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REVIEW ARTICLE

Brave New Worlds: The Expanding Universe of Lyme Disease

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Abstract

Projections around the globe suggest an increase in tick-vectored disease incidence and distribution, and the potential for emergence of novel tick-borne pathogens. Lyme disease is the most common reported tick-borne illness in the Unites States and is prevalent throughout much of central Europe. In recent years, the worldwide burden of Lyme disease has increased and extended into regions and countries where the disease was not previously reported. In this review, we discuss the trends for increasing Lyme disease, and examine the factors driving Lyme disease expansion, including the effect of climate change on the spread of vector Ixodid ticks and reservoir hosts; and the impacts of increased awareness on disease reporting and diagnosis. To understand the growing threat of Lyme disease, we need to study the interplay between vector, reservoir, and pathogen. In addition, we need to understand the contributions of climate conditions to changes in disease risk.

Keywords: *Borrelia*, expansion, *Ixodes*, Lyme disease

Introduction

In 1992, the Institute of Medicine issued a seminal report on emerging microbial threats to human health in the United States (Committee on Emerging Microbial Threats to Health 1992). The report addressed key factors involved in both the emergence of new diseases and the resurgence of old pathogens: human demographics and behavior, economic development and land use, and microbial adaptation, among others. It was the ''committee's hope that lessons from the past will illuminate possible approaches to prevention and control of these diseases in the future.''

Unfortunately, in the ensuing quarter century, microbial threats to health have not declined. In fact, vector-borne disease [defined as disease transmitted to plants, animals, or humans by arthropods (Institute of Medicine 2008)] is on the rise. Estimates from the World Health Organization suggest that vector-borne disease accounts for 17% of human global infectious disease burden (World Health Organization 2017).

While mosquitos and biting flies are recognized as major vectors of both established and novel scourges, including malaria, West Nile virus, and Zika virus, tick-transmitted disease has not received as much attention. However, projections for vector-borne disease activity in the United States include increased incidence, increased distribution of tick borne disease, and the possibility of novel tick-borne pathogens that have yet to be discovered (Forum on Microbial Threats 2016). Indeed, these predictions have already been realized, not only in the United States, but across the globe. In this review, we will focus on the expansion of the hard ticks of the genus *Ixodes* and one of the many infectious agents transmitted by the tick—Lyme disease.

Lyme disease was first recognized in the 1970s, following an epidemic of juvenile arthritis cases in eastern Connecticut (Steere et al. 1977). The peak of cases in summer and early fall and its geographic clustering led to the hypothesis that an arthropod vector was transmitting an unknown agent (Steere et al. 1977, 1978). The infectious agent of Lyme disease was discovered in 1982 by Willy Burgdorferet al., after spirochetal bacteria, subsequently named *Borrelia burgdorferi*, were isolated from *Ixodes dammini* ticks (Burgdorfer et al. 1982, Benach et al. 1983, Steere et al. 1983). Lyme disease is endemic across much of the Northern hemisphere including the United States, Europe, and parts of Asia (Kurtenbach et al. 2006).

Clinical presentation of disease often includes a characteristic skin lesion called erythema migrans. In the early stages of the disease, patients may experience secondary skin lesions, malaise, fatigue, lethargy, and joint and muscle pain (Stanek et al. 2011, 2012, Hu 2012). Patients may go on to develop oligoarticular arthritis of the large joints, frequently the knee. More serious manifestations of disease, such as cardiac and neurological complications can also occur (Hu 2012, Stanek et al. 2012). Approximately 20 closely related

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Borrelia form the *B. burgdorferi sensu lato* (*s.l.*) complex, including known causative agents of Lyme disease (in North America: *B. burgdorferi sensu stricto* (*s.s.*); in Europe and Asia: *Borrelia afzelii*, *Borrelia garinii*, *Borrelia spielmanii*, and *Borrelia bavariensis*) (Richter et al. 2004, Margos et al. 2009, 2011, 2014, Rudenko et al. 2011b, Stanek and Reiter 2011), and related borreliae that have not yet been demonstrated to cause human disease (Rudenko et al. 2011a, Cutler et al. 2017; Table 1). *B. burgdorferi s.l.* differ in pathogenicity, geographic location, Ixodidae vector, and preferred reservoir host(s). For simplicity, Lyme borreliae are frequently referred to simply as *B. burgdorferi*.

Lyme disease spreading *Ixodes* spp. ticks are distributed throughout the northern hemisphere (Stanek et al. 2012). The tick passes through three life stages: larva, nymph, and adult, generally in a 2-year life cycle. *Ixodes* spp. acquire Lyme disease spirochetes through a blood meal; there is no transovarial transmission (Piesman et al. 1986, Patrican 1997, Rollend et al. 2013). Lyme borreliae are carried and transmitted by several species of *Ixodes* ticks; the most common species are *Ixodes scapularis* and *Ixodes pacificus* in North America and *Ixodes ricinus* and *Ixodes persulcatus* in Europe and Asia.

There are other tick species that may be infected with and able to transmit *B. burgdorferi s.l.* including *Ixodes minor*, *Ixodes dentatus*, *Ixodes spinipalpis*, and *Haemaphysalis longicornis*, among others (Rudenko et al. 2011b). As these species rarely bite humans, they pose little risk of transmitting the Lyme disease pathogen. However, these other tick species play an important role in maintaining *B. burgdorferi* in nature (James and Oliver 1990, Hornok et al. 2012, Roome et al. 2017). *Ixodes* spp. are generalists when it comes to seeking a blood meal, but often like to feed on particular species at particular life stages; for instance, adult ticks in both Europe and the Northeastern United States prefer deer as their feeding source (Ostfeld et al. 2006, Gilbert et al. 2012, Levi et al. 2012, Pacilly et al. 2014). *I. scapularis* ticks carry a variety of pathogens including *Anaplasma*, *Babesia*, *Bartonella*, *Borrelia*, *Ehrlichia*, *Rickettsia*, *Theileria*, and *Flavivirus* (Nelder et al. 2016).

Worldwide Burden of Lyme Disease

Lyme disease is the most common arthropod-borne disease in the United States, with ~30,000 cases reported to the

Table 1. *Borrelia burgdorferi Sensu Lato* Complex

Species	*Published description*	*Human disease?*	*Location*	*Vector*	*Main reservoir*
Borrelia burgdorferi	Johnson et al. 1984	Yes	N. America, Europe	*Ixodes scapularis*, *Ixodes pacificus*, *Ixodes ricinus*	Rodents and birds
Borrelia afzelii	Canica et al. 1993	Yes	Europe, Asia	*I. ricinus*, *Ixodes persulcatus*	Rodents
Borrelia garinii	Baranton et al. 1992	Yes	Europe, Asia	*I. ricinus*, *I. persulcatus*	Birds and rodents
Borrelia americana	Rudenko et al. 2009	No	United States	*I. pacificus*, *Ixodes minor*	Birds
Borrelia bavariensis	Margos et al. 2009	Yes	Europe, Asia	*I. ricinus*, *I. persulcatus*	Rodents
Borrelia andersonii	Marconi et al. 1995	No	United States	*Ixodes dentatus*	Rabbit
Borrelia bissettii	Postic et al. 1998	Yes	United States, Europe	*I. scapularis*, *I. pacificus*, *I. ricinus*, *I. minor*	Birds and rodents
Borrelia spielmanii	Richter et al. 2004	Yes	Europe	*I. ricinus*	Rodents
Borrelia valaisiana	Wang et al. 1997	Yes	Europe, Asia	*I. ricinus*, *Ixodes granulates*	Birds
Borrelia lusitaniae	Le Fleche et al. 1997	Yes	Europe, N. Africa	*I. ricinus*	Rodents
Borrelia californiensis	Margos et al. 2016	No	United States	*I. pacificus*, *Ixodes jellisonii*, *Ixodes spinipalpis*	Kangaroo rat, mule deer
Borrelia carolinensis	Rudenko et al. 2011a	No	United States	*I. minor*	Rodents
Borrelia kurtenbachii	Margos et al. 2014	No	United States	*I. scapularis*	Rodents
Borrelia finlandensis	Casjens et al. 2011	No	Finland	*I. ricinus*	Unknown
Borrelia sinica	Masuzawa et al. 2001	No	China	*Ixodes ovatus*	Rodents
Borrelia yangtzensis	Margos et al. 2015	No	China, Japan	*Haemaphysalis longicornis*, *Ixodes granulatus*	Rodents
Borrelia japonica	Kawabata et al. 1993	No	Japan	*I. ovatus*	Rodents
Borrelia tanukii	Fukunaga et al. 1996	No	Japan	*Ixodes tanuki*	Unknown
Borrelia turdi	Fukunaga et al. 1996	No	Japan	*Ixodes turdus*	Birds
Borrelia chilensis	Ivanova et al. 2014	No	Chile	*Ixodes stilesi*	Rice rats?
Borrelia mayonii	Pritt et al. 2016	Yes	U.S.-Upper Midwest	*I. scapularis*	Rodents?

Adapted from Rudenko et al. (2011b) and Cutler et al. (2017).

Centers for Disease Control and Prevention (CDC) every year (CDC 2017). However, several studies conducted by the CDC and others suggest the number of diagnosed cases of Lyme disease is actually 10-fold higher (Hinckley et al. 2014, Kugeler et al. 2015, Nelson et al. 2015, Schiffman et al. 2016). In the United States, most cases occur in just 12 of the 50 states, with a concentration in New England, Mid-Atlantic, and Upper Midwest regions (CDC 2017). Lyme disease has spread into neighboring Canada, as well, with 917 cases reported in 2015 (Government of Canada 2016).

Estimated cases for all of Europe are around 85,000 cases per year (Lindgren and Jaenson 2006, Smith and Takkinen 2006, Schotthoefer and Frost 2015, World Health Organization 2017). Case numbers in England and Wales are estimated to approach 3,000 cases annually, although the number of reported cases is much lower (Public Health England 2013, Schotthoefer and Frost 2015) (Table 2). The highest reported number of cases occur in central Europe, particularly in Germany, Austria, Slovenia, and the coastal regions of Sweden (Schotthoefer and Frost 2015). Reports of Lyme disease are still relatively rare in Japan and Korea (Lee and Cho 2004), while Lyme disease is clearly established in China, though exact numbers have yet to be reported (Fang et al. 2015).

Lyme Disease Expansion: Trends in North America

Northeast

The number of reported cases of Lyme disease in the New England state of Maine alone quadrupled in the decade between 2005 and 2015, from 247 cases to 993 (CDC 2017). Not surprisingly, the emergence of Lyme disease in the extreme northeastern portion of the United States has been accompanied by an increasing number of reports from regions of Canada contiguous with the Northeastern United States, particularly in Ontario, Quebec, and the Maritime provinces. Furthermore, predicted climate change may result in continued northward expansion of suitable tick habitats and allow for the introduction of permanent *I. scapularis* populations via migratory birds (Ogden et al. 2015).

Midwest

Despite the potential barrier posed by the Great Lakes, Lyme disease has expanded into Michigan and Indiana, increasing from 62 and 33 cases in 2005 to 125 and 103 cases, respectively, in 2015 (CDC 2017). Modeling studies suggest that environmental conditions are suitable for the spread of *I. scapularis* into central and northern Michigan, the Ohio River Valley, and far northwestern Minnesota (Hahn et al. 2016). The high plains states of the Dakotas have been traditionally considered too dry and devoid of suitable habitat for the westward spread of *I. scapularis*. Indeed, 10 years ago, there was no evidence that *I. scapularis* tick-borne diseases were circulating in North Dakota. However, several *I. scapularis*-borne pathogens, including *B. burgdorferi*, have now been detected in *I. scapularis* populations in northeastern North Dakota (Russart 2013, Russart et al. 2014, Stone et al. 2015). Concurrent with this discovery is an increasing incidence of Lyme disease within the state, from 2 reported cases in 2000 to 33 in 2015 (North Dakota Department of Health 2016). Our current understanding of dynamic range expansion is incomplete; in a recent publication, four computational models based on perceived habitat suitability were compared with the most up-to-date surveillance data on *I. scapularis* occurrence in the Midwest, and only one of the four models correctly indicated that breeding populations of the tick could become established in North Dakota (Russart 2013, Russart et al. 2014, Dougherty 2015, Stone et al. 2015, Hahn et al. 2016). Recent modeling efforts show that parts of South Dakota can potentially support populations of *I. scapularis* as well, and an established population of *I. scapularis* was recently reported in Clay County, South Dakota (Maestas et al. 2016). Central Canada has not been spared the spread of *I. scapularis* and Lyme disease, with small but established foci of *B. burgdorferi*-infected ticks detected in the province of Manitoba and far western Ontario (Government of Canada 2016, Scott et al. 2016).

Southeast

In the southeast, an increase in Lyme disease cases has occurred in Virginia, particularly in the northern part of the state. However, expansion southeast through the metropolitan area of Richmond, and southwest along the Appalachian Mountains, is also occurring. In addition, if mountain ecology is favorable for the vector and its hosts, an increase of cases in neighboring mountainous areas of Kentucky, West Virginia, and Tennessee might also be expected (Lantos et al. 2015). The incidence and spread of Lyme disease in Virginia suggests more cases are likely in the near future in neighboring North Carolina. Indeed, *B. burgdorferi* is endemic among both ticks and tick hosts on the Outer Banks of North Carolina, and as of March 2015, five counties in North Carolina have been identified as endemic for Lyme disease (North Carolina Department of Health and Human Services 2015).

I. scapularis is established in the southeastern and Gulf coasts, and modeling analyses suggest *I. scapularis* is spreading inland from those areas as well (Hahn et al. 2016). While the incidence of Lyme disease is considerably lower in the Southeastern United States, *I. scapularis* are well established in this region (Barton et al. 1992, Sanders and Oliver 1995, Jacobs et al. 2003, Oliver et al. 2003, 2008, Rosen et al. 2012, Mays et al. 2014). Enzootic transmission cycles exist in coastal zones of South Carolina and in Georgia and Florida, and *B. burgdorferi* is endemic in these regions (Oliver et al.

Table 2. Lyme Disease Cases per Year; Selected Countries

	2005	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
U.S. total	23,305	19,931	27,444	28,921	29,959	22,561	24,364	22,014	27,203	25,359	28,453
Canada	NR	NR	NR	NR	144	143	266	338	682	522	917
England and Wales	595	768	797	813	863	905	959	NA	NA	NA	NA

Adapted from Public Health England (2013), Government of Canada (2016) and CDC (2017).
NA, not available; NR, not reported.

2003). However, there are differences in reservoir hosts from these regions, compared to the northeastern states (cotton mouse, cotton rat, and western woodrat) and different Ixodid ticks such as *Ixodes affinis* and *I. minor* (Clark et al. 2002, Oliver et al. 2003), which rarely bite humans. In addition, tick behavior is different in the southeast, with nymphs remaining in leaf litter rather than actively questing (Arsnoe et al. 2015). There may be some human cases acquired locally, although most cases are probably travel-related (Clark et al. 2013). A point of concern is that recent genetic studies suggest north to south gene flow of *I. scapularis*; as populations interbreed, southern ticks might acquire the behavior characteristics of their northern counterparts and become more likely to transmit *B. burgdorferi* to humans (Van Zee et al. 2015).

Texas

Presence of *B. burgdorferi* in *I. scapularis* along the Texas-Mexico boundary is controversial (Esteve-Gassent et al. 2015, Norris et al. 2015). Rodents with high prevalence of *B. burgdorferi s.l.* infection have been identified as far south as rural communities in the Yucatan, Mexico, however (Solis-Hernandez et al. 2016). A study that examined serological evidence for *B. burgdorferi* infection among white-tailed deer (*Odocoileus virginianus*) in Texas found 4.7% seropositive by enzyme-linked immunosorbent assay, but only 0.5% positive by western blot. There has been an increased incidence in Lyme disease cases in Texas (Adetunji et al. 2016), although the increase could be due to travel-associated cases or misdiagnoses with Southern Tick Associated Rash Illness (STARI) (Philipp et al. 2006, Blanton et al. 2008, Goddard 2017). Eastern Texas provides suitable habitat for *I. scapularis*, but remains a low risk area for acquisition of Lyme disease (Feria-Arroyo et al. 2014, Szonyi et al. 2015).

West

I. pacificus is the vector of Lyme disease in California and the west coast of the United States and Canada. California, in particular, presents a different type of habitat than that observed in the Northeastern United States, mainly coastal oak forests and semi-desert scrub (Salkeld et al. 2014, 2015). Furthermore, the mild climate allows infected ticks to be active year-round (Salkeld et al. 2014). Risk of human infection has remained stable over the last decade in California, Oregon, and Washington state, in addition to the province of British Columbia (Government of Canada 2016, CDC 2017), suggesting that *I. pacificus* may already be established in all regions where there is suitable habitat (Hahn et al. 2016). Population expansion of known reservoirs for *B. burgdorferi*, such as the American robin, due to urbanization and chaparral removal, could increase the risk of transmission to humans (Newman et al. 2015); but, rising temperatures and drought due to climate change may restrict any potential increases in human disease risk to coastal and higher elevation habitats (Salkeld et al. 2014).

Lyme Disease Expansion: Trends in Europe

Trends in Europe are difficult to track due to differences in agencies and reporting across the continent (Smith and Takkinen 2006, Schotthoefer and Frost 2015). Across Western Europe, there are estimated to be 22 cases per 100,000 persons (Sykes and Makiello 2016). In England and Wales, however, there has been a steady increase in Lyme disease cases over the last several years (Table 2). The Scottish Highlands are also an area of high endemicity. Between 2008 and 2013, the prevalence of Lyme disease in all of Scotland was 6.8 cases per 100,000 persons, while it was 44.1 per 100,000 in Highland region (Mavin et al. 2015, Munro et al. 2015). The Tayside region adjacent to Highlands saw a dramatic rise in Lyme disease cases recently, an increase that has been attributed to changes in climate (Slack et al. 2011).

Lyme Disease Expansion: Trends in Asia

Six genospecies of *B. burgdorferi s.l.* and over 100 species of the Ixodidae family of hard ticks have been identified in China (Fang et al. 2015). Human cases of Lyme disease caused by genospecies *B. garinii*, *B. afzelii*, and *Borrelia valaisiana* have been reported in most provinces of mainland China (Fang et al. 2015). Exact numbers of cases are unclear, as the disease is likely underreported due to lack of surveillance and a lack of awareness by most physicians, and the lack of appropriate diagnostic facilities (Fang et al. 2015). The Lyme disease incidence rate per 100,000 population is 0.008 in Japan (Infectious Disease Surveillance Center 2011), and remains rare in Korea (Lee and Cho 2004).

Factors Driving Lyme Disease Expansion: Vectors, Hosts, and Reservoirs

The traditional view of the *I. scapularis* life cycle holds that ticks are found in deciduous and mixed forests, where larvae and nymphs feed primarily on the white-footed mouse (*Peromyscus leucopus*) and adult females feed primarily on white-tailed deer (*O. virginianus*) (Kurtenbach 2006, Piesman and Schwan 2010). This notion is being challenged as more knowledge of Lyme disease cycles outside of the Northeastern United States is acquired (Brisson et al. 2008, Brinkerhoff et al. 2011, Russart et al. 2013, Fedorova et al. 2014, Russart 2014, Dougherty 2015, Loss et al. 2016, Wodecka et al. 2016).

The general factors driving the escalation of Lyme disease, however, are similar in North America, Europe, and Asia, irrespective of differences in habitat, hosts, and behavior (Mannelli et al. 2012, Kulkarni et al. 2015, Medlock and Leach 2015). These factors, discussed below, include climate change (Ostfeld and Brunner 2015), host and reservoir expansion (Diuk-Wasser et al. 2012, Roy-Dufresne et al. 2013, Roome et al. 2017), and enhanced monitoring, detection, and reporting of *Ixodes* spp. and Lyme disease (*e.g.*, Aenishaenslin et al. 2016).

Ixodes *spp.*

The geographic distribution of *Ixodes* spp. is governed by the distribution of hosts and limited by temperature and humidity, with ticks preferring environments with warm, humid summers and mild winters (Ostfeld and Brunner 2015). While off-host *I. scapularis* are highly susceptible to desiccation and low temperature in laboratory experiments, established populations have been found in regions that experience frigid and dry winters (Galloway 1989, Russart et al. 2014, Stone et al. 2015, Eisen et al. 2016). This suggests that microclimates are invaluable for *I. scapularis* survival. Deciduous and mixed forests provide leaf litter that maintain high relative humidity and are regarded as the classic microhabitat for ticks. However, several temperate biomes, including coniferous forests, grasslands, and pastures also maintain microclimates that sustain *Ixodes* spp. (Estrada-Pena 2001, Walker et al. 2001, Richter and Matuschka 2006, Millins et al. 2016) some urban, peri-urban, and recreational environments support or are capable of supporting *Ixodes* spp. and host populations (Rizzoli et al. 2014, Mackenstedt et al. 2015, Hansford et al. 2017).

Temperature and precipitation changes projected by the Intergovernmental Panel on Climate Change (IPCC) could have significant impacts on the distribution of *Ixodes* spp. Current models suggest a gradient of increasing precipitation at northern latitudes and decreasing precipitation closer to the equator. Increasing precipitation would increase humidity and could aid in the spread of *Ixodes* spp. into novel areas, assuming other conditions for survival are met. IPCC models are highly confident temperatures will increase (Collins et al. 2013, Kirtman et al. 2013).

An increase in temperature at northern latitudes would also expand suitable *Ixodes* spp. habitat. A longer spring and summer would lengthen the exposure window as *Ixodes* spp. are most actively questing during warm, humid periods (Ogden et al. 2004). For these reasons, *Ixodes* spp. will likely extend northward within North America, Europe, and Asia. In California and the southern United States, however, frequent drought is likely to prohibit the spread of *I. pacificus* and *I. scapularis* populations into new areas (Jones and Kitron 2004).

The degree and direction of *Ixodes* spp. expansion is not completely understood, as established populations have been found in and beyond transition zones (Leighton et al. 2012, Eisen et al. 2016, Jaenson et al. 2016). These populations are often found by researchers flagging for ticks and capturing animals. As surveillance increases, especially long-term surveillance, a fuller picture of how and where *Ixodes* spp. is to spread will become apparent.

Hosts and reservoirs

Climate change is driving *P. leucopus*, the common host for larvae and nymphs and reservoir for *B. burgdorferi*, north along the eastern half of North America (Roy-Dufresne et al. 2013). Similarly, the predominant host for adult *I. scapularis*, white-tailed deer, are also extending their range throughout Canada, due to changes in both climate and land use (*e.g.*, agriculture, forestry) (Dawe and Boutin 2016). Land changes in the Western United States, specifically the removal of fire-prone chaparral, could lead to an increase of Lyme disease in California (Newman et al. 2015). Birds inhabiting chaparral tend to be less infested by larvae and nymphs (Newman et al. 2015). New habitats would bring new bird species, some of which may be more suitable hosts for larvae and nymphs.

Other Factors Driving the Expansion of Lyme Disease

With the geographic spread of *Ixodes* spp., hosts, and reservoirs, is the inevitable increase in Lyme disease. A concern in both emerging and established regions of Lyme disease infection is a lack of detection.

Diagnostics

Lyme disease can present as a nondescript influenza-like illness (exceptions are the European *B. bavariensis* and *B. garinii*, which are neurotropic, and *B. afzelii*, which causes acrodermatitis chronica atrophicans) (Coipan et al. 2016). An additional diagnostic complication is associated with cases where Lyme disease presents without erythema migrans. As a result, Lyme disease frequently escapes the notice of some physicians, particularly in areas where Lyme disease is still emerging, resulting in incorrect diagnoses and underreporting. Indeed, underreporting is a significant problem associated with Lyme borreliosis surveillance, leading to an incomplete picture of disease epidemiology (Hinckley et al. 2014, Nelson et al. 2015).

For diagnosis in the United States, the CDC recommends a two-tiered serological test based on *B. burgdorferi s.s.* strains. The first tier is an enzyme immunoassay (EIA) or immunofluorescent assay using a *B. burgdorferi s.s.* lysate or whole cells, respectively; and the second tier is an immunoblot for IgM or IgG using a whole cell lysate of *B. burgdorferi s.s.* Sensitivity is low during the early (localized) stage of infection but significantly increases as Lyme disease progresses to the early and late disseminated stages (Moore et al. 2016, Waddell et al. 2016). Europe uses a similar two-tiered test; however, the European test takes into account the multiple Lyme disease species present. This multi-species approach increases the sensitivity of the test in Europe (Branda et al. 2013). An additional EIA using the C6 peptide from VlsE has been developed, which has increased sensitivity over traditional EIA, though not commonly used in the United States (Branda et al. 2013).

Some of the increase in Lyme disease cases is likely due to better detection, reporting, and informed medical professionals. It is difficult at present, however, to isolate the proportion of cases that are due to an increased prevalence of disease and are simply the product of improved detection.

Novel Borrelia *species*

The emergence of new species causing Lyme disease, such as *Borrelia mayonii* in North America, may contribute to an increase in the number of reported cases (Dolan et al. 2016, 2017, Pritt and Petersen 2016, Pritt et al. 2016, Scott 2016, Eisen et al. 2017). The two-tiered serological test is based on *B. burgdorferi s.s.* As cross-reactivity has been noted with several *Borrelia* spp., including relapsing fever spirochetes (Rath et al. 1992, Johnson et al. 1996), thorough evaluations of the two-tiered test to detect other Lyme disease spirochetes is necessary to distinguish between Lyme borreliae and novel species.

Co-infections

A single *I. scapularis* tick can be infected with and transmit several bacterial, viral, and protozoan pathogens (Durand et al. 2017). Interactions between some of these pathogens, with significant clinical implications, have been noted. *Babesia microti*, the causative agent of babesiosis, is poorly transmitted and maintained in hosts unless *B. burgdorferi* is also present (Dunn et al. 2014). In contrast, competition can occur between different *B. burgdorferi* strains (Levin and Fish 2001, Devevey et al. 2015, Rynkiewicz et al. 2017). Not all strains of *B. burgdorferi* are pathogenic or able to survive in known reservoirs, yet these nonpathogenic strains are still maintained through the enzootic cycle. One explanation for the persistence of these nonpathogenic *Borrelia* in the environment is through co-feeding (the passage of microbes from an infected vector to an uninfected vector feeding in close proximity) (States et al. 2017); however, Rego et al. (2014) demonstrated that when ticks are infected with multiple strains of *B. burgdorferi*, a bottleneck exists that limits the number of strains transmitted. Another explanation may be that, in addition to co-feeding, these nonpathogenic strains persist in different, yet to be identified, reservoirs. Clearly, more research is needed on the effects of pathogen competition and cooperation within the tick and how this affects transmission of infectious agents to vertebrate hosts.

Refractory, incompetent, and dilution hosts

Larvae and nymphal *I. pacificus* primarily feed upon lizards in California, particularly the western fence lizard (*Sceloporus occidentalis*) and the southern alligator lizard (*Elgaria multicarinata*), in addition to rodents, birds, and mammals (Castro and Wright 2007). Both lizards are refractory hosts for *B. burgdorferi s.l.* (Lane and Loye 1989, Lane and Quistad 1998, Lane et al. 2013). The presence of such refractory hosts decreases the prevalence of infected ticks and, thus, the prevalence of Lyme disease.

Incompetent hosts can decrease the prevalence of infected ticks, particularly when no competent reservoirs are available for infected larvae and nymphs (Richter and Matuschka 2006). This effect is most notable in regions with heavy animal grazing. Both wild and domestic ungulates, predominately deer and cattle, can sustain all life stages of *I. ricinus* but are unable to maintain *B. burgdorferi*, which could lead to a decrease in the prevalence of infected ticks (Richter and Matuschka 2006). However, agriculture and grazing animals also significantly alter the landscape, possibly enough to impact the sustainability of Lyme disease-competent reservoirs. Thus, in regions with few or no competent hosts, Lyme disease should be extremely low or not present.

The idea that vertebrate biodiversity reduces the incidence of Lyme disease (*i.e.*, dilution hosts) may hold true in some regions (LoGiudice et al. 2003). However, as we are finding from studies in California (Brown and Lane 1996), the Midwestern United States (*e.g.*, Dougherty 2015), the Southern United States, and Europe (Wodecka et al. 2016), a dilution host in one area is not a dilution host in another. In addition, increased vertebrate biodiversity does not appear to decrease the incidence of Lyme disease in areas where ticks actively bite humans (*e.g.*, Northeastern United States, Upper Midwestern United States, Europe).

The list of *I. pacificus* hosts is lengthy in California and several species are competent reservoirs for *B. burgdorferi*, including western gray squirrels (*Sciurus griseus*), California kangaroo rats (*Dipodomys californicus*), and dusky-footed wood rats (*Neotoma fuscipes*) (Brown and Lane 1996, Castro and Wright 2007, Salkeld et al. 2008). Moreover, these species are the primary reservoirs, not *Peromyscus* spp. found in California (Brown and Lane 1996). Likewise, in Europe and Asia, there does not appear to be a single, predominant reservoir as a diverse population of rodents, small and medium mammals, and birds serve as adequate reservoirs (Gern et al. 1998).

In addition, species-rich areas have been postulated to contain dilution hosts. Dilution hosts are able to sustain *Ixodes* spp. populations but are not highly competent reservoirs of *B. burgdorferi s.l.* complex species (less than ∼50% of individuals from examined species were identified as competent) (LoGiudice et al. 2003). In areas where Lyme disease is emerging and highly competent reservoirs are not present, these less competent hosts may be able to sustain a *Borrelia* population until highly competent reservoirs arrive (Estrada-Pena et al. 2016, Ruyts et al. 2016, Wodecka and Skotarczak 2016, Jahfari et al. 2017). Host competency may also rely on the genetics of *Borrelia*, thus different strains of pathogenic *Borrelia* may survive in different reservoirs (Becker et al. 2016, Wodecka and Skotarczak 2016, Raberg et al. 2017).

Final Thoughts

The available data suggest that Lyme disease cases will continue to increase. Concomittant with *I. scapularis*, *I. ricinus*, and *I. persulcatus* invasion of new ecosystems, climate change will also affect the diversity and composition of vertebrate fauna in those habitats. As a consequence, nontraditional hosts may assume greater roles in maintaining zoonoses. Opportunistic expansion of species into altered ecological niches may be driven in large part by abiotic factors such as changing climate (Sahney et al. 2010). In addition to the spread of vector ticks, the potential exists for the Lyme borreliae to adapt to novel hosts and reservoirs. As the character Dr. Ian Malcolm stated in Jurassic Park, ''Life breaks free. Life expands to new territories. Painfully, perhaps even dangerously. But life finds a way.'' (Crichton 1990).

Management of Lyme disease (and other tick-borne infections) in check, will require further study on the interplay between vector, reservoir, and pathogen. In addition, we need to understand the contributions of climate to changes in disease risk. Integration and better coordination across a spectrum of public health agencies is crucial, particularly in Europe (Smith and Takkinen 2006, Schotthoefer and Frost 2015). A One Health approach with cooperation among the biological, medical, agricultural, social, and veterinary sciences would mitigate Lyme disease risk, particularly through improved surveillance; for instance, veterinarians may notice an uptick in Lyme disease among dogs or horses in a community before physicians and public health official see increased human cases. Facts do not cease to exist because they are ignored (Huxley, 1927), but the concerted efforts of all stakeholders can mitigate the risks of Lyme disease expansion in this brave new world.

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