An estimate of Lyme borreliosis incidence in Western Europe†

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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 will be used to calculate the mean incidence. The mean incidence rates will then be combined to estimate the regional burden and a population-weighted regional burden of disease based on the standardized incidence rate from the included studies and the total population at risk.

Methods Reviews and surveillance reports identified by the initial database search were assessed for eligibility first by their title and abstract and subsequently by a more detailed review of the source by two independent authors for the most recent data regarding LB. Eleven 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 464/100 000 and the lowest in Italy of 0.001/100 000. The unweighted mean for the included data provided an incidence rate of 56.3/100 000 persons per year, equating to ∼232 125 cases in 1 year throughout the region. The calculated population-weighted average incidence rate for the regional burden of LB in Western Europe was 22.05 cases per 100 000 person-years.

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 rate has been estimated by this study to be 22.04/100 000 person-years. Concordant and well-conducted surveillance and disease awareness should continue to be encouraged to monitor LB, as tick numbers and activity are increasing, leading to greater risks of infection.

Keywords epidemiology, public health, research

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 LB is known as *Borrelia burgdorferi* sensu lato. Five of these are known human pathogens (*B. afzelii*, *B. garinii*, *B. burgdorferi* sensu stricto, *B. baverensis* and *B. spielmanii*) and three 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

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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 for LB such as 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 coinciding 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 presenting with symptoms (2–30 days).[10]

The incidence of LB has been increasing across the globe, with the number of reported cases in Europe rising from the early 1990s as well as expanding in geographic distribution.[11] These rises in LB have been linked with not only improved diagnostics and awareness, increased tick density and burden of tick disease, but the changes in climate that have allowed ticks to spread into higher latitudes and altitudes in recent decades have also been associated.[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] Over-diagnosis of LB is also an important factor and it is estimated that in some settings, less than a quarter of those referred with LB may 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 differing collection methods in the included sources, over-diagnosis as well as under-diagnosis should still be considered when analysing these data. Although surveillance is increasing for LB, at the moment, a global estimate of disease burden and incidence does not exist, with previous reports of incidence in Europe having only included 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 in their surveillance of LB cases and at which stage (early/disseminated) a recorded diagnosis is made. 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 underreporting 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 policymakers and health providers to understand the current burden in their region especially when 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 LB is an untreated LB, which 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] Knowledge of this misclassification is important with regards to search strategy for two reasons, as omission of chronic LB as a search term to enhance specificity may lead to missed results related to disseminated LB, while its inclusion for sensitivity requires thorough assessment of each paper using this term to avoid unrelated inclusions.

The objectives of this review are as follows:

- To assess the presence and quality of existing surveillance data regarding LB for countries defined as being in Western Europe by the World Bank.
- To standardize this data in order to calculate standardized mean incidence rates per 100 000 people per year for each country where available.
- To use population data for each country to establish a weighted mean incidence rate as an estimate for the entire region.
- From existing reports and studies, provide possible explanations for any increase or decrease so as to hypothesize possible reasons for any increase or decrease in incidence rate from previous estimations.

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, which were available at The University of Edinburgh under licence. These were searched with no restriction on language for data from inception of each database up until the beginning of March 2013. A search strategy is supplied in Appendix 1 that consists of synonymous terms for LB, countries of Western Europe as well as epidemiological terms of interest. A list of the countries searched for is included as part of Table 1. Boolean operators were employed to link these terms and exclude countries not defined by The World Bank as being in Western Europe, which had returned results as part of the search (Poland, Slovakia, Russia and Croatia). The only exception to this criterion is being the Republic of Ireland, which was included by the author.[33] Western Europe as a region within

Table 1 Non-standardized measures, case definitions of included studies as extracted from the included studies and summary of included studies

Reference	*Country/region*	*Disease measurement*	*Non-standardized value (per year)*	*Case definition*	*Study type*	*Study period*	*Standardized incidence rate (cases/100 000/year)*
Smith and Takkinen[5]	Austria	Incidence rate	135 cases per 100 000 population	Estimate based on a survey of physicians	Surveillance report	2005	135
Vanthomme *et al.*[25]	Belgium	Number of cases	338 cases of erythema migrans	Cases reported to General Practitioners with erythema migrans in Belgium	Case reports	2008–09	90.2
EpiNorth[26]	Denmark	Incidence rate	1.7 cases per 100 000 population	Diagnosis with LB	Surveillance report	2011	1.7
EpiNorth[26]	Finland	Incidence rate	30.92 cases per 100 000 population	Diagnosis with LB	Surveillance report	2011	30.92
Letrilliart *et al.*[27]	France	Number of cases	86 cases of LB	Diagnosis with LB	Case reports	1999–2000	9.4
Fülöp and Poggensee[28]	Germany	Incidence rate	37.3 cases per 100 000 population	Diagnosis of erythema migrans	Surveillance report	2006	37.3
No data	Greece						
EpiNorth[26]	Iceland	Incidence rate	7 cases per 100 000 population	Diagnosis with LB	Surveillance report	2011	7
Lindgren and Jaenson[10]	Ireland	Incidence rate	0.6 cases per 100 000 population	Diagnosis with LB	Review	1995	0.6
Smith and Takkinen 2006[5]	Italy	Incidence rate	0.001 cases per 100 000 population	Diagnosis with LB	Surveillance report	2001–05	0.001
No data	Luxembourg						
Hofhuis *et al.* 2010[29]	The Netherlands	Incidence rate	134 cases of erythema migrans per 100 000 population	Diagnosis of erythema migrans	Case reports	2009	134
EpiNorth[26]	Norway	Incidence rate	4.96 cases per 100 000 population	Diagnosis with LB	Surveillance report	2011	4.96
Smith and Takkinen[5]	Portugal	Incidence rate	0.04 cases per 100 000 population	Diagnosis with LB	Surveillance report	2005	0.04
Lindgren and Jaenson[10]	Spain (La Rioja)	Incidence rate	9.8 cases per 100 000 population	Diagnosis with LB	Review	2003	9.8
Bennet *et al.*[30]	Sweden	Cumulative incidence	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
Hubálek[31]	Switzerland	Cumulative incidence	25.1 cases per 100 000 population	Diagnosis with LB	Review	1988–98	25.1
	UK						
Health Protection Agency[32]	England and Wales	Incidence rate	Diagnosis with LB	Government figures	2011	1.73	1.7 cases per 100 000 population
Slack *et al.*[12]	Scotland	Incidence rate	Diagnosis with LB	Surveillance study	2009–10	5.53	5.53 cases per 100 000

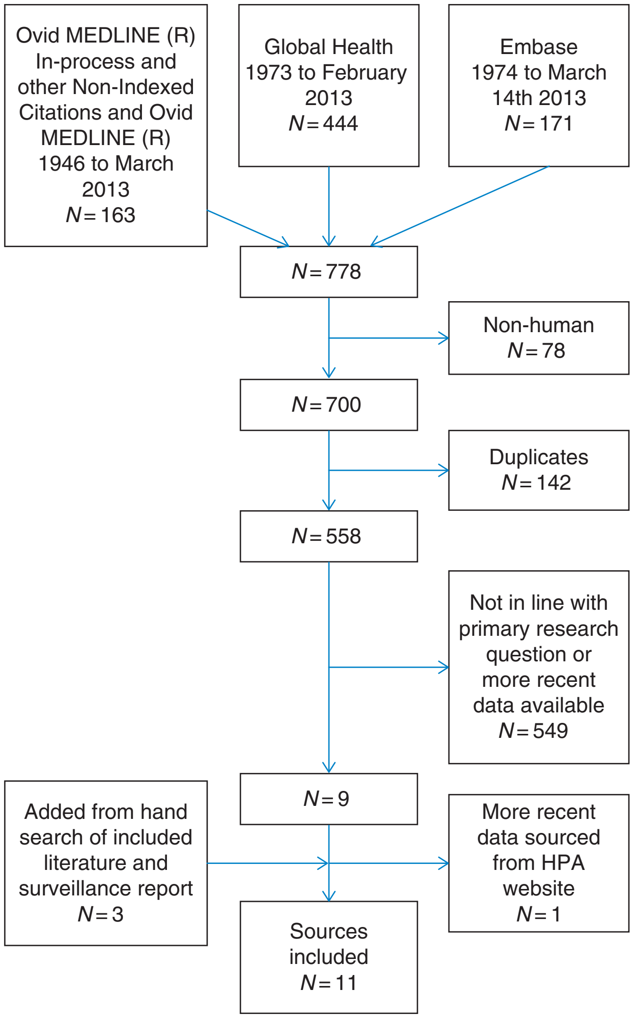

Fig. 1 Search strategy flow diagram.

this World Bank definition includes countries of a similar economic background and healthcare provision, as well as by 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 was either published or in the process of being published. A flow diagram to illustrate the flow of information throughout this review is found in Fig. 1.

Inclusion criteria

The search was performed independently by each author and identical results were obtained. Sources identified by the initial database search were exported into Mendeley Desktop reference management software (Version 1.1.2, 2011, Mendeley Ltd, London, UK) and any duplicate studies merged, and non-human studies excluded. The remaining studies were then assessed for eligibility separately by the two authors, 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 were 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 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 were included, this was the case for data concerning Switzerland, Spain and Ireland.[13,31] Surveillance reports were included and were especially useful for more Northern countries in providing recent data.[5,10,26] For England and Wales, information was gathered from the Health Protection Agency, as this provided the most up-to-date figure of incidence.[32] 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

Data were extracted by hand and analysed using Microsoft Excel 2007. The 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 exceptions being information for Belgium, France and Sweden, which was 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.[34,35] This population information was also used to back calculate incidence into a case notification rate, which allowed greater accuracy when approximating the sub-regional burden of disease. The mean incidence rates for each region 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 rates from the included studies and the total population at risk.

Results

Of the sources included in this review, three were surveillance reports of which two were on a multi-national level and one on a national level.[5,26,28] Two reviews were also used as sources for data as the origins of their estimates were unobtainable.[10,31] Incidence data for England and Wales were accessed through the Health Protection Agency, a government body.[32] Datum 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, which provided incidence rates for their relevant country. No figures 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 1.

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 incidence rates for LB were reported in southern Sweden with 464/100 000 and the lowest in Italy of only 0.001/100 000.[10,30] 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 9.4/100 000, first and third quartiles of 1.73 and 37.4/100 000, respectively) equating to an interquartile range of 35.57/100 000. As a result of these 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 ∼232 125 cases in 1 year throughout the region—based on a total population of 412.2 million living in Western Europe in 2011.[34,35] Using the total population at risk from the included studies or the year-specific population data for surveillance reports, a population-weighted average incidence rate was calculated. This weighted mean for the regional burden of LB in Western Europe being 22.05 cases per 100 000 person-years. A summary of these results can be found in Table 2.

Table 2 Summary of results

Mean incidence rate[a]	56.31/100 000
Median incidence rate[a]	9.4/100 000
Maximum reported incidence rate[a]	464/100 000
Minimum reported incidence rate[a]	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
Interquartile range	35.57
Weighted mean incidence rate[a]	22.05/100 000

[a]Incidence rate is expressed in person-years.

Discussion

Main finding of this study

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 22.04/100 000 person-years. This review calls for the 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.

What is already known on this topic?

When compared with previous studies, these data indicate that the incidence of LB in certain European countries may be increasing faster than would be expected by population growth alone. Such increases have been observed in Germany, the Netherlands and the UK as well as in others.[28,29,36] These increases may simply be due to an improvement in reporting practices, raised awareness of the disease or over-diagnosis 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, similar to other arthropods, are sensitive to changes in climate, since 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, and as humans venture into the greener areas of a country either for work or recreation, the likelihood of them becoming hosts inevitably increases.[40,41] The increase in the number of ticks as well as their natural host organisms has been hypothesized to be associated with the temperate warming of the climate, since the ideal conditions for ticks are among vegetation that maintains a high level of humidity.[41] One review has provided a theoretical projection of the effect which climate change will have on the burden of disease attributed to LB. It predicts 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, extreme heat or severe floods.[10]

What this study adds?

This study suggests that Western Europe requires continued epidemiological surveillance of LB, 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 that have 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.[42] Indeed, this review highlights the variation in the definition of LB throughout the literature. The diagnosis of LB relies on a combination of clinical signs and symptoms as well as appropriate laboratory testing. Serology testing alone should not be encouraged as this in itself is not diagnostic, particularly in early infection where only 17–40% of those tested will yield positive results.[43]

Conversely, while erythema migrans is a diagnostic symptom of LB, it is not present in up to 30% of cases. There are complexities surrounding a definitive criterion 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 should also be conducted aiming to minimize the risk of being bitten by a tick, as this is the only certain way to avoid being infected.

Limitations of this study

A large level of heterogeneity was found throughout the incidence data for LB in Western Europe. The reasons for this include differences in case definitions or collection methods, as well as that very few countries include LB as a compulsorily notifiable disease. Over- and under-diagnosis of LB is another important factor with a significant impact on the number of reported cases. Alternatively, 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 as in some cases.[10] However, despite these limitations, the incidence rates provided by this study enable an estimate of the burden of disease in Western Europe. Indeed, this review calls attention to LB as an infection of growing importance to healthcare authorities and governments throughout the region, and will hopefully encourage a more standardized approach to data collection.

Differences in population structure are another factor that is likely to underlie the heterogeneity in our data, evidenced by the large maximum to minimum range and interquartile range. The degree of urbanization differs between countries, affecting the risk of being infected with LB, as tick populations are largely confined to greener rural areas. The effect of differences in levels of urbanization is difficult to quantify however, as it has been suggested that the increased risk to rural dwellers is offset by the decreased levels of awareness of urban dwellers who visit areas with a higher risk of contracting LB.[44] Some studies have also identified differences in the age groups of those affected, and 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.[12,28] 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 or Luxembourg. The countries reporting very low incidence rates such as Italy are likely to be under-estimating the true levels of LB as studies exist demonstrating the existence of *B. burgdorferi* in these countries and the presence of at-risk areas.[45] These gaps in data could be improved by a region-wide initiative towards improved reporting LB as a notifiable disease; however, currently, there seems to be little progress in this area. This ought to be reviewed both on account of the disease burden and from a financial point of view, as the cost of LB to European Health systems is estimated to be over €1000 million.[5,44,46]

What is known already:

- LB is an important disease with wide-ranging health and economic impact 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 in part to climate change.

What this study adds:

- This study estimates that the population-weighted incidence of LB in Western Europe to be 22.04/100 000 person-years.
- There is no unified approach to surveillance or diagnostic criteria for the disease.
- Further evidence that LB 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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Appendix 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/
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