

Research Paper

A Simple Spatial Model to Explain the Distribution of Human Tick-Borne Encephalitis Cases in Hungary

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ABSTRACT

Tick-borne encephalitis (TBE) is a common medical problem in Hungary and throughout much of Europe and Asia. This paper develops a geographic model that helps to predict the distribution of human tick-borne encephalitis cases in Hungary. The model is tested on a dataset of serologically confirmed TBE cases mapped by patients' residences. Case densities (incidence rates) are compared to predicted distributions of TBE derived from digital land-cover data. Maps are analyzed at the county level and on a smaller spatial scale. The analyses identified three major factors that shape the geographic distribution of human TBE cases in Hungary. The most important component is the distribution of forest habitat. TBE incidence correlates positively with the amount of forested habitat in each county. On a finer scale, the amount of forests within a 2500-meter radius of each town and village correlated significantly with TBE incidence rate. Based on these data, about 30% of the variation in TBE incidence is accounted for by the specific distribution of forest habitats in Hungary. Besides the distribution of forests, differences in human land-use practices among regions also affect the distribution of TBE cases. Additionally, because of the low transmission rate of the virus to humans, the perceived distribution of TBE cases is affected by random stochastic events. As a consequence of stochastic variation, meaningful patterns in the distribution of TBE cases can be only recognized when data are analyzed over broader temporal and spatial scales. **Key Words:** Tick-borne encephalitis—Landscape ecology—GIS modeling—Hungary. *Vector-Borne Zoonotic Dis.* 6, 369–378.

INTRODUCTION

TICK-BORNE ENCEPHALITIS (TBE) is caused by viruses belonging to the family Flaviviridae, genus *Flavivirus* (Westaway et al. 1985). The virus infects a wide variety of hosts such as roe deer (Gerth et al. 1995), sylvan rodents (Kozuch et al. 1990), or humans. The infection is transmitted between mammalian species via tick (*Ixodes ricinus*) bites. The disease is widespread, its range extends from Central Europe to Far-Eastern Asia (Calisher 1988) and within this enormous area different subtypes of the

virus can be distinguished. The mortality rate of the illness is low (<1%) in Europe, while the slightly different viral subtypes in Far-Eastern Asia take a much higher (5–20%) toll on human populations (Gustafson 1994). Presently, prevention of the infection is the most effective way to decrease the impact of TBE on human communities. State-organized and state-aided vaccination campaigns against TBE started in Hungary in 1977, and the commercially available vaccine was free of charge for occupationally endangered people living and working in known endemic areas. In 1991, free vaccina-

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tion campaigns ceased as TBE vaccine became publicly available in pharmacies throughout Hungary. Today, approximately 5% of the Hungarian population has received adequate vaccination. Because most vaccinated people live in the low-risk urbanized areas, TBE is still a serious problem in rural areas.

It has been known for a long time that TBE cases are not uniformly distributed. There have been more cases reported from so-called endemic areas which are also called natural foci of infection (Nosek et al. 1970, Pavlovskii 1939, 1966). It is also well understood that TBE is associated with forested areas. Yet many ecological aspects of tick-borne encephalitis still remain unexplained. Recent pioneering epidemiological studies tried to analyze the distribution of various infectious diseases using geographic information system (GIS) and satellite imagery (Barinaga 1993, Kitron 1998). The main goals of these studies were to estimate the risk of infection (Dister et al. 1997, Glass et al. 1995), increase the efficiency of protective measures (Beck et al. 1994), and help to understand factors influencing the geographic extent of disease (Rogers and Randolph 1991). Following the framework of these studies, recent papers have focused on TBE risk assessment utilizing satellite data (Daniel et al. 1998, Zeman 1997) and the possible effects of climate change on the prevalence of TBE (Lindgren 1998, Randolph 2005). In our study, we utilized GIS technology to test the hypothesis that the extent and distribution of forested areas is significantly correlated with the number of human TBE cases in Hungary.

METHODS

Medical records of 7959 serologically confirmed TBE cases, reported in 1958–2004, were compiled in the Johan B. National Center for Epidemiology, Budapest Hungary (former National Institute of Public Health). Based on the clinical symptoms, if hospital physicians suspected that a patient contracted tick-borne encephalitis, blood samples were sent to the National Center for Epidemiology for further testing. In cases where the first serological test was inconclusive, the serological test was re-

peated during the convalescent period of the illness to obtain conclusive serological results. Until 1980, serum and cerebrospinal fluid (CSF) of suspected patients were tested by hemagglutination inhibition (HI) and complement fixation (CF) tests. Antigen was prepared from sucrose-acetone extracts of infected mouse brain following procedures described by Clarke and Casals (1958). Positive results were confirmed by virus neutralization in the early years of the TBE monitoring. Since 1981, indirect immunofluorescence assay (IFA) has been the primary diagnostic method to demonstrate the presence of both TBEV specific IgM and IgG antibodies. IFA slides are prepared from virus infected cell lines (PS, Vero, Vero E6). Sera are separated by ion-exchange chromatography before the IgM demonstration (Nagy and Mezey 1977). Results are confirmed by both HI and various commercial ELISA tests. The first Hungarian tick-borne encephalitis virus isolate has been used for the preparation of all in-house reagents (Fornosi and Molnár 1954). In most cases, hospital physicians attempted to determine where and when the infection took place. Since people usually get infected with the TBE virus in the vicinity of their hometown or village, patients' residences were recorded as the primary site of TBE infection. In few cases, however, patients were able to recall where they had been bitten by ticks; specifically, whether infection occurred at a location other than their residence (e.g., on a weekend trip in the countryside). Then, each patient's residence or the nearest named place where a patients had been bitten was georeferenced and geographic coordinates were assigned to each case using digital maps of Hungary. To determine the incidence rate, we used the 2000 population census data. Because the population of Hungary has not changed substantially in the last 40 years (e.g. the country's population was the same size in 1999 and as it was in 1962); using the 2000 census data was a reasonable element of our study.

To analyze the spatial distribution of TBE encephalitis, the ArcInfo program (ESRI 1997) was used. Maps were edited for display in ArcView. Land-cover maps (scale 1:100,000) were obtained from the Authority of Nature Conservation of the Ministry of Environment. These land-cover maps were created as part of

the pan-European CORINE program (Coordination of Information on Environment) in an effort to record the current state of the environment in Europe (Rodwell et al. 1995). Hungarian CORINE land-cover maps show the distribution and extent of major habitat types and land use categories, such as towns and villages, agricultural areas, natural forests, grasslands, wetlands, open water and other (Büttner et al. 1995). The smallest unit shown on the map is 25 hectares. The CORINE map, overlaid by point distribution maps of human TBE cases, was used to determine general distribution patterns.

Working hypotheses were proposed and two simple spatial models were created to estimate viral prevalence in different regions of Hungary. The first hypothesis was based on the assumption that the incidence rate, calculated from the number of reported TBE cases and the number of local residents at each region (county or grid cell), would correlate with the proportion of forested areas in the same region. To test this hypothesis, the CORINE land-cover map was superimposed upon county maps, the sums of the forested and non-forested areas were calculated and compared with TBE incidence rates.

The second hypothesis was based on the idea that the number of TBE cases and incidence rates would correlate with the amount and the proximity of human habitats (villages, cities) to forests. To test this hypothesis, various buffer polygons (250, 1000, 2500, and 5000 m) were created around towns and villages, forest maps were overlaid and clipped by the buffer polygons, and the correlation between the abundance of forest habitats within the buffer zone and TBE incidence were calculated. Because the area of each buffer polygon depends on the area of the original town or village, the forest abundance (in percentage of the total area) was calculated within each buffer zone. The correlation between incidence rate and forest abundance was repeatedly calculated using the four designated buffer zones. Optimal buffer width was selected where the correlation between the incidence rate and the forest area was the strongest. The resulting maps were analyzed at two different spatial scales: risk estimates were averaged at the county level and by using a 25-

km mesh grid. Finally, estimated risk was contrasted with the TBE incidence rate from the same region. A linear regression model was used to statistically test the spatial model's ability to predict the observed number of human TBE cases. It was assumed that the better the model, the higher the correlation between the predictor variable (the amount of forest habitat) and TBE incidence rate would be.

RESULTS

The distribution of TBE cases shows a distinct, non-uniform pattern (Fig. 1A,D) in Hungary. More patients are reported from the western and northern parts of the country, while the southeastern part of the country is relatively free of infection with a few sporadic exceptions. The fact that the distribution of TBE cases does not show any similarity to the map of human population densities in Hungary supports the idea that the particular disease pattern is mostly controlled by environmental factors and not by the distribution of the human populace.

The general pattern of observed human TBE incidence rates grouped by counties (Fig. 1A) is accurately reflected on the risk assessment map based on the proportion of forested areas (Fig. 1B). The spatial model was able to pinpoint two high-risk counties, one in western Hungary (Zala county), and the other in northern Hungary (Nógrád county). Furthermore, the spatial model based on the distribution of forests elucidated a relatively low risk area in the southeastern part of Hungary. Statistical testing of the model confirmed that there is a significant correlation ($r = 0.51$) between the proportion of forested areas and human TBE cases (Fig. 2A).

Examining the distribution pattern of TBE incidence rate on a finer scale and using equal areas, additional variation can be identified within the broader geographic pattern (Fig. 1D). To the south of Zala county, a smaller, distinct, previously unrecognized endemic area in Baranya county exists. This newly recognized endemic area does not show up on county level maps. A third endemic area is in the northern part of Hungary in Nógrád

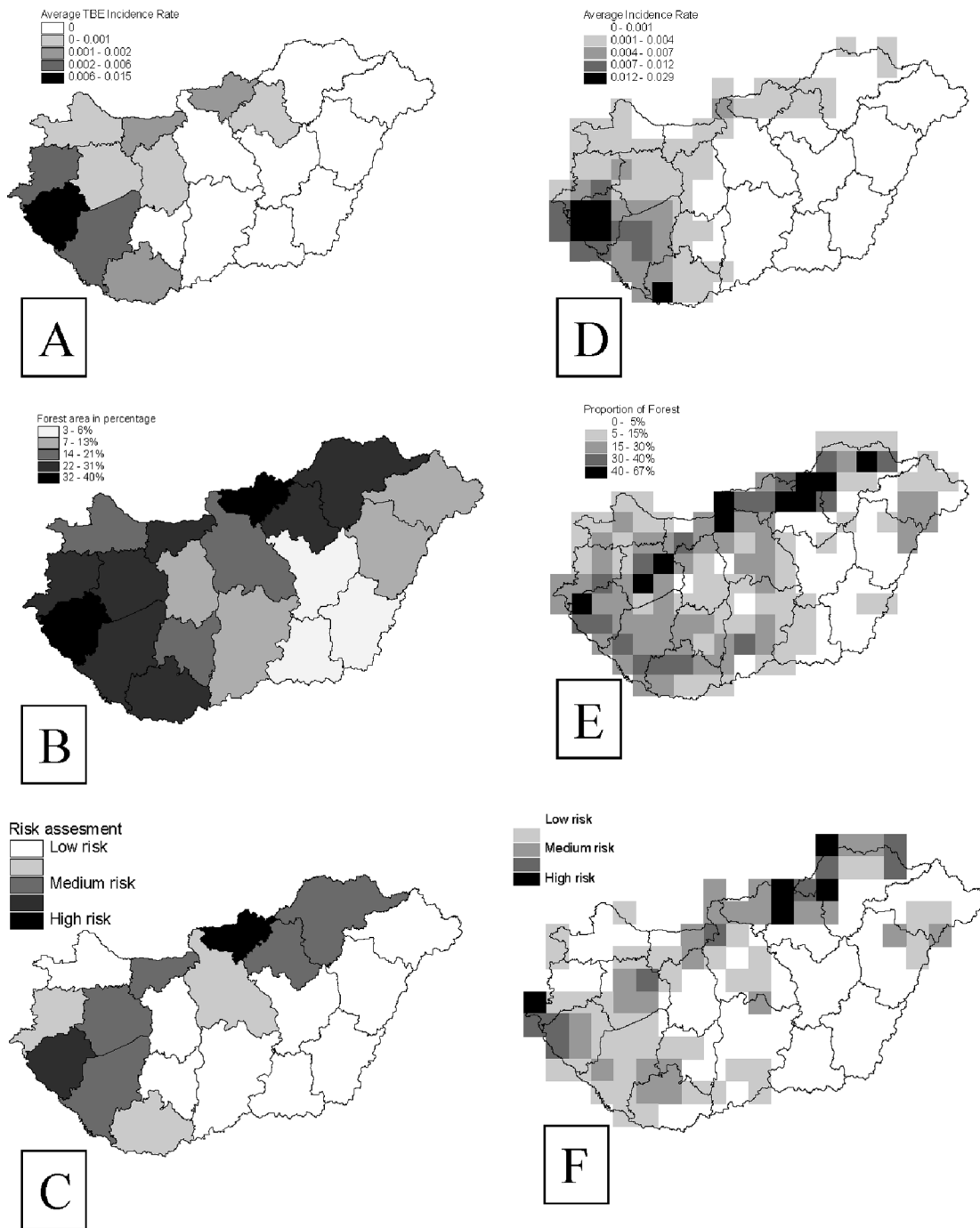


FIG. 1. The distribution of TBE cases and predicted incidence rates based on two geographic models at two different scales. (A) Average TBE incidence within counties. (B) Proportion of forest areas in each county. (C) TBE risk assessment at each county calculated from the level of forestation around each locality (town/village) using the 2500-m buffer zone. (D) Average TBE incidence within each 25-km wide grid cell. (E) Proportion of forest areas in 25 × 25 km wide grid cells. (F) Risk assessment within each cell calculated from the level of forestation around each locality using a 2500-m wide buffer zone.

county and has a lower TBE incidence rate when compared to other endemic areas, yet, the contrast is more apparent on the county level map because this endemic region is sur-

rounded by low-incidence rate areas (Fig. 1A). The map in Figure 1D also shows a fourth, small area (single 25km wide square) in northern Hungary with high incidence

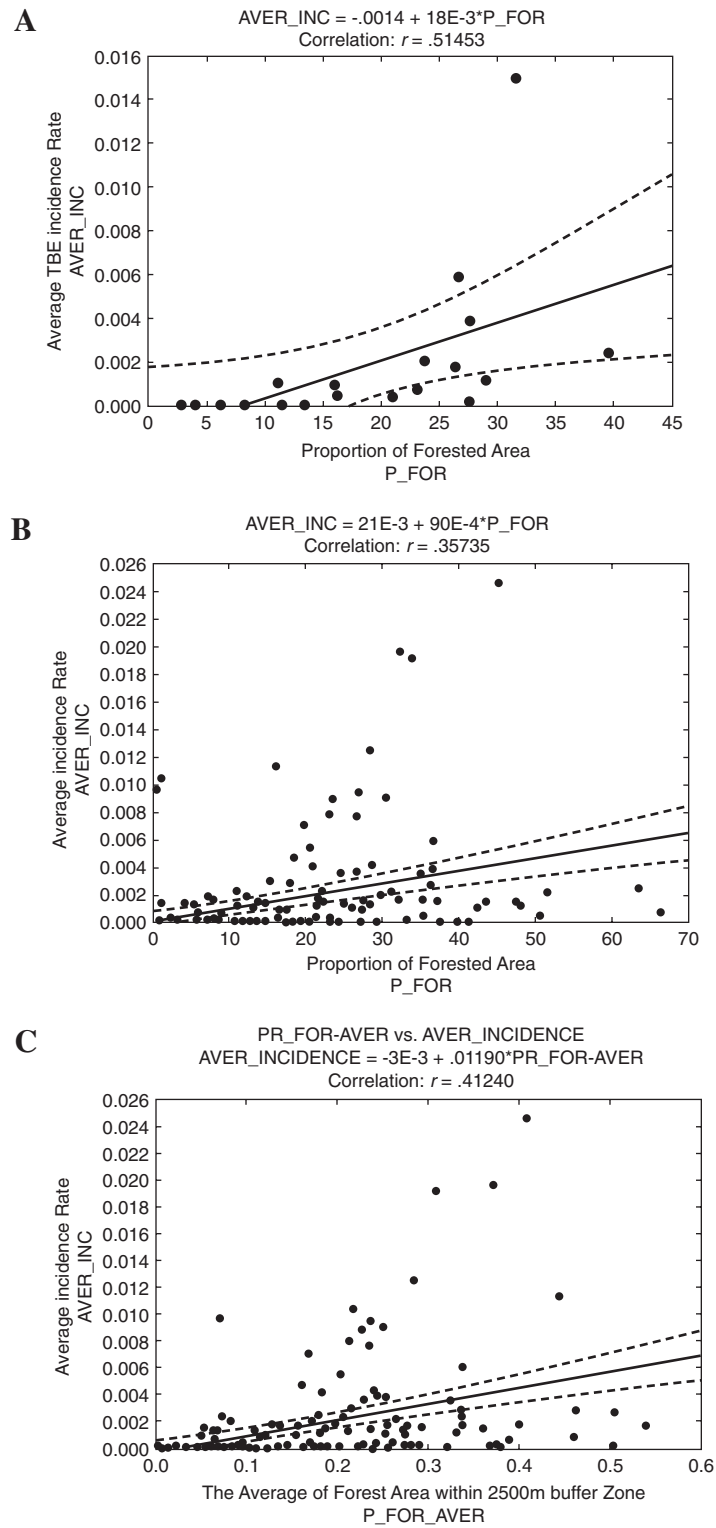


FIG. 2. Correlation between TBE incidence and the level of forestation at different geographic scales (county vs. 25-km grid) and using different geographic models. Solid lines show the linear regression model, dotted lines indicate the 95% confidence interval. (A) Correlation between the number of reported TBE cases and the proportion of forest calculated for each county. (B) Correlation between TBE incidence and the proportion of forest calculated for each grid cell (25 × 25 km). (C) Risk assessment (based on forested areas within the 2500-m buffer zone) vs. average incidence rate tabulated for each 25-km wide grid cell.

rate. This area, called the Börzsöny Mountains, is a known natural focus of TBE.

The particular distribution pattern of TBE shows correlation with the overall distribution of forests (Figs. 1D and 2B). The forest distribution map tabulated by the 25-km-wide grid (Fig. 1E) resembles the TBE incidence rate map (Fig. 1D). For example, all the endemic areas in Zala, Baranya, and Nógrád counties have large forests. The Börzsöny Mountains, a natural focus of TBE, is one large contiguous forest area. The general forest-cover pattern (more forest in the west and north) explains the low incidence rate of TBE in the east. However, compared to the county level correlations, the correlation between the amount of forest habitat and TBE incidence rate becomes weaker ($r = 0.35$) at this spatial level (Fig. 2B). Moreover, there are a few areas that appear as "high risk" on the forest map, but in reality, have low incidence.

From the maps of Figure 1A,B,D,E, it is evident that a good predictive spatial model of TBE has to examine the distribution of forest habitats in relation to the distribution of the human population. The new GIS model examined the amount of forest habitat in the vicinity of the towns and villages. In a preliminary analysis, buffer polygons were drawn around localities using varying widths (250, 1000, 2500, and 5000 m). The strength of correlation between forest habitats and TBE incidence depended on the width of the buffer polygons rising from low levels at 250 m and peaking at 2500 m (Table 1 and Fig. 3). Examining a narrow buffer polygon around villages, such as natural habitats within 250 m of the city limits (Table 1), does not capture the area's overall landscape characteristics. As larger and larger buffer polygons were selected around villages, the correlation between calculated local TBE incidence rates and

TABLE 1. CORRELATIONS BETWEEN THE LEVEL OF FORESTATION AROUND LOCALITIES AND INCIDENCE RATES

	INCIDENCE	PR_FOREST	PR_311	PR_312	PR_313	POPULATION
Buffer 250m						
INCIDENCE	1.00	0.04	0.03	0.02	0.02	-0.19
PR_FOREST		1.00	0.89	0.17	0.32	-0.16
PR_311			1.00	-0.02	-0.11	-0.14
PR_312				1.00	0.02	-0.02
PR_313					1.00	-0.07
POPULATION						1.00
Buffer 1000m						
INCIDENCE	1.00	0.18	0.15	0.08	0.08	-0.16
PR_FOREST		1.00	0.89	0.26	0.36	-0.18
PR_311			1.00	0.04	-0.07	-0.16
PR_312				1.00	0.17	-0.02
PR_313					1.00	-0.08
POPULATION						1.00
Buffer 2500m						
INCIDENCE	1.00	0.24	0.16	0.17	0.16	-0.16
PR_FOREST		1.00	0.90	0.31	0.35	-0.21
PR_311			1.00	0.05	-0.06	-0.19
PR_312				1.00	0.33	-0.05
PR_313					1.00	-0.09
POPULATION						1.00
Buffer 5000m						
INCIDENCE	1.00	0.23	0.15	0.20	0.21	-0.16
PR_FOREST		1.00	0.92	0.35	0.35	-0.22
PR_311			1.00	0.08	-0.04	-0.19
PR_312				1.00	0.47	-0.08
PR_313					1.00	-0.11
POPULATION						1.00

Significant correlation values are highlighted with bold numbers. Correlation between forested areas (PR_FOREST = proportion of total forested areas within the buffer zone, PR_311 = proportion of deciduous forests, PR_312 = proportion of coniferous forest, PR_313 = mixed deciduous-coniferous forest) and incidence rate were calculated using different distances (buffers) around localities. In addition, the number of inhabitants (POPULATION) was included in the correlation analysis.

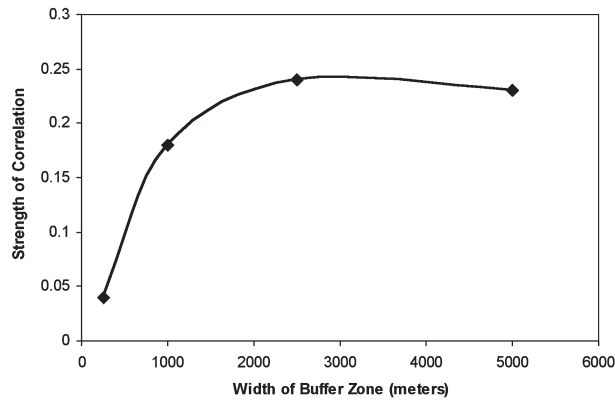


FIG. 3. Width of buffer zones around localities (villages/towns) determine how well forest area correlates with incidence rate.

forested habitats increased (Fig. 3). On the other hand, correlation values did not improve over a certain buffer radius (5000 m), signifying that larger buffer areas did not capture additional information on the quality of the natural habitats at a given locality (Table 1).

The new spatial model based on proximity and the amount of forest in the vicinity of a village resulted in the additional ability to explain the distribution pattern of TBE cases (Fig. 1C,F). Overall, the model highlights additional factors that influence the distribution of TBE. The county-level risk assessment map (Fig. 1C) shows more similarity to the incidence rate map (Fig. 1A) than the forest map (Fig. 1B). The model explains the low TBE incidence rate in certain southeastern counties (Bács-Kiskun, Borsod-Abaúj-Zemplén, Szabolcs-Szatmár-Bereg, Hajdú-Bihar counties), although these counties have significant amounts of forest habitats. It appears that the forest habitats in these counties are farther from villages and towns. In addition, the human population is more aggregated in this area and as a consequence, there are fewer, but larger towns and villages than in the western part of the country. Agricultural lands, immediately surrounding and dominating the area around these towns and villages, effectively separate forest habitats from human settlements even further. As a result, the majority of the human population has lower risk of TBE infection from ticks in these counties. Analyzing the performance of the model on a 25×25 km wide grid showed

some improvement compared to the analysis based solely on forest distribution. The amounts of forest habitats surrounding towns, averaged by grid cells (Fig. 1F), reflects the overall distribution of TBE cases in Hungary, showing the higher infection rates in west and north and a lower infection rate in the southeast. The higher correlation coefficient ($r = 0.41$) between the amount of forest habitat and incidence rate (Fig. 2C) compared to the analysis based solely on forests (Fig. 2B) where the correlation was weaker ($r = 0.35$) indicates that a model which incorporates the distribution of both human townships and forest habitat provides a better predictive model.

Correlations between the amount of forested habitat and TBE incidence in the vicinity of townships revealed that not only forest habitat, but the structure (e.g., distribution, land-use practices) of human populations significantly affects the distribution of TBE cases (Table 1). While the incidence rate was standardized by human population density (incidence rate = number of TBE cases/number of local residents), it still shows a negative correlation ($r = -0.16$; Table 1) with population size. This indicates that people who are living in smaller villages (<1000 people) are more likely to work in or visit a forested environment than people from larger villages and towns. Moreover, the negative correlation between population size and the amount of forestation around villages ($r = -0.21$; Table 1) shows that agricultural communities aggregate into larger towns, while communities relying on forestry remain small and scattered.

DISCUSSION

This study tested the hypothesis that particular landscape characteristics could be used to explain the distribution and incidence rate of human tick-borne encephalitis patients in Hungary. First, we demonstrated that the proportion of forested habitats could partially explain the number of reported patients in each county or a smaller geographic area. In a similar way, a spatial model based on the proximity of human habitats and forests explained the observed pattern of TBE incidence in Hungary. It

is important to emphasize that the two working hypotheses and models are based on different assumptions. The first spatial model simply assumed that the amount of forested habitat was the key factor for determining the distribution of TBE. In contrast, the second spatial model put the emphasis on the spatial arrangement of towns, villages, and natural habitats by calculating the risk of infection based on the accessibility/proximity of forested areas to people. This approach is supported by previous studies: conservation biologists regard a high edge/area ratio of protected lands as a sign of degradation because more edge provides better accessibility to the area for invading species (Gustafson and Crow 1994). The spatial model we present incorporates this biological view by putting more emphasis on quality rather than on quantity of forest habitat.

There are additional signs that forest qualities (species composition, size, connectedness) play an important role in shaping the distribution and incidence of TBE. Plots on Figure 2 show a few points that can be regarded as statistical "outliers." While these points fit poorly on the regression line, they tend to line up along a second line with different slope. This specific pattern might indicate that there are alternative stable states and multiple equilibria for either the reservoir species or the virus. In cases of multiple equilibria, the transmission rate of the virus to humans can be significantly different among regions. Presently, there is not enough data to decide whether the poorly fitting data points are outliers or part of a larger pattern; further studies are necessary at a larger geographic scale.

Based on the results, our second important conclusion is that the distribution of human TBE infections can be only partially explained by environment. The distribution of TBE cases is also shaped by variation in human land-use pattern, the distribution of the human populace, and socioeconomic differences among regions. The negative correlation between human population size and the level of forestation in the area shows the human impact on the landscape. Regional differences in land-use not only shape the landscape, but also have an effect on

how the human population is structured. The major economic difference between the eastern part of Hungary (mostly agricultural) and the western part of Hungary (mostly tourism, forestry, and wildlife management) is also responsible for the particular pattern of TBE distribution. While there are no great differences in human population densities between the two regions, the structure of the human settlements differ. In western Hungary, the human population is evenly distributed, while in the east, people aggregate into larger cities surrounded by agricultural areas. Consequentially, while the level of forestation is not drastically different between the regions, there is a much higher contrast in TBE incidence rates between the two regions.

In addition, random stochastic events also mask the effect of environmental factors on the distribution of human TBE infections. Because of the low rate at which ticks transmit the TBE virus to humans, the appearance of human cases in a given year will be strongly influenced by chance. An approximate calculation shows how the low incidence rate of TBE affects the ability of the GIS model to estimate TBE risk at smaller geographic scales. The annual incidence rate of TBE varied between 1.1 and 2.5 TBE patients/100,000 citizens during the period of 1990–2004. Because the average number of local residents in a 25×25 km grid is about 61000 citizens, the expected number of TBE cases per grid cell is 0.67–1.5 cases per year. Obviously, if the incidence rate of TBE is this low, the reported cases will be scattered among villages that can be regarded as "high-risk." Moreover, it is possible that no TBE patients are reported from high-risk areas for years, because of low human population density and low TBE incidence.

For our study, we analyzed the data of patients who had clinically and serologically confirmed TBE. Based on our criteria, the annual number of reported TBE patients is a very conservative estimate of the actual number of TBE infections. A recent randomized serological survey among Hungarians 20 years or older (Ferenczi et al. 2005) indicates that the TBE infection rate is high (5–10%), but many people seroconvert without presenting serious clinical

symptoms, which would require hospitalization. Our decision to apply strict criteria to include data points has certain advantages. Neurological symptoms of TBE usually appear 3 weeks after infection and patients are still able to recall where the infection took place, for example out of town on a trip. The serological confirmations of TBE virus infections were also a necessary step since several other viral infections can cause similar symptoms.

We pooled and analyzed the spatial distribution of TBE cases recorded over four decades. While there are certain pitfalls associated with this method, this step was necessary to obtain adequate statistical power. The two major factors that might have biased the analysis were variation in climate and demographic changes in the human populace during the study period. It appears that climate change has had an effect on the number of TBE cases in Europe (Randolph 2004), but the overall spatial distribution of TBE cases has remained the same in Hungary over the last four decades (Ferenczi et al. 2005). In respect to demographic processes, while the overall birth rate has decreased in Hungary, immigration rates have compensated for the drop in birthrate and the population of Hungary has remained stable over the last four decades. While there are signs of internal migration, yet shifts in the distribution of the Hungarian populace is a very slow process because the middle-aged and older generations have very low mobility (Illés 2000).

Our study strongly supports the original hypothesis and predictions that TBE risk assessments made on simple landscape characteristics are acceptably accurate. Predictions from our study, such as, that the amount and the arrangement of forests can explain the distribution of TBE cases and that they are an important factor influencing disease prevalence, are consistent with the data provided here. However, discrepancies experienced between the observed and predicted values indicate that the entire problem has not been resolved yet. Other ecological and geographic factors (e.g., forest type, soil type), inevitably important, should be included in more complex spatial models.

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