An estimate of Lyme borreliosis incidence in Western Europe†

Robert A. Sykes, Phoebe Makiello

College of Medicine, University of Edinburgh, Edinburgh, Midlothian, UK
Address correspondence to Robert A. Sykes, E-mail: rasykes@doctors.org.uk; rob_sykes@msn.com.

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. bavariensis and B. spielmanii) and three are suspected human pathogens (B. valaisiana, B. bissetti 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

†This article was originally written as part of intercalated degree in Epidemiology at The University of Edinburgh 2012–13 and amended for publication with the assistance of Phoebe Makiello who contributed to the manuscript, confirmed the search strategy and methods and independently reviewed papers for inclusion.

Robert A. Sykes, Final Year Medical Student
Phoebe Makiello, Final Year Medical Student
a systemic disease affecting the joints, nervous system and less frequently the heart. 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. Orienteering, hunting, picnicking and gardening also expose individuals to more ticks and therefore increase the risk of infection. 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). Over-diagnosis of LB is also an important factor and it is estimated that in some settings, less than a small 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). 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. 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. 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.

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. 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. 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. 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country/region</th>
<th>Disease measurement</th>
<th>Non-standardized value (per year)</th>
<th>Case definition</th>
<th>Study type</th>
<th>Study period</th>
<th>Standardized incidence rate (cases/100 000/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith and Takkinen</td>
<td>Austria</td>
<td>Incidence rate</td>
<td>135 cases per 100 000 population</td>
<td>Estimate based on a survey of physicians</td>
<td>Surveillance report</td>
<td>2005</td>
<td>135</td>
</tr>
<tr>
<td>Vanthomme et al.</td>
<td>Belgium</td>
<td>Number of cases</td>
<td>338 cases of erythema migrans</td>
<td>Cases reported to General Practitioners with erythema migrans in Belgium</td>
<td>Case reports</td>
<td>2008–09</td>
<td>90.2</td>
</tr>
<tr>
<td>EpiNorth</td>
<td>Denmark</td>
<td>Incidence rate</td>
<td>1.7 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Surveillance report</td>
<td>2011</td>
<td>1.7</td>
</tr>
<tr>
<td>EpiNorth</td>
<td>Finland</td>
<td>Incidence rate</td>
<td>30.92 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Surveillance report</td>
<td>2011</td>
<td>30.92</td>
</tr>
<tr>
<td>Letrilliart et al.</td>
<td>France</td>
<td>Number of cases</td>
<td>86 cases of LB</td>
<td>Diagnosis with LB</td>
<td>Case reports</td>
<td>1999–2000</td>
<td>9.4</td>
</tr>
<tr>
<td>Fülöp and Poggensee</td>
<td>Germany</td>
<td>Incidence rate</td>
<td>37.3 cases per 100 000 population</td>
<td>Diagnosis of erythema migrans</td>
<td>Surveillance report</td>
<td>2006</td>
<td>37.3</td>
</tr>
<tr>
<td>No data</td>
<td>Greece</td>
<td>Incidence rate</td>
<td>7 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Surveillance report</td>
<td>2011</td>
<td>7</td>
</tr>
<tr>
<td>EpiNorth</td>
<td>Iceland</td>
<td>Incidence rate</td>
<td>0.6 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Review</td>
<td>1995</td>
<td>0.6</td>
</tr>
<tr>
<td>Lindgren and Jaenson</td>
<td>Ireland</td>
<td>Incidence rate</td>
<td>0.001 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Surveillance report</td>
<td>2001–05</td>
<td>0.001</td>
</tr>
<tr>
<td>Smith and Takkinen</td>
<td>Italy</td>
<td>Incidence rate</td>
<td>9.8 cases per 100 000 population</td>
<td>Diagnosis of erythema migrans</td>
<td>Surveillance report</td>
<td>2006</td>
<td>9.8</td>
</tr>
<tr>
<td>No data</td>
<td>Luxembourg</td>
<td>Incidence rate</td>
<td>134 cases of erythema migrans per 100 000 population</td>
<td>Diagnosis of erythema migrans</td>
<td>Case reports</td>
<td>2009</td>
<td>134</td>
</tr>
<tr>
<td>EpiNorth</td>
<td>The Netherlands</td>
<td>Incidence rate</td>
<td>4.96 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Surveillance report</td>
<td>2011</td>
<td>4.96</td>
</tr>
<tr>
<td>Smith and Takkinen</td>
<td>Portugal</td>
<td>Incidence rate</td>
<td>0.04 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Surveillance report</td>
<td>2005</td>
<td>0.04</td>
</tr>
<tr>
<td>Lindgren and Jaenson</td>
<td>Spain</td>
<td>Incidence rate</td>
<td>9.8 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Review</td>
<td>2003</td>
<td>9.8</td>
</tr>
<tr>
<td>Bennet et al.</td>
<td>Sweden</td>
<td>Cumulative incidence</td>
<td>Annual mean incidence of 464 cases of erythema migrans per 100 000 population</td>
<td>Cases reported with erythema migrans in Blekinge County</td>
<td>Case reports</td>
<td>1997–2002</td>
<td>464</td>
</tr>
<tr>
<td>Hubalek</td>
<td>Switzerland</td>
<td>Cumulative incidence</td>
<td>25.1 cases per 100 000 population</td>
<td>Diagnosis with LB</td>
<td>Review</td>
<td>1988–98</td>
<td>25.1</td>
</tr>
<tr>
<td>Health Protection Agency</td>
<td>UK</td>
<td>Incidence rate</td>
<td>Diagnosis with LB</td>
<td>Government figures</td>
<td>Surveillance study</td>
<td>2009–10</td>
<td>5.53</td>
</tr>
<tr>
<td>Slack et al.</td>
<td>Scotland</td>
<td>Incidence rate</td>
<td>Diagnosis with LB</td>
<td>Government figures</td>
<td>Surveillance study</td>
<td>2009–10</td>
<td>5.53 cases per 100 000 population</td>
</tr>
</tbody>
</table>
this World Bank definition includes countries of a similar eco-
nomic 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 inclu-
sion, that was either published or in the process of being pub-
lished. 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 refer-
ence 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 compa-
red 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. Surveillance reports were included and were es-
pecially useful for more Northern countries in providing
recent data.

For England and Wales, information was gathered from the Health Protection Agency, as this provided
the most up-to-date figure of incidence. This search located
11 sources of incidence data for inclusion in the review repre-
senting 17 countries in total. No information was found to be
available for Greece or Luxembourg concerning the epidemi-
ology 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 informa-
tion 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 practi-
tioners. 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. This search located
11 sources of incidence data for inclusion in the review repre-
senting 17 countries in total. No information was found to be
available for Greece or Luxembourg concerning the epidemi-
ology of LB.
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. Two reviews were also used as sources for data as the origins of their estimates were unobtainable.\textsuperscript{10,31} Incidence data for England and Wales were accessed through the Health Protection Agency, a government body.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10}

What this study adds?

This study suggests that Western Europe requires continued epidemiological surveillance of LB, as well as investigation

### Table 2  Summary of results

<table>
<thead>
<tr>
<th>Statistic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean incidence rate\textsuperscript{a}</td>
<td>56.31/100 000</td>
</tr>
<tr>
<td>Median incidence rate\textsuperscript{b}</td>
<td>9.4/100 000</td>
</tr>
<tr>
<td>Maximum reported incidence rate\textsuperscript{a}</td>
<td>464/100 000</td>
</tr>
<tr>
<td>Minimum reported incidence rate\textsuperscript{a}</td>
<td>0.001/100 000</td>
</tr>
<tr>
<td>Max./Min. ratio \textsuperscript{a}</td>
<td>464 000 : 1</td>
</tr>
<tr>
<td>Range</td>
<td>463.999</td>
</tr>
<tr>
<td>25th percentile</td>
<td>1.73/100 000</td>
</tr>
<tr>
<td>75th percentile</td>
<td>37.3/100 000</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>35.57</td>
</tr>
<tr>
<td>Weighted mean incidence rate\textsuperscript{a}</td>
<td>22.05/100 000</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Incidence rate is expressed in person-years.
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. 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.

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. 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. 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. 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. These gaps in data could be improved by a region-wide initiative towards improved reporting of 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.

---

**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.

**References**


108(2)


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/
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