial scan statistics were applied to the annual number of TBE cases assigned to municipal centroids. The model also uses municipal population data for the period from 2000 to 2020 (data is sourced from Rosstat). The use of this method made it possible to obtain spatial clusters of municipalities for a specific period of time, where the observed number of TBE cases statistically exceeds the expected number of cases.

To examine overall spatial clustering of TBE incidence, Global Moran's I spatial autocorrelation tool was additionally used. TBE incidence data were also tested for the presence of local spatial autocorrelation using Getis-Ord Statistics (Getis and Ord, 1992). Calculations were implemented in GeoDa software (Anselin et al., 2006). As a result, spatial clusters with high and low incidence could be identified and compared to the spatio-temporal clusters that had already been found.

Table 1. Environmental and socio-economic variables

Drivers	Variable	Data source
Natural	Altitude (m)	ALOS World 3D - 30m (AW3D30) is a global digital surface model (DSM) dataset
	Share of forest territories (%)	Dynamic World (a 10m near-real-time (NRT) Land Use/ Land Cover (LULC) dataset) (Brown et al., 2022)
	Precipitation in the warm period, (May — September, °C)	Copernicus Climate Change Service (C3S) (2017): ERA5: Fifth generation of ECMWF atmospheric reanalyses of the global climate. Copernicus Climate Change Service Climate Data Store (CDS), (date of access 08-10-2023), https://cds.climate.copernicus.eu/cdsapp#!/home
	Depth of snow cover (mm)	
	Air temperature for the cold period (November — March, °C)	
	Land surface temperature for the warm period (May — September, °C)	MODIS daily Land-surface Temperature at 1 km grids https://doi.org/10.5067/MODIS/MOD11A1.061
Socio-economic	Population density (people per sq. km)	Federal State Statistics Service (Rosstat)
	Share of people employed in agriculture, hunting, and forestry; fishing and fish farming (%)	
	Share of people employed in mining (%)	
	Share of the total area of residential premises equipped with sewerage (%)	
	Share of dilapidated housing (%)	
	Density of paved roads (km per 1000 sq. m)	

Regression analysis

Due to the fact that the incidence rate is highly biased and does not correspond to a normal distribution, which makes it difficult to use multiple linear regression, the number of years of registration of TBE cases in the municipality was used as the dependent variable. This approach seems justified, since the number of cases in the study area is usually no more than 1–2 per year, with rare exceptions of up to 10–15 cases (maximum 18) confined to cities. In addition, in a number of municipalities, TBE was not registered at all during the study period, which creates a significant number of zero values in the sample. In contrast to the incidence rate, there were no outliers for the variable of the number of years of registration.

We used zero-inflated negative binomial regression, which is appropriate for modeling count variables with excessive zeros that may be overdispersed (the count mean was 5.76, with a variance of 28.64, indicating overdispersion). According to theory, the count values and excess zeros are produced by different processes and can be represented separately (Hilbe, 2011).

Zero-inflated negative binomial regression models have two sets of predictors. One is used in a negative binomial model that predicts counts of the years of TBE registration and other is used in a logistic model to predict zero values (current absence of TBE registration in municipality). In that case we used a set of environmental and social predictors as the share of forest area, precipitation during warm period, population density, the share of population employed in mining. All variables were tested for multicollinearity by with the variance inflation factor (VIF < 5 that indicated moderate correlation). The goodness of regression model fit was assessed by an adjusted R-squared (R^2_{adj}) – a coefficient of determination adjusted for the number of predictions in the model, and a Root Mean Square Error (RMSE) - an average difference between values predicted by a model and the actual values. Regression analysis was carried out using R packages *ggplot2, car, pscl, easystats, sjPlot*.

Regression residuals were tested for the absence of spatial autocorrelation using Anselin Local Moran's I test (Anselin, 1995). This test is aimed at finding clusters of polygons with increased/decreased residual values based on the local Moran's I index and its statistical significance metrics (z-score and p-value). Statistical significance was assessed using 999 random permutations, and FDR correction was applied to eliminate the influence of multiple testing. Moran's I index values close to 1 or -1 and having a p-value<0.05 indicate the presence of clustering.

Results

Spatio-temporal clusters

Spatio-temporal analysis of TBE incidence allowed us to identify several statistically significant clusters. The most stable spatio-temporal cluster occurred between 2009 and 2018, and was characterized by a high relative risk of incidence (RR = 24.9), observed in the southwest of Zabaikalsky Krai (Fig. 2). The cluster includes two municipal districts, Krasnochikoisky and Petrovsk-Zabaikalsky. The remaining statistically significant spatio-temporal clusters belong to the period from 2000 to 2002, and are confined to the entire study area.

When considering the time dynamics for the entire study period, it was revealed that the period from 2000 to 2002 was characterized by a high incidence rate, after which the number of cases in the region stabilized (Fig. 3). It should be noted that in these years, no increase in incidence was observed in the Krasnochikoysky and Petrovsk-Zabaykalsky districts.

The Global Moran's I test for overall spatial clustering of incidence indicated the existence of a possible positive spatial autocorrelation (0.375, p-value<0.001) in the region. A spatial cluster of high incidence was identified in Zabaikalsky Krai, more specifically, in the central (Sretensky, Shelopogunsky) and southwestern (Kyrinsky, Krasnochikoysky, Petrovsk-Zabaikalsky, Khiloksky, Uletovsky) districts, while a low incidence cluster, including areas where the incidence was not recorded at all, was recorded in the southern districts of Amur Oblast (Fig. 4).

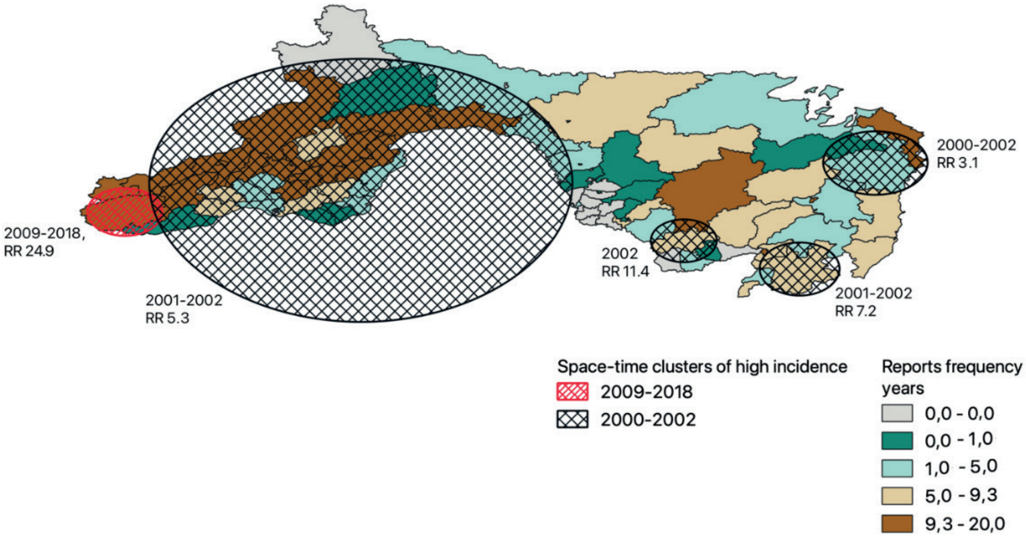

Fig. 2. Spatio-temporal patterns of TBE incidence (retrospective Space-Time analysis scanning for clusters with high rates using the Discrete Poisson model, RR – relative risk, cluster p-value < 0.05)

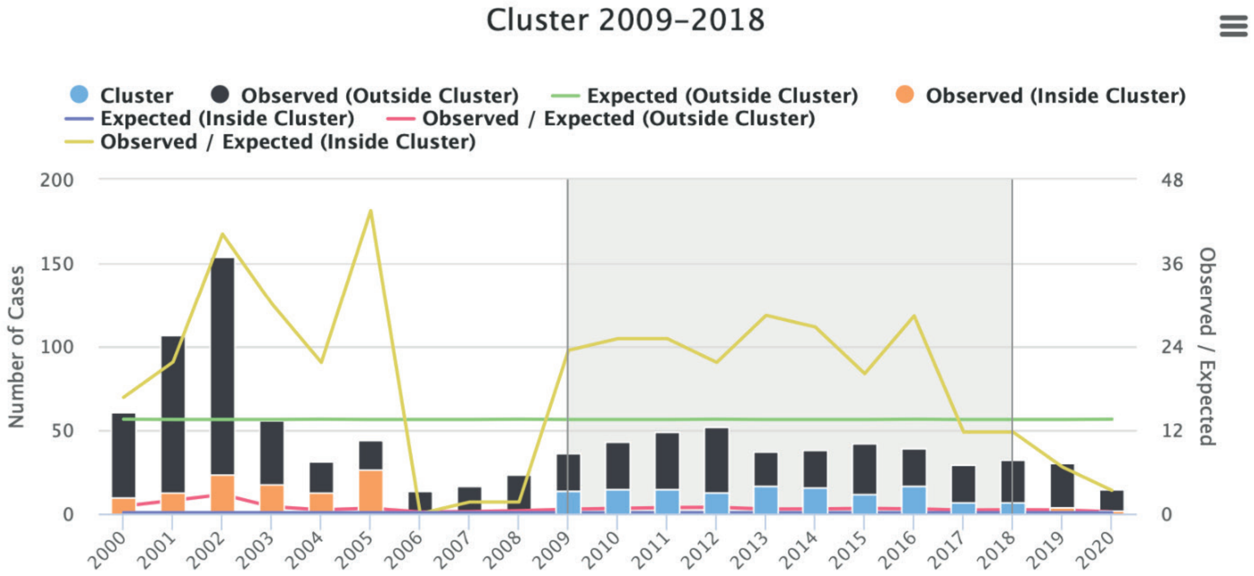

Fig. 3. TBE incidence dynamic (2000-2020) inside and outside of incidence cluster 2009-2018

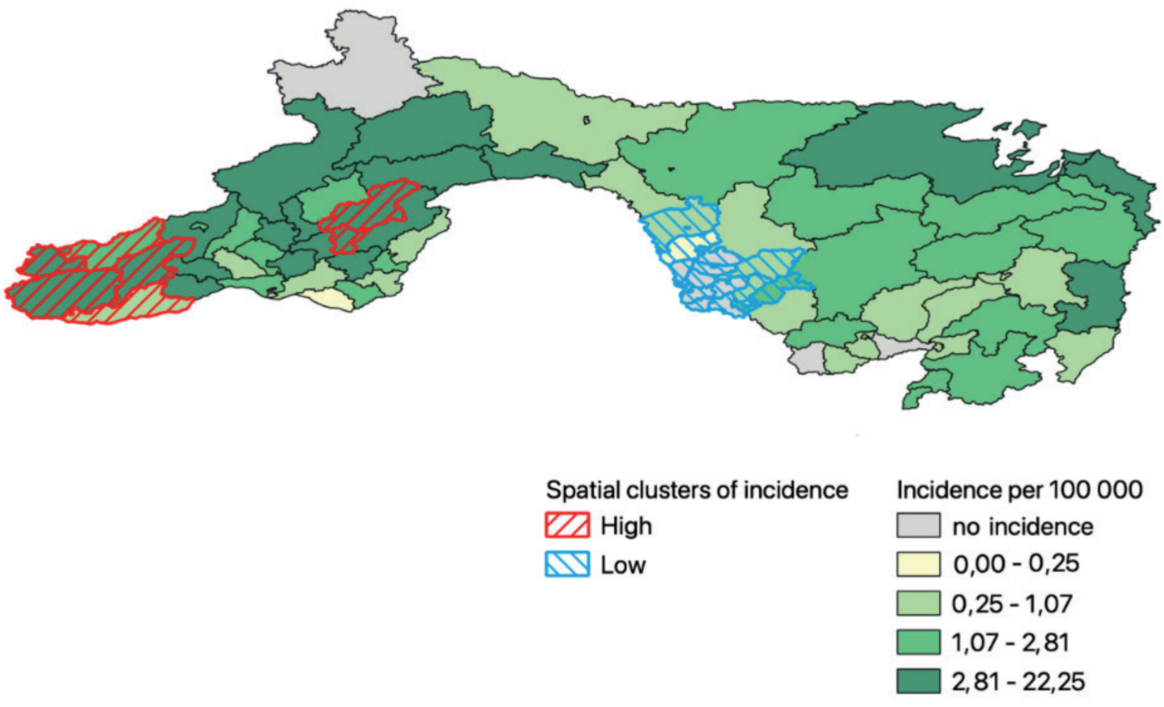

Fig. 4. Spatial patterns of high and low TBE incidence, 2000-2009 (Getis-Ord Statistics, cluster p-value < 0.05)

Potential drivers of TBE distribution

The results of Zero-inflated negative binomial regression showed good explanatory power of the TBE model (R2adj=0.90, RMSE =3.28). No overdispersion in the model, nor clustering of residuals were recorded. Registration of TBE on the territory was significantly related to such indicators as altitude, the share of forests, precipitation for the warm period, population density, the share of people employed in agriculture, hunting and forestry, fishing and fish farming, the share of people employed in mining, the share of dilapidated housing. Table 2 summarizes the model coefficients with their 95% confidence intervals, as well as statistical significance metrics (p-value) indicating a performance of particular variable as an explanatory factor in the regression. (Table 2).

Discussion

Population morbidity in 85 municipalities in the southern part of the Russian Far East for the period between 2000 and 2020 was analyzed, and a set of potentially influencing factors that shape the spatial heterogeneity of the distribution of TBE were identified.

In the study region, there are two focal territories: the Central Siberian-Transbaikal region, which includes Zabaikalsky Krai, and the Khingano-Amur region, which ties all other territories together (Korenberg and Kovalevsky, 1981). The results of the analysis showed that currently these focal areas are characterized by different intensities of the epidemic process. The territory where the epidemic process has been most active and stable for a long time is the southwest of Zabaikalsky Krai. This includes the Krasnochikoisky and Petrovsk-Zabaikalsky districts, that are forming a stable spatio-temporal cluster. This conclusion coincides with the results of other studies, where these two areas are classified as areas with high epidemiological risk (Turanov et al., 2020). This may be due both to the most favorable environmental conditions for tick populations represented in mid-mountain cedar-larch forests (National Atlas of Russia, vol. 2, 2007), and the influence of the peculiarities of economic activities carried out by residents

Table 2. Results of zero-inflated negative binomial regression models

Variables	Model coefficients	CI 95%	Std. Error	z value	Pr(>|z|)
Truncated poisson with log link					
(Intercept)	1.306	–0.527, 3.138	0.935	1.397	0.163
Altitude (m)	0.000	0.000, 0.001	0.000	2.557	0.011*
Share of forest territories (%)	0.016	0.009, 0.022	0.003	4.872	<0.001***
Precipitation in the warm period, (May — September, °C)	–13.266	–20.001, –6.531	3.436	-3.861	<0.001***
Depth of snow cover (mm)	–0.133	–2.025, 1.758	0.965	-0.138	0.890
Air temperature for the cold period (November — March, °C)	0.011	–0.043, 0.065	0.027	0.403	0.687
Land surface temperature for the warm period (May — September, °C)	0.020	–0.017, 0.057	0.019	1.042	0.298
Population density (people per sq. km)	0.001	0.001, 0.002	0.000	5.531	<0.001***
Share of people employed in agriculture, hunting, and forestry; fishing and fish farming (%)	–0.095	–0.136, –0.055	0.021	-4.634	<0.001***
Share of people employed in mining (%)	–0.171	–0.310, –0.032	0.071	-2.412	0.016*
Share of the total area of residential premises equipped with sewerage (%)	0.001	–0.005, 0.008	0.003	0.345	0.730
Share of dilapidated housing (%)	0.039	0.010, 0.068	0.015	2.628	0.009**
Density of paved roads (km per 1000 sq. m)	–0.002	–0.010, 0.006	0.004	-0.546	0.585
Zero hurdle model coefficients (binomial with logit link)					
(Intercept)	6.214	2.513, 9.914	1.888	3.291	<0.001***
Share of forest territories (%)	0.067	0.025, 0.108	0.021	3.147	0.002**
Precipitation in the warm period, (May — September, °C)	–78.206	–125.583, –30.829	24.172	-3.235	0.001**
Population density (people per sq. km)	0.005	0.000, 0.009	0.002	1.949	0.051
Share of people employed in mining (%)	–1.197	–1.911, –0.483	0.364	-3.285	0.001**

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Testing of regression residuals revealed no clusters or outliers.

of the areas associated with active interaction with natural environment.

Residents of the Krasnochikoysky district are mainly engaged in agricultural production (livestock raising), wood processing and procurement of wild plants: mushrooms, berries, pine nuts, wild garlic (Official portal of the Trans-Baikal Territory. Krasnochikoysky district. https://chikoy.75.ru/o-rayone/168914 -description). Labor employment of the population is low, which is why there are high risks of people coming into contact with the vector, especially during the period of active taiga fishing (Turanov et al., 2020). The metallurgical plant in the Petrovsk-Zabaikalsky district ceased its operation in 2002 (Rogov, 2023), which could also have contributed to a decrease in employment and people switching to actively visiting natural biotopes for hunting, fishing and collecting wild plants.

It should be noted that the administrative units neighboring the Krasnochikoisky and Petrovsk-Zabaikalsky districts form a spatial cluster of high incidence, which can also serve as confirmation of an active epidemic process in this territory.

Areas with low activity of the epidemic process include districts of the south of Amur Oblast, where a cluster of low incidence was identified, including areas with zero registration of TBE cases. This is the most populated and developed territory of the region, located in the landscape zone of deciduous forests on the Zeya-Bureya Plain and the southern part of the Amur-Zeya Plain. Natural conditions are less favorable for the circulation of the virus compared to the rest of the study region, which is mainly determined by the low proportion of forests in these districts (no more than 40%). The low activity of the epidemic process is confirmed by the lowest detection rates of antibodies to the TBE virus in the population (Dragomeretskaya et al., 2018).

A distinctive feature of the 2000–2002 clusters was the even distribution throughout the study region. In general, TBE is characterized by periodic cycles of rising incidence, usually occurring every 3–5 years (Korenberg et al., 2013). However, these clusters are, apparently, an echo of the deterioration of the epidemic situation with TBE throughout the entire focal territory of the Eurasian continent in 1990–1999, when there was a multifold increase in incidence rates not only in Western and Eastern Siberia, but also in the European and Far Eastern parts of the country (Zlobin et al., 2015; Leonova, 2020). The deterioration of the epidemiological situation could be caused by both the increased risk of infection of urban residents and the almost complete absence of methods and opportunities for mass prevention during the years of the socio-economic crisis (Voronkova, Zakharycheva, 2007; Korenberg et al., 2013). In subsequent years, on the contrary, there was a persistent trend towards a pronounced decrease in the incidence of TBE.

It should be noted that the Russian focal area of TBE continues into China, covering the northeast of the country and the provinces of Inner Mongolia, Heilongjiang, and Jilin, taking that that Heilongjiang is of the foremost priority (Yi et al., 2017) . Approximately 99% of cases have been reported in forested areas with mixed broadleaf-coniferous forests as the dominant vegetation, as well as in mixed broadleaf-coniferous forests and broadleaf forests. Moreover, most cases were in farmers or forestry workers (Sun et al., 2017; Chen et al., 2019).

The results of the regression analysis contribute to the understanding of the distribution of TBE in the study region, as well as the location of the identified spatio-temporal clusters. The spread of infection is the result of both natural and social factors; however, the role of the latter cannot be underestimated. According to the regression model, factors influencing the likelihood of infection primarily include the share of forest, the amount of precipitation during the warm season, population density, and employment in the mining industry.

The share of forests in the territory of a municipality is one of the main drivers, as it determines the possibility of the existence of the main vector of the virus, *I. persulcatus*. This is supported by consistent results from both spatio-temporal cluster analysis and regression model analysis. This is one of the most influential factors associated with the vector ecology.

The amount of precipitation during the warm period was also a significant variable in the model: the higher the amount of precipitation, the lower the probability of the spread of TBE. However, the influence of this factor should be interpreted with caution. Several other studies have also shown mixed results regarding the nature of the influence of precipitation (Brabec et al., 2017; Li et al., 2017). For example, in northeastern China, the risk of TBE infection in southwestern Heilongjiang Province was found to decrease with increasing precipitation, whereas in the center, it intensified along with increasing precipitation (Li et al., 2017). Ticks are sensitive to humidity, and increased humidity caused by increased precipitation helps to maintain optimal conditions in tick refuges, reduces moisture loss during hunting, improves their survival, and lengthens hunting periods (Uusitalo et al., 2020). However, the mechanism for synchronizing the complex life cycle of ixodid ticks under natural conditions is based on the reaction to day length. Therefore, the most generally important hydrothermal conditions are those under which ticks can receive an amount of heat and moisture that guarantees the completion of a certain developmental stage within a strictly defined time frame (Korenberg et al., 2013).

The lack of significance of the temperature factor in the model is probably explained by fairly favorable temperature conditions for the tick population and virus circulation throughout the entire study area; therefore, it is not limiting and does not appear on the regional scale of the study. In addition, it should be noted that little studies have been made about the impact of temperature or other meteorological factors directly on the TBE virus population (Korenberg et al., 2013).

Among other natural factors that significantly influence the spread of TBE, is altitude that can also reflect the environmental requirements of ticks. However, as in the case of the relationship with precipitation, the threshold values may be important when assessing the influence of a factor on the distribution of TBE. In northeast China, a non-monotonic and segmental effect of altitude was shown, with the highest risk of infection at altitudes of 400–600 m, then 1400–1700 m and 2000–3000 m (Sun et al., 2017). The affinity of *I. persulcatus* to medium and low altitudes has been noted in studies on Altai (Shchuchinov et al., 2015) and Tuva (Kholodilov et al., 2019).

Among socio-economic factors, the greatest influence was found for indicators of population density and employment, as well as the share of dilapidated housing. High population density appears to be a factor contributing to the spread of TBE. It is often associated with a high proportion of urban areas and a large population, which naturally increases the risk of TBE (Uusitalo et al., 2020). Employment of the population, which in our case was characterized by the share of people employed in agriculture, hunting, forestry, fishing, and fish farming, as well as in mining, probably restrained the spread of taiga foraging among the population and, accordingly, caused less contact with natural biotopes. In addition, those formally employed in hunting and forestry are more likely to be vaccinated, which also limits the spread of the disease. The influence of the share of dilapidated housing and the share of the total area of residential premises equipped with sewerage, as an indirect indicators of the socio-economic well-being of the population, support the hypothesis that one of the main factors in the spread of TBE in districts may be the lack of employment of the population or low level of income. The finding of the impact of unemployment and low-wage work on forest visits to gather resources for sale is in agreement with other studies (Stefanoff et al., 2012; Stefanoff et al., 2018).

Thus, the analysis not only made it possible to identify territories with different levels of manifestation of the epidemic process and determine the factors influencing the formation of a spatially heterogeneous picture in the spread of TBE, but also led to an indirect conclusion about the most vulnerable group: the economically marginalized population living in areas that are depressed in the socio-economic context. At the same time, the rest of the sick population might be vacationers resting in nature or working on private plots of land. These differences can be illustrated by the example of larger cities of the region (Chita, Khabarovsk, and Komsomolsk-on-Amur), where cases of TBE are recorded almost annually; however, taking into account population density and socio-economic characteristics, the likelihood of population contact with a vector and the risk of TBE infection cannot be considered together with districts included in the stable spatio-temporal cluster of Krasnochikoisky and Petrovsk-Zabaikalsky districts.

The identified spatio-temporal differences within the study region and their potential drivers must be considered when carrying out preventive measures, including vaccine prevention, anti-tick treatments, health education, and informing the population about personal protection. Despite the fact that at least 95% of the child and adult populations living in endemic areas are subject to mandatory vaccination, as well as the entire population that is exposed to occupational risks or travels to areas endemic for TBE (Sanitary Rules..., 2022), the vaccination plan is not completely fulfilled. The information on the partial volume of the vaccination campaign carried out is available in the reports "On the state of sanitary and epidemiological well-being of the population" for all subjects studied. Immunization coverage of TBE among the population living in endemic areas was no more than 10%. In addition, there are problems in evaluating the epidemiological effectiveness of vaccine prevention (Pen'evskaya et al., 2018). To improve the vaccine prevention program and analyze its effectiveness, a wider use of assessing the seroprevalence of IgG antibodies to the tick-borne encephalitis virus is necessary (Tokarevich et al., 2022). Despite the existence of natural cycles in the epidemiological manifestations of TBE, the influence of socio-economic components can have a strong impact on the incidence rate. A clear confirmation of this is the rise in incidence in the 1990s. Therefore, a set of preventive measures should be developed with consideration for the socio-economic characteristics of districts.

Strengths and limitations

The research carried out has certain limitations. Firstly, due to the lack of data, the influence of such factors as the size of tick populations, species composition and the level of their infestation in the study area, as well as the presence of rodents and large mammals that act as feeders for a significant number of both immature and adult stages were not considered (Cagnacci et al., 2012). Secondly, we were unable to compile a cohesive picture of the south of the Far East due to the absence of publicly available statistical data for Primorsky Krai. Lastly, the accuracy of threshold estimations for the response of influencing factors is limited by statistics that are combined across municipal units. However, the set of methods used allowed us to obtain consistent results regarding the spatial picture and potential drivers in the spread of TBE.

CONCLUSION

The study's findings allowed for the identification of two distinct clusters: one in the south of Amur Oblast, which was non-endemic and had a low incidence rate, and the other in the southwest of Zabaikalsky Krai, which showed a temporally stable cluster of active TBE viral circulation among the population. Simultaneously, various drivers in the creation of these spatial clusters can be identified. While the lack of ideal conditions for the virus vector, primarily caused by a small percentage of forests, determines a cluster of non-endemic areas, the socio-economic component plays a major role in the formation of a cluster of active virus circulation among the population. Despite the fact that TBE is a natural focal disease (as evidenced by the identified influence of the proportion of forests, the amount of precipitation in the warm season and altitude), the socio-economic parameters, such as population density, employment and financial well-being of the population, might also have quite the impact on the viral processes of TBE. Therefore, the underestimation of the socio-economic components may negatively affect the effectiveness of preventive measures.

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