Emerging vector-borne diseases and environmental change:

The rise of Lyme borreliosis in Western-Europe

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SUMMARY
During the last decade several infectious diseases started to emerge in Western-Europe. At the same time numerous environmental factors were changing. One of the diseases that apparently emerged is Lyme borreliosis (LB). This thesis aims to increase the understanding of emerging diseases LB is taken as an example. Therefore the research question is: To what extent contributed changing environmental factors to the emergence of LB and how might this contribution change in the future?

An analysis of the characteristics of LB demonstrates that this disease was indigenous to Western-Europe for thousands of years and that its symptoms were already described in the beginning of the 20th century. The pathogen, \textit{Borrelia burgdorferi} s.l., needs a complex network of vectors (the tick \textit{Ixodes ricinus}) and reservoirs for transmission. Humans act as accidental dead-end hosts for the vector, but the pathogen is able to infect if the tick-bite lasts longer than 24 hours. Infection can result in multi-system manifestations, but usually the symptoms are limited to the development of an expanding ring-like lesion. If not treated in time with antibiotics, the infection can result in chronic arthritis or neurological symptoms.

Combining several sources of reported incidence data demonstrates a near linear increase of the average number of reported cases: a doubling since 2002. This trend is confirmed by trends found in tick field studies and comparison with trends in other world regions.

Several contributing factors are identified for this emergence, these factors are categorized into three groups. Factors that influence the \textit{Borrelia}-infected population size are: temperature, precipitation, weather extremes, biodiversity, season length and land use. The latter two are considered to be of increased contribution. Factors that influence the human exposure to infected ticks: pets in the household, community size, wealth and outdoor activities. From this category, the presence of pets is also regarded to be of increased contribution. Factors from the third category do not influence the absolute number of LB cases, but influence the number known through reporting: public and professional awareness. Analysis showed that the public awareness towards LB did not change, but the professional awareness is increasing. The identified factors and the expected change in contribution are modeled with three modeling approaches: extrapolative, static and dynamic. It is found that a doubling of the reported case of LB can be expected in 2030.

It is concluded from the example of LB is that emerging vector-borne diseases take place in complex systems with high uncertainty of data. However, an estimate prediction can be made with knowledge of the major drivers only. Therefore, it is recommended to standardize the reporting of these diseases and make them mandatory. Moreover, for policymakers opportunities lie in mobilizing the general population more.
SAMENVATTING

Uit verschillende bronnen is gebleken dat gedurende het afgelopen decennium verschillende infectieziektes in opmars zijn in West-Europa. Op het zelfde moment waren een groot aantal omgevingsfactoren aan verandering onderhevig. Een van de ziektes die een toename vertoonde is de ziekte van Lyme, ook wel Lyme-borreliosis (LB) genoemd. Dit onderzoek heeft als doel het begrip omtrent deze infectieziektes met een sterke toename te vergroten. Daartoe richt dit onderzoek zich op LB, en heeft als onderzoeksvraag: In welke mate hebben de veranderende omgevingsfactoren mogelijk bijgedragen aan de toename in LB incidentie en hoe zal de bijdrage van deze omgevingsfactoren mogelijk gaan veranderen in de toekomst?

Een beschouwing van LB in West-Europa laat zien dat deze ziekte al duizenden jaren voorkomt en dat de symptomen reeds aan het begin van de vorige eeuw in de literatuur werden beschreven. De ziekteverwekker, *Borrelia burgdorferi* s.l., maakt voor zijn overdracht gebruik van een complex netwerk waarin de vector *Ixodes ricinus* en verschillende reservoirs een belangrijke rol spelen. De overdracht op mensen is het gevolg van een tekenbeet die langer dan 24 uur duurt. Mensen maken gewoonlijk geen deel uit van de natuurlijke levenscyclus van teken, een menselijke tekenbeet gebeurt dan ook per ongeluk en betekent vaak het einde van het leven van de teek. Infectie kan leiden tot een grote verscheidenheid aan humane systeemreacties, maar vaak blijven de symptomen beperkt tot de ontwikkeling van een rode uitbreidende ring op de huid. Wanneer er echter niet op tijd met antibiotica behandeld wordt kan de ziekte zich door het lichaam verspreiden en leiden tot chronische klachten als artritis of neurologische klachten.


In deze studie zijn drie verschillende groepen factoren geïdentificeerd die hebben bijgedragen aan de opkomst van LB. Factoren die de omvang van de *Borellia*-geïnfecteerde tekenpopulatie kunnen beïnvloeden zijn: temperatuur, neerslag, weerextremen, biodiversiteit, seizoen lengte en landgebruik. Van deze factoren worden de laatste twee geacht een verhoogde bijdrage te hebben op LB. Factoren die die blootstelling van mensen aan geïnfecteerde teken beïnvloeden zijn: aanwezigheid van een huisdier in het huishouden, omvang van de woongemeenschap, rijkdom en buitenhuis activiteiten. Van deze categorie van factoren wordt de aanwezigheid van huisdieren geacht een verhoogde bijdrage te hebben aan de toename in LB incidentie. De derde groep van factoren beïnvloedt niet de absolute hoeveelheid geïnfecteerde teken maar wel de bekende incidentie als gevolg van rapportage. Dit zijn de factoren met betrekking tot de mate van bewustzijn van de bevolking en de mate van bewustzijn van mensen die beroepsmatig met LB te maken hebben. Uit analyse blijkt dat de mate van bewustzijn onder de bevolking niet is toegenomen ondanks de toename van LB incidentie, maar dat het professionele bewustzijn wel toenemende is.

De geïdentificeerde factoren samen met de verwachte toekomstige verandering in de bijdrage aan LB zijn gemodelleerd door gebruik te maken van drie verschillende modellen gebaseerd op een geëxtrapoleerde, statische en dynamische aanpak. De resultaten hiervan laten zien dat een verdubbeling van het aantal gerapporteerde LB gevallen verwacht kan worden in 2030.

Uit dit voorbeeld van LB kan geconcludeerd worden dat infectieziektes met een sterke toename voorkomen in een complex systeem met een hoge mate van dataonzekerheid. Toch kunnen aannemelijke toekomstvoorspellingen gemaakt worden met bijna alleen kennis over de belangrijkste factoren. Daarom wordt aanbevolen dat de rapportage van deze ziekten wordt gestandaardiseerd en verplicht gesteld. Voor beleidsmakers liggen er kansen om de gevolgen van deze ziekten in de toekomst te verminderen door de bevolking meer te mobiliseren.
CHAPTER 1: GENERAL INTRODUCTION

1.1 Emerging infectious diseases
During the last decade outbreaks of several non-indigenous infectious diseases occurred under the both the human and the veterinary populations in the western part of Europe. Examples of this are: the first occurrence of the Schmallenberg virus in 2011 in Germany and other European countries, which infected cattle, sheep and goat (Garigliany et al., 2012); the outbreak of Q-fever in the Netherlands in 2008 (Roest et al., 2011); the midge-borne blue tongue epidemic starting in 2006 (Carpenter et al., 2009); indigenous mosquito-borne dengue and chikungunya fever in Southern France in 2010 (Gould et al., 2010); the increase in incidence and geographical spreading of tick-borne Lyme borreliosis and tick-borne encephalitis over the last decade (Lindgren & Jaenson, 2006; Lindquist & Vapalahti, 2008). For most of those diseases, a vector transfers the pathogens. Some of those diseases were commonly assumed to be restricted to (sub)tropical latitudes, instead of the temperate climate of Western Europe. Other diseases were assumed to be limited to a certain region and with a relative constant incidence. The above-mentioned examples indicate that this assumption might be incorrect; somehow factors in Western-Europe changed over the last few decades and are now favorable for occurrence of those diseases.

1.2 Changing environmental factors
During the last decades, numerous environmental factors were changing in Western Europe. For example, in the biophysical environment, due to anthropogenic actions the levels of greenhouse gasses (most notably CO₂) have increased. This change in turn resulted in altered climatological characteristics, e.g. precipitation patterns or average and extreme annual temperatures (Purse et al., 2005). Also other environmental factors were changing, for example transportation frequency, speed and distances traveled by people and cargo. For certain infectious diseases, there is already a proven, or alleged, correlation between temperature and occurrence of diseases and/or vectors (Gray et al., 2009; Karagiannis et al., 2009; Kyle & Harris, 2008; Lindgren & Jaenson, 2006; Purse et al., 2005). For the other environmental parameters, the correlation between environmental changes and the manifestation of diseases is yet unclear (Lindgren et al., 2012; Myers & Patz, 2009).

1.3 Lyme borreliosis
One of the vector-borne diseases currently emerging and allegedly correlated with changing environmental factors is Lyme borreliosis (LB), also known as Lyme disease. This disease is characterized by the typical features inherent to many epidemiological problems: data scarcity, data uncertainty and a high system complexity. Therefore, this disease might serve as a useful case study how this and other emerging diseases became emerging and how these diseases will behave in the future.

1.4 Aim
Using LB as a case study, this research aims at providing a better understanding of the effect of changing environmental factors on emergence of LB by identifying significant factors. Moreover, this research aims at providing an outlook for the future to aid policymakers to construct a strategy addressing the increased occurrence of LB and other vector-borne infectious diseases.
1.5 Research question
This research has the following research question:

To what extent did environmental factors contribute to the emergence of Lyme borreliosis in the past and how will the contribution of these factors change in the future?

1.6 Methodology
To answer the research question, the different aspects of this question are subdivided into four separate sub-questions. For each of these questions a separate general methodology is discussed, however, an overall used method for data accumulation is triangulation. This method uses data from multiple sources to gain insight in a certain topic. Triangulation uses multiple methods for data collection and is combining and complementing quantitative with qualitative data, thereby increasing the understanding of why certain quantitative relationships exists, i.e. giving meaning to quantitative findings (Brownson et al., 2009). For a more comprehensive methodology for each sub-question see the corresponding chapters.

Chapter 2
What is the scientific knowledge about Lyme borreliosis in Western Europe?
This sub-question is addressed by means of an extensive literature survey. The aim of this survey is to find which (f)actors are involved during the pathogen transmission and to discuss the possible consequences of a human infection with LB. To answer this sub-question, articles from online journals and books from the university library are used. The online papers are mainly found using LB related keywords on two online search tools: ISI Web of Knowledge and Google Scholar. However, also searches are performed on the individual journals. Recent articles are used from the period from 2008, however for some topics it is necessary to use more dated articles. Because this study limits itself to Western-Europe, the majority of the information describing LB of originates from this region. However, if relevant information from other regions is found, and if there was no Western-European specific source, this information is also discussed. The result of this literature survey is an overview of the current state of the scientific knowledge about LB in Western-Europe and the significant factors during the infection of humans.

Chapter 3
To what extent is Lyme borreliosis emerging in Western-Europe?
To answer this question regarding the past and current LB incidence, quantitative data is obtained from several (inter)national health agencies, statistical agencies and literature from Western-European sources. Subsequently the found quantitative data is processed with the spreadsheet software Microsoft Excel to construct an average Western-European trend. Also, qualitative data from literature sources is discussed. For verification and for completeness, the Western-European trends are compared with literature from other regions.

Chapter 4
Which significant environmental factors contributed to the past emergence of Lyme borreliosis and how does the contribution of these factors change in the future?
To address the question how LB have become emerging, several factors are identified and discussed on basis of analysis of scientific literature and analysis of statistical data. The focus of these analyses is to find possible (cor)relations between the occurrence of LB and environmental factors. Sources for data are online journals, national statistical agencies, European
climatological agencies, experts and online behavior from Wikipedia and Google. Furthermore, the expected future contribution of the identified factors to the LB incidence is discussed.

Chapter 5

What will be the future incidence of Lyme borreliosis in Western-Europe?
The answers from the previous sub-questions are used to give a projection of the future LB incidence by means of modeling approaches. Three different modeling approaches are used: extrapolative, static and dynamic. For the extrapolative and static model Microsoft Excel is used. The dynamic model is constructed using the software modeling program STELLA from ‘isee systems’. Based on these findings, policy recommendations are formulated.

1.7 Boundaries
This research is focused on LB in Western-Europe only. The first reason for this focus is that in this part of the world the in §1.1 mentioned emerging infectious vector-borne diseases are from a scientific perspective novel and unexplained. The second reason is the occurrence of these infectious diseases in this magnitude is unusual, therefore the inhabitants of this region are at risk because they are unprepared for these diseases, both immunologically and practically. The third reason is the unique combination of the LB vector and the pathogen sub-species for Western-Europe, therefore the situation in other regions is not compatible with the situation in Western-Europe. Nevertheless, as some important data is unavailable for Western-Europe some significant findings from other regions are discussed.
The second boundary is that this research is literature based; it does therefore not generate new knowledge and is thus dependent on the availability data. However, experts are consulted to incorporate the latest ideas and to possibly create new insights.
CHAPTER 2: CHARACTERISTICS OF LYME BORELIOSIS

2.1 Introduction

This chapter gives an overview of the current scientific knowledge concerning the infection with LB found in literature. The knowledge is discussed according to the schematic overview of the transmission of the disease agent depicted in figure 2.1. However, the overview begins with a discussion of the history of LB.

![Figure 2.1: Overview of the transmission of the LB pathogen](image)

2.2 History

LB was not identified until three decades ago. In 1977 in the small towns Lyme and Old-Lyme (Connecticut, northeastern USA) an epidemic of arthritis (i.e. inflammation of joints) occurred among 39 children and 12 adults. An investigation excluded juvenile rheumatoid arthritis (an autoimmune disorder) as the cause of the epidemic because the occurrence was 100 times greater than the expected occurrence in these communities. The specific geographic clustering of the cases lead the investigators to suspect an arthropod vector as the cause. This suspicion was strengthened by the occurrence of skin lesions in a third of the cases which were previously described in the literature in Europe to be associated with ticks. This newly identified disease was therefore named after the place it was identified, Lyme disease (Steere et al., 1977). Several years later, the causative pathogen, a spirochaete (i.e. a spiral-shaped bacterium), later named *B. burgdorferi*, was discovered to be tick-borne (Burgdorfer et al., 1982).

As mentioned, prior to the identification and naming of Lyme disease in the USA, symptoms of the disorder had been described in Europe. In contrast to the manifestation of arthritis in the USA, in Europe characteristic skin lesions were described at the beginning of the twentieth century. In 1909 the Swedish dermatologist Afnélius reported ring like expanding lesions (now known as erythema migrans) he observed on the patients skin at the site of a bite by the tick *Ixodes ricinus* (Benach & García-Moncó, 2010; Marconi & Earnhart, 2010). The same manifestations were also described a few years later in Austria (Lipschütz, 1913).

Also neurological symptoms after tick bites were already described in the early twentieth century. In 1922 two French neurologists, Garin and Bujadoux, described neurological complications and skin lesions after a tick bite (Garin & Bujadoux, 1922).

The idea that spirochetes and ticks might be involved in causing the skin lesions arose already in 1950. Unfortunately the author was not able to corroborate his idea (Hellerstrom, 1950). Around the same time, even successful skin treatments, injecting penicillin into the skin, were reported (Hollstrom, 1951).

The European symptoms were not linked to the American symptoms until 1984. In this year *B. burgdorferi* was detected in a European patient with skin lesions after a tick bite (Asbrink et al., 1984).

This non-recognition of arthritis as a symptom of Lyme disease in Europe can be illustrated by the following example. In a publication about ticks by the Dutch association for field biology (KNNV) in 1979, the authors only mention the skin manifestations (*erythema migrans* and *acrodermatitis chronica atrophicans*) after a tick bite. According to this publication the micro-organisms injected into the skin by the feeding of ticks manifest themselves only by symptoms of the human skin (van Bronswijk et al., 1979).
Recent discoveries demonstrated that Lyme disease in its current state has been around much longer. Analysis of the genome of a 5,300 year old mummy, “Ötzi the Iceman”, found in the European Alps, revealed that he was infected with the genetic material for Lyme disease, the bacteria *Borrelia burgdorferi* (Keller et al., 2012).

After the classification of LB, pharmaceutical research aimed at a vaccine resulted in the availability of the recombinant vaccine, known as LYMErix, against LB available on the US market in December 1998. This vaccine was targeting the lipoproteins (i.e. the bacterial cell membrane). Although medical trials indicated that this vaccine had good protection for people between 15 and 70 years of age, the vaccine was suddenly removed from the market in February 2002. The reason for this withdrawal was commercial (i.e. bad sales), probably as result from the public concerns about the possibility of an unwanted autoimmune response to the vaccine (Marconi & Earnhart, 2010; Nigrovic & Thompson, 2007). Currently, the only vaccines available on the market to prevent LB are for dogs. But, human pharmaceutical research is focusing its attention on the possibility to provoke immunity by targeting components of the ticks’ saliva (McDowell et al., 2011). However, the pharmaceutical companies are questioning the economic feasibility of developing a human vaccine against LB (Plotkin, 2011). Besides, for a vaccine to be suitable for usage in Europe the vaccine must deal with more different genospecies compared to that in the USA. So the future of human LB vaccines is uncertain.

### 2.3 Pathogen

Lyme borreliosis is caused by a specific type of bacterium, a spirochete, a member of the *Borrelia* genus. The spirochetes from this genus associated with LB are known as *Borrelia burgdorferi* sensu lato (s.l.). The bacterium resides a significant part of its life cycle inside gut of its vector, the tick. Here, *B. burgdorferi* s.l. is able to multiply as a result from the blood the tick is feeding on. After 24 hours of feeding by the tick (i.e. a tick bite), a fraction of the spirochetes is able to relocate to the saliva glands of the tick, where they transfer to the vertebrate the tick is feeding on at that moment (des Vignes et al., 2001). In this case an infected tick is infecting a naive host. But, this can also happen the other way around. During the blood meal of the tick, spirochetes can also transfer from the blood of the vertebrate host to the ticks gut, thus infecting a naive vector (Schwan & Piesman, 2002). Because transovarian transmission of the bacterium is extremely rare (Bellet-Edimo et al., 2005), ticks normally get infected after feeding on a suitable infected host, known as a reservoir.

Although the disease is known all over the northern hemisphere, and the main clinical features are very similar, there are differences between regions/continents. This is the result of infection by one of at least thirteen different LB related genospecies of *B. burgdorferi* s.l. (Dykhuizen & Brison, 2010). In Europe *B. afzelii, B. garinii* and to a lesser extent *B. burgdorferi* sensu stricto (s.s.) are responsible for the disease (Habálek & Halouzka, 1997). This in contrast to the USA where generally only *B. burgdorferi* s.s. is responsible for the clinical manifestations (see figure 2.2). The other genospecies are also capable of infecting humans and other vertebrate hosts, however these species are rarely found in patients diagnosed with LB (Derdakova & Lencakova, 2005; Habálek & Halouzka, 1997). The three different genospecies found in Europe are suggested in literature to be associated with distinct clinical manifestations: arthritis (*B. burgdorferi* s.s.), skin manifestations (*B. afzelii*) and neuroborreliosis (*B. garinii*) (Habálek & Halouzka, 1997; Lindgren & Jaenson, 2006). This association might give an explanation as to why the identification of LB took until the 1977, despite the first reports early in the twentieth century (§2.2).

As illustrated in figure 2.2, multiple genotypes are endemic in Western-Europe. Therefore, ticks infected with multiple genospecies of *Borrelia* are observed. This multiple infection results from
feeding on the same host by different ticks, resulting in an exchange of *Borrelia* species (Gern & Rais, 1996). These ticks are subsequently capable of infecting human hosts with multiple genospecies of *Borrelia*. (Schaarschmidt et al., 2001). The distinct geographical genospecies distribution is not only the result of different evolution processes of the bacterium, but the genospecies are also associated with specific vectors. For example, in Europe the main vector for the bacterium is the sheep tick *I. ricinus*, whereas the blacklegged tick *I. scapularis* is the main vector of *B. burgdorferi* s.l. in the USA (Kurtenbach et al., 2006).

**Figure 2.2:** Global distribution of Borrelia species (Kurtenbach et al., 2006).

### 2.4 Vector

In Europe, three tick species are described as a vector for *B. burgdorferi*: *Ixodes ricinus*, *Ixodes uriae* and *Ixodes hexagonus*. Of these three vectors, *I. ricinus*, also known as the sheep or castor bean tick, is the most common vector in Western Europe. The tick has the typical 3-stage lifecycle (larva, nymph and adult) common for the hard tick family (see figure 2.3). The tick requires a fresh blood meal to be able to enter the next development stage through moulting. When the ambient temperatures are right, i.e. >7° C., the tick can engage in host-seeking activity (Mannelli et al., 2012). To acquire blood *I. ricinus* climbs the vegetation in its hunt for a vertebrate host, this behavior is known as questing (Piesman & Gern, 2004). The height the tick climbs onto vegetation is depending on the development stage of the tick. In every stage the host animal preference differs, therefore, and to avoid desiccation, larvae remain close to the ground. Nymphs and adults climb higher to be able to feed on larger vertebrates. Adults can even be found at a height of 1.5 meters (Mejlon & Jaenson, 1993). On basis of cues (e.g. movement or heat), the tick decides to drop itself onto the host passing by. Through the fur of the host the tick crawls to a suitable feeding site. Here, the tick feeds for 3-7 days on the blood of the host, resulting in a significant increase in the ticks’ body size. When the stomach of the tick is full, it drops itself onto the ground and starts the metamorphosis into the next development stage. The third and final host is important for the reproduction of *I. ricinus*, after this final blood meal the female adult lays eggs and dies subsequently. Depending on the environmental conditions, most ticks will complete their life cycle within 2-6 years (Piesman & Gern, 2004).
The length of this lifecycle is significantly influenced by the temperature of the environment in combination with photoperiod length. In Western Europe these factors usually determine the questing activity and provide the cue for diapause during the winter, when temperatures are below 4°C. Ticks that did not feed prior to entering hibernation usually die of fat exhaustion. This means that almost all ticks are entering a new development stage during autumn (i.e. a single cohort of each stage starting in autumn) (Piesman & Gern, 2004; Randolph et al., 2002). For example in the Netherlands, the activity of I. ricinus is not constant during the whole year but has peaks. An example of this activity trend is depicted in figure 2.4. This graph shows the monthly distribution of collected tick numbers from a study performed in the Netherlands in 2007 (Gassner et al., 2011). However, a recent study in Southern Italy shows that ticks from all three stages can be active all year round, and have the possibility to complete their lifecycle within only one year (Dantas-Torres & Otranto, 2012).

The tick is able to survive under a large variety of environmental conditions as I. ricinus is well adapted to survive harsh winters while diapausing. Still, the mortality rates will increase sharply when the ambient temperatures are below -10°C (Dautel & Knülle, 1997). Because of this good adaptation, its latitudinal range expands from Portugal and Israel to Sweden and Russia (Erster et al., 2012; Gem & Humair, 2002). Nevertheless, I. ricinus requires a high humidity (>85%) to
avoid to get desiccated (Daniel et al., 1998). The tick is therefore often found in or near vegetation types that are capable of providing this humidity: deciduous woodlands and mixed forests where the tick restores its water balance in the high humidity of the leaf litter (Piesman & Gern, 2004). However, *I. ricinus* is also capable to survive in grassy meadows and even urban environments (Lindgren & Jaenson, 2006). Nevertheless, because of the necessity to feed on vertebrate blood, the occurrence of hosts is commonly a good predictor of habitat suitability for *I. ricinus*.

### 2.5 Reservoir

The tick *I. ricinus* is able to feed on a large variety (>300) of vertebrate hosts species, including reptiles, birds and mammals (Anderson, 1991). However, only few of these are competent of acting as a reservoir for *B. burgdorferi* s.l.. A species capable of being a reservoir has the ability to ‘store’ the pathogen and transfer it to future generations *Ixodes*. Therefore, the pathogen depends for its maintenance on a small group of animals. These are small and medium sized mammals: mice, voles, squirrels, birds (most notably migratory birds) and reptiles. These animals acquire the infection from nymph stage ticks and subsequently transmit *B. burgdorferi* s.l. to larvae. The adult tick feeds mostly on large animals (deer, cattle or horses) which are non-competent reservoirs. Whilst not important in the pathogen life-cycle, these hosts play an important role in maintaining the tick population, because these large mammals are required for reproduction of the tick (Lindgren & Jaenson, 2006; Mannelli et al., 2012; Piesman & Gern, 2004). It is demonstrated that through the specificity of parts of the hosts’ immune system (i.e. complement), the *Borrelia* bacterium has host preference (Gern, 2008; Kurtenbach et al., 2006). Therefore, the genospecies *B. afzelii* is mostly found in small and medium sized mammals and *B. garinii* is mostly found in birds (Mannelli et al., 2012).

### 2.6 Humans

While humans are not part of the natural lifecycle of ticks, humans can act as hosts and provide the desired blood meal for *I. ricinus*. During the bite of an infected tick, after 24 hours the pathogen is able to spread through the human body. Despite the fact that humans usually are dead-end hosts for *B. burgdorferi* s.l., the infection with the spirochete can lead to clinical manifestations. Genomic sequencing of the *B. burgdorferi* genome revealed that the bacterium is not capable of excreting cytotoxins, thus the LB associated symptoms are the result of the hosts’ immune systems response against the spirochete (Wooten & Weis, 2001). Typically, this response results in multi-system manifestations of clinical symptoms. Because of the multi-system nature of the disease, the order, number and degree of manifestations differ among patients, with also the possibility of an asymptomatic infection in some patients. Currently the clinical picture shows five important distinct human manifestations. See also table 2.1 for an overview for an example of the characteristic distribution of LB symptoms. A description of the symptoms, in order of occurrence, is listed below.

1. *Erythema migrans*:
   The most common manifestation of the pathogen is on the skin, *erythema migrans* (EM). An epidemiologic study in Sweden shows that in 77% of all cases of LB EM is one of the manifestations (Berglund et al., 1995). In the majority of the patients the skin lesion starts within 7 to 14 days at the site of the tick bite, but it can occur at other places at a later time as well when the bacteria are moving through the body. Characteristic for the lesion is the round or oval shape and the quick expanding speed (up to 20 cm² per day). In 80% of the cases the lesion had a central clearing, i.e. the shape of a bull’s eye (Dandache & Nadelman, 2008). Other
manifestations accompanied by EM are headache, fatigue and fever. A case study reported in 17% of the cases headache and/or fatigue (Strle et al., 2002).

2. Arthritis
Arthritis is, as result of the discovery of Lyme disease by Steere et al. through this manifestation, commonly incorrectly regarded to be one of the often occurring symptoms of LB. Actually, only 10-20% of the infected European patients develop symptoms of arthritis. This is mainly the result of arthritis being an expression of late untreated LB. Presently LB is generally diagnosed before the infection can progress into arthritis in most cases. But also the difference in *Borrelia* genospecies occurrence between Europe and the USA might explain this low European percentage. Lyme arthritis is characterized by inflammation of large joints, in most cases resulting in a swelling of the knee (Radolf et al., 2010).

3. Neuroborreliosis
An infection with *B. burgdorferi* s.l. can also lead to nervous system manifestations. In the Swedish study 16% of the pathogen-infected patients reported neurological symptoms (Berglund et al., 1995). Lyme neuroborreliosis, also known as Garin-Bujadoux-Bannwarth syndrome, sets in after an average incubation period of seven weeks. The disorder often starts with acute severe radiculoneuritis (i.e. radiating nerve pain) and severe headaches, usually followed by partial paralysis of the facial muscles after two weeks. The pain is for some patients so severe that it can lead to personality changes. When left untreated, the symptoms usually disappear within 25 weeks (Stanek & Strle, 2008; Stanek et al., 2011).

4. *Acrodermatitis chronica atrophicans*
Another dermatological manifestation of LB is *acrodermatitis chronica atrophicans* (ACA). This type of skin lesion is seen in a late stage of untreated LB in adults. It is characterized by red or blue-red lesions, in most cases on the extensor surfaces of extremities. The lesions will develop over time into atrophic tissue areas (Stanek et al., 2011).

5. Carditis
In rare cases an infection of LB can manifests as cardiac symptoms. The rhythm disturbances in these rare cases were reported shortly after an EM, or in association with arthritis or nervous system manifestations (Stanek et al., 2011).

Tabel 2.1: An example of the distribution of the LB associated symptoms in Sweden (Berglund et al., 1995).

<table>
<thead>
<tr>
<th></th>
<th>Erythema migrans</th>
<th>Neuroborreliosis</th>
<th>Arthritis</th>
<th>Acrodermatitis</th>
<th>Lymphocytoma</th>
<th>Carditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythema migrans</strong></td>
<td>1075</td>
<td>40</td>
<td>10</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Neuroborreliosis</td>
<td>40</td>
<td>176</td>
<td>8</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Arthritis</td>
<td>10</td>
<td>8</td>
<td>65</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Acrodermatitis</em></td>
<td>1</td>
<td>2</td>
<td>8</td>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytoma</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Carditis</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>&gt;3 Manifestations</td>
<td>3</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1139</strong></td>
<td><strong>235</strong></td>
<td><strong>98</strong></td>
<td><strong>47</strong></td>
<td><strong>41</strong></td>
<td><strong>7</strong></td>
</tr>
<tr>
<td><strong>Percentage</strong></td>
<td><strong>77%</strong></td>
<td><strong>16%</strong></td>
<td><strong>7%</strong></td>
<td><strong>3%</strong></td>
<td><strong>3%</strong></td>
<td><strong>&lt;1%</strong></td>
</tr>
</tbody>
</table>
The most common way of treating a patient diagnosed with Lyme is administering antibiotics. The prognosis of treating an early detected LB case with oral antibiotics is good. However, the prognosis of a late stage LB case is much worse. When the infection progresses, the pathogen is able to cross the blood-brain barrier, and is therefore much more difficult to treat with antibiotics. Therefore, an infection with LB might in some cases result in long-lasting symptoms. There are some controversies about the antibiotics treatment. One group regards Lyme disease as a chronic one, therefore advocating long-term antibiotic therapy. The other group believes on the basis of scientific research that this prolonged treatment does not result in substantial improvement in quality-of-life and can potentially harm a patient through the side effects of antibiotics (Benach & García-Moncó, 2010).

2.7 Conclusion
This chapter gave an overview of the scientific knowledge about the tick-borne infectious disease Lyme Borreliosis. The pathogen *B. burgdorferi* s.l. is for its maintenance highly dependent on its transmission between several animal species. During these transmissions, the vector, the tick *I. ricinus*, plays a key role. In turn, the vector is also highly dependent on several animal species for maintenance. Therefore, conditions of the external environment can significantly influence the life-cycle of the tick and consequently the life-cycle of the pathogen. When an uninfected tick feeds on a reservoir for the pathogen, the tick becomes a carrier of the pathogen and has the possibility to infect new reservoir species or dead-end hosts. For both the vector and the pathogen, humans are incidental hosts, usually a dead-end one. The pathogen can infect humans when the bite of an infected tick lasts longer than 24 hours. Infection with the pathogen may lead to a condition known as Lyme borreliosis. This disease is characterized clinically by its multi-system manifestations. When treated with antibiotics in time, the chances on recovery are good. However, left untreated, the infection may lead to chronic symptoms.
CHAPTER 3: EMERGENCE OF LYME BORRELIOSIS

3.1 Introduction
As discussed in the general introduction, LB is considered to be an emerging disease by several literature sources. However, the discussed evidence to what extent this disease is emerging quantitatively has to be analyzed. Therefore, this chapter tries to make the considered emergence measurable by combining several sources of incidence statistics.

To determine the incidence rate of LB in Western-Europe there are several complicating factors. The most important one is that Western-Europe consists of a number of different countries. While efforts of the European Union (EU) members resulted in the establishment of one (European) Center for Disease Prevention and Control (ECDC), still each individual country has its own reporting standards. This means is that on top of misclassification and under-reporting inherent to all surveillance data, the situation for Western-Europe as a whole is even worse (CDC, 2012; Smith & Takkinen, 2006).

Another complicating factor is that in most Western-European countries LB is not a mandatory nationally notifiable condition. Therefore, reliable long-term national surveillance data are lacking for most countries. Fortunately, some regions decided to report the incidence of LB on a regional level.

To deal with this unavailability of sufficient reliable national or European LB surveillance data and still be able to establish the extend of LB emergence, data is discussed from a wide variety of European sources. Also, data from adjacent regions is included. The found incidence data is summarized into one average European LB incidence trend. To indicate whether the European trends are plausible, also surveillance data from other non-European regions is discussed.

3.2 Incidence data

3.2.1 EpiNorth surveillance
EpiNorth is a co-operation project for communicable disease control in Northern-Europe and is currently partly funded by the ECDC. The participating countries are depicted in figure 3.1. According to EpiNorth, the epidemiological data they publish is provided by the national or regional institutes for infectious disease control. Therefore, the published data will be influenced by the different reporting standards in the individual countries. However, combining the data should give an average LB incidence trend in these regions, thus an impression of the average situation in the EpiNorth participating countries. (EpiNorth, 2012).

Figure 3.1: EpiNorth participating countries (EpiNorth, 2012).
The obtained surveillance data from the different counties is normalized for the inhabitant size of each individual country and subsequently combined. The results in figure 3.2 show a clear trend of increased reported LB incidence since 1999. The linear trend shows an increase in LB incidence of 88% when comparing 1999 and 2011. Similar trends are confirmed for all the EpiNorth participating countries individually (data not shown).

The trend of increased LB incidence in Northern-Europe during the last decade is evident. Because these trends occur in countries in close vicinity to Western-Europe, a similar trend for Western-Europe might be assumed. However, there are differences between those two regions (e.g. social-economical and climatological), therefore the demonstrated incidence trend might not be totally representative for the situation in Western-Europe.

![Figure 3.2: Average LB incidence for countries participating in EpiNorth, normalized for inhabitant size (EpiNorth, 2012).](image)

### 3.2.2 Dutch GPs consults

Surveillance data can also originate from professionals in the primary health care. This survey conducted among all general practitioners (GPs) in the Netherlands is based on voluntarily filled in forms about the number of patients that consulted their GP for a tick bite or for an *erythema migrans*. The data the researchers received is used to first calculate the incidence based on the population size visiting a specific GP and consequently used to extrapolate to all the patients in the Netherlands. The study started in 1994, and was repeated in 2001, 2005 and 2009. The number of participating GPs was 79% in 1994 and reduced to 50% in 2009 (Hofhuis *et al.*, 2010).

The results in figure 3.3 show an almost linear increase in the number of patients consulting their GP with *erythema migrans*: for the whole Netherlands from 6,000 patients in 1994 to 22,000 patients in 2009. Moreover, the real incidence of LB in the Netherlands is even higher, because EM symptoms are only present in 77% of the cases (§2.6). This means an 80% increase from 2001 to 2009. The number of people visiting their GP after a bite of a tick shows again a linear increase.

These results indicate that the LB incidence among Dutch GPs is significantly higher than in the other discussed sources of LB surveillance data. This may the result of the used methodology. Still, the witnessed trend is comparable to the other surveillance data.
3.2.3 Laboratory-based surveillance in England and Wales
Professionals in the primary healthcare (usually GPs) have the possibility to submit blood samples from suspected LB patients for laboratory analysis. In most countries samples for diagnostic tests are sent to a many different laboratories for analysis. In two countries part of the United Kingdom, England and Wales, every single test is performed by a single laboratory from the Health Protection Agency (HPA). Epidemiology results from this surveillance should therefore exclude the inaccuracy resulting from different analytical methods (HPA, 2012). Results from these diagnostic tests show an increase in incidence from 268 cases (incidence of 0.50/100,000) in 2001 to 971 cases (1.73/100,000) in 2011. This means an increase of 262% in laboratory confirmed LB cases in ten years. These results indicate that LB in England and Wales has a low incidence of LB compared to other countries in Europe. However, incidence data from the diagnostic test is only based on samples submitted actively by GPs. Therefore, it might be that a significant part of the cases of LB is not registered. Still, a significant and comparable increase of LB incidence is demonstrated during the last decade.

3.2.4 Eastern-German incidence
Like in many West-European countries, in Germany there is no nationwide mandatory reporting of LB patients. However, national health regulations provide the possibility for German states to expand the number of mandatory notifiable infectiousness diseases. As result, surveillance data is available for the six eastern German states (Berlin, Brandenburg, Mecklenburg-Vorpommern, Sachsen, Sachsen-Anhalt and Thüringen). The states reported the cases of LB to the federal institute for disease control and prevention, the Robert-Koch-Institut (Adlhoch & Poggensee, 2010).

Figure 3.4 shows the LB surveillance data from the six eastern German from 2002 to 2009. The results show a strong increase in LB incidence: the number of cases nearly doubled from 17.8 cases per 100,000 inhabitants in 2002 to 34.7 cases in 2009, a 94% increase. The increase of LB incidence in Eastern-Germany from 2002 to 2009 shows an increase comparable with that from other sources.
3.2.5 Average Western-European incidence

Because the four previously discussed LB incidences consist of a wide variety of data sources, the used methodologies between sources differ significantly and therefore the trends cannot be integrated into one trend spanning the average LB incidence in Western-Europe. However, the data can still be combined to attain an overview of the development of the average LB incidence change during the last decade. This can be done because although different methodologies are used among the sources of LB incidence data, within each source these methodologies did not change over the years. Therefore, the change within one source of data is comparable with other sources of LB incidence data. Moreover, by generating an average Western-European incidence change, the accuracy of the past LB incidence trend is increased as result from using data from multiple sources.

To give an overview of the average situation in Western-Europe, the four previously discussed sources are taken together based on the incidence data from 1999 to 2011. Missing incidence data for some years from sources discussed in §3.2.2-4 is generated based on the linearity of the past trend. To acquire an equal average, the data from the four sources is recalculated in index numbers, with 2011 set at 100. Subsequently an equally weighted average of the four sources is calculated. The result is shown in figure 3.5. The figure of the average Western-European LB incidence shows that the incidence more than tripled since 1999. Also, the increase in the past years shows a near linear increase, with an $R^2$ of 0.97.
While the previous discussed sources concerned the change in reported cases of LB patients, another indicator for the LB emergence might be the number of infected ticks. Higher numbers of infected ticks increases the chances of human LB infections (for a more comprehensive discussion see §4.1).

In the relatively isolated Western-German nature reserve Siebengebirge researchers examined the composition and number of the local tick species and determined the *B. burgdorferi* s.l. prevalence among those ticks. For this research, data was used from the same field studies in 1987, 1989, 2001, 2003, 2007 and 2008. Therefore, this field study constitutes a long-term analysis of the local situation.

A comparison of data from different years shows that tick densities decreased in two of the three investigated vegetation types. The increase on the other vegetation type was continuously from 13 ticks/100 m² in 1987 to 146 ticks/100 m² in 2008. Because this specific vegetation type is covering 10% of the total area of the nature reserve (the third largest local plant community), this increase might have a large effect on the absolute number of ticks in the reserve. The *Borrelia* prevalence in 2011 (16.5%) is twice the prevalence of 1987 (7.6%). The number of genospecies *Borrelia* found in infected ticks in 2009 was significantly higher compared to that of earlier years, indicating a higher host-seeking activity by the ticks (Schwarz *et al.*, 2012).

The results from this long-term field study indicate more than a doubling in the number of *Borrelia*-infected ticks over the last two decades. Moreover, it suggests that the ticks have moved to another type of vegetation with the possibility of sustaining larger tick populations.

While the discussed field study concerns a very specific location, the vegetation type and environmental conditions of the Siebengebirge are very common among natural reserves across Western-Europe. Therefore, conclusions from this field study are applicable to the situation in entire Western-Europe.
3.4 Geographical range

Another indicator for the LB emergence is increasing occurrence area. When the habitat size of ticks is increasing, larger tick populations can be sustained and the chances of a human tick bite are also increasing. Several studies over the last years indicate that the geographical range of ticks is expanding, both altitudinally and latitudinally. The altitude where ticks could be found increased significantly over 23 years in the Czech Republic. Researchers compared current data with historical data from the Bohemian Forest, a low mountain range bordering Germany and Austria. They found that the maximum altitude where *Ixodes ricinus* was found shifted upwards from 800 meters above sea level in 1980 to 1,100 meter in 2003 (Daniel *et al.*, 2003).

During the same time, the latitude where ticks could be found was also increasing in Sweden. Local researchers recently compared tick prevalence (i.e. occurrence) and abundance (i.e. quantity) between the early 1990s and 2008. The results are depicted in figure 3.6. The researchers concluded that during the last sixteen years ticks increased their range with 9.9% and can now be found up to 66° parallel north (Jaenson *et al.*, 2012). It is assumed that this range expansion is the result of lower mortality rates during the winter, corresponding with changing winter temperatures (for a further discussion see §4.2.1.1).

![Figure 3.6: Estimated ranges of I. ricinus in Sweden in the early 1990s (left map) and 2008 (right map) (Jaenson *et al.*, 2012).](image)

3.5 Trends in non-European regions

The previously discussed statistics all concerned European sources. However, ticks do not occur solely in Europe. To increase the validity of witnessed European trends, a comparison is made with incidence data from other non-European sources.

In contrast to the countries of Western-Europe, LB is a mandatory notifiable disease in the USA. Reports of Lyme disease are collected and verified by state and local health departments. Subsequently the information is shared with the national Center for Disease Control (CDC). Therefore, clear uniform incidence statistics are available for this large region. As depicted in figure 3.7, the occurrence of LB in the USA is almost completely restricted to the thirteen northeastern states: the reported cases from these states make up 96% of the total USA national cases in 2011 (CDC, 2012).
Figure 3.7: LB Distribution of LB cases in the USA in 2011 (CDC, 2012).

Depicted in figure 3.8 is the surveillance data from these thirteen states during 2002 to 2011. When the linear trend line is analyzed, the numbers of reported cases increased with 50%. The increase is comparable with the other discussed European statistics.

Figure 3.8: Number of reported LB cases in the thirteen most LB prevalent states of the USA from 2002 to 2011 (CDC, 2012).

While LB used to be found only on the northern hemisphere, recent research shows that LB is now also prevalent in Australia on the southern hemisphere. Reports of patients with neurological symptoms and cases of EM are described during the last decade. Analysis of these reports revealed that those patients did not leave the country, thus the infections must have happened in Australia. This led researchers to the conclusion that LB must be regarded endemic to Australia (Maud & Berk, 2012; Mayne, 2012).
3.6 Conclusion

In this chapter several national statistical sources of LB incidence were discussed to establish to what extent LB can be considered emerging in Western-Europe. Additionally, due to the scarcity of reliable Western-European incidence data, regional data and data from adjacent regions were discussed. Also, data from indicators for LB were included.

The discussed incidence data indicate a trend of emerging LB incidence in Western-Europe, the observed increase in LB incidence varies between 80% and 262% during the last decade. When the change in LB incidence from these sources is taken together, it is shown that the current LB incidence is on average double the 2002 incidence.

This conclusion is strengthened by the fact that several indicators for LB, concerning the distribution of the vector, also point at an emergence of LB. During the last decades the range and habitat characteristics of *I. ricinus* are favoring larger tick populations. This increase in LB incidence is not unique for Europe. Incidence data from other countries in the world, more specifically USA and Australia, also point at LB emergence. Because LB is increasing in incidence in many European countries and is expanding its range, LB is considered to be an emerging disease in Western-Europe.
CHAPTER 4: FACTORS FOR LYME BORRELIOSIS EMERGENCE

4.1 Introduction
To identify how LB has become an emerging disease during the last decade, in this chapter possible changing factors contributing to the witnessed trend of increasing LB incidence are identified and discussed. These factors are classified into one of the following three categories:

1. *Borrelia*-infected tick population size
   This category includes factors that could influence the number of infected ticks. When the environmental conditions are favoring the infected tick population to expand and/or to increase, the odds that someone will encounter a tick shall also increase. This results in more tick bites, thus more LB infections.

2. Human exposure to infected ticks
   This category includes factors that could influence human behavior. When these factors alter, they can change the behavior of people. An outcome of this changed behavior may be a higher possibility of being exposed to an infected tick, which will result in more tick bites, thus more LB infections.

While the factors belonging to those two categories are contributing to (changes in) the absolute number LB infections, the numbers known are dependent on the quality and quantity of reporting. This means that the reported number of LB infections could change, while in reality the absolute number of LB infections was not changing. Therefore, reporting is regarded as the third category of factors responsible for LB to be considered an emerging disease.

3. Reporting
   This category consists of factors influencing the reporting of infected ticks and LB infections. When the quality of LB reporting increases, the result will also be an increase in the number of positive LB cases, thus, more known LB infections.

In the following analysis, possible altering risk factors for LB prevalence are discussed. The discussed factors are selected on the basis of an alleged relationship to LB in literature and an apparent relation to LB incidence as result from the discussion in the previous two chapters. An overview of identified factors is depicted in figure 4.1. For each of the factors the significance of changing the LB incidence is discussed. If data was available, also past and future trends are analyzed. This chapter concludes with a general conclusion based on all factors discussed.

As discussed in chapter 2, LB is occurring within a system comprised of many actors, e.g. vectors, hosts, reservoirs and humans. All these actors are acting in response to environmental parameters. But also actors could influence each other, and environmental parameters might have an influence on each other as well. As noted in chapter 3, solid reliable data regarding this system is sketchy. As a result, this system has a high level of complexity and a high level of uncertainty. For analytical purposes it is impossible to assess the system as a whole. Therefore, in the following analysis of risk factors for LB, only individual parameters of the system are assessed and their influence on the outcome of the system, the LB incidence, is analyzed.

The role of the causative agent, the *Borrelia* bacterium, is assumed to be unchanged. As discussed in §2.3, the bacterium survives during its life cycle inside a wide variety of hosts (i.e. in the ticks gut and in the blood of rodents, birds, large mammals), thus within a broad range of environmental conditions. Furthermore, because the pathogen is residing within hosts, it is relatively isolated from the external environment. Due to the time scale, possible genomic mutations are also regarded insignificant. Therefore, this analysis assumes that the *Borrelia* bacterium is not significantly affected by the in this context small environmental changes.
Figure 4.1: Overview of the identified and discussed probable risk factors for LB incidence increase.
4.2  *Borrelia*-infected tick population
Factors in this category are contributing to the change in absolute numbers and/or geographical distribution of infected ticks in Western-Europe. These factors are all influencing the condition of the external environment of the tick and its hosts.

4.2.1  Climate
Because the vector for LB spends a large part of its lifecycle questing in the external environment, changes in this environment may strongly affect the tick. Not only the vector can be affected, but also the hosts are likely to react on changes of the climate. This paragraph discusses two major environmental characteristics for the external environment of the tick and its hosts: temperature and precipitation. Also the occurrence of extreme weather conditions is discussed. Not only the change over the last decades is discussed, but also an outlook for the decades to come is given.

4.2.1.1  Temperature
Figure 4.2 shows the change in average temperature per decade during the winter and summer in Europe. Practically everywhere the average temperatures have increased during the last three decades. However, the observed temperature change can vary strongly among regions. Most notably are the higher average temperatures in Scandinavia during the winter months December, January and February compared to the rest of Europe.

![Figure 4.2: Observed temperature change over Europe 1976-2006 (European Environment Agency, 2012b).](image)

In general, higher temperatures will increase the transmission of vector-borne pathogens in three aspects: vector development rate, vector biting rate and pathogen replication. However, at the same time higher temperatures will decrease vector survival, for example from more extreme environmental conditions (Kilpatrick & Randolph, 2012). To what extent each of the general vector-borne aspects will change under the influence of changing temperature averages and to what extent they will apply to the average tick in Europe is difficult to determine due to the complexity of the affected system. For example, increasing temperatures in Northern-Europe will increase deer winter survival chances and induces earlier deer birth dates. This results in higher roe deer abundance, the most
important host for maintaining tick populations. At the same time, the environment will be able
to sustain this higher deer abundance, because the higher temperatures will increase plant
growth. This stands in sharp contrast to Southern Europe: here, higher temperatures will evoke
the opposite, i.e. decreased deer abundance in these regions (Mannelli et al., 2012).

Thus, the effects are difficult to determine and can also vary greatly among different regions.
Nevertheless, several scientists are arguing that the in §3.6 described expansion of the
geographical range of ticks, both latitudinally as well altitudinally, is driven by the warming
climate (Daniel et al., 2003; Jaenson et al., 2012; Lindgren et al., 2000). This assumption is
understandable when considering the rise in average winter temperatures coincides
geographically with the expansion of LB.

While the temperature effects on the system as a whole are difficult to assess, the effects of
higher average temperatures might have a clear effect with regard to temperature thresholds.
For ticks to be able to engage in questing a temperature of at least 7° C. is required. When the
ambient temperature is lower than 4° C. the ticks usually go to diapause (§2.3).
A good indicator for the length of the winter is the change in number of frost days (< o° C.). The
map shown in figure 4.3 demonstrates that over the last three decades the numbers of frost days
in a large part of Europe are decreasing. These shorter and milder winters enables the tick to
survive the winter and to extend its activity period, ultimately resulting in higher tick activity
during the winter (Mannelli et al., 2012).

![Figure 4.3: Observed changes in warm spells and frost days between 1976-2006 (European Environment
Agency, 2012a).](image)

In the future the witnessed trend of increasing temperatures is expected to continue, albeit the
pace slows down a bit. For the projection shown in figure 4.4 a scenario from the IPCC’s Fourth
Assessment Report is used. The chosen scenario, A1B, is characterized by a world with global
population of 9 billion in 2050, with a rapid economic growth where technologies spread quickly
and will be applied on both fossil and non-fossil fuels. With this scenario, the average temperatures during the winter months are expected to increase with approximately 4° C. for Northern-Europe and with approximately 3° C. for the rest of Europe in the coming 58 to 87 years.

The effects of the warming of Europe on the occurrence of ticks on a system level are difficult to predict. However, it can be expected that changing temperatures will have a significant effect on the tick activity during the winter and also will affect the geographical distribution of the tick in Western-Europe.

4.2.1.2 Precipitation
Figure 4.5 shows the changes in annual precipitation in Europe per decade since 1961. The distribution of the annual precipitation change shows that the southern and southern western parts of Europe experienced a trend of less annual precipitation, i.e. these regions have become drier. Other parts of Europe have become wetter, in general these are the northern and north western parts of Europe. However, as figure 4.5 demonstrates, the distribution of the precipitation change is not evenly distributed across Europe.
For ticks to survive during questing they require a high level of humidity (§2.3). Thus in areas where the annual precipitation has gone up, the odds that a tick can survive will increase. However, a change in annual precipitation will also have an effect on the external environment, with opposite effects for the tick population. For example, if a drier summer coincides with higher average temperatures, these conditions will cause decreasing survival rates for the tick during questing, because of the higher chance of desiccation. However, at the same time these conditions will favor growth of the beech (*Fagus sylvatica*) over growth of the Norway spruce (*Picea abies*) (Ammer *et al.*, 2008). The fallen leafs of the beech will in turn create a suitable habitat for the tick to avoid desiccation, thus increasing survival rates.

In figure 4.6 is depicted a projection for the future precipitation change in Europe using the IPCCs A1B scenario (§4.2.1.1). This prediction shows that the trend of a drier south and a wetter north is continued. However, it is expected that the division between north and south becomes stricter. By 2100, the average summer precipitation of southern Europe is 20%-30% lower than the 1990 level. In the same time, northern Europe will become on average 5% to 15% wetter during the summer and 10% to 20% annually.

Thus, the effects of the change in annual precipitation over the last decades on the prevalence of LB are hard to predict. This results from the uneven distribution of the change in precipitation across Europe. Moreover, the effects on the system on a whole are hard to foresee. For the future it is predicted that the trend as seen the last four decades is likely to continue.
4.2.1.3 Extremes

The two previous paragraphs discussed the average developments of Europe’s future climate, but the occurrence of weather extremes is predicted to change as well. While the *Ixodes* tick is characterized by its resistance to a broad variety of environmental conditions (§2.3), some conditions will negatively affect the survival of these ticks. However, other changing extreme conditions might favor the survival of ticks.

Extreme precipitation is seen to increase in amount and intensity already the last decade, a significantly high number of devastating rainfalls occurred since 2000 in Western-Europe (Coumou & Rahmstorf, 2012). For the future more extreme rainfall is predicted for the northern part of Europe, whereas for the Mediterranean earlier and longer droughts are predicted (Beniston *et al.*, 2007). For ticks the extreme rainfall could result in drowning, whereas drought could result in desiccation.

Besides higher average temperature during the winter, also periods of cold spells, i.e. short periods of extreme cold, are expected to increase in temperature. By the end of this century, cold spells are expected to still occur with the same duration, return period and intensity, however, they become approximately 5° C. warmer. This means that in Western-Europe the temperatures remain above freezing point during a cold spell, thus ticks will have increased chances of surviving the winter (de Vries *et al.*, 2012).

4.2.1.4 Conclusion

Climate change will affect the environment where the pathogen, the vector and host are residing. From the three paragraphs above it can be concluded that currently Western-Europe is getting more attractive as a habitat for ticks. The northern part is getting wetter and hotter and
the ticks are found expanding to this regions (§3.7). In the southern part of Europe, ticks can be active all year round if they are able find sufficient humidity, for example in Southern-Italy (§2.4). However, the increasing number of extreme precipitation events as seen during the last decade might affect tick survival.

For the future, Europe might become less suitable as a habitat for *Ixodes*. The southern part is expected to become too hot and too dry for survival of ticks. Although the northern part is developing into a more suitable habitat with regard to temperature, the average winter temperatures are expected to become more suitable for ticks, the expected rise in extreme rainfall creates an opposing effect as result from increased risk of drowning. However, the effects will be variable (in time, in location and in intensity) as expected from a system with this level of complexity. So there is still a lot of controversy about the extent to which climate change is contributing to the incidence of this disease (Rohr *et al.*, 2011). Therefore, most scientists acknowledge the influence of climate on the transmission and distribution of LB, but climate change is not seen as the main cause of the increasing LB prevalence. The scientific consensus is that other factors (e.g. land use and social factors) played and will play a role of more significance in the increased LB prevalence (Gray *et al.*, 2009; Kilpatrick & Randolph, 2012; Rohr *et al.*, 2011).

### 4.2.2 Biodiversity

Over the last decades several theoretical models and laboratory experiments demonstrated that an increasing biodiversity correlates with a decreased risk of infection among several diseases including LB. This so-called dilution effect is suggested to be the result from the fact that higher species-rich communities contain a higher fraction of less competent hosts. For LB this means that ticks more often feed on hosts that are not able to provide an adequate environment for the *Borrelia* bacterium. Therefore, the number of ‘wasted’ transmission increases, thus the overall number of infected ticks will decline. However, also the opposite occurs. When the biodiversity is reduced, and this concerns the loss of those less competent hosts, the number of optimal transmissions will increase. From literature it is known that this increased pathogen transmission as result from biodiversity loss occurs among several infectious diseases (e.g. West Nile virus, malaria and LB). Apparently these vector-borne infectious diseases all use an optimal host for transmission of the pathogen more ecological resilient than other species. A relatively well documented example for LB is the resilience of the white footed mouse, the optimal host for LB, in the USA. This mouse is found along infected ticks regardless of species richness, whereas the poor host Virginia possum, which will kill the vast majority of ticks during feeding, disappears when biodiversity is reduced (Johnson & Thieltges, 2010; Keeling *et al.*, 2010; Ostfeld & Keesing, 2012). Recent European Union policy plans are aiming to halt the current biodiversity loss with 2012 adoption of a new resolution. One of the targets of this resolution is to create legislation to preserve biodiversity. Ultimately the policy plans are aiming at restoring biodiversity as far as feasible (The European Parliament, 2012).

### 4.2.3 Season length

As a result from environmental conditions (low temperature and low light intensity), ticks usually enter diapause during winter. When ticks were not able to find a suitable blood meal prior to diapausing, the changes that ticks will survive the winter are low (§2.4).

However, if ticks are able to shorten the diapause period, thus have a longer questing period, there is a higher chance to find suitable blood hosts. Consequently the tick population does not decrease, because these ticks survived. Moreover, these ticks also have higher chances to complete their life cycle, and will produce offspring. The questing period can be extended by an earlier seasonal onset.
Data from well documented species is used to analyze if the onset of questing period of ticks might be changed. The data in figure 4.7 shows that both the onset of flying periods of butterflies and dragon flies, and the egg laying period of birds tend to start earlier over the last decades in the Netherlands. For example, when looking at the trend line of the onset of oviposition period for birds: in 1986 this was at day number 134 (May 14), currently this happens 10 days (=7.5%) earlier.

This trend is not only found in the Netherlands, but also at a European level. During 1959-1993 the spring (defined as tree leaf unfolding) started on average six days earlier, at the same time the start of autumn (defined as tree leaf coloring) was on average delayed by about five days. This means that in 34 years, the average annual growing season was extended by almost eleven days (Menzel & Fabian, 1999).

Thus, for these species (insects, birds and trees) the environmental conditions (most likely temperature) are suitable to start their season on an earlier date. Ticks are also heavily dependent on environmental conditions, therefore it is expected that ticks will express a similar behavior as the discussed species. Thus, ticks will have a lengthened season of activity by a reduced diapause length. This will increase their window to find suitable hosts, thus increasing its changes on survival.

4.2.4 Land use
The way humans change and manage the surroundings can have a great impact on the occurrence of ticks. This paragraph discusses two effects of the human land use on ticks. Because ticks rely during questing on characteristics of their habitat (i.e. high humidity under fallen leaves and vegetation to climb in), the availability of this habitat has a major influence on the tick population size. The kind of land use most suitable as a habitat for ticks is deciduous
forest. This means that if this habitat would increase in size (i.e. more forests), the total number of ticks would also increase.

The other effect of land use concerns the host availability for ticks. To complete their three-stage life-cycle, ticks need blood from three different hosts. While for survival of a single tick, all these hosts are required and thus equally important, for the whole tick population the availability of the third host is of more importance. The following two examples will demonstrate this.

During the last century in the northeastern of USA abandoning of large farms caused a major change in landscape. Large open fields, used during the 18th and 19th centuries for agriculture, changed through natural succession into deciduous forests. As the large forests returned, so did the white-tailed deer. This event initiated the invasion by the \(I.\ scapularis\) tick, resulting in the current LB epidemic in the North-Eastern USA (Barbour & Fish, 1993; §3.8).

Another example of the connection between ticks and deer is found in Scotland, UK. Researchers performed a field study where large numbers of ticks were collected at many different locations. Analysis of the ticks revealed that more questing nymphs and higher incidences of \(B.\ burgdorferi\ s.l.\) among ticks were found at deciduous forest sites with high deer abundance (James et al., 2013).

These two examples illustrate that ticks can reproduce in larger numbers if the necessary third-stage host is available. Thus if the land is used as a large forest, the result will be a larger tick population.

An overview of the total surface area of forest within a country, the Netherlands (§3.2), with a large increase in LB incidence is shown in figure 4.8. The graph indicates that amount of forest in has been increasing since 1900. Most notably is the sharp increase between 1990 and 2000 (13.3% increase).

The extent to which this is an international phenomenon is shown in figure 4.9. Over the last two decades the total surface area of forest in Western-Europe increased with 8.1%. However, the highest increase is seen during the first decade, and the pace of the increase is slowing down since 2000.
Therefore during the last 20 years the possible habitat in Western-Europe for ticks has increased with 8.1%. Also for the important third-stage host the environment is more suitable for harboring higher population numbers. This effect might be enhanced by natural conservation policies developments at the same period. In the Netherlands a policy was developed called the 'Ecologische Hoofdstructuur' (English: National Ecological Network). This policy aims to connect different natural preservation parks with each other to preserve biodiversity by increasing habitat size (Ministry of Economic Affairs (Netherlands), 2012). Since the habitat of deer is increasing in size, it should be able to sustain a higher population of deer.

However, this effect of increasing habitat size on more ticks does not necessarily have to result in a higher number of *Borrelia*-infected ticks. Many vertebrate species cannot survive in forest smaller than two hectares. One species however, the white-footed mice (an important reservoir of *Borrelia*), is not affected by the size of the forest. Moreover, because the non-surviving species tend to be predators or competitors of the white footed mice, the population density of the mice will increase with an opposite direction to forest size. Because these mice are an important reservoir for the LB bacterium, this results in higher densities of *Borrelia*-infected ticks (Allan *et al.*, 2003; §4.2.2). Thus, larger forests might result in a lower mice density, leading to a lower number of *Borrelia*-infected ticks.

Concluding, the change in land use in Western-Europe over the last two decades favors larger tick population, by an increase of habitat size and by an increase of the third stage host crucial for reproduction. In contrast, the disappearance of small and/or fragmented forest patches is bound to reduce the density of *Borrelia*-infection among ticks.
4.3 Human exposure to infected ticks
Factors in this category influence the chance that a human being encounters an infected tick.

4.3.1 Pets in households
One way of increasing the chances of tick-human interaction, is by taking the tick to the natural environment of humans, i.e. the house. A contributing risk factor could be the presence of pets in the household. For example, the pet could pick up a tick, which can be brought into the house via the fur of the pet. Or, having a pet could increase the chance to going to areas with high tick density, i.e. forests.

In a 2012 large serology study \((n=12,297)\) performed among the German population, researchers looked at the prevalence of IgG antibodies (an indicator of present of past LB infection) against \(B.\ burgdorferi\) present in the blood in combination with potential risks factors. This study was performed only in children and adolescents aged one to seventeen, because the researchers regard this age group more prone to LB infection due to recreational activities, e.g. playing outdoors. Nevertheless, using data from this study will still give important insights into the significance of pets in a household as a risk factor for LB.

Serology data revealed that average prevalence of LB antibodies among the entire researched age group is 4.0%, among people without a pet in the household is 3.3% and among people with a pet is 4.8% (45% higher). The kind of pet matters: people holding cats have a prevalence of 6.2% (88% higher than no pet) and people holding dogs have in 4.8% of the cases IgG antibodies against LB in their blood (Dehnert et al., 2012).

During the last years to total number of pets in Germany increased from 7.5 million cats and 5.3 million dogs in 2004 to 8.4 million cats (+9.3%) and 5.4 million dogs (+1.9%) in 2011 (Industrial Association of Pet Care Producers, 2011).

This study reveals that the odds of a present or past LB infection among children under the age of eighteen are higher if there is a pet in the household. Having a cat is a higher risk factor, than having a dog. The number of German households with cats increased with almost ten percent during the last decade.

However, these correlations found do not imply a causal relationship between having a pet and higher LB infectious. Other risk factors might also play a significant role in the higher prevalence of LB antibodies. For example, one might argue that dog owners are proportionally living more often in rural areas or in small villages. When taking the results of the next paragraph into consideration (higher prevalence in rural areas), the serology results for pets might not be totally representative for the entire population.

4.3.2 Community size
A risk factor for LB infection might be the proximity to the natural habitat of the tick. When someone’s distance to the habitat is larger, his likelihood of encountering an infected tick decreases. The size of the community is regarded a determinant for distance to the ticks’ habitat. Therefore, the odds of encountering an infected tick would increase in the following order of urbanization: metropolitan areas (>100,000 inhabitants), the mid-sized towns (>20,000), small towns (>5,000) and rural areas (<5,000).

The 2012 German serology study confirms this hypothesis. Inhabitants of large metropolitan areas have 2.9% antibody prevalence, people from mid-sized towns 3.5%, people from small towns 4.5% and people from rural areas 5.7% (Dehnert et al., 2012).

The results demonstrate that for German children under the age of eighteen the chances of having a previous or current LB infection are correlated with community size. As mentioned in paragraph 4.3.1, these correlations do not imply causal relationships. For example, people living in rural areas are likely to be more involved in outdoor activities. Thus, not necessarily the size of residential area is the risk factor, but one’s lifestyle when living in a smaller community might
be the “true” risk factor. However, the size of the community can be still be used as an indicator (or predictor) for LB seroprevalence.

Figure 4.10 shows is the trend of urbanization in the European Union since 1960. In this graph urbanization is defined as people living in urban areas with urban-type land use and with no gaps larger than 200 meter between individual settlements. The trend shows a steady increase in the percentage of the total population living in urban areas. Therefore, the influence of community size is regarded to have contributed negatively to the LB prevalence during the last decade. This trend of urbanization is expected to continue in the future, although the pace may slow down a bit.

Figure 4.10: Urbanization of the European Union (consisting of the 2013 members) since 1960 (The World Bank, 2012).

4.3.3 Wealth

Paragraph 4.3.2 indicates that the size of residential areas can be a risk factor for LB, but also the type (i.e. size) of residence can also be a risk factor. People with an above average wealth tend to live in larger houses on larger pieces of land. Belgian researchers analyzed spatial distribution maps of LB incidence in Belgium. When this data was combined with social-economic statistics the analysis showed a higher likelihood of LB infection among people living in the wealthier peri-urban areas. The researchers assumed that this higher probability results from more space between the individual settlements (i.e. larger gardens), thus more suitable habitat for ticks (Catherine et al., 2007).

Figure 4.11 shows the income inequality in the European Union 15 countries, consisting of the 1995 EU members. The measure used to assess the income inequity is the Gini-index. Using this index, a Gini-coefficient of zero means perfect income equality, whereas a coefficient of 100 means perfect inequity. The graph shows that the past development of income distribution is relatively constant, although a small increase in inequality is observed. But in general the number of people with an above average income did not significantly change. Therefore, the contribution of more or less numbers of wealthier people is not regarded as a significant contributor to the increase LB prevalence.
4.3.4 **Outdoor activities**

An important risk factor for humans to get infected with LB is their behavior regarding outdoor activities. One of the outdoor activities that is considered to increase significantly the chances of such an infection, is going to the natural environment of the tick, i.e. forests. Here, the tick density is relatively high, therefore the chances of getting bitten by a *Borrelia*-infected tick are substantially higher.

Figure 4.12 shows the annual percentage of the Dutch population that is visiting a forest at least once a month, or at least more than three times a year. The results show no significant change over the last fifteen years. This result is confirmed by the constant annual visitor attendance of the most visited Dutch national park 'The Hoge Veluwe' since 2003 (data not shown) (Stichting...
Het Nationaal Park De Hoge Veluwe, 2011). More detailed statistics for The Netherlands or comparable statistics of other Western-European countries are difficult to obtain because long-term monitoring data or reliable statistics are non-existent (Sievänen et al., 2008). However, if Europeans would act in a similar fashion as Americans, an increase of outdoor activities is to be expected. In the USA, the fastest increase in participant numbers in outdoor activities is seen in hiking, sightseeing and picnicking (Bell et al., 2007). Due to unavailability of reliable European data concerning the outdoor activity behavior of people, the past and future developments concerning this behavior are hard to predict. Based on the two discussed Dutch sources the trend of getting LB as result from outdoor activities was not assumed to contribute to the increase in LB in the past. However if Europeans would follow the USA trends, more outdoor activities are to be expected.

4.4 Reporting
Factors in this category do not account for changes in the absolute numbers of infected ticks or the absolute number of infections. They do however contribute to the awareness, which in turn could result in more and/or improved reporting of LB cases. Factors from this category can result in a higher LB incidence, because a significant share of the LB cases was not reported. The seroprevalence data discussed in §4.3.1 shows that 4.0% (prevalence of 4,000 per 100,000 inhabitants) of the examined German juvenile people was infected with LB. Because this group of people consisted only of people under 18, the average number of reported LB cases annually to completely cover the found seroprevalence should be on average 222.2 (=4,000/18). As the discussed data in §3.5 indicate, the 2009 number of reported Western-German LB cases was 34.7. Therefore, in this year on average 84% of the LB cases were not reported. Moreover, even the in §3.3 discussed high reported incidence in the Netherlands of 133.9 in 2009 means that on average 40% of the LB cases were not reported. Therefore, if the reporting would be more sensitive or if more people are aware of LB, the result would be more positive LB cases.

4.4.1 Public awareness
The quality and quantity of LB reporting is assumed to be affected by the public awareness and/or interest by the public. When the public is more aware of LB, the result may be more or sooner GP consultations, which in turn would result in a higher known incidence. Note, this can happen when the absolute numbers of infected ticks and cases of LB remain unchanged.

In this analysis tools are used that evaluate the use of large medium, the internet, to assess if there is a change in public awareness regarding LB over the last years. For this analysis it is assumed that if someone wants to have information about something, the internet is among the first sources of information. Whilst Europe has a big disadvantage concerning the different reporting standards, the diversity between different countries is for this analysis is of great importance. In Western Europe many regions have their geographically specific own language, e.g. the majority of Germany is only spoken in Denmark and adjacent regions. Thus, for each region highly specific data can be obtained by looking at local language page visits regarding LB information.

Wikipedia is an online encyclopedia where reliable and accurate information can be obtained. Also, if one would search for “lyme” in any of the countries to be analyzed using the largest internet search tool Google, in every local language the number one search result is the corresponding Wikipedia lemma. Therefore, the number of Wikipedia page views is assumed to
be representative for the number of people interested in recent and easy accessible information regarding this infection.

Figure 4.13 shows the daily page views for the German “Lyme-Borreliose” lemma since December 2007. The results show two remarkable things. The first is that the annual cycle of tick activity (§2.3) is almost perfectly copied as number of Wikipedia page views. Because of this similarity, the assumption that people use Wikipedia as source of information regarding Lyme is plausible. The second is that there is no increasing trend in number of daily page views when comparing different years. Similar results are shown by other language Wikipedia lemma regarding LB from The Netherlands, Denmark, Sweden, France and Italy (data not shown).

Since 2007, the use of the internet as a result of technological developments has increased significantly. Therefore, to arrive at a correct public interest into the subject of LB on Wikipedia, these results have to be corrected for change in the total usage of Wikipedia. Figure 4.14 shows the total local Wikipedia monthly page views per language. The German Wikipedia shows an increase of 12% in the period 2009 – 2012. Combining this with the page views for “Lyme-Borreliose” lemma, a slight decrease of the public interest might be assumed.

Another source of public interest regarding LB on the internet is not if people are looking at the source of information itself, but if the people are looking for the information. As mentioned, if people are looking for data on the internet they often use a search tool. During the last decade the most frequently used one is Google. Statistics from this medium gives highly accurate information how often people are searching for information regarding LB.
Figure 4.14 shows how much interest there is for, i.e. how often people search for, terms related to LB. The third term, “malaria”, is shown for comparative purposes. The graph shows similar results as figure 4.13: a reflection of the annual tick activity and no significant change in how often people search for LB related terms when comparing different years.

Therefore, it can be concluded that using statistics from an important source of information and an important search tool on the internet, that there is no change in public awareness or interest in topics regarding LB when comparing different years. Moreover, when the increasing number of Wikipedia views is compared with the views for LB, a slight decrease of general interest can be assumed. However, this trend is not observable in the interest for LB related topics in Google’s search volume. Thus, it is concluded that the interest from the public in recent years did not significantly influence the reporting of LB cases.

Figure 4.15: The interest from people residing in Germany into two LB related search terms: “zeckenbiss” (tick bite) and “borreliose”. The third term (“malaria”) is for comparison. The y-axis represents search volume relative to the highest point on the chart (set at 100) (Google, 2013).
4.4.2 Professional awareness

The quality and quantity of LB reporting is also assumed to be affected by the awareness of professionals towards LB. If professionals are more aware of LB, the quality and quantity of reporting would presumably increase. Professionals dealing with LB are: doctors, GPs, scientists or politicians.

![Figure 4.16: Number of LB related scientific papers published annually on the Web of Knowledge (Thomas Reuters, 2013).](image)

The first tool to assess if there might be an altered interest is the number of scientific articles published annually on LB. It is assumed that if professionals have more interest towards LB, there would be more funding available. With more funding available, more research done can be done, resulting in more publications. Note, of course scientists are independent in their research topics, but if scientists cannot get the funds to perform their research, it is assumed that the interest of the professional world is lower.

Figure 4.16 shows the annual numbers of published scientific articles with the topic “Lyme borreliosis” available on Web of Knowledge. The graph shows that the number of published articles is relatively constant since 1994, with an average number of 160±28. This is confirmed by the trend line, which shows no significant change.

The second tool to assess if there is an altered interest in a certain field is by consulting professionals in the field, i.e. general practitioners. The Dutch GP educational program in Groningen mentions no specific education in the curriculum of the GP education, but argues that tick bites or *Borrelia* infections usually are studied in practice. Here, additional information is available from a 2007 standard guideline of the national GP organization (NHG) or a 2012 directive of the national health agency (RIVM) to aid GPs how to deal with LB patients (Bruinsma, 2013). The available guidelines are subject to development over the last years, as a guideline update from 2003 introduced an encouragement for GPs to treat severe cases of LB with intravenous antibiotics in a hospital. It is argued that this encouragement might have contributed to the increase of reported LB cases in the Netherlands (§3.3; Hofhuis et al., 2006).

The third tool to assess the interest is by looking at initiatives from the national level with regard to LB. An example of a new project to get more information about ticks in the Netherlands is called Tekenenradar.nl (‘tick radar’). This initiative is launched in March 2012 as a collaboration of
the RIVM, the Wageningen University and De Natuurkalender (the nature calendar, a public animal observation network). This initiative aims to inform people about LB by providing a risk level on tick bites and to increase knowledge about LB in the Netherlands by allowing people to report tick bites or to send in ticks for research. Also the RIVM is focusing its LB prevention attention to the risk group of children by targeted study material and online movies (van Vliet, 2013).

4.5 Key findings
This chapter discussed which factors could be contributing to the emergence of LB. Moreover, for the identified contributing factors a projection of the future contribution was discussed. From these discussions the following key findings can be extracted:

**Borrelia-infected tick population size**
- The changing climate is affecting the incidence of LB, however the direct effects are regarded not to be one of the main drivers behind the emergence.
  - The effects of higher average temperatures will probably result in a larger suitable tick habitat, mainly as result from warmer winters.
  - The change in precipitation is likely to shift the habitat of the tick northwards, as result from a drier south and a wetter northern-Europe.
  - Changing weather extremes result in harsher environmental conditions, but on the other hand periods of extreme cold during the winter become more mildly, thus less deadly for ticks.
- Reduction of the biodiversity is increasing the tick population as result from the host resilience; however policy plans are halting biodiversity loss.
- The increasing season length is increasing the survival chances of ticks, as a result from higher odds of finding a suitable host and therefore is favoring higher tick populations. This contributing factor is therefore regarded as one of the main drivers behind the emergence of LB.
- The increasing total surface area of forest in Western-Europe is increasing the habitat size for both ticks and the for reproduction important third stage host. The increase in forest area was over the last two decades 8.1% and is therefore regarded as one of the major drivers behind LB emergence.

**Exposure to infected ticks**
- The presence of pets in the household is positively correlated with LB seroprevalence. Because the last years the number of pets in households was increasing, this contributing factor is regarded as one of the major drivers behind LB emergence.
- People living in small communities are positively correlated with LB seroprevalance. However, as result from urbanization, the number of people living in small communities is declining.
- Above-average incomes tend to increase the odds on LB infection as result from more spacious lot sizes. However, the proportion of the Western-European population with above-average incomes did not significantly change the last decades.
- The last years no increase in outdoor activities is seen, however, in the future a trend of more outdoor activities is expected.

**Reporting**
- From analysis of the online behavior of people, no increase of interest is seen from the general population the last years
- The professional interest towards LB seems to increasing, by national health campaigns and regularly updated guidelines for doctors.
CHAPTER 5: FUTURE INCIDENCE OF LYME BORRELIOSIS

5.1 Introduction
The previous chapters gave a comprehensive qualitative discussion about the past of LB in Western-Europe. However, for policy makers, researchers and even the general population the future development of LB might be more relevant. Therefore the knowledge from this qualitative discussion is quantified and used as an input for a useful tool to project the future: a theoretical model.

A model widely used in the epidemiology is the SIR (susceptible-infected-recovered) compartment model (Kermack & McKendrick, 1932). However, this model cannot be used for this analysis as it requires a level of comprehension about the entire LB system, specifically infection rates of the different hosts, which are currently unknown for LB (chapter 3). Other modeling approaches described in literature usually focus on one specific changing factor, often climate change (e.g. Brownstein et al., 2003) or range expansion of the tick (e.g. Leighton, et al., 2012). However, as the discussed factors in chapter 4 indicate, it is expected that not one, but several changing factors are increasing the number of annual LB infections. For this reason, and because of the complexity and the deep uncertainty of the LB infection system, a more general model is required. Such a modeling approach of a qualitative discussion of the entire LB infection system is currently not adequately described in literature.

Thus, to model the future LB incidence based on the qualitative discussion, a new model is constructed. To be comprehensive, three different modeling approaches are used: extrapolative, static and dynamic. Because the LB incidence can vary between regions and the used reporting standards also differ, the input for the models is the Western-European average of all aspects concerning LB. Consequently, the output of the modeling is the average increase in the number of reported cases of LB expected in the near future. The near future is defined as the year 2030. The three different models are discussed in order of complexity, followed by a discussion of the results.

5.2 Extrapolating
A simplistic method to predict the future is by extrapolating past trends to the future. For LB incidence this approach is convenient as low data quantities are required. However, by using past trends for the future, the model assumes that these trends do not change in the predicted future. Nevertheless, by using this approach, still an indicative projection of the future can be constructed.

This model uses as input the average LB incidence change in Western-Europe and adjacent regions from 1999 to 2011 as discussed in chapter 3. The incidence data summarized in figure 3.5 shows that the past LB incidence increase is almost linear with an $R^2$ of 0.97. Therefore, extrapolating this past trend linearly could be a relevant predictor of the average LB increase in the future.

The graph in figure 5.1 shows that on basis of past the past LB incidence, using a linear extrapolation, the future LB incidence in is expected to be more than twice as high (+110.2%) than the 2011 incidence.
5.3 Static modeling

As mentioned, extrapolating the past to the future uses the assumption that past trends do not change. However, as discussed in chapter 4, the contributing factors for LB incidence are subjective to change. To be able to incorporate these changing trends into the extrapolation model, a static model is constructed. This model calculates the 2030 LB average incidence increase based on the extrapolation, but now corrected for possible changes of the contributing factors on the LB incidence in the future. To be able to assess this, first the influence and change of the contributing factors on the LB incidence have to be quantified.

5.3.1 Quantification

On the basis of the discussion in chapter 4 the contributing factors for LB incidence are quantified as shown in table 5.1. Based on the discussion of literature three factors are regarded to have the most influence on the past LB incidence: ‘season length’, ‘land use’ and ‘pets in household’. Therefore, their influence is rated at 4. Other factors are regarded to have less influence on the past LB incidence, these factors are rated between 1 and 2. On basis of the qualitative discussion an expected change of this past influence in the future is assumed. This change is shown as a positive or negative percentage in the ‘Expected future change (%)’ column. For example, for ‘temperature’ the past influence of ‘2’ is increased with expected to increase with 20%, thus an expected 2030 influence on the LB incidence of ‘2.4’.

Figure 5.1: The future of LB incidence in Western-Europe based on a linear extrapolation of the past.
Table 5.1: Quantified influence on the LB incidence in the past (1999-2011) and in the future (2030) based on the qualitative discussion in chapter 4.

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>Past influence on LB incidence</th>
<th>Expected future change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Borellia-infected tick population</strong></td>
<td>Temperature</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Precipitation</td>
<td>1</td>
<td>-20</td>
</tr>
<tr>
<td></td>
<td>Extremes</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Biodiversity</td>
<td>1</td>
<td>-10</td>
</tr>
<tr>
<td></td>
<td>Season length</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Land use</td>
<td>4</td>
<td>-50</td>
</tr>
<tr>
<td><strong>Exposure to infected ticks</strong></td>
<td>Pets in household</td>
<td>4</td>
<td>-20</td>
</tr>
<tr>
<td></td>
<td>Community size</td>
<td>2</td>
<td>-20</td>
</tr>
<tr>
<td></td>
<td>Wealth</td>
<td>1</td>
<td>-10</td>
</tr>
<tr>
<td></td>
<td>Outdoor activities</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td><strong>Reporting</strong></td>
<td>Public awareness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Professional awareness</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

5.3.2 Model
The now quantified data of each factor can be incorporated into the static model. This model uses the linear extrapolation from §5.3.1 as a basis, however now the influence and future change of the contributing factors is included. This is done by calculating the future influence of each contributing factor (past influence * future change) as a part of the projected 2030 average LB incidence from the linear extrapolation. This can be summarized into the following formula:

\[
LB_f = \left( \frac{ex}{tp} \right) \times p \times \left( 1 + \left( \frac{fc}{100} \right) \right)
\]

Symbols:
- \(LB_f\) = the LB incidence increase as a result from one factor
- \(ex\) = the 2030 average LB incidence increase based on linear extrapolation
- \(tp\) = the total past influence of all factors together
- \(p\) = the past influence of a specific factor
- \(fc\) = the future change of a specific factor

The sum of the twelve LBs is the expected LB incidence increase in 2030 based on static modeling of the expected future change of the influence of the contributing factors. This result is shown as a graph in figure 5.2. Additionally two extreme scenarios with regard to the influence of the climate are shown. In table 5.2 is shown the used future change values for these two scenarios. The graph shows that the expected future LB incidence is almost twice as high (+91%) as the 2011 incidence. The two extreme scenarios demonstrate what the influence is of a change beyond expectation. When the influence of climatological factors in the future is half of the current influence the number of annually reported LB cases increases with 69%. When the influence should double, the number of reported cases increases with 106%.
Table 5.2: Characteristics of two extreme scenarios regarding the climatological influence on the LB incidence in the future.

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
<th>Weak influence of climate</th>
<th>Strong influence of climate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Borrelia-infected tick population</strong></td>
<td>Temperature</td>
<td>-50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Precipitation</td>
<td>-50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Extremes</td>
<td>-50</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Biodiversity</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Season length</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Land use</td>
<td>-50</td>
<td>-50</td>
</tr>
<tr>
<td><strong>Exposure to infected ticks</strong></td>
<td>Pets in household</td>
<td>-20</td>
<td>-20</td>
</tr>
<tr>
<td></td>
<td>Community size</td>
<td>-5</td>
<td>-5</td>
</tr>
<tr>
<td></td>
<td>Wealth</td>
<td>-10</td>
<td>-10</td>
</tr>
<tr>
<td></td>
<td>Outdoor activities</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td><strong>Reporting</strong></td>
<td>Public awareness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Professional awareness</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Figure 5.2: The future of LB incidence in Western-Europe based on static modeling of the changing contributing factors. Also shown are two extreme scenarios regarding the influence of climatological factors on the LB incidence.
5.4 Dynamic modeling

Using the static modeling approach it is assumed that change of the influence of the contributing factors is linear, i.e. only the change in 2030 is modeled. However, as the discussion of the contributing factors in chapter 4 demonstrates, not all effects are expected to be linear. For example, the change in land use shows a convexed development in the past, it is therefore expected that this change will work on in the future. Also some factors are dynamic, i.e. they could influence each other. For example, a higher professional awareness would not only have a direct effect on more reported cases by doctors, but would also have an indirect effect on less tick bites from outdoor activities. As more professional awareness results in more prevention programs, people are more aware of the risks on LB when performing outdoor activities, people will wear more protective clothing or check themselves more carefully on tick bites.

To incorporate dynamic effects into the static model, a dynamic model is constructed by using the dynamic modeling software program STELLA. This software program is used due to its proven qualities regarding dynamic modeling and its ease to construct a dynamic model. The diagram of the dynamic model and the used future influences are shown in appendix A.

The results of this dynamic modeling approach are shown in figure 5.3. This model projects a future LB incidence almost twice as high (+98%) than in 2011. This result is as expected comparable with static modeling approach. But in addition the dynamic model gives insights in how the LB incidence is expected to develop in the years to come. The model projects that the pace of LB incidence increase will increase a bit compared with the past trend in the years towards 2020. From 2020 the pace slows down, however, after a few years the pace of increase in LB incidence is increased again.

Figure 5.3: The future of LB incidence in Western-Europe based on dynamic modeling of the changing influence of the contributing factors.
5.5 Conclusion

An overview of all modeling approaches is shown in figure 5.4. The three approaches project an increase in the incidence of LB for 2030 ranging from +91.9% based on static modeling to +110.2% based on an extrapolation of the past trend. Dynamic modeling projects an increase of +97.6% in the future. Which of these three approaches gives the most accurate result is hard to assess, however, because the outcome of the dynamic modeling approach is between the outcomes of the two other approaches, this approach is considered to be the most informative about the future trend.

In general, it might be concluded that based on the modeling it is projected that the increase of the LB incidence is going to continue in the future, with a doubling of the 2011 annually reported LB cases in the year 2030.

![Figure 5.4: The future of LB incidence in Western-Europe based on three modeling approaches: extrapolative, static and dynamic.](image-url)
CHAPTER 6: GENERAL DISCUSSION

This thesis aimed to use the emergence of LB as an example of other emerging infectious diseases (EID) in Western-Europe. By using LB as an example, consequently the assumption was made that the emergence of LB is comparable to other EIDs. However, there are significant differences between the different EIDs. For example the mentioned diseases in §1.1 all use different vectors, therefore large parts of the system behind the human infection differ. But although these differences exist, there are also many similarities: these diseases are emerging, vector-borne and are unexplained. Therefore, this thesis focused on the similarities between these diseases, by exploring the problems associated with diagnosing, reporting and predicting. Moreover, because of the focus on these characteristics, this thesis did only discuss aspects of the emergence of LB. However, there are also other diseases associated with ticks. For example, currently a large upsurge in the reported cases of tick-borne encephalitis (TBE) is happening in Eastern-Europe (Lindquist & Vapalahti, 2008). Therefore, a topic for further research might be to include data from this disease.

The generate an average Western-European LB incidence, quantitative data from a wide variety of sources was used to deal with the uncertainty as a result from the data reporting (§3.2). While this thesis focused on the occurrence of LB in Western-Europe, during the discussion of the incidence data it was found that data for Western-Europe was relative scare. To still generate an average European trend with sufficient data sources, data from North- and Eastern-Europe was included. While this region is adjacent to the focus area, and is therefore comparable with the situation in Western-Europe, some differences do exist. To validate the found trends as result from including this data, trends found in literature from field studies was discussed.

The selection of the contributing factors for the tick population (§4.2) and the human exposure (§4.3) was based on discussions found in literature. Consequently, important contributing factors could be missed as a result from not being available in literature. Moreover, the assumed contribution to the emergence of LB results from careful consideration of the found qualitative connections. This implies that results might differ if new literature would be available.

The discussed incidence statistics, resulting in the conclusion that LB is emerging, is based on the reporting of LB cases. Because in most cases the reporting was not mandatory, the quality of LB reporting is variable and not in all cases clear symptoms are present, the found incidence is not equal to the absolute number of LB cases. Therefore, the found LB emergence might be the result of an emergence of the LB reporting. This possibility was analyzed by the third category of contributing factors (§4.4). The main conclusion drawn from this analysis is that the reporting was not biased as result from more awareness online, however, it also demonstrated that the emergence of LB did not result in more information searches. This result is contradictory and in sharp contrast with the latest information technological developments (i.e. the overall increase in the availability of internet access). Because if one would assume that the internet is among the first sources to obtain information about the found tick on someone’s body, or a suddenly appearing expanding ring-like lesion, the conclusion of this assumption would be that the number of LB cases is not increasing. Therefore, in further research other channels of communication might be included.

An important plausible contributing factor not included, but also impossible to include, is the occurrence of unexpected, extreme events. For example, if someone nationally well-known would be diagnosed with LB, or if any other reason would get the occurrence and/or emergence of LB prominently in the news, the awareness and available funds for research and prevention would probably dramatically increase. The result would be a local change of in the distribution of the contribution of the risk factors for LB.
The question how the emergence of LB would develop into the future was addressed by means of a modeling approach (§5.5). For this modeling approach, it was necessary to assume that the discussed contributing factors together were causing the total reported LB incidence. As this is probably not the case, i.e. it is not likely that all contributing factors are described in literature, the modeling approaches are only using data which could be identified from literature. Based on this data, a modeling approach was chosen that would combine all the available quantitative data from the past with qualitative data about the future. This required that some qualitative data had to be transformed into quantitative data to be included in a model. This transformation required a level of abstractness and simplicity that inevitably resulted in the deletion of some details. Because of this transformation and the limited available data, the basis of the model was therefore kept as compact and straightforward as possible to avoid further assumptions and data malformations. The result of the modeling approach is a rough projection based on the data found in literature. For future research it might be interesting to develop a model with more complexity and more data inputs.

Instead of focusing on one changing factor, this research attempted to incorporate a wide-ranging variety of factors possibly contributing to the past and current LB emergence into a future projection on a macro level. Similar approaches are currently not yet described in literature. However, in line with this research, several researchers are concluding that the emergence of LB can only be explained by using an integrated approach by incorporating more than one possible factor for the LB emergence (Mannelli et al., 2012; Myers & Patz, 2009). As demonstrated in the modeling approaches, action in the future is strongly advisable. This advice is also found in literature from multiple disciplines. From a microbiological point of view, research advice the development of a successful European vaccine against LB (Embers & Narasimhan, 2013). From an ecological and climatological point of view researches are arguing that more knowledge should be generated to convince clinicians and public health professionals to take action to minimalize the effect of LB on the general health (Kilpatrick & Randolph, 2012).
CHAPTER 7: CONCLUSION

7.1 General conclusions
To answer the research question to what extent environmental factors contributed to the emergence of Lyme borreliosis in the past and how this contribution could change in the future, several conclusions from the different aspects of this question are formulated.

LB is a disease indigenous to Europe for thousands of years. During the transmission, the pathogen *Borrelia burgdorferi* s.l. relies on a complex network of hosts, reservoirs and vectors. In turn, these components of this network also have complex relationships with their (natural) environment. While the pathogen is relatively insensitive to environmental changes, these components are not. When the infected vector, *I. ricinus*, feeds on a human being, the pathogen is able to infect after 24 hours. Infection results in multisystem symptoms in most patients.

The average emergence of LB in Western-Europe is characterized by a linear increase during the last decade, with a doubling in 2011 of number of reported LB since 2002. This increase is confirmed by the increase in range found in field studies and incidence trends from other world regions.

Three factors are identified as being the major drivers behind this emergence. The first factor is the increasing active season length of ticks, resulting in higher possibilities for ticks to find a suitable host or to infect a human. For reference animal species in the Netherlands the onset of this season started over the last 24 years 10 days earlier. Prior to that, the same trends are documented at a European level: from 1959 to 1993 the activity season was extended with eleven days. The second factor is the increasing total surface area of forest in Western-Europe. This increase of 8.1% and the increasing forest patch size over the last 2 decades, favors a larger tick population by an increased habitat size for the for tick reproducing important third host. The third identified factor is the presence of a pet in the household. Serology studies demonstrate that in households with a pet the chances on an infection with the LB pathogen are 45% higher compared to no pet present. If the pet is a cat, the chances are even 88% higher. Next to these major drivers, two other less contributing factors to the emergence are worth mentioning. While they certainly contribute to the emergence of LB, the direct effects of changing climatological characteristics are regarded to primarily influence the LB occurrence to shift northwards in the future. The assumed contributing factor of the awareness of the general public towards LB is seen unaffected by the current emergence, and is therefore assumed to be of low contribution.

Modeling approaches of the future LB incidence project that the number of annually reported LB cases is going to double in the year 2030.

Altogether, the system behind the human infection with LB is characterized by a high complexity, numerous interrelationships and highly uncertain data. However, if the past trends are combined with the projected change of the contributing factors project that the current LB incidence is continuing to emerge in the future. Therefore, this vector-borne disease has the possibility to become a real threat to public health if not acted accordingly by the (inter)national health agencies to increase the general awareness towards this disease.

7.2 Policy implications
This thesis aimed at providing a better understanding of the effects of changing environmental factors on the emergence of infectious vector-borne diseases, thereby developing an outlook for policymakers to construct a strategy coping with this emergence, by analyzing the current emergence of LB.

This analysis of LB exemplifies that vector-borne diseases take place in a system with tight connections to numerous of environmental components. Because these components form a complex network of chained events, changing parameters of these components can change the outcome of the system in many unforeseen ways. Moreover, next to the complexity, general solid
quantitative data about these systems is scarce as result from being difficult to obtain. The majority of the quantitative data currently available about these systems primarily results from reporting, and is therefore highly error-prone as a consequence of different reporting standards. Therefore, the future emergence of these diseases is hard to accurately predict. However, as the example of LB in this thesis demonstrates, the major drivers behind the reported emerging vector-borne diseases are limited to a relative small number of contributing factors. Thus, an approximate projection of future prevalence can be constructed without absolute knowledge about the entire system, but just with data of these drivers only. Therefore, to be able to predict the occurrence of emerging infectious diseases in the future it is strongly advisable to make the reporting of the incidence of these diseases mandatory and to use one standard, European, reporting protocol. Also it is advisable to increase the knowledge of the system, with a focus on the major drivers.

Next to these recommendations, for policymakers it is advisable to increase the public awareness in order to deal with the possible public health threat from emerging infectious diseases. As demonstrated by the example of LB the emergence of LB did not lead to a corresponding increase in the public awareness. Therefore, opportunities lie in mobilizing the general population to act in a more precautionary manner with regard to emerging infectious diseases.
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CHAPTER 9: REFERENCES


van Vliet, A. (2013). Wageningen University, Personal communication


Figure A1: Overview of the dynamic model in STELLA
Figure A2: Overview of the future projection of the change of the contributing factors for LB as used in the dynamic STELLA model.