Lyme borreliosis in Europe

A Rizzoli (annapaola.rizzoli@iasma.it)[1,2], H C Hauffe[1,2], G Carpi[1], G I Vourc'h[3], M Neteler[1], R Rosà[1]
1. Department of Biodiversity and Molecular Ecology, Research and Innovation Centre, Fondazione Edmund Mach, San Michele all'Adige (Trento), Italy
2. Both authors contributed equally to this work.
3. Unité d'Epidémiologie Animale, Institut National de la Recherche Agronomique (INRA), St Genès Champanelle, France

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Despite improvements in prevention, diagnosis and treatment, Lyme borreliosis (LB) is still the most common arthropod-borne disease in temperate regions of the northern hemisphere, with risk of infection associated with occupation (e.g. forestry work) and certain outdoor recreational activities (e.g. mushroom collecting). In Europe, LB is caused by infection with one or more pathogenic European genospecies of the spirochaete *Borrelia burgdorferi* sensu lato, mainly transmitted by the tick *Ixodes ricinus*. Recent surveys show that the overall prevalence of LB may be stabilising, but its geographical distribution is increasing. In addition, much remains to be discovered about the factors affecting genospecific prevalence, transmission and virulence, although avoidance of tick bite still appears to be the most efficient preventive measure. Uniform, European-wide surveillance programmes (particularly on a local scale) and standardisation of diagnostic tests and treatments are still urgently needed, especially in the light of climate change scenarios and land-use and socio-economic changes. Improved epidemiological knowledge will also aid development of more accurate risk prediction models for LB. Studies on the effects of biodiversity loss and ecosystem changes on LB emergence may identify new paradigms for the prevention and control of LB and other tick-borne diseases.

Introduction

Lyme disease (or Lyme borreliosis, LB) is a multisystemic inflammatory disorder caused by an immune response to the pathogenic genomic species of *Borrelia burgdorferi* sensu lato (sl), which are transmitted by the hard ticks of the *Ixodes ricinus* species complex [1,2]. Despite substantial efforts to improve surveillance and control of LB in recent decades, it is still the most prevalent arthropod-borne disease in the temperate regions of the northern hemisphere [1], with approximately 65,500 patients annually in Europe (including notified cases and qualified estimates per country from 1987 to 2006, although the years covered vary) [3]. In the last few decades, the incidence of LB has been increasing in some countries and areas of Europe, but not in others. However, the effect of improvements in diagnosis and reporting of the disease on such statistics is unknown (see [3] for a review). Less controversial is the fact that the geographical distribution of LB is still expanding, especially towards higher altitudes and latitudes ([3] and references therein). Moreover, LB is likely to become an increasingly relevant health risk in the near future due to complex interactions between diverse environmental and socio-economic factors, which will affect various aspects of disease ecology and epidemiology, as outlined below.

The importance of LB has led to a surge in research effort, on all aspects of LB biology, ecology and epidemiology. The purpose of this review is to summarise the most recent findings (especially those of the last five years) and indicate where there is still controversy and lack of knowledge.

Transmission, epidemiology and clinical symptoms

Ecology and disease transmission

The ecology of LB is based on interactions between the pathogenic agent (*B. burgdorferi* sl), the vector (*Ixodes* ticks) and vertebrate reservoir hosts.

The *B. burgdorferi* sl complex currently comprises at least 18 genospecies [2]. In Europe, several of these are pathogenic to humans: *B. afzelii, B. garinii, B. burgdorferi* sensu stricto (ss), *B. bavariensis* (previously *B. garinii* OspA serotype 4) and *B. spielmanii*, while the pathogenicity of others such as *B. lusitaniae, B. valaisiana*, and *B. bissetii* is still uncertain [4]. In ticks, *B. afzelii and B. garinii* are the most common European circulating genospecies, followed by *B. burgdorferi* ss and *B. valaisiana* [5], whereas *B. lusitaniae* has a more focal distribution, especially in the Mediterranean basin [6]. Several genospecies may also be present simultaneously in a vector [5]. Although all pathogenic genospecies may cause erythema migrans (a red rash or patch on the skin), different genospecies are also associated with other clinical manifestations of the disease: *B. burgdorferi* ss is most often associated with arthritis and neuroborreliosis, *B. garinii* with neuroborreliosis, and *B. afzelii* with the chronic skin condition acrodermatitis chronica atrophicans [7].

The distribution and prevalence of various genospecies is known to vary on a local and regional scale, both temporally and spatially [5,8] with a higher biodiversity of genospecies between 4 °W and 20 °E, where there is a higher prevalence of ticks infected with *Borrelia* [8]. In addition, there is an uneven geographical distribution of LB manifestations across Europe: in Norway, for example, 71% of LB cases have neuroborreliosis, while in Germany, 85% of cases have erythema migrans [9]. *Borrelia* genospecies are also associated with particular reservoir hosts: for example, *B. afzelii* and *B. bavariensis* tend to be associated with rodents, *B. valaisiana* and most *B. garinii* serotypes with birds [4], *B. lusitaniae* with lizards and *B. spielmanii* with dormice [10]. On the basis of the sequence of housekeeping genes, it has been shown that the genetic structuring of *Borrelia* genospecies is dependent on the migration pattern of host populations [11], so that genospecies that are associated with birds are dispersed further than those associated with mammals. *Borrelia* can also be classified according to outer surface protein (Osp) sequences (there are 21 OspC major groups) and recent research suggests that these genotypes are ecologically and epidemiologically diverse [12,13]. However, despite its relevance to development of preventive measures and treatment, knowledge of the distribution and symptoms associated with each genospecies and genotype is still far from complete, and the genetics of *Borrelia* transmission and virulence are starting to be unravelled [10,14].

The bridge vectors (vectors that feed on more than one host species) that transmit *B. burgdorferi* to humans in Europe are primarily the tick *I. ricinus* and, less frequently, *I. persulcatus*. Ticks have three life stages: larva, nymph and adult, each lasting one to two years. Hard ticks seek hosts by 'questing' or climbing up grass stems or onto the edge of leaves, and extending their forelegs in response to thermal and chemical cues. They then drop or crawl onto hosts that pass or brush their forelegs. Larvae, nymphs and female adult ticks take one blood meal, lasting several days, from a vertebrate host (while adult males mate with feeding adult females). Between meals, the larvae and nymphs remain in leaf litter until moulting is complete, while adult females lay a batch of eggs in the litter then die). *Borrelia* may be acquired by a tick from feeding on an infected host or when feeding very close to an infected tick on the same, even uninfected, host (transmission by co-feeding) or from the site where an infected tick has recently finished its blood meal, (transmission by localised extended co-feeding) [10]. Once infected, competent tick species retain the pathogen even between moults, effectively transmitting the pathogen to the next feeding stage and/or to a host.

The most recent meta-analysis of surveillance data indicates that the overall mean prevalence of *Borrelia* infection in ticks in Europe is 13.7% (range: 0–49.1) although the prevalence is higher in adults (18.6%) than in nymphs (10.1%); Central Europe (Austria, Czech Republic , Germany, Switzerland, Slovenia and Slovakia) has by far the highest rates (in nymphs, >11%; in adults, >20%) [5]. In fact, peak prevalence has recently been confirmed between 5 °E and 25 °E longitude [8].

The capacity of ticks to transmit *Borrelia* to various hosts is influenced by a series of factors, including those intrinsic to ticks (e.g. questing behaviour, diapause duration, host preference, mating strategy [15] and tick density [16]), as well as extrinsic biotic and abiotic factors (e.g. climatic conditions, vegetation type and management, and host behaviour, abundance, susceptibility, tick burden and reservoir competence [17-20]). It has been shown that ticks infected with *Borrelia* may actually have an increased host-finding capability [21]. The tick–host interaction is particularly important for *Borrelia* infection dynamics, since the feeding tick secretes salivary vasoactive mediators and immunomodulators that facilitate the transmission of the pathogen from the tick to the host and vice versa [22]. Transmission efficiency can also vary in relation to *Borrelia* genospecies and duration of host infectivity [23,24].

Tick nymphs are mainly responsible for transmitting *Borrelia* to humans and quest most actively from spring to autumn in microenvironments with more than 85% relative humidity, such as in deciduous or mixed woodland with high ecotonal indices [17,25], as well as in suburban and urban environments [26] and roadsides [27]. For humans, exposure risk in a known tick-infested site can be as high as one infected tick per person per hour of exposure, or 0.25 infected ticks per 100 metres walking distance [21]. Transmission does not usually occur within the first 24 hours of the blood meal [28], so immediate removal of ticks is a highly recommended preventive measure (see below).

In Europe, confirmed competent reservoir hosts (i.e. tick hosts that can be infected with *Borrelia* and transmit this agent to uninfected ticks) include many common species of small and medium-sized rodent (mice, rats, squirrels, hares and rabbits), as well as several bird species (especially passerines), reptiles and insectivores [10,29]. Conversely, many large wild and domesticated vertebrates (e.g. deer and sheep) are considered non-competent reservoirs (i.e. ticks feeding on them do not acquire Borrelia; however, ticks may transmit *Borrelia* to each other when feeding very close together on these non-competent hosts). Host specificity is the result of the resistance or sensitivity of *Borrelia* genospecies to the serum complement of various host species, which leads to the survival or death of the pathogen, respectively [30]. Importantly, non-competent reservoir hosts, such as deer, may also serve as crucial maintenance hosts for feeding ticks of all stages [10]. The presence and density of these hosts is associated with the density of ticks, but their effect on tick-borne infection dynamics is complex [31]. The presence of non-competent reservoir hosts can decrease the transmission potential of Borrelia, reducing the prevalence in the vector and subsequent

disease risk to humans (a dilution effect [32,33]). Ogden and Tsao [34] have shown that any host that feeds enough ticks to reduce the overall infection prevalence in nymphs, by diverting them away from competent host species, would be likely to increase the tick population density by improving the chances of successful tick feeding. However, the overall effects of changes in biodiversity on LB emergence have yet to be thoroughly investigated [35].

Epidemiology

Although LB is not a particularly new emerging disease, an accurate description of LB epidemiology in Europe is still not possible because few countries have made this disease mandatorily notifiable [3,9,36]. Unfortunately, there appears to be no plan to continuously monitor LB at the European level [37]; instead this is recommended only 'Where the epidemiological situation in a Member State so warrants …', although such situations are not defined [38]. Therefore, surveillance statistics in Europe are based on non-standardised case criteria and uncoordinated systems of data collection [39,40]. Moreover, these data are inaccurate because patients with erythema migrans and other clinically diagnosed cases may be under-reported, the geographical distribution of referrals for testing is unknown, the criteria for serological diagnoses are not standardised, seropositivity due to past infection may be included, and data from remote regions may be lacking [41,42]. In addition, patients may be infected by one or two (rarely three) pathogenic *B. burgdorferi* genospecies and heterogeneity in symptoms caused by these various agents complicates surveillance [43].

A summary of the currently available epidemiological data is available in [3]. Epidemiological studies indicate the mean annual number of LB notified cases (including qualified estimates) in Europe is more than 65,400 (incidence rates per country range from less than one per 100,000 population to about 350 per 100,000 population). In Europe, LB occurs between 35 °N and 60 °N, and generally below 1,300 metres above sea level. However, there is strong heterogeneity in spatial distribution: the level of antibodies to *B. burgdorferi* sl is highest in residents of northern and central countries and lowest in those in the southern countries. In addition, at a local level, there is a focal pattern of distribution related to suitable tick habitat, including some hotspots where more than 100 cases per 100,000 population per year are recorded (e.g. parts of Slovenia, Germany and Austria, the Baltic coastline of southern Sweden, and some Estonian and Finnish islands).

LB risk is specifically linked to tick abundance and exposure. Therefore, although higher risk is no longer considered to be correlated with residency in rural areas, higher LB risk is associated with occupation (e.g. forestry work and farming) and especially with certain leisure activities (e.g. hunting, mushroom collecting and berry picking) and age (with two groups mainly affected: children aged 5–14 years and adults aged 50–64 years).

Since infection is correlated with tick abundance and exposure (and, therefore, tick activity), diagnosis of acute LB peaks in June and July in many northern and central countries of Europe, while a second smaller peak may occur in southern countries in late summer or early autumn; however, both erythema migrans and chronic forms of the disease can be diagnosed throughout the year [3]. Although the number of LB cases seems to be increasing in some areas, such trends are extremely heterogeneous and/or remain to be confirmed [3].

Clinical symptoms

The clinical presentation of LB ranges from acute to chronic illness, with wide variation attributed to the different *Borrelia* genospecies and/or genotypes implicated in the infection (as described above and in [44]), although the exact mechanisms maintaining chronic symptoms have yet to be confirmed. Diagnosis is primarily clinical and takes into account the risk of tick bite. Clinical case definitions for use in Europe – although not official European Union case definitions – are available in [45].

Briefly, several days or weeks after a tick bite, if *Borrelia* infection occurs, in 60–80% of cases this will be characterised by erythema migrans (the rash or patch on the skin about 10 cm across that may expand peripherally as a palpable band, and may or may not be itchy) [46], although early infection may be completely asymptomatic. Other early symptoms include influenza-like symptoms, fever, fatigue, headaches and muscle or joint pain. Several weeks or months after infection through a tick bite (with or without a previous history of erythema migrans), neuroborreliosis (noted in 10–20% of symptomatic patients) in the form of meningoradiculitis, meningitis or meningoencephalitis [47], Lyme arthritis or Borrelia lymphocytoma may occur [45]. Less frequently, multiple erythemata, or carditis are diagnosed [45,48]. Months or even years after *Borrelia* infection, acrodermatitis chronica atrophicans, lymphocytoma, chronic arthritis (fairly rare in Europe), encephalomyelitis or chronic neuroborreliosis (very rare in Europe) may be observed [45].

Microbial or serological confirmation of *Borrelia* infection is needed for all manifestations of the disease except for typical early skin lesions [49]. The diagnosis of some chronic forms of LB is currently controversial [50], and it has also been suggested that the overdiagnosis and overtreatment of LB may be an important problem [51].

Diagnostic methods

Direct detection of *B. burgdorferi* sl

Although the diagnosis of LB is primarily based on the most obvious clinical sign, erythema migrans, diagnosis of other forms of LB require confirmation by

means of a diagnostic test [52]. A wide range of methods have been developed for the direct detection of *B. burgdorferi* sl in clinical tissue specimens, including microscopic examination, detection of *B. burgdorferi*-specific proteins or nucleic acids, and cultivation. Although culture is the most commonly used method of direct detection, success rate depends on sample type. While mean recovery rates of *Borrelia* from skin biopsies of patients with erythema migrans and acrodermatitis chronica atrophicans are up to 70% [43], those for cerebrospinal fluid (CSF) are much lower. Future diagnostic methods may include PCR-based molecular techniques that can rapidly confirm clinical diagnosis of LB, and identify *Borrelia* genospecies in tissue specimens or cultured isolates [53]. However, even molecular methods have not yet been standardised since protocols and gene targets vary between laboratories and more clinical validations are needed [53]. Importantly, a negative PCR result does not necessarily indicate the absence of *Borrelia* [54]; therefore, the use of a PCR-based assay to confirm diagnosis of LB in the absence of serological evidence of *Borrelia* infection is not currently recommended.

Indirect diagnosis of *B. burgdorferi* sl

The complexity of the antigenic composition of *B. burgdorferi* sl and the temporal appearance of antibodies to different antigens at successive time intervals after *Borrelia* infection means the development of a serological test with high sensitivity and specificity is a challenge. The most commonly used serological methods for the detection of antibodies to *B. burgdorferi* sl include indirect immunofluorescent antibody assay (IFA) and an enzyme-linked immunosorbent assay (ELISA) [54]. Nevertheless, specific antibodies are often not detectable in the early stage of infection with the use of currently available test methods.

In more than 50% of cases, diagnosis of LB can be made on the basis of an expanding erythema (confirmed after a one-week follow-up). In the absence of erythema migrans at least one other clinical manifestation must be noted and confirmed using serological diagnosis of *Borrelia* in blood or CSF. According to the most recent German Society for Hygiene and Microbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie, DGHM) guidelines [43], serological diagnosis for patients in Europe should follow a two-step procedure: (i) ELISA and if reactive, followed by (ii) an immunoblot, if possible using recombinant antigens (p100, p58, p41i, VlsE, OspC, DbpA), including those expressed primarily in vivo (VlsE and DbpA), instead of whole-cell lysate antigen blots. OspC and VlsE are the most sensitive antigens for IgM antibody detection [54]. European standardisation of these diagnostic tests and new markers for detecting active infections are urgently required [55].

Treatment

Surprisingly, our review found that there is no European consensus on treatment and that economic considerations and national guidelines on avoidance of drug resistance also impact the current treatment of choice (no comparative costs are available). Treatment of the vast majority of LB cases is based on antibiotics, with drug type, dose, route (oral or intravenous) and duration varying with stage of the disease, as well as with symptoms. Treatment regimes and recommendations are summarised from the regularly updated European Union Concerted Action on Lyme Borreliosis (EUCALB) website [1] and [49], where doses can also be found. See also [49,51,56] for recent reviews on evaluation of treatments.

In general, in almost all LB cases, the disease is resolved with short courses of antibiotics [51,57], although longer courses are recommended for relapses or more serious and/or chronic forms. Some authors advocate that all symptomatic LB cases should be treated in order to avoid progression to later stages of the disease, and suggest that the earlier treatment begins, the less likely it is that more severe forms will follow [58]. However, overtreatment is considered a problem by others [51], although thus far, drug resistance has been noted only in vitro [59]. On the other hand, few data are available on the risk of long-term effects of non-treatment in asymptomatic LB patients [60]. Several studies have now shown that a few so-called chronic or 'post-LB' forms of the disease do not respond to antibiotics, although the reason for this is subject to some debate [50,51,61].

The main risks involved in treatment appear to be inappropriate patient management following inaccurate diagnosis. As mentioned above, both over- and under-diagnosis of LB is suspected.

Prevention

It has been suggested that individual or community measures to reduce the probability of tick bites and LB infection could be extremely effective preventive methods [62-64]. For example, in order to decrease the risk of tick bites and *Borrelia* transmission, people living in or visiting tick-infested areas are advised to avoid tick habitats, to wear long, light-coloured trousers (tucking them into socks) and to use insect repellent that contains permethrin (on clothes) or N,N-Diethyl-meta-toluamide (DEET) (on clothes or directly on skin). After visiting or working in such areas, a shower is recommended and a thorough check for ticks should be done, including careful inspection of the neck, armpits and groin. Tick bites can also be avoided by carefully inspecting and removing ticks from pets [65]. Any attached ticks should be removed immediately with tweezers if available, by seizing and pulling steadily on the mouthparts, without twisting [66] and the attachment site disinfected. Since ticks do not have a high probability of transmitting *Borrelia* until 12–24 hours after beginning to feed, immediate removal of ticks is one of the most effective ways of avoiding *Borrelia* infection. The site should be monitored for 30 days after the bite for signs of erythema migrans (there are

many websites that clearly illustrate these procedures, e.g. [67]).

There is currently no vaccine available on the European market. Thus far, the development of a vaccine for humans against *B. burgdorferi* sl infection has concentrated on the highly immunogenic outer surface proteins of this pathogen. Although an OspA-based vaccine was developed and licensed in 1998, it was withdrawn from the market in 2002 for economic reasons, as well as doubts as to its long-term efficacy (it was also not recommended for children under the age of 15 years or for people with arthritis). The future of vaccines of this type is uncertain; vaccine research continues, with the aim of generating protection against all pathogenic genospecies of *B. burgdorferi* sl [68]. New approaches include transmission-blocking vaccines, which act on proteins produced by ticks that appear to improve the transmission of the *Borrelia* spirochaetes from vector to host [69]. Factors critical to an effective and accepted vaccine will probably include the following: a detailed knowledge of the host–parasite cycle on a local, regional and European scale and of the distribution and prevalence of *Borrelia* genospecies; a better understanding of the symptoms associated with infection with each genospecies; and standardised serological confirmation of all suspected LB cases, including genospecies identification. Further studies on the role of surface lipoproteins of *B. burgdorferi* sl are also urgently needed [70]. In addition, enhancement of the epidemiological surveillance of LB, both of the disease itself and the abiotic and biotic factors that affect it, would improve risk assessment and aid prevention immeasureably [71].

Current geographical distribution of LB

LB occurs across Europe, with a distribution closely matching that of the vector *I. ricinus*. This tick species can be infected with *Borrelia* throughout its wide latitudinal range, from northern Turkey and the Atlas Mountains of Tunisia to northern Sweden [8,72,73]. Infected tick density also decreases with increasing altitude, although the ticks are now found at up to 1,300 metres [74,75]. Consequently, the incidence of LB decreases from the endemic areas of central Europe to the southern and northern limits [3,8]. However, studies on a local scale often reveal a higher incidence than previously recorded at a regional scale [16], so that monitoring LB locally may be important for treating and preventing the disease.

Factors triggering changes in LB incidence

The changes in capacity of *I. ricinus* to transmit *B. burgdorferi* sl in Europe could be due to changes in elements of the transmission process [40,76], such as: transmission coefficient (due to genetic changes in pathogen, vector and/or host [10]); survival rates of ticks (as a result of favourable abiotic changes [72]); increased tick abundance (resulting from increased availability of reservoir hosts and/or habitat [77]); increased exposure of humans to tick bites (due to an increase in outdoor activities [76]). Theoretical studies indicate that complex interactions between these factors will probably yield wide spatio-temporal fluctuations in the relative abundance of different *Borrelia* genospecies and LB incidence [23].

Global climate change inducing higher minimum temperatures (night-time and winter) and earlier springs are likely to affect many aspects of tick phenology [78], such as their local distribution, density and survival rates. For example, as a result of climate change, ticks have already spread into higher latitudes and altitudes in many European countries [72,75,78], while tick abundance is mainly affected by host abundance and habitat structure [25,79]. Regional studies with reliable long-term surveillance data show that an increase in tick abundance has also resulted in an increased incidence of LB, and that this increase is correlated with climatic factors [77]. However, climate change may not contribute to an overall increase in LB, since there may be an extended and more intense LB transmission season in some areas, while the risk of LB could decrease, at least temporarily, in locations with repeated droughts or severe floods, as shown in [80].

Instead, climate-related changes in land use and socio-economic influences on human behaviour are more likely to have a strong impact on the distribution and abundance of ticks and *Borrelia* infection risk (as noted for tick-borne encephalitis; [81]), especially in highly disturbed ecosystems, such as managed forests, peri-agricultural and urban and peri-urban sites [79]. A concomitant increase in the density of wild and domestic vertebrates, paralleled with expansion of suitable habitats for competent reservoir hosts, is expected to increase tick density, *B. burgdorferi* circulation and hence LB incidence [22,35,40,78,82]. The specific and combined contributions of all environmental and socio-economic factors to the observed pattern and predicted future impact of several tick-borne diseases in Europe were assessed within the Framework 6 Integrated Project Emerging Diseases in a changing European eNvironment (EDEN) [83].

Assessing the risk of infection

The complex multi-strain multi-host interactions associated with *B. burgdorferi* sl infection make it difficult to determine the risk of infection to humans [29,84,85]. While risk assessment may be based on well-planned surveillance of tick and *Borrelia* genospecies distribution and abundance [86,87] and/or serological surveillance of *Borrelia* infection in humans [88-90], it has been also been suggested that high-risk biotopes should be identified [91]. Spatial models have been developed to identify high-risk areas based on environmental and climatic features [92]. A model based on the long-term trends of habitat suitability for *I. ricinus* in Europe shows that the distribution of such habitats has remained relatively stable, although parts of Europe show increasing (Ireland, and parts of the United Kingdom, France, Spain, Portugal and Italy) or

a decreasing (Balkans, countries in the central parts of Europe and southern Scandinavia) suitability [80]. On a smaller spatio-temporal scale, the risk of exposure to Borrelia-infected ticks in the Italian Alps was predicted with a model based on bootstrap aggregation of tree-based classifiers within a geographic information system (GIS) [93]. The resulting map of the probability of encountering a questing *I. ricinus* nymph infected with *B. burgdorferi* sl has provided an important risk assessment tool for local human health authorities and policymakers.

Although the above methods can be used for risk and human exposure assessments, they cannot be used for addressing these as dynamic processes during a growing or declining epidemic. A detailed Ro (basic reproduction number) map would be an easy-to-interpret overview of LB risk following the introduction of *B. burgdorferi* sl into an area and could be suitable for following an LB epidemic (Ro being a measure of the risk of establishment of a disease in a certain area or population, defined as the expected number of new infections induced by a typical infectious individual during the full infectious period in a susceptible population [94]). For tick-borne pathogens, Ro can now be estimated using a next-generation matrix method [95], based on accurate biological conditions. However, Rosà and Pugliese [96] found that the effect of host densities on the Ro of tick-borne infections depends strongly on the regulation of tick populations. Since there is currently very little information on which factors affect natural tick populations, more complete, long-term field data are still needed before accurate Ro maps can be produced.

Conclusion

In Europe, the annual number LB cases is increasing in some areas, and tick vectors are expanding their range, to higher altitudes and latitudes, suggesting that LB will remain an important health concern in the coming decades, especially in light of economic, land use and climate change predictions. In addition, the effect of the resulting biodiversity loss and ecosystem changes on LB emergence should be an important focus of investigation, especially to identify new paradigms for the prevention and control of LB and other tick-borne diseases. It emerges from our review that standardised diagnoses are crucial to treating and combatting LB in Europe, as are European-wide reporting systems and datasets concerning all aspects of the molecular ecology and epidemiology of LB [10]. Preventive measures aimed at minimising tick-bite risk are promoted as one of the best ways to avoid *Borrelia* infection. Many authors agree that a concerted effort to improve surveillance is essential for monitoring this disease [9,36,49,55] and we consider that more complete eco-epidemiological knowledge is also needed to develop accurate risk prediction models.

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