Relative Risk for Ehrlichiosis and Lyme Disease in an Area Where Vectors for Both Are Sympatric, New Jersey, USA

Andrea Egizi, Nina H. Fefferman, Robert A. Jordan

Author affiliations: Rutgers University, New Brunswick, New Jersey, USA (A. Egizi, N.H. Fefferman, R.A. Jordan); Monmouth County Mosquito Control Division, Tinton Falls, New Jersey, USA (A. Egizi, R.A. Jordan); University of Tennessee, Knoxville, Tennessee, USA (N.H. Fefferman)

The lone star tick, *Amblyomma americanum*, is a vector of *Ehrlichia chaffeensis* and *E. ewingii*, causal agents of human ehrlichiosis, and has demonstrated marked geographic expansion in recent years. *A. americanum* ticks often outnumber the vector of Lyme disease, *Ixodes scapularis*, where both ticks are sympatric, yet cases of Lyme disease far exceed ehrlichiosis cases. We quantified the risk for

ehrlichiosis relative to Lyme disease by using relative tick encounter frequencies and infection rates for these 2 species in Monmouth County, New Jersey, USA. Our calculations predict >1 ehrlichiosis case for every 2 Lyme disease cases, >2 orders of magnitude higher than current case rates (e.g., 2 ehrlichiosis versus 439 Lyme disease cases in 2014). This result implies ehrlichiosis is grossly underreported (or misreported) or that many infections are asymptomatic. We recommend expansion of tickborne disease education in the Northeast United States to include human health risks posed by *A. americanum* ticks.

Tickborne diseases are a growing public health concern in the United States (*1*). Lyme disease, caused by the bacterium *Borrelia burgdorferi,* is the most frequently reported vectorborne illness in the Northeast (*2*) and has been the subject of widespread education campaigns aimed at preventing human encounters with its vector, *Ixodes scapularis* (the black-legged tick). Unfortunately, such campaigns focus comparatively less attention on other medically important ticks in Lyme disease–endemic areas (*3*); therefore, persons living in these areas may not fully recognize the threat posed by these species. Specifically, the much more aggressive lone star tick, *Amblyomma americanum*, transmits the agent of human monocytic ehrlichiosis and may serve as the vector for several other emerging tickborne pathogens (*3–5*). Historically found primarily in the Southeast United States but with established distributions along the Atlantic Coast and into the Midwest (*6*), *A. americanum* ticks are active concurrently with *I. scapularis* ticks; aggressively attack humans in all tick life stages (adult, nymph, and larvae); and are typically by far the more numerous of the 2 ticks where they are sympatric (*7,8*).

Given the abundance and aggressive host-seeking behavior of *A. americanum* ticks, it is reasonable to expect high rates of human encounters with them (*8–10*). In recent
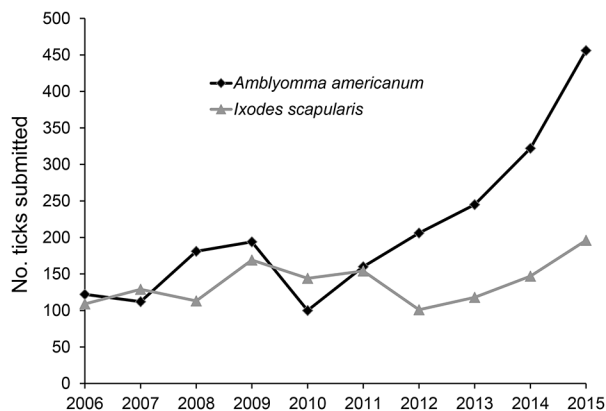
Figure 1. Number of ticks submitted each year to Monmouth County Mosquito Control Division's passive surveillance program during May–August, by year, Monmouth County, New Jersey, USA, 2006–2015.

years, submissions of *A. americanum* ticks to the Monmouth County Mosquito Control Division's passive tick surveillance program (Tinton Falls, New Jersey, USA; offering free tick identification to residents since 2006) have been increasing steadily while submissions of *I. scapularis* ticks remain nearly level (Figure 1), suggesting increased human exposure to *A. americanum* ticks relative to *I. scapularis* ticks.

A. americanum ticks are known vectors of >2 human pathogens, *Ehrlichia chaffeensis* and *E. ewingii* (*10,11*), which cause human ehrlichiosis, an illness often marked by an initial prodrome of undifferentiated fever, headache, myalgia, nausea, malaise, thrombocytopenia, leukopenia, and hepatic injury (elevated serum transaminase levels) (*12*). More severe complications (including toxic shock–like symptoms and meningitis or meningoencephalitis) may occur in some untreated persons (including immunocompromised patients), and death rates as high as ≈3% have been reported (*12,13*).

The number of ehrlichiosis cases attributable to *E. chaffeensis* that have been reported to the Centers for Disease Control and Prevention (Atlanta, GA, USA) has increased steadily since the disease became reportable, from 0.8 cases/million persons/year in 2000 to 3.0 cases/million persons/year in 2007 (*13,14*). However, some evidence suggests that ehrlichiosis may be substantially underreported (*12*) and even reported cases may be misclassified because of cross-reactivity between *E. chaffeensis*, *E. ewingii*, and other *Ehrlichia* and *Anaplasma* agents in widely used serologic tests (*15–17*). Health risks may be compounded if physicians are less familiar with ehrlichiosis than Lyme disease, particularly because initial symptoms may be relatively vague, resembling a viral syndrome typical of an array of tickborne diseases (*14*), which creates the potential for diagnostic confusion where *I. scapularis* and *A. americanum* ticks are sympatric (*10*). Ehrlichiosis could also be misdiagnosed as Rocky Mountain spotted fever if a patient is co-infected with *Ehrlichia* sp. and *Rickettsia amblyommatis,* (formerly *Candidatus* Rickettsia amblyommii [*18*]), a species cross-reactive in tests for rickettsial pathogens (*19*) and commonly present in ≥40% of field-collected *A. americanum* ticks (*4*).

This study quantified the risk to humans of ehrlichial infections, relative to Lyme disease risk. We used data obtained from tick surveillance programs in Monmouth County, New Jersey, an area with a high reported incidence of Lyme disease and increasing *A. americanum* tick encounter rates.

Methods

Site Description
Monmouth County (40°44′N, 74°17′W) is located in eastern-central New Jersey, a US state on the mid-Atlantic

coast. The county is 468.8 mi^2 in size and had a population of 630,380 (1,344.7 persons/mi^2) as of the 2010 census (http://www.census.gov/quickfacts/table/PST045215/34025). The geomorphologic break separating the Inner and Outer Coastal Plain physiographic provinces in New Jersey runs horizontally across the center of the county, and the resulting soil differences are reflected in vegetative differences between these 2 regions (20). The Outer Coastal Plain region is characterized by sandier soils that are often dry and acidic, with pine forests and cedar swamps. Previously, the distribution of *A. americanum* ticks in Monmouth County was restricted to this southern part of the county (21), whereas *I. scapularis* ticks were found throughout. However, recently specimens of *A. americanum* ticks have been captured in the far north and west of the county.

The county reports several hundred cases of Lyme disease annually, with a 10-year average (during 2005–2014) of 361 cases/year. By contrast, during that same period, there were on average 5.5 cases/year of *E. chaffeensis* infection and no cases of infection attributed to *E.ewingii* (22).

Risk Model

The relative risk for infection with a tickborne pathogen depends on multiple factors, including risk for exposure to a competent vector, risk for exposure to the pathogen from exposure to the vector, and risk for transmission from exposure to a pathogen-infected vector. To characterize the risk for human exposure to ticks, we define the parameter C_x as the relative proportion of each species (*x*) of tick submitted to the Monmouth County Mosquito Control Division's tick identification and testing service. This passive surveillance program, initiated in 2006, allows county residents to submit ticks they have encountered (e.g., found on their skin or clothing) for species identification. This program averages 658.9 submissions/year, although this number has increased markedly in recent years (R.A. Jordan, unpub. data). For C_x, we used the 10-year average of relative submissions data (2006–2015) during peak Lyme disease transmission season in New Jersey (May–August) (Table). Although in Monmouth *A. americanum* ticks are often 3 times as abundant as *I. scapularis* ticks in field collections (9), using the passive surveillance data in our model (where *A. americanum* ticks are only encountered 1.5 times as often; Table) provides a more direct measure of human exposure to ticks as well as a more conservative risk estimate.

To characterize risk for exposure to the disease from the vector, we define I_x as the prevalence of the pathogen in ticks (i.e., percentage infected), weighted by life stage. Both *I. scapularis* and *A. americanum* ticks have a 3-host life cycle, meaning that adults have had more opportunities to feed on an infected host than nymphs and consequently infection rates differ between life stages. Because transovarial transmission of either *B. burgdorferi* or *E. chaffeensis* does not occur (23,24), host-seeking larvae are not infected and therefore were not included in the calculations. Relative abundance of nymphs and adults of each species submitted to our passive tick surveillance program during May–August were reported ($C_{X,N}$ and $C_{X,D}$) and used to weight the infection prevalence of each (Table). Infection rates of *I. scapularis* ticks with *B. burgdorferi* for both life stages ($I_{IS,D}$ and $I_{IS,N}$) also were obtained from our passive surveillance program, whereby residents submitting an *I. scapularis* tick can elect to have it tested for *B. burgdorferi* through nested PCR assay (following established protocols [8]). Our records show that during a 10-year period of our program, 90.5% of residents submitting *I. scapularis* ticks during May–August have chosen to have them tested (R.A. Jordan, unpub. data), including 153 adults and 1,146 nymphs. However, the program does not test *A. americanum* ticks, so infection rates for this species were obtained from other sources. Rates of adult tick infection with *E. chaffeensis* and *E. ewingii* ($I_{AA,D}$) in Monmouth County were derived from Schulze et al. (21) and summed, yielding a total value (accounting for co-infected ticks) of 11.7% infection with human *Ehrlichia* pathogens (N = 291). Nymphal infection rates with both ehrlichia species were obtained from an unpublished dataset consisting of field-collected nymphs from 4 sites in eastern and western Monmouth County in 2014 (R.A. Jordan unpub. data). Nymphal specimens were disrupted by using a TissueLyser and DNA isolated with QIAgen DNeasy 96 well-plate blood and tissue kits (QIAGEN, Valencia, CA, USA). Specimens were tested for pathogens by using real-time PCR protocols for

Table. Parameters used in relative risk calculations for ehrlichiosis and Lyme disease, by vector, Monmouth County, New Jersey, USA*

Parameter	Ixodes scapularis		Amblyomma americanum	
Relative abundance of each species	C_{IS} = 38.32		C_{AA} = 61.68	
	Adults	Nymphs	Adults	Nymphs
Relative abundance of each life stage	$C_{IS, D}$ = 19.96	$C_{IS, N}$ = 80.04	$C_{AA, D}$ = 35.34	$C_{AA, N}$ = 64.66
Infection rates per life stage	$I_{IS, D}$ = 39.87	$I_{IS, N}$ = 23.3	$I_{AA, D}$ = 11.7	$I_{AA, N}$ = 9.04
Infection rates, weighted	I_{IS} = 26.60		I_{AA} = 9.98	

*Values are in percentages. Relative abundances (denoted by C_X) are derived from specimens submitted to the Monmouth County Mosquito Control Division's tick identification and testing service during peak Lyme disease transmission season (May–August) and during a 10-year period (2006–2015). Infection rates of *I. scapularis* ticks with *Borrelia burgdorferi* (I_{IS}) also from passive surveillance program. Infection rates of *A. americanum* ticks (I_{AA}) encompass both *Ehrlichia chaffeensis* and *E. ewingii* (accounting for co-infection).

E. chaffeensis (*25*) and *E. ewingii* (*26*). Both probes were modified slightly (shortened) to allow the use of an MGB quencher as follows (5′–3′): VIC-CGGACAATTGCT-TATAACC-MGBNFQ for *E. chaffeensis* and 6FAM-AACAATTCCTAAATAGTCTCTGAC-MGBNFQ for *E. ewingii*. Sequence detection primers and reaction conditions were as described previously (*26*). A subset of samples was compared with conventional PCR methods established by this laboratory for detection of these pathogens (*21*), and the 2 methods were found to be in agreement. The resulting infection prevalence of *Ehrlichia* pathogens in *A. americanum* nymphs ($I_{AA,N}$) (encompassing *E. chaffeensis* and *E. ewingii*, accounting for coinfection) was 9.04% (N = 752). Overall infection prevalence (I_x) in each species of tick, weighted by life stage, was calculated by multiplying the relative abundance of each life stage times its infection rate and summing across life stages (Table).

To characterize transmission risk, we defined T_X as the likelihood of successful pathogen transmission from an infected tick to a human. The general concept of vector competence includes both this direction of transmission from vector to host as well as the probability of the vector becoming infected from feeding on infected hosts, which in our calculations is already reflected in tick infection rates (I_x). Data on transmission efficiency to animals for both species is scarce because most studies feed multiple infected ticks on 1 host (so the risk imposed by a single feeding tick is unknown) and, because of the difficulty in working with large vertebrates in a laboratory setting, have very small sample sizes (*27–30*). Further, whether probabilities of transmission obtained from animal studies are applicable to humans is

unknown. Therefore, although we are including the parameter T_X in the equation so that it can be applied when such data become better known, for purposes of these analyses we are setting it equal to 1 for both diseases, yielding no functional impact on the model.

Calculations

Based on our definitions, we calculate the relative risk for ehrlichiosis compared to Lyme disease as risk = $(C_{AA} \times I_{AA} \times T_{AA})/(C_{IS} \times I_{IS} \times T_{IS})$. To then translate this value into expected cases of observed human infection, we move from risk to reported case numbers by using the reported number of cases of Lyme disease in Monmouth County as a benchmark. In other words, if there were X Lyme disease cases, then the expected number of ehrlichiosis cases would be X multiplied by the relative risk estimate calculated as described.

Results

The relative risk for ehrlichiosis cases compared to Lyme disease was calculated as risk = $(61.68 \times 9.98 \times 1)/(38.32 \times 26.61 \times 1) = 0.604$. These numbers mean that we should expect to see ehrlichiosis cases occur 0.604 times as often as Lyme disease cases.

In 2014, a total of 439 cases of Lyme disease were reported in Monmouth County (*22*). By using the risk estimates described, we would expect there to be ≥265 cases of ehrlichiosis, >2 orders of magnitude higher than the number of cases actually observed (Figure 2).

Discussion

We demonstrate that in Monmouth County, New Jersey, ehrlichiosis infections from *A. americanum* ticks should be occurring, at a minimum, one half as often as Lyme disease (e.g., 1 ehrlichiosis case for every 2 Lyme disease cases). This rate of occurance is clearly not the case (Figure 2), and these numbers suggest that ≈99% of potential ehrlichiosis infections are not recognized. It is possible that not all persons who become infected in Monmouth are county residents (and so their case would be recorded elsewhere) making the total number of Monmouth County–derived infections likely to be somewhat higher than the observed 2 cases. However, even if one assumes all ehrlichiosis reported for the entire state of New Jersey to originate in Monmouth County (64 cases in 2014) (*22*) these values still indicate a substantial discrepancy between numbers of observed and expected cases.

When selecting values for the parameters used in our calculations, every opportunity to be conservative was taken to avoid biasing estimates of relative risk. For example, infection (I_x) probabilities were higher for Lyme disease than ehrlichiosis (39.87% vs. 11.7% for adult ticks and 23.3% vs. 9.04% for nymphs). Although reported *B. burgdorferi* infection rates in *I. scapularis* adults frequently
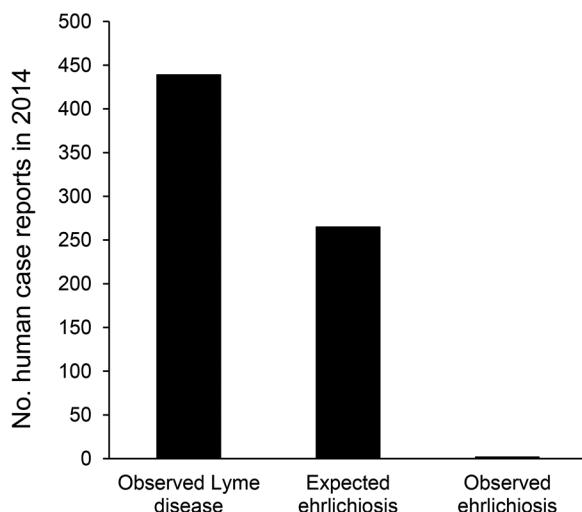
Figure 2. Number of observed versus expected ehrlichiosis cases, Monmouth County, New Jersey, USA, 2014. Expected values calculated by using number of observed Lyme disease cases as benchmark.

range from 40% to 50% in hyperendemic areas, several studies have reported lower rates (*9,31*). Our weighted infection prevalence estimate of 9.98% (encompassing both *E. chaffeensis* and *E. ewingii* across adults and nymphs) is probably lower than the actual value, given that many studies have reported infection prevalence in the range of 5%–15% for *E. chaffeensis* alone and in some locations twice that rate (*3,32*). Last, use of passive surveillance numbers (C_x) probably underestimates the actual risk for exposure to *A. americanum* ticks; residents who recognize the tick species may be less likely to bring in *A. americanum* ticks to the passive surveillance program, because we only test *I. scapularis* (as stated on our website), and taking the 10-year average for relative abundances (2006–2015) does not account for the recent surge in *A. americanum* tick submissions from 2012 onward (Figure 1). In light of these considerations, the actual risk for *A. americanum* tick–associated ehrlichioses in Monmouth County may be much higher than we have estimated.

One caveat should be noted. Differences in PCR sensitivity between *B. burgdorferi* and *Ehrlichia* sp. assays could affect our ability to compare infection rates, although to mitigate this problem as much as possible, we relied on established primers and checked that infection rates were within ranges reported by other studies as described previously. Thus, any difference in our ability to detect pathogens between the 2 tick species is unlikely to alter our conclusions.

One possible explanation for the lower-than-expected number of reported ehrlichiosis cases is a lack of awareness about ehrlichial disease on the part of the public and physicians, leading to misdiagnosis and underreporting. The infection tends to manifest as a general influenza-like illness, and onset of a rash is rare (*12*), so persons may be less likely to visit a doctor unless more severe symptoms emerge or they are aware of a recent tick bite and the presence of tickborne diseases in the area. Awareness of non–Lyme disease tickborne illnesses is startlingly low, even in parts of the country where ehrlichiosis cases outnumber Lyme disease cases (*33–35*). One study found that >50% of respondents in the United States had heard of Lyme disease, whereas only 1.4% had heard of ehrlichiosis (*35*). As a consequence of these factors, when active screening for ehrlichial infections is performed, the resulting case rates are often much higher than those reported to governmental agencies (*3,36,37*). For example, Olano et al. (*37*) found that the incidence of ehrlichiosis observed when actively screening patients was as much as 2 orders of magnitude higher than the passively reported incidence.

Another explanation could be the existence of asymptomatic infections. Several studies of *E. chaffeensis* antibody seroprevalence in adults found that most of those carrying the antibodies had no recollection of a symptomatic infection (*38–40*). Further, a study screening blood samples from children from the Southeast United States for *E. chaffeensis* revealed that many more children had been exposed than showed clinical signs (*41*). Most documented cases of *E. chaffeensis* and *E. ewingii* infection come from older adults (*13,15*), so when younger adults and children become infected, they may be less likely to have symptoms or seek treatment (*41*), accounting for the large number of unreported infections. Other vectorborne diseases, such as West Nile virus, transmitted by mosquitoes, also demonstrate large numbers of asymptomatic infections and increased severity among the older population (*42*). However, because of cross-reactivity in the serologic test for *E. chaffeensis* and the lack of specific testing for *E. ewingii*, one could argue that many presumed asymptomatic cases of *E. chaffeensis* were actually incidences of infection with *E. ewingii*, which tends to be more mild (*16*). Although our study considered *E. chaffeensis* and *E. ewingii* interchangeably, if we repeat our calculations by using *E. chaffeensis* infection rates alone, we would expect Monmouth County to have seen 84 cases of *E. chaffeensis* in 2014, when only 2 were reported. Therefore, 97.6% of *E. chaffeensis* infections are potentially going unnoticed (versus 99% of ehrlichiosis infections overall), which is still a troubling discrepancy.

Across the entire United States, the number of Lyme disease cases dwarfs ehrlichiosis cases. During 2004–2013, the Centers for Disease Control and Prevention annually reported 279–528 Lyme disease cases/1 million persons (*2*). In contrast, during that same period, annual ehrlichiosis cases ranged from 3.3 to 26 cases/1 million persons (*43*). If our numbers can be extrapolated to other areas in the country, this implies that, on a national scale, potentially thousands of ehrlichiosis cases are going undiagnosed. The *A. americanum* tick appears to be expanding into geographic areas where it did not occur previously (*6,32*) and is becoming more abundant within its existing range (*9,21,44*). Because ehrlichiosis cases have steadily increased since becoming reportable (*13,15*), the spread of *A. americanum* ticks and the emergence of ehrlichiosis as a human pathogen in the United States may parallel increases in *I. scapularis* tick populations and the emergence of Lyme disease that occurred 30 years prior (*14*). Even if most unrecognized infections are mild or asymptomatic, these could still have consequences for public health; for example, blood donors who are unknowingly infected could pass the infection to immunocompromised patients (*45*), or prescription of sulfa drugs for unrelated ailments could result in worsened disease presentation (*46*).

Our findings indicate a need to increase public education efforts about the risks for acquiring tickborne diseases other than Lyme disease in the United States, and in particular, to expand prevention awareness of medically important tick species other than *I. scapularis*. Fortunately, many of these diseases, including ehrlichiosis, can be

prevented in the same manner as Lyme disease (e.g., avoidance of tick bites) and are treated similarly to Lyme disease (*12,47*); also, the number of ehrlichiosis cases peaks during spring and summer months, corresponding with peak Lyme disease transmission months (*13,15*). Consequently, refocusing existing public health education efforts to encompass the full spectrum of tickborne diseases could be accomplished without changing much of its content, although some attention should be given to the risks imposed by viruses and protozoa as well as unique characteristics of the questing behavior of *A. americanum* ticks. To better inform these educational efforts and more accurately assess tickborne disease risk, more research into diseases other than Lyme disease is required.

Humans can alter their environment in many ways that affect disease transmission, from localized changes affecting tick habitat and host abundance, to larger changes affecting the planet's climate. As these changes continue to occur, the study of vector and pathogen distributions and abundance will be critical to understanding the potential risk to humans posed by emerging pathogens. Our calculations imply that infections with *E. chaffeensis* and *E. ewingii* are underrecognized, at least in Monmouth County, New Jersey, if not throughout a larger portion of the United States where *A. americanum* ticks are abundant or becoming abundant. Additional effort is needed to determine the causes for this apparent discrepancy and to characterize the actual prevalence of ehrlichiosis in the human population, as well as to raise awareness about the risk for exposure to these pathogens in areas where *A. americanum* ticks are common.

Acknowledgments

Dr. Egizi oversees a research laboratory for the Monmouth County Mosquito Control Division located in the Center for Vector Biology at Rutgers University in New Brunswick, New Jersey, USA. She is interested in using molecular tools to gain insight into the ecology and evolution of vectors and vectorborne disease in the northeastern United States.

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Address for correspondence: Andrea Egizi, Rutgers University, 180 Jones Ave, New Brunswick, NJ 08901, USA; email: andrea.egizi@co.monmouth.nj.us