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The negative relationship between mammal host diversity and Lyme disease incidence strengthens through time

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Abstract. Since its discovery in 1975, Lyme disease has spread and increased in much of central and eastern United States. Host diversity is thought to play a role in Lyme disease risk, and it has been suggested that the direction of the relationship between host diversity and disease risk may vary depending on the spatial scale of observation. Here we modelled the effect of mammal host species richness on the incidence of Lyme disease from 1992 to 2011 across all states in the United States with reported or established black-legged tick (*Ixodes scapularis*) populations. We tested two contrasting hypotheses: a positive vs. a negative relationship between host species richness and Lyme disease incidence. We also tested the hypothesis that the strength of the diversity–disease-risk relationship increased over time, as Lyme disease spread. We observed a strong negative relationship between mammal host species richness and Lyme disease incidence, and this relationship became more negative over time. Lyme disease increased over time more rapidly in host species-poor states than host species-rich states. Our findings support the importance of mammal host richness on Lyme disease risk at large spatial scales, and the importance of spatial and temporal scales on the diversity–disease relationship.

Key words: *amplification;* Borrelia burgdorferi; *dilution; diversity; emergence;* Ixodes; *Lyme disease; United States.*

Introduction

Lyme disease is the most commonly reported vector-borne disease in the temperate zone and, if left untreated, can lead to neurological, cardiac, and arthritic symptoms (reviewed in Ogden et al. 2009). It was first identified in 1975 in Lyme, Connecticut (Steere et al. 1977), although it had existed in North America at low levels for at least 50 years before (Barbour and Fish 1993). Lyme disease has increased in prevalence and spatial extent since 1975 (Bacon et al. 2008; Centers for Disease Control and Prevention [CDC] data *available online*),[4] and is now endemic to most of the central and eastern United States (Steere et al. 2004). The disease is caused by the bacterium *Borrelia burgdorferi* and is transmitted to humans via ticks belonging to the genus *Ixodes*, primarily the black-legged tick (*I. scapularis*) in eastern and central North America. Larval and nymphal *I. scapularis* tend to take blood meals from small mammals and birds, while adults take blood meals from deer. Many of the small mammal and bird hosts are reservoirs of *B. burgdorferi*, but they differ in their ability to transmit *B. burgdorferi* to feeding black-legged ticks, the most effective reservoir being the white-footed mouse (*Peromyscus leucopus*; Brunner et al. 2008).

A diversity of host species are involved in the Lyme disease system, and it is thought that this diversity mediates Lyme disease risk, but the nature of this relationship is a matter of ongoing debate (Dobson 2004, Keesing et al. 2006, Ogden and Tsao 2009, Randolph and Dobson 2012). Previous studies have found that in areas of emergence of Lyme disease, the prevalence of infected ticks is driven by the interaction between host species richness and the relative abundance of the white-footed mouse, the most competent host for *B. burgdorferi* (Simon et al. 2014, Werden et al. 2014). Schmidt and Ostfeld (2001) hypothesized that Lyme disease risk decreases with biodiversity, suggesting that disease protection is an ecosystem service provided by biodiversity (the "dilution effect" hypothesis). They propose, among other possible mechanisms (Keesing et al. 2006), that increased host diversity reduces the relative abundance of white-footed mice, resulting in tick bites being diverted from the white-footed mouse. The white-footed mouse is among the most competent reservoirs for *B. burgdorferi*, and so this will result in a decrease in disease incidence via a decreased prevalence of infection in host-seeking ticks. An alternative hypothesis, the amplification effect, states that Lyme disease risk increases with biodiversity (Keesing et al. 2006); a mechanism that may also affect risk for other human infectious disease (Wood et al. 2014). Again,

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many possible mechanisms could lead to this relationship, but several authors (Gilbert et al. 2001, Keesing et al. 2006, Ogden and Tsao 2009) argue that increased host diversity may increase overall host abundance, which would result in increased tick abundance, and therefore higher disease risk.

The ecology of Lyme disease is complex with many interacting variables, making it difficult to disentangle the relationship between Lyme disease incidence and host diversity. First, temporal scale should play a role in the diversity–disease relationship: in regions where Lyme disease is emerging, many of the key populations involved in the dynamics of Lyme disease transmission are unstable and increasing (most notably black-legged ticks, white-footed mouse, and *B. burgdorferi* populations), and so there is no reason to believe that the relationship between host diversity and disease risk should remain constant over time in these systems (e.g., Tuite et al. 2013). Consequently, the relationship between Lyme disease incidence and any given regionally dependent variable, including host diversity, may change over time. A change in the strength of the relationship between Lyme disease incidence and host diversity can be expected if host species-poor regions have some characteristics that allow Lyme disease to emerge more rapidly than in host-species-rich regions, or vice versa.

Second, Wood and Lafferty (2013) proposed that the biodiversity–Lyme disease relationship may operate in different directions at the within-forest scale and at the landscape scale. They argue that, historically, an amplification effect has occurred at the landscape scale because reforestation has driven an increase in host diversity resulting in an increase in competent host density; in areas with increased forest cover there is thus a higher host diversity and greater Lyme disease incidence. At the within-forest scale, a dilution effect may take place through the reduction in white-footed mouse relative abundance within host communities.

The relationship between host diversity and Lyme disease incidence may thus be dependent on both the temporal and spatial scales of observation. Here, we investigated the nature of the relationship between host species richness and Lyme disease incidence at the scale of the central and eastern United States, and how it has changed over the past two decades. We explored and controlled for several variables that may confound the relationship between host diversity and Lyme disease. Lyme disease cases have been reportable in the United States since 1992 and cases in each state are reported each year to the Centers for Disease Control (Bacon et al. 2008, Centers for Disease Control 2012). This database provides a record of the emergence of Lyme disease in the United States, allowing study of the relationship between disease cases and host species richness over time. Here, Lyme disease cases in the United States from 1992 to 2011 and the species richness of *I. scapularis* mammal hosts in each state with reported or established *I. scapularis* populations were analyzed, along with a number of covariates. The analyses were at a broad geographic scale, and we therefore hypothesized that an amplification effect of host species richness is expected. In other words, a positive relationship between Lyme disease cases and host species richness should be observed across states of varying host species richness. Furthermore, we hypothesized that the strength of the species-richness–disease-risk relationship changed significantly over time between 1992 and 2011, because the disease incidence has increased during this period. We expect an increase in the strength of the relationship between mammal host diversity and Lyme disease cases, as the overall number of cases of the disease is increasing in time.

Methods

Data

The number of cases of Lyme disease per 100 000 people for each of the 48 contiguous states from 1992 to 2011 was obtained from the United States Centers for Disease Control (see footnote 4). The *I. scapularis* mammal host species richness was obtained by tallying the number of *I. scapularis* mammal host species (Appendix C, provided by L. A. Durden) whose range overlaps with each of the 35 states (Smithsonian Institution, National Museum of Natural History, North American Mammals database, *available online*)[5] with established or reported *I. scapularis* populations (Dennis et al. 1998). All of these states with reported or established *I. scapularis* are located in the east and central United States. All years from 1992 to 2011 were included in the analysis. The tick behavior varies across its range and Stromdahl and Hickling (2012), identified states falling south of 35° N as having populations of ticks that differ from northern tick population (southern nymphs rarely feed from humans). We thus categorized the states into northern (27) and southern (8) states based on whether the state's mid-latitude fell north or south, respectively, of 35° N (United States Census Bureau, data *available online*).[6]

Six other variables that could affect Lyme disease incidence were also included in our model as covariates. The distance of the closest border of each state to the closest border of Connecticut and to the closest border of Wisconsin, the two areas recognized as the points of origin of Lyme disease in North America (Barbour and Fish 1993, Hoen et al. 2009), was measured using Google Earth (Version 6.2.2.6613; Google, Mountain View, California, USA). This variable aimed to capture how the spatial pattern of spread of *B. burgdorferi* from its likely source foci might have influenced Lyme disease incidence in any one state. We also included in our models the human population of each State (United

[5] http://www.mnh.si.edu/mna/search_name.cfm
[6] http://www.census.gov/geo/reference/state-area.html

TABLE 1. Log-normal Poisson mixed models of Lyme disease cases from 1992 to 2011 fit by maximum likelihood.

Parameters	Estimate	SE	*Z*	*P*
All states				
(Intercept)	7.262	6.408	1.133	0.2575
Host species richness	−4.614	1.991	−2.317	0.0271
Year	0.964	0.1314	7.338	<0.0001
Forest area	−0.013	0.005	−2.559	0.0107
Distance to Connecticut	−0.002	0.0003	−6.451	<0.0001
Host species richness × Year	0.285	0.040	−7.092	<0.0001
Northern states				
(Intercept)	10.289	6.052	1.700	0.0897
Host species richness	−6.248	1.815	−3.442	0.0022
Year	0.884	0.152	5.819	<0.0001
Distance to Connecticut	−0.001	0.0004	−2.855	0.0090
Distance to Wisconsin	0.001	0.0006	2.160	0.0414
Host species richness × Year	−0.252	0.0465	−5.411	<0.0001

Note: The first model includes all 35 states in the United States with established or reported populations of *Ixodes scapularis*, while the northern states model includes the subset of states with a mid-latitude above 35° N.

States Census Bureau data *available online*)[7] for each year from 1992 to 2011, as well as the total area of the state (USDA data *available online*),[8] the area of each state covered by deciduous or coniferous forest (see footnote 8), the preferred habitat of *I. scapularis* (Ostfeld et al. 1995), and the average January temperature (NOAA data *available online*).[9]

Data analysis

We investigated the relationship between host species richness and disease incidence with a nonlinear mixed model of Lyme disease cases fit using glmer in the lme4 (Bates et al. 2013) packages in R version 3.0.2 (R Core Team 2013). The outcome variable was the reported number of Lyme disease cases per year for each state from 1992 to 2011. We used a Poisson model with an observation-level random effect (also known as a log-normal Poisson model; Elston et al. 2001). The log of human population was included as an offset in the model. The model included host species richness, year, forest area, land area, distances from Connecticut and from Wisconsin, the interaction between host species richness and year and the interaction between host species richness and forest area as fixed effects and state as a random effect. We checked for colinearity among the variables using the variance inflation factor (vif) from the HH package in R version 3.0.2 (Heiberger 2013); all variables had vifs <10 (Miles 2005), and so were kept in the model (Appendix A). The full model was simplified by backward selection with the function drop1 from the stats package in R version 3.0.2, which uses the Akaike information criterion (AIC) to rank the models based on both goodness of fit and complexity. The model with the lowest AIC after backward selection was kept as the final model. The model was applied twice: to all the states with *I. scapularis* and to the northern states subset. Spatial autocorrelation in the number of Lyme disease cases was tested using the Moran index, using the Moran.I function in the package ape in R (Venables and Ripley 2002). A Gaussian spatial correlation matrix was selected on the basis of a variogram, using the variogram function in the package spatial in R (Venables and Ripley 2002) and added to the final models (all states and northern subset) to account for spatial autocorrelation. The models with a spatial correlation matrix were built using glmmPQL (MASS package in R).

RESULTS

Spatial autocorrelation was present with Moran's *I* ranging from 0.12 to 0.31 with a mean of 0.21 and a standard deviation of 0.061 ($P < 0.0001$) for all years. The addition of the spatial correlation matrix controlled for autocorrelation in the residuals of the final models. Lyme disease cases decreased with mammalian host species richness and increased over time across the central and eastern United States (Appendix B, Table 1). The number of Lyme disease cases decreased with an increasing distance to Connecticut and the amount of forest area. There was no significant effect of the distance to Wisconsin, January temperature, or land area on Lyme disease incidence.

The model for the northern states subset was similar (Appendix B). Again, Lyme disease cases decreased with host species richness (Table 1). The relationship between Lyme disease cases, the distance to Connecticut, and the distance to Wisconsin was negative, while all other variables were nonsignificant.

As indicated by the significant negative interaction between host species richness and year in the models above (Table 1), the slope of the relationship between Lyme disease cases and host species richness became more negative over time (Fig. 1). In both the total and the northern models, the rate of increase in Lyme disease

[7] http://www.census.gov/popest/data/index.html

[8] http://www.ers.usda.gov/data-products/major-land-uses.aspx#.Uado_5y1t8E

[9] http://gis.ncdc.noaa.gov/map/cag/#app=cdo

cases was most marked in states with lower host species richness (Table 1, Fig. 2).

Discussion

A dilution effect

The negative relationship between tick host species richness and Lyme disease incidence is consistent with a dilution effect of host diversity from 1992 to 2011 in the United States. Both theory and observations suggest that a dilution effect will only occur under certain conditions and disease systems (Gilbert et al. 2001, Dobson 2004, Keesing et al. 2006, Begon 2008, Ogden and Tsao 2009, Wood and Lafferty 2013). Our observations at the scale of the central and eastern United States provide evidence of a dilution effect, with host species richness having the strongest effect on Lyme disease incidence at low levels of host species richness.

The dilution effect we observed across the United States could be due to regional mechanisms such as metacommunity processes in hosts (Leibold et al. 2004), since ticks have little capacity for movement other than on very mobile hosts. Furthermore, a positive local-regional species richness relationship has been found in field observations across many taxa (Caley and Schluter 1997), and a high-diversity state should be on average made up of high-diversity communities. If the overall Lyme disease risk in a region is determined by the disease risk of the communities of which it is composed, then a dilution effect can result at the regional scale from mechanisms operating at the community level.

Wood and Lafferty (2013) proposed that an amplification effect of biodiversity should occur at the regional scale, with a dilution effect occurring under specific conditions at the local scale. This proposition was based on the historical associations and observations of expansion of northern *I. scapularis* populations in response to reforestation and the resulting expansion of key tick host populations (particularly white-tailed deer, *Odocoileus virginianus*), empirical observations relating the degree of forest cover and Lyme disease incidence at a broad regional scale (reviewed in Wood and Lafferty 2013), as well as local observations of dilution effects (Ostfeld and Keesing 2012).

Our observations do not support this hypothesis however, and we did not observe a positive relationship between host species richness and Lyme disease incidence for any year from 1992 to 2011. Instead, the incidence of Lyme disease decreased with the proportion of forest in the full model (Table 1) and forest area had no effect in the northern states (Table 1). This suggests that while reforestation during the last century may have driven Lyme disease emergence (Wood and Lafferty 2013), this is no longer a significant driver of variations in Lyme disease risk and incidence.

Spatial heterogeneity in tick behavior may further modulate the relationship between Lyme disease and host diversity. Northern and southern *I. scapularis* represent two distinct clades (Diuk-Wasser et al. 2006, 2012, Pepin et al. 2012), which also differ behaviorally. Southern *I. scapularis* ticks tend to take blood meals from reservoir-incompetent lizard hosts and rarely take blood meals from humans (Stromdahl and Hickling 2012). Lyme disease cases are reported by the CDC based on state of residence, so an unknown proportion of Lyme disease cases reported in each state are travel acquired, and this proportion is likely high in southern states. However, while ticks and human Lyme disease incidence may behave differently in the southern states, this did not affect our results, and a dilution effect was still observed when southern states were excluded from the analyses.

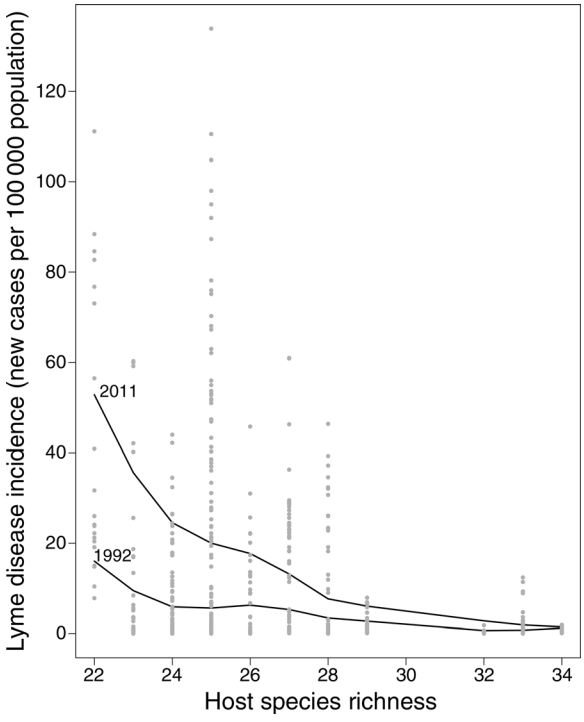

Fig. 1. Lyme disease incidence (number of cases per 100 000 people) from 1992 to 2011 in all 35 states of the United States with established or reported *Ixodes scapularis* populations against tick host mammalian species richness. Trend lines were generated for two years: 1992 and 2011 by applying a locally weighted scatterplot smoothing function (loess in the stats package in R), with points weighted by number of states per host species richness level.

A strengthening effect over time

Another important finding is the increase in the strength of the dilution effect over time (Fig. 1). The diversity–disease-risk relationship became increasingly negative, providing empirical evidence that the diversity–disease-risk relationship can indeed change through time as a zoonotic disease emerges. Management of Lyme disease may therefore become increasingly effective over time if it targets the diversity of host species within forest habitats.

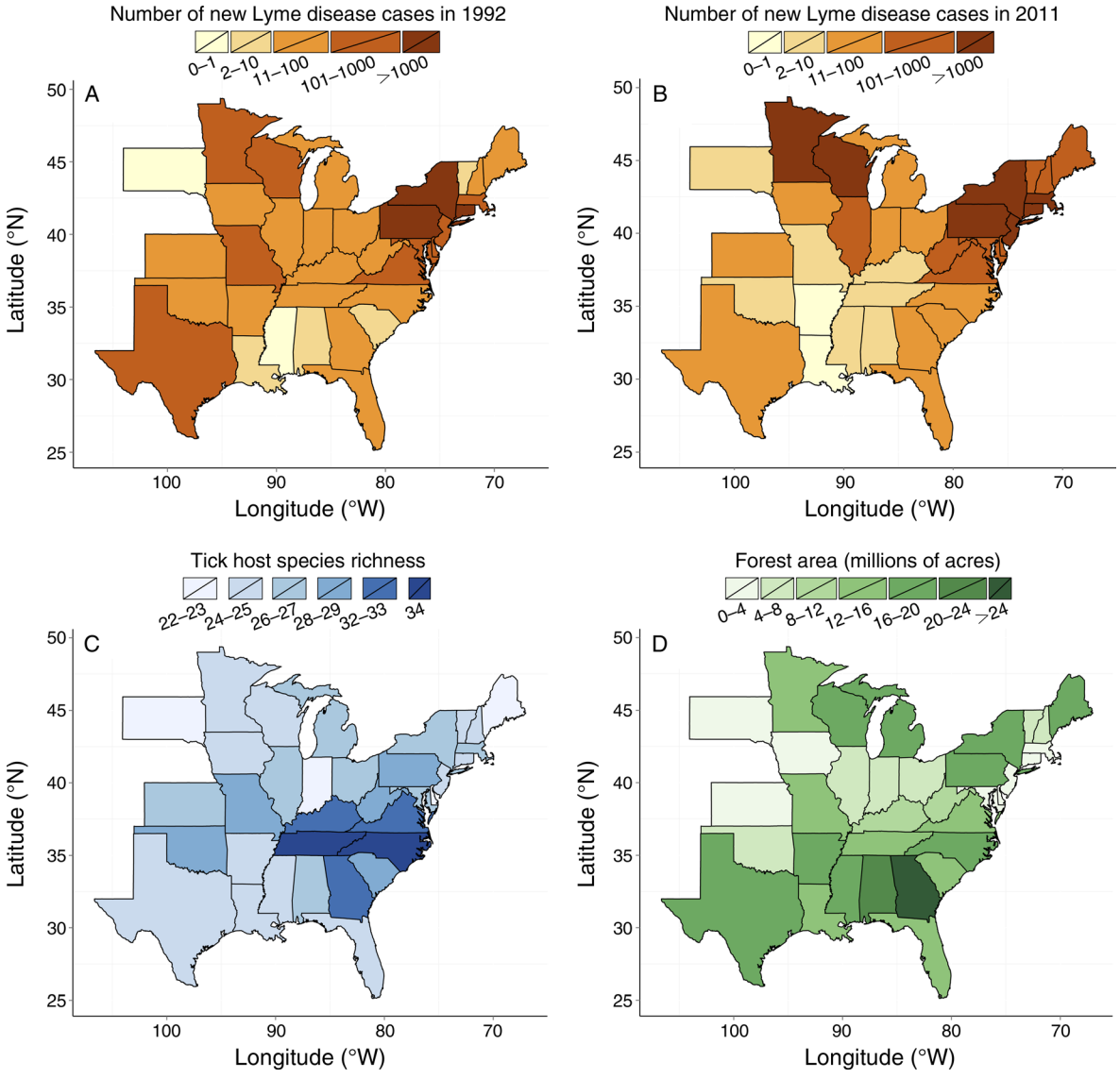

FIG. 2. The number of Lyme disease cases in (A) 1992 and (B) 2011 in the 35 states of the United States with established or reported *Ixodes scapularis* populations, compared with the (C) tick host mammalian species richness and (D) forest area (1 acre = 0.405 ha) in these States. Lyme disease increased at a larger rate in host species-poor states than in host species-rich states (Table 1).

While the widespread reforestation during the 20th century across a wide geographic area of the United States may have led to an increase in biodiversity to threshold levels needed to support tick and *B. burgdorferi* population expansion, the change in the diversity–disease relationship over time is mediated by a mechanism causing Lyme disease to increase more rapidly in low host species richness states than in high host species richness states. The change of Lyme disease incidence from 1992 to 2011 decreased with host species richness. If the absolute or relative abundance of white-footed mice, the most competent reservoir host for *B. burgdorferi*, is reduced by high host richness (Nupp and Swihart 2000), this could provide a plausible mechanism. Decreased white-footed mouse abundance would lead to a decreased transmission rate due to a lower encounter rate, leading to a slower emergence of Lyme disease in host species rich states. This hypothesis differs from the dilution effect hypothesis in that it predicts a decrease in the rate of disease emergence with diversity, while the dilution effect predicts a decrease in disease incidence or risk with diversity.

The increasing dilution effect seen at the scale of the United States could also be due to a change in the relative importance of host dispersal and host community structure over time. Empirical modeling by Ogden et al. (2013) found that early in the emergence of Lyme disease, the tick immigration rate is more important in determining the speed of *B. burgdorferi* invasion in a community than the host diversity of the community

(but see also Simon et al. 2014). This is supported by our observation that states with the highest incidence of Lyme disease are located closer to Connecticut, one of the sources of *Borrelia* in the United States. As Lyme disease emerges, there may then be an increasing dilution effect as host diversity becomes relatively more important in determining disease risk in communities.

Lyme cases are likely underreported (by two-thirds) during the early stages of emergence (Naleway et al. 2002) and are currently underreported by a factor of 10 in states with high Lyme disease incidence (data *available online*).[10] In some states, a decrease in the number of cases was observed. Rhode Island, Missouri, and New York all reported relatively large decreases (decrease of >100 cases from 1992 to 2011), likely due to changes in collections of surveillance data, as Lyme disease is still emerging in the United States. For example, officials at the Rhode Island Department of Health, the state with the largest per capita decrease in Lyme disease cases, attribute the decrease to a change in surveillance methods following a decrease in available funds in 2004–2005 (Rhode Island Department of Health, *personal correspondence*).

We assumed that the mammal host ranges remained constant over time, but climatic and human land use changes over the past decades may have resulted in range shifts (e.g., Roy-Dufresne et al. 2013) or contractions (Channell and Lomolino 2000). These range shifts could conceivably affect the diversity–disease relationship and could merit further study.

Given that the diversity–disease-risk relationship can change over time, it may be important that researchers establish whether their focal system is at equilibrium. This could be tested by investigating whether some measure of disease incidence, such as reported incidences by clinics to a governmental agency, has increased over time in the study area. If the disease system has not reached equilibrium, there is no reason to expect that the relationship will remain constant. Ostfeld and Keesing (2000), concluded that a dilution effect occurred in the United States using CDC data from 1997 and 1998. In 1998, however, Lyme disease was still emerging in the United States (Bacon et al. 2008). Here, we also performed an analysis at the level of the United States, this time considering data covering a much greater span of time, as well as other variables. We also found a dilution effect, but demonstrated that the diversity–disease-risk relationship had not remained constant.

Conclusions and future directions

When accounting for time, spatial scale, forest cover, tick phenotype, and spatial pattern of disease spread, we found a dilution effect of diversity on Lyme disease in the United States, and revealed that this effect was getting stronger over time. While adding to the body of evidence for a dilution effect (reviewed in Ostfeld and Keesing 2012), our findings also have management implications for Lyme disease in the United States. We provide evidence that the strength of the relationship between Lyme disease and host diversity is dynamic. Our findings also have land management and public health implications for other regions in which Lyme disease is currently emerging, including southern Canada. Future studies should focus on intermediate spatial scales; studies at the mesoscale may connect patterns at the very largest scales to the local process occurring within communities. Landscape studies offer the opportunity to examine within and between patch dynamics of Lyme disease emergence and spread (Simon et al. 2014). By bridging scales, we may reconcile the shifts in the strength and direction of the relationship between diversity and Lyme disease risk seen across studies.

[10] http://www.cdc.gov/lyme/stats/humanCases.html

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Supplemental Material

Ecological Archives

Appendices A, B, and C are available online: http://dx.doi.org/10.1890/14-0980.1.sm