

Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures

By: Elisabet Lindgren Thomas G.T. Jaenson



ABSTRACT

Stockholm University and WHO, within a project funded by the European Commission (EVK2-2000-00070), reviewed the impacts of climate change and adaptation on Lyme borreliosis (LB) in Europe.

LB is the most common vector-borne disease in Europe. The highest incidence is reported from Austria, the Czech Republic, Germany, and Slovenia, as well as from the northern countries bordering the Baltic Sea. LB is a multi-system disorder that is treatable with antibiotics, but may lead to severe complications of the neurological system, the heart, and the joints.

LB is caused by a spirochete (*Borrelia burgdorferi* s.l.), which is transmitted to humans by ticks, in Europe mainly the species *Ixodes ricinus*. Reservoir animals are small rodents, insectivores, hares and birds.

Ticks may live for more than three years and are highly sensitive to changes in seasonal climate. Daily seasonal climatic conditions directly impact tick survival and activity. Indirectly, climate affects both tick and pathogen occurrence through effects on habitat conditions and reservoir animal density. In addition, climate-induced changes in land use and in recreational behaviour influence human exposure to infected ticks and thus disease prevalence.

Since the 1980s, tick vectors have increased in density and spread into higher latitudes and altitudes in Europe. It can be concluded that future climate change in Europe will facilitate a spread of LB into higher latitudes and altitudes, and contribute to increased disease occurrence in endemic areas. In some locations, where climate conditions will become too hot and dry for tick survival, LB will disappear.

There is a need to strengthen preventive measures such as information to the general public, surveillance activities within a pan-European network and to use standardized methods to provide data for future research activities.

Keywords

BORRELIA BURGDORFERI LYME DISEASE - diagnosis - epidemiology TICK-BORNE DISEASES - prevention and control DISEASE TRANSMISSION CLIMATE EPIDEMIOLOGIC SURVEILLANCE EUROPE

EUR/04/5046250

Address requests about publications of the WHO Regional Office for Europe to: Publications WHO Regional Office for Europe Scherfigsvej 8 DK-2100 Copenhagen Ø, Denmark Alternatively, complete an online request form for documentation, health information, or for permission to quote or translate, on the

Regional Office web site (http://www.euro.who.int/pubrequest).

© World Health Organization 2006

All rights reserved. The Regional Office for Europe of the World Health Organization welcomes requests for permission to reproduce or translate its publications, in part or in full.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Where the designation "country or area" appears in the headings of tables, it covers countries, territories, cities, or areas. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use. The views expressed by authors or editors do not necessarily represent the decisions or the stated policy of the World Health Organization.

CONTENTS

Page

Acl	nowledg	ement	4
1.	Introdu	ction	5
	1.1.	The scope and framework of the cCASHh project	5
	1.2.	Lyme borreliosis	5
2.	Geogra	phical distribution	6
	2.1.	Distribution	6
	2.2.	Incidence	7
	2.3.	Population at risk in Europe	10
	2.4.	High-risk periods	11
3.	Pathoge	n transmission cycle	11
	3.1.	The pathogen	11
	3.2.	The tick	12
	3.3.	Reservoir hosts	12
	3.4.	Pathogen circulation in nature	13
4.	Influence	e of environmental and climatic factors on disease risk	14
	4.1.	Climate and the life-cycle dynamics of the tick	15
	4.2.	Indirect effects of climate	16
5.	Observe	ed effects of recent climate variations in Europe	18
6.	Possible	e future effects of climate change in Europe	19
7.	Adaptat	ion and preventive measures	20
	7.1.	Diagnosis and treatment	20
	7.2.	Vaccination	21
	7.3.	Control targeted at the vector	22
	7.4.	Control targeted at the reservoir host	22
	7.5.	Information and health education	22
	7.6.	Surveillance and monitoring	23
	7.7.	Future research needs	24
8.	Conclus	vions	24
Ref	erences		25

Acknowledgements

This document was prepared by Elisabet Lindgren, Department of Systems Ecology, Stockholm University, Sweden, and Thomas G.T. Jaenson, Department of Systematic Zoology, Uppsala University, Sweden.

The authors wish to thank José A. Oteo of Hospital de La Rioja, Logroño, Spain; Bohumir Kriz and Milan Daniel of the National Institute of Public Health, Prague, Czech Republic; and Kuulo Kutsar of Health Protection Inspectorate, Tallinn, Estonia, for making original data available.

This document was reviewed by Clive Davies, Disease Control and Vector Biology Units, London School of Hygiene and Tropical Medicine, United Kingdom; Agustin Estrada-Peña, Department of Parasitology, Veterinary Faculty, Zaragoza, Spain; Milan Daniel, National Institute of Public Health, Czech Republic; and Glenn McGregor, School of Geography and Environmental Sciences, University of Birmingham, United Kingdom; Sari Kovats and Katrin Kuhn from London School of Hygiene and Tropical Medicine, and Kristie L. Ebie, Exponent, United States. Findings were also discussed at a WHO workshop in 2004 on climate change and vector-borne diseases.

The authors would like to thank Jeremy Gray from the Department of Environmental Resource Management, University College, Dublin, Ireland and Norman Gratz from Switzerland for their detailed comments, suggestions and support during the process.

The authors would like to thank Anne Blessy Corda for the layout and format of the document and Kathy Pond for editing the document.

The preparation of this document was funded through the European Commission funded project "Climate Change and Adaptation Strategies for Human Health" (EVK2-2000-00070), coordinated by the WHO Regional Office for Europe, Global Change and Health Unit, Rome, Italy.

Bettina Menne from the WHO Regional Office for Europe coordinated the cCASHh project, organizing meetings and discussion frameworks.

1. Introduction

1.1. The scope and framework of the cCASHh project

Climate and weather are important determinants of human health and well-being. Important changes in climatic conditions are predicted and these will have implications for human health in Europe.

The project "Climate Change and Adaptation Strategies for Human Health" (cCASHh) was funded by the European Commission within its fifth framework programme under Thematic Programme: Energy, Environment and Sustainable Development (EESD-1999) and the Key action: Global change, climate and biodiversity. The project started on 1 May 2001 and ended on 31 July 2004. The assessment mainly includes all 25 countries of the European Union.

The overall objective of the cCASHh project is:

- to identify the vulnerability to adverse impacts of climate change on human health;
- to review current measures, technologies, policies and barriers to improving the adaptive capacity of populations to climate change;
- to identify for European populations the most appropriate measures, technologies and policies to successfully adapt to climate change;
- to provide estimates of the health benefits of specific strategies or combinations of strategies for adaptation under different climate and socioeconomic scenarios.

To this end several health impact assessments, adaptation assessments, cost–benefit analysis and integrated assessment modelling (health futures) were carried out. The main health outcomes that were investigated in the cCASHh project are:

- health impacts of thermal stress
- health impacts of floods
- foodborne diseases
- vector- and rodent-borne diseases.

This document presents the results of an extensive literature review on Lyme borreliosis (LB) combined with input from leading experts in this field.

1.2. Lyme borreliosis

LB is the most common vector-borne disease in temperate zones of the northern hemisphere. About 85 000 cases are reported annually in Europe (estimated from available national data). However, this number is largely underestimated as case reporting is highly inconsistent in Europe and many LB infections go undiagnosed. In the United States between 15 000 and 20 000 cases are registered each year and the disease is currently endemic in 15 states (Steere, 2001).

LB is transmitted to humans during the blood feeding of hard ticks of the genus *Ixodes*: in Europe mainly *Ixodes ricinus*, and to a lesser extent *I. persulcatus*. The symptoms of LB were described almost a century ago by the Swedish dermatologist Arvid Afzelius, but the disease

was not identified until 1977, in the area of Lyme in the United States – hence the name Lyme disease. Following the discovery in 1982 of the spirochete (spiral-shaped bacterium) *Borrelia burgdorferi* s.l. as the causative agent of LB, the disease emerged as the most prevalent arthropod-borne infection in northern temperate climate zones around the world. In Europe the disease is nowadays commonly called LB. LB is a multi-system disorder that is treatable with antibiotics. Neither subclinical nor symptomatic infections provide immunity. If early disease manifestations are overlooked or misdiagnosed, LB may lead to severe complications of the neurological system, the heart and the joints. Spirochetes are maintained in nature in ticks and in the blood of certain animal species: in Europe particularly insectivores, small rodents, hares and birds. Humans as well as larger animals, such as deer and cattle, do not act as reservoirs for the pathogen.

Current knowledge of the impact of different climatic factors on vector abundance and disease transmission is rather extensive. Climate sets the limit for latitudinal and altitudinal distribution of ticks. In addition, daily climatic conditions during several seasons (as ticks may live for more than three years) influence tick population density both directly and indirectly. The pathogen is not in itself sensitive to ambient climatic conditions, except for unusually high temperatures, but human exposures to the pathogen – through tick bites – may be influenced by weather conditions.

During the last decades ticks have spread into higher latitudes (observed in Sweden) and altitudes (observed in the Czech Republic) in Europe and have become more abundant in many places (Tälleklint & Jaenson, 1998; Daniel et al., 2003). These tick distribution and density changes have been shown to be related to changes in climate (Lindgren et al., 2000; Daniel et al., 2004). The incidences of LB and other tick-borne diseases have also increased in Europe during the same time period. In some places this may be an effect of better reporting over time. However, studies from localized areas that have reliable long-term surveillance data show that such incidence increases are real, and that they are related to the same climatic factors that have been shown to be linked to changes in tick abundance (Lindgren, 1998; Lindgren & Gustafson, 2001; Daniel et al., 2004).

2. Geographical distribution

2.1. Distribution

The geographical distribution of LB worldwide correlates with the known distribution of the ixodid vectors (Fig. 1). In Europe, the distribution of *I. ricinus* overlaps with the distribution of *I. persulcatus* in the coastal regions east of the Baltic Sea and further south along that longitude into middle Europe, from where the range of *I. persulcatus* stretches to the Pacific Ocean. Where the two species overlap there are microclimatic conditions separating their distribution. *I. persulcatus* is more flexible and less sensitive to hydrothermal changes in the environment than *I. ricinus* (Korenberg, 1994). Recent studies of the Baltic regions of the Russian Federation showed for example that 11.5% of *I. ricinus* ticks (development stages not stated) were carriers of *B. burgdorferi* s.l. in contrast to 26.3% of *I. persulcatus* (Alekseev et al., 2001). In addition, a large number of other tick species have been reported as carriers of *B. burgdorferi* s.l., but this does not necessarily mean that these ticks are effective in transmitting the disease. Seasonal climatic conditions limit the latitude and altitude distribution of ticks in Europe (Daniel, 1993; Lindgren et al., 2000; Daniel et al., 2003, 2004). Both altitude and latitude distribution limits of *I. ricinus* have changed during recent years in Europe, as described in detail

in Section 5. Ticks are now found in abundance up to 1100 m above sea level (a.s.l.) in the Czech Republic (Daniel et al., 2003), up to 1300 m a.s.l. in the Italian Alps (Rizzoli et al., 2002), and along the Baltic Sea coastline up to latitude 65°N in Sweden (Jaenson et al., 1994; Tälleklint & Jaenson, 1998). At high northern latitudes, where the inland climate generally is too harsh for ticks to survive, small tick populations can be found in locations where the landscape characteristics help in modifying the climatic conditions. That is, close to large bodies of water, i.e. in river valleys, around inland lakes and along the coastlines (Lindgren et al., 2000).





2.2. Incidence

Surveillance in Europe varies and does not allow direct comparison between countries. In some regions the general public is not aware of the risk, and as the symptoms of LB are easily neglected — especially if the characteristic skin rash called erythema migrans does not occur initially — LB may go undetected. In addition, data obtained from various European laboratories are often not directly comparable because of different serological tests used to detect antibodies to *B. burgdorferi* s.l. (Santino et al., 2002). Even if LB is diagnosed, there is often a lack of reporting as few countries have made LB a compulsorily notifiable disease. Despite these caveats, it appears that both disease incidence and antibody prevalence are higher in the central and eastern parts of Europe than in the western parts (Table 1). A gradient of decreasing incidence from south to north in Scandinavia and from north to south in Italy, Spain and Greece has also been noted (e.g. Epinorth, 2003; EUCALB). The highest incidences of LB in Europe are found in the Baltic States and Sweden in the north, and in Austria, the Czech Republic, Germany, Slovenia and central Europe (Figures 1, 2a and 2b).

In much of Europe, the number of reported cases of LB has increased from the early 1990s (e.g. the Czech Republic, Estonia, Lithuania; see Fig. 2), and the geographic distribution of cases has also expanded. This is partly due to an increased level of awareness in the general population and among medical personnel, and to better reporting. However, studies from the Czech Republic and Sweden show changes in vector abundance as well as changes in latitudinal or altitudinal distribution of ticks during the same time period (Tälleklint & Jaenson 1998; Daniel et al., 2003). The possible factors underlying these reported changes will be discussed in the sections below.

Country	Incidence per 100 000 population (annual average)	Annual number of cases (average)	Antibody prevalence (in human blood) ^a	
Austria 300		14-24 000	1997: General 7.7% ¹	
Belgium	No data	500	No data	
Bosnia and Herzegovina	LB is prevalent			
Bulgaria	55	3500	No data	
Croatia		>200 (LB absent in sout	hern parts) ²	
Czech Republic	27-35 (Fig. 2a)	3500	No data	
Denmark	0.8 (Table 2)	<50	No data	
Estonia	30-40 (Fig. 2b)	<500	1997: Risk pop. 2.7% ¹	
Finland	12.7 (Table 2)	<700	1995: Risk pop. 16.9% ³ 1998: High risk area 19.7% ⁴	
France	16.5 40 (Berry-Sud)	7-10 000	1997: Risk pop. 15.2% ⁵	
Germany	25 111 (Wurzburg) ⁶	15–20 000	1997: General 5.6% ¹	
Greece	No data	No data	1997: General 1–3% ¹ 2000: Young males 3.3% ⁷	
Hungary	Neuroborreliosis 2.9 (Baranya) ⁸	No data	No data	
Iceland	B.garinii present in I.uri	iae ⁹		
Ireland	0.6	<50	1998: General 3.4% ¹⁰	
Italy	~17 (Liguria)	<20 (Central Italy)	1997: General: 1.5–10% ¹ 1998: Risk pop. 27% ¹¹	
Latvia	15.6 (Table 2)	<400	No data	
Lithuania	25-35 (Fig. 2c)	<1300	1994: General 4–32% ¹²	
Luxembourg	LB is prevalent ¹³			
Malta	Uncertainty whether the	pathogen is endemic or no	ot	
Netherlands	43	6500	1993: Risk pop 28%; non- risk pop 5% ¹⁴ 1997: General 9% ¹⁵ 2001: Risk pop. 15% ¹⁶	
Norway	2.8 (Table 2)	124	No data	
Poland	4.8 32.2 (Podlasie Province) ¹⁷	No data	1995: Risk area 49.7% ¹ 1999: General 33%; Risk pop. 48% ¹⁷ Podlasie Province: Risk pop. 1995: 39%; 2000: 4% ¹⁷	

Table 1. Incidence and annual number of cases of LB, and seroprevalence of
antibodies (in human blood) in different European countries

Portugal	Borrelia prevalent in ticks ¹⁸				
Romania	No data	No data	1999: General 4–8%; Risk pop 9.3–31.7% ¹⁹		
Serbia and Montenegro	LB is prevalent	No data	No data		
Slovakia	No data	1000	2001: General 5.4%; Risk pop. 16.8% ²⁰		
Slovenia	155	>2000	Children 12.6% ²¹		
Spain	9.8 (La Rioja) 22	26 (La Rioja) 22	No data		
Sweden	80 (South)	10 000 (South)	1992: General 7% ²³ 1995: General 34% (south) ²⁴		
Switzerland	30.4	2000	No data		
United Kingdom	Before 1992: 0.06 After 1996: 0.3 ²⁵	>2000	1998: Risk pop. 0.2% ²⁶ 2000: Risk area.5–17% ²⁷		

^a General = general population; Risk pop. = risk population, such as hunters; Risk areas = people living in high risk areas, such as forests, etc.

Forests, etc.
Source: ¹ Santino et al., 1997; ² Mulic et al., 2000; ³ Oksi & Viljanen, 1995; ⁴ Carlsson et al., 1998; ⁵ Zhioua et al., 1997;
⁶ Huppertz et al., 1999; ⁷ Stamouli et al., 2000; ⁸ Pal et al., 1998; ⁹ Olsen et al., 1993; ¹⁰ Robertson et al., 1998; ¹¹ Ciceroni & Ciarrocchi, 1998; ¹² Montiejunas et al., 1994; ¹³ Reiffers-Mettelock et al., 1986; ¹⁴ Kuiper et al., 1993; ¹⁵ De Mik et al., 1997; ¹⁶ Goossens et al., 2001; ¹⁷ Pancewicz et al., 2001; ¹⁸ De Michelis et al., 2000; ¹⁹ Hristea et al., 2001; ²⁰ Štefančiková et al., 2001; ²¹ Cizman et al., 2000; ²² José A. Oteo, 2003, personal communication; ²³ Gustafson et al., 1993; ²⁴ Berglund et al., 1995; ²⁵ Smith et al., 2000; ²⁶ Thomas et al., 1998; ²⁷ Robertson et al., 2000.

		1999	2	2000		2001	2	2002
Area	No. of	Incidence	No. of	Incidence	No. of	Incidence	No. of	Incidence
	cases		cases		cases		cases	
Archangelsk								
Region	Ν	o data	33	2.3	32	2.3	39	2.7
Denmark	18	0.3	64	1.2	53	1	41	0.8
Estonia	321	22.2	601	43.8	342	25	319	23.3
Finland	404	7.8	895	17.2	691	13.3	884	17
Iceland	No data					0	0	
Kaliningrad Region	Ν	o data	189	19.9	Ν	o data	68	7.2
Latvia	281	11.5	472	19.4	379	16	328	14
Leningrad Region			140	8.5	107	6.5	111	6.7
Lithuania	766	20.7	1713	46.3	1153	33	894	25.7
Murmansk Region	Ν	o data	1	0.1	3	0.3	2	0.2
Nenets area	Ν	o data	0	0	0	0	0	0
Norway	Ν	o data	138	3.1	124	2.8	109	2.4
Republic of Karelia	Ν	o data	44	5.8	21	2.8	25	3.3
St. Petersburg (city)	Ν	o data	541	11.3	323	6.7	398	8.5

Table 2. Reported annual number of LB cases and LB incidence per 100 000 inhabitants in northern Europe and neighbouring areas 1999 – 2002

Source: Epinorth, 2003.

Reliable epidemiologic data are sparse for most of the endemic LB areas. However, there exist valid serological data from some extensive studies, such as those of Berglund et al. (1995, 1996), who conducted a prospective, population-based study over one year in parts of southern Sweden. National data from countries where LB is a notifiable disease are important, such as the Czech

Republic where national surveillance of LB started in 1990 (Fig. 2a). Possible causes of interannual variations in incidence will be discussed in the sections below.





Figure 2 a,b,c. Annual incidence of Lyme borreliosis in the Czech Republic, and both Lyme borreliosios and TBE in Estonia and Lithuania.

Annual incidence = cases per 100 000 inhabitants /year. *Sources:* Milan Daniel, 2003, personal communication (Fig. 2a); Kuulo Kutsar, 2004, personal communication (Fig. 2b, Fig. 2c).

2.3. Population at risk in Europe

High-risk groups are people living and/or working in LB endemic locations such as forested areas (Smith et al., 1991; WHO, 1995; Santino et al., 1997; Carlsson et al., 1998; Robertson et al., 2000). Occupations such as forest workers, hunters, rangers, gamekeepers, farmers and military field personnel have an especially high risk of contracting LB. This has been shown in several studies on antibody prevalence in human blood and on disease incidence (Cristofolini et al., 1993; Kuiper et al., 1993; Nuti et al., 1993; Oksi & Viljanen, 1995; Santino et al., 1997; Zhioua et al., 1997; Ciceroni & Ciarrocchi, 1998; Stamouli et al., 2000; Goossens et al., 2001; Pancewicz et al., 2001; Štefančiková et al., 2001). Certain recreational habits are linked to increased risk of disease, such as orienteering, hunting, gardening and picnicking (EUCALB; Zeman, 1997; Gray et al., 1998a). Higher seroprevalence of antibodies has been reported for men, probably owing to higher exposure to ticks (Carlsson et al., 1998). In some studies LB is more common among children (EUCALB), whereas in others the highest incidences of LB are found in the working age group (Pancewicz et al., 2001).

Awareness of LB is generally lower in city dwellers than in long-term residents of endemic areas. Little knowledge of ticks and inaccurate perception of the disease increase the risk of acquiring infection and of not recognizing the condition (EUCALB).

2.4. High-risk periods

Reports of cases often show distinct seasonality (Fig. 3). Symptoms of disease normally occur within 2–30 days of a tick bite; hence the seasonal pattern of LB cases lags slightly behind the seasonal pattern of tick activity (see Section 4.1). The highest risk periods from a public health point of view take place when peaks in tick activity occur simultaneously with peaks in human visits to tick infested areas. During the tick activity season there are no "safe" times as ticks may be active day and night (Mejlon, 1997).



Figure 3. Reported Lyme borreliosis cases per month in Estonia.

Source: Kuulo Kutsar, 2004, personal communication.

In Sweden cases of LB are reported throughout the year but with the majority of affected people having been infected during July and August (Åsbrink et al., 1986). A study from southern Sweden showed that tick bites occur most frequently in July, with the highest number of cases with erythema migrans consequently being reported in August, and other LB manifestations peaking in September (Berglund et al., 1995). These seasonality patterns are explained by the fact that more people than usual visit *B. burgdorferi* s.l. infested areas during these periods since July is the main summer holiday month in Sweden, and the forest berry and mushroom picking season as well as the hunting season begins in July/August.

3. Pathogen transmission cycle

3.1. The pathogen

B. burgdorferi s.l., the causative agent of LB, is a gram-negative bacterium, which belongs to the family Spirochaetaceae. To date, *B. burgdorferi* s.l. can be divided into eleven genospecies, of which those with pathogenic significance are *B. afzelii*, *B. burgdorferi* sensu stricto, *B. garinii* and, possibly, *B. valaisiana* (Gylfe et al., 2000; Kurtenbach et al., 2002). The only pathogenic strain found in the United States is *B. burgdorferi* s.s. (Steere, 2001). In contrast, all four pathogenic genospecies of *B. burgdorferi* s.l. are present in Europe, although most of the LB cases are caused by *B. afzelii* and *B. garinii* (Fraenkel et al., 2002; Oehme et al., 2002; Ornstein

et al., 2002; Santino et al., 2002). *B. afzelii* predominates in the northern, central and eastern parts of Europe, and *B. garinii* in the western parts.

Several genospecies may be present simultaneously both in infected ticks (Schaarschmidt et al., 2001; Oehme et al., 2002) and in patients diagnosed with LB in Europe (Tazelaar et al., 1997; Schaarschmidt et al., 2001). Different clinical manifestations are often associated with the different genospecies, as are different reservoir hosts; see Table 5, in Section 7.1 (Humair & Gern, 2000; Kurtenbach et al., 2002). However, this does not seem be the case in the Russian Federation and eastern parts of Europe where non-specific maintenance cycles involving small mammals and various borrelia species have been described (Gorelova et al., 1995; Richter et al., 1999).

3.2. The tick

The European *I. ricinus* and *I. persulcatus*, as well as the closely related North American vectors of Lyme disease, *I. scapularis* and *I. pacificus*, belong to the hard tick family Ixodidae. Of about 850 described species of ticks world-wide this family is the most important from a medical and veterinary point of view (Sonenshine, 1991). In addition to *Borrelia* spirochetes, *I. ricinus* is capable of transmitting a whole range of other pathogens including viruses, bacteria (e.g. rickettsiae), protozoa and nematodes (see Table 6 in Section 7.1).

I. ricinus is usually found in vegetation types that maintain high humidity. Woodlands are preferred to open land, with a preference for deciduous compared to coniferous woodlands (Adler, 1992; Glass et al., 1995; Tälleklint 1996; Gray et al., 1998a; Memeteau et al., 1998; Zeman & Januska, 1999). On-going studies show that not only are woodland habitats important but habitat configuration, i.e. forest patch structure and connectivity, appears to play a crucial role in determining tick abundance (Agustin Estrada-Peña, 2003, personal communication). In the United Kingdom ticks are more abundant in open grassy meadows (Gray et al., 1998a; Estrada-Peña, 1999). Ticks may also be found in suburban and urban environments (Spielman, 1994; Dister et al., 1997; Gray et al., 1998a; Junttila et al., 1999). Preferred habitats often have thick undergrowth and ground litter, which provide cover against cold and drought and create microclimatic conditions with high humidity (Daniel et al., 1977; Mejlon 1997; Gray et al., 1998a).

Ticks may live for more than three years, depending on climatic conditions (Balashov, 1972; Gray, 1991). Most of the tick's life is spent on the ground restoring water balance, undergoing metamorphosis (egg-larvae-nymph-adult), laying eggs, or hibernating. However, when the tick is in active search of a blood meal it climbs the vegetation. Larvae normally stay closer to the ground as they are more sensitive to ambient humidity than more mature stages (Gigon, 1985; Mejlon & Jaenson, 1997), whereas adults may be found on vegetation even as high as 1.5 metre (Mejlon & Jaenson, 1997). This is one reason why larvae are more often found to parasite smaller animals than nymphs and adults (e.g. Tälleklint & Jaenson, 1994).

3.3. Reservoir hosts

Even though ticks feed on a large range of species, including mammals, birds and reptiles, only a few may act as reservoirs for the pathogen. The abundance of reservoir hosts in a particular habitat is the most important factor in the establishment of infected tick populations. Important competent reservoirs of *B. burgdorferi* s.l. in Europe are rodents, such as *Apodemus* mice and voles; insectivores, such as shrews and hedgehogs; hares; and several bird species, including migratory birds (Aeschlimann et al., 1986; Hovmark et al., 1988; Gern et al., 1991; Matuschka et

al., 1992; De Boer et al., 1993; Olsen et al., 1993; Tälleklint & Jaenson, 1993,1994; Gray et al., 1994; Ciceroni et al., 1996; Jaenson & Tälleklint, 1996; Craine et al., 1997; Gern et al., 1998; Kurtenbach et al., 1998a, 1998b; Zeman & Januska, 1999; Zore et al., 1999; Gylfe et al., 2000). Small mammals, which often are reservoir-competent hosts, are mainly infested by larval ticks, to a lesser extent by nymphs, but rarely by adult ticks. Medium-sized mammals, such as hares, and large mammals, such as game, cattle and horses, are infested by all tick stages. These latter mammals are reservoir-incompetent but are nevertheless important for pathogen transmission as they provide food for large numbers of adult females, thereby contributing to higher tick abundance (Jaenson & Tälleklint, 1999; Robertson et al., 2000). Studies have shown that in areas where game, such as roe deer and cattle, is present ticks are more abundant (Gray et al., 1992; Jensen et al., 2000; Jensen & Frandsen, 2000; Robertson et al., 2000) and the number of reported LB cases is higher (Zeman & Januska, 1999).

3.4. Pathogen circulation in nature

Once a tick has become infected with spirochetes it will harbour the pathogens for the rest of its life. Transmission of pathogens often takes place between one and three days after an infected tick has attached itself to a host/human (Kahl et al., 1998). Thus, if a tick is detected and immediately removed after attachment the risk of infection in humans is reduced substantially. Little is known about the duration of borrelia infection in vertebrate hosts. In England and Wales pheasants are important reservoirs and may be infective for ticks for as long as three months (Kurtenbach et al., 1998a). At present only small rodents — apart from the ticks themselves — are known to remain infected during the winter period (Humair et al., 1999). The transmission of *B. burgdorferi* s.l. in nature is less sensitive to seasonal variations in tick activity patterns than the TBE virus transmission cycle (Randolph, 2001) because of the longer period that the reservoir hosts stay infectious with *B. burgdorferi* s.l.

Borrelia spirochetes may be transferred directly from the female tick to its offspring, but such vertical transmission is rare (e.g. Mejlon & Jaenson, 1993; Gray et al., 1998a; Humair & Gern, 2000). In general, less than 1% of host-seeking larvae are infected, compared with between 10% and 30% of the nymphs and between 15% and 40% of adults (Aeschlimann et al., 1986; Jaenson, 1991; Mejlon & Jaenson 1993; Gray et al., 1998a). The majority of the different tick stages become infected when feeding on blood from an infective reservoir animal. The skin of some host species (including some reservoir-incompetent hosts, such as sheep) can constitute an interface for the transmission of spirochetes between infected and non-infected ticks that are co-feeding closely together (Randolph et al., 1996; Ogden et al., 1997). However, six times as many ticks acquire infection when feeding on infected mice as when co-feeding with infected ticks and only 1 out of 100 larvae appears to acquire spirochetal infection when co-feeding with infected nymphs (Richter et al., 2002).

The tick is attached to the host for several days during feeding. This allows the tick to be carried passively into new locations by the host it is attached to. Small mammals such as rodents have rather limited territories. Larger animals such as roe deer normally move around within a range of between 50 and 100 hectares (Cederlund & Liberg, 1995), while birds may deposit ticks far from their original habitat. Birds are often passive carriers of ticks infected with *B. burgdorferi* s.l. (Olsen et al., 1995). Therefore, migrating birds play a role in the introduction of pathogens into new locations along their migratory routes. In addition migratory birds have recently been found to be able to carry LB as a latent infection for several months, and this infection can be reactivated and passed on to ticks as a result of the stress the birds experience during migration (Gylfe et al., 2000).

The dispersal of borrelia pathogens by birds into the European Region may occur along the migrating routes northward/southward in Europe, from Africa in the south and along the western-eastern routes from Eurasia, depending on the bird species. Even though birds account for most of the long-range spread of ticks and pathogens this rarely leads to any major new colonization of ticks or to LB outbreaks in previously nonendemic areas (Jaenson et al., 1994), unless local ecological conditions have been altered, either by land use/land cover changes or climate change (Lindgren, forthcoming). However, transport of ticks and pathogens by migratory birds does have an impact on tick abundance and, in the case of *B. valaisiana* and *B. garinii* (see Table 5 in Section 7.1), on the infectivity in areas that are already LB endemic and/or where suitable ecological conditions are present.

4. Influence of environmental and climatic factors on disease risk

Invertebrate disease vectors, such as ticks, are highly sensitive to climatic conditions, but human infections are only the end product of a complex chain of environmental processes (Epstein, 1999). Some of the most important factors that may influence disease burden are listed below.

Table 3. Factors influencing changes in the disease burden of LB Source: modified from Lindgren, forthcoming.

Factors influencing vector and reservoir animal abundance

- Land use and land cover changes (the latter due to human activities or from natural causes) that affect tick habitats and host animal populations.
- Global changes, such as climate change, with direct effects on the survival and development of ticks, and indirect effects on tick abundance and pathogen transmission through impacts on the composition of plant and animal species, and on the on-set and length of the seasonal activity periods of the tick.

Factors influencing human-tick encounters

- Changes in human settlements and other demographic changes in relation to the proximity to risk areas.
- Changes in human recreational behaviour, including changes caused by altered climatic conditions.
- Changes in use of areas for commercial purpose, e.g. forestry, game-keeping, hunting and eco-tourism.
- Effectiveness of information campaigns on LB disease risk, and the use of different self-protective methods.

Factors affecting society's adaptive capability to changes

- Socioeconomic and technological level.
- Presence of monitoring and surveillance centres and networks.
- Capability of the public health sector and local communities to handle acute and long-term changes in disease outbreaks and risk.
- Type of energy and transportation systems in use and other factors influencing the society's contribution to present and future greenhouse gas emissions.

Climatic and environmental factors can affect LB risk in several ways by determining: the spatial tick distribution (at a range of scales from microhabitat to geographic region); daily variability in risk of infective tick bites; seasonal patterns in risk of infective tick bites; inter-annual variability in risk of infective tick bites; and long-term trends.

4.1. Climate and the life-cycle dynamics of the tick

Both the length of each season as well as daily temperatures and humidity are important factors for the survival, development and activity of ticks. Ticks become active when the ambient temperature increases above 4–5 °C, below which they are in a chill coma (Balashov, 1972; Duffy & Campbell, 1994; Clark, 1995). Higher temperatures are needed for metamorphosis and egg hatching, i.e. between 8 °C and 10–11 °C respectively (Daniel, 1993).



Figure 4. Average seasonal activity of tick vectors in Latvia 1999–2002. *Source:* Kuulo Kutsar, 2004, personal communication.

I. ricinus activity has a prominent annual cycle. Depending on location, ticks start to search for blood meals in early or late spring: in the Czech Republic this usually occurs in March or April, whereas in Latvia the start is later (Fig. 4). Both unimodal and bimodal (with peaks in both spring and autumn) seasonal tick activity peaks have been reported and seasonal occurrence of the different tick stages may vary between years and regions (Nilsson, 1988; Mejlon & Jaenson, 1993; Tälleklint & Jaenson, 1997; Gray et al., 1998a; Zakovska, 2000; Randolph et al., 2002). In habitats where desiccation is common, such as open areas, periods of activity will be shortened to only a few weeks, as opposed to several months in dense woodlands where moisture is higher (Gray, 1991).

I. persulcatus behaves similarly to *I. ricinus*, except that autumn activity rarely occurs (Piesman & Gray, 1994; Korenberg 2000).

The earlier the arrival of spring and the more extended the autumn season, the longer the period that allows ticks to be active and undergo metamorphosis. This may lead to a faster life-cycle with a reduction in the duration between tick bites (Balashov, 1972; Dobson & Carper, 1993). *I. ricinus* larvae and nymphs that feed in the early parts of the season moult into the subsequent life stage in 1–3 months, whereas larvae and nymphs feeding in the latter part of the season enter diapause, hibernate, and moult the following year (Tälleklint, 1996).

There is always a risk that the tick will not survive during the winter; the survival rate of *I*. ricinus larvae is approximately 5% and around 20% for nymphs (Sonenshine, 1991). The longer the season of activity, the larger the proportion of the tick population that hibernates in a more advanced developmental stage. Winter survival depends on minimum temperatures, duration of exposure to cold, the tick's developmental stage and feeding status. Even if the tick survives the winter, further ability to undergo metamorphosis the following spring depends on the length and magnitude of exposure to the cold (Lindsay et al., 1995). Nymphs and adults may resist freezing temperatures well below -7 °C, whereas eggs and larvae, especially if fed, are slightly more sensitive to the cold (Table 4) (Balashov, 1972; Daniel et al., 1977; Gray, 1981). Laboratory studies have shown that ticks survive a couple of months at -5 °C (Fujimoto, 1994) and can resist air temperatures as low as -10 °C for up to one month if not in direct contact with ice (Dautel & Knülle, 1997). Ticks overwinter in ground-cover vegetation. Deep snow conditions could be favourable for winter survival of the tick since deep snow may increase the ground temperature by several degrees (Berry, 1981). The effect of snow cover on ground temperatures depends on such factors as snow depth and duration, physical characteristics of soil and air temperatures (Berry, 1981).

During the host-seeking periods when ticks climb onto vegetation the tick is particularly vulnerable to low air humidity. Larvae are more sensitive than adults and nymphs to both temperature (Table 4) and desiccation (Daniel, 1993). The need for host-seeking ticks to maintain a stable water balance is an important factor in determining the location and duration of activity (Randolph & Storey, 1999). The non-parasitic (off-host) phases of *I. ricinus* require a humidity of at least 80–85% at the base of the vegetation (Kahl & Knülle, 1988; Gray, 1991). Vegetation characteristics are thus important for the maintenance of tick populations (see also Section 3.2).

I. ricinus		Humidity			
life-stages	Minimum	Activity threshold		Optimum	
	survival	Air	Soil		
Larvae	-57°C ^{a,1}	No	data	15–27°C ²	
Nymph	No data	$4-5^{\circ}C^{4}$	$4-5^{\circ}C^{4}$	10–22°C ²	80–85% ^{5,6}
Adult female	-20°C ^{a,1}	7 °C ³	4–5°C ³	18–25°C ²	

Table 4. Climate factors linked to tick vector survival and activity

^aTicks have been shown to resist very low temperatures; however the length of the cold exposure is important. *Source*: ¹ Dautel & Knülle, 1997; ² Daniel & Dusabek, 1994; ³ Sonenshine, 1993; ⁴ Balashov, 1972; ⁵ Gray, 1991; ⁶ Kahl & Knülle, 1988.

B. burgdorferi is not sensitive to ambient climatic conditions except for unusually high temperatures. Optimum temperatures for *B. burgdorferi* s.l. are between 33 °C and 37 °C (Barbour, 1984; Heroldova et al., 1998; Hubalek et al., 1998) and the maximum temperature threshold is 41 °C (Hubalek et al., 1998).

4.2. Indirect effects of climate

Tick density at a given time in a given place is the combined effect of climatic and environmental conditions that have occurred over several years. Long-term studies covering several decades have shown that tick density, as well as disease risk during a particular year, is linked to the number of days per season with temperatures favourable for tick activity, development and year-round survival during two successive years previous to the one studied (Lindgren, 1998; Lindgren et al., 2000; Lindgren & Gustafson, 2001). Such climatic conditions do not only have direct effects on the tick's survival and life-cycle dynamics but create indirect implications for tick prevalence and disease risk (Fig. 5).

Weather conditions, such as temperatures and precipitation, affect the microclimate of the tick habitat, which in turn impacts the tick's immediate survival and activity. However, long-term effects of climate variability may affect the length of the vegetation period and cause changes in plant species composition, thus affecting the spatial distribution and prevalence of both tick and host animal populations. The effect on vegetation affects the ecological dynamics between host animals and ticks through a complex chain of environmental processes, as described for north American conditions by Jones et al. (1998). Snow conditions, in turn, may impact the winter survival of both ticks and host animals. Deep snow conditions are favourable for small hibernating mammals as they create higher ground temperatures, whereas crusty deep snow may be lethal for larger hosts such as the roe deer that feed on sprigs and similar vegetation that are accessible to the animal if the snow cover is thin or easy to remove (Cederlund & Liberg, 1995).



Figure 5. Schematic over-view of the inter-linked relationships between human society, climate change, ecological and demographic changes, and changes in tickborne disease incidence. Source: Lindgren, 1998.

The risk of human LB infection in a specific area depends both on the number of infective ticks in active search for a blood meal and on factors influencing human exposure to ticks. Variations in weather conditions influence human recreational behaviour and hence the risk of exposure to infected tick bites (Jaenson, 1991; Kaiser, 1995). Recreational surroundings such as forests and their marginal grasslands as well as parks are areas often preferred by ticks. Long-term climatic changes may affect vegetation zones and hence influence the commercial use of an area (Table

4) with, in some cases, increased exposures of humans to ticks and, in others, decreased encounters between humans and disease vectors.

5. Observed effects of recent climate variations in Europe

Since 1950, night-time temperatures (i.e. minimum temperatures) have risen proportionally more in the northern hemisphere than daytime temperatures (Easterling et al., 1997; Beniston & Tol, 1998; IPCC, 2001). Winter temperatures have increased more than other seasons, particularly at higher latitudes (Easterling et al., 1997; Beniston & Tol 1998). In Europe, the spring now starts two weeks earlier than it did before the 1980s and the length of the vegetation season has increased (IPCC, 2001). These are all factors of importance for tick vectors and LB risk.

Early signs of effects from changes in climate are more easily recognized in areas located close to the geographical distribution limits (latitudinal or altitudinal) of an organism. Latitudinal changes in tick distribution between the early 1980s and mid-1990s have been reported from northern Sweden (Jaenson et al., 1994; Tälleklint & Jaenson, 1998), (Fig. 6). Spatial and temporal analyses showed that these distribution shifts were correlated to changes in daily seasonal climate (Lindgren et al., 2000). The establishment of new tick populations at the highest latitudes was related to less severe winter temperatures and increased number of days with temperatures vital for tick reproduction (i.e. >10 °C) (Lindgren et al., 2000). Increases in tick population density in the central parts of Sweden were significantly correlated to "accumulated temperature days" that represented milder winters, earlier start of the tick activity period in spring (i.e. >4 °C), and prolonged autumn seasons over a consecutive number of years (Lindgren et al., 2000).

Figure 6. Differences in tick prevalence in central and northern Sweden (southern parts not included).

The left map illustrates conditions before 1980 and the right map illustrates tick distribution after the mid 1990s. *Source*: Lindgren et al., 2000.

Mountain studies on *I. ricinus* populations have been performed in the same locations in the Czech Republic in 1957, 1979–1980 and 2001–2002. A shift in the upper altitude boundary of permanent tick population from 700 m to 1100 m a.s.l. has been observed (Daniel et al., 2003). Specifically, tick surveys (on permanently resident dogs and by flagging) were carried out between 2001 and 2002 at altitudes between 700 m and 1200 m a.s.l. in the Sumava mountains.

Ticks were found on all dogs up to 1100 m a.s.l. and similarly up to this altitude by flagging. These findings contrasted with analogous surveys carried out in the same region in 1957 at altitudes between 780 m and 1200 m a.s.l., when no ticks were detected above 800 m a.s.l., and few between 780 m and 800 m a.s.l. Similarly no ticks were detected in the same region during surveys at 760 m a.s.l. between 1979 and 1980. These tick distribution changes have been shown to be linked to changes in climate (Daniel et al., 2004).

The impact of climate variability on disease occurrence is more complex than the effects that the climate may have on the distribution and population density of the vectors (see Fig. 5, Section 4.2). Studies on the effects of long-term climate variations on tick-borne disease prevalence are affected by several scientific problems. Data vary between places and over time owing to differences in awareness, surveillance, and diagnostic methods, which so far have made longterm studies on LB difficult to perform. However, reliable data on TBE are available from some localized areas, for example from Stockholm County in Sweden where a surveillance programme ran for four decades after an outbreak in the late 1950s. Changes in incidence of TBE in the county during this time period have been shown to be related to changes in daily seasonal climate represented by "accumulated temperature days" (Lindgren, 1998; Lindgren & Gustafson, 2001). These TBE findings are of interest for the understanding of changes in LB prevalence as the incidences of both diseases show similar annual patterns, as shown in Fig. 2b and 2c. However, it has been suggested that TBE transmission should be negatively affected by a warmer climate, with the hypotheses being that rapid cooling in autumn will allow more larvae and nymphs to feed together in the following spring, and that this is more important for pathogen transmission for TBE than for LB due to shorter viremia (Randolph, 2001). No such relationships have been found at higher latitudes or altitudes (Lindgren & Gustafson, 2001; Randolph, 2001; Zeman & Benes, 2004).

6. Possible future effects of climate change in Europe

Global temperatures are predicted to continue to increase, and at a rate faster than at any time before in human history with the risk of causing greater instability in regional climates with changes in precipitation and wind patterns. In the latest report from the United Nations' Intergovernmental Panel on Climate Change (IPCC, 2001) the following predictions for Europe are listed: in northern Europe and the Alps the climate is likely to become generally milder and precipitation will increase over the next 50 to 100 years. Winter temperatures will rise proportionally more at high latitudes; the region as a whole will experience higher increases in night compared to day temperatures; the vegetation season is projected to increase in length (for example in Sweden this could be as much as 1–2 months) (Christensen et al., 2001); increased risk for flooding is expected to occur, particularly in the northern and north-western parts of Europe, whereas more summer droughts are expected in the southern parts. These are all conditions that could affect the distribution and population density of ticks and their host animals and alter the vegetation composition of tick habitats over the coming decades.

The possible impact of future climate change on LB risk in Europe can be surmised by investigating the impact of climate on the observed spatial and temporal heterogeneities described above. Soon it should be possible to generate biological "process-based" (i.e., taking into account the multiyear life cycles) models of *I. ricinus* abundance, seasonality, and distribution (Randolph et al., 2002). However, to date, attempts to predict *I. ricinus* or LB distributions have largely been limited to statistical "pattern-matching" models (e.g. Daniel & Kolar, 1991; Daniel & Dusabek, 1994; Estrada-Peña, 1997, 1998, 1999, 2002; Zeman, 1997;

Daniel et al., 1999; Zeman & Januska, 1999; Randolph, 2001; Rizzoli et al., 2002;). Such statistical models provide some insight into possible impacts of climate change, but conclusions should be drawn with caution (Randolph et al., 2002).

Taking current knowledge from different disciplines it is possible to make theoretical projections of future changes in disease burden in Europe. Based on the results of the studies reviewed for this extensive report it seems most probable that a future climate change in Europe will:

- facilitate a spread of LB into higher latitudes and higher altitudes;
- contribute to an extended and more intense LB transmission season in some areas;
- diminish the risk of LB, at least temporarily, in locations with repeated droughts or severe floods.

7. Adaptation and preventive measures

7.1. Diagnosis and treatment

LB is a multisystem disorder, which can affect a complex range of tissues. The clinical presentations can generally be divided into three stages, but progress from an early to a later stage does not always occur. The early infection consists of localized erythema migrans (stage 1), which occurs in about 60–80% of cases within 2–30 days of a tick bite and consists of a red skin rash or lesion spreading from the site of the bite. If left untreated, a disseminated infection that affects the nervous system, joints and/or the heart (stage 2) may follow within days or weeks. Neuroborreliosis occurs in about 20% of LB cases, arthritis in 10%, while carditis is rare. Among children, *B. burgdorferi* s.l. is now the most common bacterial cause of encephalitis and facial palsy/paralyses. Chronic LB (stage 3) is nowadays uncommon. In the United States chronic LB causes symptoms mainly in the joints, particularly the knee, whereas in Europe chronic symptoms are more diverse and include a rare degenerative skin condition called acrodermatitis chronica atrophicans, which mainly occurs in elderly women. It has been suggested that different genospecies of *B. burgdorferi* s.l. are associated with different clinical manifestations, as shown in Table 5. However the symptoms often overlap between genospecies (Schaarschmidt et al., 2001; Ornstein et al., 2002).

Laboratory evidence of infection, by demonstration of specific antibodies, is not required for the diagnosis of erythema migrans but for all other clinical manifestations of LB; especially as *I. ricinus* may transmit several other zoonotic pathogenic organisms, some of which may interact with *B. burgdorferi* s.l. and affect LB diagnosis and epidemiology (Table 6). Co-infection can result in one of the diseases being overlooked, particularly when symptoms are similar, for example for TBE and early LB neuroborreliosis. Some other diseases transmitted by ticks, such as human erlichiosis and babesiosis, are immunosuppressive and can affect the severity of the infections and lead to treatment difficulties (EUCALB; Krause et al., 1996, 2002). Co-infection with human erlichiosis has, for example, been found in 11.4% of LB cases in a study from southern Germany (Fingerle et al., 1999).

Most infections with *B. burgdorferi* are asymptomatic and self-limiting, so no treatment is required if antibodies are found in individuals without clinical symptoms. However, patients showing symptoms with adequate supporting laboratory evidence for diagnosis should be treated to prevent possible progression of the disease. A range of antibiotics is available such as penicillin, cephalosporin and tetracycline but their selection and use vary between countries. If

treatment is initiated in a local or disseminated early stage, healing rates of more than 85% can be achieved (Hofmann, 2002).

Table 5. Distribution of the different pathogenic European genospecies of *B. burgdorferi* sensu lato, their main reservoir hosts, and their predominant LB symptoms

Genospecies	Predominant clinical manifestation	Main distribution	Predominant reservoir host
B. garinii	Neurological symptoms ^{1,2}	Western Europe ³	Birds ^{4,8,12} (Rodents) ⁴
B. afzelii	Acrodermatitis chronica atrophicans ^{1,2}	Central, eastern ³ and northern Europe and Scandinavia ^{5,6}	Rodents ⁷
B. burgdorferi s.s.	Arthritis ⁷	USA ⁹	Rodents ⁴
		Sparsely in Europe and the Russian Federation ¹⁰	Birds
<i>B. valaisiana</i> (suspected to be pathogenic)	Unknown	Mainly Ireland, but also the United Kingdom, Netherlands, Scandinavia, Switzerland, Italy ^{10,11}	Birds ^{4,12}

Source: ¹ Van Dam et al., 1993; ² Balmelli & Piffaretti, 1995; ³ Ruzic-Sabljic et al., 2002; ⁴ Kurtenbach et al., 1998b; ⁵ Jenkins et al., 2001; ⁶ Fraenkel et al., 2002; ⁷ Humair et al., 1999; ⁸ Gylfe et al., 2000; ⁹ Steere, 2001; ¹⁰ Alekseev, 2001; ¹¹ Santino et al., 2002; ¹² Humair et al., 1998

Dogs, horses and possibly cattle can suffer from manifestations of LB, particularly joint-associated symptoms (Stanek et al., 2002).

Table 6. Pathogens that may be co-transmitted with B. burgdorferi s.l. by ixodid ticks

Organism	Disease
Babesia divergens	Babesiosis
Babesia microti	Babesiosis
Coxiella burnetii	Q fever
Anaplasma spp.(previously named Ehrlichia)	Erlichiosis
Francisella tularensis	Tularaemia
Tick-borne encephalitis virus	Tick-borne encephalitis

Source: EUCALB.

7.2. Vaccination

There has been uncertainty whether a vaccine is cost-effective, owing to the high cost of the vaccine, the low risk of LB in many areas and the largely curable nature of the disease. It has been shown that a vaccine is cost-effective only for people living or working in endemic areas who are frequently exposed to tick bites (Hsia et al., 2002). Since there appears to be much more heterogeneity among the different pathogenic European genospecies of *B. burgdorferi* s.l. (Ciceroni et al., 2001) it will probably be necessary to produce a "cocktail" of surface proteins

The WHO Regional Office for Europe

The World Health Organization (WHO) is a specialized agency of the United Nations created in 1948 with the primary responsibility for international health matters and public health. The WHO Regional Office for Europe is one of six regional offices throughout the world, each with its own programme geared to the particular health conditions of the countries it serves.

Member States

Albania Andorra Armenia Austria Azerbaija Belarus Belgium Bosnia and Herzegovina Bulgaria Croatia Cyprus **Czech Republic** Denmark Estonia Finland France Germany Greece lungary Ireland Israel Italv Kazakhsta Kyrgyzstan Latvia Lithuania Malta Monaco Monteneo Vetherlan Vorwav Portugal Republic of Moldova Romania Russian Federation San Marino ovenia Switzerland aiikistan The former Yugoslav Republic of Macedonia Turkey Turkmenistar Ukraine United Kingdom Uzbekistan

ISBN 92 890 2291 4 WHOLIS no.:E89522 Original: English

LYME BORRELIOSIS IN EUROPE: INFLUENCES OF CLIMATE AND CLIIMATE CHANGE, EPIDEMIOLOGY, ECOLOGY AND ADAPTATION MEASURES

Stockholm University and WHO, within a project funded by the European Commission reviewed the impacts of climate change and adaptation on Lyme borreliosis (LB) in Europe.

LB is the most common vector-borne disease in Europe. The highest incidence is reported from Austria, the Czech Republic, Germany, and Slovenia, as well as from the northern countries bordering the Baltic Sea. LB is a multi-system disorder that is treatable with antibiotics, but may lead to severe complications of the neurological system, the heart, and the joints.

LB is caused by a spirochete (*Borrelia burgdorferi* s.l.), which is transmitted to humans by ticks, in Europe mainly the species *Ixodes ricinus*. Reservoir animals are small rodents, insectivores, hares and birds.

Ticks may live for more than three years and are highly sensitive to changes in seasonal climate. Daily seasonal climatic conditions directly impact tick survival and activity. Indirectly, climate affects both tick and pathogen occurrence through effects on habitat conditions and reservoir animal density. In addition, climate-induced changes in land use and in recreational behaviour influence human exposure to infected ticks and thus disease prevalence.

Since the 1980s, tick vectors have increased in density and spread into higher latitudes and altitudes in Europe. It can be concluded that future climate change in Europe will facilitate a spread of LB into higher latitudes and altitudes, and contribute to increased disease occurrence in endemic areas. In some locations, where climate conditions will become too hot and dry for tick survival, LB will disappear.

There is a need to strengthen preventive measures such as information to the general public, surveillance activities within a pan-European network and to use standardized methods to provide data for future research activities.

By: Elisabet Lindgren Thomas G.T. Jaenson

World Health Organization Regional Office for Europe

Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark Tel.: +45 39 17 17 17. Fax: +45 39 17 18 18. E-mail: postmaster@euro.who.int Web site: www.euro.who.int

Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures

for an effective vaccine in Europe. However, it is unlikely that adequate protection against all strains will be achieved.

7.3. Control targeted at the vector

Acaricides used on vegetation have been shown to reduce the density of ticks throughout the activity season if applied in late spring (Schulze & Jordan, 1995). However, most of the chemicals are costly, short-lived and non-specific and may cause ecological disturbances. They should not be recommended unless severe, epidemic situations are prevalent (Jaenson et al., 1991). Acaricides such as permethrin may be applied on animals that serve as tick hosts, and could be used successfully on livestock (Gray et al., 1998a). Permethrin should be used with caution, though, as it is known to be highly toxic to aquatic organisms including fish, and to honeybees (Begon et al., 1996).

The role of biological agents in regulating tick populations has so far been poorly investigated. Hill (1998) argues for the possibility of releasing certain nematode species that are pathogenic to engorged female ticks as a measure of tick control. The risk of unexpected negative ecological effects should be carefully considered before such types of method are used.

Private gardens and city parks could be landscaped in such a way that it helps reduce tick and host animal abundance. Short-cut lawns hold few ticks for example (Duffy & Campbell, 1994). Choosing plants that are not attractive as forage for larger hosts such as roe deer and hares helps reduce the risk of accidental tick introduction into gardens and parks (Jaenson et al., 1991). Repeated removal of undergrowth and leaf litter has been shown to reduce considerably the amount of *I. scapularis* (Schulze & Jordan, 1995).

Controlled burning of the vegetation affects ticks directly by exposure to lethal temperatures and indirectly by removing suitable vegetation for surviving ticks. Tick mortality will depend on the intensity of the fire, the time of the year that the burning takes place and the post-burn vegetation conditions (Schmidtmann, 1994). However, other species will be negatively affected, and extensive burning contributes to emissions of greenhouse gases.

7.4. Control targeted at the reservoir host

Changes in the composition of host species in an area could change the risk of infection. However, to what degree depends on the new proportion between reservoir competent and incompetent host animals in relation to the density of the different tick stages (Jaenson & Tälleklint, 1999). Effective disease control would require massive population reduction of both reservoir species and larger host animals, such as roe deer (Tälleklint & Jaenson, 1994), and is therefore not feasible. A less radical method is to use deer fences. They significantly reduce the abundance of immature tick stages in the non-deer area, but it does not result in elimination of ticks. Medium-sized mammals play a role in introducing adult ticks into areas where deer have been excluded, so the density in the non-deer area will be related to the density of ticks on the other side of the deer fence (Daniels & Fish, 1995). The domestic cat can be used in residential areas for the control of mice populations, but this will only have limited effects on disease prevention.

7.5. Information and health education

The most effective preventive method available for LB is information to the general public (Gray et al., 1998b; O'Connell et al., 1998). Knowledge about LB has been shown to be notably higher

in endemic areas compared to non-endemic ones – a difference mainly due to differences in media coverage (Gray et al., 1998b). Swedish media, for example, broadcast or print information about risk areas, risk periods and personal preventive measures at the beginning of the tick activity period in spring each year. With increasing tourism within the European Region it is important to target visitors to tick endemic areas as well. Several informative web sites about LB risk and prevention are now available for the general public, for example the National Public Health Service for Wales (http://www.phls.wales.nhs.uk/lyme.htm), and the Lyme Disease Network, Lymenet, in the United States (http://www.lymenet.org).

There are several effective methods available for personal protection against tick bites in addition to knowledge about risk areas, risk periods and the use of adequate gardening practices.

- Proper clothing, such as boots, should be worn when visiting tick-infested locations. Trousers and sweaters should be tightened or tucked in at ankles, wrists and waist (Tälleklint & Jaenson, 1995).
- Chemical repellents can be applied on the clothes. N-diethyl-toulamide (DEET), the agent used in mosquito-repellents, has been shown to be effective in preventing *I. ricinus* from adhering to clothing (Jaenson et al., 2003).
- Routine control of body and clothes directly after activities in tick-infested vegetation can reduce tick attachment. Daily self-inspection and prompt tick removal is protective against LB.
- The fur of pet animals that are kept in tick-infested areas should be inspected regularly for ticks, particularly for attached female adults. Otherwise, such pets could contribute considerably to an increasing density of ticks in adjacent gardens and surroundings (Thomas GT Jaenson, unpublished observations).

In addition, in-depth education about clinical symptoms, diagnosis, treatment, risk factors, surveillance, etc. should be provided to health personnel not only in endemic areas but also in potential new risk regions.

7.6. Surveillance and monitoring

Several initiatives have been taken lately to address LB in Europe and to promote monitoring and the sharing of information. The European Union concerted action on Lyme borreliosis (EUCALB) targets professional groups, ranging from scientific researchers to public health workers. Their web site provides up-to-date information about scientific publications and other LB activities around Europe. The Network for Communicable Disease Control in Northern Europe (Epinorth) consists of infectious disease control institutes in Denmark, Norway, Iceland, Sweden, Finland, the Russian Federation, Estonia, Latvia and Lithuania. The aim of this network is to share information and register data on major infectious diseases, including LB, in this region.

There is a need for the establishment and funding of several surveillance centres throughout Europe. These should be set up within a pan-European network to record changes in the reported number of human cases and in tick and pathogen prevalence in nature, including areas that have previously not been investigated. The following recommendations should be considered when data is collected.

• Standardized methods for tick collection should be employed. The methods should – if possible – not be changed over time to allow future comparisons. Sampling should be sufficiently frequent in time and space.

- Standardized methods for estimating spirochete prevalence in ticks in Europe should be employed.
- Other tick-borne pathogens, such as the TBE virus, should be included in surveillance.
- Samples of ticks from a number of localities in Europe should be preserved at low temperature (<-80 °C) for future use (when new and better diagnostic methods are available) to allow future scientists to analyse potential changes of infection rates of ticks with "old" and "newly emerged" pathogens.

7.7. Future research needs

The impact of climatic factors (ambient temperatures, air and soil humidity, etc.) on the lifecycle dynamics of the different vector species of LB has been thoroughly documented in many laboratory studies. In addition, some parts of Europe have been rather well investigated with regard to tick distribution, habitat vegetation, host composition, infectivity of ticks/hosts/humans and seasonality patterns. However, more of these latter types of local studies are needed for the whole European Region. Also, better transdisciplinary-based mathematical scenario models need to be developed, as discussed in Section 6, to address alterations in LB risk areas and disease burden in Europe from a future climate change.

8. Conclusions

It is likely that climate change has already led to changes in *I. ricinus* populations in Europe. Even if existing data are in general not reliable enough to allow comparisons over time and in space of changes in tick prevalence and disease incidence on a pan-European level, some studies from specific areas have been based on particularly reliable long-term data sets (Daniel et al., 2003). These studies have shown that recently observed increases in density and expansion in the distribution of *I. ricinus* into higher altitudes and latitudes are correlated to changes in local climate, just as observed variations in tick-borne disease incidence in places with long-term surveillance data have been shown to be linked to variations in local climatic conditions.

Based on the results of all the different studies that have been reviewed it can be concluded that future climate change in Europe will facilitate a spread of LB into higher latitudes and altitudes, and contribute to an extended and more intense LB transmission season in some areas. In other areas, where future climate change will cause climate conditions too hot and dry for tick survival, LB will disappear.

References

Adler GH et al. (1992). Vegetation structure influences the burden of immature *Ixodes dammini* on its main host, *Peromyscus leucopus*. *Parasitology*, 105:105–110.

Aeschlimann A et al. (1986). *B.burgdorferi* in Switzerland. *Zentralblatt für Bakteriologie, Mikrobiologie, und Hygiene, Series A*, 263:450–458.

Alekseev AN et al. (2001). Identification of *Ehrlichia* spp. and *Borrelia burgdorferi* in Ixodes ticks in the Baltic regions of Russia. *Journal of Clinical Microbiology*, 39(6):2237–2242.

Åsbrink E, Olsson I, Hovmark A (1986). Erythema chronicum migrans Afzelius in Sweden. A study on 231 patients. *Zentralblatt für Bakteriologie, Mikrobiologie, und Hygiene, Series A*, 263:229–236.

Balashov YS (1972). Bloodsucking ticks (Ixodoidea) - vectors of diseases of man and animals. *Miscellaneous Publications of the Entomological Society of America*, 8:163–176.

Balmelli T, Piffaretti JC (1995). Association between different clinical manifestations of Lyme disease and different species of *Borrelia burgdorferi* sensu lato. *Research in Microbiology*, 16:329–340.

Barbour AG (1984). Isolation and cultivation of Lyme disease spirochetes. *The Yale Journal of Biology and Medicine*, 57(4):521–525.

Begon M, Harper J, Townsend CR (1996). Ecology. Oxford, Blackwell Science Ltd.

Beniston M, Tol RSJ (1998). Europe. In: *The Regional impacts of climate change: An assessment of vulnerability*. A Special Report of IPCC Working Group II. New York, Cambridge University Press, 149–187.

Berglund J et al. (1995). An epidemiologic study of Lyme disease in southern Sweden. *New England Journal of Medicine*, 333(20):1319–1327.

Berglund J, Eitrem R, Norrby SR (1996). Long-term study of Lyme borreliosis in a highly endemic area in Sweden. *Scandinavian Journal of Infectious Diseases*, 28(5):473–478.

Berry MO (1981). Snow and climate. In: Gray DM, Male DH, eds. *Handbook of snow*. Toronto, Pergamon Press, 32–59.

Carlsson SA et al. (1998). IgG seroprevalence of Lyme borreliosis in the population of the Åland Islands in Finland. *Scandinavian Journal of Infectious Diseases*, 30(5):501–503.

Cederlund G, Liberg O (1995). Rådjuret. Viltet, ekologin och jakten. [*The roe deer. Wildlife, ecology and hunting*]. Uppsala, Almqvist and Wiksell.

Christensen JH et al. (2001). A synthesis of regional climate change simulations. A Scandinavian perspective. *Geophysical Research Letters*, 28:1003–1006.

Ciceroni L, Ciarrocchi S (1998). Lyme disease in Italy, 1993-1996. *The New Microbiologica*, 21(4):407–418.

Ciceroni L et al. (1996). Antibodies to *Borrelia burgdorferi* in sheep and goats. Alto Adige-South Tyrol, Italy. *The New Microbiologica*, 19(2):171–174.

Ciceroni L et al. (2001). Isolation and characterization of *Borrelia burgdorferi* sensu lato strains in an area of Italy where Lyme borreliosis is endemic. *Journal of Clinical Microbiology*, 39(6):2254–2260.

Cizman M et al. (2000). Seroprevalence of erlichiosis, Lyme borreliosis and tick-borne encephalitis infections in children and young adults in Slovenia. *Wiener klinische Wochenschrift*, 112(19):842–845.

Clark DD (1995). Lower temperature limits for activity of several Ixodid ticks (Acari: Ixodidae): effects of body size and rate of temperature change. *Journal of Medical Entomology*, 32(4):449–452.

Craine NG et al. (1997). Role of grey squirrels and pheasants in the transmission of *Borrelia Burgdorferi* sensu lato, the Lyme disease spirochaete, in the UK. *Folia Parasitologica*, 44:155–160.

Cristofolini A, Bassetti D, Schallenberg G (1993). Zoonoses transmitted by ticks in forest workers (tick-borne encephalitis and Lyme borreliosis): preliminary results. *La Medicina del Lavoro*, 84:394–402.

Daniel M (1993). Influence of the microclimate on the vertical distribution of the tick *Ixodes ricinus* (L.) in central Europe. *Acarologica*, XXXIV(2):105–113.

Daniel M, Dusabek F (1994). Micrometerological and microhabitat factors affecting maintenance and dissemination of tick-borne diseases in the environment. In: Sonenshine DE, Mather TN, eds. *Ecological dynamics of tick-borne zoonoses*. New York, Oxford University Press, 391–1138.

Daniel M, Kolár J (1991). Using satellite data to forecast the occurrence of the common tick *Ixodes ricinus*. *Modern Acarology*, 1:191–196.

Daniel M et al. (1977). Influence of microclimate on the life cycle of the common tick *Ixodes ricinus* (L.) in an open area in comparison with forest habitats. *Folia Parasitologica*, 24:149–160.

Daniel M et al. (1999). Tick-borne encephalitis and Lyme borreliosis: comparison of habitat risk assessments using satellite data (an experience from the Central Bohemian region of the Czech Republic). *Central European Journal of Public Health*, 7(1):35–39.

Daniel M et al. (2003). Shift of the tick *Ixodes ricinus* and tick-borne encephalitis to higher altitudes in central Europe. *European Journal of Clinical Microbiology and Infectious Disease*, 22(5):327–328.

Daniel M et al. (2004). An attempt to elucidate the increased incidence of tick-borne encephalitis and its spread to higher altitudes in the Czech Republic. *International Journal of Medical Microbiology*, 293(37):55–62.

Daniels TJ, Fish D (1995). Effect of deer exclusion on the abundance of immature *Ixodes scapularis* (Acari: Ixodidae) parasitizing small and medium-sized mammals. *Journal of Medical Entomology*, 32(1):5–11.

Dautel H, Knülle W (1997). Cold hardiness, super cooling ability and causes of low-temperature mortality in the soft tick, *Argas reflexus*, and hard tick, *Ixodes ricinus* (Acari: Ixodoidea) from Central Europe. *Journal of Insect Physiology*, 42(9):843–854.

De Boer R et al. (1993). The woodmouse (*Apodemus sylvaticus*) as a reservoir of ticktransmitted spirochetes (*Borrelia burgdorferi*) in The Netherlands. *Zentralblatt für Bakteriologie: International Journal of Medical Microbiology*, 279(3):404–416.

De Michelis S et al. (2000). Genetic diversity of *Borrelia burgdorferi* sensu lato in ticks from mainland Portugal. *Journal of Clinical Microbiology*, 38(6):2128–2133.

De Mik EL et al. (1997). The geographical distribution of tick bites and erythema migrans in general practice in The Netherlands. *International Journal of Epidemiology*, 26(2):451–457.

Dister SW et al. (1997). Landscape characterization of peridomestic risk for Lyme disease using satellite imagery. *American Journal of Tropical Medicine and Hygiene*, 57(6):687–692.

Dobson A, Carper R (1993). Biodiversity. Lancet, 342:1096–1099.

Duffy DC, Campbell SR (1994). Ambient air temperature as a predictor of activity of adult *Ixodes scapularis* (Acari: Ixodidae). *Journal of Medical Entomology*, 31:178–180.

Easterling DR, Horton B, Jones FD (1997). Maximum and minimum temperature trends for the globe. *Science*, 277:363–367.

Epinorth (2003) [web site]. A co-operation project for communicable disease control in Northern Europe. Epidata on Lyme borreliosis (http://www.epinorth.org, accessed 13 December 2003).

Epstein PR (1999). Climate and health. Science, 285(5426):347-348.

Estrada-Peña A (1997). Epidemiological surveillance of tick populations: A model to predict the colonization success of *Ixodes ricinus* (Acari:Ixodidae). *European Journal of Epidemiology*, 13(5):573–580.

Estrada-Peña A (1998). Geostatistics and remote sensing as predictive tools of tick distribution: a cokriging system to estimate *Ixodes scapularis* (Acari: Ixodidae) habitat suitability in the United States and Canada from advanced very high resolution radiometer satellite imagery. *Journal of Medical Entomology*, 35(6):989–995.

Estrada-Peña A (1999). Geostatstics as predictive tools to estimate *Ixodes ricinus* (Acari: Ixodidae) habitat suitability in the western palearctic from AVHRR satellite imager. *Experimental and Applied Acarology*, 23(4):337–349.

Estrada-Peña A (2002). Increasing habitat suitability in the United States for the tick that transmits Lyme disease: a remote sensing approach. *Environmental Health Perspectives*, 110(7):635–640.

EUCALB, European Union concerted action on Lyme borreliosis [web site]. (http://www.dis.strath.ac.uk/vie/LymeEU/, accessed 13 December, 2003).

Fingerle V et al. (1999). Epidemiological aspects of human granulocytic Ehrlichiosis in southern Germany. *Wiener Klinische Wochenschrift*, 111(22–23):1000–1004.

Fraenkel CJ, Garpmo U, Berglund J (2002). Determination of novel borrelia genospecies in Swedish *Ixodes ricinus* ticks. *Journal of Clinical Microbiology*, 40(9):3308–3312.

Fujimoto K (1994). Comparison of the cold hardiness of *Ixodes nipponensis* and *I. persulcatus* (Acari: Ixodidae) in relation to the distribution patterns of both species in Chichibu Mountains. *Japanese Journal of Sanitary Zoology*, 1:333–339.

Gern L et al. (1991). *Ixodes (Pholeoixodes) hexagonus,* an efficient vector of *Borrelia burgdorferi* in the laboratory. *Medical and Veterinary Entomology*, 5:431–435.

Gern L et al. (1998). European reservoir hosts of *Borrelia burgdorferi* sensu lato. *Zentralblatt für Bakteriologie: International Journal of Medical Microbiology*, 287:196–204.

Gigon F (1985). Biologie d'Ixodes ricinus L. sur le Plateau Suisse – une contribution à l'écologie de ce vector. [Biology of Ixodes ricinus on the Plateau Suisse – a contribution to the vector's ecology] [Dissertation]. Faculty of Sciences, University of Neuchâtel.

Glass GE et al. (1995). Environmental risk factors for Lyme disease identified with geographic information systems. *American Journal of Public Health*, 85(7):944–948.

Goossens HA, van der Bogaard AE, Nohlmans MK (2001). Dogs as sentinels for human *Lyme borreliosis* in The Netherlands. *Journal of Clinical Microbiology*, 39(3):844–848.

Gorelova NB et al. (1995). Small mammals as reservoir hosts for borrelia in Russia. Zentralblatt für Bakteriologie: International Journal of Medical Microbiology, 282:315–322.

Gray JS (1981). The fecundity of *Ixodes ricinus* (L.) (Acarina: Ixodidae) and the mortality of its development stages under field conditions. *Bulletin of Entomological Research*, 71:533–542.

Gray JS (1991). The development and seasonal activity of the tick, *Ixodes ricinus*: a vector of *Lyme borreliosis*. *Review of Medical and Veterinary Entomology*, 79:323–333.

Gray JS et al. (1998a). Lyme borreliosis habitat assessment. Zentralblatt für Bakteriologie: International Journal of Medical Microbiology, 287(3):211–228.

Gray JS et al. (1998b). Lyme borreliosis awareness. Zentralblatt für Bakteriologie: International Journal of Medical Microbiology, 287(3):253–265.

Gray JS et al. (1992). Studies on the ecology of Lyme disease in a deer forest in County Galway, Ireland. *Journal of Medical Entomology*, 29(6):915–920.

Gray JS et al. (1994). Acquisition of *Borrelia burgdorferi* by *Ixodus ricinus* ticks fed on the European hedgehog, *Erinaceus europaeus* L. *Experimental and Applied Acarology*, 18(8):485–491.

Gubler DJ et al. (2001). Climate variability and change in the United States: potential impacts on vector- and rodent-borne diseases. *Environmental Health Perspectives*, 109 Suppl 2:223–233.

Gustafson R et al. (1993). Clinical manifestations and antibody prevalence of Lyme borreliosis and tick-borne encephalitis in Sweden: a study in five endemic areas close to Stockholm. *Scandinavian Journal of Infectious Diseases*, 25(5):595–603.

Gylfe A et al. (2000). Reactivation of borrelia infection in birds. Nature, 403(6771):724–725.

Heroldova M, Nemec M, Hubalek Z (1998). Growth parameters of *Borrelia burgdorferi* sensu stricto at various temperatures. *Zentralblatt für Bakteriologie: International Journal of Medical Microbiology*, 288(4):451–455.

Hill DE (1998). Entomopathogenic nematodes as control agents of developmental stages of the black-legged tick, *Ixodes scapularis*. *Journal of Parasitology*, 84(6):1124–1127.

Hofmann H (2002). Early diagnosis of Lyme borreliosis. Do not look only for erythema migrans. *MMW Fortschritte der Medizin*, 144(22):24–28.

Hovmark A et al. (1988). First isolation of *Borrelia burgdorferi* from rodents collected in northern Europe. *Acta Pathologica et Microbiologica Scandinavica*, 96:917–920.

Hristea A et al. (2001). Seroprevalence of *Borrelia burgdorferi* in Romania. *European Journal of Epidemiology*, 17(9):891–896.

Hsia EC et al. (2002). Cost-effectiveness analysis of the Lyme disease vaccine. *Arthritis and Rheumatism*, 46(6):1651–1660.

Hubalek Z, Halozka J, Heroldova M (1998). Growth temperature ranges of *Borrelia burgdorferi* sensu lato strains. *Journal of Medical Microbiology*, 47(10):929–932.

Humair PF, Gern L (2000). The wild hidden face of Lyme borreliosis in Europe. *Microbes and Infection*, 2:915–922.

Humair PF et al. (1998). An avian reservoir (*Turdus merula*) of the Lyme disease spirochetes. *Zentralblatt für Bakteriologie:International Journal of Medical Microbiology*, 287:521–538.

Humair PF, Rais O, Gern L (1999). Transmission of *Borrelia afzelii* from Apodemus mice and Clethrionomys voles to *Ixodes ricinus* ticks: differential transmission pattern and overwintering maintenance. *Parasitology*, 118:33–42.

Huppertz HI et al. (1999). Incidence of Lyme borreliosis in the Wurzburg region of Germany. *European Journal of Clinical Microbiology and Infectious Diseases*, 18(10):697–703.

IPCC (2001). *Climate change 2001: The third assessment report of the Intergovernmental Panel on Climate Change*. Cambridge, Cambridge University Press.

Jaenson TGT (1991). The epidemiology of Lyme borreliosis. Parasitology Today, 7:39-45.

Jaenson TGT, Tälleklint L (1996). Lyme borreliosis spirochetes in *Ixodes ricinus* and the varying hare on isolated islands in the Baltic sea. *Journal of Medical Entomology*, 33(3):339–343.

Jaenson TGT, Tälleklint L (1999). The reservoir hosts of *Borrelia burgdorferi* sensu lato in Europe. In: Needham G, Mitchell R, Horn DJ, Welbourn WC, eds. *Acarology IX. Vol. 2, Symposia*. Columbus, Ohio Biological Survey, 409–414.

Jaenson TGT, Lindström A, Pålsson K (2003). Repellency of the mosquito repellent MyggA (*N*,*N*-diethyl-3-methyl-benzamide) to the common tick *Ixodes ricinus* (L.)(Acari: Ixodidae) in the laboratory and field. *Entomologisk Tidskrift*, 124:245–251.

Jaenson TGT et al. (1991). Methods for control of tick vectors of Lyme borreliosis. *Scandinavian Journal of Infectious Diseases*, 77(Suppl):151–157.

Jaenson TGT et al. (1994). Geographical distribution, host associations, and vector roles of ticks (Acari: Ixodidae, Argasidae) in Sweden. *Journal of Medical Entomology*, 31(2):240–256.

Jenkins A et al. (2001). *Borrelia burgdorferi* sensu lato and *Ehrlichia* spp. in Ixodes ticks from southern Norway. *Journal of Clinical Microbiology*, 39(10):3666–3671.

Jensen PM, Frandsen F (2000). Temporal risk assessment for Lyme borreliosis in Denmark. *Scandinavian Journal of Infectious Diseases*, 32(5):539–544.

Jensen PM, Hansen H, Frandsen F (2000). Spatial risk assessment for Lyme borreliosis in Denmark. *Scandinavian Journal of Infectious Diseases*, 32:545–550.

Jones CG et al. (1998). Chain reactions linking acorns to gypsy moth outbreaks and Lyme disease risk. *Science*, 279(5353):1023–1026.

Junttila J et al. (1999). Prevalence of *Borrelia burgdorferi* in *Ixodes ricinus* ticks in urban recreational areas of Helsinki. *Journal of Clinical Microbiology*, 37(5):1361–1365.

Kahl O et al. (1998). Risk of infection with *Borrelia burgdorferi* sensu lato for a host in relation to the duration of nymphal *Ixodes ricinus* feeding and the method of tick removal. *Zentralblatt für Bakteriologie: International Journal of Medical Microbiology*, 287:41–52.

Kahl O, Knülle W (1988). Water vapour uptake from subsaturated atmospheres by engorged immature ixodid ticks. *Experimental and Applied Acarology*, 4(1):73–83.

Kaiser R (1995). Tick-borne encephalitis in southern Germany. Lancet, 345:463.

Korenberg EI (1994). Problems of epizootiology, epidemiology and evolution associated with modern borrelia taxonomy. In: Yanagihara Y and Masuzawa T, eds. *Present status of Lyme disease and biology of Lyme borrelia*. Shizuoka, Japan, 18–47.

Korenberg EI (2000). Seasonal population dynamics of *Ixodes* ticks and tick-borne encephalitis virus. *Experimental and Applied Acarology*, 24:665–681.

Krause PJ et al. (1996). Concurrent Lyme disease and babesiosis. Evidence for increased severity and duration of illness. *JAMA: the Journal of the American Medical Association*, 275(21):1657–1660.

Krause PJ et al. (2002). Deer-Associated Infection Study Group. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. *Clinical Infectious Diseases*, 34(9):1184–1191.

Kuiper H et al. (1993). One year follow-up study to assess the prevalence and incidence of Lyme borreliosis among Dutch forestry workers. *European Journal of Clinical Microbiology and Infectious Diseases*, 12(6):413–418.

Kurtenbach K et al. (1998a). Competence of pheasants as reservoirs for Lyme disease spirochetes. *Journal of Medical Entomology*, 35(1):77–81.

Kurtenbach K et al. (1998b). Differential transmission of the genospecies of *Borrelia burgdorferi* sensu lato by game birds and small rodents in England. *Applied and Environmental Microbiology*, 64(4):1169–1174.

Kurtenbach K et al. (2002). Host association of *Borrelia burgdorferi* sensu lato - the key role of host complement. *Trends in Microbiology*, 10(2):74–79.

Lindgren E (1998). Climate and tick-borne encephalitis. *Conservation Ecology*, 2(1)5:1–14 (http://www.consecol.org/Journal/vol2/iss1/art5/, accessed 13 December, 2003).

Lindgren E (forthcoming). Managing the human life-supporting environment for disease transmission.

Lindgren E, Gustafson R (2001). Tick-borne encephalitis in Sweden and climate change. *Lancet*, 358:16–18.

Lindgren E, Tälleklint L, Polfeldt T (2000). Impact of climatic change on the northern latitude limit and population density of the disease-transmitting European tick, *Ixodes ricinus*. *Environmental Health Perspectives*, 108(2):119–123.

Lindsay IR et al. (1995). Survival and development of *Ixodes scapularis* (Acari: Ixodidae) under various climatic conditions in Ontario, Canada. *Journal of Medical Entomology*, 32:143–152.

Matuschka FR et al. (1992). Capacity of European animals as reservoir hosts for the Lyme disease spirochete. *The Journal of Infectious Diseases*, 165:479–483.

Mejlon HA (1997). Diel activity of *Ixodes ricinus* Acari: Ixodidae at two locations near Stockholm, Sweden. *Experimental and Applied Acarology*, 21:247–255.

Mejlon HA, Jaenson TGT (1993). Seasonal prevalence of *Borrelia burgdorferi* in *Ixodes ricinus* (Acari: Ixodidae) in different vegetation types in Sweden. *Scandinavian Journal of Infectious Diseases*, 25:449–456.

Mejlon HA, Jaenson TGT (1997). Questing behaviour of *Ixodes ricinus* ticks (Acari: Ixodidae). *Experimental and Applied Acarology*, 21:747–754.

Memeteau S et al. (1998). Assessment of the risk of infestation of pastures by *Ixodes ricinus* due to their phyto-ecological characteristics. *Veterinary Research*, 29(5):487–496.

Montiejunas L et al. (1994). Lyme borreliosis in Lithuania. *Scandinavian Journal of Infectious Diseases*, 26(2):149–155.

Mulic R et al. (2000). Lajmska borelioza u Hrvatskoj od 1987. do 1998 - epidemioloski aspekt. [Lyme borreliosis in Croatia from 1987 to 1998 – epidemiological aspects]. *Lijecnicki Vjesnik*, 122(9–10):214–217.

Nilsson A (1988). Seasonal occurrence of *Ixodes ricinus* (Acari) in vegetation and on small mammals in southern Sweden. *Holarctic Ecology*, 11:161–165.

Nuti M et al. (1993). Infection in an Alpine environment: antibodies to hantaviruses, leptospira, rickettsiae and *Borrelia burgdorferi* in defined Italian populations. *The American Journal of Tropical Medicine and Hygiene*, 48(1):20–25.

O'Connell S et al. (1998). Epidemiology of European Lyme borreliosis. Zentralblatt für Bakteriologie: International Journal of Medical Microbiology, 287:229–240.

Oehme R et al. (2002). Foci of tick-borne diseases in southwest Germany. *International Journal of Medical Microbiology*, 291(33):22–29.

Ogden NH, Nuttall PA, Randolph SE (1997). Natural Lyme disease cycles maintained via sheep by cofeeding ticks. *Parasitology*, 115:591–599.

Oksi J, Viljanen MK (1995). Tick bites, clinical symptoms of Lyme borreliosis, and borrelia antibody responses in Finnish army recruits training in an endemic region during summer. *Military Medicine*, 160(9):453–456.

Olsen B, Jaenson TGT, Bergström S (1995). Prevalence of *Borrelia burgdorferi* sensu latoinfected ticks on migrating birds. *Applied and Environmental Microbiology*, 61:3082–3087.

Olsen B et al. (1993). A Lyme borreliosis cycle in seabirds and *Ixodes urinae* ticks. *Nature*, 362:340–342.

Ornstein K et al. (2002). Three major Lyme Borrelia genospecies (*Borrelia burgdorferi* sensu stricto, *B. afzelii* and *B. garinii*) identified by PCR in cerebrospinal fluid from patients with neuroborreliosis in Sweden. *Scandinavian Journal of Infectious Diseases*, 34(5):341–346.

Pal E et al. (1998). Neuroborreliosis in county Baranya, Hungary. *Functional Neurology*, 13(1):104.

Pancewicz SA et al. (2001). Wybrane aspekty epidemiologiczne boreliozy z Lyme wsrod mieszkancow wojewodztwa podlaskiego. [Epidemiologic aspect of Lyme borreliosis among the inhabitants of Podlasie Province]. *Przeglad epidemiologiczny*, 55(3):187–194.

Piesman J, Gray JS (1994). Lyme disease/Lyme borreliosis. In: Sonenshine DE, Mather TN, eds. *Ecological dynamics of tick-borne zoonoses*. New York, Oxford University Press, 327–350.

Randolph SE (2001). The shifting landscape of tick-borne zoonoses: tick-borne encephalitis and Lyme borreliosis in Europe. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 356(1411):1045–1056.

Randolph SE, Storey K (1999). Impact of microclimate on immature tick-rodent host interactions (Acari: Ixodidae): implications for parasite transmission. *Journal of Medical Entomology*, 36(6):741–748.

Randolph SE, Gern L, Nuttall PA (1996). Co-feeding ticks: epidemiological significance for tick-borne pathogen transmission. *Parasitology Today*, 12, 472–479.

Randolph SE et al. (2002). An empirical quantitative framework for the seasonal population dynamics of the tick *Ixodes ricinus*. *International Journal for Parasitology*, 32(8):979–989.

Reiffers-Mettelock J, Glaesener G, Schroell M (1986). Burgdorfer's borreliosis or Lyme disease. The first Luxembourg cases. *Bulletin de la Société des sciences medicales du Grand-Duche de Luxembourg*, 123(2):103–110.

Richter D, Allgower R, Matuschka FR (2002). Co-feeding transmission and its contribution to the perpetuation of the Lyme disease spirochete *Borrelia afzelii*. *Emerging Infectious Diseases*, 8(12):1421–1425.

Richter D et al. (1999). Genospecies diversity of Lyme disease spirochetes in rodent reservoirs. *Emerging Infectious Diseases*, 5:291–296.

Rizzoli A et al. (2002). Geographical information systems and bootstrap aggregation (bagging) of tree-based classifiers for Lyme disease risk prediction in Trentino, Italian Alps. *Journal of Medical Entomology*, 39(3):485–492.

Robertson JN et al. (1998). Seroprevalence of *Borrelia burgdorferi* sensu lato infection in blood donors and park rangers in relation to local habitat. *Zentralblatt für Bakteriologie: International Journal of Medical Microbiology*, 288(2):293–301.

Robertson JN, Gray JS, Stewart P (2000). Tick bite and Lyme borreliosis risk at a recreational site in England. *European Journal of Epidemiology*, 16(7):647–652.

Ruzic-Sabljic E et al. (2002). [Characterization of *Borrelia burgdorferi* sensu lato strains isolated from human material in Slovenia.] *Wiener klinische Wochenschrift*, 114(13–14):544–550.

Santino I et al. (1997). [Geographical incidence of infection with *Borrelia burgdorferi* in Europe.] *Panminerva Medica*, 39(3):208–214.

Santino I et al. (2002). Detection of four *Borrelia burgdorferi* genospecies and first report of human granulocytic ehrlichiosis agent in *Ixodes ricinus* ticks collected in central Italy. *Epidemiology and Infection*, 129(1):93–97.

Schaarschmidt D et al. (2001). Detection and molecular typing of *Borrelia burgdorferi* sensu lato in *Ixodes ricinus* ticks and in different patient samples from southwest Germany. *European Journal of Epidemiology*, 17(12):1067–1074.

Schmidtmann ET (1994). Ecologically based strategies for controlling ticks. In: Sonenshine DE, Mather T, eds. *Ecological dynamics of tick-borne zoonoses*. New York, Oxford University Press.

Schulze TL, Jordan RA (1995). Potential influence of leaf litter depth on effectiveness of granular carbaryl against subadult *Ixodes scapularis* (Acari: Ixodidae). *Journal of Medical Entomology*, 32(2):205–208.

Smith HV, Gray JS, Mckenzie G (1991). A Lyme borreliosis human serosurvey of asymptomatic adults in Ireland. *Zentralblatt für Bakteriologie: International Journal of Medical Microbiology*, 275(3):382–389.

Smith R, O'Connell S, Palmer S (2000). Lyme disease surveillance in England and Wales, 1986–1998. *Emerging Infectious Diseases*, 6(4):404–407.

Sonenshine DE (1991). Biology of ticks. Oxford, Oxford University Press.

Sonenshine DE (1993). Biology of ticks, Vol 2. Oxford, Oxford University Press.

Spielman A (1994). The emergence of Lyme disease and human babeosis in a changing environment. *Annals of the New York Academy of Sciences*, 740:146–155.

Stamouli M et al. (2000). Very low seroprevalence in young Greek males. *European Journal of Epidemiology*, 16(5):495–496.

Stanek S ET AL. (2002). History and characteristics of Lyme borreliosis. In: Gray JS et al. eds. Lyme borreliosis: *Biology, Epidemiology and Control*. CAB International, Wallingford, Oxon, UK, 1–28.

Steere AC (2001). Lyme disease. The New England Journal of Medicine, 345:115-125.

Štefančiková A et al. (2001). Epidemiological survey of human borreliosis diagnosed in Eastern Slovakia. *Annals of Agricultural and Environmental Medicine*, 8:171–175.

Tälleklint L (1996). *Transmission of Lyme borreliosis spirochetes at the tick vector - mammal reservoir interface* [Dissertation]. Department of Zoology, Uppsala University, Sweden.

Tälleklint L, Jaenson TGT (1993). Maintenance by hares of European *Borrelia burgdorferi* in ecosystems without rodents. *Journal of Medical Entomology*, 30:273–276.

Tälleklint L, Jaenson TGT (1994). Transmission of *Borrelia burgdorferi* s.l. from mammal reservoirs to the primary vector of Lyme borreliosis, *Ixodes ricinus* (Acari: Ixodidae), in Sweden. *Journal of Medical Entomology*, 31(6):880–886.

Tälleklint L, Jaenson TGT (1995). Control of Lyme borreliosis in Sweden by reduction of tick vectors: An impossible task? *International Journal of Angiology*, 4:34–37.

Tälleklint L, Jaenson TGT (1997). Infestation of mammals by *Ixodes ricinus* ticks (Acari:Ixodidae) in south-central Sweden. *Experimental and Applied Acarology*, 21(12):755–771.

Tälleklint L, Jaenson TGT (1998). Increasing geographical distribution and density of *Ixodes ricinus* (Acari: Ixodidae) in central and northern Sweden. *Journal of Medical Entomology*, 35(4):521–526.

Tazelaar DJ et al. (1997). Detection of *Borrelia afzelii*, *Borrelia burgdorferi* sensu stricto, *Borrelia garinii* and group VS116 by PCR in skin biopsies of patients with erythema migrans and acrodermatitis chronica atrophicans. *Clinical Microbiology and Infection*, 3(1):109–116.

Thomas DR et al. (1998). Low rates of ehrlichiosis and Lyme borreliosis in English farm workers. *Epidemiology and Infection*, 121(3):609–614.

Van Dam AP ET AL. (1993). Different genospecies of *Borrelia burgdorferi* are associated with distinct clinical manifestations of Lyme Borreliosis. *Clinical Infectious Diseases*, 17:708–717.

WHO (1995). *WHO Workshop on Lyme Borreliosis Diagnosis and Surveillance, Warsaw, Poland, 20-22 June 1995*. Geneva, World Health Organization (document WHO/CDS/VPH/95.141).

Zakovska A (2000). Monitoring the presence of borreliae in *Ixodes ricinus* ticks in Brno Park Pisarky, Czech Republic. *Biologia*, 55(6):661–666.

Zeman P (1997). Objective assessment of risk maps of tick-borne encephalitis and Lyme borreliosis based on spatial patterns of located cases. *International Journal of Epidemiology*, 26(5):1121–1129.

Zeman P, Benes C (2004). A tick-borne encephalitis ceiling in Central Europe has moved upwards during the last 30 years: possible impact of global warming? *International Journal of Medical Microbiology*, 293(37):48–54.

Zeman P, Januska J (1999). Epizootic background of dissimilar distribution of human cases of Lyme borreliosis and tick-borne encephalitis in a joint endemic area. *Comparative Immunology, Microbiology and Infectious Disease*, 22:247–260.

Zhioua E et al. (1997). Prevalence of antibodies to *Borrelia burgdorferi* in forestry workers of Ile de France, France. *European Journal of Epidemiology*, 13(8):959–962.

Zore A et al. (1999). Infection of small mammals with *Borrelia burgdorferi* sensu lato in Slovenia as determined by polymerase chain reaction (PCR). *Wiener Klinische Wochenschrift*, 111(22–23):997–999.