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Critical Evaluation of the Linkage Between Tick-Based Risk Measures and the Occurrence of Lyme Disease Cases

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Abstract

The nymphal stage of the blacklegged tick, *Ixodes scapularis* Say, is considered the primary vector to humans in the eastern United States of the Lyme disease spirochete *Borrelia burgdorferi* sensu stricto. The abundance of infected host-seeking nymphs is commonly used to estimate the fundamental risk of human exposure to *B. burgdorferi*, for the purpose of environmental risk assessment and as an outcome measure when evaluating environmentally based tick or pathogen control methods. However, as this tick-based risk measure does not consider the likelihoods of either human encounters with infected ticks or tick bites resulting in pathogen transmission, its linkage to the occurrence of Lyme disease cases is worth evaluating. In this Forum article, we describe different tick-based risk measures, discuss their strengths and weaknesses, and review the evidence for their capacity to predict the occurrence of Lyme disease cases. We conclude that: 1) the linkage between abundance of host-seeking *B. burgdorferi*-infected nymphs and Lyme disease occurrence is strong at community or county scales but weak at the fine spatial scale of residential properties where most human exposures to infected nymphs occur in Northeast, 2) the combined use of risk measures based on infected nymphs collected from the environment and ticks collected from humans is preferable to either one of these risk measures used singly when assessing the efficacy of environmentally based tick or pathogen control methods aiming to reduce the risk of human exposure to *B. burgdorferi*, 3) there is a need for improved risk assessment methodology for residential properties that accounts for both the abundance of infected nymphs and the likelihood of human–tick contact, and 4) we need to better understand how specific human activities conducted in defined residential microhabitats relate to risk for nymphal exposures and bites.

Keywords

Borrelia burgdorferi; *Ixodes scapularis*; blacklegged tick; Lyme disease

The blacklegged tick, *Ixodes scapularis* Say (including the junior synonym *Ixodes dammini* Spielman, Clifford, Piesman & Corwin), is the primary vector to humans in the eastern United States of the Lyme disease spirochete *Borrelia burgdorferi* sensu stricto (Dennis et al. 1998, Eisen et al. 2016a). Most human infections are considered to result from bites by infected nymphs (Spielman et al. 1985; Piesman 1987a; Falco et al. 1996, 1999; Mead

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2015). As collection of data for either human infection with *B. burgdorferi* or human bites by nymphs infected with this pathogen can be challenging, the abundance of infected host-seeking nymphs in the environment has emerged as a convenient surrogate measure for human risk of exposure to *B. burgdorferi*. The abundance of infected host-seeking nymphs can be viewed as the fundamental risk of a person encountering infected nymphs while engaging in behaviors within tick habitat that may place him or her into contact with nymphs. Common reasons to estimate the abundance of infected host-seeking nymphs include: 1) evaluation of the outcome of environmentally based control methods to suppress *I. scapularis* nymphs and *B. burgdorferi*; 2) assessment of spatial and temporal variability in the fundamental risk of encountering infected nymphs, and 3) development of spatial models for the fundamental risk of encountering infected nymphs.

However, the linkages between the abundance of host-seeking infected nymphs and human contact with infected ticks or Lyme disease cases are strongly dependent on how humans use the landscape and for how long nymphs that contact humans remain attached before being discovered and removed. For human infection to occur, an infected tick must first come into contact with a human, then attach and feed for a duration (typically >24–48 h) sufficient for transmission of *B. burgdorferi* to take place (Piesman 1993). Ginsberg (1993) noted that the abundance of host-seeking infected ticks is not linearly correlated with the risk of human exposure to *B. burgdorferi*, and Poland (2001) further stated that determining the abundance of host-seeking infected ticks is insufficient to estimate human Lyme disease risk because, in addition to not being linearly correlated with human risk of spirochete exposure, this tick-based risk measure does not consider the likelihoods of either human encounters with infected ticks or bites by infected ticks resulting in pathogen transmission. Moreover, a recent study found that a 69% reduction in nymphal abundance along residential property ecotones did not result in reduced numbers of either tick bites or cases of Lyme disease or other tick-borne diseases (Hinckley et al. 2016). On the other hand, studies have reported significant positive correlations between the abundance of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and Lyme disease incidence across years (Stafford et al. 1998), between communities in a given year (Mather et al. 1996), or among counties or segments of a state for a given time period (Nicholson and Mather 1996, Pepin et al. 2012).

These observations raise important questions. First, under which circumstances is the abundance of host-seeking infected nymphs most representative of the risk for occurrence of Lyme disease cases? Second, are self-recognized human encounters with nymphs or actual bites by nymphs, or infected nymphs, better tick-based surrogates for risk of occurrence of Lyme disease cases as compared with measures based upon collection of host-seeking infected nymphs? Third, can we develop a novel fundamental risk measure based upon collection of host-seeking infected nymphs with improved potential for linkage to actual human bites by infected nymphs and Lyme disease cases, particularly on residential properties where most nymphal exposures are considered to occur in the Northeast? Here, we describe different tick-based risk measures, based on host-seeking ticks collected from the environment as well as ticks collected from humans, discuss their strengths and weaknesses, and review the evidence for their capacity to predict the occurrence of Lyme disease cases. We also propose a concept for a new risk measure based on collection of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs with improved potential for linkage to risk for human bites by infected nymphs on residential properties.

Risk Measures Based on Collection of Host-Seeking Nymphs From the Environment

Introduction to Risk Measures Based on Collection of Host-Seeking Nymphs

Neither abundance of host-seeking *I. scapularis* nymphs nor the prevalence of infection with *B. burgdorferi* in the nymphs should be considered a robust stand-alone measure for the risk of humans to encounter infected nymphs. The abundance of host-seeking *I. scapularis* nymphs infected with *B. burgdorferi*, sometimes referred to as DIN (density of infected nymphs) or ERI (entomological risk index), is a far more meaningful risk measure, as it combines data for nymphal abundance and the likelihood of infection (Mather et al. 1996, Pepin et al. 2012). Compared with abundance of host-seeking nymphs alone, the abundance of host-seeking infected nymphs is a better predictor of Lyme disease incidence (Pepin et al. 2012). The abundance of infected host-seeking nymphs has been expressed in different ways, including the number of infected host-seeking nymphs collected per unit area sampled (in which case it also can be referred to as the density of infected host-seeking nymphs), the number of infected host-seeking nymphs collected per unit of active sampling time, and the average distance of sampling resulting in the encounter with one infected nymph (Kahl et al. 2002, Estrada-Peña et al. 2013). As efforts to estimate the abundance or density of infected host-seeking nymphs within a given sampling area typically are based on a limited number of sampling occasions, they will contact only a portion of the total population of nymphs present within that area even if the entire area is sampled (Daniels et al. 2000). Our use of the terms abundance or density therefore should be interpreted as relative abundance and relative density rather than as absolute estimates of the nymphal population present.

A main benefit of estimating the density of host-seeking infected nymphs is that this fundamental risk measure can be based on standardized tick sampling and pathogen detection methodology to compare the density of infected nymphs across space and over time (Eisen and Eisen 2008, Eisen et al. 2010, Diuk-Wasser et al. 2012). In addition to tick collection and pathogen detection being time-consuming and costly activities, the main shortcoming of the density of host-seeking infected nymphs to predict the occurrence of Lyme disease cases is that this risk measure does not account for the likelihood of human contact with the sampled host-seeking nymphs. Consequently, the linkage between density of host-seeking infected nymphs and Lyme disease occurrence may be weak if areas with high fundamental risk of exposure to infected nymphs are infrequently visited by humans. At the fine spatial scale of a residential property, a frequently used portion of the property with very low density of host-seeking infected nymphs (e.g., an open expanse of lawn) may present higher risk for human contact with infected nymphs than an adjacent but rarely used portion of the property with much higher density of host-seeking infected nymphs (e.g., a lawn/woods edge or wooded area). The association between the density of host-seeking infected nymphs and the number of human bites by infected nymphs therefore is very sensitive to how humans use their local environment and engage in specific behaviors that result in contact with host-seeking nymphs.

Estimation of the Density of Host-Seeking *B. burgdorferi*-Infected *I. scapularis* Nymphs

Because host-seeking *I. scapularis* exhibit limited horizontal movement, typically ≤5 m for all life stages (Falco 1987, Daniels and Fish 1990, Stafford 1992, Goddard 1993, Lord 1993, Carroll and Schmidtmann 1996), estimation of their density is best achieved by active sampling that covers a large area, typically ≥100 m^2 (Ginsberg and Ewing 1989b, Falco and Fish 1992, Schulze et al. 1997). Although carbon dioxide-baited traps can be effective over short distances up to a few meters (Falco 1987, Falco and Fish 1989b, Solberg et al. 1992), the catches are strongly influenced by specific trap placement and trap-based results therefore very likely are less representative of *I. scapularis* abundance across a large area as compared with an active collection method that covers more ground. Active tick sampling by walking and then stopping periodically to remove ticks from the clothing is well suited for collection of the adult stage, whereas dragging or flagging is well suited also for collection of immatures that seek hosts closer to the ground substrate (Ginsberg and Ewing 1989b, Falco and Fish 1992, Schulze et al. 1997). The tick drag or flag typically consists of a piece of flannel or similar light-colored cloth that is moved horizontally across vegetation or ground substrate (drag) or more vertically along higher vegetation (flag). The more easily maneuvered tick flag also can be used to stir leaf litter to sample ticks within this substrate. Various modifications to the basic drag or flag aim to increase contact with the tick host-seeking substrate by weighting down the trailing end (for example by sewing a chain into the trailing end), cutting part of the drag or flag into strips rather than using a solid piece of cloth, or using a modified handle for improve maneuverability (Sonenshine 1993). One recent study showed similar overall efficacy for dragging versus flagging in collecting *I. scapularis* nymphs, although dragging did produce more nymphs in some cases (Rulison et al. 2013).

Standardized tick drag or flag sampling that provides comparable data across space and over time can be achieved as long as key methodological drawbacks are understood and pitfalls avoided (Estrada-Peña et al. 2013). Determination of tick density per unit area sampled is preferred, but this is not always feasible and tick abundance per unit time of active sampling (not including the time required to check the flag or drag for ticks and removing them) can be used as an alternative measure. The flag or drag should be examined frequently (ideally every 10–20 m or 15–30 s) to avoid *I. scapularis* ticks becoming dislodged as the cloth moves across the substrate (Schulze and Jordan 2001), and sampling should not be conducted when the substrate is wet enough to prevent ticks from questing or to saturate the cloth potentially leading to reduced ability of ticks to grip the cloth fibers.

Factors known to impact the efficiency of flag or drag sampling for *I. scapularis* include weather conditions and time-of-day, which influence microhabitat temperature and humidity and therefore impact the host-seeking behavior of the tick, and the type of substrate sampled, which influences the ability of the sampling cloth to penetrate down to the microhabitat in which the ticks are questing (Goddard 1992; Schulze et al. 1997, 2001; Vail and Smith 1998, 2002; Schulze and Jordan 2003). One important consideration is that the ticks collected by a single drag or flag sample represents only a small fraction of the total host-seeking population in the sampled area. Of the total population in the area sampled, some ticks will have retreated to protected microhabitats to rehydrate and are not actively seeking hosts during the few moments when the sampling cloth moves across the substrate, some ticks will be actively host-seeking but not well positioned to grip the cloth fiber as it briefly moves past their host-seeking location, and some ticks will succeed in contacting the sampling cloth. Daniels et al. (2000) estimated from multiyear data that a single drag sample resulted in collection of 3–9% of the total population of host-seeking *I. scapularis* nymphs in a mixed deciduous forest habitat with relatively little understory. Data from field arenas similarly indicated a low probability (<3.5%) of observing host-seeking *I. scapularis* nymphs on wooden dowels mimicking vegetation stems (Arsnoe et al. 2015). Drag sampling efficiency could conceivably be higher in certain habitats, such as on short-cropped lawns, and lower in others, such as forested habitats with more emergent vegetation. On a day-to-day basis, drag sampling efficiency also will be impacted by weather conditions in the preceding days influencing the proportion of the nymphal population that is well hydrated and seeking hosts actively during a sampling session. Comparisons of tick density among habitat types, for a given habitat type in different geographic areas, or over time in fixed sampling sites therefore need to account for these potential confounders and standardize the sampling scheme to the extent possible with regards to time-of-day and weather conditions when sampling is conducted and the physical attributes of the sampled substrate.

The temporal sampling scheme is another key consideration, particularly when removal of nymphs is required for detection of *B. burgdorferi* to calculate the density of host-seeking infected nymphs. In the Northeast, *I. scapularis* nymphs become active in late March, peak numbers of nymphs occur from late May to early July, and lower numbers of nymphs can be encountered through October (Sonenshine 1993, Eisen et al. 2016b). One potential scheme is to sample repeatedly (weekly or every 2 wk) across a large part of the season when nymphs are active. The main drawbacks are workload if many sites need to be sampled over large geographic areas and repeated removal of nymphs artificially deflating nymphal density with successive removal samples as the season progresses, particularly in settings where nymphal numbers are low. When a more limited number of removal samples is used, they typically focus on the period of time when nymphs can be assumed to be most abundant. Dobson (2013) noted that sampling on single dates within a 2-mo window of assumed peak tick activity is too error prone and that at least two and preferably three samples should be conducted within the peak activity window. Conducting two to three removal samples during the peak activity period should have only limited impact on the population of host-seeking nymphs (likely removing <10% of the population in the first sample and <20% for the first two samples combined) while having a reasonable chance of producing an adequate number of nymphs for pathogen detection.

The minimum sample size for nymphs to examine for presence of *B. burgdorferi* to produce robust data for infection rate and density of infected nymphs depends upon the local infection rate. As infected nymphs tend to cluster in the environment (Telford et al. 1992), it also is important that subsets of tested nymphs from sites yielding larger numbers of nymphs than necessary to test are representative of the entire sampled area rather than using nymphs from only a portion of the sampled area.

Human–Tick Encounter Locations

One key but still poorly understood component of the linkage between host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and the occurrence of Lyme disease cases is where people most commonly encounter host-seeking infected nymphs. The better we understand where and how people encounter host-seeking infected nymphs, the better we can design informative sampling schemes to estimate the density of host-seeking infected nymphs. Early studies demonstrated that: 1) host-seeking *I. scapularis* can be encountered in the Northeast both on residential properties and in heavily used recreational areas (Wallis et al. 1978; Falco 1987; Falco and Fish 1988a, 1989a; Ginsberg and Ewing 1989a; Lastavica et al. 1989; Maupin et al. 1991; Schulze et al. 1991; Carroll et al. 1992; Stafford and Magnarelli 1993; Duffy et al. 1994; Schulze and Jordan 1996), and 2) host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs tend to be clustered in the environment (Telford et al. 1992), presumably in microhabitats used heavily by larval hosts serving as *B. burgdorferi* reservoirs (e.g., near rodent nests or landscape features such as rock walls, wood piles, and habitat ecotones along which rodents move or where they seek food).

However, published studies on the most likely specific locations in which people think that they encountered *I. scapularis* nymphs are very scarce. Falco and Fish (1988b) reported that 69% of bites, by *I. scapularis* nymphs or females, were considered to result from exposures in the backyard, whereas the remaining 31% were thought to result from exposures off the residential property including schools or camps (11%), parks or recreational areas (9%), places of employment (4%), while hunting (3%) or in other areas (4%). Similarly, based on unpublished data collected by the Stamford (CT) Health Department for ticks submitted to The Connecticut Agricultural Experiment Station (CAES) for identification and pathogen testing between 1989 and 2001, Stafford (2007) reported that about 75% of the Lyme disease cases were probably associated with activities (play, yard, or garden work) around the home and, in addition, roughly 20% of the tick bites most likely were acquired in activities away from the home (Kirby Stafford III, CAES, personal communication). Another more recent study conducted in Connecticut similarly indicated that the majority of tick bites result from exposure on one’s own residential property (Mead et al. 2015). Although these studies point to the residential property as the source of most human encounters with *I. scapularis* nymphs in Lyme disease endemic areas of the Northeast, they provide very limited information about which specific portions of the properties that present the greatest risk for human–nymph encounters. Such information is critical to enable the development of effective measures to reduce human tick bites on residential properties. Moreover, the studies also demonstrate that nymphal bites occur commonly, accounting for roughly one quarter to a third of all nymphal bites, during activities away from the residential property. This finding points to a need for Lyme disease prevention strategies that reduce risk not only on residential properties, but also on heavily used public lands. Additional research on the most likely specific locations where people consider nymphal encounters to have occurred is needed in a wide range of Lyme disease endemic areas.

Habitat-Related Variation in Abundance of Host-Seeking Nymphs Across Residential Properties and Human Behaviors Leading to Increased Risk for Tick Contact

The recognition of the residential property as a key exposure site for *B. burgdorferi*-infected *I. scapularis* nymphs led to additional studies to determine if host-seeking nymphs are evenly distributed across the residential landscape or clustered within certain habitats. A study based on drag sampling to collect host-seeking *I. scapularis* nymphs on residential properties in New York revealed that nymphs were most numerous in the wooded portions of the properties (average distance traveled to collect one nymph of 37 m), followed by the unmaintained woods/lawn edge (75 m), ornamental vegetation including perennial ground cover (154 m), and lawns (1,035 m; Maupin et al. 1991). Nymphs infected with *B. burgdorferi* were collected in all four habitat types, with infection prevalences ranging from 25% for nymphs collected from ornamental vegetation to 38% for nymphs collected from the ecotone. Moreover, the density of infected ticks per unit area sampled was positively correlated with property size, presumably because larger properties were more likely to include wooded portions as compared with smaller properties. Others examined residential properties in Connecticut (Stafford and Magnarelli 1993) or New York (Duffy et al. 1994, Frank et al. 1998) with similar results: host-seeking *I. scapularis* nymphs were more abundant in woodland and woodland ecotone as compared with lawns and grassy ecotone. Increased forest fragmentation due to residential property development, with fewer properties that contain or adjoin wooded areas, has been suggested to result in overall reduced peridomestic risk of exposure to infected ticks and acquisition of Lyme disease (Glass et al. 1995; Dister et al. 1997; Cromley et al. 1998; Brownstein et al. 2005; Jackson et al. 2006a,b). Repeating these types of studies to more specifically account for variable maturity of residential landscapes and different levels of forest fragmentation would be of interest.

Focusing on lawns adjacent to other lawns versus wooded areas, Carroll et al. (1992) reported ~5-fold greater density of host-seeking *I. scapularis* nymphs on lawns bordering on wooded areas as compared with lawns bordering on other lawns in Rhode Island. The prevalence of infection in nymphs with *B. burgdorferi* was similar for both types of lawns (31% in both cases). For those lawns that bordered on a wooded area, the sampling scheme included the lawn edge and lawn habitat 1–2, 2–4, and >4 m distant from the edge. The density of host-seeking nymphs decreased gradually from the lawn edge to the more interior parts of the lawn. The decrease in nymphal density, as compared with the density at the lawn edge (0–1 m), was approximately 43, 64, and 70%, respectively, for distances of 1–2, 2–4, and >4 m from the edge. Stafford and Magnarelli (1993) reported similar decreases in the density of host-seeking *I. scapularis* nymphs from the lawn edge to the more interior part of a lawn. Moreover, the highest numbers of nymphs on lawns were recorded for lawns that bordered on wooded areas or stone walls, or had ≥50% of shaded lawn area.

Specific activities resulting in exposure to host-seeking *I. scapularis* nymphs have been explored directly in a single field study where subjects engaged in specific behaviors and then examined their clothing for nymphs and indirectly in a few Lyme disease case-control studies. In the former case, Carroll and Kramer (2001) reported that crawling on hands and knees on the ground, mimicking play or yard work, resulted in more frequent encounters with nymphs as compared with walking. They also noted that *I. scapularis* nymphs commonly were found on logs, such as may be used by tired hikers. Data from Lyme disease case-control studies also suggest that increased risk for Lyme disease acquisition, and thus presumably also the risk for tick bites, is associated with spring and summer activities such as yard work and brush clearing (Orloski et al. 1998, Smith et al. 2001). Additional studies are urgently needed to improve our understanding of how specific human activities conducted in defined residential microhabitats, and with different types of summer weight clothing, relate to risk for nymphal exposures and bites for children and adults.

Evidence for Linkage of the Abundance or Density of Host-Seeking *B. burgdorferi*-Infected *I. scapularis* Nymphs to the Occurrence of Human Tick Bites or Lyme Disease Cases

Core questions regarding the relationship between the density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and the occurrence of Lyme disease cases are: 1) what is the general shape of this relationship? and 2) is the shape or strength of the relationship dependent on the spatial scale examined? Ginsberg (1993) noted that the density of host-seeking infected ticks is not linearly correlated with the risk of human exposure to *B. burgdorferi* and that control interventions that lower the density of infected ticks therefore do not necessarily result in equivalent declines in risk of human exposure to *B. burgdorferi*. Key components of the linkage between host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and the occurrence of a Lyme disease case include: 1) the density of host-seeking infected nymphs in a given area; 2) the likelihood of a person engaging in activities resulting in contact with at least one infected nymph in that area; and 3) the likelihood of an infected nymph that contacts the person to bite and remain attached for long enough to transmit *B. burgdorferi*. Of these, component (2) is perhaps the most difficult to quantify and parameterize in a model.

If the density of infected nymphs is not assessed in the areas where humans are most likely exposed to nymphs, then the value of this risk measure to predict human exposure to infected nymphs and Lyme disease cases is very limited. The risk for this to occur likely is greater when the tick sampling focuses on very specific perceived high risk habitats—such as the lawn/woods edges of residential properties—rather than a broader set of risk habitats, and perhaps also is more pronounced for tick sampling conducted at a fine spatial scale such as residential properties (linking to occurrence of Lyme disease cases in residents) as compared with a coarser scale such as communities or counties (linking to Lyme disease incidence across communities or counties).

These general considerations agree with data from published studies. Conally et al. (2006) did not find the density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs in lawn/woods ecotones of residential properties within a single Rhode Island community to be predictive of the probability of Lyme disease occurrence. A more recent large multistate study, albeit restricted to evaluating abundance of *I. scapularis* nymphs rather than infected nymphs, similarly found that reducing nymphal abundance on residential properties by 69% did not result in reduction of Lyme disease cases (Hinckley et al. 2016). In contrast, strong correlations were reported between the abundance or density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and Lyme disease incidence across 8 yr for a set of

Connecticut communities ($r = 0.944$) and between six Rhode Island communities in a single year ($r = 0.978$) (Mather et al. 1996, Stafford et al. 1998). The abundance or density of infected nymphs was estimated based on data from residential properties in the Connecticut study and from forested sites within the towns included in the Rhode Island study. Weaker but still significant correlations between the abundance or density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs and Lyme disease incidence were reported based on data for 10 km^2 quadrats in Rhode Island ($r = 0.51$) or counties in the eastern United States ($r = 0.60$ and 0.69 for observed and model-predicted density of infected nymphs, respectively) (Nicholson and Mather 1996, Pepin et al. 2012). Similar analyses for individual states in the latter study yielded strong correlations ($r > 0.80$) for some states but no significant correlations for other states. Possible reasons for the overall weaker correlations in these studies include a lower density of sampling sites to determine the abundance or density of infected nymphs, sampling sites exclusively or commonly located outside of residential areas (state parks or other publicly accessible forested areas), differences across geographical regions in the genotypes of *B. burgdorferi* commonly found in nymphal ticks, and variable quality of Lyme disease case reporting between and within states.

As noted above, the association between density of host-seeking infected nymphs (fundamental risk) and the occurrence of Lyme disease (realized risk) is strongly dependent on how humans interact with tick habitat. For example, assuming similar human behavior and an even distribution of infected ticks across a landscape, one would expect a linear or sigmoidal association between fundamental and realized risk. However, differences in human activity space, particularly with regards to encroachment on tick habitat, the type of activities performed when spending time in tick habitat, and the likelihood of detecting and removing attached nymphs all contribute to decouple, or add noise to the relationship between fundamental and realized risk. Measures of both the density of host-seeking infected nymphs and Lyme disease occurrence are imperfect, which contributes further noise to this relationship. In addition, as infected nymphs tend to cluster in the environment, a person exposed to one infected nymph may be at elevated risk, as compared with others, for exposure to additional infected nymphs. Additional research to further our understanding of these confounding issues is urgently needed.

Nevertheless, there should come a point when host-seeking infected nymphs are so scarce that the likelihood of encountering them is greatly reduced for all persons using a given area. It would be of great practical value to determine actual thresholds for density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs above and below which reduction in density of infected nymphs has negligible impact on the occurrence of Lyme disease cases. To do so would require the elucidation of the linkage between density of host-seeking nymphs and human–nymph encounter rates. The higher threshold would serve as a minimum target for interventions aiming to suppress the density of infected nymphs, and the lower threshold would be an ultimate target for the interventions. Between these thresholds, the relationship between density of infected nymphs and occurrence of Lyme disease cases could take different shapes but should at least be positive.

Risk Measures Based on Collection of Ticks From Humans

Introduction to Risk Measures Based on Collection of Ticks From Humans

Risk measures based on collection of *I. scapularis* from humans have the greatest potential to predict the occurrence of Lyme disease cases. However, most Lyme disease patients in the United States are unaware of a tick bite prior to symptom onset: the proportion of Lyme disease patients that remember a tick bite preceding their illness most commonly is in the range of 30–50% (Table 1). This finding implies: 1) that the majority of bites by *I. scapularis* ticks that result in transmission of *B. burgdorferi* go unnoticed; and 2) that the range of 10–37% of respondents, regardless of Lyme disease status, who report finding attached ticks over a preceding 12-mo period in Lyme disease endemic areas (Hanrahan et al. 1984, Rand et al. 1996, Burke et al. 2005, Gould et al. 2008, Finch et al. 2014, Hook et al. 2015) represents a gross underestimate of the true proportion of persons that experience tick bites annually.

Estimation of Tick–Human Contact

The seasonal pattern of peak occurrence of Lyme disease cases during late spring and early summer mirrors that seen for the nymphal stage of *I. scapularis* in the Northeast, but is distinct from the seasonal activity pattern of females which seek hosts primarily from fall to early spring (Spielman et al. 1985; Piesman 1987a; Falco et al. 1996, 1999; Mead 2015). Moreover, the smaller nymphs are more likely, as compared with the females, to remain attached for long enough (typically >24–48 h) to transmit *B. burgdorferi* (Piesman et al. 1987b, 1991; Piesman 1993; Piesman and Dolan 2002). We therefore consider it very likely that the majority of *I. scapularis* bites that go unnoticed are nymphal rather than female bites. Moreover, even for those ticks that are discovered, nymphs typically remain attached longer before being removed as compared with females. Nadelman et al. (2001) found that a higher proportion of *I. scapularis* nymphs recovered from humans were partially engorged, rather than unfed (flat), as compared with females biting humans (61% partially engorged nymphs verssus 34% partially engorged females). Based on a tick engorgement index, Yeh et al. (1995) reported that 64% of tick bite victims that did find and remove *I. scapularis* females had done so by 36 h of attachment whereas 41% that found and removed nymphs had done so by 36 h of attachment. Falco et al. (1996) similarly reported that, for those *I. scapularis* that were detected and removed, attached females were more likely than attached nymphs to have been removed by 24 h (73% for females vs. 54% for nymphs).

These findings collectively imply that data for nymphs are more informative to predict the occurrence of Lyme disease cases as compared with data for female ticks. Moreover, data for attached nymphs are preferable to data that combine attached nymphs and crawling nymphs that were detected and removed prior to attachment and therefore did not have any chance to transmit *B. burgdorferi*. Most *I. scapularis* nymphs biting humans are free of *B. burgdorferi* infection even in Lyme disease endemic areas (Costello et al. 1989, Magnarelli and Anderson 1989, Shapiro et al. 1992, Sood et al. 1997), and host-seeking infected nymphs tend to be clustered in the environment (Telford et al. 1992). Therefore, data for attached and infected nymphs will be most closely linked to the risk for occurrence of Lyme disease cases. Estimating the duration of attachment, particularly if it is greater than 24 or 48 h, with an engorgement index (Piesman and Spielman 1980, Yeh et al. 1995, Falco et al. 1996, Sood et al. 1997) can provide additional information for the likelihood of an attached infected nymph to have transmitted *B. burgdorferi*. As a case in point, Sood et al. (1997) reported higher risk of *B. burgdorferi* infection for humans on which *I. scapularis* nymphs or females had been attached, based on an engorgement index, for ≥72 h as compared with <72 h. To conclude, the optimal risk measure to determine for ticks collected from humans is attached *B. burgdorferi*-infected *I. scapularis* nymphs, particularly those that were attached for >48 h. The duration of attachment is best estimated from a tick engorgement index, as poor correlations between self-assessed likely feeding duration and the feeding duration revealed by the engorgement index have been reported both for *I. scapularis* (Sood et al. 1997) and the closely related *Ixodes ricinus* (L.) in Europe (Logar et al. 2002, Wilhelmsson et al. 2013). In these studies, the subjects typically underestimated the time a tick had been attached.

One important consideration for all risk measures based on collection of ticks from humans is that the quality of the tick identification will vary depending on who is responsible for the identification, which life stage is identified, and the composition of locally occurring human-biting ticks. The most reliable data will be generated if an entomologist is responsible for the tick identification. Falco et al. (1998) determined the accuracy of tick identification by physicians and the public for nearly 3,800 putative tick specimens collected in New York. Of the examined specimens, 6% were arthropods other than ticks, including beetles, true bugs, mites, lice, and spiders. Moreover, Sood et al. (1997) reported that ~25% of tick submissions from the public in New York were non-*I. scapularis* specimens, including other tick species as well as insects and skin fragments. The scenario producing the least reliable data therefore is when members of the public report on bites by what they consider to be *I. scapularis* ticks, particularly for the smaller and less readily identifiable nymphal stage in areas where human-biting nymphs of other species occur that are incapable or less capable than *I. scapularis* of transmitting *B. burgdorferi*.

For example, nymphs recovered from humans included both *I. scapularis* and *Ixodes cookei* Packard in Connecticut (Magnarelli and Anderson 1989), both *I. scapularis* and *Amblyomma americanum* (L.) in New York and Maryland (Falco 1987, Falco and Fish 1988b, Armstrong et al. 2001), and multiple *Ixodes* spp.—*I. cookei, I. scapularis, Ixodes marxi* Banks, and *Ixodes muris* (Bishopp and Smith)—in Maine (Smith et al. 1992). Moreover, *I. cookei* has been reported to bite humans also in Michigan, New York, Vermont, and West Virginia (Hall et al. 1991, Sood et al. 1997, Walker et al. 1998, Lubelczyk et al. 2010), and bites by *A. americanum* occurs commonly in the Mid-Atlantic States (Merten and Durden 2000, Schulze et al. 2006, Rossi et al. 2015). *Ixodes scapularis* accounted for most (83–94%) of the nymphs recovered from humans in Connecticut and New York (Magnarelli and Anderson 1989, Falco 1987, Falco and Fish 1988b), whereas they made up only a small proportion (<10%) of the human-biting nymphs in Maine and Maryland (Smith et al. 1992, Armstrong et al. 2001). Based on data from United States Armed Forces personnel, which may be less reflective of residential settings as compared with the data from civilians presented above, *I. scapularis* (with no distinction with regards to life stage) accounted for 79–92% of recognized human bites in the Connecticut-Rhode Island-New York-Massachusetts area; ~45% of bites in the Minnesota-Wisconsin-Ohio area; 10–20% of bites in the Mid-Atlantic States of Pennsylvania, New Jersey, Delaware, Maryland, Washington D.C., and Virginia (northern part of the state); and 2–7% of bites in southern Virginia, North Carolina, and South Carolina (Rossi et al. 2015).

It also should be noted that the local contribution of *I. scapularis* to all nymphal bites of humans may change over time, either increasing as this tick becomes more abundant in some parts of its range (e.g., Maine and Michigan) or decreasing as other human-biters, particularly *A. americanum*, invade and proliferate in new areas (e.g., the Mid-Atlantic and Lower Northeast States; Rand et al. 2007, Hamer et al. 2010, Springer et al. 2014). Surveillance data therefore need to be reasonably recent (no more than a few years old) to be informative of the current local tick fauna.

Evidence for Linkage of Risk Measures Based on Collection of Ticks From Humans to the Occurrence of Lyme Disease Cases

The evidence for using risk measures based on collection of ticks from humans to predict occurrence of Lyme disease cases is weak and the results of existing studies are contradictory. Steere et al. (1978) found that a higher proportion of Lyme disease patients reported tick bites as compared with their neighbors (44 vs. 26% experiencing a tick bite), Smith et al. (1988) reported increased seropositivity for persons with >4 known *Ixodes* bites during the past year as compared with those with ≤4 bites, and Phillips et al. (2001) reported increased risk of Lyme disease for persons recalling exposure to >5 ticks per year as compared with those with exposure to 5 or fewer ticks (18 vs. 10% with Lyme disease diagnosis). Moreover, Krause et al. (2006) reported that tick bites were reported more frequently by persons who experienced repeated episodes of Lyme disease than by those who experienced only a single episode. Contrasting results were reported from other studies. Schwartz and Goldstein (1990) found no difference in self-reported quantitative tick exposure for *B. burgdorferi* seropositive versus seronegative outdoor workers; Klein et al. (1996) found no difference among children with Lyme disease versus controls for the likelihood of deer ticks having been identified on the children; Smith et al. (2001) found that those who reported discovering ticks on their person while checking had similar Lyme disease risk to those who reported never finding ticks while searching; and Finch et al. (2014) found no difference between *B. burgdorferi* seropositive and seronegative persons in the proportion having experienced a tick bite within the past year (29 vs. 26% experiencing a tick bite). These contradictory findings may stem from: 1) variable accuracy in detecting tick bites across decades and in areas with different awareness of Lyme disease and vector ticks: 2) tick species identification not being done by entomologists in any of the eight above-mentioned studies; and 3) sample sizes that were not sufficiently large to overcome the low quality of data for self-reported tick bites.

One recent study on the relationship between tick bites and Lyme disease in United States Armed Forces personnel working in military installations across the eastern United States was able to overcome these shortcomings by including large numbers of both Lyme disease cases (>1,300) and submitted ticks (>11,000), using expert tick identification, and determining the *B. burgdorferi* infection status for submitted *I. scapularis* (Rossi et al. 2015). Unexpectedly and discouragingly, neither the submission rate of *I. scapularis* nor the submission rate of *B. burgdorferi*-infected *I. scapularis* ticks were significantly associated with Lyme disease incidence across military treatment facilities. Paradoxically, some of the analyses showed significant positive associations between the submission rate for *Amblyomma* and *Dermacentor* ticks and Lyme disease incidence, and for all ticks (*Amblyomma* and *Dermacentor* and *Ixodes*) combined and Lyme disease incidence. One possible explanation for why this study failed to link bites by *I. scapularis* or *B. burgdorferi*-infected *I. scapularis* to the occurrence of Lyme disease cases is a low rate of detection of bites by *I. scapularis* nymphs: data from other studies indicate that the proportion of Lyme disease patients that remember a tick bite prior to illness onset ranges from 14–67% (most commonly 40–50%) and that the proportion recalling a tick bite at the erythema migrans rash site is even lower, typically 10–25% (Steere et al. 1978, 1983; Hanrahan et al. 1984; Williams et al. 1986, 1990; Benach and Coleman 1987; Berger 1989; Agger et al. 1991; Szer et al. 1991; Bowen et al. 1984; Jung et al. 1994; Gerber et al. 1996; Nadelman et al. 1996; Orloski et al. 1998, Wormser et al. 2005). Additional studies are warranted to clarify the circumstances under which collection of *I. scapularis* from humans may predict Lyme disease cases.

Data to indicate the proportion of tick bites that result in Lyme disease manifestations are scarce and also must be viewed in light of tick bites often going unrecognized. Based on previously published studies (Falco and Fish 1988b, Costello et al. 1989, Shapiro et al. 1992, Agre and Schwartz 1993), Campbell et al. (1998) suggested a best point estimate of 2%, with a plausible range of 1–5%, for the proportion of recognized *I. scapularis* bites that result in an erythema migrans in persons not receiving prophylactic treatment after the tick bite. Later studies are in agreement, with the proportion of recognized *I. scapularis* bites resulting in *B. burgdorferi* infection estimated to be 3.2–3.7% (Sood et al. 1997, Nadelman et al. 2001). To further complicate matters, there is evidence that repeated bites by *I. scapularis* can result in hypersensitivity and increased itching in humans, leading to increased likelihood of nymphs being detected and removed and reduced risk of acquisition of Lyme disease (Burke et al. 2005). This finding underscores the importance of quantifying the number of tick bites, rather than using the qualitative distinction of bites versus no bites, to accurately link nymphal bites to risk for occurrence of Lyme disease cases.

Specific Uses for Different Tick-Based Risk Measures

Use of Field-Estimated or Model-Predicted Density of Host-Seeking *B. burgdorferi*-Infected *I. scapularis* Nymphs to Predict Lyme Disease Occurrence

As described above, field-estimated abundance or density of host-seeking infected nymphs has been shown to be positively correlated with Lyme disease incidence at coarse spatial scales such as communities (Mather et al. 1996, Stafford et al. 1998). Moreover, environmental and climatic variables perform reasonably well at predicting the density of host-seeking infected nymphs at coarse spatial scales. For example, within a large (~9,090 km^2), ecologically and climatically diverse county in northwestern California, a climate-based model yielded an overall accuracy of 86% in predicting the density of host-seeking infected *Ixodes pacificus* Cooley and Kohls nymphs (Eisen et al. 2010). At an even larger spatial scale that spanned the eastern United States, Diuk-Wasser et al. (2012) similarly modeled the density of host-seeking infected *I. scapularis* nymphs based on elevation, temperature, humidity, and forest patch size with an overall accuracy of 91%. One therefore might wonder how well such model projections for the density of host-seeking infected nymphs predict Lyme disease incidence.

Pepin et al. (2012) explicitly evaluated how well model-predicted density of host-seeking infected nymphs, from Diuk-Wasser et al. (2012), correlated with incidence of Lyme disease reported by county. Overall, model-predicted density of host-seeking infected nymphs explained 69% of the variation in Lyme disease incidence within counties across a 23 state region representing low and high incidence of Lyme disease. Analyses for individual states produced variable results, with only 60% of states yielding a significant positive association between model-predicted density of host-seeking infected nymphs and Lyme disease incidence at the county scale. Greater exploration of the discordant areas, particularly where tick populations are still expanding geographically or increasing rapidly, may provide valuable insights. For example, Pepin et al. (2012) suggested the lower than expected incidence of Lyme disease in the Upper Midwest compared with the Northeast, might be explained by differences in the predominant genotypes of *B. burgdorferi* circulating in ticks. Further exploration of areas where Lyme disease incidence is higher than expected from model-predicted density of host-seeking infected nymphs might indicate either a misclassification of this tick-based risk measure or a concentration of human activity in settings where infected nymphs are especially abundant. Alternatively, areas where Lyme disease incidence is lower than expected based on model-predicted density of host-seeking infected nymphs might indicate disease underreporting, or infected ticks being concentrated in areas where human activity is infrequent.

Model-predicted density of host-seeking infected nymphs appears to be a valuable tool for predicting Lyme disease incidence at coarse spatial scales, and exploration of causes for local discordance between model-predicted risk and Lyme disease surveillance data can aid in improving both tick-based and human-based surveillance. However, as noted above, the association between field-observed density of host-seeking infected nymphs and Lyme disease occurrence seems to weaken as the spatial scale decreases, particularly when considering the fine spatial scale of residential properties at which current tick and pathogen control efforts primarily are focused.

Evaluation of the Outcome of Environmentally Based Control Methods to Suppress *I. scapularis* Nymphs and *B. burgdorferi* and to Reduce Human Tick Bites and Lyme Disease Cases

Outcome measures based on collection of host-seeking nymphs and determination of infection with *B. burgdorferi* in the nymphs can provide valuable information about the efficacy of an environmentally based intervention to suppress host-seeking infected nymphs on residential properties in terms of: 1) the percentage reduction of host-seeking infected nymphs attributable to the intervention; 2) the relative density of host-seeking infected nymphs present after the intervention; and 3) the estimated absolute density of infected nymphs present in different habitat types. For control methods that kill host-seeking nymphs regardless of their infection status, such as application of acaricides to the ground substrate, the density of host-seeking nymphs can serve as a proxy for the density of host-seeking infected nymphs when assessing percentage reduction of host-seeking infected nymphs attributable to the intervention. Similarly, for control approaches that reduce infection in host-seeking nymphs without impacting their numbers, such as rodent reservoir-targeted baits treated with antibiotics or vaccines, the prevalence of *B. burgdorferi* infection in host-seeking nymphs can serve as a proxy for the density of host-seeking infected nymphs when assessing percentage reduction of host-seeking infected nymphs attributable to the intervention. Using these proxies, however, will result in loss of data for the relative or estimated absolute density of host-seeking infected nymphs present after an intervention.

Although a 90% reduction in the density of host-seeking infected nymphs on a residential property attributable to a given intervention is a strong outcome in general terms, it still needs to be understood in terms of the number of infected nymphs still present after the intervention. For example, in a scenario with 1,000 nymphs present on the property before the intervention and a *B. burgdorferi* infection rate of 20% (1,000*0.2 = 200 infected nymphs), there would still be 20 infected nymphs present after an intervention with 90% control efficiency. One possible goal for a residential-based intervention would be to reduce the absolute number of infected nymphs present on each property to no more than 1. To reach this goal, the efficacy of the intervention would need to exceed 50% if a mere 10 nymphs (i.e., 2 infected nymphs assuming a 20% infection rate) were present on the property before the intervention, 90% if 50 nymphs (10 infected nymphs) were present, 95% if 100 nymphs (20 infected nymphs) were present, and 99% if 500 nymphs (100 infected nymphs) were present.

Our limited understanding of the linkage between the density of host-seeking infected nymphs on residential properties and the occurrence of Lyme disease cases confounds the use of this tick-based risk measure to assess the capacity for a given environmentally based tick–pathogen control intervention to reduce Lyme disease. Data for attached and *B. burgdorferi*-infected nymphs should be more closely linked to the risk for occurrence of Lyme disease cases than any other conceivable tick-based risk measure, and therefore should be promoted for use to evaluate the potential for environmentally based tick–pathogen control interventions to reduce bites by infected nymphs and Lyme disease cases. However, as nymphal ticks are notoriously difficult to spot while biting, and there will be substantial variation among individuals in their ability to detect nymphal bites, data for self-recognized nymphal bites also must be viewed with caution. Assessing exposure in humans to *B. burgdorferi* based on clinical findings is the ultimate method to determine whether a given environmentally based tick/pathogen control intervention did reduce human exposure to the Lyme disease agent. However, in the absence of complementary data for tick-based risk measures, a potential failure of the intervention to reduce Lyme disease cases becomes difficult to explain in terms of whether it resulted from the intervention failing to sufficiently reduce the density of host-seeking infected nymphs within the treated areas, from lack of reduction of human-nymph encounters, or from other causes.

Based on these considerations, we caution against the use of any single outcome measure—be it density of host-seeking infected nymphs, human bites by nymphs or infected nymphs, or clinically diagnosed Lyme disease—for studies on the capacity of environmentally based interventions aiming to suppress host-seeking infected nymphs to ultimately reduce Lyme disease cases. To gain a full picture of both the outcome of the intervention and to understand why it succeeded or failed, we recommend measuring all of the following parameters: 1) the density of host-seeking *B. burgdorferi*-infected *I. scapularis* nymphs on residential properties and in other relevant settings; 2) the occurrence and number of bites by *I. scapularis* nymphs, particularly infected nymphs, among the study subjects; 3) the most likely specific locations in which human–nymph encounters occurred, particularly with respect to if they occurred within versus outside of areas that should have been protected by the intervention; and 4) clinically diagnosed Lyme disease among the study subjects. Although this is an onerous task, it is nevertheless necessary to generate data with high potential for producing conclusive findings while also shedding light on the underlying causes for why an intervention succeeded or failed.

Can We Develop a New Risk Measure Based on Collection of Host-Seeking *B. burgdorferi*-Infected *I. scapularis* Nymphs With Improved Potential for Linkage to Risk for Human Bites by Infected Nymphs on Residential Properties?

The commonly used tick-based risk measures of relative abundance or density of host-seeking infected nymphs may have weak linkages to actual human bites by infected nymphs on residential properties, especially if the tick sampling effort covers only a small portion of the property. We propose that a new risk measure for residential properties could be developed that aims to estimate the absolute number of infected nymphs present within the full range of habitats on a property, and also accounts for the level of human use of these habitats. Our reasoning builds upon that the risk for human bites by infected nymphs on a property is a function of the actual number of infected nymphs present and in which property habitats they occur. A single infected nymph located in a heavily used portion of a backyard presents greater risk for a human bite by an infected nymph as compared with manifold more infected nymphs located in a rarely frequented portion of the same backyard. To arrive at an improved risk measure for human exposure to infected nymphs on a residential property we propose the concept of summing data, by property habitat classification, generated by multiplying the following data for each habitat class: 1) the relative density of infected nymphs per unit area of the given habitat as determined by drag sampling and subsequent pathogen detection in collected nymphs; 2) the inverse of the estimated drag sampling efficiency for the habitat; 3) the estimated area covered by the habitat within property limits; and 4) the estimated frequency of use of the habitat from May to July, tentatively classified as minimal with a multiplication factor of 0.1, low with a multiplication factor of 1, moderate with a multiplication factor of 5, and high with a multiplication factor of 10. Relevant property habitat classes could include: 1) open lawn >3 m from woods or other vegetation or landscape features such as rock walls; 2) lawn edge within 3m from woods or other vegetation or landscape features such as rock walls; 3) ornamental vegetation; 4) woods within 10m of the lawn edge; and 5) woods >10 m from the lawn edge. We are not aware of any existing data-sets that can be used to explore this concept for a new tick-based risk measure. Fieldwork to generate such data and subsequent data evaluations may well lead to changes in the proposed risk measure components or in the way they are measured. Research to determine the feasibility of this type of new tick-based risk measure, to uncover its pitfalls, and to assess the strength of its linkage with human bites by infected nymphs is encouraged.

Conclusions

- A main benefit of using risk measures based on collection of host-seeking *I. scapularis* nymphs is that the sampling methodology, and thus the quality of the data, can be standardized. Although all data for abundance or density of host-seeking infected nymphs are underestimates of the total population of infected nymphs, the level of underestimation should be constant, or nearly so, with standardized tick sampling and pathogen detection methodology.
- A main benefit of using risk measures based on collection of *I. scapularis* nymphs from humans is that they reflect actual rather than potential tick encounters. Data for attached and *B. burgdorferi*-infected nymphs should be more closely linked to the risk for occurrence of Lyme disease cases than any other tick-based risk measure.
- A main disadvantage of estimating risk for human exposure to *B. burgdorferi* based on the density of host-seeking infected nymphs is our poor understanding of the linkages between this risk measure and the occurrence of human bites by infected nymphs or Lyme disease cases. The development of a new risk measure based on collection of host-seeking infected nymphs with a strong linkage to actual human bites by infected nymphs would be beneficial.
- A main disadvantage of using risk measures based on collection of nymphs from humans lies in the difficulty of generating high-quality data for self-recognized nymphal bites. No more than half of attached nymphs can be assumed to be detected while feeding, and the detection efficiency will vary greatly among people based on their level of diligence in scanning their bodies for ticks and their sensitivity to tick bites resulting in itching.
- The linkage between the density of host-seeking infected nymphs and Lyme disease occurrence appears to be strong at community or county scales but weak at the fine spatial scale of residential properties. The evidence for risk measures based on collection of ticks from humans to predict occurrence of Lyme disease cases is weak and study results are contradictory.
- The combined use of risk measures based on infected nymphs collected from the environment and ticks collected from humans is preferable to either one of these risk measures used singly when assessing the efficacy of environmentally based tick or pathogen control methods aiming to reduce the risk of human exposure to ticks infected with *B. burgdorferi*.
- We need to better understand how specific human activities conducted in defined residential microhabitats relate to risk for nymphal exposures and bites.
- It would be of great practical value to determine actual thresholds for the density of host-seeking infected nymphs above and below which reduction in density of

infected nymphs has negligible impact on the occurrence of Lyme disease cases. The higher threshold would serve as a minimum target for interventions aiming to suppress the density of infected nymphs, and the lower threshold would be an ultimate target for the interventions.

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Table 1

Proportion of Lyme disease (LD) patients that were aware of a tick bite prior to the onset of symptoms

Study population	Proportion LD patients aware of a tick bite	No. aware of tick bite / total no. LD patients	Note from study description	Year(s) of study	Study location	Reference
Recall of tick bite						
Children and adults	0.14	34 / 237	Aware of having been bitten by a deer tick.	1981–1987	Multiple communities, NY	Berger 1989
Children and adults	0.22	32 / 144	Tick bite known to physician treating patient.	1990–1991	Multiple communities, MD	Jung et al. 1994
Children and adults	0.31	97 / 314	Recall of a tick bite.	1976–1982	Multiple communities, CT	Steere et al. 1983
Children and adults	0.40	274 / 679	Recalled tick bite prior to illness onset.	1983–1984	Multiple communities, NY	Benach and Coleman 1987
Children and adults	0.41	87 / 210	Recall of a definite tick bite.	1982–1983	Westchester Co., NY	Williams et al. 1986
Children and adults	0.44	19 / 43	Remembered having been bitten by a tick within 3 mo before the illness.	1977	Multiple communities, CT	Steere et al. 1978
Children and adults	0.49	40 / 82	Recalled a tick bite (early Lyme disease).	1985–1987	Upper Midwest	Agger et al. 1991
Children and adults	0.63	60 / 95	Definitely been bitten by one or more ticks.	1981–1982	Monmouth Co., NJ	Bowen et al. 1984
Children and adults	0.67	10 / 15	Recalled tick bite.	1982	Fire Island, NY	Hanrahan et al. 1984
Children	0.36	47 / 132	Recognized a tick bite within the preceding month.	1992–1993	Multiple communities, CT	Gerber et al. 1996
Children	0.49	44 / 90	Reported a tick bite before the onset of symptoms.	1982–1983	Westchester Co., NY	Williams et al. 1990
Recall of tick bite at the erythema migrans rash site						
Children and adults	0.10	5 / 51	Recalled a prior tick bite at the rash site.	1993	Hunterdon Co., NJ	Orloski et al. 1998
Children and adults	0.21	9 / 43	Remembered having been bitten by a tick at the site of the initial lesion before its onset.	1977	Multiple communities, CT	Steere et al. 1978
Children and adults	0.25	20 / 79	Recalled tick bite at primary erythema migrans site.	1991–1993	Westchester Co., NY	Nadelman et al. 1996
Children	0.22	22 / 132	Recognized a tick bite at the site of the erythema migrans within the preceding month.	1992–1993	Multiple communities, CT	Gerber et al. 1996
Children	0.52	24 / 46	Remembered a tick bite at the site of the skin lesion.	1976–1979	Multiple communities, CT	Szer et al. 1991
Adults	0.20	20 / 101	Recalled tick bite at skin-lesion site.	2001–2003	Multiple communities, NY	Wormser et al. 2005