Fall and rise of Lyme disease and other *Ixodes* tick-borne infections in North America and Europe

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Lyme disease is a spirochaetal infection with acute and chronic manifestations. Lyme disease and other infections transmitted by *Ixodes* species ticks are increasing in temperate and Holarctic regions of the Northern hemisphere. These zoonotic infections are most commonly acquired in suburban residential areas and outdoor recreation areas close to cities. Different enzootic cycles, which include a variety of large and small mammals as well as migratory birds, maintain and distribute in nature the *Borrelia* species that cause Lyme disease. The rise in cases of Lyme disease and the other *Ixodes* tick-borne infections is, in part, the consequence of reforestation and the increase in deer populations in developed countries.

What we now call ‘Lyme disease’ or ‘Lyme borreliosis’ was first described earlier this century in Europe under a variety of other names, such as ‘erythema chronicum migrans’ (ECM) or ‘Bannwarth’s syndrome’. Few practitioners now, even in Europe, use these other terms, so complete and widespread has been ascendancy of a name that stems from a town in the northeastern US. Ironically, the 17th century founders of Lyme, Connecticut, originally took for their village the name of an English seaside town.

The story of Lyme disease terminology is also a metaphor for the evolution of the infection. At first this disease appeared to be restricted to Europe; the first Americans reported to have ECM acquired their infections in Europe and not in the US. Later, Steere and colleagues described the infection so comprehensively to leave little doubt that, if this disorder had occurred in North America previously, it had escaped the general notice of generations of physicians. After the aetiological agent of Lyme disease was discovered, first in the US and soon after in Europe, comparison of the isolates suggested that the infection had recently been imported to North America from Europe. More recent studies, however, indicate these organisms have been long established on both continents.
Whatever its geographical origins, Lyme disease is at present the most common vector-borne disease in Europe and the US. In the US, approximately 10,000 cases are officially reported annually; the actual incidence is likely to be 5 times as many. Trailing Lyme disease in numbers but transmitted by the same, or similar, ticks are the infections erhrlichiosis, babesiosis, and viral encephalitis. While Lyme disease rarely, if ever, is fatal, cumulative morbidity from untreated infection has been considerable. Contributing to the popular concern about Lyme disease is the fact that the usual victims of the infection are suburban in residence and middle class or higher in socio-economic status.

Although some of the increased incidence of Lyme disease can be attributed to recent migrations of humans into previously uninhabited areas, a more important factor has been a different kind of change in the landscape: the return to forests of lands formerly used for agriculture or industry.

Biology

The cause of Lyme disease is a spirochaete in the genus *Borreli*a. *Borreli*a species shuttle between an arthropod vector, which is usually a tick, and a mammalian or avian reservoir. The other major human disease caused by *Borreli*a species spirochaetes is relapsing fever.

| Table 1 Vectors of Lyme disease *Borreli*a species (underlined) and related species |
|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| **Tick**                                     | **Distribution**                             | **Borreli*a spp**                             |
| Ixodes ricinus*,#                            | Western & central Europe                      | afzelii, burgdorferi, garinii, valaisiana, group DN127 |
| I. scapularis*,#                             | Eastern & central US & Canada                 | burgdorferi, group DN127                      |
| I. pacificus*,#                              | Far-western US & Canada                       | burgdorferi, group DN127                      |
| I. persulcatus*,#                            | Far-eastern Europe & Asia                    | afzelii, garinii, miyamotoi, garinii          |
| I. uriae                                      | North & South Atlantic                       | afzelii, burgdorferi                          |
| I. hexagonus                                  | Western & central Europe                     | burgdorferi                                  |
| I. minor                                      | Southeastern US                               | burgdorferi                                  |
| I. affinis*                                   | Southeastern US                               | andersonii, burgdorferi                       |
| I. dentatus                                   | Northeastern US                               | Group DN127                                  |
| I. spinipalpis                                | Western US                                   | japonica                                     |
| I. ovatus                                     | Japan                                        | afzelii                                      |
| I. granulatus                                 | China                                        | garinii                                      |
| I. tanuki                                     | Japan                                        | tanukii                                      |
| I. turdus                                     | Japan                                        | turdæ                                        |
| I. nipponensis*                               | Korea                                        | afzelii, garinii, valaisiana, garinii         |
| Haemaphysalis spp.                            | China                                        |                                              |

*Member of the Ixodes ricinus complex of species

#Frequent vectors of Lyme disease *Borreli*a species to humans
Fall and rise of Lyme disease

Deer and other large mammals

Tick eggs → Not infected → Adult ticks → Infected

Ixodes ticks that frequently feed on humans in suburban and rural areas

Larval ticks → Infected → Nymphal ticks

Rodents, other small mammals, and birds

Nymphal ticks → Infected → Larval ticks

Ixodes ticks that rarely feed on humans

Adult ticks → Tick eggs

Fig. 1 This diagram shows the life cycles of *Ixodes* species ticks that frequently or rarely bite humans (Table 1) and the reservoir animals for Lyme disease *Borrelia* species that they may have in common. 'Infected' means that in the change from the one stage to another the infection is acquired, passed on, or is lost. For instance, larval ticks acquire the infection after feeding on infected reservoir mammals or birds, but infected adult ticks do not pass the infection on to their progeny through the eggs. Humans are inadvertent hosts and not critical for maintaining the ticks in nature. On the other hand, the small mammals, bird, and a large mammal, usually a deer, are critical.

Most *Borrelia* spp. humans are inadvertent hosts and transmission dead-ends for the infecting spirochaete population. This means that to understand the epidemiology of this infectious agent we need to know its epizootology, that is, what happens in nature among animals.

Species of *Borrelia* that cause Lyme disease have been found in a variety of ticks (Table 1)\(^9,17-24\). With the exception of two species of *Haemaphysalis* in China, the tick vectors of these *Borrelia* spp. are in the genus *Ixodes*, a type of hard ticks. Table 1 lists several different types of *Ixodes*...
ticks. Only those of the *I. ricinus* complex of ticks are known to transmit the infection to humans. The vector species in this complex are *I. ricinus* (sheep tick), *I. scapularis* (deer or black-legged tick), *I. pacificus* (western black-legged tick), and *I. persulcatus* (taiga tick). The other species listed in Table 1 seldom bite people. Yet species, such as *I. uriae*, *I. hexagonus*, and *I. spinipalpis*, are important for maintaining the Lyme disease agents in nature by transmitting the *Borrelia* spp. among animals and by carrying them from one location to another (Fig. 1). For example, *I. uriae* ticks are the *Borrelia* vectors for a cycle involving seabirds that migrate north and south between subarctic and subantarctic regions.

The types of *Borrelia* presently known to cause Lyme disease are classified into three species: *B. burgdorferi*, which occurs in North America and western Europe; *B. afzelii*, which occurs in western and central Europe and parts of Russia; and *B. garinii*, which occurs in Europe, across Russia, and in northern Asia. These *Borrelia* species can be found in more than one *Ixodes* species (Table 1). For instance, *I. ricinus* ticks have been found to carry at least four different species, sometimes two or more at a time. Table 1 also lists species of *Borrelia*, such as *B. andersonii* in North America, *B. valaisiana* in Europe, and *B. japonica* in Asia, that are not established disease agents for humans. This is because they are associated mainly with ticks that rarely feed on humans or because they are inherently non-infectious or non-virulent for people. Some *Borrelia* strains, such as DN127 and similar isolates, have not been given a separate species name yet.

The geographic areas providing a risk for Lyme disease can be predicted by understanding the tick vectors, the hosts for the ticks, and the reservoir for the spirochaetes. *I. ricinus* complex ticks proliferate and survive between temperatures of -10°C and +35°C, and then only tolerate the extremes for short periods. The relative humidity in the atmosphere should be 80% or greater, and the soil should be near-saturated with water. These ticks flourish in areas with forests and damp soil covered by a dense layer of undergrowth. They also do well in moist bushy and tall grassy areas that border forested lands.

One of the characteristics of ticks that transmit Lyme disease to humans is that they feed on a variety of hosts, including large and small mammals, birds, and reptiles (Fig. 1). In general, the immature stages of larva and nymph feed on small mammals, ground feeding birds, and lizards. The adults usually feed on large or medium-sized mammals and, less frequently, on birds. Some ticks are closely associated with only one type of host by reason of anatomy, physiology, or behaviour. But *I. ricinus* complex ticks are less discriminating in their tastes. The 'preferred' hosts may be those animals that are both abundant in the area and not very efficient at grooming themselves.
There are numerous actual or potential reservoirs for Lyme disease *Borrelia* spp. and closely related species (Table 1)\(^{17,18,23,29-32}\). Indeed, this group of *Borrelia* spp. is notable for its wide host range, which includes a variety of small mammals and birds, but not reptiles. Most other *Borrelia* spp. have more limited host ranges\(^6\). The ability of Lyme disease *Borrelia* spp. to infect so many types of animals may explain in part its current success in adapting to local and global environmental changes.

For the *I. ricinus* complex ticks to be maintained within an area and to spread to new areas, they need large free roaming animals as hosts. In most areas of the world where Lyme disease is common, deer serve this role\(^{33-35}\). Deer themselves are not suitable reservoirs for maintaining the spirochaete in nature, but by providing the adult ticks with a meal, a necessity before reproduction can occur, the presence of deer in an area assures a new generation of ticks (Fig. 1).

**Evolution**

The increase of Lyme disease in North America has paralleled the explosive growth of deer populations on that continent over the last several decades\(^2\). The Lyme disease agent and vectors had probably been present in North America when the first European settlers arrived but, through hunting and clearing of the forests for agriculture and industry, the numbers of deer and the ticks that parasitized were drastically reduced. Forests and woodlots have return to regions of North America and Europe where high technology parks and residential areas have replaced farms and smokestack factories. Contributing to the increase in deer herds in developed countries in the North has been an absence of significant predators, other than the sports hunter.

The reduction of deer and their ticks in the northeastern US probably produced an evolutionary bottleneck for *B. burgdorferi* in that region. Whereas other parts of North America, such as southern and the far-western US, have *B. burgdorferi* strains of several different genetic types, the strains of *B. burgdorferi* in *I. scapularis* ticks of New York, Connecticut, and nearby states are more limited in diversity\(^9\). When deer and tick populations increased again, the *B. burgdorferi* strains that proliferated represented a few clones or a single clone. Curiously, *B. burgdorferi* isolates of Europe have been found to be no more genetically diverse than those of the northeastern US, a finding that contrasts with the greater genetic variety noted among *B. azelii* and *B. garinii* isolates of Europe and Asia\(^8\). If *B. burgdorferi* was imported from North America to Europe, it was more than a century ago; museum
specimens of European ticks from 1884 revealed the presence of both B. garinii and B. burgdorferi.

Pathogenesis and clinical manifestations of Lyme disease

Infection almost always begins with a tick bite. Maternal-fetal transmission is rare among humans, and transmission by oral, faecal, respiratory, urinary, or sexual routes or by fomites does not occur. The biting ticks for humans are usually in the nymphal stage of their life cycle (Fig. 1). Infected adult ticks also bite humans but this stage is less important as a vector for humans. For one thing, adults are more easily detectable than the tiny nymphs. Moreover, in geographic areas far enough north to have four seasons, the adults tend to feed in the Spring and Fall when fewer people are active outdoors.

In highly endemic areas, up to 70–80% of the ticks are infected with B. burgdorferi or other species. For the first 24–48 hours of feeding, the spirochaetes already present in the tick's intestine remain dormant. As the intestine fills more with blood, the spirochaetes begin to multiply and migrate through the intestinal wall into the body fluid that bathes the internal organs. From there, the spirochaetes move to the salivary glands of the ticks. With multiplication and this passage, the predominant surface antigens change from one pair of lipoproteins, OspA and OspB, to a single abundant lipoprotein, OspC.

The spirochaetes enter the skin with the tick's saliva. Dissemination through the skin or blood may occur a few days later. It is possible that spirochaetes also disseminate via lymph channels or peripheral nerves. Whatever the route, the bacteria can be found in experimental animals and in infected humans at sites distant from the tick bite within days to weeks of the start of the infection. The infection can be roughly divided as three stages: early localized; early disseminated; and late (Table 2).

At the tick bite, the majority of infected humans have erythema migrans, the flat, nonpainful erythema often with central clearing or concentric ring pattern. This is early localized infection and may be accompanied by mild constitutional symptoms or lymphadenopathy. As the spirochaetes move peripherally, the rash expands over several days to diameters of several centimeters. At one time, this localized skin rash was considered synonymous with Lyme disease, but similar or identical rashes can occur in the absence of B. burgdorferi transmission. Another sign of early localized infection in Europe, but not in North America, is a benign lymphocytoma of ear lobe or nipple. In Europe, the initial region of invasion of the skin may become a chronic inflammatory condition known as acrodermatitis chronica atrophicans.
Table 2  Clinical stages and manifestations of Lyme disease

<table>
<thead>
<tr>
<th>Period</th>
<th>Time from onset</th>
<th>Manifestations</th>
<th>Treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early localized</td>
<td>1–8 weeks</td>
<td>Solitary erythema migrans</td>
<td>7–21 days</td>
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<td></td>
<td></td>
<td>Regional lymphadenopathy</td>
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<td></td>
<td></td>
<td>Lymphocytoma</td>
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<td></td>
<td></td>
<td>Mild constitutional symptoms</td>
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<tr>
<td>Early disseminated</td>
<td>3–26 weeks</td>
<td>Multiple erythema migrans</td>
<td>14–30 days</td>
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<td></td>
<td></td>
<td>Cranial neuritis</td>
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<td></td>
<td></td>
<td>Meningoencephalitis</td>
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<td></td>
<td></td>
<td>Radiculitis</td>
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<td></td>
<td></td>
<td>Polyarthritis</td>
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<td></td>
<td></td>
<td>Carditis</td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>≥ 6–12 months</td>
<td>Oligoarticular arthritis</td>
<td>21–60 days</td>
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<tr>
<td></td>
<td></td>
<td>Acrodermatitis chronicum atrophicans</td>
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<tr>
<td></td>
<td></td>
<td>Meningoencephalitis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Peripheral neuropathy</td>
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</tbody>
</table>

Organs and tissues likely to be seeded with *B. burgdorferi* during dissemination are the following: (i) the heart; (ii) large joints, such as the knee; (iii) the peripheral and central nervous system; and (iv) distant parts of the skin\(^3\text{,}^{4,41}\). More likely than not, the affected limb in a case of neuropathy or arthritis will be the same limb bitten by the tick.

Oligoarticular arthritis with frank joint swelling appears to be more common with *B. burgdorferi* than with other species of Lyme disease agents. On the other hand, certain strains of *B. garinii* are frequently represented among isolates from the cerebrospinal fluid, and *B. afzelii* is more likely to be confined to the skin than the other two species\(^43,44\).

Spirochaetes have been few in number in whatever tissue they have been found\(^2,41\). For instance, at the height of the blood infection, the number of spirochaetes in a milliliter of blood is about 1000. Pathologists examining histological preparations with a silver stain, such as Warthin Starry, or immunofluorescence, may have to search many fields to find an organism in the heart or skin. A consequence of this low bacterial burden and slow progression is an infectious disease with low fever, low mortality, and a course measured in weeks to years rather than days.

Spirochaetes express OspC during the early phase of the infection in humans and experimental animals. IgM antibodies to OspC appear beginning about 2 weeks after the start of infection\(^45\). Selection by the immune systems of countless reservoir animals likely accounts for the considerable strain-to-strain differences in OspC sequences and epitopes. OspA, which is expressed within the tick and seldom if ever within mice, shows less sequence variability between strains\(^46\).
Resurgent/emergent infectious diseases

The surface proteins of the spirochaetes during late or latent infection are not known but may be related to variable antigens of relapsing fever Borrelia spp. The bacteria are even fewer in number than during acute infection. The inflammation that occurs in a knee or patch of acrodermatitis chronicum atrophicans is out of proportion to the numbers of organisms present. While some investigators have proposed a predominantly intracellular location for the spirochaetes during late or latent infection, the bulk of experimental evidence indicates that while the spirochaetes may be sequestered in immunologically protected locations, such as brain and eye, the majority, if not all, remain extracellular.

When infections are localized, oral antibiotics for 2–4 weeks are sufficient to cure almost all patients. After dissemination has occurred, treatment is more difficult. The neurotropism and slow growth of the Lyme disease Borrelia spp. mean that treatment with antibiotics that penetrate the central nervous system and for durations of a few weeks are needed. Successful therapy with β-lactam antibiotics of these infections is another indication that intracellular localization is not a prominent feature of the pathogenesis of this infection.

Other emerging tickborne infections

The same Ixodes ticks that transmit Lyme disease to humans are vectors for at least three other infectious agents: Ehrlichia phagocytophila, Babesia microti, and tickborne encephalitis (TBE) virus. The same factors in the increase in Lyme disease, that is, reforestation and growth of deer populations, also explain changes in the incidence of infections caused by these microorganisms. Co-infections with two or more of these organisms are not uncommon in people living in or visiting the endemic areas.

Ehrlichiae are obligate intracellular Gram-negative bacteria related to rickettsiae. Only recently have the human pathogens been cultivated in the laboratory. There are several different species of Ehrlichia. Representatives are found on different continents and associated with different types of reservoir animals. In North America, E. phagocytophila, which is transmitted by I. scapularis and I. pacificus ticks, causes human granulocytic ehrlichiosis. The reservoir is the field mouse, Peromyscus leucopus, that harbours B. burgdorferi. Human granulocytic ehrlichiosis is suspected to also occur in Europe. Two other ehrlichial diseases of humans are human monocytic ehrlichiosis, which is caused by E. chaffeensis and transmitted by other types of ticks in central and southern US, and Sennetsu fever, which is caused by E. sennetsu in Japan and has
an as yet indecipherable transmission cycle. Features distinguishing human granulocytic and monocytic ehrlichiosis from Lyme disease are higher body temperature, leukopenia, and thrombocytopenia.

TBE is a spring–summer encephalitis caused by a flavivirus in the temperate and sub-arctic regions of Eurasia. It is one of the few arboviral infections transmitted to humans by ticks, in this case *I. ricinus*, *I. persulcatus*, and possibly *I. ovatus*. A TBE-like virus has recently been identified in North America, where this type of tickborne infection had not been frequently observed.

Babesiosis resembles malaria in many aspects. The piroplasms that cause babesiosis are intraerythrocytic parasites. Infected individuals have fever and haemolytic anaemia. Those without spleens have more severe courses and may die of the complications of acute infection. There are many different species of *Babesia*, and the distribution of these infections is worldwide. *B. microti* in North America and *B. divergens* in Europe are the commonest agents of babesiosis for humans. The reservoirs for both *Babesia* species are rodents. The vectors are *I. scapularis* for *B. microti* and *I. ricinus* for *B. divergens*. Unlike ehrlichiosis, which usually is a shortlived infection if the patient survives, babesiosis can cause a persistent infection and may, in endemic areas, be another infectious risk of blood transfusion.

**Prevention**

Lyme disease and the other infections are one of the costs we bear for living close to nature and for the ‘re-greening’ of parts of Europe and North America. These diseases are not spread from person-to-person and, thus, can be prevented by avoiding exposure to ticks, or by taking personal precautions against tick bites when in an endemic area. For instance, a resident of New York City or Vienna has a very low to nonexistent risk of getting Lyme disease, babesiosis, ehrlichiosis, or TBE. If they go to the New Jersey seashore or the Vienna Woods, repellents can be sprayed and light-coloured trousers and a long-sleeved shirt can be worn. A nightly check for ticks can further reduce the odds of getting ill.

However, the suburban environment for the vector ticks means that exposure may be unavoidable for those who on a daily basis work outdoors or live in the area. Reduction of deer and tick populations can be achieved but the current strategies for this, such as deer eradication or community pesticide use, are not socially acceptable to one constituency or another. A vaccine has been available to prevent TBE, and a recombinant vaccine based on the OspA protein has just completed successful human trials in the US.
Resurgent/emergent infectious diseases

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