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TICK ASSOCIATED DISEASES

Lyme Disease

Lyme disease is caused by the spirochete *Borrelia burgdorferi*, a corkscrew-shaped bacterium. It is associated with the bite of certain *Ixodes* ticks, particularly the blacklegged tick, *Ixodes scapularis* (commonly known as the deer tick). This disease was first recognized in a group of arthritis patients from the area of Lyme, Connecticut in 1975 and occurs in North America, Europe, and Asia. The emergence of Lyme disease is associated with reforestation and increased white-tailed deer populations and populations of small animal hosts. Deer are the principal hosts for adult *I. scapularis*. White-footed mice, chipmunks, shrews, and certain birds are important hosts for the larval and nymphal stages and serve as reservoirs (source of infection for the ticks) for *B. burgdorferi*.

There are around 30,000 cases of Lyme disease reported to the Centers for Disease Control and Prevention (CDC) each year (Fig. 1), with 13 states from the northeast, mid-Atlantic, and upper mid-west accounting for 95% of the cases (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, Wisconsin). With only about 10% of the cases estimated to be reported, there are probably around 300,000 cases of Lyme disease actually diagnosed each year.

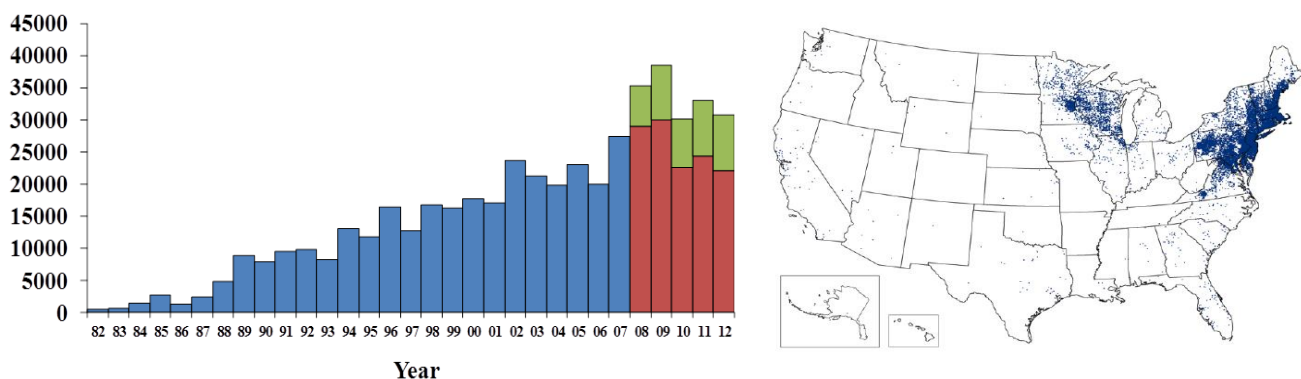


Figure 1. Left; number of Lyme disease cases reported to the CDC, 1982-2012. The surveillance case definition changed in 2008 and cases are classified as probable (green) or confirmed (rust). Right; reported cases of Lyme disease for 2012, each dot placed randomly within county for a confirmed case (Data: CDC).

In Connecticut, the number of reported Lyme disease cases steadily increased from a few hundred in the mid-to late 1980s to around 3,000 annually. The incidence of Lyme disease by town is available at the Connecticut Department of Public Health's (DPH) web site and the result of tick testing by town is available on the Connecticut Agricultural Experiment Station's (CAES) website (www.ct.gov/dph and [/caes](http://www.ct.gov/caes)).

Signs and symptoms of Lyme disease . . .

Localized infection - Approximately 70 - 80% or more of patients develop a red rash (erythema migrans or EM) within 2 to 32 days (typically 8 or 9 days) after the tick bite. The rash gradually expands over a period of a week or more and will fade after several weeks. Rashes vary in size and shape, and may occur anywhere on the body, although common sites are the thigh, groin, trunk, and armpits. The rash is not the small, quarter-sized redness just due to the tick bite.

Many rashes reach about 5-6 inches in diameter, but some can be 8-16 inches or more in size. The rash often remains red, but swelling, blistering, scabbing or central clearing may occur, resulting in a "bull's-eye" appearance (photos courtesy Pfizer Central Research). The rash may be warm to the touch, but it is usually not painful or itchy. Mild nonspecific, flu-like symptoms may be associated with the rash. In most cases, symptom onset occurs during the summer months when the nymphal stage of *Ixodes* is active. Lyme disease affects all age groups, but the greatest incidence has been in children under 14 years and adults over 40 years of age. There may be no early symptoms in some cases.

Disseminated infection - The course and severity of Lyme disease is variable. Days or weeks after the bite of an infected tick, multiple rashes, migratory joint and muscle pain (also brief, intermittent arthritic attacks), debilitating malaise and fatigue, neurologic or cardiac problems may occur. Early neurologic symptoms develop in about 15% of untreated patients and these can include paralysis of facial muscles (Bell's palsy), meningitis (fever, stiff neck, and severe headache), and radiculoneuropathy (pain in affected nerves and nerve roots, can be sharp and jabbing or deep). A year or more after the tick bite in untreated or inadequately treated individuals, symptoms of persistent infection may include numbness or tingling of the extremities, sensory loss, weakness, diminished reflexes, disturbances in memory, mood or sleep, and an intermittent chronic arthritis (typically swelling and pain of the large joints, especially the knee). Approximately 50-60% of untreated patients develop arthritis and about 10% of these will progress to chronic arthritis. Ocular manifestations may include conjunctivitis and other inflammatory eye problems.

Diagnosis . . .

Consult a physician if you suspect Lyme disease. In the absence of an EM, Lyme disease may be difficult to diagnose because its symptoms and signs vary among individuals and mimic those of many other diseases. Conversely, other arthritic or neurologic diseases may be misdiagnosed as Lyme disease. A diagnosis of Lyme disease is made on signs, symptoms, history, and supporting laboratory data. A blood test to detect antibodies to Lyme disease spirochetes can aid in the diagnosis of the disease. Testing is generally a two stage process with a sensitive enzyme-linked immunosorbent assay (ELISA), which if positive or equivocal, is followed by a more specific Western immunoblot test for the presence of multiple, specific, anti-*Borrelia* antibodies (the "bands" on a Western blot test). Antibody tests should not be used as the sole criterion for a diagnosis, especially during the early stages of the disease. One issue is the use of antibody testing before a serodiagnosis can be made. Antibodies can usually only be detected 3-4 weeks after infection. Negative results do not necessarily exclude Lyme disease, but reliability of the test does improve in later stages of the disease. Prompt treatment may also abort any detectable antibody response. Patients are also known to have detectable antibodies for years after successful treatment (i.e., absence of further clinical symptoms). There is no reliable, readily available clinical test for direct detection or culture of the spirochetes.



Treatment . . .

Lyme disease is treated with several antibiotics, including tetracycline, doxycycline, amoxicillin, penicillin, cefuroxime, or ceftriaxone. Early treatment can prevent the later symptoms of Lyme disease from developing. Oral antibiotics are effective in treating most cases of Lyme disease. In some cases, antibiotics may be given intravenously. Patients treated in the early stages of the disease usually recover completely. Full recovery is possible for patients treated in the later stages of the disease, but resolution of symptoms may take weeks or months. Persistent signs and symptoms after treatment have been reported in some patients, though the cause(s) are unclear and remain controversial. Possible reasons for treatment failure include inadequate treatment, coinfection with another tick-borne pathogen, remnants of dead spirochetes causing inflammation, persistent infection with live spirochetes, or a triggered autoimmune response. People can be re-infected and develop Lyme disease with subsequent tick bites, requiring another course of treatment.

Lyme disease in animals . . .

Dogs, cats, horses, and cows can also contract Lyme disease. Lameness, fever, reduced appetite, and a reluctance to move are the usual symptoms in these animals. Animals are treated with antibiotics. Canine vaccines are available. Consult your veterinarian about the prevention and treatment of Lyme disease in your animals. The extent to which pet owners may be at increased risk of tick bite is unknown. Animals may carry ticks into the home, or outdoor activities with animals may increase the exposure of pet owners to ticks and their habitat (photo courtesy Pfizer Central Research).



Table 1. Summary of the tick-borne diseases, the causal pathogen, and associated tick vectors in the United States.

| Disease | Pathogen | Tick Vector |
|-------------------------------|----------------------------------|--|
| Anaplasmosis | <i>Anaplasma phagocytophilum</i> | <i>I. scapularis</i> , <i>I. pacificus</i> |
| Babesiosis | <i>Babesia microti</i> | <i>I. scapularis</i> , <i>I. pacificus</i> |
| Colorado tick fever | Reoviridae (virus) | <i>Dermacentor andersoni</i> |
| Ehrlichiosis (HME) | <i>Ehrlichia chaffeensis</i> | <i>A. americanum</i> |
| Ehrlichia muris-like agent | <i>Ehrlichia spp.</i> | <i>I. scapularis</i> |
| Heartland virus disease | Heartland virus | <i>A. americanum</i> (?) |
| Lyme disease | <i>Borrelia burgdorferi</i> | <i>I. scapularis</i> , <i>I. pacificus</i> |
| Spotted fever <i>Borrelia</i> | <i>Borrelia miyamotoi</i> | <i>I. scapularis</i> |
| STARI | Unknown | <i>A. americanum</i> |
| Powassan Encephalitis | Powassan Virus, deer tick virus | <i>I. cookei</i> , <i>I. scapularis</i> |
| Rocky Mountain spotted fever | <i>Rickettsia rickettsia</i> | <i>D. variabilis</i> , <i>D. andersoni</i> |
| Relapsing fever | <i>Borrelia spp.</i> (4) | <i>Ornithodoros spp.</i> |
| Tularemia | <i>Franciscella tularensis</i> | <i>Dermacentor</i> , <i>A. americanum</i> |

Human Babesiosis

Babesiosis is a malaria-like illness caused mainly by *Babesia microti*, a protozoan parasite of red blood cells. The protozoan is spread principally by the bite of the blacklegged tick, *Ixodes scapularis*, although cases by blood transfusion or transplacental/perinatal transmission have been reported. White-footed mice carry this parasite in nature. The majority of human cases (82%) have occurred in June, July and August. Signs and symptoms include fever, fatigue, chills, sweats, headache, and muscle pain, beginning usually 1-6 weeks after the tick bite. Human babesiosis has been recognized since the 1960's in parts of Massachusetts (particularly Nantucket and Martha's Vineyard), and parts of Long Island, New York. It also occurs in Wisconsin and Minnesota.



Figure 2. *Babesia microti* in red blood cells (CDC).

The first Connecticut case of human babesiosis was reported from Stonington in 1988. There were 8 cases in 1989 and babesiosis became a physician reportable disease in October 1989 and laboratory-reportable in 1990. A study by Experiment Station scientists in 1989 found no evidence of this pathogen in Fairfield County at that time. From 1991 through 2013, 2,155 confirmed or probable cases of babesiosis have been reported to the Connecticut Department of Public Health (Fig. 2), still mainly in New London County, although the disease is spreading in the state (Fig. 3). From 2001-2010, most (37.1%) cases reported were from residents in New London County, followed by Fairfield County (17.7%). The remaining cases were reported from Middlesex (9.7%), Windham (6.1%), Tolland (4.7%), New Haven (6.9%), Hartford (5.9%), and Litchfield (3.7%) counties.

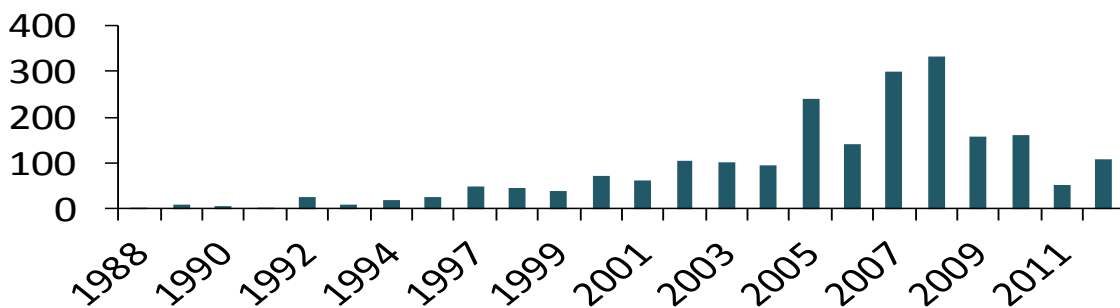


Figure 2. Number of reported cases of human babesiosis in Connecticut, 1988-2012 (Data courtesy Connecticut Department of Public Health).

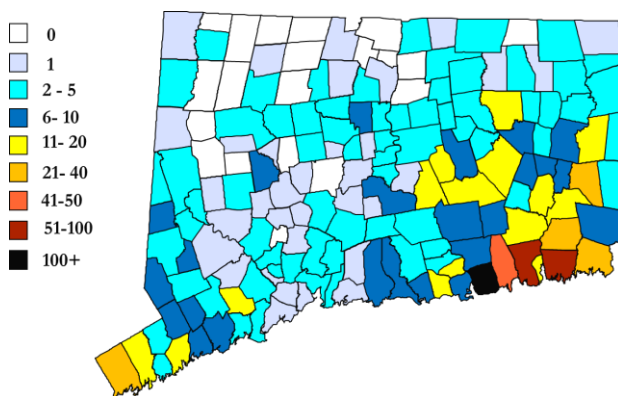


Figure 3. Distribution of reported human babesiosis cases, 2001-2010.

Human babesiosis became a nationally notifiable disease in January 2011 and there were 1,228 and 940 cases reported in 2011 and 2012, respectively. Cases were reported from New England, New York, Wisconsin and Minnesota.

Infection usually produces no or only mild symptoms in healthy children and adults, though all ages can be severely affected. Babesiosis can be severe or fatal in the elderly, immunocompromised individuals, and people without spleens. Death has been reported in about 5% of cases. The greatest incidence of severe babesiosis occurs in those older than 50 years of age

(median age of CT patients was 67 years). Co-infection with the agents of ehrlichiosis or Lyme disease can result in more severe or prolonged illness and overlapping clinical symptoms. Asymptomatic infection can persist for months or even years with a risk of transmission to others through blood donations. Blood donations are not accepted from people with a history of babesiosis.

Diagnosis can be confirmed from blood smears by observing the organism in red blood cells, detection of antibodies, or amplification of the disease agent's DNA by polymerase chain reaction (PCR) methods. Laboratory tests may show anemia and a decrease in blood platelets. Babesiosis in children and adults is treated with quinine and clindamycin. In recent clinical trials, a combination of atovaquone and azithromycin was effective in treating babesiosis in adults with fewer side effects. An exchange transfusion may be used in very severe cases with a high rate (> 5%) of infected red blood cells.

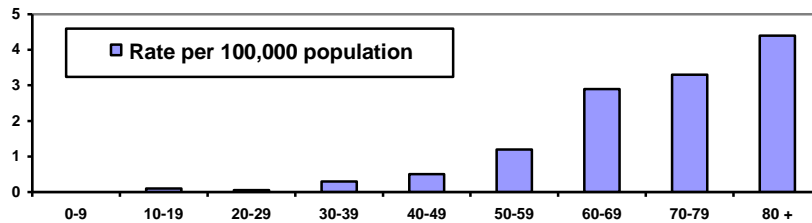


Figure 4. Rate per 100,000 population of babesiosis by age group, 1991-2000 (Data courtesy Connecticut Department of Public Health).

¹Connecticut Epidemiologist 23(2): 9-11; May 2003.

Human Anaplasmosis and Ehrlichiosis

Anaplasmosis and ehrlichiosis are diseases of both animals and humans caused by several bacteria in the genus *Anaplasma* and *Ehrlichia*. Two main forms of these diseases in humans are currently recognized in the United States: human monocytotropic ehrlichiosis (HME), caused by *Ehrlichia chaffeensis*, and human granulocytic anaplasmosis (HGA), caused by *Anaplasma phagocytophilum*, which was reclassified from the genus *Ehrlichia* to the genus *Anaplasma*. Human disease caused by the recently recognized *E. ewingii* has also been reported in the south central United States.

Human monocytotropic ehrlichiosis (HME) was first described in the mid-1980s. The lone star tick, *Amblyomma americanum*, is the vector for *E. chaffeensis* in south central and southeastern regions of the country where most cases of HME occur. White-tailed deer, a major host for all motile stages of the lone star tick, are a reservoir host for *E. chaffeensis*. The lone star tick is common as far north as New Jersey and Long Island, New York. It is also abundant on Prudence Island, Rhode Island. The lone star tick is uncommon in Connecticut with residents living mainly in coastal communities in Fairfield and New Haven Counties occasionally being bitten by these ticks. The DNA of *E. chaffeensis* has been detected in 7.6% (of 106) and 11.5% (of 52) lone star ticks from Connecticut and Prudence Island, respectively. Human granulocytic anaplasmosis (HGA) was first reported from Wisconsin and Minnesota in 1994. Most cases of anaplasmosis have been reported from states where Lyme disease is highly endemic as the blacklegged tick, *Ixodes scapularis* is the principal vector in the northeastern and upper mid-western states. The western blacklegged tick, *I. pacificus*, is the vector along the Pacific coastal states. White-footed mice, and possibly deer, are reservoirs for *A. phagocytophilum*. Most cases of these two diseases occur during the summer in May, June, and July.



Figure 5. *A. phagocytophilum* in cytoplasm of a granulocyte (CDC).

Nonspecific signs and symptoms for both diseases include fever, headache, muscle pain, nausea, vomiting, and malaise. Most patients show a decrease in their white blood cell and blood platelet counts. Illness may be mild, moderate or severe and is generally self-limited, resolving in a few weeks. However, fatalities do occur and treatment should be started promptly. Doxycycline is the drug of choice for the treatment of ehrlichiosis. Although all age groups may be affected, the number of cases increases with age. The highest rates have been observed for patients 60 years of age or older. HME has been confused with Rocky Mountain spotted fever. Diagnosis can be confirmed by a serological blood test, observing the organism in white-blood cells, culturing the organism, or by polymerase chain reaction (PCR).

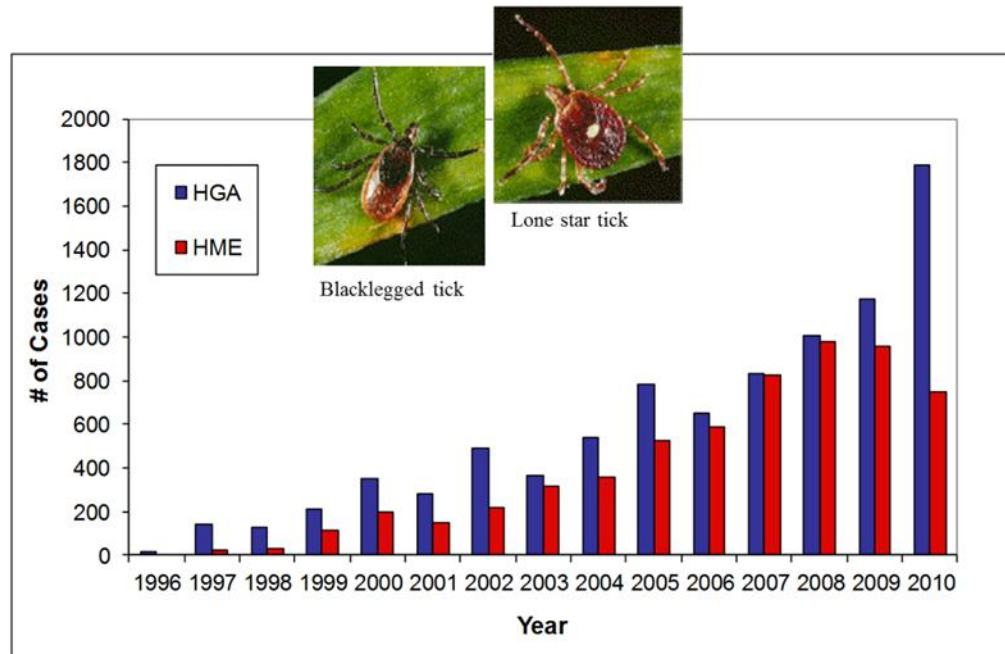


Figure 6. Number of reported cases of human anaplasmosis and ehrlichiosis in the United States, 1996-2010 (Data CDC).

Connecticut, New York, New Jersey, Rhode Island, Wisconsin, and Minnesota account for 90% of the cases with 1,761 cases reported in 2010. Both HGE and HME have been reportable diseases in Connecticut since 1995 and cases of HGA are distributed across all eight Connecticut counties. Cases of HME in Connecticut are possible, as the DNA of *E. chaffeensis* has been detected in lone star ticks in Connecticut. In New York, both HGE and HME have been reported mainly from the lower Hudson River Valley and eastern Long Island.

A diagnosis of anaplasmosis should be considered for patients with a flu-like febrile illness and possible exposure to *I. scapularis* ticks. Co-infections by the HGA and Lyme disease agents have been reported and may result in more severe disease and complicate the clinical presentation and diagnosis of Lyme disease.

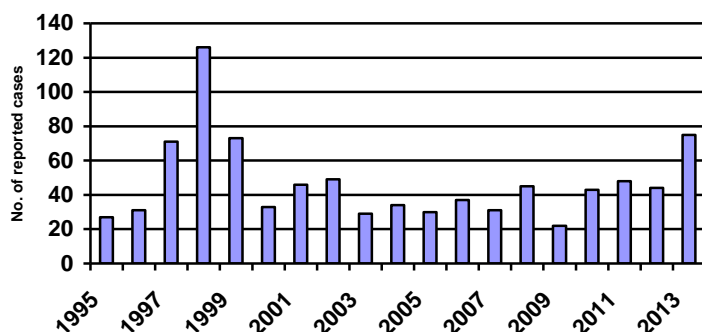


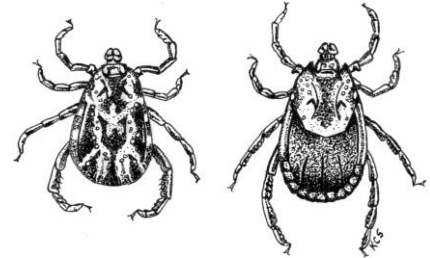
Figure 7. Confirmed cases of HGA reported in Connecticut 1995-2013 (Data courtesy Connecticut Department of Public Health).

Rocky Mountain Spotted Fever



Rocky Mountain spotted fever (RMSF), caused by *Rickettsia rickettsii*, is rare in Connecticut and New England. This disease occurs throughout the United States, but most cases of RMSF are in the South Atlantic and West Central states. However, cases have occurred in New York City. In the eastern U.S., the American dog tick, *Dermacentor variabilis*, transmits *R. rickettsii*.

Figure 8. Far left: Female American dog tick (Photo courtesy Pfizer Central Research); **Figure 9.** Below: Adult American dog ticks (left, male; right, female).



Scientists at the Connecticut Agricultural Experiment Station found that less than 1% of 3,000 American dog ticks examined in Connecticut contained spotted fever-group organisms. Not all spotted fever-group rickettsiae are infectious to humans. Between 1983 and 1993, 27 human cases were reported to the Connecticut Department of Public Health. Seventy percent of these cases were in Fairfield and New Haven counties. Between 1994 and 1999, an additional 21 cases were reported.

Symptoms usually appear within 2 to 9 days after a tick bite. Symptoms include sudden fever (90% of 1989 cases), headache (89% of cases), muscle pain (83% of cases), and rash (78% of cases). The rash is noticed 2-4 days after illness begins and may include the palms (50% of cases) and soles of the feet. Prompt antibiotic treatment (doxycycline is the drug of choice) for suspected cases of RMSF is important, because it can be fatal in 15-20% of untreated cases. Delays in diagnosis because of the absence of a rash or no knowledge of a tick bite could be dangerous for the patient. In recent years, about 1-4% of cases in the United States have been fatal. A clinical diagnosis may be confirmed by antibody blood tests.

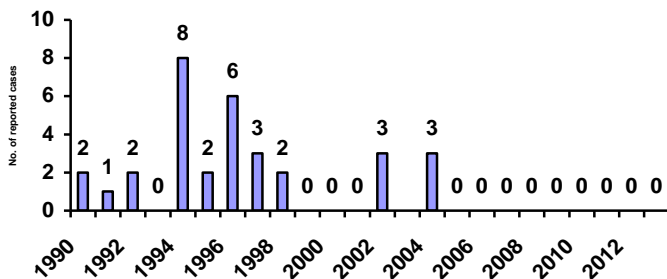
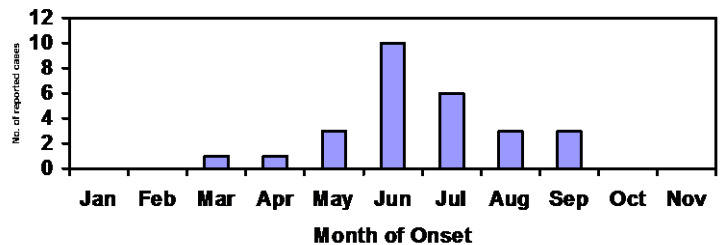


Figure 10. Reported cases of Rocky Mountain spotted fever in Connecticut, 1990-2013. (Data courtesy Connecticut Department of Public Health).

Figure 11. Reported cases of Rocky Mountain spotted fever in Connecticut by the month on onset between 1983 and 1993 (Data courtesy Connecticut Department of Public Health).



Tick Paralysis

The feeding by certain *Dermacentor* ticks can cause a progressive paralysis, which is reversed upon removal of the tick. Recovery is usually complete. The paralysis is not caused by a disease pathogen, but by a toxin produced by the tick. Paralysis begins in the extremities of the body with a loss of coordination. It progresses to the face with corresponding slurred speech, and finally shallow, irregular breathing. Failure to remove the tick can result in death by respiratory failure. Most cases of tick paralysis are caused by the Rocky

Mountain wood tick (*Dermacentor andersoni*) in northwestern states. The American dog tick has also been known to cause tick paralysis.

Tularemia

The bacterium, *Francisella tularensis*, that causes tularemia (Rabbit Fever) is transmitted mainly by the bite of several species of ticks and contact with infected animals. Highly infectious, it is also considered a potential biological warfare agent. The disease may be contracted while handling infected dead animals, eating under cooked infected meat, an animal bite, drinking contaminated water, inhaling contaminated dust, contact with contaminated materials, or bites from deer flies and horse flies. Tularemia occurs naturally throughout the United States, but most cases are reported from the south central states of Missouri, Arkansas, Kansas, and Oklahoma. There has been a decline in the number of cases over the past several decades. National reporting stopped after 1994 and resumed in 2003 with 1,304 cases reported nationally between 2003 and 2011. Reports of tularemia in New England are not common. Connecticut and Vermont had one case each in 2009. However, Massachusetts had 89 cases. There is a persistent focus of tularemia on Martha's Vineyard, an island off the coast of Massachusetts. Many cases were pneumonic and appear related to gardening or landscape activities.

Ticks associated with tularemia are the American dog tick, *D. variabilis*; lone star tick, *A. americanum*; and Rocky Mountain wood tick, *D. andersoni*. Most cases occur during the summer (May-September). The clinical symptoms of tularemia depend upon the means of infection. With infection by a tick, an ulcer often occurs at the site of the bite with occasional swelling of the regional lymph nodes. Fever is the most commonly reported symptom. Diagnosis can be confirmed by an antibody blood test. Streptomycin or gentamicin are generally used for the treatment of tularemia. Tetracycline may also be used, but it is less effective and there can be relapses.

Other Tick-Associated Diseases

Powassan (POW) Virus is the only member of tick-borne (TBE) group viruses present in the United States and Canada. It was first described in 1958 in Powassan, Ontario. The principal vector is the tick *Ixodes cookei*, which feeds on a variety of small and medium-sized mammals, especially carnivores such as woodchucks, raccoons, skunks, foxes, etc., and occasionally people. Cases of Powassan encephalitis are rare and sporadic, but may be more common than previously realized. While there were only 24 known cases in North America from 1958 to 1994 (mainly in the eastern U.S. and Canada, of which six were fatal), additional cases were identified in Maine and Vermont from 1999-2001 as a result of testing for West Nile virus, and a total of 58 cases have been documented from 2001-2013, mainly in Michigan, Minnesota, and New York. Cases of Powassan encephalitis may result in severe long-term morbidity and has a fatality rate of 10-15%. Patients generally have a history of tick bite, or a history of exposure to tick habitat or exposure to hosts such as

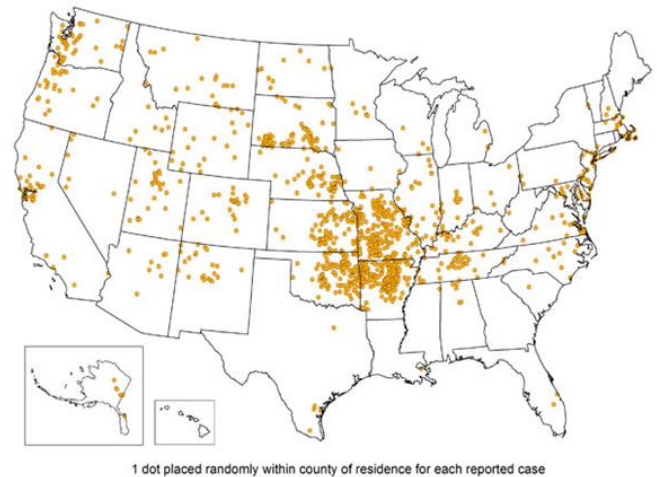


Figure 12. Distribution of reported human cases of tularemia, 2003-2010 (CDC).



Figure 13. Characteristic type of ulcer or lesion from tick transmitted tularemia (CDC).

squirrels, skunks, or woodchucks. Two woodchucks and two skunks at the home of a Maine patient tested positive for antibodies to POW virus.

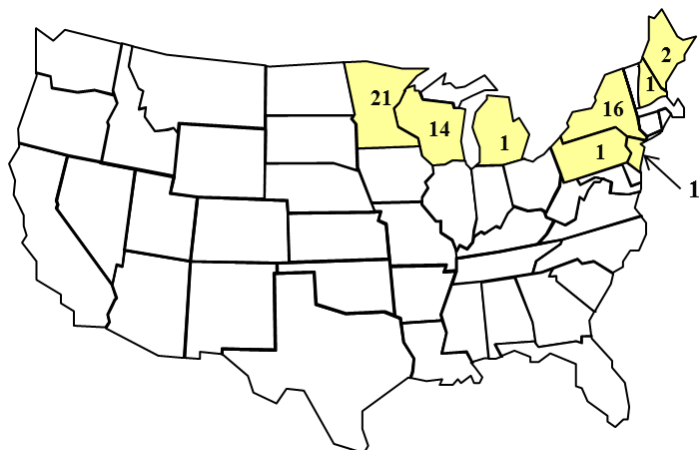


Figure 14. Cases of Powassan encephalitis in the United States, 2001-2013 (CDC).

A virus extremely similar to the POW virus, called the deer tick virus (DTV) was isolated from two *I. scapularis* and is considered a strain (Lineage II) of the Powassan virus. Infection rates with DTV in blacklegged tick adults averages about 1.4%. Unlike the other pathogens transmitted by *I. scapularis*, transmission of this virus is quick, within 15 minutes of attachment.

Relapsing Fever, caused by over 10 *Borrelia* species worldwide, is transmitted by soft ticks (tick family Argasidae) of the genus *Ornithodoros* in the United States. These relapsing fever ticks are found through the western states and are associated with rodent burrows, nests, and caves. The ticks can live for many years without feeding. Human cases are relatively uncommon and are often associated with people staying in shelters or cabins infested with these ticks. The disease is characterized by cycles of high fever and is treated with antibiotics.

Blacklegged ticks have been found to transmit a *Borrelia* spirochete, named *Borrelia miyamotoi*, that belongs to the relapsing fever group of *Borrelia* rather than the Lyme *Borrelia* group. The spirochete was first described in Connecticut in 2001 and found to be present in *I. scapularis* and white-footed mice. However, human infections weren't described until 2011 in Russia and several human cases were subsequently reported from the northeast U.S. in 2013. The prevalence of infection with *B. miyamotoi* in the blacklegged tick is lower than that of *B. burgdorferi*, about 1-2% on average. Clinical infections manifest as a viral-like illness with fever, fatigue, muscle aches, chills, sweats and nausea. It is treated with doxycycline, ceftriaxone, or penicillin.

Colorado Tick Fever, caused by a virus, occurs in mountainous areas above 5,000 feet in the western United States and Canada. There are 200-400 cases each year. Scientists believe cases are underreported. The virus is transmitted by female Rocky Mountain wood ticks. Symptoms begin with an acute high fever, often followed by a brief remission, and another bout of fever lasting 2-3 days. Other symptoms included severe headache, chills, fatigue, and muscle pain. Illness may be mild to severe. Treatment is symptomatic. Recovery takes several weeks to occasionally months.

Heartland Virus, a new phleovirus associated with severe febrile illness, was described from 2 human cases in Missouri in 2009. The patients presented with fever, fatigue, anorexia, and diarrhea and had a low white blood cell and platelet count. Both had a history of multiple tick exposures. The new virus was isolated from lone star ticks, *Amblyomma americanum*, which is the presumptive vector. An additional seven cases have been reported from Missouri, Tennessee, and Oklahoma in 2012, 2013, and 2014.

STARI (Southern Tick-Associated Rash Illness), got its name from the Lyme-like rash and illness associated with bites by the lone star tick. The cause of STARI remains unknown.

