Potential drivers of human tick-borne encephalitis in the Örebro region of Sweden, 2010-2021

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Abstract

Incidence of tick-borne encephalitis (TBE) has increased during the last years in Scandinavia, but the underlying mechanism is not understood. TBE human case data reported between 2010 and 2021 (N = 81) was aggregated into postal codes within Örebro County, south-central Sweden, along with tick abundance and environmental data to analyse spatial patterns and drivers of TBE. We identified a substantial and continuing increase of human TBE incidence in Örebro County during the study period. Although the spatial pattern varied between years, spatial cluster analyses showed significant hotspots (higher number of cases than expected) in the southern and northern parts of Örebro County, whereas a cold spot (lower number of cases than expected) was found in the central part comprising Örebro municipality. Generalised linear models showed that the risk for residents of acquiring TBE increased by approximately 141% for every percent increase in the proportion of wetland forest, however models had relatively low goodness of fit ($R^2 < 0.25$). Results suggest that incidence of TBE in Örebro County is spatially clustered, however variables used in this study, i.e., forest cover, water, tick abundance, sheep as indicator species, alone do not explain these patterns.

Introduction

Tick-borne encephalitis (TBE) is a severe infection, affecting the central nervous system and can cause lesions in the brain and spinal cord in humans[1]. TBE is caused by TBE virus (TBEV) belonging to the genus flavivirus of the family Flaviviridae, and consists of three subtypes: European, Siberian, and Far Eastern TBEV[1–3]. TBEV is predominantly tick-borne but has been known to infect via intake of unpasteurised milk products from infected livestock[2–4]. The hard tick *Ixodes persulcatus* is the main vector of the Siberian and Far Eastern subtype, whereas the closely related *Ixodes ricinus* is the main vector for the European TBEV subtype[2]. Morbidity and mortality differ between subtypes, with Far Eastern subtype causing more severe disease and a case-fatality of up to 20–40%[2,3] compared to milder symptoms and case-fatalities of 1–2% for the European subtype and 6–8% for the Siberian subtype[3]. It has however been speculated that this difference in disease severity and case-fatality may at least partly be explained by other factors such as differences in clinical alert and reporting routines which varies between countries[2,5]. As there is no specific antiviral treatment for TBE, active immunisation is the most effective protection against infection with TBEV[4]. In Sweden, recommendations for vaccination vary between geographic areas and counties according to the epidemiological situation, following the recommendations from the Public Health Agency of Sweden[6] and the county medical officer for communicable diseases.

Incidence of TBE has been increasing globally during the last decades[2,4] and since 2012, the European Centre for Disease Prevention and Control (ECDC) included TBE in the list of notifiable diseases in the European Union[7]. The increase in TBE incidence is likely due to several factors such as changes in climate[8,9], as well as changes in the availability of tick host species[10,11], which all impact tick life cycle and thus tick distribution[11,12]. In Europe, *I. ricinus* has expanded its geographical range northwards and to higher altitudes[9,11, 13–15]. Consequently, TBEV has also been found at higher altitudes[14,16] and in areas that were previously non-endemic[8,17]. In Sweden, since 2004, all human TBE cases are notifiable by law, which provides a reliable knowledge of distribution. The endemic area for European TBEV subtype was first described in the Stockholm area[18] which later expanded to provinces in the south-west and the south of Sweden[13]. TBEV seems to have a focal distributional pattern in endemic areas as the virus is not uniformly present in the tick population[19,20], and thus the risk for TBE infection is restricted to small geographical foci[21]. During 2021, a record high of 533 TBE cases were reported to the Public Health Agency of Sweden, representing an incidence of 5.1 cases per 100.000 inhabitants, where most of the cases were autochthonous[6]. Although the geographical distribution of TBE cases in Sweden has expanded, most of the cases are reported in southern and central Sweden[6]. In Örebro County sporadic cases of TBE were reported until 2014 followed by an increase in reported cases over the last years. Since 2015 vaccination is recommended for people at risk of TBEV infection (local county recommendations from the county medical officer for communicable diseases).

The geographical distribution of *Borrelia burgdorferi* and TBEV corresponds to the geographical range of their vectors. However, *B. burgdorferi* demonstrates a fairly even distribution within the range of its vector whereas TBEV shows a patchy distributional pattern, which suggests that other factors may play a part in restricting the range of TBEV[2,22]. Studies from arctic Russia and Italy found that the increase in TBE incidence was correlated with changes in (increasing) air temperature[23], forest structure and roe deer density[24]. In addition, other studies suggest that changes in human activities, such as use of forest resources and changes in agricultural practises, are the ultimate causes of increasing TBE incidence and that these activities are impacted by differences in socio-economic circumstances thus causing different epidemiological patterns in different countries[25,26].

Several studies have found TBEV specific antibodies in cattle, goat, and sheep milk[27–29] and it has been argued that livestock kept on natural pastures and exposed to ticks can be used as sentinels for TBEV distribution and the emergence of new TBEV foci[29]. Wallenhammar et al.[29] analysed milk and colostrum from sheep and goats and were able to identify three previously unknown TBEV foci within Örebro County, based on TBEV specific antibodies found within the milk. Thus, analysing milk from pasture-raised livestock may be an interesting and non-invasive surveillance method for revealing TBEV[29].

In this study we investigated both temporal and spatial patterns as well as potential drivers of TBE usingregistered human TBE case data from Örebro County in South-Central Sweden. We present maps of human TBE prevalence and identify areas with high or low clustering of TBE cases within the county. In addition, we explore whether tick abundance, land cover types, and presence of sheep as a sentinel for TBEV prevalence and distribution[29] can explain human TBE spatial patterns and whether handling of sheep could be associated with human TBE cases within the county.

Methods

Study area and postal codes

The study was conducted in Örebro County situated in South-central Sweden (59.5350° N and 15.0066° E), a total area of 8,545.6 km^2. Örebro County is named after its capital city Örebro and consists of 12 municipalities (Fig. 1) accounting for approximately 305,000 residents. Örebro County is surrounded by four major freshwater lakes, having borders with two of them (Vättern and Hjälmaren). The southern part of the county is characterised by agriculture and hemiboreal forests and a climate in-between oceanic and continental with warm summers and cold winters, with mean temperatures below 0 C during approx. December to February. The northern part of the county is within the boreal zone, agriculture is sparse, and the climate is slightly cooler year-round.

We obtained a shapefile of 291 postal codes in Örebro County from ArcGIS online data[30], which contained data on area and population size of each postal code.

TBE data

We obtained data on human TBE cases reported from 2010–2021 through the surveillance of the Communicable Diseases Register, called SmiNet, maintained by the Public Health Agency of Sweden[6]. A total of 118 TBE cases were reported in Örebro County within the study period. However, we only included data where the probable place of infection, given in the clinical reports, (or patient home address, see below) happened within Örebro County, i.e., postal codes were within the Örebro region. This left us with 81 TBE cases. In 12 of these cases that happened within Örebro County the postal code of the infection site was not known, and thus we used the postal code of these patients' home address (as all 12 patients resided within Örebro County). We combined the TBE data with the Örebro County postal code shapefile, and based on the postal code population sizes, we calculated the period prevalence of TBE for each postal code in Örebro County both for individual years and summarised over all 12 years. Furthermore, we calculated the TBE incidence/100,000 inhabitants each year (over all postal codes), assuming constant human population size over the 12 years, using human population data from the shapefile of postal codes in Örebro county from ArcGIS online data[30]. All methods were performed in accordance with the relevant guidelines and regulations.

Cluster analyses

To explore potential spatial clustering within individual postal codes in Örebro County, we ran a simple χ^2 test case prevalence data for the summarised years to investigate whether cases were randomly distributed over the different postal codes or clustered within specific postal codes. To identify potential spatial clusters of human TBE cases across postal codes, we used the program SatScan[31] and the package rsatscan[32] in R 4.1.2[33]. We performed spatial scan analyses for summarised years and for separate years with an elliptical scanning window, using the Poisson probability model, where the number of cases within our study area is assumed to be Poisson-distributed, according to a known underlying population at risk (human population within the different postal codes). We used a maximum spatial window size of less than or equal to 50% of the total population at risk. The method identifies significant spatial clusters where there is a higher (hotspots) or lower (cold spots) incidence of cases within the scanning window than expected based on the Poisson probability of the entire study area. SatScan then reports the ratio of observed number of cases within a cluster to the expected number (ODE). Interpretation of an ODE of 1 means that there is no difference from the expected number of cases. We used the Gini coefficient[34] for cluster selection, as it measures the heterogeneity of the cluster collection, aiding us in which clusters to report (multiple smaller clusters versus large joint clusters).

Tick abundance data

As a part of the RåFäst project ("The interplay between ticks, tick-borne diseases and wildlife in Sweden", the Swedish University of Agricultural Sciences (SLU) at Grimsö Wildlife Research Station[35]), a tick abundance study was conducted in the southern parts of Örebro County. Questing ticks were collected using the cloth dragging technique[35]. At each site a cloth was dragged 200 m in two directions (north/south and east/west), i.e., 400m in total, and after every 50 m, the cloths were controlled for ticks. We calculated the mean abundance of tick larvae, nymphs, and adult ticks (both combined as total number of ticks and separately for each life stage and sex) in each postal code encompassed by the RåFäst study by averaging over multiple sites within each postal code. All ticks detected were morphologically identified to species by trained technicians and all were classified as *I. ricinus*.

Sheep data

As sheep can be used as a potential sentinel for TBEV prevalence[29], we were interested in investigating the relation between human TBE incidence and the presence of sheep farms in Örebro County. We obtained location data on all sheep farms within Sweden, provided by the Swedish agricultural agency[36]. We calculated the total number of sheep farms for each postal code within Örebro County.

Landscape data

As forest type and water may affect tick abundance[37], we looked specifically at these landscape variables. We obtained land cover data[38] for Örebro County from The Swedish Environmental Protection Agency[39] as a raster image with a resolution of 10 x 10 metres. This raster image contained 25 different land cover classes, ranging from agricultural fields to open water, waterways and forests. We overlaid this raster with the Örebro postal codes shapefile and calculated the number of 10 x 10 m water (lakes, rivers and streams) and forest raster cells within each postal code. To obtain land cover proportions, we multiplied the number of calculated water and forest raster cells by 100 (as each raster cell in the NMD raster represents 100 m^2) and calculated the respective proportions within each postal code using the postal code area provided by the shapefile. We stratified and merged different forest types within the NMD raster into two forest types: wetland forest and dry forest and total forest (dry forest + wetland forest, Table 1). Dry forests here represent mainly dry coniferous forest types with a less abundant shrub layer, while wetland forests contain both coniferous and deciduous moist forest types with abundant shrubs layers of bilberry (*Vaccinium myrtillus*), lingonberry (*Vaccinium vitis-idaea*), heather (*Calluna* *vulgaris*) and mushrooms (Fungi), whereof several species are popular for human consumption (*Cantharellus sp. and Boletus sp.*, among many other).

Table 1
Land cover definition of the Swedish land cover data[38] and stratification into water, dry- and wetland forest.

Stratification	NMD description
Water	Lakes and streams
Dry forest	Broadleaved forest (not on wetland)
	Mixed coniferous forest (not on wetland)
	Mixed coniferous and deciduous forest (not on wetland)
	Mixed trivial deciduous and broadleaved forest (not on wetland)
	Pine forest (not on wetland)
	Spruce forest (not on wetland)
	Trivial deciduous forest (not on wetland)
Wetland forest	Broadleaved forest (on wetland)
	Mixed coniferous forest (on wetland)
	Mixed coniferous and deciduous forest (on wetland)
	Mixed trivial deciduous and broadleaved forest (on wetland)
	Pine forest (on wetland)
	Spruce forest (on wetland)
	Trivial deciduous forest (on wetland)

Statistical analysis

To investigate the trend in yearly incidence/100,000 inhabitants between 2010 and 2021, we used R 4.1.2[33] to fit a logistic and an exponential growth model to our data. Changes in annual incidence is most likely determined by its relationship with one or more external factor (such as tick abundance, available blood hosts etc.). When such factors are unlimited, incidence rate can be described by an exponential growth model that would be the simplest model to describe an increase in the number of TBE cases that is directly proportional to incidence at each point in time, with no sign of levelling off. Alternatively, a logistic model could be fitted, implying that incidence is approaching an asymptote as there is some sort of intrinsic regulatory (depressing) response to the number of TBE cases as incidence increase. Here we test for the best fit of either one of these two models to investigate potential trends in the development of future TBE incidence in Örebro County.

To identify potential drivers of TBE occurrence, we ran our statistical analyses as the prevalence of TBE cases over the years (2010–2021), calculated as the number of cases out of the total population within a postal code. Due to the limited number of cases within the region, we did not calculate yearly prevalence but summarised prevalence over all the 12 years. To test for associations between human TBE cases and landscape and sheep farms, we used generalised linear models (GLMs) with a logit link assuming a quasibinomial distribution. A quasi-binomial distribution adds an extra parameter (dispersion parameter) compared to the binomial distribution to describe extra variance in the data that cannot be explained by the binomial distribution alone. First, univariate GLMs were used to examine whether there was an association between the dependent and independent variable and thereafter we ran a multivariate model with all significant independent variables from the univariate tests. We used R 4.1.2[33] for statistical analysis. When testing for associations between TBE and tick abundance, only postal codes with estimates of tick abundance were included in the GLMs. For multivariate models, we used backwards stepwise elimination by removing the variable with highest P-value and re-running the GLM. We also performed an analysis of variance (ANOVA) between the original and the reduced model to check whether a reduction in the residual sum of squares (SS) was statistically significant or not and compared Quasi AIC-values (QAIC) between models. We checked the final model for spatial autocorrelation by plotting the residuals, calculating Moran's I and looking at a Spline (cross-) correlogram. The latter estimates spatial dependence as a continuous function of distance and shows the correlation of pairs of spatial observations with increasing distance (lag) between them[40].

Results

Distribution and incidence of TBE cases within Örebro County

The 81 human TBE cases reported between 2010 and 2021 were distributed over 46 different postal codes. The annual incidence of TBE cases in Örebro County showed a substantial increase over a 12-year period, from 0.7 cases/100,000 inhabitants (n = 2) in 2010 to 7.3 cases/100,000 inhabitants (n = 22 cases) in 2021 (assuming constant population size of 303,348 inhabitants obtained from the postal code shapefile from ArcGIS online data[30]) (Fig. 2). The prevalence and clustering of TBE cases were depicted at the postal code level in Örebro County (Fig. 3). TBE cases appeared to be located in the south of the county mainly in postal codes belonging to Laxå municipality and in the north of the county in postal codes belonging to Lindesberg municipality.

Cluster analyses

The χ^2 test to detect spatial clustering within individual postal codes showed that the case prevalence data (summarised over all 12 years) were not randomly distributed (χ^2_{290}= 422.57, $P < 0.0001$) thus indicating that TBE cases were clustered within individual postal codes in Örebro County. For clustering across postal codes, the SatScan analysis detected significant clusters for the combined years 2010–

2021 in the south-western and north-eastern part of the county, with a cold spot in the central Örebro County (Fig. 3). For individual years, only the years 2018–2021 had significant clusters with hotspots found in the southern part of the county in 2018, 2019 and 2021 but in the northern part in 2020. A cold spot was found around central Örebro County in both 2020 and 2021 (Fig. 4).

Tick abundance, forest type and sheep farms

The RåFäst project had sampled questing ticks from 110 sites within 107 postal codes in southern Örebro County. The total sum of larvae, nymphs and adult ticks was 3,144, where the average abundance for all ticks for each postal code spanned from 0–200 ticks. The total abundance of larvae, nymphs, adult females, and males was 1,185 (found in 41 postal codes), 1,819 (found in 102 postal codes), 69 (found in 39 postal codes) and 71 (found in 45 postal codes) respectively. Among the tick sampling sites, 73 were located in dry forest (mean total tick abundance = 33.95), and 2 in wetland forest (mean total tick abundance = 7). The relative proportions of dry- and wetland forest within the study area were 89% and 11%, respectively. Highest overall abundance was found in postal codes within the municipalities Lekeberg, Laxå, Hallsberg, Kumla, Askersund and Örebro (Supplementary File, Fig. S1).

The total number of sheep farms in Örebro County was 487 farms within 105 postal codes and the farms were evenly distributed across all postal codes with highest numbers (12–14 farms) in postal codes within Lindesberg and Nora municipalities in the north and Örebro municipality in the central part the county (Supplementary File, Figure S2)

Landscape variables

Örebro County consisted of 16.1% forest, which comprised 14.7% dry forest and 1.4% wetland forest, with less forest in postal codes bordering the central city of Örebro. Water in the form of lakes, rivers and streams made up 3.7% of the county. Supplementary Figure S3 shows the distribution of forest and water proportions across the different postal codes in Örebro County.

Statistical analysis

Fitting both an exponential- and a logistic model to our TBE incidence data, indicates that the logistic model had stronger support compared to the exponential model (R^2 = 0.84 vs 0.72), implying that incidence will continue to increase but ultimately reach an asymptote – according to the logistic model here at approximately 10 cases every year/100,000 inhabitants in Örebro County (Fig. 2B). This may however not be accurate as it will also depend on the extend of immunisation within the county.

The dispersion parameters for all GLM models were larger than 0, suggesting that the quasibinomial distribution fitted our data better than a simple binomial distribution (Table 2). The univariate tests showed that the incidence of human TBE was not significantly associated with tick abundance for any life stage or combined number of ticks. However, we found a significant association between human TBE incidence and the number of sheep farms (Table 2). When separating forest land cover into dry and wetland forest, we found significant associations between both types of forest and incidence of human

TBE (Table 2). Combining dry and wetland forest into an all-forest category also showed a significant association with incidence of human TBE (Table 2). We suspected that the effect of sheep farms could be related to them being mostly in forested areas, thus we ran a Pearson's product-moment correlation test between total number of sheep farms and proportion of forest (wetland + dry) within a postal code. The result indicated a significant correlation between these two variables ($t_{289} = 8.0$, $P < 0.001$) with a correlation coefficient of 0.43. Thus, number of sheep farms was omitted from further analyses. The multivariate model included the significant variables from the univariate tests, dry and wetland forest. In the multivariate model, dry forest was not significant ($P > 0.05$, Table 3), and removing it from the model produced a lower QAIC (Table 3). Furthermore, an ANOVA comparing the full and reduced model proved no significant differences in the residual SS of the 2 models (Table 3), thus the reduced model including only wetland forest was chosen as the final model. In the final model, odds ratios showed that for every percent increase in wetland forest, the likelihood of TBE increased by 141% (Table 3). However, goodness of fit (R^2) for the final model was less than 0.25, showing poor predictive power.

Table 2
GLM results from univariate tests, testing for significant associations between human TBE cases and proportion of dry and wetland forest, proportion of water, tick abundance and number of sheep farms. Note that the sample size and thus degrees of freedom (df) were smaller for models including tick abundance, as we only included postal codes with measures of tick abundance.

Variables	Coefficient estimate	t-value	df	p-value	Dispersion parameter
Abundance all ticks	-0.009	-0.577	46	0.567	5.008
Abundance larvae	-0.009	-0.454	46	0.652	5.274
Abundance nymphs	-0.020	-0.620	46	0.539	5.006
Abundance females	0.055	0.105	46	0.916	5.582
Abundance males	0.106	0.201	46	0.841	5.726
Number of sheep farms	0.179	3.044	289	< 0.01	5.883
Dry forest	0.135	2.944	289	< 0.01	4.711
Wetland forest	0.881	5.487	289	< 0.0001	3.232
All forest	0.146	3.472	289	< 0.001	4.138
Water	0.062	1.184	289	0.237	5.733

Table 3
GLM results from the multivariable test, investigating associations between human TBE cases and dry and wetland forest. The ANOVA p-value is from comparing the reduced model to the full model. OR = odds ratio, QAIC = Quasi AIC, CIs = 95% confidence intervals.

Variables	Coefficient estimate	p-value	ANOVA, p-value	OR (CIs)	QAIC
Dry forest	0.084	0.062		1.088 (0.996-1-188)	394.334
Wetland forest	0.711	< 0.001		2.035 (1.411–2.936)	
Wetland forest	0.881	< 0.0001	0.060	2.414 (1.762–3.307)	390.215

Spatial plots of the residuals of the final model including wetland forest showed some spatial autocorrelation, particularly in the south of the region (Supplementary File Fig. S4). This was confirmed with Moran's I ($I = 0.12$, $z = 3.35$, $P < 0.001$). However, a spline (cross-) correlogram of the final model residuals showed a generally weak spatial autocorrelation, with weak negative and positive autocorrelation (correlation coefficients between − 0.03 and 0.02) at distances up to 100 km (Supplementary File Fig. S5). Despite weak autocorrelation, our results indicate that we did not account for all the spatial variation within the TBE data.

Discussion

We analysed surveillance data of 81 cases on human TBE with probable place of infection within Örebro Country from 2010–2021 and noticed a ten-fold increase in incidence during this period from 0.7 cases/100,000 inhabitants in 2010 to 7.3 cases/100,000 inhabitants in 2021. Compared to the overall increase in incidence in Sweden from approximately 1.9/100,000 inhabitants in 2010 to 5.1/100,000 inhabitants in 2021, the increase in Örebro County was more drastic than in Sweden as a whole[6]. A similar trend has been reported in Europe where TBE showed a steady increase from 0.6 to 0.9 cases per 100,000 inhabitants from 2016 to 2020[41]. Analysing 12 years of reported TBE incidence in Örebro County, suggested incidence numbers fit a logistic growth curve. If this is the case, incidence in Örebro County seems to be in the rapid growth phase, and we may expect a higher incidence in the future. With the current logistic fit, incidence reaches an asymptote at 10 cases/100,000 inhabitants annually or approximately 30 individual cases per year. However, the fitted model assumes that all other factors remain constant (weather, tick abundance, host animals, level of vaccination, human behaviour etc.). This is most likely not the case as factors such as weather, tick abundance, and host animals are highly variable and furthermore the increasing incidence in Örebro County, might give rise to an increase in immunisation and tick protective behaviour within the county. We furthermore found that TBE cases were not spatially evenly distributed within Örebro County but were clustered both within and across postal codes. The cluster analyses revealed repeated hotspots of TBE in the south of the county and a consistent cold spot with significantly lower incidence around the city of Örebro in the central part of the county. Given the presence of spatial clustering, we sought out to identify potential drivers causing these spatial patterns.

We found that forest was associated with TBE prevalence which is in accordance with other studies from Europe. Models on human TBE in Finland and Hungary have both found the amount of forest to be among the top predictors for the distribution of TBE cases[42,43]. These findings seem to be correlated with tick abundance, as the European *I. ricinus* is highly abundant in forested habitats that provide environmental and climatic conditions optimal for tick survival[44–46].

When stratifying forest into dry- and wetland forest, we found that wetland forest had a stronger association with human TBE cases than dry forest. The risk of getting TBE increased with an increasing proportion of wetland forest even though mean tick abundance was much higher in dry forests than wetland forests (though low sample size in wetland forest may attribute to this). Clearly closed habitats appear to be one of the most favourable for ticks[47] and high questing activity is most likely related to preserved humidity in such habitats during summer[48] corresponding to the habitat we classified as wetland forests. However, we cannot rule out that host community composition may differ from dry to wet forest habitats, explaining a difference in TBE prevalence related to unidentified host species. Even though we have not been able to find other studies confirming this finding, dry forests offer ideal habitats for many important tick hosts from small rodents, insectivores and birds to larger mammals such as hares and deer which are believed to have a positive effect on tick abundance[11], wetland forests are important habitats for many insectivorous bird species[49]. Several bird species are often infested with *Ixodes* ticks and birds are known to disseminate TBEV infected ticks into new areas[50]. In addition, Csank et al.[51] detected TBEV neutralisation antibodies in a local breeding bird in Drienovská wetland, Slovakia. It has been suggested that birds may play an important role in TBEV ecology as they may act as amplifying hosts or reservoirs[50,51]. This could potentially explain our findings. However, it could also be that our findings may not as much reflect tick abundance but more so human behaviour. In general, wetland forests provide an excellent habitat for mushroom growth[52], so these habitats may be popular for mushroom hunting for human consumption. When hunting for mushrooms, people tend to wander into the forest off the forest tracks thus exposing themselves to ticks in the understory. Unfortunately, we do not have information on the activity performed while contracting TBE (or a tick bite) for any of our human TBE cases, which could have been interesting to include in our models.

With our GLMs, we were, not able to establish an association between tick abundance in the ÖrebroCounty and human TBE cases. It could be due to only a smaller part of the county (approx. 30–40%) being surveyed for tick abundance, and thus we could not run our analysis with all the TBE cases in the region. It could however also be due to other factors affecting the distribution of TBE cases, not considered in our model, such as availability of host species or forest structure [52]. Sheep are considered an important tick host where they occur and as it has previously been demonstrated that sheep may function as a sentinel species for TBEV prevalence[29]. Thus, we here tested for associations between human TBE prevalence and the number of sheep farms in Örebro County. We did find a significant association; however the sheep farms were strongly related to forest habitats, making it impossible to separate the cause and effect between the two. Sheep farms were thus omitted as a predictor in our model. Other studies have found that host species composition and abundance[24,43] are among the drivers of TBEV thus incorporating such data could greatly improve our models. Örebro County is surrounded by lakes and bordering the two large lakes Vättern and Hjälmaren, that attract migrating birds during the spring and autumn migrations[53]. These birds may introduce TBEV-infested ticks to the county and could thus be of importance when investigating spatial patterns of TBE in Örebro. Unfortunately, we do not have data on host species for the entire Örebro region, but this may be considered for future studies.

The establishment of TBEV within a region is furthermore dependent on the microclimate and population density of small rodent hosts[13]. Warmer climate may be a positive factor for both ticks and hosts and increases the possibility for TBEV establishment due to viral transmission via co-feeding of larvae and nymphs[54–56]. However, within Örebro County itself we could not discern any differences in temperature when looking at meteorological data, and unfortunately no data on micro climatic conditions exists for all postal codes.

During the study period we identified hotspot clusters in the southern and northern parts of the county. This trend indicates that TBEV has the potential to establish permanently in the region. Other studies have also found that TBEV may remain endemic in the same area over many years – for example genetic analysis revealed establishment of specific TBEV strains in certain regions, which persisted even after decades[57,58]. However, we found no evidence of a higher amount of wetland forest habitats within the postal codes in the cluster. A significant incidence cold spot around Örebro City is not surprising as this area has very little forest and highly urbanised surroundings.

We aggregated our data to the postal code level using postal codes of probable infection site. Furthermore, we used the home address postal code of 12 TBE cases, as information on infection sites were lacking. Both the latter and the coarse aggregation of our data can obfuscate details that may have importance in the occurrence of TBEV. A possible solution could have been to assume that most infections happen close to home and only used data on patient home addresses. However, a given probable place of infection seemed more accurate. Moreover, due to guidelines on human health research ethics, we were not allowed to get exact addresses on human TBE patients thus limiting our study to aggregation by postal codes.

Conclusion

We found that human TBE incidence in Örebro County has been increasing continuously since 2010 resembling a logistic growth curve and thus may potentially stabilize in the future. TBE cases were spatially clustered, with higher prevalence in the south and a consistently low prevalence in postal codes in and around Örebro city. The prevalence of TBE was associated with the proportion of forest within a postal code, particularly the amount of wetland forest. However, our models had relatively low goodness of fit, suggesting that other factors not considered in this study may be important for the spatial distribution of TBE within Örebro County. The explored drivers of TBE (land cover) were not changing over time and the underlying causes of the geographical spread of human TBE cases to Örebro County and the ongoing increase in human incidence remain unexplained.

Declarations

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Author contributions:

LJK: Conceptualization, methodology, resources, validation, writing – review and editing. Writing – original draft. **MJ:** Conceptualization, funding acquisition, methodology, resources, validation, writing – review and editing. **PEL:** Conceptualization, funding acquisition, methodology, resources, validation, writing – review and editing. **NA:** Methodology, writing – review and editing. **PW:** Formal analysis, methodology, validation, writing - review and editing. **HF:** Conceptualization, funding acquisition, methodology, resources, validation, writing – review and editing. **MC:** Formal analysis, methodology, validation. **AW:** Methodology. **RB:** Conceptualization, methodology, validation, writing – review and editing. **GR:** Conceptualization, funding acquisition, methodology, resources, validation, writing – review and editing. **PK:** Conceptualization, funding acquisition, methodology, resources, validation, writing – review and editing.

Data availability

The data on human TBE cases that were used in our analyses have been collected and stored in the Communicable Disease Register in Örebro County Council and at the Public Health Agency of Sweden.

Competing interests

PEL has been an external scientific expert to Valneva Austria GmbH, Vienna, Austria, and external senior advisor to Pfizer Inc.

Ethics approval

The data on human TBE cases that were used in our analyses are collected and stored in the Communicable Disease Register in Örebro County Council and at the Public Health Agency of Sweden. Since these data do not contain any personal information there is no requirement to obtain ethical permission to use these data sets for analyses as described in this paper. The TBE county level incidence data are freely available on the internet.

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Figures

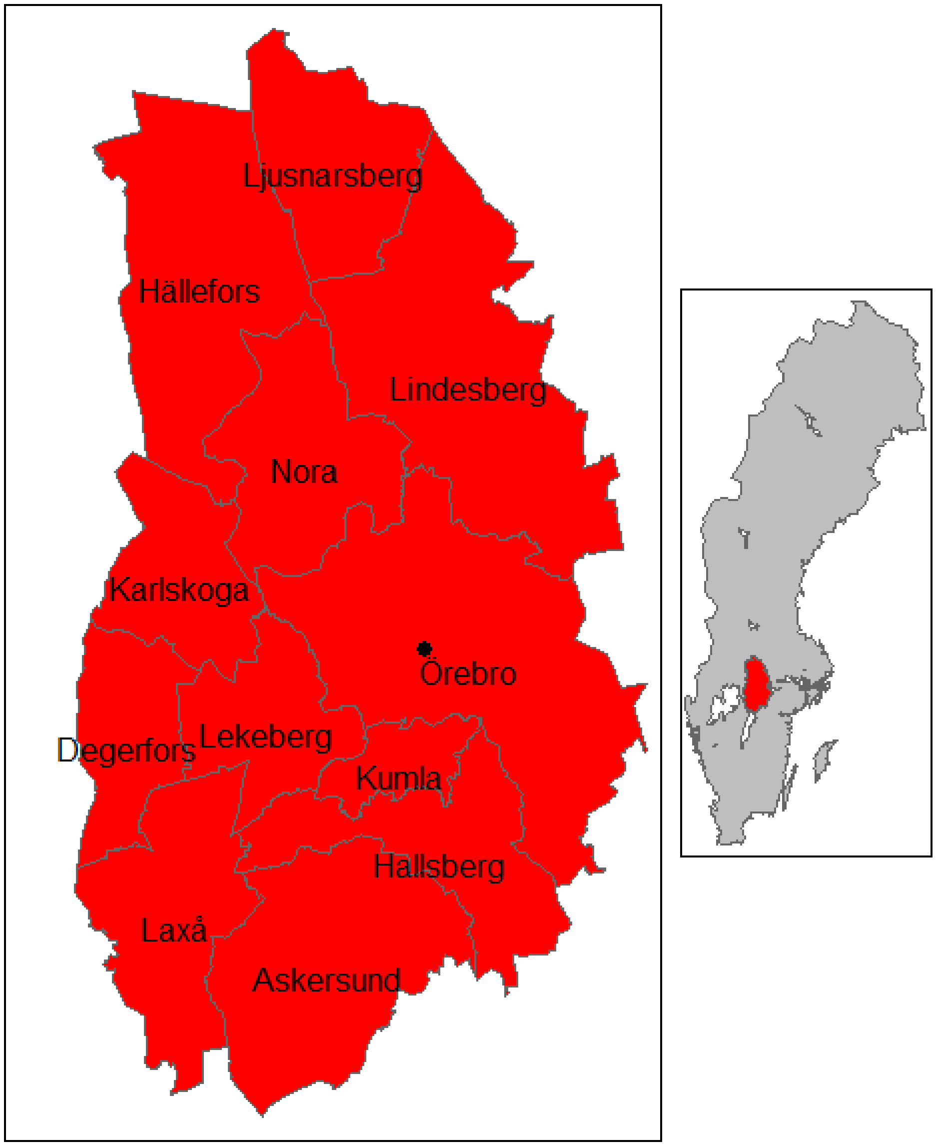

Figure 1

Örebro County with the 12 municipalities depicted. Black dot depicts the county capital of Örebro. Inset map shows the location of Örebro County in Sweden.

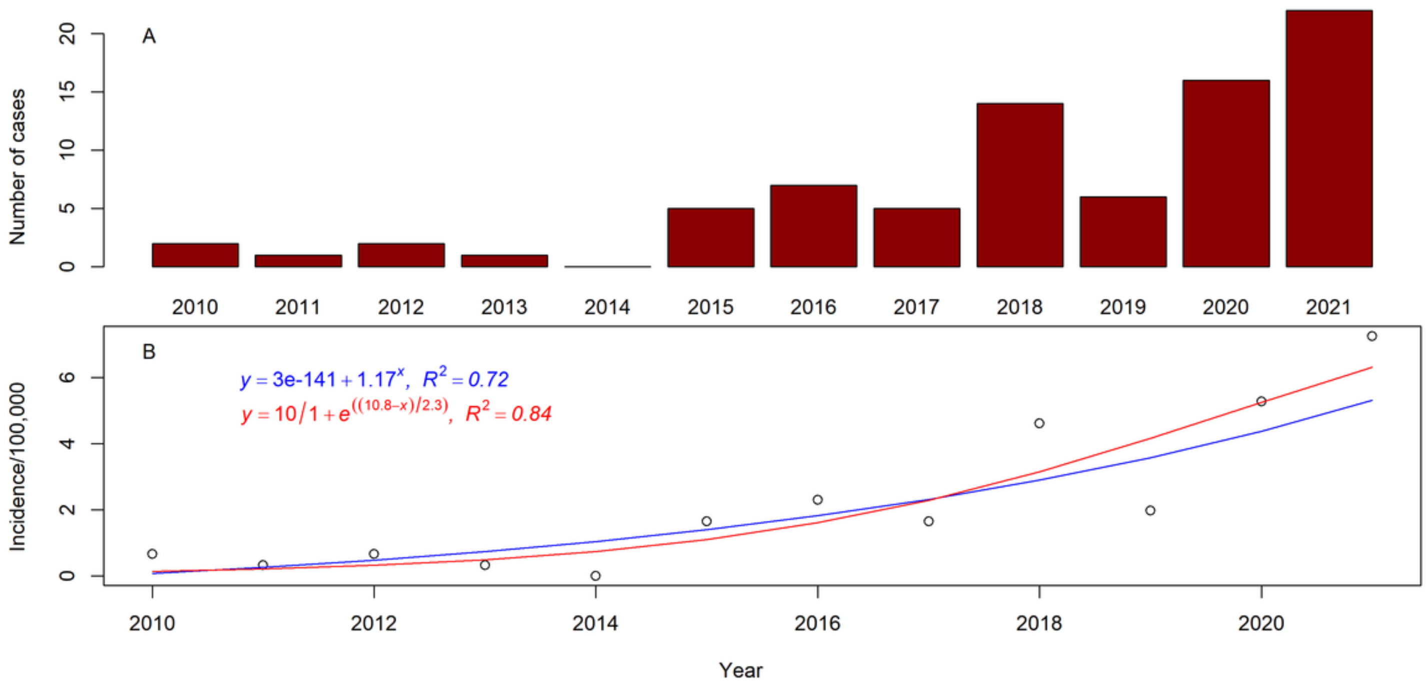

Figure 2

TBE in Örebro County, south central Sweden from 2010 to 2021. The data are depicted as A) Total number of cases (n = 81, and B) incidence and curves fitted from a logistic model (red) and an exponential model (blue) to show incidence trend based on 12 years. The R^2 depicted for the logistic model is the Nagelkerke (Cragg and Uhler) pseudo R^2, calculated using the rcompanion[59] package in R 4.1.2.[33]

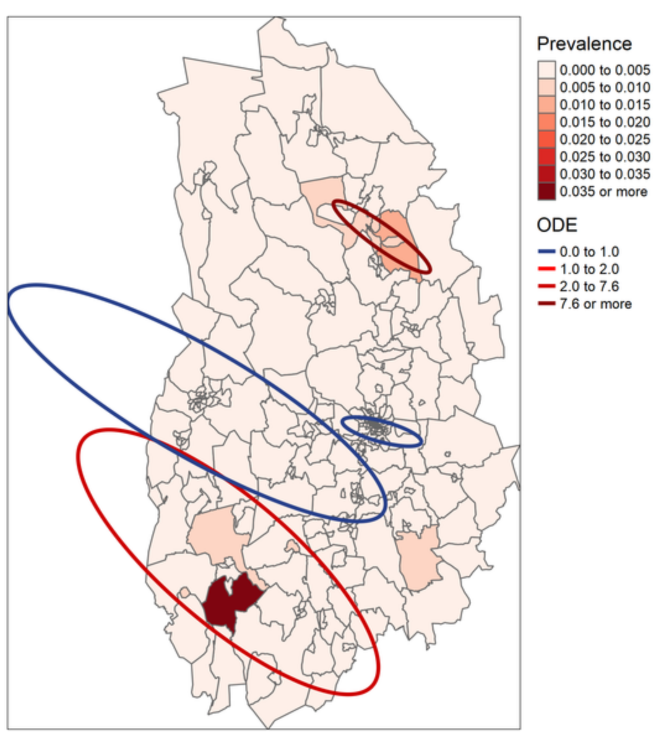

Figure 3

Prevalence (depicted at the postal code level) and estimated clusters for the combined years of human TBE (2010 - 2021). Prevalence was calculated using population data from each postal code within the postal code shapefile obtained through ArcGIS Online[30]. Clusters were analysed using SatScan[31] and only significant clusters with the maximum Gini coefficient are depicted. Satscan calculates ODE, which is the observed number of cases divided by expected number of cases based on the Poisson probability of the entire study area.

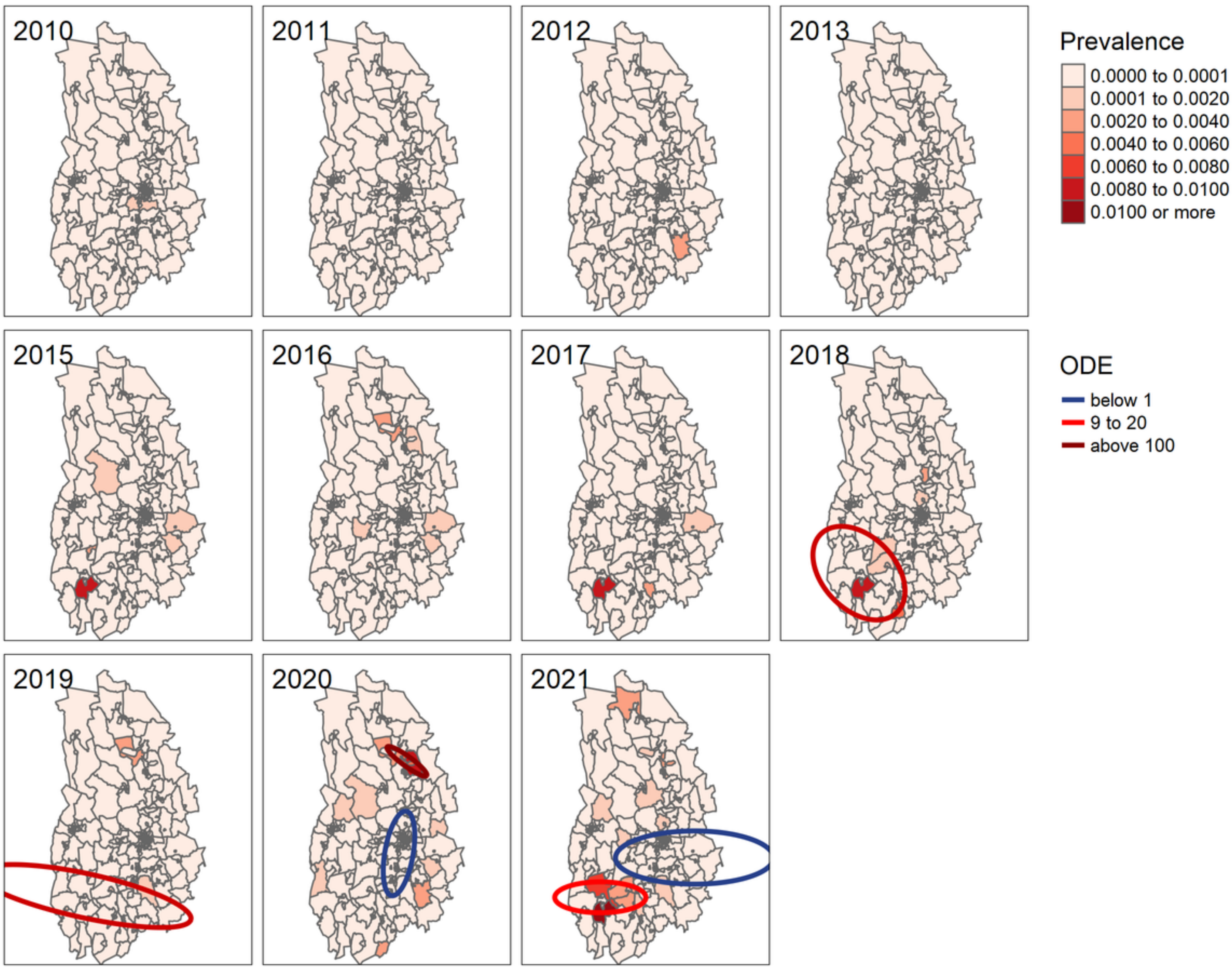

Figure 4

Human TBE prevalence (depicted at the postal code level) and estimated clusters for the individual years 2010 - 2021. Note that the year 2014 is missing, as no human TBE cases were reported that year. Clusters were analysed using SatScan and only significant clusters with the maximum Gini coefficient are depicted. Satscan calculates ODE, which is the observed number of cases divided by expected number of cases based on the Poisson probability of the entire study area.

Supplementary Files

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