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REVIEW ARTICLE

An Estimate of Lyme Borreliosis Incidence in Western Europe

Robert A Sykes BMedSci (Hons)[1]

[1]Medical Student, University of Edinburgh
Correspondence email: R.Sykes@sms.ed.ac.uk

Abstract

Background: Lyme borreliosis (LB) is the most common zoonotic disease transmitted by ticks in the USA and Europe. This review aims to estimate the regional burden of LB in Western Europe. Data from previous publications were used to calculate the mean incidence. The mean incidence rates were then combined to estimate the regional burden and a population-weighted regional burden of disease based on the standardized incidence from the included studies and the total population at risk.

Methods: Reviews and surveillance reports identified by the initial database search were first assessed for eligibility by their title and abstract, and subsequently by a more detailed review of the source for the most recent data regarding LB. 11 sources of incidence data were included in the review, representing 17 countries in total. Incidence estimates were calculated from reported values and population data.

Results: Countries in Western Europe have a large variance in the incidence rates. The highest reported incidences for LB were reported in southern Sweden with 464 per 100 000 and the lowest in Italy of 0.001 per 100 000. The unweighted mean for the included data provided an incidence of 56.3 per 100 000 persons per year, equating to approximately 232 125 cases in one year throughout the region. The calculated population-weighted average incidence for the regional burden of LB in Western Europe was 22.05 cases per 100 000 person-years.

Conclusions: LB is an emerging disease and the most common zoonotic infection in Western Europe approaching endemic proportions in many European countries. The population-weighted incidence has been estimated by this study to be 22.04 per 100 000 person-years. Concordant and well-conducted surveillance and disease awareness should continue to be encouraged to monitor LB as tick numbers and activity increases.

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An Estimate of Lyme Borreliosis Incidence in Western Europe

Background

Lyme borreliosis (LB), or Lyme disease, is the most common zoonotic disease transmitted by ticks in the USA and Europe.[1] The complex of Borrelia bacteria that causes Lyme borreliosis is known as *Borrelia burgdorferi* sensu lato. 5 of these are known human pathogens (*B. afzelii*, *B. garinii*, *B. burgdorferi* sensu stricto, *B. baverensis*, and *B. spielmanii*) and 3 are suspected human pathogens (*B. valaisiana*, *B. bissettii*, and *B. lusitaniae*).[2,3] This bacterium is transmitted to humans and other vertebrates during the blood feeding of Ixodid ticks, of which the most common in Europe is the *Ixodes ricinus*, or sheep tick.[4,5] Early stages of LB will commonly present with erythema migrans, a skin lesion or rash that can occur between 2 and 30 days after being bitten by an infected tick, which can be successfully treated with antibiotics.[6] However, if the infection is not treated at this early stage, the bacteria will disseminate and the localized infection will progress into a systemic disease affecting the joints, nervous system and, less frequently, the heart.[7]

Those at highest risk are people residing or working in endemic areas of LB, such as in forested areas, and have occupations such as forestry workers, gamekeepers, farmers, military personnel, and rangers.[8] Orienteering, hunting, picnicking, and gardening also expose individuals to more ticks and therefore increase the risk of infection.[9] There is also a distinct degree of seasonality associated with the risks of LB that coincides with the seasonal pattern of tick activity. Activity is higher in the warmer parts of the year; however, there is a slight lag between tick activity and case reporting due to the period between infection and symptom presentation (2–30 days).[10]

The incidence of LB has been increasing across the globe, with the number of reported cases in Europe rising since the early 1990s and expanding in geographic distribution.[11] These rises in LB have been linked to improved diagnostics and awareness, increased tick density, increased burden of tick disease, and changes in climate in recent decades that have allowed ticks to spread into higher latitudes and altitudes.[12,13] There are an estimated 85 000 cases of LB in Europe each year; however, the reporting in Europe is inconsistent and, as such, many infections go undiagnosed.[10] Overdiagnosis of LB is also an important factor and it is estimated that, in some settings, less than a quarter of those referred with LB have confirmed LB.[14,15] Serological testing as part of surveillance reporting within several sources may help to address this factor, although this in itself is not confirmation of LB. However, due to

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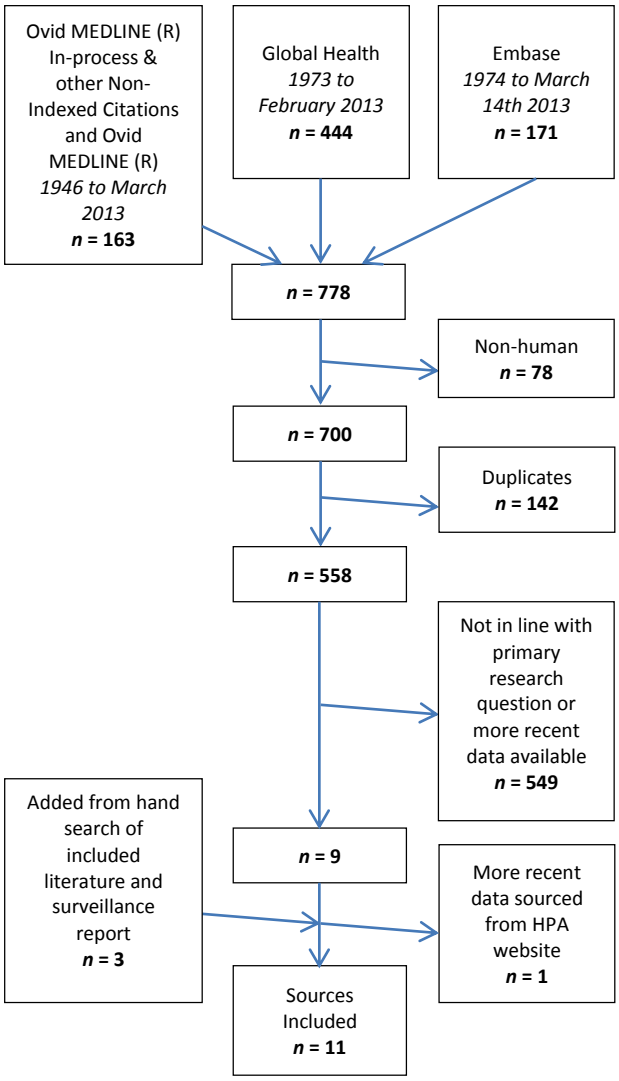
differing collection methods in the included sources, overdiagnosis as well as underdiagnosis should still be considered when analysing these data. Although surveillance is increasing for LB, a global estimate of disease burden and incidence does not exist at the moment, with previous reports of incidence in Europe only including an overview of selected countries.[10,16] Differences in the methods of case reporting also lead to a more problematic estimation of a regional burden of disease. While some countries continually report LB diagnoses, there is a great disparity between countries concerning surveillance of all or only some of the early and/or disseminated LB cases. An example of this is erythema migrans which, while present in a large proportion of LB (70–80%), does not occur in all cases and may have led to an under-reporting of the true burden of disease.[5,17] For a disease of such increasing importance and which is likely to affect more and more people, it is important for policy makers and health providers to understand the current burden in their region, especially considering that LB and chronic LB have been highly controversial subjects in politics and the media in recent years.[18,19] The term chronic LB is often used inappropriately. The definition of chronic LB is an untreated LB that has developed over a long period of time into late-stage disseminated LB or into acrodermatitis chronica atrophicans (ACA), also known as "Herxheimer disease". Referral to a condition of "chronic LB" may in many instances actually be a reference to a "post-Lyme syndrome", where symptoms have persisted despite treatment with antibiotics and resolution of the infection.[20-24]

This review aims to estimate the regional burden of LB in Western Europe. Data extracted from included papers were standardized in order to calculate the mean incidence per 100 000 people per year.

Figure 1. Search strategy flow diagram



The mean incidence rates were then combined in order to achieve an estimate of the regional burden and a population-weighted regional burden of disease based on the standardized incidence from the included studies and the total population at risk.

Methods

Search strategy

Articles of importance and relevance were identified by an electronic search of MEDLINE, Embase, and Global Health databases through the Ovid Gateway. These were searched with no restriction on language for data, from the inception of each database up until the beginning of March 2013. A search strategy is supplied in Box 1, which consists of synonymous terms for LB, countries of Western Europe, and epidemiological terms of interest. A list of the countries searched for is included as part of Table 2. Boolean operators were employed to link these terms and exclude countries that had returned results as part of the search but are not defined by the World Bank as being in Western Europe (Poland, Slovakia, Russia, and Croatia). The only exception to this criterion is the Republic of Ireland, which was included by the author.[25] Western Europe as a region within this World Bank definition includes countries of a similar economic background, healthcare provision, and geographical location. Furthermore, a hand search of included and relevant reference materials was undertaken to identify other sources of primary surveillance data for inclusion that were either published or in the process of being published. A diagram to illustrate the flow of information throughout this review is found in Figure 1.

Box 1. Search Terms for Medline through Ovid Gateway

Search terms for Lyme disease and Lyme borreliosis

1 lyme disease/ 2 erythema migrans/ 3 erythema chronicum migrans/4 lyme borreliosis/5 neuroborreliosis/6 1 or 2 or 3 or 4 or 5

Search terms for Western European countries

7 exp Western Europe/8 Austria/9 Belgium/10 Denmark/11 Finland/12 France/ 13 Germany/14 Greece/15 Iceland/16 Italy/17 Luxembourg/18 Netherlands/19 Norway/20 Portugal/ 21 Spain/22 Sweden/23 Switzerland/ 24 United Kingdom/25 Scotland/26 England/27 Wales/ 28 Northern Ireland/29 Ireland/30 Great Britain/31 Poland/ 32 Slovakia/33 Russia/ 34 Croatia/35 or/31-34/ 36 or/7-30/ 37 36 not 35 / 38 37 and 6

Search terms for epidemiological studies

39 Epidemiologic studies/ 40 epidemiology/ 41 epidemiology.mp./ 42 incidence/ 43 incidence.mp. 44 or/39-43/ 45 38 and 44

Inclusion criteria

Sources identified by the initial database search were exported into Mendeley Desktop reference management software

(Version 1.1.2, 2011, Mendeley Ltd, London, UK) – duplicate studies were merged and non-human studies excluded. The remaining studies were then assessed for eligibility first by their title and abstract and subsequently by a more detailed review of the source for data regarding confirmed cases of LB. Where multiple reports for countries were available, the most recent data was selected.

Papers that reported only partial sections of a population were excluded, unless the sample was representative of the entire population by design, so as not to bias data when compared with the population as a whole. Papers that only publish information on laboratory tests were not included as there was no way of knowing the demographics of the people from which the samples had been obtained.

Reviews were analysed for appropriate data and, if found to be relevant, had their reference lists examined for the original source of data where possible. However, if the original source was unobtainable, then the review data was included. This was the case for data concerning Switzerland, Spain, and Ireland.[13,26] Surveillance reports were included and were especially useful for more northern countries in providing recent data.[5,10,27] For England and Wales, information was gathered from the Health Protection Agency, as this provided the most up-to-date figure of incidence.[28] This search located 11 sources of incidence data for inclusion in the review, representing 17 countries in total. No information was found to be available for Greece or Luxembourg concerning the epidemiology of LB.

Data extraction

The data extraction of incidence information from the included sources was dependent on the type of information provided. Most sources reported incidence rates per 100 000 persons per year. Belgium, France, and Sweden were exceptions, for which incidence rates were reported as the number of cases of erythema migrans or confirmed LB in general practices. Austria had only an estimate of LB per 100 000 person-years based on a survey of general practitioners. In order to calculate the population-weighted averages, the mean population for the observation period was obtained from the World Bank for each country, with the exception of England, Wales, and Scotland, for which the 2011 census data were extracted.[29,30] This population information was also used to back-calculate incidence into a case notification rate which allowed greater accuracy when approximating the subregional burden of disease.

Results

Of the sources included in this review, 3 were surveillance reports, of which 2 were on a multinational level and 1 on a national level.[5,27,31] 2 reviews were also used as sources for data as the origins of their estimates were unobtainable.[10,26] Incidence data for England and Wales was accessed through the Health Protection Agency, a governmental body.[28] Data for Austria was obtained only through an estimate based on a survey of physicians in primary care, but has been included in previous reporting of Austrian incidence and, as such, was included in this review. The remaining included studies were observational studies undertaken at a national level that provided incidence rates for their relevant country. No data were obtained for Greece or for Luxembourg due to a lack of reporting in these countries. A summary of the initial extraction of results and standardized incidence rates are provided in Table 2.

Countries in Western Europe have a large variance in the incidence rates of LB between both the countries themselves and regions within the countries. The highest reported incidences for LB were reported in southern Sweden with 464 per 100 000 and the lowest in Italy with only 0.001 per 100 000.[10,35] This provides a large ratio between these two values of 464 000:1. The unweighted mean for the included data provided an incidence of 56.3 100 000 (median value 9.4 per 100 000, first and third quartiles of 1.73 and 37.4 per 100 000 respectively), equating to an interquartile range of 35.57 per 100 000. As a result of this data, the unweighted burden of disease for LB in Western Europe is estimated to be 56.3 new cases per 100 000 population per year, equating to approximately 232 125 cases in one year throughout the region based on a total population of 412.2 million living in Western Europe in 2011.[29,30] Using the total population at risk from the included studies or the year-specific population data for surveillance reports, a population-weighted average incidence was calculated. This weighted mean for the regional burden of LB in Western Europe is 22.05 cases per 100 000 person-years. A summary of these results can be found in Table 1.

Table 1. Summary of results

Statistic	Value
Mean Incidence	56.31/100 000
Median incidence	9.4/100 000
Maximum reported incidence	464/100 000
Minimum reported incidence	0.001/100 000
Max/Min ratio	464 000:1
Range	463.999
25th percentile	1.73/100 000
75th percentile	37.3/100 000
Inter-quartile range	35.57
Weighted mean incidence	22.05/100 000

*Incidence is expressed in person-years.

Table 2. Non-standardised measures, case definitions of included studies as extracted from the included studies and summary of included studies

Reference	Country/Region	Disease Meaurement	Non-Standardised Value (per year)	Case Definition	Study Type	Study Period	Incidence rate (cases/100 000/year)
Smith *et al.*, 2006[5]	Austria	Incidence rate	135 cases per 100 000 population	Estimate based on a survey of physicians	Surveillance report	2005	135
Vanthomme, 2012[32]	Belgium	Number of cases	338 cases of erythema migrans	Cases reported to GPs with erythema migrans in Belgium	Case reports	2008–2009	90.2
EpiNorth, 2011[27]	Denmark	Incidence rate	1.7 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance report	2011	1.7
EpiNorth, 2011[27]	Finland	Incidence rate	30.92 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance report	2011	30.92
Letrilliat *et al.*, 2005[33]	France	Number of cases	86 cases of Lyme borreliosis	Diagnosis with Lyme borreliosis	Case reports	1999–2000	9.4
Fulop *et al.*, 2008[31]	Germany	Incidence rate	37.3 cases per 100 000 population	Diagnosis of erythema migrans	Surveillance report	2006	37.3
No data	Greece						
EpiNorth, 2011[27]	Iceland	Incidence rate	7 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance report	2011	7
Lindgren *et al.*, 2006[10]	Ireland	Incidence rate	0.6 cases per 100 000 population	Diagnosis with Lyme borreliosis	Review	1995	0.6
Smith *et al.*, 2006[5]	Italy	Incidence rate	0.001 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance report	2001–2005	0.001
No data	Luxembourg						
Hofhuis *et al.*, 2010[34]	Netherlands	Incidence rate	134 cases of erythema migrans per 100 000 population	Diagnosis of erythema migrans	Case reports	2009	134
EpiNorth, 2011[27]	Norway	Incidence rate	4.96 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance report	2011	4.96
Smith *et al.*, 2006[5]	Portugal	Incidence rate	0.04 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance report	2005	0.04
Lindgren *et al.*, 2006[10]	Spain (La Rioja)	Incidence rate	9.8 cases per 100 000 population	Diagnosis with Lyme borreliosis	Review	2003	9.8
Bennet *et al.*, 2006[35]	Sweden	Incidence rate	Annual mean incidence of 464 cases of erythema migrans per 100 000 population	Cases reported with erythema migrans in Blekinge County	Case reports	1997–2002	464
Hubalek *et al.*, 2009[26]	Switzerland	Incidence rate	25.1 cases per 100 000 population	Diagnosis with Lyme borreliosis	Review	1988–1998	25.1
Health Protection Agency, 2011[28]	United Kingdom (England & Wales)	Incidence rate	1.7 cases per 100 000 population	Diagnosis with Lyme borreliosis	Government figures	2011	1.73
Slack *et al.*, 2011[12]	United Kingdom (Scotland)	Incidence rate	5.53 cases per 100 000 population	Diagnosis with Lyme borreliosis	Surveillance study	2009–2010	5.53

Discussion

A large level of heterogeneity was found to be present throughout the incidence data for LB in Western Europe. The reasons for this include different case definitions, collecting methods, and that very few countries include LB as a compulsorily notifiable disease. Overdiagnosis and underdiagnosis of LB is another important factor with a significant impact on the number of reported cases. In other countries, it is suggested that the general public are simply not aware of the risk of LB and as such neglect symptoms, especially if erythema migrans does not develop.[10] However, with such limitations in mind, the estimates provided by this study will give at very least a minimum illustration of the burden of disease in Western Europe, which demonstrates the importance of LB as a continually emerging infection to healthcare authorities and governments throughout the region. This will hopefully encourage a more standardized approach to data collection.

When compared with previous studies, these most recently available data indicate that the incidence of LB in certain European countries may be increasing faster than expected by population growth alone. Such increases have been observed in Germany, the Netherlands, and the United Kingdom, among others.[31,34,36] These increases may simply be due to an improvement in reporting practices, raised awareness of the disease, or overdiagnosis of LB. However, tick numbers and activity are closely associated with the number of cases of LB and an amplification of these reported by other studies cannot be ignored.[37,38] Ticks, similarly to other arthropods, are sensitive to changes in climate as most of their life cycle is dependent on climatic variables, especially development and survival.[39] A smaller factor is that of vegetation levels and host availability – as humans venture into the greener areas of a country either for work or recreation, the likelihood of them becoming a host inevitably increases.[40,41] The increasing number of ticks has been hypothesized to be associated with the warming of the climate as the ideal conditions for ticks are amongst vegetation that maintains a high level of humidity.[41] One review has provided a theoretical projection of the effect that climate change will have on the burden of disease attributed to LB, predicting that LB will continue to spread into higher latitudes and altitudes, will have an extended and more intense transmission season in certain areas of Europe, and that the risk of LB may decrease in areas where there are repeated droughts or severe floods.[10]

Another factor influencing the observed heterogeneity of results, as displayed by the large maximum to minimum range and interquartile range of the included data,

could be differences in population structures. While all individuals who expose themselves to the environment in which these arthropods thrive will be at risk, differences in urban and rural populations between countries would therefore have an effect on the risk of being infected with LB. This could work in either direction as, although rural workers and populations are at increased risk from their local environment, urban dwellers tend to have a decreased awareness which increases the risk of being infected and not recognizing the disease.[42] Some studies have also identified differences in the age groups of those affected. While some studies have found that children and older people are more often affected by LB, others note the opposite with predominantly adult working age groups affected.[12,31] This demonstrates that there are likely to be differences in exposure risk for age groups between countries and, as such, both geographical and population demographics may influence incidence, although the direct mechanism remains unclear.

Although data for the majority of countries were obtainable, there are clear information gaps created by lacking or absent disease reporting, such as in Greece and Luxembourg. The countries reporting very low incidences such as Italy are likely underestimated, as studies exist demonstrating the existence of *Borrelia burgdorferi* in these countries and the presence of at-risk areas.[43] These gaps in data could be improved by a region-wide initiative towards improved reporting of LB as a notifiable disease. However, there currently seems to be little progress in this area, which should be reviewed both for disease burden and the financial burden on European health systems, which is estimated to be over €1000 million.[5,42,44]

A suggestion for future research into LB in Western Europe is continued epidemiological surveillance as well as investigation into the disease status in countries for which there is little or no data. In countries where different areas vary greatly in incidence, it would be of interest to continue surveillance within different regions, as it is sensible to expect that areas with different tick densities will have different incidence rates. This is important in countries where only one region is reported, such as in Spain, as it is likely that these smaller reported areas are not representative of the whole country. Where studies are designed on a smaller scale, it is important to focus on a unified approach to case definition, and an example of a consensus case definition has been published.[45] Variation on the definition of a case of LB across the included sources is evident in this review. LB is a diagnosis made on a combination of clinical signs and symptoms as well as appropriate laboratory

testing. Serology testing alone should not be encouraged because this in itself is not diagnostic. Conversely, while erythema migrans is a diagnostic finding for LB, it is not present in up to 30% of cases. There are complexities surrounding definitive criteria for diagnosis due to current variations between countries; however, a region-wide case definition used in reporting may help to improve the accuracy and reporting of LB diagnoses. Further research into preventative measures aiming to minimize the risk of being bitten by a tick should also be conducted, as this is the only certain way to avoid being infected.

Conclusions

LB is a continually emerging disease and the most common zoonotic infection in Western Europe, approaching endemic proportions in many European countries. The population-weighted incidence has been estimated by this study to be 22.04 per 100 000 person-years. This review encourages further establishment of well-conducted and concordant surveillance research in order to monitor the disease in the ever-changing climate where tick numbers and activity are increasing, leading to greater risks of infection.

Learning Points

What is already known

- Lyme borreliosis is an important disease with wide-ranging health and economic impacts and a substantial global health burden.
- It is the most common zoonotic infection in Western Europe.
- Incidence of LB is increasing and little is being done to address this increase.
- Increase in tick numbers may be partly due to climate change.

What this article adds

- This study estimates the population-weighted incidence of Lyme borreliosis in Western Europe to be 22.04 per 100 000 person-years.
- There is no unified approach to surveillance or diagnostic criteria for the disease.
- Further evidence that Lyme borreliosis is established within Western Europe and that it is an important topic that requires further research and investment from governing bodies.

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