Global Importance of Ticks and Associated Infectious Disease Agents

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Abstract

Ticks are medically important ectoparasites that have global distribution. They live in diversified habitats, have close contact with a wide range of vertebrate hosts, and can transmit a variety of disease agents to human beings, domesticated animals, and wildlife. Tick-borne infections can cause acute or chronic illnesses, such as Lyme disease, relapsing fever, Crimean Congo hemorrhagic fever, human babesiosis, Texas cattle fever, Rocky Mountain spotted fever, ehrlichiosis, Boutonneuse fever, tularemia, Colorado tick fever, and encephalitis. Human fatalities have been reported for some of these diseases. Certain tick species are also suspected vectors of *Bartonella* organisms. Having high reproductive potential, few natural parasites and predators, the ability to live several months or years, and relatively broad host ranges, ticks are well adapted for survival and difficult to control. Certain practices, however, such as early removal of attached ticks from skin, use of repellents, and landscape modifications near human dwellings can reduce tick bites and risk of infection.

Introduction

Ticks transmit a variety of pathogenic organisms that can cause mild to severe illnesses, even death, in human beings, domesticated animals, and wildlife ([1],2). These highly specialized ectoparasites, which suck blood, lymph, and digested tissues from mammals, birds, reptiles, and amphibians, can also cause tick paralysis (toxicosis) and allergic reactions. There are about 877 named species worldwide ([1]), with more than half assigned to the following genera: *Ixodes* ($n = 245$), *Haemaphysalis* ($n = 164$), and *Amblyomma* ($n = 131$). These arthropods occur from the tropics to subarctic areas and are well adapted to living in harsh, diversified habitats, including animal nests. For example, *Hyalomma dromedarii* (the camel tick) lives in deserts and burrows in the sand

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to prevent desiccation. When a host approaches, the ticks rapidly emerge from the sand and attach to the animal. In West Africa, *Ornithodoros sonrai* feeds on rodents, which burrow in the earthen floors of human dwellings built with mud walls, and can transmit the spirochete *Borrelia crocidurae* when they feed on people at night. These ticks tend to remain in these settings, particularly during droughts. The eyeless tampan, *Ornithodoros moubata*, also lives in or near human dwellings in sub-Saharan Africa and transmits *Borrelia duttoni*.

Although most ticks have close associations with vertebrate animals, these arthropods spend most of the time in surrounding habitats seeking hosts, digesting blood meals, and developing through different life stages to adulthood. Some tick species have limited host preferences, while others have broad host ranges. For example, *Ixodes texanus* feeds almost exclusively on raccoons in the northeastern United States. *Ixodes scapularis*, most abundant in forested areas of the north-

eastern and upper midwestern U.S., feeds on a wide range of vertebrate hosts. Adult ticks prefer white-tailed deer (*Odocoileus virginianus*) but also will parasitize horses, cattle, and a variety of medium-sized mammals. The immature stages (larvae and nymphs) will likewise feed on these hosts but will take blood from rodents and several species of birds as well. *Ixodes scapularis* and *I. pacificus* (a related species found in the western U.S. and Canada) feed on more than 100 host species, while *Ixodes ricinus* and *Ixodes persulcatus* parasitize more than 200

host species in Eurasia [1]. The potential for acquiring and transmitting pathogens is greatest for those tick species that have broad host ranges and when pathogens are efficiently passed from one life stage to another (trans-stadial transmission). In some tick species, there is passage of disease organisms from the female to the eggs (transovarial transmission).

Public Health Significance

Several diseases have been linked to tick bites, and there are certain tick species that are considered to be of high public health importance. In the U.S., *I. scapularis* and *I. pacificus* transmit *Borrelia burgdorferi* sensu stricto, the etiologic agent of Lyme disease (also known as Lyme borreliosis), *Anaplasma phagocytophilum* (the causative agent for human granulocytic anaplasmosis, formerly known as human granulocytic ehrlichiosis), and *Babesia microti* (the pathogen for human babesiosis) or a related *Babesia* species. *Dermacentor andersoni* and *Dermacentor variabilis* are important vectors of *Rickettsia rickettsii* (the agent for Rocky Mountain spotted fever) and *Francisella tularensis* (the pathogen for tularemia). In Europe, *I. ricinus* transmits *B. burgdorferi* sensu stricto, *Borrelia garinii*, and *Borrelia afzelii*, pathogens associated with general patterns of arthritis, neurologic abnormalities, and skin disorders of Lyme borreliosis, respectively [3]. These associations among the genospecies of the *B. burgdorferi* sensu lato complex and certain clinical manifestations are not absolute, however. Some features, such as the occurrence of flu-like illnesses and the presence of an expanding skin lesion (erythema migrans), are shared among the different infectious agents in this complex [4]. It was once believed that there were prominent differences in clinical manifestations occurring in North America

and Europe, such as greater prevalence of Lyme arthritis in the U.S. However, the arthritis aspect of *B. burgdorferi* infections appears to be more prevalent in Europe than previously thought. Clinical differences exist between the two continents, but in general, the manifestations appear to be less distinct than reported earlier [3]. Other pathogens transmitted by *I. ricinus* include *Rickettsia conori* (the agent for Boutonneuse fever), *Babesia divergens*, *A. phagocytophilum*, and viruses that cause tick-borne encephalitis and Crimean Congo hemorrhagic fever [1]. *I. persulcatus*, which replaces *I. ricinus* in northeastern Europe and extends eastward to northern Asia, also transmits different *Borrelia* species and the virus that causes tick-borne encephalitis. The latter disease also has been associated with *Dermacentor marginatus* and *Dermacentor silvarum* in Eurasia. *Amblyomma cajennense* and *Carios rudis* are vectors of *R. rickettsii* and *Borrelia venezuelensis*, respectively, in Central and South America.

The lone star tick (*Amblyomma americanum*), widely distributed in southern and eastern regions of the U.S., transmits *Ehrlichia chaffeensis*, the etiologic agent of human monocytic ehrlichiosis; *Ehrlichia ewingii*; *F. tularensis*; and *Borrelia lonestari* [5]-10). The last organism is the putative disease agent that causes southern tick-associated rash illness (also known as STARI or Master's disease). *B. lonestari* has been cultured [8], but the success rate is low. There are several reports of human cases from Missouri [7], where annular skin lesions are very similar to erythema migrans described for *B. burgdorferi* infections. Larval and nymphal ticks feed on small, medium, and large mammals and on birds, while adult ticks heavily parasitize white-tailed deer and cattle. The connection between lone star ticks

and deer is important because these mammals are reservoirs for *E. chaffeensis* [10] and probably play a similar role in the ecology of *B. lonestari* [9]; transmission of multiple disease agents from wild-caught lone star ticks to captive, reared deer has been reported [9]. Lone star ticks are also known or suspected vectors of *Coxiella burnetii* (the Q fever agent), spotted fever group rickettsiae, and possibly an organism closely related to *Ehrlichia ruminantium* [6, 11-14). *E. ewingii*, first described as a human pathogen in 1999, invades neutrophils, similar to *A. phagocytophilum* infections. In dogs, *E. ewingii* delays spontaneous neutrophil apoptosis and, consequently, may exacerbate the effects of other diseases [15].

The geographic range of *A. americanum* has expanded northward in the U.S. during the past three decades [7,16], with records as far north as Maine [16]. The DNA of *E. chaffeensis* has been detected in lone star ticks from southern New England [17]. This expansion in geographic range is probably due, in part, to movement of ticks on their hosts, particularly birds, and increased deer populations. It is unknown if global warming is enhancing tick survival in the more northern latitudes.

Although numerous disease agents have been isolated from ticks and characterized worldwide, Lyme disease is the most prevalent arthropod-associated illness in North America. Based on very conservative reporting, the numbers of human Lyme disease cases in the U.S. during 2006 ($n = 19,931$) and 2007 ($n = 20,599$) greatly exceeded those recorded for other arthropod-related diseases [18]. National figures for human cases of Rocky Mountain spotted fever were 2,288 in 2006 and 2,106 in 2007. Moreover, the maximum number of reported cases of human monocytic

ehrlichiosis (n = 685), human granulocytic anaplasmosis (n = 786), and tularemia (n = 154) were relatively low during the period 2002 to 2007. National figures for documented human cases of West Nile encephalitis, caused by a mosquito-transmitted flavivirus, were likewise lower in 2006 (n = 2,774) and 2007 (n = 2,332) than reported cases of Lyme disease. Recognizing that these figures are conservative, the records still give overall perspective on the impact that Lyme disease is having on human health in the U.S. The rise in deer populations and corresponding increases in numbers of *I. scapularis* ticks, reversion of agricultural land to forested areas, and the building of human dwellings in or near foci for *B. burgdorferi* infections have contributed greatly to the increased incidence of this multisystemic disease. White-footed mice (*Peromyscus leucopus*), the chief reservoir of *B. burgdorferi*, are abundant in forested areas and serve to infect larval and nymphal ticks. Birds also play an important role by introducing infected ticks to previously non-infested areas and in some cases have been found carrying ticks between continents. These ecological factors are also important in Europe, where several thousands of human Lyme borreliosis cases have been reported.

Clearly, there is worldwide distribution of a multitude of tick-transmitted pathogens. Certain tick species can harbor multiple agents, thereby increasing the potential for coinfections in vertebrate hosts. Using a variety of molecular probes, several investigators have reported on the presence of multiple pathogens in ticks (2,7). There also are numerous reports of coexisting antibodies to different pathogens in human beings and other mammals (2). Although it is unclear how prevalent coinfections are in humans or domesticated animals, it is important for physicians and veterinarians to consider possible activity of multiple disease agents in the differential diagnosis and treatment protocols.

Antibiotic treatment during early onset of tick-borne bacterial or protozoan infections is more effective than treating advanced stages of disease. In instances when prompt antibiotic treatment is lacking in *B. burgdorferi* infections, prolonged illnesses can include Lyme arthritis, Lyme carditis,

or neurologic disorders. *R. rickettsii* and *F. tularensis* are highly pathogenic organisms that can cause fatalities if untreated. Similarly, in untreated, immunocompromised patients, *B. microti* infections can cause death, as well.

Laboratory Diagnosis

Serologic tests for antibodies and highly sensitive and specific molecular procedures to detect the DNA of pathogens are relied on heavily to diagnose tick-borne infections, particularly when the clinical picture is unclear or if there are coinfections. For example, erythema migrans, the hallmark sign associated with early onset of Lyme disease, is sometimes lacking. In these instances, it can be extremely difficult to determine the cause(s) of arthritic, cardiac, or neurologic disorders as this disease progresses. Supportive laboratory work can aid clinical diagnoses of Lyme disease. In analyses of skin biopsy specimens, blood, synovial fluids, or other tissues, laboratory confirmation of *B. burgdorferi* infection can be accomplished by using nucleic acid detection techniques and culturing procedures (19). Polymerase chain reaction (PCR) procedures target the amplification of chromosomal and plasmid genes of *B. burgdorferi*. Although several primers and probes have been tested, high assay sensitivity and specificity were reported when primers for outer surface protein A were applied. Using larger volumes of blood to culture this spirochete has improved isolation yields. However, *B. burgdorferi* is a low-density parasite in blood, and because of costs and generally low-yielding results, culture methods are not widely used for diagnosis. Clearly, the performance of PCR methods on synovial fluids, cerebrospinal fluids, and skin tissues has been better than in analyzing blood. Serologic testing for antibodies also can be helpful in detecting past or current *B. burgdorferi* infections. Two-tier testing protocols using enzyme immunosorbent assay (EIA) and Western blot methods are frequently used. Replacing whole-cell, lysate antigens with highly specific recombinant or peptide antigens in serologic tests has improved assay performance (20-24).

Molecular techniques are available to detect the nucleic acids of other tick-

borne pathogens. Similar to work done on *Borrelia* species, nucleotide sequence comparisons have been particularly useful in determining phylogenetic relationships for strains of other pathogens isolated from ticks and wild-caught mammals in different continents. Exhaustive studies on the DNA of ehrlichiae, species of *Anaplasma* and *Bartonella*, and *F. tularensis* have contributed immensely to clarifying the taxonomic, pathogenic, and ecological relationships of diverse groups of closely related organisms (25-28). For example, PCR amplification and cloning procedures were recently used along with culturing blood from six persons who exhibited chronic neurological or neurocognitive syndrome (28). *Bartonella henselae* or *Bartonella vinsonii* subspecies *berkhoffii* were isolated and identified. There was notable animal contact or recent arthropod exposure, including ticks, as a risk factor for four of these subjects. Although definitive proof is lacking for tick transmission of *Bartonella* organisms, there is case-based and sero-epidemiological evidence suggesting possible transmission by *Rhipicephalus sanguineus* (the brown dog tick) and *I. scapularis* ticks. Moreover, *Bartonella* DNA has been detected in questing ticks.

Molecular procedures were also relied on to investigate the RNA extracted from the Ipswich, Massachusetts strain of the deer tick virus (DTV), which appears to be a subtype of Powassan virus (29). Based on experimental results (30), *I. scapularis* ticks are competent vectors of Powassan virus, but *Ixodes cookei*, which feeds heavily on woodchucks (*Marmota monax*) and occasionally on people, is probably an important enzootic vector. A recombinant DTV envelope glycoprotein has been used as an antigen in an EIA. Antibodies have been detected in white-footed mice and meadow voles (*Microtus pennsylvanicus*) captured at sites in Massachusetts, Rhode Island, and Wisconsin (29), where the *I. scapularis* abounds, but seropositivity rates were less than 4%; the prevalence of infected *I. scapularis* ticks, collected in four sites, ranged from zero to 1.3%. It is unknown if the DTV is a human pathogen or if this flavivirus is prevalent in other tick species or non-rodent, vertebrate host populations.

Reducing Risk of Tick Bites and Infection

The risk of acquiring one or more tick-borne infections is high in certain areas. There are some specific measures, however, that one can follow to reduce the risk of tick bites and infection. Ticks of several species congregate along animal trails and rest on the tips of vegetation awaiting a passing host. Animal odors, vibration caused by an approaching host, visual appearance of hosts, and carbon dioxide are important factors in host detection. Daily checks for attached ticks and early removal of these ectoparasites from skin are of paramount importance in preventing infections. Compared to mosquitoes, blood feeding in ticks is a relatively slow process. Several hours are needed for a tick to fully implant its hypostome, a hold-fast organ, into host skin tissue. Although transmission rates vary with tick species and the type of pathogen, the passage of disease organisms to hosts occurs when blood is ingested hours after the initial tick bite. It has been estimated that *I. scapularis* ticks need to be attached for about 36 hours to transmit *B. burgdorferi* to hosts. The probability of transmission increases thereafter as feeding continues. Proportionately higher dosages of these spirochetes are transmitted by ticks as they ingest larger volumes of blood nearing full engorgement. Therefore, promptly removing attached ticks soon after attachment and before blood feeding begins greatly reduces the risk of infection. Use of tick repellents on skin or clothing, as directed on the product label, is another important preventive measure for people who enter tick-infested habitats. In addition, certain landscape management practices in yards adjacent to homes can reduce the number of questing ticks (31). High humidity is a key factor for survival of *I. scapularis* ticks. Therefore, removing trees and brush to increase direct sunlight and air flow in lawn areas near homes and creating barriers with brick, paving, gravel, or woodchips between lawns and tick-infested areas adjacent to or in woodlands are helpful. The use of registered pesticides to control questing ticks on vegetation at the edges of woodlands can be effective, too, if treatment is applied in a timely manner to target certain tick stages. For example, a chemical spray applied from late May through mid-June in the northeastern U.S. can reduce the number of *I. scapularis* nymphs, which are the most efficient vectors of *B. burgdorferi, A. phagocytophilum, and B. microti*. Treatment during April or October will reduce adult ticks. Repeated chemical treatment in subsequent years may be required to address reinvasion of ticks in the treated areas.

References

1. Anderson, J.F. and L.A. Magnarelli. 2008. Biology of ticks, p. 195-215. *In* J.A. Edlow (ed.), Infectious disease clinics of North America: tick borne diseases, Lyme Disease. W.B. Saunders, Philadelphia, PA.

2. Swanson, S.J. et al. 2006. Coinfections acquired from *Ixodes* ticks. Clin. Microbiol. Rev. 19:708-727.

3. Stanek, G. and F. Strle. 2008. Lyme disease — European perspective, p. 327-339. *In* J.A. Edlow (ed.), Infectious disease clinics of North America: tick borne diseases, Lyme Disease. W.B. Saunders, Philadelphia, PA.

4. van Dam, A.P. et al. 1993. Different genospecies of *Borrelia burgdorferi* are associated with distinct clinical manifestations of Lyme borreliosis. Clin. Infect. Dis. 17:708-717.

5. Anderson, B.E. et al. 1993. *Amblyomma americanum*: a potential vector of human ehrlichiosis. Am. J. Trop. Med. Hyg. 49:239-244.

6. Childs, J.E. and C.D. Paddock. 2003. The ascendancy of *Amblyomma americanum* as a vector of pathogens affecting humans in the United States. Annu. Rev. Entomol. 48:307-337.

7. Masters, E.J., C.N. Grigery, and R.W. Masters. 2008. STARI, or Masters Disease: lone star tick-vectored Lyme-like illness, p. 361-376. *In* J.A. Edlow (ed.), Infectious disease clinics of North America: tick borne diseases, Lyme Disease. W.B. Saunders, Philadelphia, PA.

8. Varela, A.S. et al. 2004. First culture of *Borrelia lonestari*, putative agent of southern tick-associated rash illness. J. Clin. Microbiol. 42:1163-1169.

9. Varela, A.S. 2007. Transmission of bacterial agents from lone-star ticks to white-tailed deer. J. Med. Entomol. 44:478-483.

10. Lockhart, J.M. et al. 1997. Isolation of *Ehrlichia chaffeensis* from wild white-tailed deer (*Odocoileus virginianus*) confirms their role as natural reservoir hosts. J. Clin. Microbiol. 35:1681-1686.

11. Parker, R.R. and G.M. Kohls. 1943. American Q fever: the occurrence of *Rickettsia diaporica* in *Amblyomma americanum* from eastern Texas. Publ. Hlth. Rep. 58:1510-1511.

12. Philip, C.B. and J.J. White. 1955. Disease agents recovered incidental to tick survey of the Mississippi Gulf Coast. J. Econ. Entomol. 48:396-399.

13. Buller, R.S. et al. 1999. *Ehrlichia ewingii*, a newly recognized agent of human ehrlichiosis. N. Engl. J. Med. 341:148-155.

14. Loftis, A.D. et al. 2006. Infection of a goat with a tick-transmitted *Ehrlichia* from Georgia, USA that is closely related to *Ehrlichia ruminantium*. J. Vector Ecol. 31:213-223.

15. Xiong, Q. et al. 2008. *Ehrlichia ewingii* infection delays spontaneous neutrophil apoptosis through stabilization of mitochondria. J. Infect. Dis. 197:1110-1118.

16. Keirans, J.E. and E.H. Lacombe. 1998. First records of *Amblyomma americanum*, *Ixodes dentatus*, and *Ixodes* (Ceratixodes) *uriae* (Acari: Ixodidae) from Maine. J. Parasitol. 84:629-631.

17. Ijdo, J.W. et al. 2000. Detection of *Ehrlichia chaffeensis* DNA in *Amblyomma americanum* ticks in Connecticut and Rhode Island. J. Clin. Microbiol. 38:4655-4656.

18. Centers for Disease Control and Prevention. 2008. MMWR Morb. Mortal. Wkly. Rep. 56:1357-1365.

19. Aguero-Rosenfeld, M.E. 2008. Lyme disease: laboratory issues, p. 301-313. *In* J.A. Edlow (ed.), Infectious disease clinics of North America: tick borne diseases, Lyme Disease. W.B. Saunders, Philadelphia, PA.

20. Lawrenz, M.B. et al. 1999. Human antibody responses to VIsE antigenic variation protein of *Borrelia burgdorferi*. J. Clin. Microbiol. 37:3997-4004.

21. Liang, F.T. et al. 1999. Sensitive and specific serodiagnosis of Lyme disease by enzyme-linked immunosorbent assay with a peptide based on an immunodominant conserved region of *Borrelia burgdorferi* vlsE. J. Clin. Microbiol. 37:3900-3906.

22. Magnarelli, L.A. et al. 2002. Comparative reactivity of human sera to recombinant VIsE and other *Borrelia burgdorferi* antigens in class-specific enzyme-linked immunosorbent assays for Lyme borreliosis. J. Med. Microbiol. 51:649-655.

23. Bacon, R.M. et al. 2003. Serodiagnosis of Lyme disease by kinetic enzyme-linked immunosorbent assay using

recombinant VlsE1 or peptide antigens of *Borrelia burgdorferi* compared with 2-tiered testing using whole-cell lysates. J. Infect. Dis. 187:1187-1199.

24. Nyman, D. et al. 2006. VlsE C6 peptide and IgG ELISA antibody analysis for clinical diagnosis of Lyme borreliosis in an endemic area. Clin. Microbiol. Infect. 12:496-497.

25. Dumler, J.S. et al. 2001. Reorganization of genera in the families Rickettsiaceae and Anaplasmataceae in the order Rickettsiales: unification of some species of *Ehrlichia* with *Anaplasma*, *Cowdria* with *Ehrlichia*, and *Ehrlichia* with *Neorickettsia*, descriptions of six new species combinations and designation of *Ehrlichia equi* and "HGE agent" as subjective synonyms of *Ehrlichia phagocytophila*. Int. J. Syst. Evol. Microbiol. 51:2145-2165.

26. Kim, C.-M. et al. 2006. Tick-borne rickettsial pathogens in ticks and small mammals in Korea. Appl. Environ. Microbiol. 72:5766-5776.

27. Ellis, J. et al. 2002. Tularemia. Clin. Microbiol. Rev. 15:631-646.

28. Breitschwerdt, E.B. et al. 2008. *Bartonella* sp. bacteremia in patients with neurological and neurocognitive dysfunction. J. Clin. Microbiol. 46:2856-2861.

29. Ebel, G.D. et al. 2000. Enzootic transmission of deer tick virus in New England and Wisconsin sites. Am. J. Trop. Med. Hyg. 63:36-42.

30. Costero, A. and M.A. Grayson. 1996. Experimental transmission of Powassan virus (Flaviviridae) by *Ixodes scapularis* ticks (Acari: Ixodidae). Am. J. Trop. Med. Hyg. 55:536-546.

31. Stafford, K.C., III. 2007. Tick management handbook. CT Agric. Exp. Station Bull. 1010. Connecticut Agricultural Experiment Station, New Haven, CT.