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Tick-borne disease risk in a forest food web

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Abstract. Changes to the community ecology of hosts for zoonotic pathogens, particularly rodents, are likely to influence the emergence and prevalence of zoonotic diseases worldwide. However, the complex interactions between abiotic factors, pathogens, vectors, hosts, and both food resources and predators of hosts are difficult to disentangle. Here we (1) use 19 yr of data from six large field plots in southeastern New York to compare the effects of hypothesized drivers of interannual variation in Lyme disease risk, including the abundance of acorns, rodents, and deer, as well as a series of climate variables; and (2) employ landscape epidemiology to explore how variation in predator community structure and forest cover influences spatial variation in the infection prevalence of ticks for the Lyme disease bacterium, *Borrelia burgdorferi*, and two other important tick-borne pathogens, *Anaplasma phagocytophilum* and *Babesia microti*. Acorn-driven increases in the abundance of mice were correlated with a lagged increase in the abundance of questing nymph-stage *Ixodes scapularis* ticks infected with Lyme disease bacteria. Abundance of white-tailed deer 2 yr prior also correlated with increased density of infected nymphal ticks, although the effect was weak. Density of rodents in the current year was a strong negative predictor of nymph density, apparently because high current abundance of these hosts can remove nymphs from the host-seeking population. Warm, dry spring or winter weather was associated with reduced density of infected nymphs. At the landscape scale, the presence of functionally diverse predator communities or of bobcats, the only obligate carnivore, was associated with reduced infection prevalence of *I. scapularis* nymphs with all three zoonotic pathogens. In the case of Lyme disease, infection prevalence increased where coyotes were present but smaller predators were displaced or otherwise absent. For all pathogens, infection prevalence was lowest when forest cover within a 1 km radius was high. Taken together, our results suggest that a food web perspective including bottom-up and top-down forcing is needed to understand drivers of tick-borne disease risk, a result that may also apply to other rodent-borne zoonoses. Prevention of exposure based on ecological indicators of heightened risk should help protect public health.

Key words: blacklegged tick; bottom-up control; Lyme disease; predator; tick-borne disease; top-down control; white-footed mouse; zoonoses.

Introduction

Infectious diseases of humans are emerging and spreading at unprecedented rates (Jones et al. 2008, Smith and Guegan 2010, Murray et al. 2015). Most of the emerging infectious diseases of humans are zoonotic, being transmitted from non-human vertebrates to humans via direct transmission, environmental deposition, fomites, or arthropod vectors (Jones et al. 2008). Mammals are the primary sources of zoonotic pathogens, and rodents are the most prevalent reservoir hosts worldwide (Han et al. 2015, 2016). For example, the pathogens causing Lyme disease, leptospirosis, monkey pox, several hantavirus diseases, plague, leishmaniasis, and various hemorrhagic fevers, are transmitted most efficiently by rodents and other small mammals (Han et al. 2015, 2016). In the North Temperate Zone, Lyme disease, which is caused by the spirochete *Borrelia burgdorferi* and transmitted by *Ixodes* ticks, is the most frequently reported vector-borne disease of humans, costing an estimated USD 712M to 1.3B per year to the United States healthcare system alone (Adrion et al. 2015). In addition, the emerging pathogens that cause human granulocytic anaplasmosis (caused by *Anaplasma phagocytophilum*) and human babesiosis (caused by *Babesia microti*) are also transmitted by *Ixodes* ticks (Hersh et al. 2012, Keesing et al. 2012, 2014, Nelder et al. 2016).

The transmission of these vector-borne zoonotic pathogens to humans depends on a complex network of species interactions that influence host and vector abundance and infection prevalence. None of the three major tick-borne pathogens is transmitted transovarially; hence, each generation of larval ticks hatches free of infection. Larval ticks can acquire the infection during a blood meal on a reservoir host, after which they molt into the nymph stage that is responsible for the vast majority of tick-borne disease cases (Barbour and Fish 1993). In eastern North America, the primary reservoir hosts for all three pathogens are small mammals—the white-footed mouse (*Peromyscus leucopus*), eastern chipmunk (*Tamias striatus*), masked shrew (*Sorex cinereus*), and short-tailed shrew (*Blarina brevicauda*; Table 1, Fig. 1A, Ostfeld et al. 2014, Levi et al. 2016). Mice have particularly high reservoir competence for *B. burgdorferi*, and larval ticks attempting to feed on mice are more likely to survive to the nymphal stage, compared to ticks feeding on other hosts (Keesing et al. 2009). Consequently,

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TABLE 1. The estimated percentage of nymphal ticks fed and infected by each host based on estimates of population density, body burden of larval ticks, and realized reservoir competence for each *B. burgdorferi* (Bb), *B. microti* (Bm), and *A. phagocytophilum* (Ap).

Species	Density (ha)	Body Burden	Reservoir Competence (Bb)	Reservoir Competence (Bm)	Reservoir Competence (Ap)	Percentage of fed ticks (%)	Percentage of infected ticks (Bb; %)	Percentage of infected ticks (Bm; %)	Percentage of infected ticks (Ap; %)
Peromyscus leucopus	40	27.8	0.91	0.29	0.07	18.12	38.62	26.91	30.37
Tamias striatus	20	36	0.57	0.17	0.07	11.74	15.70	10.20	20.04
Sorex cinereus	25	55.5	0.33	0.29	0.02	22.62	17.51	33.69	9.50
Blarina brevicauda	25	62.9	0.45	0.19	0.04	25.63	26.80	25.15	23.50
Sciurus carolinensis	8.1	142	0.02	0.03	0.03	18.75	1.01	2.76	15.73
Small birds	31.6	1.7	0.12	0.03	0.02	0.88	0.24	0.12	0.37
Odocoileus virginianus	0.25	239	0.02	0.19	0.00	0.97	0.05	0.96	0.00
Mephitis mephitis	0.05	66.8	0.08	0.24	0.01	0.05	0.01	0.07	0.02
Procyon lotor	0.2	127	0.01	0.02	0.01	0.41	0.01	0.05	0.06
Didelphis virginiana	0.2	254	0.03	0.02	0.02	0.83	0.05	0.08	0.42

Notes: We assume equivalent molting success and overwinter survival among hosts. Data on population density, body burden, and reservoir competence are compiled from (LoGiudice et al. 2003, Keesing et al. 2009, 2012, 2014, Hersh et al. 2012, 2014, Ostfeld et al. 2014).

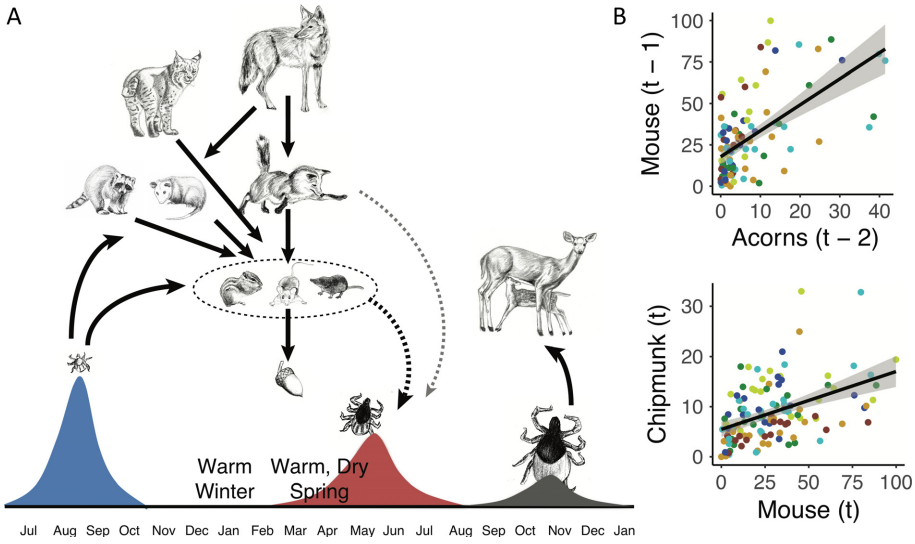

FIG. 1. Tick life cycle (A) in the context of the food web and climate, and (B) highlighting bottom-up forcing of mice and chipmunks by correlation, via the size of the previous year acorn crop. Results from each of six grids are separated by color. Drawings by Yiwei Wang and Taal Levi.

prior abundance of mice is hypothesized to affect density and infection prevalence of nymphs (Ostfeld et al. 1996, 2006). Mice and chipmunks are granivorous and omnivorous, and their population densities in summer are correlated with acorn production by oaks (*Quercus* spp.) the prior autumn (Fig. 1B, Ostfeld et al. 1996, Elkinton et al. 2004; see also supplementary materials), leading to the hypothesis that acorn production might predict tick-borne disease risk nearly two years in advance (Ostfeld et al. 1996, 2006).

These small mammals are preyed upon by various mammalian predators that can potentially reduce their abundance or modify their behavior with consequences for disease risk (Fig. 1A, Levi et al. 2012, Hofmeester et al. 2017*a*). Red foxes (*Vulpes vulpes*) may be particularly important predators of reservoir hosts because foxes are abundant and prey readily on small mammals (Major and Sherburne 1987), but coyotes (*Canis latrans*), bobcats (*Lynx rufus*), raccoons (*Procyon lotor*), and opossums (*Didelphis virginiana*) all prey on small mammals (Hamilton 1951, Sandidge 1953, Hopkins and Forbes 1980, Rivest and Bergeron 1981, Major and Sherburne 1987, Litvaitis and Harrison 1989, McLean et al. 2005). Although not as abundant, bobcats are likely to be key predators because they are obligate carnivores while the other species are omnivores. In addition, raccoons and opossums can divert tick blood meals away from competent hosts and can kill, via grooming, a large portion of larval ticks that they encounter (Keesing et al. 2009, Levi et al. 2016).

Species interaction among predators may also influence predation of reservoir hosts. In particular, substantial evidence indicates that coyotes (*Canis latrans*), which expanded into the US Northeast and Upper Midwest during the mid-20th century, locally displace smaller predators (Crooks and Soule 1999, Henke and Bryant 1999, Ritchie and Johnson 2009), especially foxes (Harrison et al. 1989, Ralls and White 1995, Crooks and Soule 1999, Henke and Bryant 1999, Fedriani et al. 2000, Kamler et al. 2003, Fener et al. 2005, Mezquida et al. 2006, Karki et al. 2007, Moehrenschlager et al. 2007, Thompson and Gese 2007, Levi and Wilmers 2012). Levi et al. (2012) hypothesized that displacement of foxes and other carnivores by coyotes would benefit reservoir hosts and therefore be expected to increase human risk of contracting tick-borne disease. Reservoir hosts are thus embedded in a complex food web, which is itself influenced by anthropogenic disturbances such as forest fragmentation and overexploitation.

A diversity of other factors has been postulated to affect population density and infection prevalence of nymphal *I. scapularis* (Fig. 1). In particular, the abundance of white-tailed deer (*Odocoileus virginianus*), an important host for feeding and reproduction by adult *I. scapularis*, is thought to correlate positively with oviposition rate and therefore with abundance of larvae the following year (Barbour and Fish 1993, Rand et al. 2004). Abundance of larvae might subsequently affect density of nymphs via demographic forcing, leading to a postulated 2-yr lagged correlation between deer and nymph densities (Barbour and Fish 1993). In addition, *I. scapularis* are sensitive to extremes in temperature and humidity during the 95% of their lives spent away from a host (Ogden et al. 2005, 2013, Levi et al. 2015, Ostfeld and Brunner 2015). Winter cold as well as spring and summer heat and dryness could reduce larval and nymphal survival, and snow cover is thought to increase survival through insulation (Hayes et al. 2015, Ostfeld and Brunner 2015, Burtis et al. 2016).

The complexity of factors potentially regulating risk of human exposure to tick-borne disease has previously made disentangling the biotic and abiotic drivers of disease risk intractable. Here we: (1) use 19 yr of data from six large field plots in southeastern New York to compare the effects of hypothesized drivers of interannual variation in Lyme disease risk, including the abundance of acorns, rodents, and deer, as well as a series of climate variables; and (2) employ landscape epidemiology to explore how variation in predator community structure influences spatial variation in the infection prevalence of ticks for the Lyme disease bacterium and two other important tick-borne pathogens.

Materials and Methods

Longitudinal field studies

Monitoring of populations of small mammals, blacklegged ticks, tick-borne pathogens, and tree seeds occurred in forests at the Cary Institute of Ecosystem Studies in Millbrook, NY (41°47′5.13″ N; 73°44′0.83″ W), which is centrally located within the Lyme disease endemic zone of the northeastern United States. These forests are typical of the temperate mixed deciduous/conifer forests of the mid-Atlantic and New England regions (Foster and Aber 2006), and are dominated by oaks (*Quercus rubra* and *Q. prinus*) and maples (*Acer rubrum* and *Acer saccharum*) in the overstory (Ogden et al. 2005), with oak and maple seedlings, maple-leaved viburnum (*Viburnum acerifolium*), witch hazel (*Hamamelis virginana*), and ironwood (*Ostrya virginiana*) common in the understory. Two 2.25-ha plots (150 × 150 m) were established in 1991, and four more were added in 1995 to comprise three pairs of plots with ca 150–250 m separating members of a pair and >700 m separating pairs.

Acorn sampling

Acorn production has been monitored since 1992 on the original 2 plots, and since 1999 on all 6 plots. Seed rain is sampled through the use of seed traps (circular fine-mesh baskets suspended ca 1 m above the ground, supported by monofilament line attached to nylon stakes to render them resistant to seed predators). Intact, mature acorns were counted monthly during autumn of each year, and the total number of acorns from all baskets within a plot was divided by the total basket area to derive an estimate of annual acorn production on each plot. The original two plots had 20 0.5 m^2 baskets located beneath different species of trees. Beginning in 1999, all six plots used a grid of 25 1.0 m^2 baskets located at small mammal trap stations (in addition to the 20 traps that continued to be monitored on the two original sites). Given the differences in the layout of the two sets of seed traps, the relationships between acorn production from 1999 to 2016 estimated from the two different sets of seed traps were used to correct the 1992–1998 data on the two original plots. Acorn density in year $t - 2$ was used as an independent variable potentially affecting Lyme-disease risk factors.

Small-mammal sampling

We have monitored abundance of small mammals at the Cary Institute using capture-mark-recapture techniques since 1991 (the two original plots) or 1995 (remaining four plots). On each plot we established an 11 × 11 point grid of Sherman live traps (one plot had a 10 × 12 point grid), with 15 m between trap stations and two traps per station, for a total of 242 traps per grid. Trapping is conducted for 2–3 consecutive days every 3–4 weeks generally from May to November of each year. Traps are baited with crimped oats (with sunflower seeds and cotton batting added during cold weather), set in late afternoon and checked between 08:00 hours and about 12:00 hours the following morning. This schedule allows us to capture both diurnal (chipmunks) and nocturnal (mice) small mammals. These two species comprised >90% of captures. Small mammals are marked with individually numbered metal eartags and released after handling at the point of capture. Data on age, sex, body mass, ectoparasite burden and trap station are recorded on each capture. An Institutional Animal Care and Use Committee approved protocols for animal handling annually.

We estimate population densities of white-footed mice and eastern chipmunks by inputting data from all trap sessions in a year into the Jolly-Seber open population model in program POPAN5 (Arnason and Schwarz 2000). We

selected the Jolly-Seber model that incorporates individual heterogeneity in capture probability. Because we are interested in assessing the importance of rodent abundance on nymphal tick abundance the following year, we focused on estimating rodent densities in mid-summer, which is the time of peak activity of larval *I. scapularis* at our sites (Ostfeld et al. 2006). In order to create a standard metric when actual trapping sessions varied in time, we estimated mouse and chipmunk abundance for each grid and year on 15 August by linear interpolation between rodent abundance estimates for trap sessions immediately before and after 15 August. Rodent densities, expressed as individuals per 2.25 hectare plot, in both year $t - 1$ and year t are used as independent variables potentially affecting Lyme-disease risk factors. We excluded data from plots and years during which field manipulations (localized mouse or chipmunk removals during 3 yr, and acorn addition during 1 yr, Ostfeld et al. 2006) could influence relevant variables.

Deer abundance estimates

Deer abundance was estimated at the scale of the Cary Institute property using population estimates from the Institute's limited-access bow-hunting program, which has run continuously from 1987 to the present (Winchcombe and Ostfeld 2001*a*, *b*). Between 7 and 11 hunters per year hunt an average total of 380 h (range 219–634 h) between mid-October and mid-November. All hunters were Cary Institute staff members or volunteers working with the staff wildlife biologist. Each was given exclusive access to one of 34 discrete hunting areas averaging 22 ha (range 9.3–35.7 ha). Virtually all hunting was from tree stands. Each day, hunters reported the number of hours hunted and the number of deer sighted, and these data were converted to deer observed per hour hunted. As a validation of this method, we asked whether deer observed per hour by bow-hunters was correlated with deer counts from annual autumn spotlighting surveys conducted from 1987 to 2000 (details in Winchcombe and Ostfeld 2001*b*), and found that the two census methods were highly correlated ($r = 0.70$, df = 11, $P = 0.01$; Winchcombe and Ostfeld 2001*b*).

Climate variables

A large number of climate variables (temperature, precipitation, minimum, maximum, variance, mean, specific to months or seasons, etc.) could potentially influence tick survival and densities of nymphs. Consequently, the probability of uncovering spurious relationships between climate and tick abundance is quite high if many explanatory variables are included without clear a priori justification. To avoid this problem, we selected climate variables that have been hypothesized to influence either changes in the abundance of immature blacklegged ticks or in human Lyme-disease incidence (Ogden et al. 2006, Diuk-Wasser et al. 2010, Hayes et al. 2015, Eisen et al. 2016). Recent studies (reviewed by Ostfeld and Brunner 2015, Eisen et al. 2016) suggest that survival of overwintering larvae and emerging nymphs are influenced by both winter temperatures and snow cover, and the combination of spring temperatures and humidity (due to sensitivity of larvae and nymphs to desiccation). Consequently, we included the number of days during February through April (year t) for which the minimum relative humidity was <50% and the maximum daily temperature was >15°C to represent harsh spring conditions. We included the number of days during the previous winter (November of year $t - 1$ through March of year t) for which the minimum daily temperature was ≥−10°C to represent warm winter conditions, as well as total snowfall (during that period) in cm to represent protective snow cover. Lastly, to represent total annual exposure to warm conditions, which is positively correlated with asynchronous feeding by larval and nymphal stages, we included cumulative degree days (base of 0°C) from October of the previous year through September of the current year (t). All weather data were obtained from the Cary Institute Environmental Monitoring Station, <2.5 km from the field plots (http://www.caryinstitute.org/science-program/research-projects/environmental-monitoring-program/weather-climate).

Tick and pathogen sampling

Estimates of the abundance and infection prevalence of nymphal ticks comprised the response variables of interest. In addition, estimates of larval abundance in year $t - 1$ were used as an independent variable. We monitored the abundance of larval and nymphal ticks in each plot and year by dragging 1-m^2 white corduroy drag cloths (Ostfeld et al. 1996) along 450 m of transects approximately every 3 weeks from April through November. Drag cloths were examined and all ticks counted and removed every 30 m. Frequent sampling in the early 1990s revealed that peak host-seeking activity for larvae occurred in mid to late August, and for nymphs occurred in mid to late June, and we timed our annual sampling to coincide with these peaks. Each year we conducted full drag sampling on all plots twice during the nymphal peak (mid May to early July) and twice during the larval peak (August to early September). For each plot and year, we estimated larval and nymphal abundance as the peak density (ticks per 100 m^2) obtained during those relevant months. Peak densities were highly correlated with cumulative seasonal densities (correlation coefficients typically >0.80; R. Ostfeld, unpubl.) on each plot. Additionally, to generate estimates of the total population of larval ticks (questing plus attached to hosts), we calculated the mean larval tick burden on white-footed mice during the trapping session closest to annual peak abundance, following Levi et al. (2016). These data on larvae per mouse were multiplied by estimated mouse density for that trapping session to generate estimates of the total population of larvae attached to mice per hectare. Estimated density of attached larvae was added to estimated density of questing larvae (from drag-sampling) to generate an estimate of the total larval population on each plot as a predictor of next year's nymph abundance.

Between 1994 and 2006, infection of individual ticks with *B. burgdorferi* was determined using direct immunofluorescence assay (DIA). Ticks were washed once in 70% ethanol and twice in deionized water and ground in phosphate-buffered saline (PBS). Three 5-ml aliquots of tick suspension were placed in separate wells in a multiwell slide, air-dried, and fixed in cold acetone for 10 min. Fluorescein rabbit

anti-*B. burgdorferi* conjugate was incubated in wells at 37°C for 45 min, after which slides were washed in PBS, dried, and mounted with a coverslip. Slides were examined systematically to categorize each tick as either infected or uninfected. On average, 378 nymphs (range 146–660) were examined for infection each year. Starting in 2007, half of all nymphs on each plot continued to be tested with DIA whereas the other half were flash-frozen for testing using quantitative PCR (methods in, Keesing et al. 2009, 2014, Hersh et al. 2012). To assess the DIA estimates relative to those generated by qPCR, in 2014 we collected 60 nymphal ticks from sites throughout the Cary Institute property and dissected each tick in half longitudinally, testing each individually by both methods. We calculated the sensitivity (true positive rate) and specificity (true negative rate) of DIA relative to qPCR as 77.8% and 97.7%, respectively. Based on these values, we converted all DIA estimates of NIP by dividing the observed proportion infected by the sensitivity. For nymphal infection prevalence with *Babesia microti* and *Anaplasma phagocytophilum*, we followed the protocols of (Hersh et al. 2012, 2014, Keesing et al. 2014).

Statistical approach for longitudinal data

For each of the three response variables (NIP, DON, and DIN) we compared a set of alternative models in which the dependent variable was a function of an a priori set of independent variables identified through previous research and hypotheses (Table 1). To account for the hierarchical structure of the dataset (observations over time within the plots), plot-specific intercept terms were included in the models for all three dependent variables. Based on previous research, we tested whether NIP varied as a function of mouse or total rodent density in year $t - 1$, or as a function of acorn density in year $t - 2$ (as a potential predictor of mouse and/or rodent density in year $t - 1$). Previous research indicates a much larger set of potential independent variables for DON and DIN. Initial model evaluation for those two dependent variables revealed slight non-linearities in the functional forms of the relationships, and modest heteroscedasticity in the residuals. To account for this, we transformed those two dependent variables using the natural log, and fit additive linear functions of the independent variables, using maximum likelihood methods with the likelihood package in R version 3.1.1 (R Core Team 2017). A normal distribution was used as the likelihood function, and the ln-transform of the dependent variables yielded a homogeneous variance in the model residuals. A single zero value for DIN (because of a zero value for NIP) was replaced with the lowest non-zero DIN value before the ln-transform. Using the autocorrelation function (acf) in R, we determined that there was no temporal autocorrelation in the residuals of the within-grid models for DON, DIN, and NIP.

Because of strong collinearity between acorn density (in year $t - 2$) and small mammal abundance (in year $t - 1$), and between mouse density and total rodent density in a given year, we first tested models for DON and DIN using either acorn density (year $t - 2$), mouse density (year $t - 1$), or total rodent density (year $t - 1$) with the other variables listed in the full model for that dependent variable (Table 1). The variable that yielded the lowest AIC_c was then used in subsequent model comparisons to identify the most parsimonious (lowest AIC_c) model. To do this, we systematically dropped one variable from the full model to see if the model was improved. Variables identified in that screening were then dropped to form a reduced model for comparison to the full model (Table 2).

Landscape epidemiology field studies

To determine whether carnivore community structure influences tick infection prevalence, we monitored carnivore communities and ticks in Dutchess County, New York at 87 sites in 2012 and 63 sites in 2013 (24 of which were monitored in both years). We monitored carnivore presence using Bushnell black-LED camera traps baited with cans of cat food nailed to a tree ~3–4 m from the camera. All cameras were set for a single session beginning between late May and late July and left for 4–6 weeks (29 ± 6 d) in order to target active home ranges rather than dispersing individuals in the fall and winter. The black-LED cameras do not produce visible light, and did not appear to be noticed by carnivores (in contrast to trials with infrared cameras). We collected ticks with drag cloths along a series of five 60 m linear transects at each site. The collected ticks were assessed for their infection prevalence with tick-borne pathogens (NIP), but we did not similarly assess intersite variation in tick density due to strong variation in understory density that could have affected sampling efficiency and phenology-driven variability in tick density across the weeks in which ticks were collected at the landscape scale. When conducted repeatedly (interannually) on the same plots, drag sampling estimates of tick density are not biased over the range of densities estimated with mark-recapture techniques (Daniels et al. 2000). Hence, we considered interannual estimates for the longitudinal study to be valid. Inefficiency is likely to vary as a consequence of the density of understory vegetation, which can affect contact between drag cloths and the ground, where larval and nymphal ticks quest, and we were less confident in the lack of bias given the large intersite variation we observed. Whole *Ixodes scapularis* nymphs were processed in the Keesing laboratory at Bard College and screened with quantitative real-time PCR for *A. phagocytophilum, B. microti,* and *B. burgdorferi*, according to protocols in (Keesing et al. 2009, 2012, 2014, Hersh et al. 2012, 2014). The human-active strain of *A. phagocytophilum* was detected using melting curve analysis, which we verified to be accurate using Sanger sequencing (Keesing et al. 2012).

We related the number of ticks infected relative to the number tested to both percent forest cover and carnivore community structure using a binomial generalized linear mixed model. We included a random effect for *site* because tick collections were nested within sites, and some sites were monitored for two years (as recommended by Warton and Hui 2011). We logit-transformed percent forest cover within a 1 km buffer and used both linear and quadratic terms in our regressions to account for this known landscape feature that may independently influence NIP (Allan et al. 2003). We included quadratic terms based on substantial support by AIC for *B. burgdorferi* and *B. microti* models ($\Delta AIC > 2$ for all models), although a quadratic term was not supported in the best models for *A. phagocytophilum*. Inclusion

of forest cover as a covariate reduced spatial autocorrelation in the residuals from all models (Moran's *I*: all *B. burgdorferi* regressions $P > 0.39$, all *A. phagocytophilum* regressions $P > 0.47$, but there was residual autocorrelation in *B. microti* $P < 0.03$).

We constructed carnivore community motifs to test a set of a priori hypotheses regarding how carnivores are expected to influence tick abundance and infection prevalence. We considered foxes and bobcats to be important small mammal predators, raccoons and opossums to be important dilution hosts that also prey on small mammals, and eastern coyotes to be a top predator that also preys on small mammals but that has an antagonistic relationship with smaller carnivores, notably foxes and opossums (Crooks and Soule 1999, Henke and Bryant 1999, Levi and Wilmers 2012) and potentially bobcats (Fedriani et al. 2000). We hypothesized that the presence of a more diverse, intact carnivore community would be correlated with reduced nymphal infection prevalence. Our previous research supported a particularly important role of foxes, and coyotes via their suppression of foxes (Levi et al. 2012), as well as opossums (Keesing et al. 2009). We also considered bobcats to be important as the only obligate carnivore (other species have more diverse diets), with substantial consumption of small mammals in the Northeastern USA (Litvaitis and Harrison 1989, Fox 1990, McLean et al. 2005). For each binomial regression model, we used a factor defining the motif to partition sites among those where a particular carnivore community was detected relative to all other sites. We considered 12 motifs. Motif 1: All mesopredators (fox, opossum, and raccoons) present or bobcats present. Bobcats were included with an or rather than and statement because they were much less common than the mesopredators, but sites with bobcats or a complete mesocarnivore community were expected to have low infection prevalence. Motif 2: Sites with all mesopredators regardless of the presence of bobcats or other carnivores. Motif 3: Foxes and opossums—an important predator and an important dilution host. Motif 4: Foxes or bobcats—a site with at least one of the hypothesized important small mammal predators. Motifs 5–8: Either foxes, opossums, bobcats, or coyotes present relative to all other observed community structures. Motifs 9–12: Coyotes present but opossums, foxes, neither opossums or foxes, and neither opossums or bobcats were observed. Detecting carnivores with camera traps can result in false negatives due to imperfect detection. We considered such non-detections as noise in our models that would reduce, rather than enhance, our ability to detect an effect of carnivore community structure on NIP. Thus, any detected signal between carnivore community structure and NIP must be strong enough to counteract the noise induced by imperfect detection.

Results

The longitudinal data comprised 78,146 captures of 19,299 individual white-footed mice and 15,646 captures of 3,755 individual eastern chipmunks. In addition, over the 19 yr for which we had a complete set of all independent and dependent variables, we counted 11,115 questing nymphs and 147,238 questing larvae.

Interannual variation in Lyme disease risk

The most parsimonious model from our set of a priori, mechanistically justified, variables (Fig. 1, Table 2) indicated that the density of *I. scapularis* nymphs infected with *B. burgdorferi* ($DIN_{Borrelia}$), was positively related to mouse density in year $t - 1$, negatively related to mouse density in year t, positively related to deer density in year $t - 2$, and negatively related to warm winter weather in the current year (Fig. 2, Table 2). A similar set of predictors was included in the best model for the total density of nymphs (DON), with the following differences: for DON, total rodent density (mouse + chipmunk) received greater support than mouse density alone, and number of spring days with warm dry conditions was better supported than warm winter weather (Table 2), but these two climate variables were correlated ($r = 0.46$). Substantial variation in DIN and DON among the six plots remained after accounting for effects of all independent variables (Fig. 2), suggesting that

Table 2. Model comparison for prediction of nymphal infection prevalence (NIP), density of nymphs (DON) and density of infected nymphs (DIN) in our longitudinal study.

Model	Terms in model	No. of parameters	AIC_{corr}	R^2
NIP ($n = 101$)				
Full	Rodent density ($t - 1$)	8	831.8	0.142
Null	Plot-specific means	7	830.2	0.135
DON ($n = 111$)				
Full	Plot-specific intercepts, Rodent density ($t - 1$), rodent density (t), larval density ($t - 1$), deer density ($t - 2$), CDD (t), warm dry spring days (t), warm winter days (t), snowfall (t), growing degree days (t)	15	243.5	0.521
Best	Plot-specific intercepts, Rodent density ($t - 1$), rodent density (t), deer density ($t - 2$), warm dry spring days (t)	11	235.8	0.509
DIN ($n = 101$)				
Full	Plot-specific intercepts, Mouse density ($t - 1$), mouse density (t), larval density ($t - 1$), deer density ($t - 2$), warm dry spring days (t), warm winter days (t), snowfall (t)	14	231.4	0.548
Best	Plot-specific intercepts, Mouse density ($t - 1$), mouse density (t), deer density ($t - 2$), warm winter days (t)	11	225.2	0.541

Notes: Presented are the terms in the full model and either the null model (for NIP) or the best reduced model (for DON and DIN), the number of parameters in each model, AIC corrected for small sample size (AIC_{corr}) and the R^2 of the models.

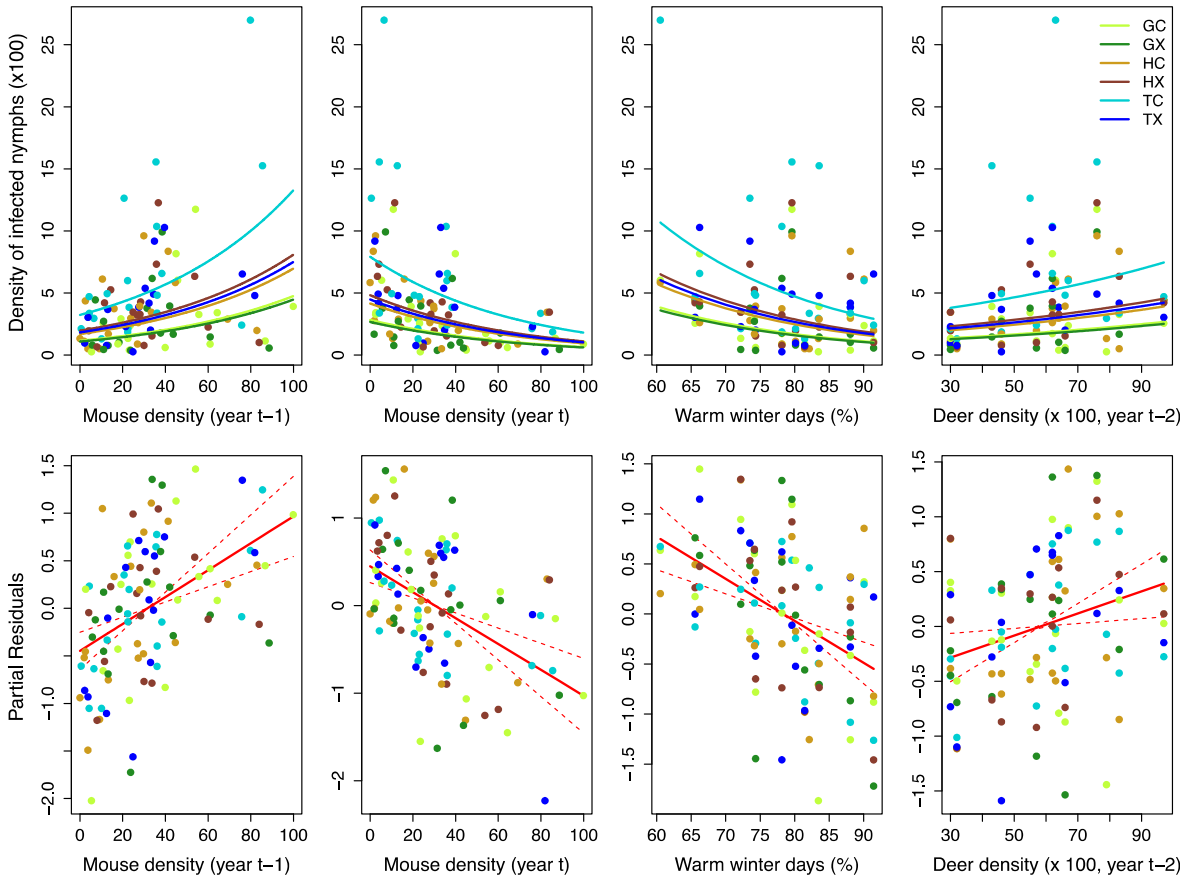

FIG. 2. Regression results of the most parsimonious linear model for predicting log (DIN). (A) Back-transformed fit of bivariate relationships from the multiple regression model, and (B) the partial residual plots demonstrating the effect and fit of each covariate when controlling for the others. Results from each grid are separated by color. Density of ticks is expressed as individuals per 100 square meters; density of white-footed mice is expressed as individuals per 2.25-ha plot; density of deer is expressed as numbers sited per hour by bowhunter-observers (times 100 for parameter estimation and comparison).

unmeasured factors operating at a scale of tens to hundreds of meters affect tick abundance. The modest positive effect of deer density in year $t - 2$ was detected despite no effect of the density of larval ticks in year $t - 1$ on either DON or $DIN_{Borrelia}$, indicating that demographic forcing from larval abundance to questing nymphs is weak. Bottom-up forcing by acorn production in year $t - 2$ was a strong, positive predictor of density of white-footed mice and of total rodents in year $t - 1$ (Fig. 1), but was not included in the most parsimonious models that included mouse and rodent density as independent variables. Our previous research (Ostfeld et al. 2006) found a positive relationship between nymphal infection prevalence ($NIP_{Borrelia}$) and acorn abundance 2 yr earlier, presumably because of the strong relationship between acorn abundance and rodent density the subsequent year (Fig. 1). Such a positive relationship remains ($P < 0.04$), but after accounting for plot-specific variation in infection prevalence, we observed no significant effect of acorns or rodent density on $NIP_{Borrelia}$ in the longer-term dataset (Table 2; Appendix S1).

Spatial (landscape) variation in Lyme disease risk

Bottom-up forcing explained between 50% and 55% of the variation in DON and $DIN_{Borrelia}$ but only 14% of the variation in $NIP_{Borrelia}$. We hypothesized that top-down effects might provide additional explanatory power for NIP. Predator community structure was not part of our longitudinal study, so we assessed potential top-down impacts using a shorter-term (2-yr) comparison of predator community structure and NIP for three tick-borne pathogens (*B. burgdorferi, Anaplasma phagocytophilum,* and *Babesia microti*) across 126 sites representing diverse landscape contexts in Dutchess County, New York, USA (Fig. 3). We predicted that sites with functionally diverse predator assemblages containing important small-mammal predators (foxes and bobcats) plus species that both prey on small mammals and deflect tick meals away from reservoir hosts ("dilution hosts" such as opossums and raccoons) would produce the lowest NIP; sites with only specialist predators or only dilution hosts would contain intermediate NIP; and sites in which coyotes displace small-mammal specialists and dilution hosts would contain the highest NIP (Fig. 4). Support for these predictions was strongest for $NIP_{Borrelia}$, which was significantly lower in sites with the most functionally diverse predator assemblages and higher in sites where coyotes displaced some or all of these predators. Similar but somewhat weaker patterns were observed for the other two pathogens. For both $NIP_{Babesia}$ and $NIP_{Anaplasma}$, the presence of assemblages containing specialist predators and dilution hosts had significantly lower

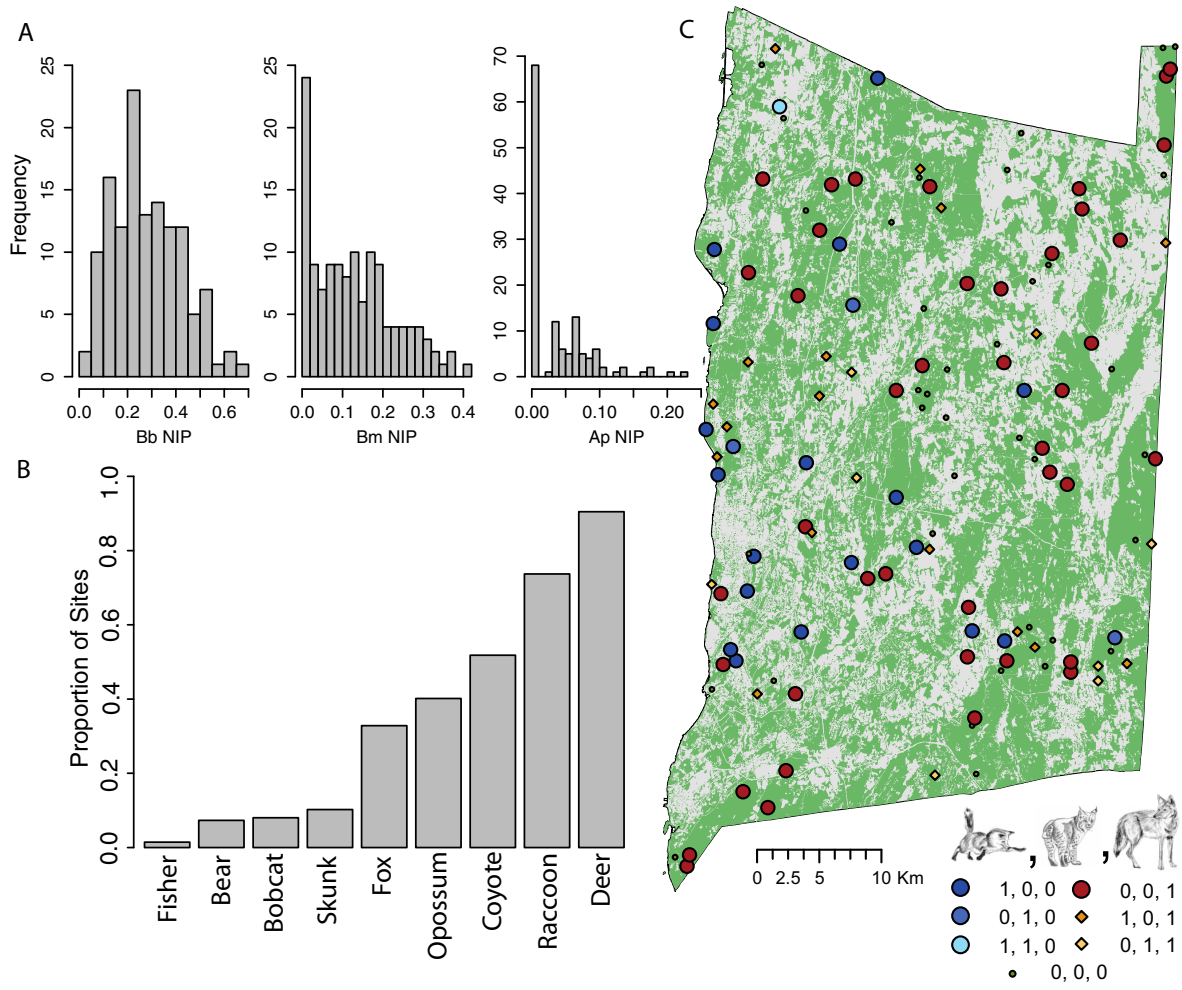

FIG. 3. Carnivore and pathogen relationships across Dutchess County, New York. (A) A histogram of the nymphal infection prevalence across sites for *Borrelia burgdorferi*, *Babesia microti*, and the human-active strain of *Anaplasma phagocytophilum* demonstrate that nymphs are much more frequently infected with *Borrelia burgdorferi* than the other two pathogens, which both had a mode of zero infected ticks. The human-active strain of *Anaplasma phagocytophilum* was particularly uncommon. (B) The proportion of sites where each species was detected by camera traps, highlighting the near complete detection of deer and raccoons, and the relative rarity of potentially important small mammal predators such as fishers, which are still expanding their range and recovering from overharvest, and bobcats. Much of the variation in carnivore detection depended on the presence of coyote, foxes, and opossums, all of which were detected at a moderate proportion of sites. Importantly, coyotes, which colonized New York during the mid-20th century, were the most frequently detected carnivore after raccoons. (C) The spatial distribution of sites with coyotes, foxes, and bobcats in relation to forest cover (green) in Dutchess County, New York.

than expected values, but the effects of coyotes in increasing NIP values were weaker (Fig. 4). For all three pathogens, NIP was highest in sites with low to moderate forest cover within a 1-km radius and was lower in sites with greater forest cover (Appendix S1: Fig. S1).

DISCUSSION

Changes to the community ecology of rodents are likely to influence the emergence and prevalence of zoonotic diseases worldwide. However, the complex network of interactions between abiotic factors, pathogens, vectors, hosts, and both food resources and predators of hosts is difficult to disentangle. Here we confront this complexity by combining nineteen years of intensive field study focused on the Lyme disease bacterium with a landscape epidemiology approach focused on three tick-borne pathogens. We found that both bottom-up forcing by acorns and top-down control by predators affected risk factors for human exposure. In both cases, the mechanism appears to depend on the regulation of small mammals that are the most competent reservoirs for tick-borne pathogens and the highest quality hosts for larval blacklegged ticks. Acorn-driven increases in the abundance of rodents are correlated with a lagged increase in the abundance of questing nymph-stage *Ixodes scapularis* ticks infected with Lyme disease bacteria ($DIN_{Borrelia}$), and the presence of a functionally diverse assemblage of predators is associated with reduced infection prevalence of *I. scapularis* ticks with zoonotic pathogens (NIP). A positive correlation between abundance of white-tailed deer and subsequent $DIN_{Borrelia}$ was also detected but the strength of the interaction was weak. Deer abundance has been postulated as a key driver of subsequent nymphal tick abundance via two sequential effects. First, adult tick populations with access to abundant deer hosts in autumn should have high reproductive rates leading to high densities of larvae the following

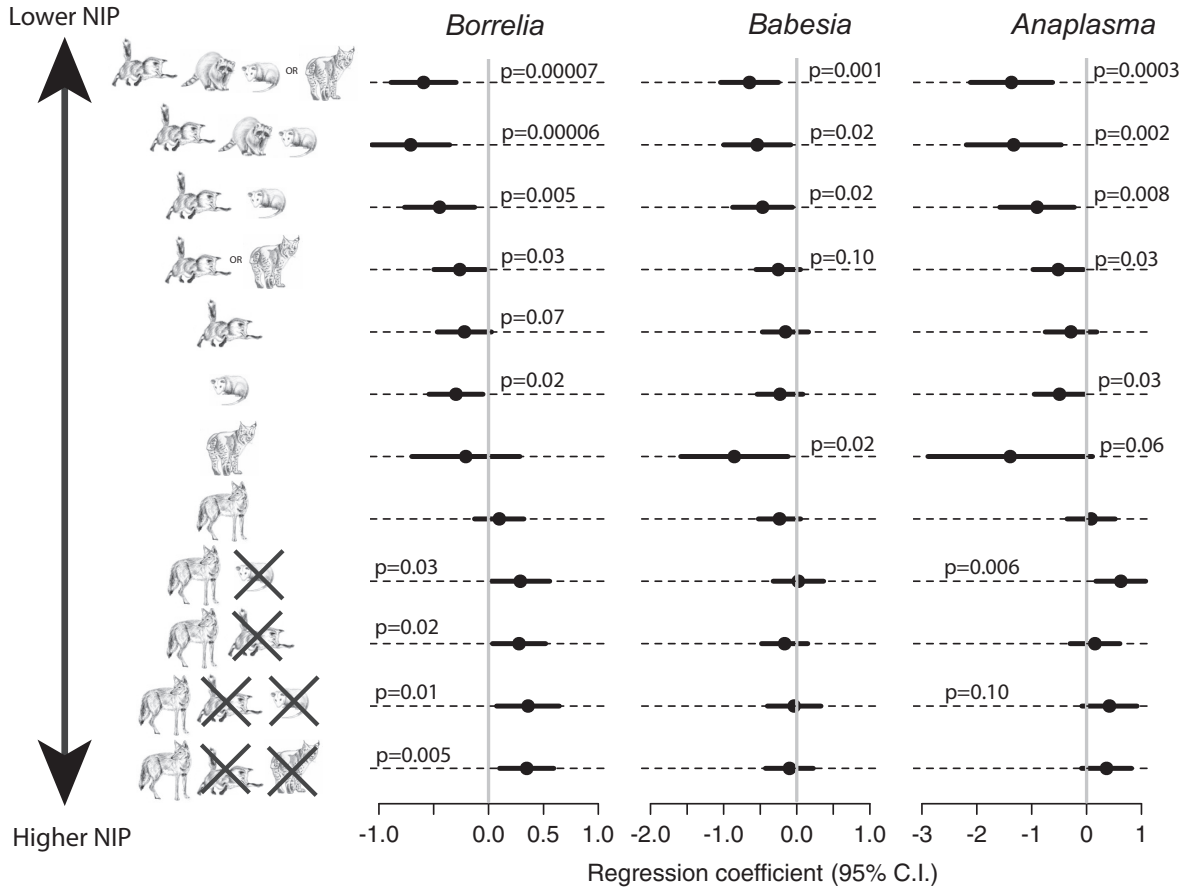

FIG. 4. The effect size of predator community structure on nymphal infection prevalence (NIP) determined from a binomial model of the number of infected ticks relative to the number tested while controlling for the proportion of forest cover within a 1 km buffer and including a random effect for the sampling site. Each row represents a separate regression testing the effect of a particular predator community motif represented as a binary factor (i.e., sites with that structure relative to all other sites). Motifs are arranged based on their expected effect on NIP. Sites where all the mesopredator dilution hosts (foxes, raccoons, and opossums) or the only obligate carnivore (bobcat) were detected were expected to have the lowest infection prevalence. Sites where coyotes are detected but not some combination of foxes, bobcats, or opossums are expected to have high risk. Some community structures were not possible to consider because no, or few, sites fit the motif. In particular, raccoons were so commonly detected that sites where raccoons were not detected but where other carnivores were present could not be considered. Bobcats, foxes, and opossums are all particularly associated with reduced NIP. Drawings by Yiwei Wang.

summer, and second, demographic forcing should drive high densities of nymphs one year later (Barbour and Fish 1993, Rand et al. 2004). However, we found no evidence that deer abundance in year $t - 2$ predicted larval abundance in year $t - 1$, and larval abundance in year $t - 1$ did not improve fit in our models of DON or $DIN_{Borrelia}$. Consequently, the mechanism underlying the weak positive effect of deer in year $t - 2$ on DON and $DIN_{Borrelia}$ is unclear. These results suggest that deer control as a Lyme disease management tool should be expected to have variable and sometimes weak impacts, in accordance with recent findings (Kugeler et al. 2016, Mysterud et al. 2016, Hofmeester et al. 2017*b*), although, due to nonlinearities, the effects may increase as deer reach very low abundance (Levi et al. 2012).

The strongly positive effect of mouse density in the prior year on $DIN_{Borrelia}$ is apparently due to both increased larval survival to the nymphal stage and efficient pathogen transmission (Keesing et al. 2009). Given the higher reservoir competence of mice than chipmunks, it is not surprising that $DIN_{Borrelia}$ was better predicted by mouse density while DON was better predicted by total rodent density. Density of mice or of total rodents in the current year was a negative predictor of $DIN_{Borrelia}$ and DON, apparently because high current abundance of these hosts can remove nymphs from the host-seeking population that might otherwise encounter people. The reduction in nymph density associated with warm, dry spring days in the current year presumably reflects desiccation-induced mortality of emerging nymphs. However, warm conditions in winter were associated with lower $DIN_{Borrelia}$ the following spring, the opposite of prior expectations that assumed cold-induced mortality. Although warming conditions, especially increases in cumulative annual degree-days, are associated with extensions of blacklegged tick populations to higher latitudes and altitudes (Ogden 2006, Ogden et al. 2008), our longitudinal study well within the tick's established range found no effect of variation in cumulative degree-days on either the overall density or density of infected nymphal ticks.

Density of nymphs and of infected nymphs varied among our six plots even after accounting for effects of all independent variables, with some plots consistently supporting higher nymph abundance (Fig. 2). The causes of this spatial

variation, which occurs at a scale of tens to hundreds of meters, are unknown but worthy of further study.

Infection prevalence of nymphal ticks with all three pathogens was lowest in sites with continuous forest (within 1 km buffer) that were occupied by a diverse assemblage of predators of small mammals (Fig. 4; Appendix S1: Fig. S1). For sites containing more effective predators of small mammals, such as red foxes and bobcats, the reduced NIP we observed was plausibly caused by reduced local abundances or activity of small rodents, disrupting host-to-tick transmission probabilities. We hypothesized that these sites would also be characterized by reduced DON but were unable to obtain reliable estimates of questing nymph density via drag-sampling because enormous variation in understory density would bias sampling efficiency, and because sampling at so many sites was necessarily protracted relative to the peak in questing activity of nymphs. For sites with more generalist predators, such as opossums and raccoons, the reduced NIP may have occurred because these hosts, which can be locally abundant, attracted ticks that might otherwise feed on rodents but failed to infect them due to low reservoir competence (Ostfeld and LoGiudice 2003, Keesing et al. 2009). Alternatively, these hosts may collectively contribute to predation on small mammals beyond that contributed by any one species. Presence of a diversity of small-mammal predators accentuated the reduction in NIP for all three pathogens. These observations, and the elevated NIP values observed where coyotes displaced these other meso-predators, are consistent with previous research showing reduced human incidence of Lyme disease where foxes are abundant and increased incidence where coyotes predominate (Levi et al. 2012). These results are also consistent with a recent study of tick-borne disease risk in the Netherlands, which found reduced tick (*I. ricinus*) burdens on small mammals with increased activity of red fox and stone marten (*Martes foina*), which appeared to indirectly reduce DON and DIN (Hofmeester et al. 2017*a*).

Taken together, our results suggest that a combination of bottom-up and top-down forcing would lead to a worst-case scenario for risk of human exposure to tick-borne pathogens. A year of acorn masting followed by a year of acorn failure should lead to a summer with highly abundant rodents followed by a summer with few rodents. High rodent abundance in one summer would elicit high densities of infected nymphal ticks that would emerge the following year, coinciding with low rodent abundance and hence low capacity to remove nymphs from the questing population. If this pattern of high-then-low acorn production occurred in areas with reduced abundance of foxes, bobcats, or dilution hosts, disease risk should be exacerbated even further. Risk would be elevated even more by a colder than average prior winter or concurrent spring.

Further studies will be necessary to evaluate the degree to which these scenarios for high risk are supported in nature. A key caveat is that our longitudinal study examined DIN, which measures the probability of human exposure to tick-borne infection given human entry into tick habitat and ignoring effects of other human behaviors such as protective clothing and self-inspections (Ostfeld 2011). In contrast, our landscape study examined NIP, which measures the probability of human exposure given a tick bite. Although NIP is generally considered less directly relevant than DIN as a predictor of tick-borne disease risk (Ostfeld et al. 2006), some studies have found spatial variation in NIP more consistently correlated with spatial variation in Lyme disease cases, as compared to variation in DIN (Connally et al. 2006). Not only do NIP and DIN differ somewhat in the aspects of disease risk they represent, they also can be affected by different processes acting at different scales. Smith et al. (2004) point out pitfalls associated with integrating different aspects of vector-borne disease risk. Modeling mosquito-borne disease, Smith et al. (2004) found that some correlates of risk, such as mosquito density and biting rate, tend to peak where breeding sites and human populations coincide and at or near peak mosquito population density; however, other correlates of risk, such as mosquito infection prevalence, tend to peak farther away from breeding sites and after the population peak because older mosquitoes that have dispersed farther away, and in declining populations, are more likely to be infected. Combining these risk elements to produce a single, average level of risk can produce biases. Because ticks are much less vagile than mosquitoes and feed only once per life stage, the processes affecting spatial and temporal variation in abundance and infection prevalence differ. However, the potential for unmeasured biases to affect heterogeneous predictors of vector-borne disease risk suggests that scenario-building from these predictors must be done cautiously.

Several key aspects of the current analyses differ from what has been established previously based on a shorter time series at these same sites (Ostfeld et al. 2001, 2006). One is that nymphal tick infection prevalence (NIP), after 19 yr, was no longer explicable based on bottom-up forcing (cf Ostfeld et al. 2006). A second is that previous analyses (Ostfeld et al. 2006) found no effect of prior abundance of deer, but we now detect a positive (albeit weak) effect. A third is that prior analyses (Ostfeld et al. 2006) found that none of several postulated weather parameters advocated in other studies affected tick-borne disease risk, but our long-term data now indicate that unusually warm, dry conditions in either winter or spring can reduce risk. This directly contradicts conventional wisdom (reviewed by Ostfeld and Brunner 2015). Fourth, although our longer time series continues to strongly support a positive impact of the prior year's density of rodents, particularly white-footed mice, on the current year's density of infected nymphal ticks, a novel result of the present study is a strongly negative impact of current year's rodent density on current year's DIN, apparently due to the removal of nymphs from the questing population as they find abundant rodent hosts. And finally, we find strong evidence that a diverse assemblage of predators can regulate an important element of zoonotic disease risk in this system.

For tick-borne diseases and many other zoonotic infections, small mammals play an outsized role as amplifiers of vectors and pathogens (Han et al. 2015, 2016). Ecological forces that regulate these small mammals appear critical to determining the risk of human infection. In the case of tick-borne pathogens in oak-dominated forests of the eastern United States, both a fluctuating acorn supply and the structure of the predator community appear to strongly affect risk of zoonotic transmission. For small-mammal reservoirs for other pathogens, other bottom-up and top-down forces, as

well as abiotic conditions, affecting abundance and hence transmission, are important (Ostfeld and Holt 2004, Krebs 2013). To anticipate patterns of top-down control by small-mammal predators, more research is necessary to increase our ability to predict predator community structure in space or time. Given the notorious challenges with diagnosis and treatment of tick-borne illnesses (Sanchez et al. 2016), and the high costs to patients and society of these reactive approaches, prevention of exposure based on ecological indicators of heightened risk should help protect public health.

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Supporting Information

Additional supporting information may be found in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/ecy.2386/suppinfo

Data Availability

Data available from the Dryad Digital Repository: https://doi.org/10.5061/dryad.d1c8046