The impact of climatic conditions on the dynamics of tick-borne encephalitis in Slovakia in 2012–2016

Hudáčková V.[1], Pekarčíková J.[1], Peťko B.[2], Mikulová K.[3], Sivčo P.[1], Rusnák M.[1]

[1]Department of Public Health, Faculty of Health Care and Social Work, Trnava University in Trnava, Slovak Republic
[2]Institute of Parasitology, Slovak Academy of Sciences, Košice, Slovak Republic
[3]Slovak Hydrometeorological Institute, Bratislava, Slovak Republic

ABSTRACT

Objectives: The main aim of our work was to analyse the development of the dynamics of tick-borne encephalitis (TBE) in connection with climatic conditions in Slovakia in 2012–2016.
Material and Methods: We performed the analysis based on the data provided by the Epidemiological Information System and the Slovak Hydrometeorological Institute. The study group consisted of 639 patients with confirmed diagnosis.
Results: The highest incidence of TBE was recorded in 2016. The highest standardized incidence rate of TBE was in the districts of the Trenčín, Žilina and Banská Bystrica regions. The relation of TBE to air temperature showed that most cases of TBE were recorded at an air temperature of 10–20 °C during the months of May to October in 2012–2016. The relationship between air temperature and number of days with snow cover and the number of TBE cases proved to be statistically significant (p-value < 0.001). There is a statistically significant difference in the average number of disease cases according to the air temperature category (p-value = 0.03). This disease occurs mainly in districts with an altitude of 200–400 m a. s. l. The dynamics of TBE in Slovakia is two-peaked with a decline in August. The main season of the disease lasts from May to October, peaking during the summer months of June and July.
Conclusion: The results of the study point to a prognosis of the development of the disease in connection with air temperature. Based on the findings that in recent years we have observed a slightly increasing trend of TBE in Slovakia due to climate change, this disease is considered a persistent public health problem.

KEYWORDS

tick-borne encephalitis – standardized morbidity – climate – altitude – seasonality

SÚHRN

Hudáčková V., Pekarčíková J., Peťko B., Mikulová K., Sivčo P., Rusnák M.: Dopad klimatických podmienok na dynamiku kliešťovej encefalitídy na Slovensku v rokoch 2012–2016

Cieľ: Hlavným cieľom našej práce bolo analyzovať vývoj dynamiky kliešťovej encefalitídy (KE) v súvislosti s klimatickými podmienkami na Slovensku v rokoch 2012–2016.
Materiál a metódy: Analýzu sme realizovali na základe údajov poskytnutých Epidemiologickým informačným systémom a Slovenským hydrometeorologickým ústavom. Sledovaný súbor tvorilo 639 pacientov s potvrdenou diagnózou.
Výsledky: Najvyšší výskyt KE bol zaznamenaný v roku 2016. Najvyššia štandardizovaná chorobnosť KE bola v okresoch Trenčianskeho, Žilinského a Banskobystrického kraja. Vzťah KE k teplote vzduchu ukázal, že najviac prípadov KE bolo zaznamenaných pri teplote vzduchu 10–20 °C v mesiacoch máj až október v rokoch 2012–2016. Vzťah medzi teplotou vzduchu a počtom dní so snehovou pokrývkou a počtom prípadov KE sa preukázal ako štatisticky významný (p-hodnota < 0,001). Existuje štatistický významný rozdiel v priemernom počte prípadov ochorenia podľa kategórie teploty vzduchu (p-hodnota = 0,03). Toto ochorenie sa vyskytuje najmä v okresoch s nadmorskou výškou 200–400 m n. m. Dynamika KE na Slovensku je dvojvrcholová s poklesom v auguste. Hlavná sezóna ochorenia trvá od mája do októbra, pričom vrcholí počas letných mesiacov jún a júl.
Záver: Výsledky štúdie poukazujú na prognózu vývoja ochorenia v súvislosti s teplotou vzduchu. Na základe zistení, že v posledných rokoch pozorujeme na Slovensku mierne stúpajúci trend KE v dôsledku klimatických zmien, je toto ochorenie považované za pretrvávajúci problém verejného zdravia.

KĽÚČOVÉ SLOVÁ

kliešťová encefalitída – štandardizovaná chorobnosť – klíma – nadmorská výška – sezonalita

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INTRODUCTION

The existence of tick-borne pathogenic microorganisms has been known since the beginning of the twentieth century [1]. Tick-borne encephalitis (TBE) is a human viral infectious disease involving the central nervous system. TBE is caused by the *tick-borne encephalitis virus (TBEV)*, a member of the family *Flaviviridae*, and was initially isolated in 1937 [2]. Three subtypes of the causative agent are known: the European (Western), the Far Eastern (spring-and-summer encephalitis) and the Siberian [3]. *Ixodes ricinus* is the major tick vector of the dominant subtype in Central and Western Europe, including the territory of Slovakia [4]. Wild animals are a reservoir of infection in nature, ticks on them become infected and accidentally transmit the disease to humans. Infected ticks occur in endemic areas where infected reservoir animals live, such as rodents, deer and foxes [5]. Due to climate change in recent years, they have also reached higher geographical locations, up to altitudes above 500 meters. The correlation between the mean altitude for TBE and the average annual air temperature suggests that the average altitude for TBE responds positively to global warming. Although there are fewer locals living in higher altitudes, these locations are frequently used for recreation and outdoor activities [6]. *I. ricinus* infectivity variations depend on the nature of the local biocenosis in each location. The dynamics of its seasonal variations, that is influenced by climatic factors, determine the annual changes [7]. In Slovakia, natural outbreaks of this disease have long occurred mainly in the west of the country, but they have moved from the southern districts to the north to the Trenčín region. Slovakia has the most reported food epidemics of TBE in Europe due to the frequent rearing of goats and sheep. The most common factors in TBE transmission are unpasteurized goat's and sheep's milk, as well as their products [8].

TBE has become a growing public health challenge in Europe and other parts of the world. The virus causes thousands of cases of meningoencephalitis in Europe annually, with an increasing trend [9]. Therefore, TBE is considered an epidemiologically serious disease. The increase may be attributed to a complex network of elements, including climatic, environmental and socio-economic factors. Immunization is the best protection against this disease [10, 11].

Slovakia is located in middle latitudes experiencing four alternating seasons. The distance from the sea creates a transitional climate between maritime and continental. The western part of Slovakia is influenced by oceans and in its eastern part the continental moderate climate prevails. The climate in Slovakia is mostly determined by altitude too [12]. The western current brings moist ocean air of moderate latitudes from the Atlantic Ocean. Continental air of moderate latitudes brings warm, sunny and less humid summers and cold winters with low total precipitation. Climate change due to global warming in Slovakia was manifested mainly by an increase in the average annual air temperature, as well as a significant decrease in relative humidity [13, 14].

To describe the epidemiological situation of TBE and to determine the relationship between the number of cases of TBE and climate conditions in Slovakia in 2012–2016, we used data from the Epidemiological Information System and the Slovak Hydrometeorological Institute to identify the dynamics of TBE due to climate change. Such a comprehensive analysis will form the basis for the design of effective interventions focusing on estimating the development of the disease in relation to climate change in risk areas and on increasing the importance of TBE vaccination.

MATERIAL AND METHODS

The study group consisted of 639 patients with a confirmed diagnosis of TBE, of which 384 men (60%) and 255 women (40%). The research sample comprised all cases reported to the Epidemiological Information System in Slovakia for the period from 1st January 2012 to 31st December 2016. The design of the epidemiological study is an ecological study.

In this study, we described the incidence of the disease using the epidemiological indicator notified new cases, which were used as a proxy for the incidence. We also focused on the occurrence of TBE in Slovakia in connection with climate change and air temperature in the period when cases arose based on measurement units of monthly average air temperature, monthly average air relative humidity, number of days with precipitation and number of days with snow cover in regions of the SR. Data on TBE cases provided by the database from the Epidemiological Information System was collected in connection with the following variables: case classification, districts of the SR (NUTS 3), regions of the SR (NUTS 2), date of receipt of the report, age of the patient and season. We obtained data in connection with climatic conditions and geographical characteristics of the regions (NUTS 2) from the Slovak Hydrometeorological Institute.

We calculated the standardized incidence of notified cases based on demographic data on the age structure and mid-year population of Slovakia in 2012–2016, which we obtained from the STATdat. database available online from the Statistical Office of the Slovak Republic [15]. To standardize the incidence rate, we used the European standard population from the Revision of the European Standard Population published on the Eurostat website [16]. From the obtained data on TBE cases in individual age categories, we calculated crude and standardized incidence of notified cases in districts and regions of the SR and confidence intervals using direct standardization for age using R-Project software. Subsequently, we compared estimated incidence among territorial units (NUTS 2,3).

Crude incidence formula:
Crude incidence rate = number of cases/mid-year population . 100 000

Standardized incidence formula:
Standardized incidence rate = crude incidence rate . European standard population/100 000

We assigned individual stations to the districts (NUTS 3) in which they were located based on the map of meteorological stations in the SR published on the SHMI website. Subsequently, we subtracted the average value of the incubation period of TBE disease (10–11 days) from the case reporting dates to minimize the difference between the reporting date and the case origin date. Data on daily and monthly average air temperature, monthly average relative humidity, number of days with precipitation, number of days with snow cover and altitude were entered into an Excel database based on available codes of meteorological stations. The association between the average air temperature in each month and the number of cases was analysed by the correlation analysis. To analyse the number of cases by the temperature category the ANOVA test was used. Statistical analysis was conducted using R-Project software [17] and the level of confidence was 0.5.

To understand the inter-relationships between new cases of TBE and meteorological variables, a multiple-correlation analysis was carried out. The value of multiple correlation coefficient varies between 0 and 1. The higher values express the stronger association. They indicate higher predictability of the dependent variable from the independent variables, with a value of 1 indicating that the predictions are exactly correct and a value of 0 indicating that no linear combination of the independent variables is a better predictor than is the fixed mean of the dependent variable [18].

RESULTS

By comparing the standardized incidence of notified cases of tick-borne encephalitis in 2012–2016, we found that the highest incidence rate 3.12 per 100,000 inhabitants (95% CI 2.67–3.63) was in 2016, followed by 2013 with incidence rate 2.99 per 100,000 inhabitants (95% CI 2.55–3.5) and 2014 with incidence rate 2.13 per 100,000 inhabitants (95% CI 1.75–2.56). On the contrary, the lowest incidence rate 1.51 per 100,000 inhabitants (95% CI 1.2–1.87) was recorded in 2015.

In terms of age, a higher age-standardized incidence of notified TBE cases has been reported in adult age groups than in children and the elderly for the long term. The highest age-standardized incidence of notified cases 0.43 per 100,000 inhabitants was recorded in 2016 in the age category 40–44 years, similar values were also recorded in the age categories 45–50 years and 55–59 years. In the age categories 70–89 years, not a single case of TBE was recorded in 2015. In the age category of 0-year-olds, only 1 case was reported for the entire monitored period with an incidence 0.02 per 100,000 inhabitants in 2014.

The regions with a long-term increased incidence of notified cases of TBE include the Trenčín, Žilina and Banská Bystrica regions. The Trenčín and Žilina regions dominated during 2012–2014. In 2015, it was mainly the Žilina region and in 2016, the incidence of notified TBE cases in the Banská Bystrica and Košice regions increased significantly. The Bratislava and Trnava regions report the lowest incidence rate of notified cases every year (Table 1).

Figure 1 shows the increased incidence of notified TBE cases in the northern districts of Slovakia. The highest values of standardized incidence of notified cases are in the districts of Považská Bystrica (PB), Púchov (PU), Bytča (BY), Žilina (ZA) in the north of the SR, and in the south, it is mainly Detva (DT), Zvolen (ZV) and Krupina (KA). For the entire monitored period, the highest incidence rate 58 per 100,000 inhabitants (95% CI 37.8–87.26) was in the district of Púchov in 2013. In

Table 1. Standardized incidence rate of TBE by regions of the SR in 2012–2016

	2012		2013		2014		2015		2016	
Region	**St.I.**	**95% CI**	**St. I.**	**95% CI**	**St.I.**	**95% CI**	**St.I.**	**95% CI**	**St.I.**	**95% CI**
Bratislava	0.48	0.1–1.6	0.17	0–1.16	0.89	0.28–2.24	0	0	0.25	0.03–1.31
Trnava	0.73	0.2–2.22	0.8	0.26–2.16	0.69	0.18–1.98	0.16	0–1.18	0.54	0.11–1.74
Nitra	1.13	0.49–2.39	1.59	0.79–2.95	2.14	1.16–3.66	1.64	0.85-2.96	1.53	0.76–2.84
Trenčín	4.23	2.78–6.34	10.96	8.48–14,00	5.45	3.74–7.75	2.13	1.09–3.81	3.38	2.09–5.27
Žilina	4.69	3.18–6.86	6.21	4.51–8.49	4.99	3.48–7.06	3.62	2.37–5.41	3.6	2.32–5.4
B. Bystrica	3.2	1.83–4.82	3.48	2.2–5.32	1.96	1.04–3.45	3.32	2.1–5.08	8.93	6.81–11.6
Košice	0.66	0.21–1.79	1.54	0.14–1.55	0.37	0.08–1.30	0.72	0.26–1.74	6.4	4.44–8.11
Prešov	0.53	0.14–1.61	1.26	0.53–2.41	1.8	0.49–2.21	0.49	0.13–1.41	0.37	0.08–1.22

St. I. – standardized incidence rate, CI – confidence interval.

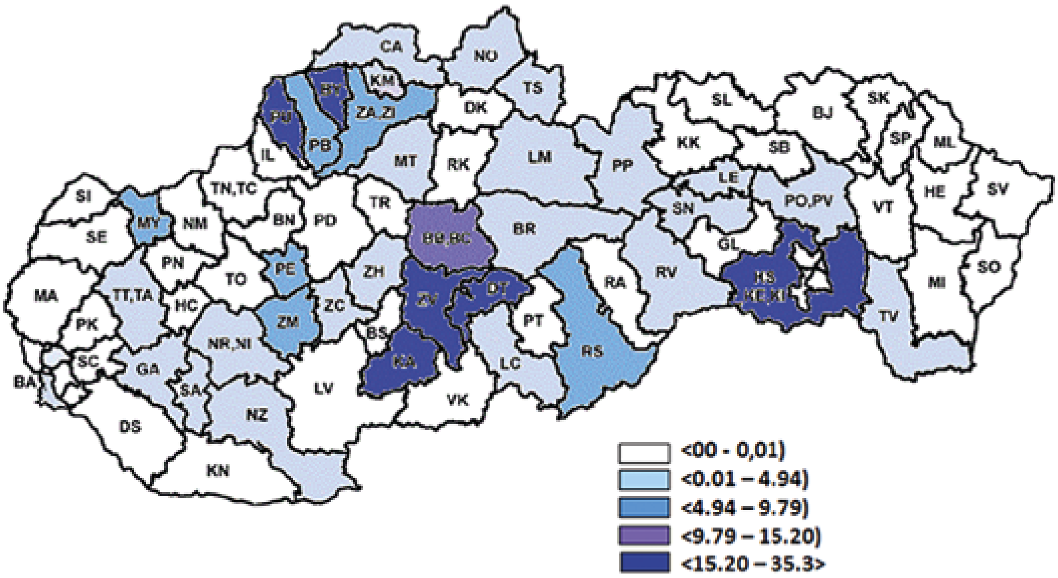

Figure 1. The map of standardized incidence rate of TBE by districts of the SR in 2016.

Source: EPIS

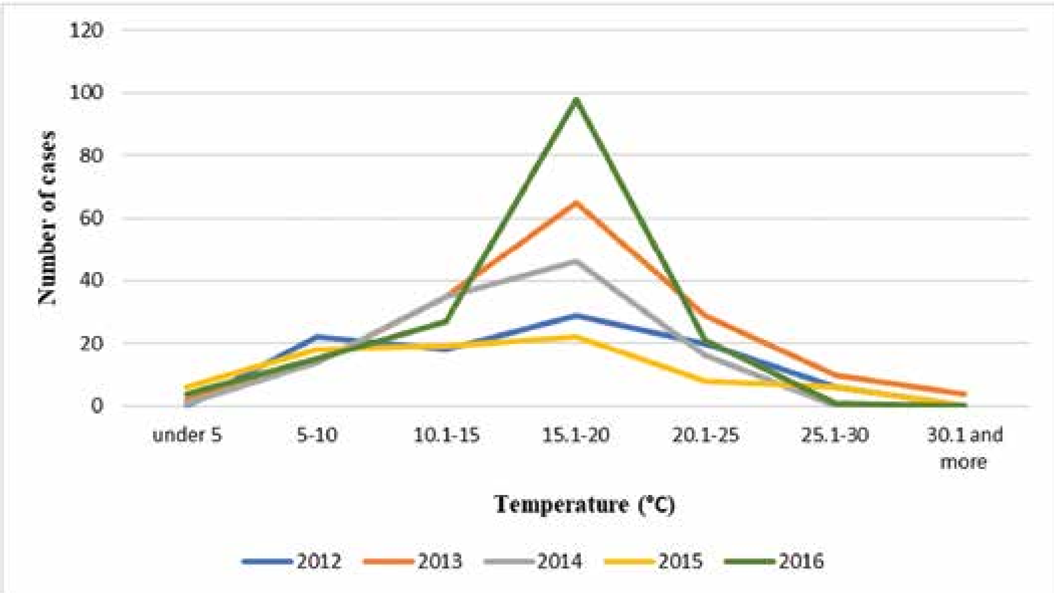

Figure 2. Number of TBE cases depending on the air temperature in 2012–2016.

Source: SHMI (1.10.2019)

this year, there was also an increase of incidence rate 14,17 per 100,000 inhabitants (95% CI 4.58–37.54) in the district of Kysucké Nové Mesto (KM). In 2012, a high incidence rate 19.31 per 100,000 inhabitants (95% CI 10.46–33.57) was recorded in the Lučenec district (LC) due to the foodborne infection. In 2015, the overall incidence of TBE was reduced, even in the northern districts. In the districts of Trnava and Bratislava regions, the incidence of TBE was low during the whole monitored period, when the incidence rate did not exceed the value 3.25 per 100,000 inhabitants (95% CI 0.39–13.43) in the district of Malacky (MA) in 2014. On the contrary, increased values in 2014 took place in the districts of the Nitra region. A significant increase of the incidence rate of TBE was observed during the 2016. The highest incidence was recorded in eastern Slovakia in the district of Košice-okolie (KS) with an incidence rate 35.3 per 100,000 inhabitants (95% CI 25.33–48.69), due to extensive foodborne epidemic from the consumption of contaminated sheep cheese. In this year, a similar incidence rate was observed in the district of Detva (DT). Moreover, compared to the previous years, high incidence rate was observed in the district of Rimavská Sobota (RS) (5.87 per 100,000 inhabitants; 95% CI 1.9–14.78).

Figure 2 shows how the dynamics of TBE in Slovakia depended on the air temperature in individual years during the 5-year monitoring period. The ticks start to be active at air temperature above zero, optimally from 5°C, when a significantly increased incidence was recorded in all years. Most cases of TBE occurred at an air temperature of 10–20 °C. The incidence of TBE at air temperature values from 25.1 °C decreased significantly in all years except 2015, when it started to decrease from 20 °C, which causes the lower activity of ticks at very high temperatures. In 2013, 4 cases of TBE were observed at tropical temperatures (above 29 °C).

Most cases of TBE took place in districts of the SR with an altitude 200–400 m a. s. l. (73%). 16% of TBE cases were reported in districts with an altitude of 100–200 m a. s. l. The lowest number of cases (11%) was recorded in districts with a location above 400 m a. s. l., but since 2012 the number of cases has increased at higher altitudes by 2016. From 400 m a. s. l. the number of cases has decreased significantly in all years, but in terms of the 5-year interval, the trend of occurrence at higher altitudes is growing.

There is a statistically significant relationship between air temperature and the number of TBE cases (p-value < 0.001). This is a moderately positive correlation ($R = 0.67$). We assume that the correlation strength is moderate as this relationship is linear only to a certain point. The number of cases increases in direct proportion to an increasing air temperature up to 20 °C and then begins to decrease. The ANOVA test demonstrated statistically significant difference in the average number of notified cases according to the air temperature category (p-value = 0.03). Statistically significant difference in the average number of cases by air temperature was confirmed between the temperatures above 20°C (24.2 cases) and 10 °C to 20 °C (78.8 cases), as well as between 10 °C to 20 °C (78.8 cases) and below 10 °C (19.2 cases).

The results of multiple correlation analysis are shown in Table 2. We found that there is a statistically significant relationship only between air temperature and the number of days with snow cover and the number of TBE cases (p-value < 0.001). From the output, we can see that the TBE case variable correlates the most with the temperature variable with the value of multiple correlation coefficient 0.61, that could be expected from a logical point of view. The snow variable shows a lower relationship coefficient ($R = 0.36$). A positive correlation was confirmed (p-value < 0.001) between the climatic factors of precipitation and air humidity ($R = 0.54$) and negative correlation between snow and temperature ($R = 0.54$); temperature and air humidity ($R = 0.48$). It means that as the number of days with precipitation increases, air humidity increases, but as the air temperature increases, the air humidity decreases. With decreasing air temperature, there is higher number of days in month with snow cover.

DISCUSSION

The results of the study confirm relations between climatic conditions and incidence of TBE in Slovakia in 2012–2016. Also, our results point to an increased incidence of TBE in northern Slovakia.

Based on data from Annual Epidemiological Reports of The European Centre for Disease Prevention and Control, there has been a decline in notification rate in 2015 compared to previous years in Slovakia and surrounding countries. The highest rates were observed in the Baltic States. The overall EU/EEA notification rate increased in 2016 compared with 2015 (0.4). In 2016, increases of over 40% in the notification rate were reported for several countries, including Slovakia. In Slovakia, this was caused by several epidemics after the consumption of unpasteurized dairy products. The overall EU/EEA notification rate decreased slightly in 2017 compared with 2016 (0.6). A 55% decrease in notification rates was observed in Slovakia [19–21].

A 2016 study in the Netherlands presents a case of endemic TBE in a 44-year-old man that occurred in June 2016 in the eastern part of the Netherlands in an area where TBE strain genetically different from common TBE strains in Europe was detected on ticks [22].

In Denmark, tick-borne encephalitis is endemic only on the island of Bornholm with an incidence 4 per 100,000 inhabitants per year. A 2019 study in Denmark reported three clinical cases of TBE in patients hospitalized within one month and all living at the border of the same forest, Tisvilde Hegn, North Zealand. New TBE viruses have been identified in tick nymphs obtained around a playground in the forest Tisvilde Hegn [23].

With an annual incidence 8–15 per 100 000 inhabitants in the period 2009–2013, Slovenia had one of the

Table 2. Multiple correlation coefficients of climatic factors and TBE cases

	Temperature	Humidity	Snow	Precipitation	TBE cases
Temperature	1	0.48	0.54	0.05	0.61
Humidity	0.48	1	0.01	0.54	0.12
Snow	0.54	0.01	1	0	0.36
Precipitation	0.05	0.54	0	1	0.13
TBE cases	0.61	0.12	0.36	0.13	1

highest reported incidences of tick-borne encephalitis in Europe [24].

In Austria, the overall incidence of TBE has remained constant, but new severely affected endemic regions have emerged in the alpine valleys in western regions. At the same time, the incidence is declining in lowland areas in the northeast of the country. There is no evidence of a transition to higher altitudes of infected sites in traditional TBE zones, but the average altitudes of some newly established endemic areas in the west are significantly higher [25]. The vaccination rate against TBE in the general population is 82% in Austria, which is the highest in the world [26].

According to a 2018 study in the Czech Republic, the ratio of TBE cases to nymphs was highest in the summer-autumn period, although the number of nymphs peaked in the spring-summer period. However, this trend has changed during the extreme weather events of floods and abnormally high temperatures, suggesting that climate change is affecting the occurrence of TBE. The relative proportions of nymphs and weeks in which they were found were higher in summer and autumn compared to spring and summer at temperatures above 5 °C and standard daily and weekly average air temperatures above 15 °C [27].

Based on the results of the study in China in 2017, 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. 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, 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 [28]. Another study from China in 2017 point to the statistical analysis of gridded geographic and environmental factors and TBE incidence. It shows that the TBE patients mainly occurred during spring and summer and that there is a significant positive spatial autocorrelation between the distribution of TBE cases and environmental characteristics. The impact degree of these factors on TBE risks has the following descending order: temperature, relative humidity, vegetation coverage, precipitation and topography [29]. In our study, a correlation between the occurrence of TBE and air temperature and number of days with snow cover in month was confirmed.

TBE cases in EU countries generally show a seasonal peak in July or early August. In 2017, cases were reported more seasonally, with most confirmed cases (94.7%) being reported from May to November, representing a 2-peak distribution, with the first peak in August and later in October 2017 [19]. In Slovakia, the dynamics of TBE is usually one-peaked or two-peaked (after a decline in August). The one-peaked represents the year 2013 and the two-peaked other years. The autumn peak in 2012, 2014 and 2016 was relatively the same. In 2012, 2014 and 2016, the start of the TBE season was early in March and April. On the contrary, in 2013 and 2015, the late start of the season in May was recorded. The main season of the disease lasts from May to October, peaking during the summer months of June and July. In the winter months, TBE is almost non-existent due to the inactivity of ticks at low air temperatures.

According to the Decree of the MH of the SR no. 585/2008 Coll., vaccination against TBE is mandatory or recommended for persons who are professionally exposed to increased danger. It is also recommended to be vaccinated if you live in endemic areas or before traveling to such areas. In Slovakia, vaccination against TBE is low, probably because of low awareness of people of this vaccine. In addition, personal protection against ticks includes the application of tick repellents; wearing protective clothing, with long sleeves and long trousers tucked into socks treated with an appropriate insecticide; inspecting the body for ticks after outdoor activities and removing ticks with tweezers or forceps; and avoiding consumption of unpasteurized dairy products in risk areas [5].

In our study, we analysed reported cases of TBE that were medically recorded. However, many cases of TBE could be asymptomatic or treated without medical assistance, thus not reported. We consider the difference between analysed and real number of cases the first limitation to our work. Another possible limitation on the relevance of the results is the fact that individual cases may have occurred in places other than the districts where they were reported by the attending physician. When evaluating data provided by SHMI on climatic conditions and altitude, we used data only from districts in which there are meteorological stations. Among them were missing data from the days when the stations were not operating. The measured values of air temperature and precipitation in the stations did not have to be completely identical with the real values at the specific place of origin of the case, which could lead to slight deviations in these values.

To confirm the more detailed connection with climate change, it would be appropriate to extend the monitoring period to 10–20 years, which would lead to a more relevant analysis of the epidemiological situation of TBE focusing importance of TBE vaccination. The resulting analysis could be the basis for creating a mathematical model to estimate the development of the disease in relation to climate change and create an application that would, based on available data (including this study), draw attention to increased risk in this area and prevention options.

CONCLUSIONS

The impact of climate change due to global warming on the incidence of tick-borne encephalitis in the region depends on how region-specific climate changes affect tick distribution and the dynamics of *tick-borne encephalitis virus* transmission. Therefore, it is still possible to expect an increase in cases of tick-borne encephalitis in the northern areas of Slovakia, which requires a continuous solution to the issue. The results of the study point to a prognosis of the development of the disease in connection with air temperature. Based on the findings that in recent years we have observed a slightly increasing trend of TBE in Slovakia due to climate change, this disease is considered a persistent public health problem.

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Conflict of interests
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Adresa pro korespondenci:
Mgr. Vladimíra Hudáčková
Fakulta zdravotníctva a sociálnej práce
Trnavská universita v Trnave
Univerzitné námestie 1
918 43 Trnava
Slovenská republika
e-mail: v.hudackova@gmail.com