What Do We Need to Know About Disease Ecology to Prevent Lyme Disease in the Northeastern United States?

REBECCA J. EISEN,1,2 JOSEPH PIESMAN,1 EMILY ZIELINSKI-GUTIERREZ,1 AND LARS EISEN3

ABSTRACT Lyme disease is the most commonly reported vector-borne disease in the United States, with the majority of cases occurring in the Northeast. It has now been three decades since the etiological agent of Lyme disease in North America, the spirochete Borrelia burgdorferi, and its primary North American vectors, the ticks Ixodes scapularis Say and I. pacificus Cooley & Kohls, were identified. Great strides have been made in our understanding of the ecology of the vectors and disease agent, and this knowledge has been used to design a wide range of prevention and control strategies. However, despite these advances, the number of Lyme disease cases have steadily increased. In this article, we assess potential reasons for the continued lack of success in prevention and control of Lyme disease in the northeastern United States, and identify conceptual areas where additional knowledge could be used to improve Lyme disease prevention and control strategies. Some of these areas include: 1) identifying critical host infestation rates required to maintain enzootic transmission of B. burgdorferi, 2) understanding how habitat diversity and forest fragmentation impacts acarological risk of exposure to B. burgdorferi and the ability of interventions to reduce risk, 3) quantifying the epidemiological outcomes of interventions focusing on ticks or vertebrate reservoirs, and 4) refining knowledge of how human behavior influences Lyme disease risk and identifying barriers to the adoption of personal protective measures and environmental tick management.

KEY WORDS disease ecology, Lyme disease, prevention, vector-borne disease, Borrelia burgdorferi

Three decades have passed since the spirochete Borrelia burgdorferi Johnson et al. was recognized as the etiological agent of Lyme disease and the tick Ixodes scapularis Say (that includes the synonym I. dammini) was incriminated as the principal vector of this pathogen in North America (Steere et al. 1977, Burgdorfer et al. 1982). Following these discoveries, numerous field and laboratory studies were conducted to elucidate the natural transmission cycle(s) of the spirochete and to identify key vertebrate spirochete reservoirs and tick vectors in different parts of North America, Europe, and northern Asia (Fiesman 2002). This was accompanied by development of novel prevention and control strategies and tools targeting: 1) host-seeking ticks, 2) ticks attached to vertebrate hosts, 3) B. burgdorferi in nonhuman vertebrate reservoirs, 4) the tick-human interface, or 5) B. burgdorferi in humans (Fiesman and Eisen 2008). Despite these efforts, Lyme disease remains the most commonly reported vector-borne disease in the United States, with annual case numbers increasing during the 1980s, 1990s, and 2000s (Bacon et al. 2008). This raises the questions of: 1) whether existing prevention and control strategies and tools are adequate to meet the challenge of reducing Lyme disease if they are implemented properly, 2) which types of novel strategies and tools with potential for reducing the burden of disease are missing in the current armamentarium, and 3) whether we know enough about the basic ecology of Lyme disease spirochete transmission, and the tick-human interface, to design effective prevention and control strategies and tools. Indeed, we find that there are numerous specific ecological and human behavioral questions with public health significance that remain to be addressed.

The aims of this article are to briefly summarize existing prevention and control strategies and tools aimed at reducing human exposure to vector ticks and B. burgdorferi, and to highlight conceptual areas where additional studies on the enzootic transmission cycle or the human-tick interface are needed to fill in the knowledge gaps preventing the development of novel, more effective Lyme disease prevention strategies and tools or the implementation of existing ones. Because the likelihood of human exposure to the tick and the pathogen both can be influenced by human behavior, we focus not only on the density of infected ticks, which represents the fundamental (or acarological) risk of human exposure to B. burgdorferi, but also provide an overview of studies that identify behavioral risk factors and explore areas where additional information in this field are needed. Our geo-

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1 Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, 3150 Rampart Road, Fort Collins, CO 80522.
2 Corresponding author, e-mail: dya2@cdc.gov.
3 Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO 80523.
Background to Tick Vectors, Vertebrate Reservoirs and Enzootic Transmission of *I. scapularis* in the Northeastern United States

The black-legged tick, *I. scapularis*, serves as the primary enzootic vector as well as the primary bridging vector to humans of *B. burgdorferi* in the northeastern United States. The tick’s life cycle (egg, larva, nymph, and adult female or male) is completed in 2 yr (Oliver 1989, Yuval and Spielman 1990, Fish 1993) and typically unfolds as follows: the female mates and feeds in the fall (Year 0) before overwintering (although some feed the following spring [Year 1]) and then lays a single egg batch, which contains 860–3,000 eggs (Fish 1993, Oliver et al. 1993), in the spring (Year 1). The larva hatches from the egg in the summer (Year 1) and begins to seek a bloodmeal host. After taking a single bloodmeal, over a 3–5 d period, the larva disengages from the host and the process of molting to the nymphal stage ensues. After this molt, the nymph overwinters and does not engage in host-seeking activities until the spring or early summer of the following year (Year 2). After finding a host and feeding to repletion, which typically takes 4–5 d, the nymph disengages from the host and molts to the adult stage. The adult female then seeks a bloodmeal in the fall of the same year (Year 2) or in the following spring. The female feeds to repletion in ∼7–10 d; the male may take small intermittent bloodmeals over the duration it is on a host (J. Piesman, unpublished data).

The larval and nymphal life stages typically infest small to medium-sized mammals (e.g., mice, voles, chipmunks, shrews, skunks, and raccoons) and birds, whereas the adult females commonly feed on larger animals, especially white-tailed deer (*Odocoileus virginianus* Zimmerman) (Piesman and Spielman 1979, Wilson et al. 1988, Mather et al. 1989, Fish and Daniels 1990, Daniels et al. 1991, Brisson et al. 2008, Mitra et al. 2010). A portion of these bloodmeal hosts (including the most important reservoir: the white-footed mouse, *Peromyscus leucopus* Rafinesque) are effective reservoirs for *B. burgdorferi*, with a high proportion of ticks becoming infected after feeding on an infected animal and retaining the infection after molting to the subsequent life stage. By contrast, white-tailed deer very rarely if ever act as a reservoir by infecting feeding ticks, but because it serves as the primary host for adults it is considered an important amplifying host for *I. scapularis* populations and thus indirectly impacts the intensity of spirochete transmission through influencing the abundance of immature infesting white-footed mice and other reservoir species (Telford et al. 1988, Mather et al. 1989). Many reservoir hosts, such as the white-footed mouse, can remain infectious to feeding ticks over long time periods, sometimes for life (Anderson et al. 1987).

A combination of epidemiological, laboratory, and field studies have convincingly demonstrated that the nymphal life stage of *I. scapularis* serves as the primary bridging vector to humans of *B. burgdorferi* (Piesman 1993, Falco et al. 1999, Connally et al. 2006). As a result, the density of infected nymphs is frequently used as an acarological measure of human risk for exposure to *B. burgdorferi* (Mather et al. 1996, Stafford et al. 1998). The seasonal host-seeking patterns of the different life stages of *I. scapularis* are well defined (Yuval and Spielman 1990, Fish 1993, Falco et al. 1999, Diuk-Wasser et al. 2006, Gatewood et al. 2009) such that nymphs typically take their bloodmeals from May through July, a time period that also coincides with the onset of symptoms for the majority of human Lyme disease cases in the northeast (Piesman 1989, Falco et al. 1999, Bacon et al. 2008). By contrast, larvae feed predominantly during June–September, with peak activity from late July through September. This seasonal asynchrony in nymphal and larval feeding provides adequate time for small mammal hosts to become infectious to feeding larvae after previously being fed upon by infected nymphs, and may, in part, explain the relatively higher prevalence of infection with *B. burgdorferi* in host-seeking *I. scapularis* nymphs in the Northeast compared with *I. scapularis* in the Upper Midwest or *I. pacificus* in the Far West where the seasonal timing of larval and nymphal feeding coincide (Spielman et al. 1985, Wilson and Spielman 1985, Ginsberg 1988, Yuval and Spielman 1990, Padgett and Lane 2001, Gatewood et al. 2009, Eisen et al. 2011).

Background to the Prevention and Control of *B. burgdorferi* Infections in Humans Through Reduction of the Density of Infected Host-Seeking Ticks and Use of Human Personal Protective Measures

The literature on Lyme disease prevention strategies was reviewed in detail previously (Fish 1995, Hayes and Piesman 2003, Stafford 2004, Schulze and Jordan 2006, Piesman and Eisen 2008). These interventions can be broadly categorized by four objectives: 1) reducing overall tick density, 2) lowering the prevalence of infection with *B. burgdorferi* in reservoir hosts and/or host-seeking ticks, 3) modifying human behavior to reduce exposure to ticks and prevent transmission by prompt removal of attached ticks, or 4) preventing Lyme disease by vaccination against *B. burgdorferi* or prophylactic treatment with antibiotics after a tick bite. The first two objectives are addressed in this section and the third objective in the final section. The last objective (vaccination and antibiotic treatment of humans) is beyond the scope of this article.

Knowledge gleaned from decades of field- and laboratory-based studies on *I. scapularis* have served as the foundation for the development of a wide range of intervention strategies that ultimately aim to reduce the density of infected ticks and thus lower the acarological risk of human exposure to *B. burgdorferi* through encounters with infected ticks, especially nymphs (Table 1). There are dual benefits to strategies aimed at reducing the overall density of ticks, such
as area-wide application of chemical or biological control agents (Curran et al. 1993, Benjamin et al. 2002, Schulze and Jordan 2006), treatment of key tick hosts with acaricides (Mather et al. 1987, Dolan et al. 2004, Brei et al. 2009), or reduction of the abundance of key tick hosts (Rand et al. 2004). First, by reducing the density of host-seeking ticks the probability of a human encountering a tick, and presumably also an infected tick, is lowered. Second, reducing the number of ticks feeding on infectious reservoir hosts should lower the force of infection (i.e., the number of secondary infections arising from a focal infection) and result in a lower prevalence of infection in the host-seeking ticks; thus, the probability of human encounters with infected ticks should be reduced. Other strategies, for example delivery of acaricides through treated bait or nesting material (Deblinger and Rimmer 1991), have focused specifically on reducing tick feeding on key reservoir hosts such as mice or chipmunks and thus lowering the intensity of enzootic spirochete transmission. Vaccination or prophylactic antibiotic treatment of key reservoir hosts may be considered as a means to reduce infection prevalence in ticks without affecting tick density (Tsao et al. 2004, Gomes-Solecki et al. 2006, Dolan et al. 2008, Schwanz et al. 2011).

Integrated tick management (ITM) strategies may combine multiple interventions aimed at reducing tick

<table>
<thead>
<tr>
<th>Purpose and method</th>
<th>Direct or time-lagged impact on risk of human exposure to ticks</th>
<th>Currently available for use</th>
<th>Representative studies</th>
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<tr>
<td><strong>Personal protection</strong></td>
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<tr>
<td>Protective human behaviors to prevent tick bites</td>
<td>Direct impact</td>
<td>Yes</td>
<td>(Hayes and Piesman 2003)</td>
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<tr>
<td>Avoidance of high risk habitat for tick exposure</td>
<td>Direct impact</td>
<td>Yes</td>
<td>(Stafford 2004)</td>
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<tr>
<td>Use of appropriate clothing to avoid tick bites</td>
<td>Direct impact</td>
<td>Yes</td>
<td>(Schreck et al. 1986, Hayes and Piesman 2003, Carroll et al. 2005)</td>
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<tr>
<td><strong>Reduction of the risk for exposure to B. burgdorferi after a bite by an infected tick</strong></td>
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<tr>
<td><strong>Prevention of Lyme disease in humans</strong></td>
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<td><strong>Household/community protection</strong></td>
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<td><strong>Reduction of density of host-seeking ticks: landscape management</strong></td>
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<tr>
<td>Deer fencing</td>
<td>Time-lagged impact</td>
<td>Yes</td>
<td>(Stafford 1993, Daniels and Fish 1995)</td>
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<td><strong>Reduction of density of host-seeking ticks: use of chemical compounds</strong></td>
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<tr>
<td>Area-wide application of synthetic acaricide compound</td>
<td>Direct impact</td>
<td>Yes</td>
<td>(Stafford 1991, Curran et al. 1993, Schulze et al. 2001)</td>
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<tr>
<td>Area-wide application of natural product acaricide compound</td>
<td>Direct impact</td>
<td>Yes</td>
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<tr>
<td>Area-wide application of desiccant compound</td>
<td>Direct impact</td>
<td>Yes</td>
<td>(Carroll et al. 2002, Solberg et al. 2003, Daniels et al. 2009)</td>
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<tr>
<td>Deer-targeted topical application of acaricide</td>
<td>Time-lagged impact</td>
<td>Yes</td>
<td>(Rand et al. 2000, Schulze and Jordan 2006)</td>
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<tr>
<td><strong>Reduction of density of host-seeking ticks: use of biological agents</strong></td>
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<tr>
<td>Area-wide application of pathogenic fungal acaricide</td>
<td>Direct impact</td>
<td>Yes</td>
<td>(Zhioua et al. 1997)</td>
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<tr>
<td>Area-wide application of nematode control agent acaricide</td>
<td>Direct impact</td>
<td>No</td>
<td>(Zhioua et al. 1995)</td>
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<td><strong>Reduction of infection with B. burgdorferi in rodent reservoirs</strong></td>
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<tr>
<td>Rodent-targeted oral vaccine</td>
<td>Time-lagged impact</td>
<td>No</td>
<td>(del Rio et al. 2008)</td>
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<td><strong>Reduction of infection with B. burgdorferi in ticks</strong></td>
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<tr>
<td>Rodent reservoir-targeted topical application of acaricide in bait box</td>
<td>Time-lagged impact</td>
<td>Yes</td>
<td>(Dolan et al. 2004)</td>
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<tr>
<td>Rodent reservoir-targeted acaricidal nesting material</td>
<td>Time-lagged impact</td>
<td>Yes</td>
<td>(Mather et al. 1987, Daniels et al. 1991, Deblinger and Rimmer 1991)</td>
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* This could also include chemical compounds targeting rodents but these are included under reduction of infection with B. burgdorferi in ticks because their primary purpose is to reduce spirochete transmission from key reservoirs rather than reducing the density of host-seeking ticks.
density or infection prevalence (Ginsberg 2001, Stafford 2004, Schulze and Jordan 2006, Schulze et al. 2007, Schwanz et al. 2011). Most of the methods that can be included in an ITM implementation are well suited for individual properties (e.g., education, landscape management, treatment of the vegetation with biological or chemical control agents, distribution of rodent-targeted acaricides, and deer fencing), whereas others require participation of a broader community (e.g., deer reduction, and application of acaricides to deer) (Table 1). Furthermore, based on their modes of action, the individual methods have different time spans before an effect is seen on the density of host-seeking nymphs. The effect can be immediate after the control implementation (e.g., landscape management and treatment of the vegetation with biological or chemical control agents) or delayed for one or more years (e.g., distribution of rodent- or deer-targeted acaricides, deer fencing, and deer reduction). The effectiveness of the above-mentioned methods to suppress the density of infected host-seeking nymphs when applied individually has been well documented but there is very little known about the additive effect of using multiple methods in an ITM framework (however, for an example of how this was incorporated into a modeling framework, see Mount et al. 1997a). This limits our ability to design locally appropriate ITM programs, and even our capacity to determine whether an ITM approach will represent an improvement over a single, effective control method.

The most effective use of these interventions, singly or as an ITM program, requires a sound understanding of the organisms targeted. For example, the timing of acaricide applications to vegetation in relation to the seasonal phenologies of different tick life stages can be critically important to determine the success of the intervention (Schulze et al. 1994). Furthermore, host community composition may affect the effectiveness of host-targeted interventions if the impact of the intervention differs between host species (Daniels et al. 1991, Mount et al. 1997a, Ginsberg 2001, Brisson et al. 2008). The spatial scale of the intervention and the landscape in which it is executed also needs to be considered. Recent landscape ecological studies have defined ecological correlates of I. scapularis density as well as the density of infected nymphs, which have been incorporated into a Geographic Information System framework to develop spatially predictive risk models (Killilea et al. 2008, Diuk-Wasser et al. 2010). Such studies may aid in determining broadly where prevention and control resources are most effective, and also can help home-owners to assess their level of risk for exposure to infected ticks. Results of fine-resolution landscape ecological studies have been used to design residential landscape modifications that aim to reduce the risk of encountering ticks in the peridomestic environment, where humans in the Northeast are most likely exposed to infected nymphs (Falco and Fish 1988, Fish 1995, Schulze et al. 1995).

Is There a Critical Host Infestation Rate Required to Maintain Enzootic Transmission of B. burgdorferi?

It has been proposed that using an ITM approach to combine interventions that reduce tick density with those that reduce infection prevalence may be the most effective strategy to reduce Lyme disease (Mount et al. 1997a, Ginsberg 2001, Dolan et al. 2004, Schulze et al. 2007). Given the documented willingness of property owners to invest only $100 per annum per household in Lyme disease prevention measures (Gould et al. 2008), one might ask if low-cost tick reduction measures alone could be sufficient to not only reduce the likelihood of human exposure to nymphs, but also to disrupt the enzootic transmission cycle resulting in a sustained reduction in infection prevalence. Furthermore, such a critical threshold(s) could be used as a bench mark by public health agencies to compare different products or interventions to assess the likelihood that they would disrupt transmission cycles. LYMESIM (Mount et al. 1997b), a simulation model of B. burgdorferi transmission by I. scapularis, is sought to identify a critical transmission threshold value above which the spirochete could be maintained in enzootic cycles and below which it could not. Results of the simulation indicated that the number of unfed nymphs per hectare required to maintain an enzootic transmission cycle ranges from 87 to 344 per ha (0.87–3.4 per 100 m²), depending on the geographic location and host composition. How this absolute density translates to the common measure of number of host-seeking nymphs per unit of time or area is unknown, which limits the utility of the model to compare the likelihood of various interventions achieving this threshold. As the relative abundance of white-footed mice, which are highly effective spirochete reservoirs, increased among the overall host population the density of nymphs required to maintain enzootic transmission decreased. The lower end in the nymphal density range mentioned above represents areas where P. leucopus is the predominant host species. The overall very low tick densities required to maintain enzootic transmission likely result from: 1) the ability of some hosts to remain infected and infectious for long time periods, 2) seasonal asynchrony of feeding by immature ticks allowing infected nymphs to infect mammalian hosts in time for them to have become infectious when larvae of the next generation engage in host-seeking and feeding, and 3) a high efficiency of transstadial transmission of B. burgdorferi in I. scapularis.

It is difficult to practically assess whether or not existing control measures are able to reduce nymphal populations below these theoretical threshold values and disrupt transmission cycles. This is in part because the threshold values identified by Mount et al. (1997) represent the total population of host-seeking nymphs. Most studies aimed at evaluating vector control measures quantify tick density based on drag sampling, which samples only a fraction (typically <10%) of the total host-seeking population (Daniels et al.
2000, Talleklint-Eisen and Lane 2000). The same basic problem occurs for tick abundance measures based on host infestation. Therefore, although at least one study (Curran et al. 1993) demonstrated that area application of acaricides could reduce sampled nymphal populations to below the minimum 87 per ha threshold identified by Mount et al. (1997), it is likely that the actual questing population was at least 10 times as high. Our attempt to compare nymphal densities from other tick control studies to this theoretical threshold value was thwarted because many studies compare tick abundance before and after treatment using number of ticks collected per unit of time sampled, or simply report the percent reduction posttreatment, rather than enumerating nymphal density per unit area. We are not aware of any field-based studies that have empirically determined host infestation rates or densities of host-seeking nymphs required to maintain enzootic transmission of B. burgdorferi but we believe that such information is critical for comparing the likelihood of any particular tick reduction intervention to disrupt the transmission cycle. Although infection persisted in host and tick populations, field-derived data suggest that reducing the abundance of immature ticks on small mammal hosts significantly reduces the force of infection. In one study, up to a 10-fold difference in infection prevalence among naïve juvenile mice was observed in areas where fipronil-treated bait boxes were used compared with untreated control sites (Dolan et al. 2004).

How Does Forest Fragmentation Impact Acarological Risk of Exposure to B. burgdorferi and the Ability of Interventions to Reduce Risk?

As summarized above, basic ecological studies have elucidated the complexity of the B. burgdorferi transmission cycle in the northeastern United States. They also indicate that the diversity of tick hosts, with variable capacity to serve as reservoirs for B. burgdorferi, may affect both the infection prevalence in host-seeking ticks and the density of infected host-seeking ticks through “zooprophylactic,” “dilution,” or “rescue” effects (Spielman et al. 1985, Mather et al. 1989, Mount et al. 1997b, LoGiudice et al. 2003, Logiudice et al. 2008, Keesing et al. 2009). This emphasizes the potential for vertebrate host community structure and diversity to impact human risk of exposure to Lyme disease spirochetes. Island biogeography theory tells us that diversity should increase with increasing island size and decreasing isolation. By the corollary, as island size decreases and isolation increases, diversity decreases (MacArthur and Wilson 1967, Simberloff and Wilson 1969). Tenets of this theory have been extrapolated to explore how forest fragmentation, which results in patches or “islands” of suitable habitat for tick and tick host populations of varying size and connectedness, impacts B. burgdorferi transmission cycles (Allan et al. 2003, Brownstein et al. 2005, Jackson et al. 2006, Estrada-Pena 2009).

It has been proposed that spatial variation in incidence of human Lyme disease or acarological risk for exposure to Lyme disease spirochetes in the northeastern United States may be associated with forest fragmentation (Frank et al. 1998, Ostfeld and Keesing 2000, Allan et al. 2003, Brownstein et al. 2005, Jackson et al. 2006). Following the island biogeography or “diversity” hypothesis, forest fragmentation influences the diversity of small and medium sized mammals and therefore influences the source for bloodmeals by immature ticks. As patch size and connectedness among patches decays, host diversity declines. Because of its generalist nature, small territory size, and ability to persist in high density populations, the white-footed mouse is often the dominant host species in small forest patches and densities of less competent B. burgdorferi reservoirs are often reduced (Ostfeld and Keesing 2000, Allan et al. 2003). As a result of the predominance of a highly effective B. burgdorferi reservoir that hosts high numbers of immature ticks, infection prevalence in nymphs and density of infected nymphs are expected to be higher than in situations (e.g., less fragmented forest stands) where alternative, less effective reservoirs present opportunities for tick bloodmeals (Logiudice et al. 2008). Indeed, one study demonstrated that small forested patches (<2 ha) in Dutchess County, NY, compared with larger patches experienced higher nymphal densities and higher infection prevalence with B. burgdorferi, leading to higher acarological risk of spirochete exposure within small patches (Allan et al. 2003). In contrast, or perhaps in addition to the diversity hypothesis, elevated tick abundance in fragmented landscapes could arise because forest fragmentation produces an increase in “forest edge” or ecotonal areas where white-tailed deer thrive from abundant forage and cover (Brownstein et al. 2005). Increases in the abundance of the preferred host of adult ticks should lead to increases in feeding and reproduction of I. scapularis resulting in elevated numbers of immature ticks in the next generation (Wilson et al. 1985) that may increase the force of infection leading to higher densities of infected nymphs.

Although forest fragmentation has been shown to have a positive association with acarological risk of exposure to B. burgdorferi in several studies (Frank et al. 1998, Allan et al. 2003, Brownstein et al. 2005), fragmentation or reduction in patch size is not necessarily indicative of increased Lyme disease incidence (Brownstein et al. 2005, Jackson et al. 2006). This nonintuitive finding may be related to human use of the peridomestic landscape that is considered to account for the majority of human exposures to B. burgdorferi-infected ticks in the Northeast. Density of host-seeking ticks typically is low on well-maintained lawns compared with residential woodland edges and adjacent wooded areas (Maupin et al. 1991). To better understand the linkage between forest fragmentation and occurrence of Lyme disease in humans we therefore need to conduct studies that generate information on forest fragmentation as well as fine scale density of infected ticks and human use patterns for different microhabitats in the peridomestic environ-
ment (e.g., lawns, woodland/lawn ecotones, and wooded areas). Furthermore, as demonstrated in California (Eisen et al. 2004), the land use category (e.g., grassland, urban, suburban) that is present in nonforested patches is likely to influence host infestation and acarological risk, but this is not typically considered. Therefore, the relationship between infected tick densities, landscape ecology, and human use patterns may be more complex than indicated by simple fragmentation indices.

We also recognize a need to further investigate how forest fragmentation may impact the effectiveness of different types of tick control interventions. Although several interventions are independent of landscape configuration (e.g., personal protective measures such as avoiding risk habitats or use of repellents) others could be more or less effective in fragmented landscapes. For example, if fragmentation consistently leads to a reduction in host diversity, host-targeted interventions could potentially be more effective in areas with low host diversity. As an example, vaccination of white-footed mice against _B. burgdorferi_ significantly reduced the density of infected _I. scapularis_ nymphs, but the magnitude of the disruption was hypothesized to be reduced because alternative reservoirs (e.g., shrews; Brisson et al. 2008) were available for immature ticks to feed upon (Tsao et al. 2004). Likewise, host-targeted acaricide interventions primarily focusing on white-footed mice (e.g., distribution of acaricide-treated nesting material) have been demonstrated to be highly effective in some areas but less successful in others, and it has been proposed that these differences could be attributed to presence of alternative reservoir hosts that were not effectively targeted in the given intervention (Mather et al. 1987, Daniels et al. 1991, Deblinger and Rimmer 1991, Ginsberg 1992, Dolan et al. 2004).

Despite lively debate in the ecological literature related to how landscape configuration may affect host diversity and _B. burgdorferi_ transmission rates, relatively few studies have focused on how _B. burgdorferi_ is maintained in enzootic cycles within the wooded suburban areas that currently dominate Lyme disease endemic areas of the Northeast. Furthermore, studies aimed at evaluating the impact of physiographic effects on transmission cycles at small spatial scales within these residential landscapes are sparse.

**What Are the Epidemiological (Lyme Disease Reduction) Outcomes of Interventions Focusing on Ticks or Vertebrate Reservoirs?**

Despite numerous and diverse options for preventing Lyme disease, there is a lack of evidence that interventions focusing on ticks or vertebrate reservoirs result in reductions not only in acarological risk measures but also in the numbers of human cases of Lyme disease. Such demonstrations may provide a more compelling reason for public health agencies to advocate for, and for individuals to practice, interventions focusing on ticks or vertebrate reservoirs. Furthermore, quantifying the association between a reduction in density of infected nymphs and a corresponding reduction in Lyme disease cases would allow public health agencies to compare the cost-effectiveness of different interventions aimed at reducing density of infected nymphs; cost-effectiveness or cost-benefit analyses typically assess value in number of cases prevented, rather than the number of ticks killed (Meltzer et al. 1999). Lack of evidence for the efficacy of vector control interventions to result in a decrease in human cases of Lyme disease is in stark contrast to other important vector-borne diseases, malaria perhaps being the best example, where epidemiological outcomes are routinely determined for control interventions that target the vector. There are also such examples emerging for West Nile virus disease in the United States, where an intervention focusing on the vector was followed up by determination of not only entomological but also epidemiological outcomes (Carney et al. 2008).

One contributing reason for the systemic lack of determination of epidemiological outcomes for studies aiming to reduce Lyme disease through decreased risk of exposure to infected ticks may be a difference in the spatial scales at which the intervention is implemented (typically individual properties) and for which reliable epidemiological data are collected as part of the passive health surveillance system (typically aggregated to administrative boundaries such as zip code or county of residence). This makes it more difficult to use existing, passively collected epidemiological data to assess reductions in Lyme disease cases. One possible solution to this problem is to scale up the intervention so that the scale matches that for passively collected epidemiological data. Such an intervention would likely focus on deer-targeted interventions that have broader spatial efficacy compared with local interventions (such as area-wide acaricides or rodent-targeted interventions). We acknowledge that there are logistical challenges associated with a large-scale evaluation that must be overcome. These include cost, variation in treatment-seeking behavior over the intervened region, and diagnostic and reporting variability. If such a study is not feasible, another solution is to design a prospective study that compares exposure to _B. burgdorferi_ between humans residing on properties impacted versus not impacted by the intervention; for example, persons residing on properties where an intervention focusing on ticks or vertebrate reservoirs were conducted compared with persons residing on control properties. One challenge related to this approach is that the intervention needs to be conducted in areas where attack rates of _B. burgdorferi_ in the human population are high enough (e.g., high densities of infected nymphs and evidence of human contact with nymphs) that the study design has adequate statistical power to detect a meaningful reduction in attack rates as evidenced by a reduction in human exposure to _B. burgdorferi_.

To date, the most commonly measured outcomes of interventions focusing on ticks or vertebrate reservoirs have been density of host-seeking ticks, abundance of ticks on hosts, and density of _B. burgdorferi-
infected ticks (Daniels et al. 1991, Ginsberg et al. 2002, Dolan et al. 2004, Hoen et al. 2009). Although only a few studies have assessed the strength of the association between density of *B. burgdorferi*-infected vector ticks and the incidence of Lyme disease in the human population, it is often and reasonably assumed that the probability of human exposure to *B. burgdorferi* increases with increasing density of infected ticks. Thus, the product of tick density and infection prevalence is frequently used as an acarological (or sometimes referred to as entomological) risk index (Mather et al. 1996). This type of risk index has been shown to be strongly and positively correlated with the number of reported Lyme disease cases or incidence of Lyme disease in Connecticut and Rhode Island (Mather et al. 1996, Stafford et al. 1998, Johnson et al. 2004). In the Rhode Island study, a significant linear association between the density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and Lyme disease case rate was identified such that the case rate per 100,000 was equal to 2,190.84 \times \text{ number of infected nymphs collected per minute of sampling}. However, it should be noted that other studies have shown that ecological variables predictive of positive associations with the density of infected ticks (i.e., landscape fragmentation) are negatively associated with Lyme disease incidence, suggesting that the density of infected ticks is not always a reliable predictor of disease incidence (Brownstein et al. 2005). This could, for example, result from human behaviors leading to minimal use of certain habitat types with high densities of infected ticks.

While a quantitative association between density of infected ticks and Lyme disease incidence could be useful for estimating an expected percentage reduction in Lyme disease incidence based on a fixed reduction in the density of infected nymphs, there are several notable caveats to such an exercise. Most importantly, it is not clear if a single functional and quantitative relationship is consistent across the geographic range of *I. scapularis*, or even between different habitat types within a given geographical area. Furthermore, incidence is a measure of Lyme disease cases per human population and tick density typically is heterogeneous across the administrative spatial unit for which incidence is derived based on passively collected data from the health system. Therefore, if a given model is used to set targets for reduction of the density of infected ticks and to determine if Lyme disease incidence declines following model predictions after an intervention, knowledge of the spatial heterogeneity on and adjacent to properties enrolled in the intervention must be taken into account, as should knowledge of the duration of time humans spend in various land class categories that are often associated with acarological risk (Killelea et al. 2008). We predict that a set of models, rather than a single one, would need to be developed and then applied as appropriate based on environment and human use patterns.

Tick control most commonly is implemented at the level of the individual property. Therefore, it is most appropriate to assess case occurrence or pathogen exposure in relation to the density of infected ticks for the particular households that are included in an intervention and the control properties. Intriguing issues that remain to be addressed in the context of tick control typically being implemented for individual properties include the potential for spill-over effects that occur, in subsequent years, between treated and adjacent nontreated properties, and the potential benefit of treating multiple adjacent properties. For example, one study (Dolan et al. 2004) demonstrated that rodent-targeted acaricide use effectively reduced the density of host-seeking nymphs and prevalence of *B. burgdorferi* in host-seeking nymphs in subsequent years. However, immigration to and emigration from the treated site was frequent and infestation rates on untreated mice that immigrated from neighboring properties that did not implement this control remained high. Given the overall low percentage of households that implement residential control measures, there is a need to evaluate how interventions applied to single properties versus clusters of properties influences the probability of Lyme disease case occurrence in persons residing in treated and neighboring untreated residences.

**How Does Human Behavior Influence Lyme Disease Risk and What Are the Barriers to Adoption of Personal Protective Measures and Environmental Tick Management?**

The success of any intervention method is dependent on the willingness of people in endemic areas to use it. More than two decades of efforts to motivate people to adopt methods to reduce the chance of tick attachment or to reduce the number of ticks and/or potential vertebrate hosts on individual properties or in community settings have been met with variable success. This can be related to shortcomings in the way the prevention message is communicated to the public, such as insufficient targeting of messages, or that some people do not consider Lyme disease a severe problem or do not see solutions to be of sufficient utility for them to take action. Theories such as the Health Belief model (Rosenstock 1974) suggest that health behaviors will be determined by an individual’s perception of susceptibility to disease and disease severity, and by the perceived efficacy versus inconvenience/cost of the behavioral change being proposed. In the case of vector-borne diseases, additional factors relating to environmental cues that are perceived to signal increased risk of pathogen exposure, for example, recognizing a specific habitat as presenting high risk of tick bites or actually being bitten by a tick, also will play a role in the decision-making process (Zielinski-Gutierrez and Hayden 2006). A more in-depth understanding of the process through which people residing in Lyme disease endemic areas assess their level of personal risk and make decisions regarding protective actions is needed to optimize the prevention message broadcast by public health agencies. Here we summarize issues related to human behavior...
which, if addressed, may improve Lyme disease prevention.

Estimates of use of personal protective measures, such as repellents, protective clothing, and tick checks, suggest that they are used more widely in the Northeast than environmental management techniques, such as acaricide application and “tick-safe” landscaping (Gould et al. 2008, Connally et al. 2009). Personal protective measures have emerged from controlled studies as factors associated with a reduction in infection with *B. burgdorferi* less frequently than one could expect (Ley et al. 1995, Klein et al. 1996, Orloski et al. 1998, Phillips et al. 2001, Smith et al. 2001, Connally et al. 2009). However, bathing within 2 hr of being outdoors as well as promptly checking for and removing ticks after coming indoors, and thus removing infected ticks before they have a chance to transmit the spirochete, were found to be associated with reduced risk of infection in a recent case-control study conducted in Connecticut (Connally et al. 2009). Several studies (Klein et al. 1996, Orloski et al. 1998, Smith et al. 2001, Connally et al. 2009) provide evidence for certain ecological characteristics of the peridomestic setting being important risk factors: for example, presence of wooded areas, leaf litter, or deer. However, relative to personal protective measures, peridomestic environmental management to mitigate these risk factors demands more planning and carries a higher cost. Communication to present these more involved options to the public may need to use different strategies than messages intended to remind people to regularly use basic personal protective measures.

The evidence for repellent use—one of the most commonly promoted methods of personal protection against tick bites—to lower the risk of *B. burgdorferi* infection is limited (Klein et al. 1996, Smith et al. 2001, Vazquez et al. 2008, Connally et al. 2009, Bissinger et al. 2011). There is no question that *I. scapularis* is repelled from skin and clothing by commercially available repellents containing DEET and other active ingredients (Carroll et al. 2004, Environmental Protection Agency 2010). However, generally only 20–40% of respondents in areas where Lyme disease is prevalent report regular use of repellents (Gould et al. 2008, Connally et al. 2009, Heller et al. 2010). Another routinely recommended, but rarely used, personal protective measure is to wear insecticide (permethrin)-treated clothing (Connally et al. 2009; Center for Disease Control [CDC], unpublished data). A recent pilot study found that outdoor workers wearing permethrin-treated clothing experienced a 93% reduction in tick bites compared with co-workers using standard tick-bite prevention measures (Vaughn and Meshnick 2011). Distaste or inconvenience often are reported as barriers to use of repellents (CDC unpublished data) and it therefore would be useful to refine guidance as to where and when repellents or insecticide-treated clothing are best used rather than recommending to “always” use these measures when outdoors.

Controversy over some environmental tick control measures influences their likelihood of being implemented. For example, survey and focus group respondents cite safety and environmental impact concerns related to the use of acaricides for tick control (Gould et al. 2008; CDC, unpublished data). When asked about willingness to apply acaricides, less than half of respondents in an area heavily exposed to educational campaigns indicated a willingness to do so (Gould et al. 2008). However investigation of consumers’ and pest control applicators’ knowledge about different acaricide options, including the use of synthetic acaricides versus those based on natural products, and communication about the relative risks and benefits of limited acaricide use may prove useful (Peterson and Higley 1993). The issue of lethal and even nonlethal management of deer is also often controversial. Motivation for deer management can be multifaceted (reducing damage to landscaping or crops, preventing deer-vehicle collisions, or reducing tick density) but costs are considerable and the social issues relating to deer management are complex and community consensus is hard to achieve (Bowker et al. 2003, Rondeau and Conrad 2003).

There are numerous unanswered questions relating to how specific human behaviors may influence risk of exposure to ticks and *B. burgdorferi*, as well as the effectiveness of specific tick control methods to prevent tick bites. One set of interrelated questions are: 1) how much of the overall risk for tick bites is accounted for by time spent on your own residential property versus private properties owned by others or public lands, 2) if personal protective measures differ for the time spent in these different environments, and 3) how commonly people venture into, and beyond, the lawn-forest ecotone that is a high-risk microhabitat within residential areas. Exploration of residents’ understanding of “risk zones” for ticks and Lyme disease, and the demographic variation in these perceptions, may provide insight into behaviors and result in opportunities to better “market” and target prevention efforts. Another set of questions relate to the spatial scale of tick control interventions, which may be important for residents’ participation and compliance: 1) how do people perceive the effectiveness of different tick control actions when they are confined to a single property versus implemented on multiple ones and 2) is there social pressure in Lyme disease endemic areas to use and support tick reduction strategies?

A third set of questions relate to intervention cost. The willingness to pay for residential property tick control has been cited as quite low, $100 per household (Gould et al. 2008), though this assessment can be critiqued as less robust than a true willingness-to-pay analysis as practiced by health economists (e.g., Gowdy and Mayumi 2001). Further attention to willingness to pay for tick control, including use of contingent valuation, analysis of household costs (monetary and otherwise) incurred because of tick avoidance and tick-borne disease, and contrasting the benefits of preventive actions may provide a more thorough understanding of consumers’ willingness to invest in tick bite prevention measures. A final issue relates to how, after the effectiveness of specific per-
sonal protective or tick control intervention methods is established, an educational program should be designed to most effectively promote their adoption. Future prioritization of evaluation efforts for educational programs, focusing not only on the resulting changes in knowledge of Lyme disease, tick bite prevention and tick control methods but also determining the specific barriers to use of personal protective measures or environmental tick management techniques, will be a critical contribution.

In conclusion. There has been significant progress made in understanding the ecological complexity of enzootic *B. burgdorferi* transmission cycles. However, there is a need for related operational research to link this knowledge to practical measures to reduce tick bites and Lyme disease in humans in the northeastern United States. Throughout this article, we note that the responsibility for acting on Lyme disease prevention recommendations falls largely upon individuals. This is in striking contrast to mosquito-borne diseases for which vector control districts shoulder much of the responsibilities for monitoring mosquito abundances and infection rates for key viral pathogens and suppressing vector populations. Whether or not communities should consider including tick control in vector control activities is a topic for debate. We argue that the knowledge gaps identified in our study would be relevant to discussions of the cost-effectiveness of community-based tick control programs, methods for setting targets for control, and assessing whether such a program would be effective in different. Key objectives for such research include:

- Quantifying the association between acarological risk of exposure to host-seeking *B. burgdorferi*-infected *I. scapularis* ticks and the extent of human spirochete exposure, particularly at the spatial scale at which tick control interventions are typically implemented (i.e., individual properties or small groups of properties).
- Evaluating how interventions applied to single properties versus clusters of adjacent properties influences the probability of Lyme disease case occurrence in persons residing in treated and neighboring untreated residences.
- Determining if intensive tick reduction can result in local elimination of *B. burgdorferi* transmission across a gradient of forest fragmentation across different habitats and gradients of forest fragmentation.
- Determining how landscape structure influences the effectiveness of different tick control strategies and identifying “landscape markers” that might suggest improved success of specific interventions.
- Improving the knowledge of how humans use different microhabitats that may pose elevated risk for exposure to infected nymphs, especially in the peridomestic environment.
- Enhancing understanding of human motivations and acceptance of personal protective measures and environmental tick control interventions with demonstrated effectiveness.

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