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Translating ecology, physiology, biochemistry and population genetics research to meet the challenge of tick and tick-borne diseases in North America

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Abstract

Emerging and re-emerging tick-borne diseases threaten public health and the wellbeing of domestic animals and wildlife globally. The adoption of an evolutionary ecology framework aimed to diminish the impact of tick-borne diseases needs to be part of strategies to protect human and animal populations. We present a review of current knowledge on the adaptation of ticks to their environment, and the impact that global change could have on their geographic distribution in North America. Environmental pressures will affect tick population genetics by selecting genotypes able to withstand new and changing environments and by altering the connectivity and isolation of several tick populations. Research in these areas is particularly lacking in the southern US and most of Mexico with knowledge gaps on the ecology of these diseases, including a void in the identity of reservoir hosts for several tick-borne pathogens. Additionally, the way in which anthropogenic changes to landscapes may influence tick-borne disease ecology remains to be fully

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understood. Enhanced knowledge in these areas is needed in order to implement effective and sustainable integrated tick management strategies. We propose to refocus ecology studies with emphasis on metacommunity-based approaches to enable a holistic perspective addressing whole pathogen and host assemblages. Network analyses could be used to develop mechanistic models involving multi host-pathogen communities. An increase in our understanding of the ecology of tick-borne diseases across their geographic distribution will aid in the design of effective area-wide tick control strategies aimed to diminish the burden of pathogens transmitted by ticks.

Keywords

Tick borne diseases; climate change; tick physiology; questing behavior; genetic diversity

Introduction

Globally, the threat of arthropod-borne infectious diseases, and in particular tick-borne diseases (TBD), on public health and the well being of domestic animals and wildlife has increased (World Bank, 2010, 2012; Dantas-Torres et al., 2012; Lemon et al., 2008; Mencke, 2013; Souza, 2011; Welburn, 2011). In the US, society benefits from the estimated \$3 billion dollars that the livestock industry saves annually by having the country free of cattle fever ticks and bovine babesiosis since 1943, through the efforts of the Cattle Fever Tick Eradication Program (Perez de Leon et al., 2010; Perez de Leon et al., 2012). In contrast, recent studies suggest that infestation with the southern cattle fever tick, *Rhipicephalus microplus*, costs \$3.24 billion dollars annually in losses to the Brazilian livestock industry (Grisi et al., 2014), and \$573.61 million dollars to producers in Mexico (Rodríguez-Vivas RI et al., 2016a). Regarding public health, it has been estimated that in the US, between \$712 million to \$1.3 billion dollars are spent annually in direct medical expenses attributed to Lyme disease (LD), which is tick-borne and considered to be the most prevalent human arthropod-borne disease in the US and Europe (Adrion et al., 2015).

Here, we present a review of current knowledge on the adaptation of ticks to their environment, and the impact that global change, including climate variability, could have on their geographic distribution in North America, principally the US and Mexico (Arsnoe et al., 2015; Bouchard et al., 2015; Dantas-Torres, 2015; de la Fuente et al., 2015a; Esteve-Gassent et al., 2014; Feria-Arroyo et al., 2014). Environmental changes are a selective pressure that induces adaptations in the physiology and behavior of ticks. How these adaptations affect tick-host-pathogen interactions remains to be fully understood. Studying these interactions is critical to understand the consequences of global change in the epidemiology of TBD of relevance to both human and veterinary medicine. However, limited information is available regarding the effects that human and animal tick-borne pathogens have on the physiological and behavioral adaptation of ticks to the environment, and how tick-pathogen interactions might modulate tick behavior and/or susceptibility to acaricides, repellents, or other behavior-modifying chemicals. Additionally, few studies have evaluated the role of tick microbiomes on the transmission and/or acquisition of pathogenic microorganisms.

This review addresses knowledge gaps on the adaptation of ticks to their environment, and how global change impacts the geographic distribution of these economically important arthropod vectors. A metacommunity perspective would enable a holistic approach that encompasses whole symbiont, pathogen, and host assemblages. This approach would allow the study of TBD ecology at different levels, always considering the intersection between organismal communities (Donaldson et al., 2016; Gog et al., 2015; Johnson et al., 2015). According to this perspective, environmental pressures (biotic and abiotic) will affect tick population genetics by selecting genotypes able to withstand new and changing environments, and by altering the connectivity and isolation among tick populations. The proposed multidisciplinary network analyses could engender mechanistic models involving multi host-pathogen communities that advance our understanding of the ecology of TBD across their geographic distribution. Practically, this foundational knowledge could facilitate the design of effective area-wide control strategies aimed at diminishing the impact of ticks and TBD in ways that are more evolutionary and epidemiologically advantageous (Hollingsworth et al., 2015).

Effect of climate variability as part of global change on species distribution and modeling

Humans, and wild and domesticated animal populations could be vulnerable to emerging and re-emerging TBD (Greer et al., 2008; Perez de Leon et al., 2012) due to climate variability among other components of global change. Continued emissions of greenhouse gases accelerate the process of climate change with evidence of increased global temperatures (Dantas-Torres, 2015; Lafferty, 2009). This climate variability directly influences the distribution and survival of ticks and the pathogens they harbor, and as a consequence, it is altering the epidemiology of TBD by changing the ecology of tick species (Greer et al., 2008).

Species distributions are influenced by a multitude of factors such as biotic (species interactions, described in the next section), abiotic (climate), historical (speciation process), dispersal capabilities and/or anthropogenic factors (Soberón and Peterson, 2005). However, climate is a prominent factor used to predict the potential distribution of arthropod vectors harboring important pathogens because its direct effect on their survival (Bouchard et al., 2015; Dantas-Torres, 2015; Fera-Arroyo et al., 2014; Gilbert et al., 2014; Monaghan et al., 2015; Williams et al., 2015). To understand and predict the distribution of arthropod vectors, research studies of R, Machado H and others. 1999. Integrated control of acaricide Information Systems (GIS). (GIS). These methodologies use complex algorithms that consider climatic variables associated to geographical distribution data (longitude and latitude) as well as climate change scenarios proposed by the Intergovernmental Panel on Climate Change (IPCC). Depending on the specific SDM, the model provides a prediction of how climatic variability is expected to affect a species' suitable habitat (Figure 1). For instance, these changes in a species' suitable habitat can provide evidence for potential shifts in distribution. It is important to note that experimental work is needed to confirm models' predictions. For example, in recent years, a higher prevalence of tick-borne encephalitis has been associated with a shift in the distribution of *Ixodes ricinus* due to climate change in Europe (Gray et al., 2009). Predictions constructed using climate change scenarios, as indicated above, support the above-mentioned association because the models show that *I.*

ricinus and *Dermacentor reticulatus*, also an important vector of tick-borne encephalitis, are expected to shift their distribution to northern European latitudes and longitudes that were previously unsuitable for these tick vectors (Gray et al., 2009; Porretta et al., 2013).

In North America, recent studies (Bouchard et al., 2015; Ogden et al., 2006) have also modeled the potential distribution of *Ixodes scapularis*, a known LD vector, under climate change scenarios, for eastern states where most cases of LD are reported. The models indicated an expansion in the distribution of *I. scapularis* to northern areas in the United States and Canada that were thought to encompass unsuitable habitat for this tick species. The predicted expansion in Canada could be explained by warmer winters that allow tick survival. Additionally, models based on simulations showing how population size is expected to change under climate change indicate that tick populations might double by 2020, pointing the influence of higher temperatures on the reproductive ability of tick populations. The distribution of *I. scapularis* was modeled using a maximum entropy approach in the southern extreme of its known distribution range in the US (Feria-Arroyo et al., 2014). Models built under climate change scenarios suggest that this LD vector would expand to northern latitudes, and western and eastern longitudes in North America (Eisen et al., 2016), which is consistent with previous studies (Ogden et al., 2006). Importantly, the models also showed that *I. scapularis* populations can persist in the Texas-Mexico border, an area thought to have the lowest suitable habitat for this tick species (Figure 2). SDM have also been used to predict the distribution of cattle fever ticks, *R. microplus* and *R. annulatus*, in this trans-boundary region in Southern US and Northern Mexico. Previously thought as contained to quarantine zones along the border, models predict an increase in the distribution of these species mainly as a result of climate variability. These results are alarming since cattle fever ticks can have detrimental effect in the US economy (George, 2008; Giles et al., 2014).

SDM have been useful to predict future suitable habitat and geographical distribution of tick vectors (Estrada-Pena and Venzal, 2007). However, the accuracy of current models in predicting vector distribution through time remains to be enhanced. Importantly, validation methods to improve time extrapolation are being developed to increase accuracy of models (Acheson and Kerr, 2015). In addition to modeling vector's distribution, SDM and GIS are useful to predict the impact of climate variability on other important aspects in the epidemiology of vector-borne diseases. For instance, models built under climate change scenarios have been used to predict the efficacy of white-tailed deer vaccination (Estrada-Pena et al., 2014) to understand the onset week of LD (Monaghan et al., 2015), and to assess how temperature affects the basic reproductive number (R_0) (Levi et al., 2015; Ogden et al., 2014). In this last case, authors formulated a model based on several complex equations that simulated the long-term effect of climatic variability on the basic reproductive number (R_0) of *I. scapularis*. They determined that climate change is expected to increase the R_0 of *I. scapularis*, and as a consequence, this could indicate a higher risk for LD in Northeastern states.

Climate change is expected to alter the epidemiology of TBD principally by changing vector distribution or their suitable habitat. Although climate is a primary factor altering the epidemiology of TBD, models could be refined by considering other biotic factors such as

the diversity of microbes infecting ticks, co-infection in ticks, and host use (Dantas-Torres, 2015). The identification and inclusion of relevant abiotic and biotic factors will enhance the predictability of models, which will allow pertinent organizations to develop more efficient tick control programs.

Effects of abiotic and biotic factors on tick behavior and physiology

Increasing evidence suggests that changes in spatial distribution and abundance of ticks, and associated tick-borne pathogen transmission are strongly influenced by climate variability and surges in tick host population density (Brownstein et al., 2003; Dantas-Torres, 2015; Means and White, 1997; Pepin et al., 2012). However, an aspect that remains to be fully understood is how predicted climate change could alter several critical features of host-tick interactions (Estrada-Pena, 2008; Estrada-Pena et al., 2012). Temperature-based simulation models were developed to predict the density of *I. scapularis* in eastern US (Diuk-Wasser et al., 2010) as well as its range expansion in Canada (Ogden et al., 2006; Ogden et al., 2013; Ogden et al., 2014). Environmental factors are thought to play important roles in driving population increases of *I. scapularis* in the US (Khatchikian et al., 2012). Nevertheless, more studies to determine how biotic and abiotic environmental factors can potentially induce changes in tick-pathogen-host interactions that shape the epidemiology of LD, and other tick-borne diseases are needed. This is important because environmental factors underlie adaptive behavioral and physiological changes in ticks.

Abiotic components of climate are known to affect the activity of ticks during off-host periods (Needham and Teel, 1991). The locomotive patterns of field collected *I. scapularis* were affected by diurnal light and temperature cycles under laboratory conditions where adult ticks collected from the field in the fall exhibited a bimodal pattern of activity, with peaks observed shortly after the lights were on and shortly after the lights were off. However, adult ticks collected in the winter and early spring exhibited a unimodal pattern of activity in the laboratory peaking shortly after the lights were off (Madden and Madden, 2005). Ticks apparently use environmental cues, including temperature and light cycle, to synchronize questing behavior with host animal activity to increase the chances of finding a suitable host and attaching to it for blood feeding. Additionally, immature *I. scapularis* ticks exhibited a diurnal detachment pattern when fed on nocturnal hosts (Mather and Spielman, 1986). Most engorged larvae (>90%) and nymphs (>80%) detached from hamsters between 12:00–20:00 h, when the 14-h photophase began at 06:00 h. The synchronous diurnal detachment is believed to allow ticks to remain in the nests of their nocturnal rodent hosts, thereby enhancing pathogen transmission.

Temperature and humidity influence the questing behavior of *I. scapularis* (Berger et al., 2014a; Schulze and Jordan, 2003; Schulze et al., 2001; Vail and Smith, 2002; Vail and Smith, 1998). Adult *I. scapularis* were found to quest earlier and later in the day when temperatures were lower and relative humidity higher, whereas adults of the lone star tick *Amblyomma americanum* were collected with greater frequency in late morning and early afternoon during periods of higher temperatures and lower humidity (Schulze et al., 2001). Ambient temperature was the best general predictor of adult questing behavior in the American dog tick, *Dermacentor variabilis*, among several micro-environmental parameters

analyzed that also included moisture, wind, and solar radiation (Harlan and Foster, 1990). Ambient temperature was also found to affect competence of *I. scapularis* as hosts for LD spirochetes. Extrinsic incubation of *I. scapularis* nymphs infected with LD spirochetes at a temperature $>27^{\circ}\text{C}$ for 2 weeks or longer had a curative effect, making the nymphs virtually non-infective (Shih et al., 1995).

Humidity has a strong effect on the survival of ticks in the non-parasitic stages. More than 85% relative humidity (RH) is required for *I. ricinus* to survive in the environment (Daniel et al., 2009). Exposure to suboptimal atmospheric moisture was found to reduce the survival of *I. scapularis* nymphs (Rodgers et al., 2007). The abundance of *I. scapularis* was negatively correlated with $<82\%$ RH for over 8h in the northeast US. Thus, adverse moisture events could be used as a good indicator to predict the seasonal abundance of *I. scapularis* (Berger et al., 2014b).

The full effects of pesticides, repellents, and other behavior-modifying chemicals on tick behavior and physiology remain to be determined. Unfed adult *A. americanum* ticks treated with a sub-lethal dose of permethrin increased tick gas exchange frequency and also caused increased water loss during CO_2 release (Zheng et al., 2013). From the comparative arthropod vector biology standpoint, it is relevant to investigate if temperature and humidity affect the efficacy of tick repellents as it was shown with mosquitoes and N,N-Diethyl-metoluamide (DEET) (Gupta and Rutledge, 1989; Rutledge and Gupta, 1999).

Biotic factors, including pathogen infection, may also affect host-seeking behavior in ticks or their response to repellents and other behavior-modifying chemicals. The infection of *I. scapularis* with *Anaplasma phagocytophilum* induces the expression of an antifreeze glycoprotein that enhances tick survival in the cold (Neelakanta et al., 2010). Infection with *Borrelia burgdorferi* s.l., the causative agent of LD, was found to increase survival of *I. ricinus* under desiccating conditions (Herrmann and Gern, 2010). The taiga tick, *I. persulcatus* infected with tick-borne encephalitis virus (TBEV) quested higher than uninfected ticks (Alekseev, 1996). *Borrelia*-infected adult *I. ricinus* were found to be significantly more tolerant of lower humidity and higher air and soil temperature and ticks of the same species infected with *Borrelia* quested at higher locations, which requires ticks to move down vegetation to rehydrate more often (Perret et al., 2000). It was hypothesized that the increased tolerance to dehydration in infected ticks may be due to higher fat reserves (Herrmann et al., 2013).

The infection of *I. scapularis* with *B. burgdorferi* had more pronounced effects on behavior in adults than in nymphs (Lefcort and Durden, 1996). Compared to uninfected adult ticks, infected adults were less able to overcome physical obstacles, less active, and quested at lower heights. However, nymphs infected with *B. burgdorferi* exhibited an increased phototaxis and attraction to vertical surfaces. By comparison, the locomotor activity of *Borrelia*-infected adults of *I. persulcatus* was found to be significantly reduced when compared with uninfected ticks (Alekseev et al., 2000). Infection with *Rickettsia* increased the locomotive speed of *D. variabilis* but did not have significant effect on *I. scapularis* (Kagemann and Clay, 2013). In contrast, *Arsenophonus* infection decreased locomotive speed of *A. americanum* and *D. variabilis*. Pathogen infection of ticks was found to have a

significant effect on both the questing behavior, sensory responses to repellent and attractant compound, as well as odorant-evoked neuronal activities in the synganglion of *I. persulcatus* (Romashchenko et al., 2012).

Infection rates with TBEV in *I. persulcatus* and *I. ricinus* were higher in ticks removed from humans and animals than unfed ticks collected from the environment, and behavioral analyses indicated TBEV infection influenced tick behavior, which resulted in increased questing activity (Belova et al., 2012; Mel'nikova et al., 1997). Infection with TBEV is known to cause increased motor activity and negative geotaxis in *I. persulcatus* (Alekseev et al., 1988). Behavioral changes in infected ticks apparently resulted in increased attachment to human and animal hosts (Belova et al., 2012; Mel'nikova et al., 1997). Infection of adult *I. ricinus* ticks with *B. burgdorferi* s.l. increased their ability to find a host under natural conditions (Faulde and Robbins, 2008). Infection of *I. ricinus* with TBEV reduced their sensitivity to DEET, which is the most commonly used compound in commercial repellent formulations (Belova et al., 2012). Although the physiological mechanisms underlying tick behavioral changes due to pathogen infection remain to be fully understood, future tick repellent evaluations should include infected ticks to fully assess their utility in preventing the transmission of TBD. Further research is also needed to determine whether *Borrelia*-induced tick behavior changes result in greater questing and host seeking activity in *I. scapularis*, which can lead to increased tick bite frequency and human exposure to pathogens.

Pathogen infection may not only change behavior but also affect the susceptibility of ticks to pesticides. Studies on virus-pesticide interactions in *I. persulcatus* and *A. hebraeum* demonstrated that treatment with a sub-lethal dose of the organophosphate acaricide chlorpyrifos reduced the survival of the TBEV-infected ticks, while increased the survival of non-infected ticks (Alekseev et al., 1997). The higher activity of TBEV-infected ticks depleted their energy reserves, weakened them, and thus became more susceptible to the acaricide.

Physiological and behavioral differences between populations of the same tick species across geographic regions may influence the epidemiology of TBD (Sakamoto et al., 2014). While *I. scapularis* populations in the US are found along the eastern seaboard from Maine to Florida, as well as west toward Texas and the northern Midwest, the incidence of LD does not occur uniformly over this distribution. Rather, LD in the US is concentrated in the northeast, and in the northern Midwest states of Minnesota and Wisconsin. Recent studies reporting questing differences between southern and northern *I. scapularis* populations showed that tick from the southern group tended to quest at lower height than ticks from the northeastern US, and to remain on the vegetation litter, which could reduce their opportunity for contact with humans (Arsnoe et al., 2015; Ginsberg et al., 2014). Molecular studies attempting to demonstrate genetic variation between southern and northern tick populations of *I. scapularis* documented different haplotypes, but the marker used (mitochondrial 16S rRNA) did not reveal evidence for population genetic structuring (Kelly et al., 2014). Genomics research that integrates physiological aspects is needed to understand the molecular basis of behavioral adaptations by ticks to environmental changes and their

interactions with pathogens that impact the epidemiology of TBD (Coates et al., 2015; Poelchau et al., 2016).

Tick Population genetics and its impact on the distribution of ticks and TBD

Several population genetic studies assessed the geographic partition of genetic variation among vector tick populations in different regions of the world (Burlini et al., 2010; Cangi et al., 2013; Dietrich et al., 2014; Dinnis et al., 2014; Kain et al., 1997; Kelly et al., 2014; Kovalev and Mukhacheva, 2012; Mechai et al., 2013). Fewer studies assessed host-associated differentiation of tick vectors (Dietrich et al., 2014; Kempf et al., 2011; McCoy et al., 2003). Host-associated differentiation refers to the formation of genetically distinct population of parasites when associated with different host species (Abrahamson et al., 2001; Booth et al., 2015; Feder et al., 1988; Kempf et al., 2011; Medina, 2012). Genetically distinct vector tick populations may differ in traits relevant to their control (Cangi et al., 2013) as well as in vector competence (Dietrich et al., 2013; Reichard and Kocan, 2006). Thus, understanding the way genetic variation of vector-ticks is partitioned is crucial in the design of sustainable and effective control strategies. For example, genetically distinct tick populations may vary in their potential to host pathogenic agents (Johnson and Thielges, 2010; Moraes et al., 2015; Scoles et al., 2006), in their questing behavior and preferences (Arsnoe et al., 2015; Ginsberg et al., 2014; Goddard et al., 2015), and in their affinity to humans (Kelly et al., 2014; Rodríguez-Vivas et al., 2016b).

Genetically distinct tick populations of the same species may differentially respond to distinct control strategies (e.g., by differing in acaricide resistance, in host preference, in probability of encountering human or animal hosts, etc.). Thus, it is important to map tick distinct genotypes to increase the effectiveness of area-wide tick management efforts. In addition, genetically distinct tick populations may differ in the time of the year at which their abundances peak. As commented above, these differences in phenology may correlate to abiotic (e.g., temperature, humidity, etc.) or to biotic (e.g., presence of specific hosts) factors. The interaction of ecological, behavioral and environmental variables may all play a role in population genetics of tick vectors and the effect of all these variables combined may determine when, where, and for how long a control strategy will work.

Several tick species have shown distinct patterns of genetic differentiation both at the geographic as well as at the host-association level (Araya-Anchetta et al., 2015). Molecular, behavioral and ecological studies revealed cryptic species within what was thought to be just one species (Beati et al., 2013). In other instances, panmictic ticks have been identified over vast geographic extensions (Delaye et al., 1997). Variation in findings may have been due in part to the different kind of molecular markers used. Most of the published studies have used microsatellites, partial sequences of mitochondrial and nuclear genes and in recent years multilocus sequence typing (MLST). More recently, single nucleotide polymorphisms (SNPs) have proven to be ideal markers to assess variation at several levels, from population to species genetic differentiation (Araya-Anchetta et al., 2015). Also, SNPs are sensitive markers, able to find population genetic structure and selective sweep signals in populations in which several other markers have failed to detect variation (Benestan et al., 2015; Neafsey et al., 2010; Stolting et al., 2013). SNPs could become the marker of choice for vector tick

studies (Araya-Anchetta et al., 2015). Armed with a new generation of more sensitive molecular markers, our knowledge of the population genetics of vector ticks is likely to increase. However, it is important to sample ticks from their entire geographic distribution and on their whole suite of hosts to have a realistic picture of their population genetic landscape.

Population genetic studies of generalist tick vectors tend to include sampling of ticks from a small portion of their potential host range. This incomplete sampling provides only a partial picture of the way genetic variation may be partitioned in tick populations. Similarly, partial covering of their geographic range also impairs our understanding of their genetic diversity. In order to fully capture the population genetic landscape of tick vectors, it is important to assess their population genetic structure in as many hosts and in as many different geographic locations as possible. Variation in relative host abundance at different locations may affect tick population genetic structure. For example, it is possible to find ticks showing host-associated population only in portions of their geographic distribution. This has been observed in plant parasites (Barman et al., 2012). Thus, it is reasonable to postulate that ticks may show similar patterns.

Another issue of importance is to assess the population genetics of pathogens harbored by ticks. Studies have assessed the geographic partitioning of genetic variation in pathogenic agents vectored by ticks (Baranton et al., 2001; Humphrey et al., 2010; Margos et al., 2011). Fewer studies have explored the partition of genetic variation in pathogens vectored by ticks among different tick host species (Jacquot et al., 2014). Understanding how pathogens are genetically distinct on ticks associated with different hosts and on the hosts themselves is crucial to fully understand the ecology of TBD. Genetically distinct pathogen populations may differ in virulence (Humphrey et al., 2010) as well as in their ability to associate with genetically distinct vectors and their hosts (Derdakova and Lencakova, 2005; Eisen et al., 2003; Giery and Ostfeld, 2007; LoGiudice et al., 2003; Nieto and Foley, 2008; Salkeld and Lane, 2010). Host-associated differentiation has been shown to cascade up trophic levels in herbivorous insects (Forbes et al., 2009; Stireman et al., 2006). Thus, it can be argued that host-associated differentiation would also cascade down to the microscopic level. The implications of this sort of differentiation have not been explored. Thus, the partition of genetic variation of all players involved in these disease systems (i.e., ticks, pathogens, and hosts) may all affect the ecology and epidemiology of TBD.

Another research area that offers exciting discovery opportunities is the study of symbiotic bacteria and their role in the population structure and in the ecological interactions between tick vectors and their hosts (Kelly et al., 2014). In other arthropods, individual symbiotic bacteria provide their hosts with ecological advantages such as heat tolerance, use of novel hosts, resistance to predators, parasites, disease, nutritional benefits and even insecticide tolerance (Douglas, 1998; Hosokawa et al., 2007; Kikuchi et al., 2012; Medina et al., 2011; Oliver et al., 2010; Scarborough et al., 2005; Tsuchida et al., 2009; Xie et al., 2011). Similar roles for tick endosymbionts remain to be fully documented. As shown in other arthropods, tick specific endosymbionts or the combined effect of several of them (i.e., the tick microbiome) may modulate vector competence, resistance to abiotic stress, to parasites, to pathogens as well as host affinity. Considering the increasing role attributed to the

microbiome harbored by several multicellular organisms in their biology, ecology, and evolution, this issue is far from trivial and will likely experience considerable development in the near future. The study of tick microbiomes and the identification of specific bacterial symbionts may provide novel targets for vector tick control.

A paradigm shift for an integrative tick community ecology approach

Historically, the study of infectious disease has been dominated by studies focusing on a single pathogen, parasite or host (Wolfe et al., 2007). Pathogen emergence or disease outbreaks have had very focused responses that derive in the isolation, study, and management efforts toward controlling the causing agent. Like in the case of some viral diseases (e.g., Variola virus, Poliovirus) these focused strategies have had a great success and have been controlled with vaccination strategies (Nelson and Williams, 2014). However, the recent increase in the prevalence of other pathogens, especially those vectored by arthropods, has made evident the limitations of this approach to manage “all” infectious agents. This current growth of Emergent Infectious Diseases (EID) is largely dominated by pathogens of zoonotic origin (Jones et al., 2008), which in many cases are agents that are closely intertwined in very complex ecological relationships with several reservoir hosts, vectors, or a combination of both. One of such examples is the case for *B. burgdorferi*, the pathogen responsible for LD (Ostfeld, 2011; Stanek et al., 2012). Moreover, anthropogenic activities are likely affecting these ecological relationships, such that human disturbances are becoming the drivers behind these increased outbreaks (Jones et al., 2008; Patz et al., 2004; Suzan et al., 2015). Thus, there has been a growing interest in addressing the study and management of pathogens and parasites with an integrated approach that considers (i) the environment where they occur, (ii) their ecological context, and (iii) their evolutionary relationships (Buckee et al., 2007; Johnson et al., 2015; Karesh et al., 2012; LoGiudice et al., 2003; Poulin, 2010). This integrated view is not only important for public health reasons but it is likely that pathogens play a strong role in shaping the distribution of life on earth (Ricklefs, 2011).

Parasites, and symbionts in general, do not occur as isolated entities but, as mentioned above, form part of potentially complex microbiomes within hosts, and vectors, with increasing evidence that these microbial communities can have substantial roles in pathogen prevalence and transmission (Narasimhan and Fikrig, 2015). However, pathogen persistence does not depend uniquely on interactions at this level. The presence, density, survival, and dispersion (i.e., transmission) of pathogens are tied to ecological processes that act at a variety of spatial and temporal scales, in the same way these processes act to determine patterns for any free living organism (Levin, 1992). Moreover, since pathogens are intimately tied to the ecology of wildlife reservoirs and vectors, the processes that regulate their arthropod and vertebrate hosts will have implications for pathogen occurrence from landscape to biome scales (Ostfeld and Keesing, 2000; Ricklefs, 2011). Throughout the range of scales from microbiomes to whole biomes, community ecology can provide analytical and conceptual approaches to understand and manage disease dynamics (Johnson et al., 2015) given that one of the main goals of community ecology is to ascertain the factors that determine the assembly, structure and dynamics of ecological communities (Weiher and Keddy, 2001).

The notion that individual communities are connected by dispersal of individuals among them, thus creating metacommunities (Figure 3), is one of the evolving concepts within community ecology that has a lot of potential application within disease ecology for both microbiome (Mihaljevic, 2012) and landscape level processes (Suzan et al., 2015). Specific applications can be vast within tick borne pathogen dynamics and analytical tools are already available (Godfrey, 2013; Poulin, 2010; Presley et al., 2010). The main goal of metacommunity theory is to ascertain patterns and mechanisms determining species diversity among sites, thereby connecting processes at focal scales to larger scales (Holyoak et al., 2005). This theoretical framework can be applied independent of spatial scale and could serve to analyze a myriad of situations within disease ecology that go from variation of symbiont component species between tissues of individuals, variation of symbionts between individuals in a population, or among different species, all the way to variation of hosts among sites in different landscapes (Mihaljevic, 2012; Suzan et al., 2015). Since multiple scenarios and potential questions that need to be addressed using this metacommunity context can be envisioned, a schematic example (Figure 3) of tick-borne diseases can be helpful to portray some possibilities: Two or more communities, connected by dispersal, can have contrasting patterns of vertebrate host diversity and composition, which in turn can sustain distinct tick communities. Mechanisms that regulate the differences and connection between communities will have a direct effect on the type and prevalence of the pathogens vectored by these tick species (see Figure 3 for details).

One of the current limitations to apply this framework to tick borne pathogen systems is data availability. At the level of individual ticks, microbiome assessments have found different microbial components among different tissues (e.g., salivary glands, midgut, ovaries, malpighian tubes) but microbiome studies that address these differences are fewer (Narasimhan and Fikrig, 2015). These microbiome comparisons among tick tissues have only been attained for *R. microplus* (Andreotti et al., 2011), *A. maculatum* (Budachetri et al., 2014), *I. scapularis* (Narasimhan et al., 2014), and *Haemaphysalis flava* (Qiu et al., 2014). Most of these studies are limited to describing microbiome bacterial components. Nevertheless, a functional link was established between the gut microbiome in *I. scapularis* and its colonization by *B. burgdorferi* (Narasimhan et al., 2014), thus evincing the relevance of these tick gut symbionts. Moreover, there is variation in tick microbiomes among species, developmental stages, environmental factors (wild vs. laboratory reared), geographical locations, feeding status, and seasons (Narasimhan et al., 2014). Characterizing and understanding the factors that create these differences in bacterial taxa, as well as the functional consequences for pathogen transmission, is paramount to develop a new paradigm for the management of tick-borne diseases using a community ecology approach.

Besides the multiple potential applications of using a community paradigm at the microbiome level (Mihaljevic, 2012) this framework can be used at the other end of the spatial scale spectrum to address vertebrate hosts and arthropod vectors from landscape to biome levels (Johnson et al., 2015; Suzan et al., 2015). A direct example of the importance of considering the ecological setting and the presence of alternative hosts for tick management is evident in the efforts to control cattle fever tick (*R. microplus*) along the US-Mexico border. Failure to consider potential wildlife hosts in an integrated management effort can lead to its failure (Perez de Leon et al., 2012). Within tick-borne diseases, another

well documented example of the epidemiological implications of host community structure and composition for pathogen spread is the case of LD (Ostfeld, 2011). The number of *B. burgdorferi* infected *I. scapularis* ticks increases, and thus the human infection risk, when biodiversity decreases at a given locale (Ostfeld and Keesing, 2000). Anthropogenic modifications of landscapes create predictable changes in biodiversity that include the reduction of mesopredators, increased abundance of white-tailed deer, and a reduction of alternative hosts for *I. scapularis*. These community level modifications have consequences on the total and infected number of ticks through several processes: (i) lack of mesopredators increases the abundance of the white-footed mouse *Peromyscus leucopus*, a main reservoir of *B. burgdorferi*; (ii) increased deer abundance sustains the reproduction of *I. scapularis*, and (iii) disappearance of alternative tick hosts increase the number of infected ticks (LoGiudice et al., 2003; Ostfeld, 2011; Ostfeld and Keesing, 2000). For this last process, a mechanistic model has been proposed that show a predictable decrease in the number of infected nymphs, a key risk factor, as community composition changes and low or non-competent reservoirs are added. This response has been named as the “dilution effect” (Civitello et al., 2015; LoGiudice et al., 2003; Lou et al., 2014; Turney et al., 2014). An increase in the abundance and types of low competence reservoirs creates a higher number of “wasted transmission events” as fewer *I. scapularis* tick larvae will bite highly competent *B. burgdorferi* reservoirs. A growing body of knowledge on the ecological interactions that are responsible for the risk of LD in humans indicates the importance of the community ecology context for the maintenance and spread of this pathogen (Buckee et al., 2007; Johnson et al., 2015; Keesing et al., 2010). Furthermore, these relationships are not limited to this pathogen as numerous examples where the importance of the ecological context for other zoonotic pathogens, with human, livestock, and wildlife health implications, are being uncovered (Johnson et al., 2015). Then, a new challenge for the management of infectious zoonotic diseases is to generate and integrate this knowledge to consider pathogens within an integrated community ecology approach, a challenge that will required an ever-growing participation of ecologists (Figure 3).

Integrated tick management

Attempts to manage the problem of diseases caused by tick-borne pathogens affecting humans, livestock, and wildlife have focused on strategies to control or eradicate tick populations (Pegram et al., 2000; Walker, 2011). Chemicals have been used widely to control or eradicate ticks (Graf et al., 2004; Guerrero et al., 2014). However, the indiscriminate use of acaricides has become a strong selective pressure for tick populations to become resistant to chemical treatments (Eiden et al., 2015; Rodríguez-Vivas et al., 2014b). Solutions to manage acaricide resistant tick populations and societal expectations for more environmentally friendly methods are driving the research and development of technologies that can be used together for the sustainable management of ticks and TBD (Ghosh and Nagar, 2014; Kiss et al., 2012; Moyer, 2015). This situation provides the opportunity to apply interdisciplinary approaches that unify current ecological, physiological, biochemical, and molecular knowledge to adapt integrated tick management strategies (Jamison et al., 2015; Pérez de León et al., 2014; Rodríguez-Vivas et al., 2014c).

Integrated management programs generally involve strategies to kill ticks infesting hosts, applying genetic selection to decrease the susceptibility of hosts to tick infestation, and making the environment less permissible, through treatment or modification, for the build up of tick populations. Different tools can be used together to mitigate the burden of ticks and TBD. Most control technologies are used to treat animal infestations, and some have been adapted for personal protection as a way to prevent ticks from biting humans (Banks et al., 2014; Childs, 2009; Cisak et al., 2012; Jordan et al., 2012). Because the majority of emerging and re-emerging TBD are zoonotic, treatment of companion animals and wildlife in domestic, peridomestic, and suburban environments against infestation can mitigate the risk of disease transmission by infected ticks that also bite humans (Fish and Childs, 2009; Jamison et al., 2015).

Progress is being made in the development and commercialization of alternative technologies that can be used together to address the challenge of acaricide resistance (Borges et al., 2011; de la Fuente and Contreras, 2015; Lonc et al., 2014), which is a situation that has been aggravated by the emergence of multiple resistance among populations of economically important tick species like *R. microplus* (Miller et al., 2012; Miller et al., 2013; Reck et al., 2014; Rodríguez-Vivas et al., 2014a). Combining registered acaricides with different modes of action is a way to overcome resistance to certain classes of commonly used acaricides like pyrethroids (Rodríguez-Vivas et al., 2013), but acaricides mixtures must be used rationally. The discovery and development of safer synthetic acaricides with new modes of action is another way to address that problem, but the research and development process is costly and risky for commercial entities (Graf et al., 2004; Guerrero et al., 2014). However, safer synthetic acaricides with new modes of action are being developed to treat tick infestations in domestic animals (Asahi et al., 2015). Genomic approaches are facilitating this process through the identification of targets for selective disruption of biological processes exclusive to ticks, and the creation of mechanism-based assays for high-throughput screening of chemicals for acaricidal properties (Gross et al., 2015; Swale et al., 2013; Yang et al., 2015).

The utility of combining vaccination against ticks with other technologies has been documented in livestock operations. An integrated system employing vaccination of cattle with Gavac[®], a Bm86-based vaccine, and with amidine treatments under field conditions, achieved nearly 100 % control of *R. microplus* populations resistant to pyrethroid and organophosphate acaricides (Redondo et al., 1999; Valle et al., 2004). In addition to controlling infestations, where tick burden decreased from 100 to 20 adult ticks per animal, a substantial reduction of acaricide treatments has been achieved (from 24 to 7–8 per year) following similar protocols in several geographic locations (de la Fuente et al., 2007). A vaccine with a high degree of efficacy could be part of an integrated program to eradicate ticks affecting livestock (Miller et al., 2012; Perez de Leon *et al.*, 2012). The precision and sustainability of control or eradication programs could be enhanced once formulations of acaropathogenic fungi, alone or in combination with acaricides, become commercially available to treat cattle. This strategy could also be applied together with vaccination against ticks (Webster et al., 2015).

As compared to ticks that affect livestock only, eradication of ticks that also bite humans and are vectors of zoonotic diseases from a large geographic area is not considered a viable option (Barnard et al., 1988; Bloemer et al., 1990; Esteve-Gassent et al., 2014; Jonsson, 2004). Community-based programs to control ticks that bite humans in the US have been developed against *A. americanum*, *I. scapularis*, and *R. sanguineus* as a way to prevent the transmission of TBD (Barnard et al., 1988; Drexler et al., 2014; Fish and Childs, 2009). Strategies to control infestations in keystone wildlife hosts of tick vectors of zoonotic diseases can decrease the human risk of exposure to tick-borne pathogens (Hoen et al., 2009). A similar effect on the risk of Rocky Mountain Spotted Fever (RMSF) transmission was observed when intervention was focused on treating companion animals infested with *R. sanguineus* in an area with high RMSF case fatality rate (Drexler et al., 2014). A promising opportunity to synergize these interventions is the integration of immunization protocols to protect companion animals and wildlife against tick infestation (Carreon et al., 2012; de la Fuente et al., 2015b). An added value of immunoprotection against tick infestation is that this approach may also mitigate the risk of pathogen transmission to susceptible hosts (Merino et al., 2013).

Advances in tick chemical ecology also offer the opportunity to translate research findings into technologies that could be used as part of integrated management programs. *R. sanguineus* was shown to discriminate substances from dogs to differentiate susceptible English Cocker Spaniels from resistant Beagles (Louly et al., 2010). Benzaldehyde and 2-hexanone were identified in Beagle odor extracts and, when used in combination, repelled *R. sanguineus in vitro* (Borges et al., 2015). A repellent formulation of these compounds could be used as part of the repertoire for integrated *R. sanguineus* management strategies. Repellents can also be used effectively for personal protection to prevent ticks bites (Pages et al., 2014).

Conclusions

The challenge to deal with ticks and TBD that affect human and animal populations in several parts of the world is recognized. Reliance on acaricides has been a principal component of programs to manage ticks as a means to mitigate the burden of TBD. Hence, attention is increasing on the integration of other technologies like anti-tick vaccines, botanicals, and biocontrol agents, into more sustainable tick and TBD control strategies. However, the impact of global change and the exquisite adaptive ability of ticks to changing biotic and abiotic factors requires continued interdisciplinary research to understand the ecological, physiological, and genetic mechanisms that allow ticks and associated pathogens to persist in changing environments. Research by others and the work by our group reviewed here shows how a holistic approach by teams involving community, evolutionary and disease ecologists, molecular biologists, entomologists, and veterinarians can advance our knowledge of the relationship between genetically distinct tick populations, the pathogens they transmit, and the host upon which they feed. Specifically, the concept of metacommunities applied to study the ecology of TBD systems provides a framework to develop tools to analyze and model the dynamics of tick-borne pathogens, which could enable new integrated tick management strategies that are evolutionarily sustainable and epidemiologically effective in North America and possibly other parts of the world.

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References

- Abrahamson WG, Eubanks MD, Blair CP, Whipple AV. Gall flies, inquilines, and goldenrods: A model for host-race formation and sympatric speciation. *Am Zool.* 2001; 41(4):928–938.
- Acheson ES, Kerr JT. Looking forward by looking back: using historical calibration to improve forecasts of human disease vector distributions. *Vector Borne Zoonotic Dis.* 2015; 15(3):173–183. [PubMed: 25793472]
- Adrion ER, Aucott J, Lemke KW, Weiner JP. Health Care Costs, Utilization and Patterns of Care following Lyme Disease. *PLoS One.* 2015; 10(2)
- Alekseev A, Korotkov J, Burenkova L. Virus–Pesticide interactions in *Ixodes persulcatus* and *Amblyomma hebraeum* ticks (Acarina: Ixodidae). *Exp Appl Acarol.* 1997; 21(8):561–568.
- Alekseev, AN. Tick pathogen interactions: behavior of infected and uninfected ticks (Ixodidae). In: Mitchell, R.; Horn, DJ.; Needham, GR.; WCW, editors. *Acarology.* Columbus; 1996. p. 113-115.
- Alekseev AN, Burenkova LA, Chunikhin SP. Behavioral characteristics of *Ixodes persulcatus* P. Sch. ticks infected with the tick-borne encephalitis virus. *Med Parazitol (Mosk).* 1988; (2):71–75. [PubMed: 3412245]
- Alekseev AN, Jensen PM, Dubinina HV, Smirnova LA, Makrouchina NA, Zharkov SD. Peculiarities of behaviour of taiga (*Ixodes persulcatus*) and sheep (*Ixodes ricinus*) ticks (Acarina: Ixodidae) determined by different methods. *Folia Parasitol (Praha).* 2000; 47(2):147–153. [PubMed: 10945740]
- Andreotti R, Perez de Leon AA, Dowd SE, Guerrero FD, Bendele KG, Scoles GA. Assessment of bacterial diversity in the cattle tick *Rhipicephalus (Boophilus) microplus* through tag-encoded pyrosequencing. *BMC Microbiol.* 2011; 11(1):6. [PubMed: 21211038]
- Araya-Anchetta A, Busch JD, Scoles GA, Wagner DM. Thirty years of tick population genetics: a comprehensive review. *Infect Genet Evol.* 2015; 29:164–179. [PubMed: 25461844]
- Arsnoe IM, Hickling GJ, Ginsberg HS, McElreath R, Tsao JI. Different populations of blacklegged tick nymphs exhibit differences in questing behavior that have implications for human lyme disease risk. *PLoS One.* 2015; 10(5):e0127450. [PubMed: 25996603]
- Asahi M, Kobayashi M, Matsui H, Nakahira K. Differential mechanisms of action of the novel gamma-aminobutyric acid receptor antagonist ectoparasiticides fluralaner (A1443) and fipronil. *Pest Manag Sci.* 2015; 71(1):91–95. [PubMed: 24591229]
- Banks SD, Murray N, Wilder-Smith A, Logan JG. Insecticide-treated clothes for the control of vector-borne diseases: a review on effectiveness and safety. *Med Vet Entomol.* 2014; 28(Suppl 1):14–25. [PubMed: 24912919]
- Baranton G, Seinost G, Theodore G, Postic D, Dykhuizen D. Distinct levels of genetic diversity of *Borrelia burgdorferi* are associated with different aspects of pathogenicity. *Res Microbiol.* 2001; 152(2):149–156. [PubMed: 11316368]
- Barman AK, Parajulee MN, Sansone CG, Suh C, Medina RF. Geographic pattern of host-associated differentiation in *Pseudatoscelis seriatus* (Reuter). *Entomol Exp Appl.* 2012; 143:31–41.
- Barnard, DR.; Mount, GA.; Kochanek, HG.; Haile, DG.; Garris, GI. *Agriculture USDo. Management of the Lone Star Tick in Recreation Areas.* U.S. Department of Agriculture; 1988. p. 33
- Beati L, Nava S, Burkman EJ, Barros-Battesti DM, Labruna MB, Guglielmone AA, Caceres AG, Guzman-Cornejo CM, Leon R, Durden LA, et al. *Amblyomma cajennense* (Fabricius, 1787)

(Acari: Ixodidae), the Cayenne tick: phylogeography and evidence for allopatric speciation. *BMC Evol Biol.* 2013; 13:267. [PubMed: 24320199]

- Belova OA, Burenkova LA, Karganova GG. Different tick-borne encephalitis virus (TBEV) prevalences in unfed versus partially engorged ixodid ticks-evidence of virus replication and changes in tick behavior. *Ticks Tick Borne Dis.* 2012; 3(4):240–246. [PubMed: 22910062]
- Benestan L, Gosselin T, Perrier C, Sainte-Marie B, Rochette R, Bernatchez L. RAD genotyping reveals fine-scale genetic structuring and provides powerful population assignment in a widely distributed marine species, the American lobster (*Homarus americanus*). *Mol Ecol.* 2015; 24(13):3299–3315. [PubMed: 25977167]
- Berger KA, Ginsberg HS, Dugas KD, Hamel LH, Mather TN. Adverse moisture events predict seasonal abundance of Lyme disease vector ticks (*Ixodes scapularis*). *Parasit Vectors.* 2014a; 7:181. [PubMed: 24731228]
- Berger KA, Ginsberg HS, Gonzalez L, Mather TN. Relative humidity and activity patterns of *Ixodes scapularis* (Acari: Ixodidae). *J Med Entomol.* 2014b; 51(4):769–776. [PubMed: 25118408]
- Bloemer SR, Mount GA, Morris TA, Zimmerman RH, Barnard DR, Snoddy EL. Management of lone star ticks (Acari: Ixodidae) in recreational areas with acaricide applications, vegetative management, and exclusion of white-tailed deer. *J Med Entomol.* 1990; 27(4):543–550. [PubMed: 1696994]
- Booth W, Balvin O, Vargo EL, Vilimova J, Schal C. Host association drives genetic divergence in the bed bug, *Cimex lectularius*. *Mol Ecol.* 2015; 24(5):980–992. [PubMed: 25611460]
- Borges LM, de Oliveira Filho JG, Ferreira LL, Louly CC, Pickett JA, Birkett MA. Identification of non-host semiochemicals for the brown dog tick, *Rhipicephalus sanguineus* sensu lato (Acari: Ixodidae), from tick-resistant beagles, *Canis lupus familiaris*. *Ticks Tick Borne Dis.* 2015; 6(5): 676–682. [PubMed: 26103925]
- Borges LMF, de Sousa LAD, Barbosa CD. Perspectives for the use of plant extracts to control the cattle tick *Rhipicephalus (Boophilus) microplus*. *Rev Bras Parasitol Vet.* 2011; 20(2):89–96. [PubMed: 21722481]
- Bouchard C, Leonard E, Koffi JK, Pelcat Y, Peregrine A, Chilton N, Rochon K, Lysyk T, Lindsay LR, Ogden NH. The increasing risk of Lyme disease in Canada. *Can Vet J.* 2015; 56(7):693–699. [PubMed: 26130829]
- Brownstein JS, Holford TR, Fish D. A climate-based model predicts the spatial distribution of the Lyme disease vector *Ixodes scapularis* in the United States. *Environ Health Perspect.* 2003; 111(9): 1152–1157. [PubMed: 12842766]
- Buckee C, Danon L, Gupta S. Host community structure and the maintenance of pathogen diversity. *Proc Biol Sci.* 2007; 274(1619):1715–1721. [PubMed: 17504739]
- Budachetri K, Browning RE, Adamson SW, Dowd SE, Chao CC, Ching WM, Karim S. An Insight Into the Microbiome of the *Amblyomma maculatum* (Acari: Ixodidae). *J Med Entomol.* 2014; 51(1):119–129. [PubMed: 24605461]
- Burlini L, Teixeira KR, Szabo MP, Famadas KM. Molecular dissimilarities of *Rhipicephalus sanguineus* (Acari: Ixodidae) in Brazil and its relation with samples throughout the world: is there a geographical pattern? *Exp Appl Acarol.* 2010; 50(4):361–374. [PubMed: 19774468]
- Cangi N, Horak IG, Apanaskevich DA, Matthee S, das Neves LC, Estrada-Pena A, Matthee CA. The influence of interspecific competition and host preference on the phylogeography of two African ixodid tick species. *PLoS One.* 2013; 8(10):e76930. [PubMed: 24130813]
- Carreon D, de la Lastra JM, Almazan C, Canales M, Ruiz-Fons F, Boadella M, Moreno-Cid JA, Villar M, Gortazar C, Reglero M, et al. Vaccination with BM86, subolesin and akirin protective antigens for the control of tick infestations in white tailed deer and red deer. *Vaccine.* 2012; 30(2):273–279. [PubMed: 22079077]
- Childs JE. Low tech versus high tech approaches for vector-borne disease control. *Vector Borne Zoonotic Dis.* 2009; 9(4):355–356. [PubMed: 19650728]
- Cisak E, Wojcik-Fatla A, Zajac V, Dutkiewicz J. Repellents and acaricides as personal protection measures in the prevention of tick-borne diseases. *Ann Agric Environ Med.* 2012; 19(4):625–630. [PubMed: 23311778]

- Civitello DJ, Cohen J, Fatima H, Halstead NT, Liriano J, McMahon TA, Ortega CN, Sauer EL, Sehgal T, Young S, et al. Biodiversity inhibits parasites: Broad evidence for the dilution effect. *Proc Natl Acad Sci.* 2015; 112(28):8667–8671. [PubMed: 26069208]
- Coates BS, Poelchau MF, Childers C, Evans JD, Handler AM, Guerrero F, Skoda S, Hopper K, Wintermantel WM, Ling K, et al. Arthropod genomics research in the United States Department of Agriculture- Agricultural Research Service: Current impacts and future prospects. *Trends Entomol.* 2015; 11:1–27.
- Daniel M, Materna J, Honig V, Metelka L, Danielova V, Harcarik J, Kliegrova S, Grubhoffer L. Vertical distribution of the tick *Ixodes ricinus* and tick-borne pathogens in the northern Moravian mountains correlated with climate warming (Jeseniky Mts., Czech Republic). *Cent Eur J Public Health.* 2009; 17(3):139–145. [PubMed: 20020603]
- Dantas-Torres F. Climate change, biodiversity, ticks and tick-borne diseases: The butterfly effect. *Int J Parasitol Parasites Wildl.* 2015
- Dantas-Torres F, Chomel BB, Otranto D. Ticks and tick-borne diseases: a One Health perspective. *Trends Parasitol.* 2012; 28(10):437–446. [PubMed: 22902521]
- de la Fuente J, Almazan C, Canales M, Perez de la Lastra JM, Kocan KM, Willadsen P. A ten-year review of commercial vaccine performance for control of tick infestations on cattle. *Anim Health Res Rev.* 2007; 8(1):23–28. [PubMed: 17692140]
- de la Fuente J, Contreras M. Tick vaccines: current status and future directions. *Expert Rev Vaccines.* 2015; 14(10):1367–1376. [PubMed: 26289976]
- de la Fuente J, Estrada-Pena A, Cabezas-Cruz A, Brey R. Flying ticks: anciently evolved associations that constitute a risk of infectious disease spread. *Parasit Vectors.* 2015a; 8(1):538. [PubMed: 26467109]
- de la Fuente J, Villar M, Contreras M, Moreno-Cid JA, Merino O, Perez de la Lastra JM, de la Fuente G, Galindo RC. Prospects for vaccination against the ticks of pets and the potential impact on pathogen transmission. *Vet Parasitol.* 2015b; 208(1–2):26–29. [PubMed: 25555312]
- Delaye C, Beati L, Aeschlimann A, Renaud F, DeMeeus T. Population genetic structure of *Ixodes ricinus* in Switzerland from allozymic data: No evidence of divergence between nearby sites. *Int J Parasitol.* 1997; 27(7):769–773. [PubMed: 9279578]
- Derdakova M, Lencakova D. Association of genetic variability within the *Borrelia burgdorferi* sensu lato with the ecology, epidemiology of Lyme borreliosis in Europe. *Ann Agric Environ Med.* 2005; 12(2):165–172. [PubMed: 16457468]
- Dietrich M, Beati L, Elguero E, Boulonier T, McCoy KD. Body size and shape evolution in host races of the tick *Ixodes uriae*. *Biol J Linn Soc Lond.* 2013; 108:323–334.
- Dietrich M, Kempf F, Boulonier T, McCoy KD. Tracing the colonization and diversification of the worldwide seabird ectoparasite *Ixodes uriae*. *Mol Ecol.* 2014; 23(13):3292–3305. [PubMed: 24888342]
- Dinnis RE, Seeliga F, Bormaneb A, Donaghyc M, Vollmera SA, Feila EJ, Kurtenbacha K, Margos G. Multilocus sequence typing using mitochondrial genes (mtMLST) reveals geographic population structure of *Ixodes ricinus* ticks. *Ticks Tick Borne Dis.* 2014; 5:152–160. [PubMed: 24361120]
- Diuk-Wasser MA, Vourc'h G, Cislo P, Hoen AG, Melton F, Hamer SA, Rowland M, Cortinas R, Hickling GJ, Tsao JI, et al. Field and climate-based model for predicting the density of host-seeking nymphal *Ixodes scapularis*, an important vector of tick-borne disease agents in the eastern United States. *Glo Ecol Biogeogr.* 2010; 19(4):504–514.
- Donaldson TG, Perez de Leon AA, Li AI, Castro-Arellano I, Wozniak E, Boyle WK, Hargrove R, Wilder HK, Kim HJ, Teel PD, et al. Assessment of the Geographic Distribution of *Ornithodoros turicata* (Argasidae): Climate Variation and Host Diversity. *PLoS Negl Trop Dis.* 2016; 10(2):e0004383. [PubMed: 26829327]
- Douglas AE. Nutritional interactions in insect-microbial symbioses: Aphids and their symbiotic bacteria *Buchnera*. *Ann Rev Entomol.* 1998; 43:17–37. [PubMed: 15012383]
- Drexler N, Miller M, Gerding J, Todd S, Adams L, Dahlgren FS, Bryant N, Weis E, Herrick K, Francies J, et al. Community-based control of the brown dog tick in a region with high rates of Rocky Mountain spotted fever, 2012–2013. *PLoS One.* 2014; 9(12):e112368. [PubMed: 25479289]

- Eiden AL, Kaufman PE, Oi FM, Allan SA, Miller RJ. Detection of Permethrin Resistance and Fipronil Tolerance in *Rhipicephalus sanguineus* (Acari: Ixodidae) in the United States. *J Med Entomol.* 2015; 52(3):429–436. [PubMed: 26334817]
- Eisen L, Dolan MC, Piesman J, Lane RS. Vector competence of *Ixodes pacificus* and *I. spinipalpis* (Acari: Ixodidae), and reservoir competence of the dusky-footed woodrat (*Neotoma fuscipes*) and the deer mouse (*Peromyscus maniculatus*), for *Borrelia bissettii*. *J Med Entomol.* 2003; 40(3):311–320. [PubMed: 12943110]
- Eisen RJ, Eisen L, Beard CB. County-Scale Distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the Continental United States. *J Med Entomol.* 2016
- Esteve-Gassent MD, Perez de Leon AA, Romero-Salas D, Feria-Arroyo TP, Patino R, Castro-Arellano I, Gordillo-Perez G, Auclair A, Goolsby J, Rodriguez-Vivas RI, et al. Pathogenic Landscape of Transboundary Zoonotic Diseases in the Mexico-US Border Along the Rio Grande. *Front Public Health.* 2014; 2:177. [PubMed: 25453027]
- Estrada-Pena A. Climate, niche, ticks, and models: what they are and how we should interpret them. *Parasitol Res.* 2008; 103(Suppl 1):S87–95. [PubMed: 19030890]
- Estrada-Pena A, Ayllon N, de la Fuente J. Impact of climate trends on tick-borne pathogen transmission. *Front Physiol.* 2012; 3:64. [PubMed: 22470348]
- Estrada-Pena A, Carreon D, Almazan C, de la Fuente J. Modeling the impact of climate and landscape on the efficacy of white tailed deer vaccination for cattle tick control in northeastern Mexico. *PLoS One.* 2014; 9(7):e102905. [PubMed: 25047078]
- Estrada-Pena A, Venzal JM. A GIS framework for the assessment of tick impact on human health in a changing climate. *Geospat Health.* 2007; 1(2):157–168. [PubMed: 18686241]
- Faulde MK, Robbins RG. Tick infestation risk and *Borrelia burgdorferi* s.l. infection-induced increase in host-finding efficacy of female *Ixodes ricinus* under natural conditions. *Exp Appl Acarol.* 2008; 44(2):137–145. [PubMed: 18273686]
- Feder JL, Chilcote CA, Bush GL. Genetic differentiation between sympatric host races of the apple maggot fly *Rhagoletis pomonella*. *Nature.* 1988; 336(6194):61–64.
- Feria-Arroyo TP, Castro-Arellano I, Gordillo-Perez G, Cavazos AL, Vargas-Sandoval M, Grover A, Torres J, Medina RF, de Leon AA, Esteve-Gassent MD. Implications of Climate Change on Distribution of Tick Vector *Ixodes scapularis* and Risk for Lyme Disease in Texas-Mexico Transboundary Re. *Parasites Vectors.* 2014; 7(1):199. [PubMed: 24766735]
- Fish D, Childs JE. Community-based prevention of Lyme disease and other tick-borne diseases through topical application of acaricide to white-tailed deer: background and rationale. *Vector Borne Zoonotic Dis.* 2009; 9(4):357–364. [PubMed: 19650729]
- Forbes AA, Powell THQ, Stelinski LL, Smith JJ, Feder JL. Sequential sympatric speciation across trophic levels. *Science.* 2009; 323(5915):776–779. [PubMed: 19197063]
- George JE. The effects of global change on the threat of exotic arthropods and arthropod-borne pathogens to livestock in the United States. *Ann N Y Acad Sci.* 2008; 1149:249–254. [PubMed: 19120223]
- Ghosh S, Nagar G. Problem of ticks and tick-borne diseases in India with special emphasis on progress in tick control research: a review. *J Vector Borne Dis.* 2014; 51(4):259–270. [PubMed: 25540956]
- Giery ST, Ostfeld RS. The role of lizards in the ecology of Lyme disease in two endemic zones of the northeastern United States. *J Parasitol.* 2007; 93(3):511–517. [PubMed: 17626342]
- Gilbert L, Aungier J, Tomkins JL. Climate of origin affects tick (*Ixodes ricinus*) host-seeking behavior in response to temperature: implications for resilience to climate change? *Ecol Evol.* 2014; 4(7): 1186–1198. [PubMed: 24772293]
- Giles JR, Peterson AT, Busch JD, Olafson PU, Scoles GA, Davey RB, Pound JM, Kammlah DM, Lohmeyer KH, Wagner DM. Invasive potential of cattle fever ticks in the southern United States. *Parasit Vectors.* 2014; 7:189. [PubMed: 24742062]
- Ginsberg HS, Rulison EL, Azevedo A, Pang GC, Kuczaj IM, Tsao JI, LeBrun RA. Comparison of survival patterns of northern and southern genotypes of the North American tick *Ixodes scapularis* (Acari: Ixodidae) under northern and southern conditions. *Parasit Vectors.* 2014; 7:394. [PubMed: 25160464]

- Goddard J, Embers M, Hojgaard A, Piesman J. Comparison of Tick Feeding Success and Vector Competence for *Borrelia burgdorferi* Among Immature *Ixodes scapularis* (Ixodida: Ixodidae) of Both Southern and Northern Clades. *J Med Entomol.* 2015; 52(1):81–85. [PubMed: 26336283]
- Godfrey SS. Networks and the ecology of parasite transmission: A framework for wildlife parasitology. *Int J Parasitol Parasites Wildl.* 2013; 2:235–245. [PubMed: 24533342]
- Gog JR, Pellis L, Wood JL, McLean AR, Arinaminpathy N, Lloyd-Smith JO. Seven challenges in modeling pathogen dynamics within-host and across scales. *Epidemics.* 2015; 10:45–48. [PubMed: 25843382]
- Graf JF, Gogolewski R, Leach-Bing N, Sabatini GA, Molento MB, Bordin EL, Arantes GJ. Tick control: an industry point of view. *Parasitology.* 2004; 129(Suppl):S427–442. [PubMed: 15938522]
- Gray JS, Dautel H, Estrada-Pena A, Kahl O, Lindgren E. Effects of climate change on ticks and tick-borne diseases in Europe. *Interdiscip Perspect Infect Dis.* 2009; 2009:593232. [PubMed: 19277106]
- Greer A, Ng V, Fisman D. Climate change and infectious diseases in North America: the road ahead. *CMAJ.* 2008; 178(6):715–722. [PubMed: 18332386]
- Grisi L, Leite RC, Martins JR, Barros AT, Andreotti R, Cancado PH, Leon AA, Pereira JB, Villela HS. Reassessment of the potential economic impact of cattle parasites in Brazil. *Rev Bras Parasitol Vet.* 2014; 23(2):150–156. [PubMed: 25054492]
- Gross AD, Temeyer KB, Day TA, Perez de Leon AA, Kimber MJ, Coats JR. Pharmacological characterization of a tyramine receptor from the southern cattle tick, *Rhipicephalus (Boophilus) microplus*. *Insect Biochem Mol Biol.* 2015; 63:47–53. [PubMed: 25958152]
- Guerrero, F.; Pérez de León, A.; Rodríguez-Vivas, R.; Jonsson, N.; MRR. Acaricide research and development, resistance and resistance monitoring. In: Sonenhine, DE.; Roe, RM., editors. *Biology of Ticks. 2.* New York: Oxford University Press; 2014. p. 353-381.
- Gupta RK, Rutledge LC. Laboratory evaluation of controlled-release repellent formulations on human volunteers under three climatic regimens. *J Am Mosq Control Assoc.* 1989; 5(1):52–55. [PubMed: 2565368]
- Herrmann C, Gern L. Survival of *Ixodes ricinus* (Acari: Ixodidae) under challenging conditions of temperature and humidity is influenced by *Borrelia burgdorferi* sensu lato infection. *J Med Entomol.* 2010; 47(6):1196–1204. [PubMed: 21175072]
- Herrmann C, Voordouw MJ, Gern L. *Ixodes ricinus* ticks infected with the causative agent of Lyme disease, *Borrelia burgdorferi* sensu lato, have higher energy reserves. *Int J Parasitol.* 2013; 43(6):477–483. [PubMed: 23416154]
- Hoen AG, Rollend LG, Papero MA, Carroll JF, Daniels TJ, Mather TN, Schulze TL, Stafford KC 3rd, Fish D. Effects of tick control by acaricide self-treatment of white-tailed deer on host-seeking tick infection prevalence and entomologic risk for *Ixodes scapularis*-borne pathogens. *Vector Borne Zoonotic Dis.* 2009; 9(4):431–438. [PubMed: 19650738]
- Hollingsworth TD, Pulliam JRC, Funk S, Truscott JE, Isham V, Lloyd AL. Seven challenges for modelling indirect transmission: Vector-borne diseases, macroparasites and neglected tropical diseases. *Epidemics.* 2015; 10:16–20. [PubMed: 25843376]
- Holyoak, M.; Leibold, MA.; Holt, RD. *Metacommunities: Spatial Dynamics and Ecological Communities.* Chicago, IL: The University of Chicago Press; 2005.
- Hosokawa T, Kikuchi Y, Shimada M, Fukatsu T. Obligate symbiont involved in pest status of host insect. *Proc R Soc B Biol Sci.* 2007; 274(1621):1979–1984.
- Humphrey PT, Caporale DA, Brisson D. Uncoordinated phylogeography of *Borrelia burgdorferi* and its tick vector, *Ixodes scapularis*. *Evolution.* 2010; 64(9):2653–2663. [PubMed: 20394659]
- Jacquot M, Bisseux M, Abrial D, Marsot M, Ferquel E, Chapuis JL, Vourc'h G, Bailly X. High-throughput sequence typing reveals genetic differentiation and host specialization among populations of the *Borrelia burgdorferi* species complex that infect rodents. *PLoS One.* 2014; 9(2):e88581. [PubMed: 24533116]
- Jamison A, Tuttle E, Jensen R, Bierly G, Gonser R. Spatial ecology, landscapes, and the geography of vector-borne disease: A multi-disciplinary review. *Appl Geogr.* 2015; 63:418–426.

- Johnson PT, de Roode JC, Fenton A. Why infectious disease research needs community ecology. *Science*. 2015; 349(6252):1259504. [PubMed: 26339035]
- Johnson PT, Thielges DW. Diversity, decoys and the dilution effect: how ecological communities affect disease risk. *J Exp Biol*. 2010; 213(6):961–970. [PubMed: 20190121]
- Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P. Global trends in emerging infectious diseases. *Nature*. 2008; 451(7181):990–993. [PubMed: 18288193]
- Jonsson, NN. Nations FaAOotU. Integrated control programs for ticks on cattle: an examination of some possible components. Rome, Italy: Food and Agriculture Organization of the United Nations; 2004. p. 82
- Jordan RA, Schulze TL, Dolan MC. Efficacy of Plant-Derived and Synthetic Compounds on Clothing as Repellents Against *Ixodes scapularis* and *Amblyomma americanum* (Acari: Ixodidae). *J Med Entomol*. 2012; 49(1):101–106. [PubMed: 22308777]
- Kagemann J, Clay K. Effects of infection by *Arsenophonus* and *Rickettsia* bacteria on the locomotive ability of the ticks *Amblyomma americanum*, *Dermacentor variabilis*, and *Ixodes scapularis*. *J Med Entomol*. 2013; 50(1):155–162. [PubMed: 23427665]
- Kain DE, Sperling FA, Lane RS. Population genetic structure of *Ixodes pacificus* (Acar: Ixodidae) using allozymes. *J Med Entomol*. 1997; 34(4):441–450. [PubMed: 9220679]
- Karesh WB, Dobson A, Lloyd-Smith JO, Lubroth J, Dixon MA, Bennett M, Aldrich S, Harrington T, Formenty P, Loh EH, et al. Ecology of zoonoses: natural and unnatural histories. *Lancet*. 2012; 380(9857):1936–1945. [PubMed: 23200502]
- Keesing F, Belden LK, Daszak P, Dobson A, Harvell CD, Holt RD, Hudson P, Jolles A, Jones KE, Mitchell CE, et al. Impacts of biodiversity on the emergence and transmission of infectious diseases. *Nature*. 2010; 468(7324):647–652. [PubMed: 21124449]
- Kelly RR, Gaines D, Gilliam WF, Brinkerhoff RJ. Population genetic structure of the Lyme disease vector *Ixodes scapularis* at an apparent spatial expansion front. *Infect Genet Evol*. 2014; 27:543–550. [PubMed: 24882702]
- Kempf F, De Meeus T, Vaumourin E, Noel V, Taragel'ova V, Plantard O, Heylen DJ, Eraud C, Chevillon C, McCoy KD. Host races in *Ixodes ricinus*, the European vector of Lyme borreliosis. *Infect Genet Evol*. 2011; 11(8):2043–2048. [PubMed: 21983685]
- Khatchikian CE, Prusinski M, Stone M, Backenson PB, Wang IN, Levy MZ, Brisson D. Geographical and environmental factors driving the increase in the Lyme disease vector. *Ecosphere*. 2012; 3(10)
- Kikuchi Y, Hayatsu M, Hosokawa T, Nagayama A, Tago K, Fukatsu T. Symbiont-mediated insecticide resistance. *Proc Natl Acad Sci U S A*. 2012; 109(22):8618–8622. [PubMed: 22529384]
- Kiss T, Cadar D, Spinu M. Tick prevention at a crossroad: New and renewed solutions. *Vet Parasitol*. 2012; 187(3–4):357–366. [PubMed: 22424918]
- Kovalev SY, Mukhacheva TA. Phylogeographical structure of the tick *Ixodes persulcatus*: a novel view. *Ticks Tick Borne Dis*. 2012; 3(4):212–218. [PubMed: 22652512]
- Lafferty KD. The ecology of climate change and infectious diseases. *Ecology*. 2009; 90(4):888–900. [PubMed: 19449681]
- Lefcort H, Durden LA. The effect of infection with Lyme disease spirochetes (*Borrelia burgdorferi*) on the phototaxis, activity, and questing height of the tick vector *Ixodes scapularis*. *Parasitol*. 1996; 113(Pt 2):97–103.
- Lemon, SM.; Sparling, PF.; Hamburg, MA.; Relman, DA.; Choffnes, ER.; Mack, A. Vector-Borne Diseases: Understanding the Environmental, Human Health, and Ecological Connections, Workshop Summary (Forum on Microbial Threats). Washington, DC: The National Academies Press; 2008. p. 350
- Levi T, Keesing F, Oggenfuss K, Ostfeld RS. Accelerated phenology of blacklegged ticks under climate warming. *Philos Trans R Soc Lond B Biol Sci*. 2015; 370(1665)
- Levin SA. The Problem of Pattern and Scale in Ecology. *Ecology*. 1992; 73(6):1943–1967.
- LoGiudice K, Ostfeld RS, Schmidt KA, Keesing F. The ecology of infectious disease: effects of host diversity and community composition on Lyme disease risk. *Proc Natl Acad Sci U S A*. 2003; 100(2):567–571. [PubMed: 12525705]

- Lonc E, Guz-Regner K, Kiewra D, Szczepanska A. Insight into tick biocontrol with special regard to fungi. *Ann Parasitol.* 2014; 60(3):169–177. [PubMed: 25281814]
- Lou Y, Wu J, Wu X. Impact of Biodiversity and Seasonality on Lyme Pathogen Transmission. *Theor Biol Med Model.* 2014; 11(1):50. [PubMed: 25432469]
- Louly CC, Soares SF, da Nobrega Silveira D, Guimaraes MS, Borges LM. Differences in the behavior of *Rhipicephalus sanguineus* tested against resistant and susceptible dogs. *Exp Appl Acarol.* 2010; 51(4):353–362. [PubMed: 20091335]
- Madden SC, Madden RC. Seasonality in diurnal locomotory patterns of adult blacklegged ticks (Acari: Ixodidae). *J Med Entomol.* 2005; 42(4):582–588. [PubMed: 16119546]
- Margos G, Vollmer SA, Ogden NH, Fish D. Population genetics, taxonomy, phylogeny and evolution of *Borrelia burgdorferi* sensu lato. *Infect Genet Evol.* 2011; 11(7):1545–1563. [PubMed: 21843658]
- Mather TN, Spielman A. Diurnal detachment of immature deer ticks (*Ixodes dammini*) from nocturnal hosts. *Am J Trop Med Hyg.* 1986; 35(1):182–186. [PubMed: 3946736]
- McCoy KD, Boulinier T, Tirard C, Michalakis Y. Host-dependent genetic structure of parasite populations: differential dispersal of seabird tick host races. *Evolution.* 2003; 57(2):288–296. [PubMed: 12683525]
- Means RG, White DJ. New distribution records of *Amblyomma americanum* (L.) (Acari: Ixodidae) in New York State. *J Vector Ecol.* 1997; 22(2):133–145. [PubMed: 9491364]
- Mechai S, Feil EJ, Garipey TD, Gregory TR, Lindsay LR, Millien V, Ogden NH. Investigation of the population structure of the tick vector of Lyme disease *Ixodes scapularis* (Acari: Ixodidae) in Canada using mitochondrial cytochrome C oxidase subunit I gene sequences. *J Med Entomol.* 2013; 50(3):560–570. [PubMed: 23802450]
- Medina, RF. Implications of host-associated differentiation in the control of pest species. In: Barbosa, P.; Letourneau, DK.; Agrawal, AA., editors. *Insect Outbreaks Revisited.* Wiley-Blackwell Publishing; 2012. p. 291-310.
- Medina RF, Nachappa P, Tamborindeguy C. Differences in bacterial diversity of host-associated populations of *Phylloxera notabilis* Pergande (Hemiptera: Phylloxeridae) in pecan and water Hickory. *J Evol Biol.* 2011; 24:761–771. [PubMed: 21261774]
- Mel'nikova OV, Botvinkin AD, Danchinova GA. Comparative data on the tick-borne encephalitis virus infectiousness of hungry and satiated taiga ticks (based on the results of an immunoenzyme analysis). *Med Parazitol (Mosk).* 1997; (1):44–49. [PubMed: 9182196]
- Mencke N. Future challenges for parasitology: vector control and 'One health' in Europe: the veterinary medicinal view on CVBDs such as tick borreliosis, rickettsiosis and canine leishmaniosis. *Vet Parasitol.* 2013; 195(3–4):256–271. [PubMed: 23680539]
- Merino O, Antunes S, Mosqueda J, Moreno-Cid JA, Perez de la Lastra JM, Rosario-Cruz R, Rodriguez S, Domingos A, de la Fuente J. Vaccination with proteins involved in tick-pathogen interactions reduces vector infestations and pathogen infection. *Vaccine.* 2013; 31(49):5889–5896. [PubMed: 24084474]
- Mihaljevic JR. Linking metacommunity theory and symbiont evolutionary ecology. *Trends Ecol Evol.* 2012; 27(6):323–329. [PubMed: 22341499]
- Miller R, Estrada-Pena A, Almazan C, Allen A, Jory L, Yeater K, Messenger M, Ellis D, Perez de Leon AA. Exploring the use of an anti-tick vaccine as a tool for the integrated eradication of the cattle fever tick, *Rhipicephalus (Boophilus) annulatus*. *Vaccine.* 2012; 30(38):5682–5687. [PubMed: 22687762]
- Miller RJ, Almazan C, Ortiz-Estrada M, Davey RB, George JE, De Leon AP. First report of fipronil resistance in *Rhipicephalus (Boophilus) microplus* of Mexico. *Vet Parasitol.* 2013; 191(1–2):97–101. [PubMed: 23026557]
- Monaghan AJ, Moore SM, Sampson KM, Beard CB, Eisen RJ. Climate change influences on the annual onset of Lyme disease in the United States. *Ticks Tick Borne Dis.* 2015; 6(5):615–622. [PubMed: 26025268]
- Moraes J, Krawczak FS, Costa FB, Soares JF, Labruna MB. Comparative Evaluation of the Vector Competence of Four South American Populations of the *Rhipicephalus sanguineus* Group for the Bacterium *Ehrlichia canis*, the Agent of Canine Monocytic Ehrlichiosis. *PLoS One.* 2015; 10(9)

- Moyer MW. The growing global battle against blood-sucking ticks. *Nature*. 2015; 524(7566):406–408. [PubMed: 26310749]
- Narasimhan S, Fikrig E. Tick microbiome: the force within. *Trends Parasitol*. 2015; 31(7):315–323. [PubMed: 25936226]
- Narasimhan S, Rajeevan N, Liu L, Zhao YO, Heisig J, Pan J, Eppler-Epstein R, Deponte K, Fish D, Fikrig E. Gut Microbiota of the Tick Vector *Ixodes scapularis* Modulate Colonization of the Lyme Disease Spirochete. *Cell Host Microbe*. 2014; 15(1):58–71. [PubMed: 24439898]
- Neafsey DE, Lawniczak MKN, Park DJ, Redmond SN, Coulibaly MB, Traore SF, Sagnon N, Costantini C, Johnson C, Wiegand RC, et al. SNP genotyping defines complex gene-flow boundaries among African malaria vector mosquitoes. *Science*. 2010; 330(6003):514–517. [PubMed: 20966254]
- Needham GR, Teel PD. Off-host physiological ecology of ixodid ticks. *Annu Rev Entomol*. 1991; 36:659–681. [PubMed: 2006871]
- Neelakanta G, Sultana H, Fish D, Anderson JF, Fikrig E. *Anaplasma phagocytophilum* induces *Ixodes scapularis* ticks to express an antifreeze glycoprotein gene that enhances their survival in the cold. *J Clin Invest*. 2010; 120(9):3179–3190. [PubMed: 20739755]
- Nelson, KE.; Williams, CM. *Infectious Disease Epidemiology: Theory and Practice*. Burlington, MA USA: Jones & Bartlett Learning, LLC; 2014.
- Nieto NC, Foley JE. Evaluation of squirrels (Rodentia: Sciuridae) as ecologically significant hosts for *Anaplasma phagocytophilum* in California. *J Med Entomol*. 2008; 45(4):763–769. [PubMed: 18714881]
- Ogden NH, Maarouf A, Barker IK, Bigras-Poulin M, Lindsay LR, Morshed MG, O’Callaghan CJ, Ramay F, Waltner-Toews D, Charron DF. Climate change and the potential for range expansion of the Lyme disease vector *Ixodes scapularis* in Canada. *Int J Parasitol*. 2006; 36(1):63–70. [PubMed: 16229849]
- Ogden NH, Mechai S, Margos G. Changing geographic ranges of ticks and tick-borne pathogens: drivers, mechanisms and consequences for pathogen diversity. *Front Cell Infect Microbiol*. 2013; 3:46. [PubMed: 24010124]
- Ogden NH, Radojevic M, Wu X, Duvvuri VR, Leighton PA, Wu J. Estimated effects of projected climate change on the basic reproductive number of the Lyme disease vector *Ixodes scapularis*. *Environ Health Perspect*. 2014; 122(6):631–638. [PubMed: 24627295]
- Oliver KM, Degnan PH, Burke GR, Moran NA. Facultative Symbionts in Aphids and the Horizontal Transfer of Ecologically Important Traits. *Ann Rev Entomol*. 2010; 55:247–266. [PubMed: 19728837]
- Ostfeld, RS. *Lyme disease : the ecology of a complex system*. New York: Oxford University Press; 2011. p. xiip. 216
- Ostfeld RS, Keesing F. Biodiversity and disease risk: The case of lyme disease. *Conserv Biol*. 2000; 14(3):722–728.
- Pages F, Dautel H, Duvallet G, Kahl O, de Gentile L, Boulanger N. Tick repellents for human use: prevention of tick bites and tick-borne diseases. *Vector Borne Zoonotic Dis*. 2014; 14(2):85–93. [PubMed: 24410143]
- Patz JA, Daszak P, Tabor GM, Aguirre AA, Pearl M, Epstein J, Wolfe ND, Kilpatrick AM, Foufopoulos J, Molyneux D, et al. Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence. *Environ Health Perspect*. 2004; 112(10):1092–1098. [PubMed: 15238283]
- Pegram RG, Wilson DD, Hansen JW. Past and present national tick control programs. Why they succeed or fail. *Ann N Y Acad Sci*. 2000; 916:546–554. [PubMed: 11193670]
- Pepin KM, Eisen RJ, Mead PS, Piesman J, Fish D, Hoen AG, Barbour AG, Hamer S, Diuk-Wasser MA. Geographic variation in the relationship between human Lyme disease incidence and density of infected host-seeking *Ixodes scapularis* nymphs in the Eastern United States. *Am J Trop Med Hyg*. 2012; 86(6):1062–1071. [PubMed: 22665620]
- Perez de Leon AA, Strickman DA, Knowles DP, Fish D, Thacker E, de la Fuente J, Krause PJ, Wikel SK, Miller RS, Wagner GG, et al. One Health approach to identify research needs in bovine and human babesioses: workshop report. *Parasit Vectors*. 2010; 3(1):36. [PubMed: 20377902]

- Perez de Leon AA, Teel PD, Auclair AN, Messenger MT, Guerrero FD, Schuster G, Miller RJ. Integrated Strategy for Sustainable Cattle Fever Tick Eradication in USA is Required to Mitigate the Impact of Global Change. *Front Physiol.* 2012; 3:195. [PubMed: 22712018]
- Pérez de León AA, Teel PD, Li A, Ponnusamy L, Roe RM. Advancing Integrated Tick Management to Mitigate Burden of Tick-Borne Diseases. *Outlooks Pest Management.* 2014; 25(6):382–389.
- Perret JL, Guigoz E, Rais O, Gern L. Influence of saturation deficit and temperature on *Ixodes ricinus* tick questing activity in a Lyme borreliosis-endemic area (Switzerland). *Parasitol Res.* 2000; 86(7):554–557. [PubMed: 10935905]
- Poelchau MF, Coates BS, Childers CP, Pérez de León AA, Evans JD, Hackett K, Shoemaker D. Agricultural applications of insect ecological genomics. *Curr Opin Insect Sci.* 2016; 13:61–69.
- Porretta D, Mastrantonio V, Amendolia S, Gaiarsa S, Epis S, Genchi C, Bandi C, Otranto D, Urbanelli S. Effects of global changes on the climatic niche of the tick *Ixodes ricinus* inferred by species distribution modelling. *Parasit Vectors.* 2013; 6:271. [PubMed: 24330500]
- Poulin R. Network analysis shining light on parasite ecology and diversity. *Trends Parasitol.* 2010; 26(10):492–498. [PubMed: 20561821]
- Presley SJ, Higgins CL, Willig MR. A comprehensive framework for the evaluation of metacommunity structure. *Oikos.* 2010; 119(6):908–917.
- Qiu Y, Nakao R, Ohnuma A, Kawamori F, Sugimoto C. Microbial population analysis of the salivary glands of ticks; a possible strategy for the surveillance of bacterial pathogens. *PLoS One.* 2014; 9(8):e103961. [PubMed: 25089898]
- Reck J, Klafke GM, Webster A, Dall' Agnol B, Scheffer R, Souza UA, Corassini VB, Vargas R, dos Santos JS, Martins JR. First report of fluazuron resistance in *Rhipicephalus microplus*: a field tick population resistant to six classes of acaricides. *Vet Parasitol.* 2014; 201(1–2):128–136. [PubMed: 24560364]
- Redondo M, Frago H, Ortiz M, Montero C, Lona J, Medellín JA, Fria R, Hernandez V, Franco R, Machado H, et al. Integrated control of acaricide-resistant *Boophilus microplus* populations on grazing cattle in Mexico using vaccination with Gavac and amidine treatments. *Exp Appl Acarol.* 1999; 23(10):841–849. [PubMed: 10581714]
- Reichard MV, Kocan AA. Vector competency of genetically distinct Populations of *Amblyomma americanum* in the transmission of *Theileria cervi*. *Comp Parasitol.* 2006; 73(2):214–221.
- Ricklefs RE. A biogeographical perspective on ecological systems: some personal reflections. *J Biogeogr.* 2011; 38(11):2045–2056.
- Rodgers SE, Zolnik CP, Mather TN. Duration of exposure to suboptimal atmospheric moisture affects nymphal blacklegged tick survival. *J Med Entomol.* 2007; 44(2):372–375. [PubMed: 17427711]
- Rodríguez-Vivas RI, Grisi L, Pérez de León AA, Silva-Villela H, Torres-Acosta JFJ, Frago H, Romero-Salas D, Rosario-Cruz R, Saldierna FDG-C. Potential economic impact assessment for cattle parasites in Mexico. *Rev Mex Ciencias Pecuarias.* 2016 In Press.
- Rodríguez-Vivas RI, Apanaskevich DA, Ojeda-Chi MM, Trinidad-Martinez I, Reyes-Novelo E, Esteve-Gassent MD, Perez de Leon AA. Ticks collected from humans, domestic animals, and wildlife in Yucatan, Mexico. *Vet Parasitol.* 2016; 215:106–113. [PubMed: 26790745]
- Rodríguez-Vivas RI, Li AY, Ojeda-Chi MM, Trinidad-Martinez I, Rosado-Aguilar JA, Miller RJ, Perez de Leon AA. *In vitro* and *in vivo* evaluation of cypermethrin, amitraz, and piperonyl butoxide mixtures for the control of resistant *Rhipicephalus (Boophilus) microplus* (Acari: Ixodidae) in the Mexican tropics. *Vet Parasitol.* 2013; 197(1–2):288–296. [PubMed: 23948559]
- Rodríguez-Vivas RI, Miller RJ, Ojeda-Chi MM, Rosado-Aguilar JA, Trinidad-Martinez IC, Perez de Leon AA. Acaricide and ivermectin resistance in a field population of *Rhipicephalus microplus* (Acari: Ixodidae) collected from red deer (*Cervus elaphus*) in the Mexican tropics. *Vet Parasitol.* 2014a; 200(1–2):179–188. [PubMed: 24365245]
- Rodríguez-Vivas RI, Perez-Cogollo LC, Rosado-Aguilar JA, Ojeda-Chi MM, Trinidad-Martinez I, Miller RJ, Li AY, de Leon AP, Guerrero F, Klafke G. *Rhipicephalus (Boophilus) microplus* resistant to acaricides and ivermectin in cattle farms of Mexico. *Rev Bras Parasitol Vet.* 2014b; 23(2):113–122. [PubMed: 25054487]

- Rodríguez-Vivas RI, Rosado-Aguilar JA, Ojeda-Chi MM, Pérez-Cogollo LC, Trinidad-Martínez I, Bolio-González ME. Control integrado de garrapatas en la ganadería bovina. Ecosistemas y Recursos Agropecuarios. 2014c; 1:295–308.
- Romashchenko AV, Ratushnyak AS, Zapara TA, Tkachev SE, Moshkin MP. The correlation between tick (*Ixodes persulcatus* Sch.) questing behaviour and synganglion neuronal responses to odours. J Insect Physiol. 2012; 58(7):903–910. [PubMed: 22497860]
- Rutledge LC, Gupta RK. Variation in the protection periods of repellents on individual human subjects: an analytical review. J Am Mosq Control Assoc. 1999; 15(3):348–355. [PubMed: 10480127]
- Sakamoto JM, Goddard J, Rasgon JL. Population and demographic structure of *Ixodes scapularis* Say in the eastern United States. PLoS One. 2014; 9(7):e101389. [PubMed: 25025532]
- Salkeld DJ, Lane RS. Community ecology and disease risk: lizards, squirrels, and the Lyme disease spirochete in California, USA. Ecology. 2010; 91(1):293–298. [PubMed: 20380218]
- Scarborough CL, Ferrari J, Godfray HCJ. Aphid protected from pathogen by endosymbiont. Science. 2005; 310(5755):1781–1781. [PubMed: 16357252]
- Schulze TL, Jordan RA. Meteorologically mediated diurnal questing of *Ixodes scapularis* and *Amblyomma americanum* (Acari: Ixodidae) nymphs. J Med Entomol. 2003; 40(4):395–402. [PubMed: 14680102]
- Schulze TL, Jordan RA, Hung RW. Effects of selected meteorological factors on diurnal questing of *Ixodes scapularis* and *Amblyomma americanum* (Acari: Ixodidae). J Med Entomol. 2001; 38(2):318–324. [PubMed: 11296842]
- Scoles GA, McElwain TF, Rurangirwa FR, Knowles DP, Lysyk TJ. A Canadian bison isolate of *Anaplasma marginale* (Rickettsiales : Anaplasmataceae) is not transmissible by *Dermacentor andersoni* (Acari : Ixodidae), whereas ticks from two Canadian *D. andersoni* populations are competent vectors of a US strain. J Med Entomol. 2006; 43(5):971–975. [PubMed: 17017236]
- Seabloom EW, Borer ET, Gross K, Kendig AE, Lacroix C, Mitchell CE, Mordecai EA, Power AG. The community ecology of pathogens: coinfection, coexistence and community composition. Ecol Lett. 2015; 18(4):401–415. [PubMed: 25728488]
- Shih CM, Telford SR 3rd, Spielman A. Effect of ambient temperature on competence of deer ticks as hosts for Lyme disease spirochetes. J Clin Microbiol. 1995; 33(4):958–961. [PubMed: 7790468]
- Soberón J, Peterson AT. Interpretation of models of fundamental ecological niches and species' distributional areas. Biodiversity Informatics. 2005; 2:1–10.
- Souza MJ. One Health: Zoonoses in the Exotic Animal Practice. Vet Clin North Am Exot Anim Pract. 2011; 14(3):421–426. [PubMed: 21872779]
- Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012; 379(9814):461–473. [PubMed: 21903253]
- Stireman JO, Nason JD, Heard SB, Seehawer JM. Cascading host-associated genetic differentiation in parasitoids of phytophagous insects. Proc R Soc B Biol Sci. 2006; 273(1586):523–530.
- Stolting KN, Nipper R, Lindtke D, Caseys C, Waeber S, Castiglione S, Lexer C. Genomic scan for single nucleotide polymorphisms reveals patterns of divergence and gene flow between ecologically divergent species. Mol Ecol. 2013; 22(3):842–855. [PubMed: 22967258]
- Suzan G, Garcia-Pena GE, Castro-Arellano I, Rico O, Rubio AV, Tolsa MJ, Roche B, Hosseini PR, Rizzoli A, Murray KA, et al. Metacommunity and phylogenetic structure determine wildlife and zoonotic infectious disease patterns in time and space. Ecol Evol. 2015; 5(4):865–873. [PubMed: 25750713]
- Swale DR, Tong F, Temeyer KB, Li A, Lam PC, Totrov MM, Carlier PR, Perez de Leon AA, Bloomquist JR. Inhibitor profile of (n)-tacrine -methylcarbamates on acetylcholinesterase from and. Pestic Biochem Physiol. 2013; 106(3)
- Tsuchida, T.; Koga, R.; Fukatsu, T. Endosymbiont that broadens food plant range of host insect. In: Bourtzis, K.; Miller, TA., editors. Insect Symbiosis. Boca Raton, FL: CTC Press; 2009. p. 408
- Turney S, Gonzalez A, Millien V. The negative relationship between mammal host diversity and Lyme disease incidence strengthens through time. Ecology. 2014; 95(12):3244–3250.

- Vail SC, Smith G. Vertical movement and posture of blacklegged tick (Acari: Ixodidae) nymphs as a function of temperature and relative humidity in laboratory experiments. *J Med Entomol.* 2002; 39(6):842–846. [PubMed: 12495181]
- Vail SG, Smith G. Air temperature and relative humidity effects on behavioral activity of blacklegged tick (Acari: Ixodidae) nymphs in New Jersey. *J Med Entomol.* 1998; 35(6):1025–1028. [PubMed: 9835697]
- Valle MR, Mendez L, Valdez M, Redondo M, Espinosa CM, Vargas M, Cruz RL, Barrios HP, Seoane G, Ramirez ES, et al. Integrated control of *Boophilus microplus* ticks in Cuba based on vaccination with the anti-tick vaccine Gavac (TM). *Exp Appl Acarol.* 2004; 34(3–4):375–382. [PubMed: 15651533]
- Walker AR. Eradication and control of livestock ticks: biological, economic and social perspectives. *Parasitol.* 2011; 138(8):945–959.
- Webster A, Reck J, Santi L, Souza UA, Dall’Agnol B, Klafke GM, Beys-da-Silva WO, Martins JR, Schrank A. Integrated control of an acaricide-resistant strain of the cattle tick *Rhipicephalus microplus* by applying *Metarhizium anisopliae* associated with cypermethrin and chlorpyrifos under field conditions. *Vet Parasitol.* 2015; 207(3–4):302–308. [PubMed: 25577676]
- Weihner, E.; Keddy, P. *Ecological Assembly Rules: Perspectives, Advances, Retreats.* New York, USA: Cambridge University Press; 2001.
- Welburn S. One Health: the 21st century challenge. *Vet Rec.* 2011; 168(23):614–615. [PubMed: 21666048]
- Williams HW, Cross DE, Crump HL, Drost CJ, Thomas CJ. Climate suitability for European ticks: assessing species distribution models against null models and projection under AR5 climate. *Parasit Vectors.* 2015; 8(1):440. [PubMed: 26310856]
- Wolfe ND, Dunavan CP, Diamond J. Origins of major human infectious diseases. *Nature.* 2007; 447(7142):279–283. [PubMed: 17507975]
- World Bank. *The International Bank for Reconstruction and Development: The World Bank.* 2010. Towards a One Health Approach for Controlling Zoonotic Diseases; p. 74 Report nr 50833-GLB
- World Bank. *International Bank for Reconstruction and Development.* 2012. The Economics of One Health; p. 65 Report nr 69145-GLB
- Xie JL, Tiner B, Vilchez I, Mateos M. Effect of the *Drosophila* endosymbiont *Spiroplasma* on parasitoid wasp development and on the reproductive fitness of wasp-attacked fly survivors. *Evol Ecol.* 2011; 25(5):1065–1079. [PubMed: 22912533]
- Yang Y, Nachman RJ, Pietrantonio PV. Molecular and pharmacological characterization of the Chelicerata pyrokinin receptor from the southern cattle tick, *Rhipicephalus (Boophilus) microplus*. *Insect Biochem Mol Biol.* 2015; 60:13–23. [PubMed: 25747529]
- Zheng H, Li AY, Fielden LJ, Liu J, Seshu J, Pérez de León AA. Effects of permethrin and amitraz on gas exchange and water loss in unfed adult females of *Amblyomma americanum* (Acari: Ixodidae). *Pest Biochem Physiol.* 2013; 107(2):153–159.

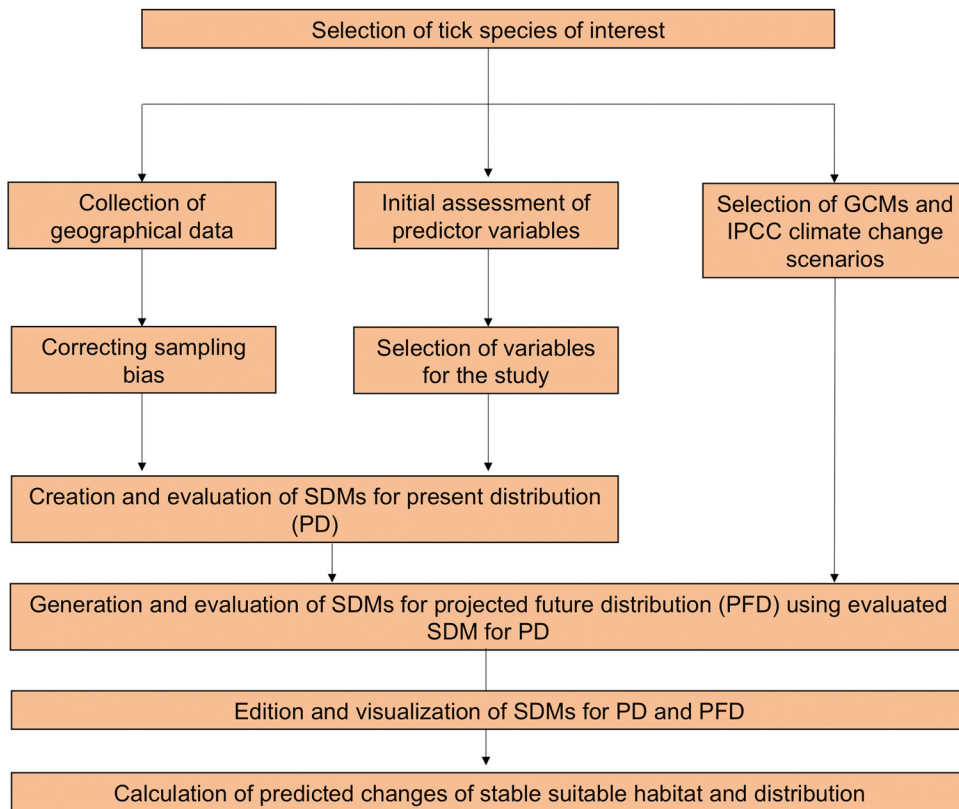


Figure 1.

General flowchart on the steps followed to create Species Distribution Models (SDMs) to predict the future distribution of tick vectors. After selecting a target tick species (e.g. *Ixodes scapularis*), geographical data (i.e. longitude and latitudes) are collected during field-work or during searches in the primary literature and databases. Importantly, geographical data should be analyzed for sampling bias, and if possible, data are corrected. Additionally, a set of climatic variables are initially selected; however, autocorrelated variables are eliminated from the study. Also, climatic variables can be selected by taking into account tick physiology. Then, a SDM (e.g. MaxEnt) for the species' present distribution is created and evaluated using corrected geographical data and predictor variables. This SDM is the basis to create SDMs that predict future distribution (FD), using climatic general circulation models (GCMs) and climate change scenarios proposed by the Intergovernmental Panel on Climate Change (IPCC). Finally, the SDMs for FD are visualized on software (e.g. Geographical Information Systems) and evaluated. As a result, these SDMs are used to calculate changes in distribution for future years.

(A)



(B)



Figure 2. Two contrasting habitats for Lyme disease integrative tick research currently conducted in Texas (A) Edwards Plateau and (B) South Central Plains

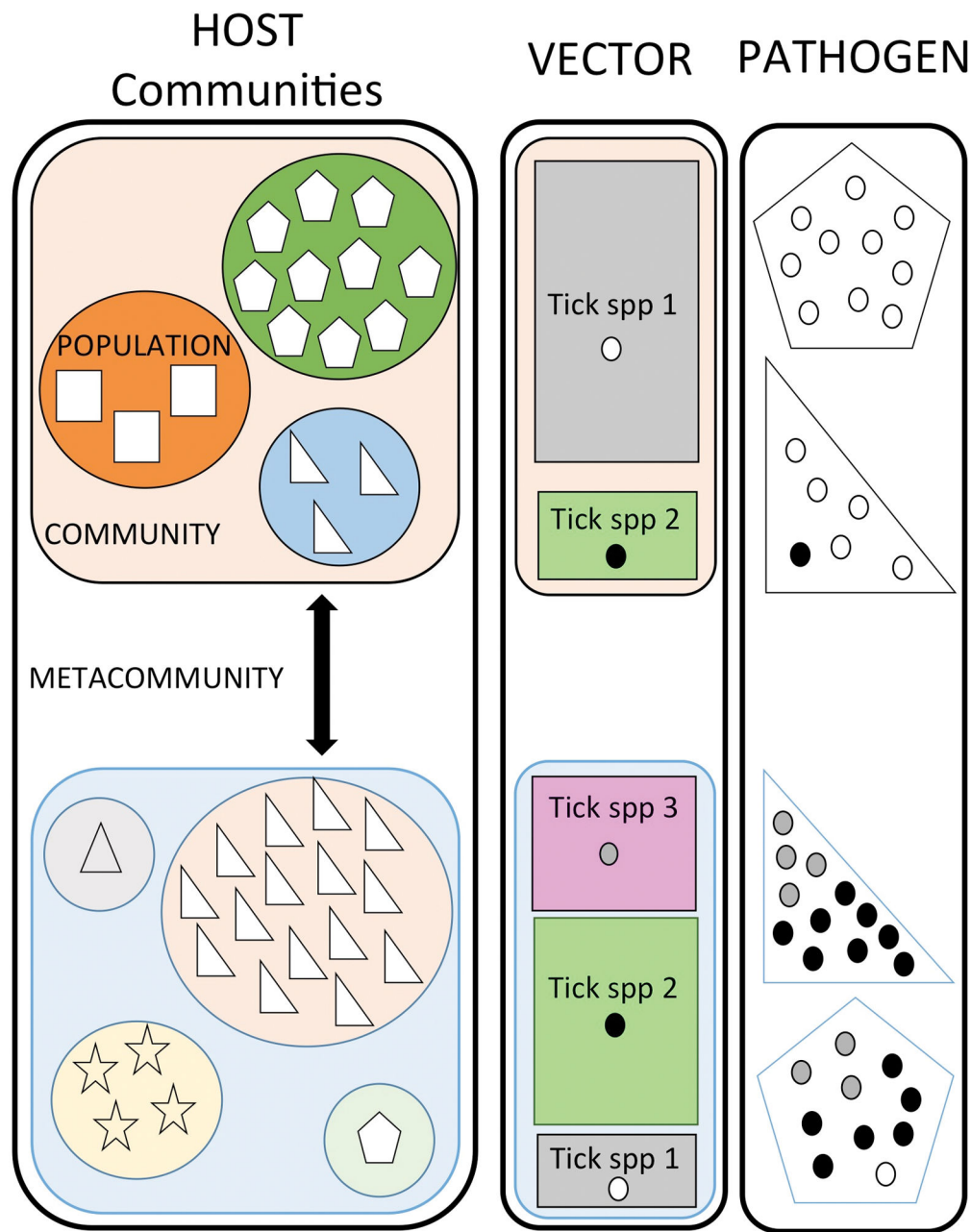


Figure 3. Interactions between vertebrate hosts (geometric shapes: square, triangle, pentagon, stars), tick vectors and pathogens can be viewed from multiple scales. At the level of individual hosts the pathogens occur in infra-communities (group of pathogens, and symbionts, coinfecting an individual and represented by the black, white or gray dots). For schematic purposes this diagram depicts a single pathogen for each tick species but these microparasites also occur in diverse symbiont and pathogen infra-communities. Thus, patterns of diversity, distribution and abundance of pathogens will be tied to both the vertebrate host and tick vectors by a series of ecological processes (dispersal, competition, etc.) and environmental variation across each scale. Changes in symbiont infra-communities,

vertebrate host, and vector diversity among sites of a metacommunity could prevent or facilitate the presence of a given pathogen across landscapes. Figure modified after Seabloom et al., 2015.

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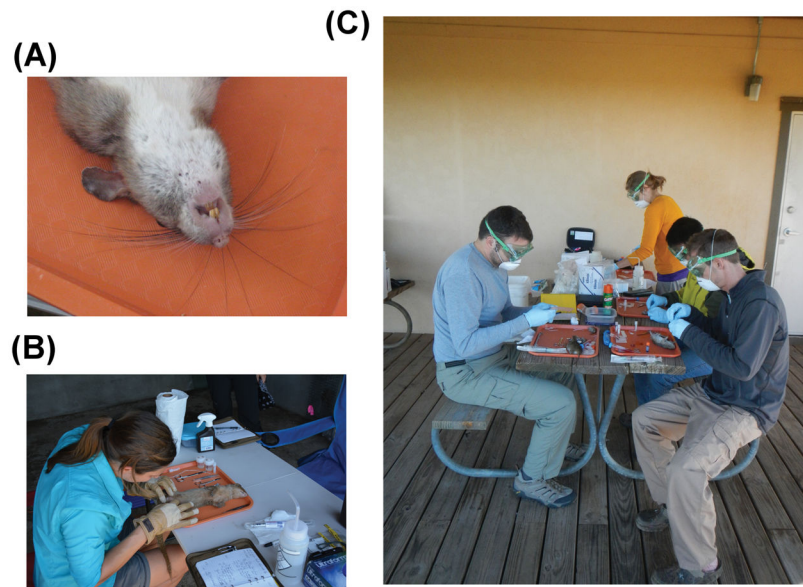


Figure 4. Multiple wildlife species are potential reservoir hosts for vector borne infectious diseases. (A) *Neotoma* spp. specimen collected in the state of Texas showing immature ticks on neck (photo courtesy of Matt Milholland). (B) Researcher inspecting a Mongoose (*Herpstes auropunctatus*) for ticks in Puerto Rico. (C) Team of researchers evaluating tick load on small mammals collected in the state of Texas.