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Predicting eastern equine encephalitis spread in North America: An ecological study

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ABSTRACT

Eastern equine encephalitis (EEE) is a rare but lethal mosquito-borne zoonotic disease. Recent years have seen incursion into new areas of the USA, and in 2019 the highest number of human cases in decades. Due to the low detection rate of EEE, previous studies were unable to quantify large-scale and recent EEE ecological dynamics. We used Bayesian spatial generalized-linear mixed model to quantify the spatiotemporal dynamics of human EEE incidence in the northeastern USA. In addition, we assessed whether equine EEE incidence has predictive power for human cases, independently from other environmental variables. The predictors of the model were selected based on variable importance. Human incidence increased with temperature seasonality, but decreased with summer temperature, summer, fall, and winter precipitation. We also found EEE transmission in equines strongly associated with human infection (OR: 1.57; 95% CI: 1.52–1.60) and latitudes above 41.9°N after 2018. The study designed for sparse dataset described new and known relationships between human and animal EEE and environmental factors, including geographical directionality. Future models must include equine cases as a risk factor when predicting human EEE risks. Future work is still necessary to ascertain the establishment of EEE in northern latitudes and the robustness of the available data.

1. Introduction

Eastern equine encephalitis (EEE) is a rare but lethal mosquito-borne zoonotic disease of equines and humans. It is endemic to parts of North and South America and the Caribbean. In the USA, EEE is maintained in a bird-mosquito cycle primarily by the black-tailed mosquito, *Culiseta melanura* (Coquillett, 1902), a species associated with freshwater hardwood swamps (Calisher, 1994). It is bridged to humans and horses by other vectors, primarily species of *Aedes*, *Coquillettidia* and *Culex* (Armstrong & Andreadis, 2010). In humans, the mortality is near 30%, with most survivors experiencing long-term neurologic issues (Villari et al., 1995). In equines the mortality is 75–90%, though it is preventable through a yearly vaccine or twice yearly in endemic areas with year-round mosquito seasons (Rood & Evans, 2008). Poultry such as turkey and quail, although being dead ends, are also susceptible to severe EEE, which can be financially damaging for poultry farmers (CDC, 1983, 2009; Lubelczyk et al., 2013).

Recently, Armstrong & Andreadis (2013) identified a shift in EEE epidemiology with increasing annual human cases and with an expansion further north in the USA. Circumstantial evidence to support this

northward expansion was the 2008 incursion of EEE into Canada (Chenier et al., 2010). In 2019, the largest number of cases reported in decades was in North America ($n = 38$), well over the annual average ($n = 8$) (Lindsey et al., 2018, 2020). Long summer, mild winter, and extreme rain events have been suggested as favorable conditions for increased mosquito abundance and therefore increased EEE transmission (Komar et al., 1999; Skaff et al., 2017; Reinhold et al., 2018). For example, in trying to understand the 12 human EEE cases in Massachusetts in 2019, Mermel (2020) found that in the same year the standard precipitation index, a drought index based on long-term local precipitation history, exceeded 2 across most of the state for the first time in 20 years. But Armstrong & Andreadis (2013) suggested a connection between increasing temperature in the Northeast and the virus spreading into new areas. However, given the scarcity and sparsity of available data for EEE and the absence of regional instead of within-state spatial analyses of human infection, the drivers for the spatial and temporal trends in EEE remain understudied.

Here, we aim to quantify the distributional pattern of human EEE incidence (HEI) in the northeastern USA using up-to-date EEE human and animal data, raw and transformed weather variables, variable

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importance selection and explicit spatial models in order to infer EEE human dynamics. Specifically, this study tested whether there is a geographical trend in HEI and if this trend has a latitudinal component while assessing if equine EEE incidence (EEI) has predictive power for HEI when controlling for weather factors (i.e. temperature and precipitation).

2. Materials and methods

2.1. Data

The study area was restricted to counties in Connecticut, Delaware, the District of Columbia, Maine, Maryland, Massachusetts, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, and Vermont for which at least one case of animal EEE was recorded over the years. The study area is characterized by a mixture of presence and absence of human and animal EEE within the study period.

The numbers of EEE cases in humans and equines between 2006 and 2019 were manually extracted from ArboNET and the United States Department of Agriculture (USDA), respectively (CDC, 2020b; USDA, 2020b). The county populations of humans and equines were assumed stable across years and collected from the 2010 US Population Census and the 2012 Census of Agriculture data respectively (United States Census Bureau, 2011; USDA, 2020a). From the data, human EEE and equine EEE annual incidence were estimated.

The weather variables and their derivatives (by transformation of the raw weather variables) were selected based on literature (Komar et al., 1999; Armstrong & Andreadis, 2013; Mermel, 2020). Specifically, daily mean temperature and precipitation between 2005 and 2019 extracted from the Parameter-elevation Regressions on Independent Slopes Model (PRISM) weather datasets at a 4 km grid resolution, were spatially aggregated to the county level (PRISM Climate Group, 2014). The spatial aggregation for each county consisted in the estimation of annual minimum, maximum, mean, median, and standard deviation (SD) for temperature and precipitation in: (i) the case reporting year; (ii) summer (June–August) in the case reporting year; (iii) autumn (September–November) in the previous case reporting year; (iv) winter (previous December–previous February); and (v) spring (March to May) preceding the transmission season in the same case reporting year.

In addition to the weather variables described above, we included the log-transformed EEI, longitude of the county centroid, dichotomized latitude of the county centroid (latitude $\leq 41.9^\circ\text{N}$ as 0 and latitude $> 41.9^\circ\text{N}$ as 1), dichotomized year of case reporting (pre-2019 as 0, post-2019 as 1). In total, 56 candidate predictors were assessed (Supplementary Table S1). The cut-off point of latitude and case reporting year were selected to reach similar sample size in each group. Because finer zones could elucidate subtle spatiotemporal patterns, we explored using latitude quartiles, terciles, and median (41.9°N) as cut-off points. Due to the small number of human cases and sparse distribution, the models converged only when using median. Additionally, latitude was not found significant when employed as continuous variable in Bayesian generalized-linear mixed-effects model (BGLMM). For completeness we also tested the model with non-dichotomized latitude (Supplementary Table S2).

2.2. Statistical analyses

This study intended to evaluate the relationships between HEI, weather, EEI and location (latitude and longitude) while accounting for spatial autocorrelation. In order to account for fixed (predictors) effects, spatial (autocorrelation) and non-spatial (noise) random effects we employed a spatial Bayesian generalized-linear mixed-effects model (BGLMM), under a lognormal assumption of human and animal incidence distributions (Anderson & Ward, 2019).

The selection of the HEI predictors constituting the fixed effect was obtained by backward and forward stepwise selection method within a

general linear regression model (GLM). Stepwise selection was based on Akaike information criteria (AIC) (Ripley et al., 2013), starting from a candidate model of 56 predictors. Because human cases are limited, we set a significance threshold at 0.1 and required minimum absolute effect sizes of the retained predictors above 0.1 to exclude insignificant or weak candidates. The total number of selected important variables was 26 (Supplementary Table S3). Moran's I test indicated spatial correlation in the residuals (Moran's I = 0.2, $P < 0.001$) confirming the validity of employing an explicit spatial model.

The BGLMM semi-informative and non-informative priors were left with wide distributions to reduce priors-driven model effects (Anderson & Ward, 2019). Predictor selection was repeated to further refine the model because the estimated effects from the GLM may change after accounting for spatial effects. The local polynomials (LP) smoothed inference likelihood was used to quantify how well each model fits the data and for model comparison (Algeri & Zhang, 2020). Additionally, variance inflation factor (VIF) was used to assess multicollinearity (Naimi et al., 2014). As results of this further variable selection, eight predictors were retained, namely, latitude, year, EEI, annual summer temperature, SD of temperature, and annual precipitation in autumn, winter, and summer. The VIFs for these eight predictors were under five, so no multicollinearity was detected (Akinwande et al., 2015). Optimization and predictions were based on a 20×20 grid spanning all study area.

Finally, we also tested for the interaction between latitude and time by testing each of the four combinations of the two dichotomized predictors (pre/post 2018 and above/below 41.9° latitude) in turn within the optimized BGLMM.

3. Results

From 2006 to 2019, 62 human cases were reported by 28 of 234 counties in the study area. A spike in 2019 ($n = 22$) was observed while the number of cases in previous years was less than 10. Among equines, 210 cases were reported from 62 counties with two peaks, in 2009 and in 2019. The counties in the upper region of the study area (latitude $> 41.9^\circ\text{N}$) were significantly different from the counties that fell below the latitudinal cut-off. Specifically, the upper area reported more human cases (56.5%) and animal cases (57.6%), had cooler summers, and slightly more rainfall but drier winters than lower area (Fig. 1; Table 1).

Eight predictors including latitude and EEI were selected for the BGLMM. The model was further improved by including the best interaction term between dichotomized latitude and time which was latitude $> 41.9^\circ\text{N}$ and case reporting year in 2006–2018 (Table 2). This final model fitted the small human case data well. The average error was 0.69 and no patterns in the errors/residuals were observed. We found a lower risk for HEI in the upper area from 2006 to 2018 (OR: 0.67; 95% CI: 0.62–0.74); while the presence of infected horses increases the risk for HEI by almost 60% (OR: 1.57; 95% CI: 1.52–1.61). Moreover, average summer temperature increasing by one degree was associated with a 23% reduction in HEI (95% CI: 0.75–0.79) at average values of the other predictors. The other weather factors only showed weak significant associations (Table 2).

4. Discussion

We found significant (although borderline) association between increased human cases and greater temperature fluctuation, cooler, drier summers, and drier winters, which are not consistent with other studies possibly due to the lack of modelling accounting for spatial autocorrelation and uncertainty (which are components of the employed Bayesian framework). The year 2019 was clearly an exceptional year, with the majority of the weather predictors for 2019 significantly different from the period before (2006–2018) in both regions (above and below 41.9°N) (Table 1). This is reflected in the exceptional number of EEE recorded in 2019. Prior to 2019, higher latitude was protective against human cases.

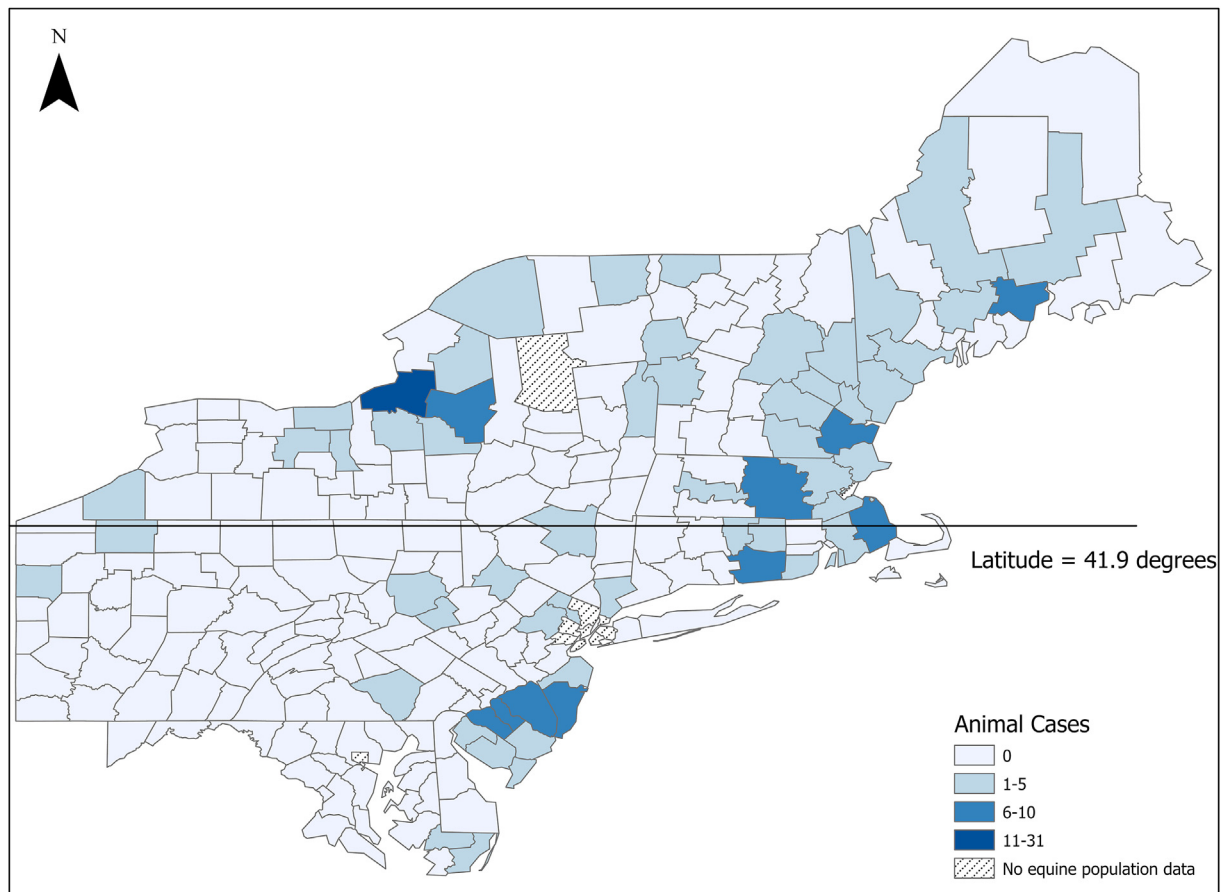


Fig. 1 Number of human cases of eastern equine encephalomyelitis in the northeastern USA, from 2006 to 2019.

Table 1
Summary statistics of selected variables for the final model

Variable	Latitude ≤ 41.9°N		Latitude > 41.9°N	
	2006–2018	2019	2006–2018	2019
Case reporting year	2006–2018	2019	2006–2018	2019
Animal cases, count	66	23	105	16
Human cases, count	13	14	27	8
Annual temperature SD [mean (SD)]	9.8 (0.66)	10.4 (0.41)***	10.6 (0.74)	11.1 (0.42)***
Summer average temperature, degrees Celsius [mean (SD)]	21.9 (1.84)	22.1 (1.86)	19.3 (1.22)	19.3 (1.11)
Last autumn average precipitation, mm [mean (SD)]	3.4 (1.19)	2.8 (0.52)***	3.5 (0.86)	3.6 (0.62)
Last winter average precipitation, mm [mean (SD)]	2.9 (0.72)	3.7 (0.40)***	2.9 (0.71)	3.2 (0.63)***
Summer average precipitation, mm [mean (SD)]	3.9 (1.12)	4.0 (0.64)***	3.8 (0.98)	3.6 (0.45)***

*** Significant difference (P -value < 0.001) between the variables' values in 2019 and 2006–2018 based on a t -test.

Abbreviation: SD, standard deviation.

In other studies, hot, wet, early summers were identified as a contributor to the 1959 EEE outbreak in New Jersey (Goldfield et al., 1969). Przelomski et al. (1988) suggested that EEE outbreaks in Massachusetts followed excessive rainfall in two consecutive years, while one year of high precipitation was not associated with the outbreaks. As with Mermel's (2020) hypothesis on the 2019 outbreak, excessive July rainfall was suggested by Feenster (1957) as an explanation for the unusually high mosquito abundance during a 1938 outbreak in Massachusetts which killed at least 200 horses and 25 humans. However, these studies focused on explaining the exceptional outbreaks rather than understanding the trends underlying them and the EEE geographical heterogeneities.

To our knowledge this is the first analysis using horse cases to predict human cases, reinforcing that equine surveillance is a key aspect in protecting the public from EEE. In studies explaining horse EEE alone, Burch et al. (2020) showed elevation and temperature seasonality as strong contributors to annual fatalities among equines. Studies using different

weather indicators, in differing locations and at differing spatial resolutions may have resulted in the contrasting findings existing in EEE literature. For example, extremely wet conditions have been suggested to lower EEE transmission in animals by reducing populations of the virus' reservoirs, mainly birds (Robinson et al., 2007; Oberg et al., 2015). Others have shown that extreme precipitation may adversely impact larval survival in container-breeding mosquitoes (Koenraad & Harrington, 2008). On the other hand, excessive precipitation has been suggested as a driver of human EEE (Komar et al., 1999; Armstrong & Andreadis, 2013; Skaff et al., 2017; Reinhold et al., 2018; Mermel, 2020). We found agreement with former studies (higher precipitation associated with lower risk) although with limited significance. This may be due to the complex non-linear association between precipitation and human EEE, or simply the 'averaging effect' that could not distinguish between precipitation experienced as light rains over long periods or extreme precipitation events over short periods. Future studies may extract environmental

Table 2
Final model for assessing the risk of human EEE incidence

Predictor	Odds ratio (95% CI) ^a
EEL	1.57 (1.52–1.61)*
Latitude > 41.9°N and Case reporting year 2006–2018	0.67 (0.62–0.74)*
Annual temperature SD	1.04 (1.01–1.08)*
Summer average temperature	0.77 (0.75–0.79)*
Last autumn average precipitation	1.01 (0.99–1.03)
Last winter average precipitation	0.95 (0.91–0.99)*
Summer average precipitation	0.97 (0.95–0.99)*

* $P < 0.05$.

Abbreviations. CI, confidence interval; EEE, eastern equine encephalitis; EEL, equine EEE incidence; SD, standard deviation.

^a Model included a binary predictor, with 1 indicating latitude > 41.9°N and case reporting between 2006 and 2018, and 0 otherwise.

factors more relevant to vectors' life-cycle and at finer scales. The effect of weather factors on behaviors of EEEV vectors and reservoirs may vary across regions, such as survival rates of migrant and resident birds (Komar et al., 1999). This reinforces our findings where the estimates of relevant environmental predictors change with latitude, in other words, they are region-specific (Brown et al., 2017). Another strength of our study is the use of PRISM Climate Data for predictor generation. PRISM interpolates weather data using sophisticated algorithms to create a continuous surface that captures complex terrain at high spatial resolution allowing for comparability of our results with many other ecological studies.

Besides weather factors, other factors not included in this analysis may have contributed to increased human infections. Land cover, for which detailed year by year changes were not available for this analysis, is usually reported as an important factor for EEEV transmission. For example, tree plantations in Florida were found to be a strong risk factor for EEE virus transmission in sentinel chickens while vegetated non-forest wetlands had a protective effect (Vander Kelen et al., 2012). In addition, urbanization may increase interaction between mosquitoes and humans (Rochlin et al., 2011). Although studies have linked land cover with mosquito abundance, evidence on mosquito infection rate or HEI is rare (Hachiya et al., 2007).

Because of the paucity of human EEE cases, creating robust models to explain the changing epidemiology of EEE is challenging (Chenier et al., 2010). In addition to the data limitation, EEE incidence may be affected by case misclassification. While EEE is a reportable disease, ArboNET is a passive surveillance system so infected animal cases with mild symptoms are unlikely to be detected. According to the CDC, clinically diagnosed EEE cases diagnosed in the USA represent 4–5% of human EEE infections that have occurred (CDC, 2020a). The study is susceptible to residual confounders, particularly interaction between human and environment. Human behavior may change with weather conditions (i.e. temperature), with regional differences in time spent outdoors (Graff Zivin & Neidell, 2014). Studies designed to quantify these factors at different spatial scales are needed.

5. Conclusions

While epidemiological studies indicate that the EEE patterns are changing with a northward shift, the rarity of this severe disease can impede a definitive answer on these dynamics. However, we find a strong association between human and equine cases, which can be harnessed to understand the changing dynamics of EEE in North America. Moreover, the association between human cases and the environmental predictors we used are different from what others have shown indicating that more research needs to be done on the drivers of human and animal EEE at regional scale. Finally, we found a northward effect that will need to be confirmed in the coming years to remove any potential risk of outlier effect in this finding.

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Ethical approval

Not applicable.

CRediT author statement

HB, LS, and XT conceived and designed the study and interpreted the data. LS and XT conducted the data analysis. HB and XT prepared the first full draft. All authors contributed to the final version of this work, read and approved the final manuscript.

Data availability

The datasets used for the present study are available from the authors website: <https://brown.lab.arizona.edu/content/research-projects>.

Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.crvbd.2021.100064>.

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