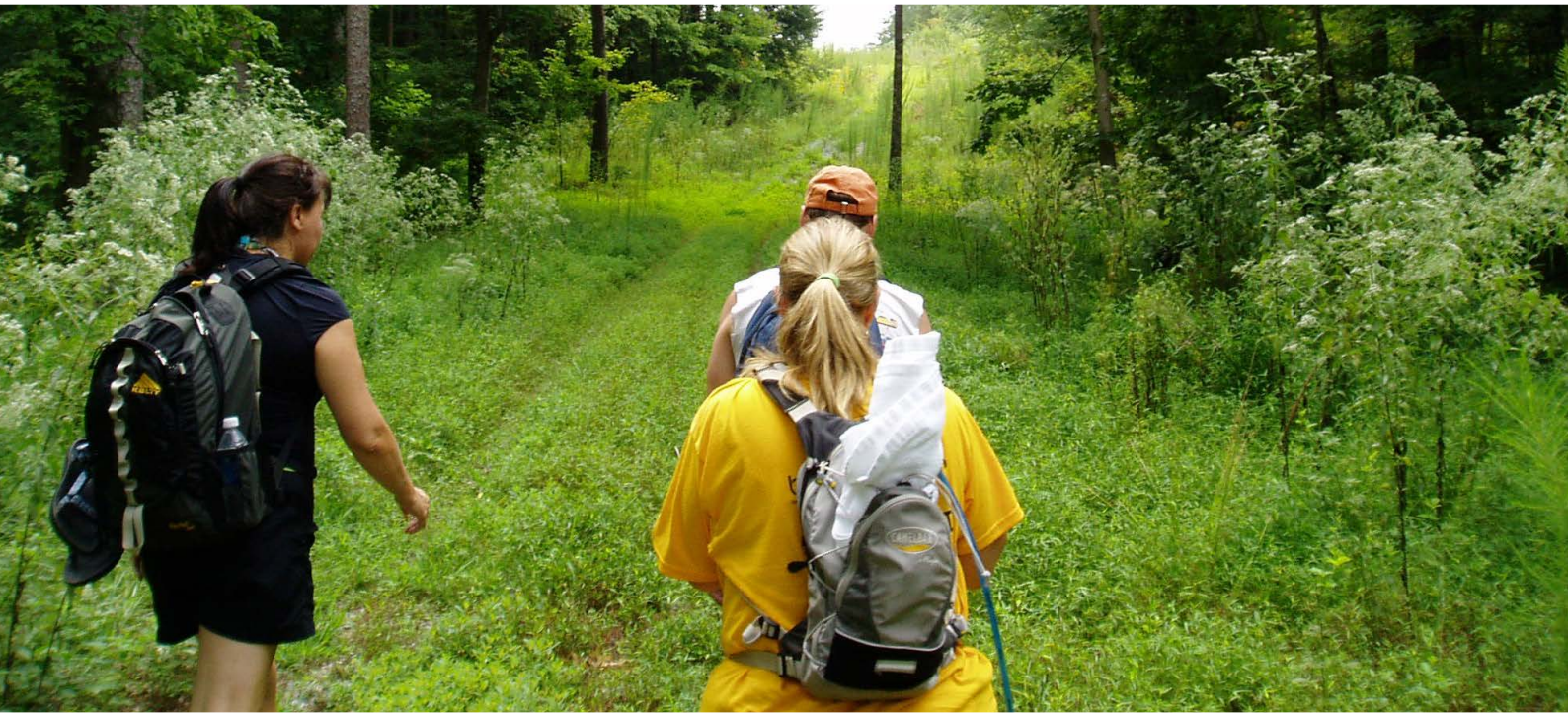
Department of Health Reviews Facility

To support national policy development and implementation

Incidence and surveillance of Lyme disease

Systematic review and policy mapping



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Conflicts of interest

There were no conflicts of interest in the writing of this report.

Contributions

The opinions expressed in this publication are not necessarily those of the Department of Health Reviews Facility or the funders. Responsibility for the views expressed remains solely with the authors.

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Abbreviations

AG	Scientific Advisory Group
CPRD	Clinical Practice Research Datalink
DEFRA	UK Department for Environment, Food and Rural Affairs
EM	erythema migrans
GP	General Practitioner
HSE	Health and Safety Executive
LD	Lyme Disease
NB	neuroborreliosis
NICE	National Institute for Health and Care Excellence
NLBTL	National Lyme borreliosis testing laboratory
PHE	Public Health England
PTLD	post-treatment Lyme disease
QA	quality assessment
QATSO	quality assessment tool for systematic reviews of observational studies
RIDDOR	Reporting of Injuries, Diseases and Dangerous Occurrences Regulations
RIPL	rare and imported pathogens laboratory
THIN	The Health Improvement Network

Summary

Background

Lyme disease is the result of an infection, caused by the Borrelia burgdorferi bacterium, which is common in ticks; people can develop Lyme disease after being bitten by an infected tick. This report describes one of a series of evidence reviews on Lyme disease commissioned by the Department of Health (England) Policy Research Programme and undertaken by the Department of Health Reviews Facility. This report focuses on the incidence and surveillance of Lyme disease. The project draws on a broader evidence map of research on Lyme disease (Stokes et al., 2017).

Review questions

The review questions were:

- *What is the incidence of Lyme disease in the UK, and how does this vary between areas and population groups?*
- *What surveillance systems and policies are in place internationally to monitor the incidence of Lyme disease?*
- *What is known about the completeness of incidence data drawn from surveillance systems?*

Following synthesis of the evidence to answer these questions we sought feedback from eight UK patient advocacy groups to assess whether the findings resonate with their experiences and concerns.

This report has three sections, corresponding to the three phases of the project.

1. A systematic review of Lyme disease incidence data for the UK
2. A map of national surveillance systems and policies for Lyme disease in Europe and North America
3. A systematic review of studies which compare Lyme disease incidence from more than one source, and so can be used to evaluate the completeness of surveillance data.

The aim of the first section is to collate all available data about the incidence of Lyme disease in the UK. The second section provides a broader international context by comparing surveillance systems in the UK to those in similar countries. The third section provides an indication of the extent of under-reporting of cases of Lyme disease to surveillance systems.

Systematic review of UK Lyme disease incidence data

Studies identified from the comprehensive evidence map of Lyme disease research (Stokes et al., 2017), along with published routine surveillance data, were synthesised to provide an overview of the incidence of Lyme disease in the UK. We located eleven studies, in addition to published routine data up to June 2017.

Routine data from recent years shows an annual incidence rate for Lyme disease in England and Wales of just under 2 per 100,000. The rate has increased slowly but

consistently over the last decade. The rate in Scotland is somewhat higher but has declined since a peak in 2008-10. The rate in Northern Ireland is very low.

Published research studies indicate that there may be geographical 'hotspots' where local incidence is much higher than found in routine data, particularly in the Highlands of Scotland. Data are lacking for England and Wales, but the situation is likely to be similar.

The highest rates are in the 40-64 age group, and rates are similar in men and women.

Map of international Lyme disease surveillance systems and policies

We used a pragmatic, non-systematic approach to describe the surveillance systems in place for Lyme disease across Europe (EU member states, plus Norway and Switzerland) and North America (USA and Canada), for a total of 34 countries (counting England and Wales, Northern Ireland and Scotland as three). We extracted data on reporting entities, case definitions, whether notification is mandatory or voluntary, and the coverage and administrative level of the system.

Most countries (N=28) have some form of surveillance for Lyme disease in place, managed in most cases at the national level. Lyme disease is notifiable by clinicians in 23 countries and by laboratories in 20; few systems rely as the UK does on laboratory notification alone (N=2 in addition to the UK). In most cases notification is mandatory, at least in principle; some countries use voluntary sentinel networks of clinicians and/or laboratories to provide data about general trends without comprehensive coverage.

Case definitions vary widely between countries. Most countries which specify a clinical case definition include both early disease (erythema migrans (EM)) and late or disseminated disease (e.g. neuroborreliosis), but in a few systems (N=3) only late disease is notifiable. There is also variation as to whether Lyme disease diagnosed on the basis of EM alone, without laboratory confirmation, is notifiable or not. A few systems collect information either on all clinician-diagnosed Lyme disease, or on patient consultations for tick bites and/or EM.

Systematic review of comparative studies of Lyme disease incidence

We undertook a systematic review using studies from the evidence map (Stokes et al., 2017) in which we compared incidence data from different sources, and estimated the extent of under-reporting of Lyme disease to surveillance systems. We located 16 studies meeting inclusion criteria. All studies were observational in nature and used either secondary data analyses or surveys to collect data. The quality of the studies overall was low. All studies were conducted in North America or continental Europe, with none from the UK.

Results from higher-quality studies, which compared data from a surveillance system with data from another source (such as hospital records or insurance data) and used consistent case definitions, suggest that the number of unreported cases is between 10% and 120% of the number of cases reported to surveillance systems, with a median estimate of 30%. All of these studies were conducted in countries with mandatory clinician reporting of Lyme disease. Findings on laboratory reporting as against clinician reporting are more limited, but do not suggest that one is markedly superior to the other in terms of under-reporting.

Most studies did not find marked disparities between systems or data sources with respect to the demographics of cases or the trends in incidence over time, although there are some divergences.

Feedback from patient advocacy groups

Feedback from patient advocacy groups suggests a concern that the evidence does not reflect the true extent of Lyme incidence and indicated that data problems undermine the accuracy of the figures. Concerns include that clinically diagnosed cases are not accounted for, that the laboratory tests are unreliable and that there is variation in clinician awareness of Lyme disease and diagnosis methods. There was also a desire for more evidence about regional differences.

Conclusions

The incidence of Lyme disease in the UK is increasing but is still low by comparison with the endemic areas of northern and central Europe and north-eastern USA.

There is almost certainly some under-reporting of cases in the UK surveillance system, but this is also likely to be true for the other systems. We would anticipate that introducing mandatory clinician notification for Lyme disease in the UK would identify some cases which are currently not reported, but would not produce substantively more reliable data, and the practical value of such a move remains unclear. Policy-makers could consider the potential value of collecting further data on the presentation and demographics of cases using questionnaires and/or using GP sentinel networks to supplement the existing surveillance system.

1. Background

This report is one of a series of reports on Lyme disease (LD) commissioned by the Department of Health (England) Policy Research Programme and undertaken by the Department of Health Reviews Facility.

The overarching project consists of a comprehensive evidence map on Lyme disease in humans and four systematic reviews on:-

1) the incidence and surveillance of Lyme disease
2) stakeholder experiences of diagnosis of Lyme disease
3) stakeholder experiences of treatment of Lyme disease; and
4) prevention of Lyme disease.

This report contains the findings from review 1) on the incidence and surveillance of Lyme disease. The primary objectives of this review are to a) systematically review UK evidence on the incidence of Lyme disease, b) to map international policies and systems for the surveillance and monitoring of Lyme disease and c) to systematically review international evidence comparing different data sources on the incidence of Lyme disease.

1.1 Lyme disease

Lyme disease is the result of an infection, caused by the Borrelia burgdorferi[1] bacterium, which is common in ticks; people can develop Lyme disease after being bitten by an infected tick (Public Health England, 2016).

In many cases, an early sign of the infection is an erythema-migrans or 'bulls-eye' rash (Stanek and Strle, 2003, Wormser et al., 2006). Clinical complications resulting from Lyme disease include joint, nervous system, and heart problems (Stanek et al., 2011, Stanek et al., 2012, Wormser et al., 2006). Some evidence suggests that presentation is not always typical (Bingham et al., 1995, Christen et al., 1993) and that complications may be more wide-ranging and persistent. However, uncertainties around persistent infection mean that the notion of chronic Lyme or post-treatment Lyme disease (PTLD) is contested and has been the subject of 'substantial and polarizing debate' in the field of medicine for many years (Rebman et al., 2017).

1.2 Surveillance of Lyme disease in the UK

Lyme disease is not a notifiable human or animal disease in the UK, so data are not collected routinely from clinical practice. However, *Borrelia burgdorferi* is a notifiable organism; that is, laboratories which test for Lyme disease are required to report positive cases to surveillance agencies. In addition, occupationally-acquired Lyme disease is

[1] We refer here to 'Borrelia Burgdoferi Sensu Lato' which includes all sub-species (including afzelii, garinii, mayonii, bissettii, lusitaniae and spielmanii). We have used the abbreviated phrase in the text for improved accessibility.

reportable under the requirements of the Health and Safety Executive (HSE) for the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations (RIDDOR).

This means that the available figures for incidence of Lyme disease in the UK refer to laboratory-confirmed cases of Lyme disease, and do not include cases where Lyme disease may be diagnosed and treated on the basis of clinical symptoms without a test being ordered. In 2013, Public Health England (PHE) estimated that an additional 1,000 to 2,000 cases of Lyme disease occur annually in England and Wales, over and above the approximately 1,000 cases notified to surveillance agencies (Public Health England, 2013).

The analysis for most samples via GP referral in England and Wales has been performed since 2012 by the PHE rare and imported pathogens laboratory (RIPL) at Porton Down. Most analyses requested in Scotland are carried out at the National Lyme borreliosis testing laboratory (NLBTL) at Raigmore Hospital, Inverness.

Data on Lyme disease are also collected within routine Hospital Episode Statistics, although this represents only cases serious enough to be admitted to hospital, which is a subset of the total cases.

1.3 Previous research on incidence of Lyme disease and surveillance systems

NICE's review of UK incidence data (National Institute for Health and Care Excellence, 2017) partly overlaps with this review, but does not explore surveillance policies in depth or evaluate completeness of data.

The most in-depth recent work on surveillance policy is reported in a paper published by van den Wijngaard et al. (2017), which we have used to inform our analysis framework. That paper is largely theoretical in orientation, with a focus on characterising indicators and reporting entities, and does not attempt to descriptively classify national systems, as does our analysis.

2. Aims and methods

This section details the review aims and provides a brief overview of the methods used for the different phases of the work. Further detail of the methods used for the different phases is found in the relevant sections below and a comprehensive account of the methods for the overarching review is in chapter 8.

2.1 Aims

The overarching aim of the review is to examine evidence on the incidence of Lyme disease in the UK and to understand the different approaches used internationally for surveying and monitoring the incidence of Lyme disease in order to illuminate the context for UK policy decision-making.

The primary objectives are to a) systematically review UK evidence on the incidence of Lyme disease, b) to map international policies and systems for the surveillance and monitoring of Lyme disease and c) to systematically review international evidence comparing different data sources on the incidence of Lyme disease.

2.1.1 Review questions

- What is the incidence of Lyme disease in the UK, and how does this vary between areas and population groups?
- What surveillance systems and policies are in place internationally to monitor the incidence of Lyme disease?
- What is known about the completeness of incidence data drawn from surveillance systems?

2.2 Review methods

Since a different approach was used for each project phase, detailed accounts are provided in chapter 0. Here we provide an overview of the ways in which the approach for each phase differed.

For phase 1, the review on UK Lyme disease incidence, and phase 3, the review on completeness of data from surveillance systems, systematic reviews were undertaken. As such these phases sought '*research evidence'* using a '*systematic approach'*; that is, research studies were identified from within the systematic evidence map produced as part of the overarching research project (Stokes et al. 2017).

However, a non-systematic or '*pragmatic'* approach was used to identify '*non-research evidence'* for both phase 2, the map of surveillance systems used internationally, and supplementary evidence for the review of UK incidence. For the UK incidence review, we examined published routine surveillance data from sources already known to the research team and recommendations from our Scientific Advisory Group (see chapter 8 for details). For the international map of surveillance systems and policies we sought information from the websites of relevant agencies, from legal or regulatory documents on the notification of communicable diseases and from surveillance reports published by national health authorities. Table 1 provides details of evidence sources and search approaches for each phase and full details are provided in chapter 8.

Table 1: Included evidence and identification procedure for each project phase

Project phase	Nature of included evidence and identification procedure	
	Research evidence (systematically identified for evidence map)	*Non-research evidence (pragmatically identified)*
1) Incidence of Lyme in the UK	Research on UK incidence	Published routine UK surveillance data
2) International map of surveillance systems and policies	-	Information from agency websites, legal documents and surveillance reports
3) Systematic review on completeness of data from surveillance systems	Research studies comparing incidence rates from more than one data source	-

2.3 Consultation with patient advocacy groups

In October 2017, we shared the key findings with eight UK-based patient stakeholder groups via an online survey and each group was invited to comment.

Prior to sharing findings, we conducted a series of face-to-face consultations with the advocacy groups in July 2017 for our review on experiences of diagnosis (Brunton et al. 2017). Whilst these face-to-face consultations did not ask participants to comment on incidence and surveillance issues directly, several participants raised issues relating to UK incidence.

Comments relating to Lyme disease incidence and surveillance from both consultation exercises are reported in chapter 6.

3. Systematic review of UK Lyme disease incidence data

3.1 Overview

- We examined information on the UK from routine data and research studies
- Incidence rates for 2005-2016 are between 3 and 6 per 100,000 in Scotland, between 1 and 2 in England and Wales, and close to 0 in Northern Ireland
- Interim 2017 data for England and Wales indicate a marked increase over 2016
- Rates are highest in the 40-64 age group, and slightly higher in men than women
- Incidence in some areas may be much higher than the national average, particularly the Scottish Highlands

3.2 Routine data

3.2.1 Data sources

The UK Department for Environment, Food and Rural Affairs (DEFRA) and PHE publish a regular Zoonoses Report which provides the number of cases of Lyme disease in England and Wales, Scotland, and Northern Ireland. The most recent provides data from 2015 and revises previously published figures for 2013-2014 (Public Health England, 2017c). Annual figures for 2016 are available separately for England and Wales (Public Health England, 2017a) and for Northern Ireland (Public Health Agency (Northern Ireland), 2017); for England and Wales there are also quarterly data up to June 2017 (Public Health England, 2017b). Data for Scotland for 2016 were not published at the time of writing, but provisional figures were communicated to us (pers. comm., Health Protection Scotland). Health and Safety Executive (HSE) data on occupationally-acquired cases are not published.

The routine data include only positive laboratory test results. Clinical practice may often focus on treatment rather than serologic testing, and such cases would not be counted in the routine data. Also, some further tests are carried out by other NHS laboratories; some of these refer to RIPL or NLBTL for confirmation, but some do not. No data are available for these other laboratories and tests conducted by them are not included in the routinely reported figures. It should also be borne in mind that the figures for Northern Ireland represent cases reported voluntarily by laboratories and may not be directly comparable with figures for the rest of the UK, where laboratory notification is mandatory.

These routinely published reports give only the number of cases. Some data are available from the Scottish system in studies in the systematic review on case demographics (e.g. gender and age) and geographical distribution; these are discussed below**Error! Reference source not found.**. However, these data are not reported routinely.

Data are also available from Hospital Episode Statistics on the number of patients with a diagnosis of Lyme disease, although obviously these only include hospital patients and not all Lyme disease cases.

3.2.2 Results: annual incidence rates

Table 2 and Figure 1 below show annual incidence rates. These represent the latest annual figures (the interim 2017 data are not included).

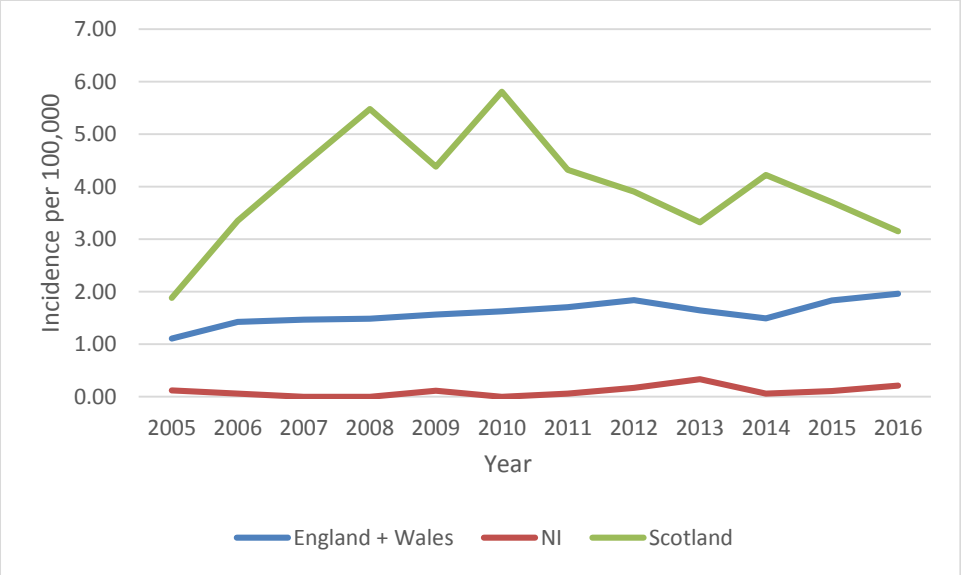
Briefly, these indicate incidence rates of between 3 and 6 per 100,000 in Scotland, between 1 and 2 in England and Wales, and close to 0 in Northern Ireland. The total number of cases per year ranged from 96 to 308 in Scotland, from 595 to 1,136 in England and Wales, and from 0 to 6 in Northern Ireland. Visual examination of the data suggests that rates in Scotland peaked in 2008-10 and then declined; the England and Wales rate shows less marked variation but a gradual rise over the period. As discussed below, these national figures may mask considerable variation in incidence between areas.

The most recent quarterly figures for England and Wales for January-June 2017 (not shown in Table 2 or Figure 1) show 483 reported cases, as compared with 283 for January-June 2016 (Public Health England, 2017b).

Table 2: Annual Lyme disease incidence rates from routine data, UK, 2005-2016

		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
England + Wales	N of cases	595	768	797	813	863	905	959	1040	936	856	1060	1136
	Population (millions)	53.6	54.0	54.4	54.8	55.2	55.6	56.2	56.6	57.0	57.4	57.9	57.9
	Incidence (per 100,000)	1.11	1.42	1.47	1.48	1.56	1.63	1.71	1.84	1.64	1.49	1.83	1.96
Scotland	N of cases	96	171	230	285	228	308	229	207	176	224	200	170
	Population (millions)	5.1	5.1	5.2	5.2	5.2	5.3	5.3	5.3	5.3	5.3	5.4	5.4
	Incidence (per 100,000)	1.88	3.35	4.42	5.48	4.38	5.81	4.32	3.91	3.32	4.23	3.70	3.15
N Ireland	N of cases	2	1	0	0	2	0	1	3	6	1	2	4
	Population (millions)	1.7	1.7	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.9	1.9
	Incidence (per 100,000)	0.12	0.06	0.00	0.00	0.11	0.00	0.06	0.17	0.33	0.06	0.11	0.21

Figure 1: Annual Lyme disease incidence rates from routine data, UK, 2005-2016



Hospital Episode Statistics for England for financial year 2015-16 show a total of 288 finished consultant episodes with a primary diagnosis of Lyme disease, and 572 with any diagnosis of Lyme disease; the cases with a primary Lyme disease diagnosis were equally distributed by gender and had a mean age of 39 (NHS Digital, 2016). Analyses by other researchers indicate an increase in hospital-recorded Lyme disease over recent years which is similar to that seen in the surveillance data (Cooper et al., 2017). However, these figures may be affected by variation both in healthcare-seeking behaviour by patients and in the willingness of clinicians to undertake consultations (as well as uncertainties in reporting), and hence should be interpreted with caution.

3.3 Systematic review

We located N=11 studies (12 reports) which met our inclusion criteria (see Appendix 3). Five of these were based on surveillance data, all but one from Scotland. Demographic data suggest that most cases occur in later middle age (40-64 years), with slightly more cases in males than females (Ho-Yen et al., 2008, Mavin et al., 2015, Milner et al., 2009). There is very wide geographical variation in incidence rates, with average incidence rates by NHS Board area in Scotland ranging from under 2 per 100,000 (with some areas reporting no cases in some years) to over 40 per 100,000 for the Highlands (Mavin et al., 2015). Three of these studies also report positive tests as a percentage of tests ordered, finding figures between 3% and 7% (Ho-Yen et al., 2008, Mavin et al., 2009, Mavin et al., 2015).

Six studies report on data other than routine surveillance data. For four of these, it is difficult to make any direct comparison with the surveillance data. One reports very limited data on travel-acquired cases from a single site (Roberts and Lever, 2003), and one reports demographic and clinical data from cases identified by a hospital laboratory (Lovett et al., 2008). One finds a seropositivity rate among Scottish blood donors of

4.2%, with regional (postcode area) rates varying up to 8.6% in the Inverness area (Munro et al., 2015). However, seropositivity rates among the general population cannot be directly compared to UK routine data, as they may include people who have no clinical symptoms. Finally, one study compares positive serological tests with hospitalisations, finding that about 10% of laboratory-confirmed cases attended hospital (Lashley et al., 2014).

The other two studies report fuller data, which is to some extent comparable with national routine data. These both report data from hospital laboratories (Dryden et al., 2015, Slack et al., 2011); in one case GPs in the local area had been targeted by an awareness-raising campaign which specifically aimed to increase reporting rates (Dryden et al., 2015).

The findings of these two studies suggest that incidence in certain areas may be considerably higher than the overall national rate. One study finds a rate of 9.8 per 100,000 in Hampshire over the period 1992-2012, with a peak annual rate of 18.5, compared with an England and Wales rate of 1.7 (Dryden et al., 2015). The other finds a rate of 16.8 per 100,000 in Tayside in 2009-2010, compared with 5.5 for Scotland as a whole (Slack et al., 2011). (However, the rates found by Slack et al. (2011) appear only slightly higher than those in published surveillance data for the same region.) Both studies also show incidence rising markedly up to 2009-2010 (Dryden et al., 2015, Slack et al., 2011); Slack et al. (2011) is consistent with surveillance data in this respect, and in Dryden et al. (2015) the rate appears to level off in subsequent years. Both these studies used similar case definitions to those used for national routine data.

Findings on demographics from these studies appear consistent with surveillance data, with the highest incidence rates in late middle age (Dryden et al., 2015, Munro et al., 2015) and similar rates in men and women (Dryden et al., 2015, Lovett et al., 2008, Munro et al., 2011, Munro et al., 2015, Slack et al., 2011).

3.4 Discussion

3.4.1 Summary of findings

Routine data shows an annual incidence rate for Lyme disease in England and Wales of just under 2 per 100,000 in recent years. The rate has increased slowly but fairly consistently over the last decade. The rate in Scotland is somewhat higher but has declined since a peak in 2008-10. The rate in Northern Ireland is very low (although data are not directly comparable). As discussed in the following subsection, these national rates conceal considerable variation between local areas, and local incidence in some areas may be several times higher.

The highest rates appear to be in people in later middle age (40-64 years). Most data show similar rates in men and women, or a slightly higher rate in men.

It should also be borne in mind that data from the UK surveillance system will under-estimate the true incidence to some extent, since cases without laboratory tests are not captured. We do not know how many cases are diagnosed and treated in the UK on the basis of clinical symptoms alone, without a diagnostic test being ordered. Hence, it is challenging to establish the true extent of under-reporting. Importantly, it is not yet clear

how much of the recent rise in notified cases reflects a rise in the true incidence, and how much may be due to changes in reporting practice, clinician awareness, clinician practice (e.g. in terms of ordering tests), and/or healthcare-seeking behaviours in patients.

3.4.2 Geographical variation and hotspots

Data for Scotland show that there are local 'hotspots' where rates are much higher than the national average, with rates in the Highland area several times those for the country as a whole (Mavin et al., 2015, Milner et al., 2009), and considerable variation at a more local level within the Highlands (Mavin et al., 2009); there are also lower-incidence hotspots in Tayside and the Western Isles.

Surveillance data are not broken down for region in England and Wales. Anecdotally, relatively high-incidence areas are found in several parts of southern England. Public Health England (2017c) list "the New Forest, Salisbury Plain, Exmoor, the South Downs, Thetford Forest and parts of Wiltshire and Berkshire" (p. 50)). Cooper et al.'s (2017) analysis of hospital episode data (published too late to be included in the map) identifies high-incidence areas in Devon and in the Chiltern Hills in south-east England.

Of the studies in the review, Dryden et al.'s (2015) findings are the closest we have to a confirmation of hotspots in England, with a local rate in Hampshire of 9.8 as compared with a national rate of 1.7 per 100,000. However, these figures also reflect a campaign to increase awareness of Lyme disease and use of Lyme disease testing services among GPs and other health professionals. Given the absence of geographically comparable routine data, we cannot determine how much of the discrepancy is due to geographical variation and how much to under-reporting or under-diagnosis of Lyme disease. It seems likely that there is some combination of both these factors, and that Dryden et al.'s results are partial confirmation of local hotspots in England.

3.4.3 Strengths and limitations of the review

We identified UK studies from the comprehensive map of literature on Lyme disease and used a systematic and transparent approach, although we did not quality assess the studies. The collation of routine data was pragmatic and non-systematic in nature, although we believe the main sources have been identified.

The evidence base relating to the UK and particularly England is sparse, and we identified gaps in knowledge about the extent of under-reporting in routine data, and of variation in geographical areas.

3.4.4 Comparison with previous research

The main existing review of UK incidence data was conducted by NICE (National Institute for Health and Care Excellence, 2017). The studies and data covered in both reviews are similar, although there is variation in search strategies and inclusion criteria. NICE included one study which was published too late to be identified by our searches (Cooper et al., 2017); this used hospital episode data for England, finding a total of N=260 completed episodes diagnosed as Lyme disease in 2011-2012, increasing to N=370 in 2014-2015.

We were able to include up-to-date routine surveillance data. As a result, our findings on the overall national incidence rate show considerably higher numbers than the NICE review (0.06 to 0.59 per 100,000, based on data from 1997 to 2005). The findings on geographical variation are similar.

4. Map of international Lyme disease surveillance systems and policies

The aim of this phase was to provide a descriptive overview of the systems and policies in place internationally for monitoring Lyme disease in humans. This provides context for UK policy decision-making as well as information for the interpretation of international incidence data.

4.1 Overview

- We examined surveillance systems and incidence rates in 34 countries in Europe and North America
- Six countries have no national or governmental systems for monitoring Lyme disease
- Systems vary across the remaining 28 countries according to whether:-
    - Reporting systems are organised at the national level (n=24) or regional level (n=4)
    - Cases of Lyme disease are reported to monitoring systems by both clinicians and laboratories (n=15), by clinicians only (n=8) or by laboratories only (n=5)
    - The notification of Lyme disease is mandatory (n=23) or voluntary (n=6).
    - Incidence is calculated from clinical presentations (e.g. EM, neuroborreliosis) (n=19), patient consultations for tick bite or EM (n=3) or positive laboratory tests (n=8)

4.2 Findings: Surveillance systems and policies

Table 3 presents the main characteristics of the surveillance systems (n=34 countries). Six of these (Austria, Cyprus, Greece, Italy, Malta and Sweden) have no national or governmental oversight in place for monitoring Lyme disease, do not place any legal obligation on clinicians or laboratories, and do not report any official statistics. Our analysis is based on the remaining twenty-eight systems (including the three UK systems).

We examine below for each country whether data are collected at a national or regional level (4.2.1), whether clinicians or laboratories are responsible for reporting data to surveillance systems (4.2.2), whether reporting of data is a legal requirement or not (4.2.3) and how a case of Lyme disease is defined (4.2.4).

4.2.1 Administrative level

Of those countries with some surveillance system in place (n=28), four are administered at sub-national level (Canada, Germany, Spain, and USA) and the remainder at national level (including the UK nations for the purposes of analysis).

In Canada, Germany, Spain and the USA, the surveillance of Lyme disease is a sub-national responsibility: each region has its own system and related laws. In Canada and the USA, all provinces collect information on Lyme disease (with the exception of the northern Canadian territories). Both countries have set national case definitions for Lyme disease, compile data submitted by states/provinces, and report them at the national level.

However, provinces in Canada do not all use the same case definitions and reporting entities: some systems were implemented before the national system and continue to use their own procedure. In addition, only some provinces participate in the Lyme Disease Enhanced Surveillance system, which collects additional information on cases and reports it to the national level. In the USA, Lyme disease is a notifiable disease but the states decide by law whether to report at the state level, and are not obliged to submit their information to the national US authorities, the Centers for Disease Control and Prevention (CDC). Nevertheless, all seem to report data on Lyme disease at the national level. In contrast, in Spain and Germany, surveillance of Lyme disease is carried out in some regions (autonomous communities in Spain, *Bundesländer* in Germany) and not in others.

Table 3: Characteristics of surveillance systems in Europe and North America

Countries (N = 34)	No govt-led activity	Administrative level		Reporting entity			Obligation and coverage				Manifestations reported (confirmed cases only)						
		National	Sub-national	Clini-cians only	Labs only	Both	Manda-tory (country -wide)	Manda-tory (some regions)	Volunta -ry Clinician sentinel	Others	EM clinical signs only	EM with lab	NB	Other late or dissem-inated	N consul-tations	Positive lab tests	Not clearly defined
UK																	
England/Wales		X			X		X									X	
North. Ireland		X			X					Volunta -ry labs						X	
Scotland		X			X		X									X	
EUROPE																	
Austria	X																
Belgium		X				X			Country -wide	Volunta -ry labs sentinel					X	X	
Bulgaria		X				X	X					X	X	X			
Cyprus	X																
Czech Rep.		X		X			X					X	X	X			
Croatia		X		X			X					X	X	X			
Denmark		X				X	X						X			X	
Estonia		X				X	X					X					
Finland		X			X		X									X	
France		X		X					Country -wide		X		X	X			
Germany			X			X		X	Some regions		X		X	X			
Greece	X																
Hungary		X				X	X					X	X				

Countries (N = 34)	**No govt-led activity**	**Administrative level**		**Reporting entity**			**Obligation and coverage**				**Manifestations reported (confirmed cases only)**						
		National	Sub-national	Clini-cians only	Labs only	Both	Manda-tory (country -wide)	Manda-tory (some regions)	Volunta -ry Clinician sentinel	Others	EM clinical signs only	EM with lab	NB	Other late or dissem-inated	N consul-tations	Positive lab tests	Not clearly defined
Ireland		X				X	X						X				
Italy	X																
Latvia		X		X			X										X
Lithuania		X				X	X										X
Luxembourg		X		X			X				X		X	X			
Malta	X																
Netherlands		X		X						Clinician surveys	X				X		
Norway		X				X	X						X	X			
Poland		X		X			X				X		X	X			
Portugal		X				X	X					X	X	X			
Romania		X				X	X					X	X	X			
Slovakia		X			X		X									X	
Slovenia		X				X	X				X		X	X			
Spain			X			X		X				X				X	
Sweden	X																
Switzerland		X		X					Country -wide						X		
NORTH AMERICA																	
USA			X			X	X				X	X	X	X			
Canada			X			X	X					X	X	X			
TOTAL (N)	**6**	**24**	**4**	**8**	**5**	**15**	**21**	**2**	**4**	**3**	**7**	**10**	**16**	**12**	**3**	**8**	**2**

4.2.2 Reporting entities of surveillance

As shown in Table 3, Lyme disease is reported by clinicians only in eight systems, by laboratories only in five systems, and by both clinicians and laboratories in the remaining 15. The Danish system is an example where both clinicians and laboratories submit data.

In systems where both clinicians and laboratories submit data, data can be reported at the national level independently for both systems, or compiled by the authority in charge (often the national public health department) in order to remove duplicates, confirm and report single cases. Belgium is an example of a country where data are reported separately. Its method includes three systems that involve clinicians and laboratories: a) a GP sentinel that participates in cross-sectional surveys approximately every five years; b) a laboratory sentinel that reports data on a weekly basis; and c) the National Reference Centre for Borrelia Burgdorferi, which provides support for diagnosis and also reports surveillance data. (Sentinels are explained in the next section.) The Public Health Scientific Institute presents data from these separately, including in different reports.

In Norway, by contrast, data from clinicians and laboratories are aggregated in a single database. Clinicians are required to send specimens of suspected cases to a laboratory, which notifies both the clinician and the surveillance system when the result is positive. Then, the clinician must send a standardised notification form to the surveillance system and the local health authority. When both clinical and laboratory notifications are received at the Institute for Public Health and match (the presence of both clinical symptoms and a positive laboratory test are required to confirm a case), they are registered as a single case in the surveillance system.

In the countries that have sub-national surveillance systems, reporting entities vary across regions. For instance, in Germany, some states require clinicians to notify cases of Lyme disease, some require laboratories to notify, some do both, and Lyme disease is not notifiable in others.

As for other reporting entities (not shown in Table 3), Belgium, the Netherlands and Switzerland invite the general population to report tick bites, EM or other symptoms via an application or website that is managed by the national public health authority or in which the government is a partner. In England and Wales, employers are required to report occupationally-acquired cases to the Health and Safety Executive, under the Reporting of Injuries, Diseases and Dangerous Occurrences Regulations.

4.2.3 Obligations and coverage

The notification of Lyme disease is mandatory by law in the majority of countries (n=21, plus some regions of Germany and Spain). Three countries (Belgium, France and Switzerland) and one German region (Bavaria) use a voluntary system called sentinels (in addition to mandatory notification in the case of Bavaria). Sentinels are groups of clinicians or organisations that are representative of the territory, trained and voluntarily registered in a network. The sentinel network in Belgium includes about 150 GPs, the French represents about 2.2% of GPs in mainland France, and the Swiss includes approximately 200 clinicians. As explained earlier, Belgium also uses a laboratory sentinel network of about 40 laboratories, representing nearly 50% of serologic tests performed in the country (not only for Lyme). The Belgian laboratory sentinels and clinician sentinels in

France, Switzerland and Bavaria are active systems that regularly report information to the authority in charge. The GP Belgian sentinel network is used as a sample to whom surveys are sent approximately every five years.

The Netherlands is a unique case where information is requested from clinicians across the whole country on a voluntary basis. Similarly to the Belgian GP sentinels, the National Institute for Public Health and Environment monitors Lyme disease through a survey sent to GPs at approximately five-yearly intervals (in some surveys other clinicians have also been surveyed). In the most recent survey questionnaires were sent to all GPs, while in previous years a random sample was contacted. The most recent survey attained a response rate of 41% of GPs, with practice populations representing 62% of the total population.

4.2.4 Case definitions for reporting Lyme disease

Surveillance systems define cases differently. The definitions used fall into the following categories:

- Clinical case definitions (N=19), of which N=3 include only early Lyme disease (EM), N=3 include only late or disseminated Lyme disease (neuroborreliosis and/or other late manifestations), and N=13 include both;
- Positive laboratory tests only (N=5);
- Number of patient consultations only (N=1).

For two countries we were unable to find a clearly stated case definition (Latvia and Lithuania). The level of detail and precision in the definitions varies between countries. Canada and the USA are examples of countries that use extensive definitions. Cases are classified into three categories (suspected, probable, confirmed), each of which is clearly defined in terms of clinical presentation, exposure and/or laboratory confirmation.

Regarding early Lyme disease (EM), seven countries consider cases assessed with clinical symptoms only. Ten require both clinical signs and a positive laboratory test. In addition to these, in the USA, confirmed cases of EM need to have clinical symptoms supported by either a laboratory confirmation or a history of tick bite. Most countries where late or disseminated Lyme disease (including neuroborreliosis, Lyme arthritis or other late manifestations) is notifiable require a laboratory confirmation.

Of the systems which use GP sentinels, two only collect data on patient consultations rather than on diagnosed disease. Consultations for tick bites and EM are notifiable in the Belgian GP sentinels, and consultations for tick bites, EM and “chronic manifestations” (no definition) are reported by the Swiss GP sentinels. The Dutch surveys measure a combination of both consultations (for tick bites) and diagnosis (of EM).

Finally, in the countries that have a laboratory-only system, only positive laboratory tests are notified (England and Wales, Northern Ireland, Scotland, Finland and Slovakia). Three further countries also report data on positive laboratory tests, as well as clinical data (Belgium, Denmark and Spain).

4.3 Discussion

4.3.1 Comparison of UK with international policies and systems

Relatively few countries operate similar systems to the UK, perhaps because few countries have centralised laboratories. Mandatory clinician reporting is fairly common across Europe and North America, but by no means ubiquitous, even in those countries which seem geographically likely to have substantial incidence rates. Some do not conduct any surveillance of Lyme disease at all, including Sweden, Austria and some regions of Germany.

There is wide variation between countries in terms of case definitions. This can be seen in terms of a 'surveillance pyramid' (Braks et al., 2011). Some systems focus on a 'higher' level of the pyramid (late or disseminated Lyme disease) and some on a 'lower' level (EM alone): those sentinel- or survey-based systems which measure all consultations for tick bites could be seen as focusing at a yet lower level.

4.3.2 Strengths and limitations of the overview

In this phase we described the different systems and policies in place for the surveillance of Lyme disease internationally using information and data from reports and websites, which for some countries is limited. We did not contact agencies directly for further information. The information and data were verified fully by a second researcher. We used Google Translate to extract information in languages not spoken by the researchers. We also scanned studies in the map to provide additional information, but did not systematically extract data from relevant studies.

To our knowledge, no previous research has produced a similar overview of surveillance systems and policies (although a project led by the European Centre for Disease Prevention and Control, which may overlap with this research, is currently underway and is due to report in December 2017). The findings complement theoretical policy discussions (e.g., van den Wijngaard et al. (2017)) by showing which policy options have actually been implemented and which have not.

This phase of the research was mainly descriptive. We did not seek to assess the implementation of surveillance systems or evaluate the completeness of data, since this would require extensive primary research. Hence, we cannot judge, for example, what proportion of cases are actually reported in countries with mandatory notification laws in force.

5. Systematic review of comparative studies of Lyme disease incidence

5.1 Overview

- We identified 16 studies which compared incidence rates for the same populations using different data sources
- Higher-quality studies comparing surveillance data to other data indicate that at least some cases identifiable from other sources are not reported to surveillance authorities; estimates range from 10% to 120% of cases, with an unweighted median of 30%
- Some evidence suggests that laboratory reporting may identify more cases than mandatory clinician reporting alone
- There are some limitations to the evidence, such as a dearth of high quality evidence, and some significant gaps such as on active surveillance systems or sentinel networks

5.2 Included studies

A total of 16 studies (17 reports) were included in the review of comparative studies. Most studies (N=10) were conducted in the USA, with five conducted in Europe and one in Canada. No comparative studies were located from the UK.

Table 4 shows the quality assessment (QA) ratings for the studies (further detail is given in Appendix 6), showing the score (minimum 0, maximum 8) of each study. On average the studies received low ratings (median score 2). This was mostly due to lack of validated data (question 2), and to discrepancies between the data sources with respect to populations (question 1) and/or case definitions (question 3), which limit the comparability of the results within studies.

Table 4: Summary Quality Assessment results (N=16)

Study reference	1. Population	2. Data validation	3. Case definition	4. Analysis	5. Comparisons	TOTAL
Bleyenheuft et al. (2015)	1	0	0	0	0	1
Bochničková et al. (2012)	0	0	0	0	0	0
Boltri et al. (2002)	1	0	0	0	0	1
Centers for Disease Control and Prevention (2008)	1	1	2	0	1	5
Clayton et al. (2015)	0	2	2	1	0	5

Dessau et al. (2015)	1	0	0	0	1	2
Ertel et al. (2012)	1	1	2	0	1	5
Henry et al. (2011)	1	2	2	1	0	6
Jones et al. (2012); Jones et al. (2013)	0	0	1	1	0	2
MacDonald et al. (2016)	1	0	0	0	0	1
Müller et al. (2012)	0	0	1	0	0	1
Naleway et al. (2002)	1	2	2	1	1	7
Nelson et al. (2015)	0	0	1	1	1	3
Robinson (2014)	1	0	0	0	0	1
Schiffman et al. (2016)	1	2	2	1	0	6
Tseng et al. (2015)	0	0	1	0	0	1

A brief overview of the types of data included in the studies is given in Tables 5 and 6. Table 5 covers the studies which compared data from a surveillance system with data from another source (N=13), in order to assess the extent of under-reporting within the former. The comparison source was either administrative records from healthcare providers (N=6), databases containing information on health insurance claims (N=5), results from laboratories conducting serologic tests (N=1) or questionnaires distributed to clinicians (N=1). The table summarises the nature of the surveillance system and case definitions (it should be noted that this information was not always explicitly reported in the study report, and had to be supplied from references given in the paper), and the comparison data source and case definition. The table also repeats the summary QA score. Finally, the table gives a summary statistic representing the reporting multiplication factor, that is, the ratio of cases found from the comparison source to those reported within the surveillance system, or calculated through modelling (Gibbons et al., 2014); this was recalculated where not directly reported in the study. As discussed below these figures should be interpreted with caution, particularly for those studies with lower quality ratings.

Table 6 covers the studies which described different data sources within a single surveillance system. (We have not calculated a multiplication factor for these studies as the data sources are generally not independent.) These studies are somewhat more heterogeneous in their aims and methods, but generally compare clinician reporting with laboratory reporting, and in one case passive surveillance (relying on clinicians to report cases) with active surveillance (a voluntary network of clinicians who reported every month) (Ertel et al., 2012).

Table 5: Studies comparing data from surveillance systems with data from other sources (N=13)

Study reference	Country	Years	Surveillance system	Case definition for surveillance source	Comparison source	Case definition for comparison source	QA score	Ratio of rate in comparison source to rate in surveillance source
Bleyenheuft et al. (2015)	Belgium	2003-2010	Sentinel laboratory network	Lab test	Medical records	Any coded (ICD-9)	1	1.06
Bochničková et al. (2012)	Slovakia	1989-2010	Unspecified	NR	Medical records	NR	0	2.17
Boltri et al. (2002)	USA	1999-2000	Mandatory clinician reporting with follow-up	(EM or disseminated) + lab test	Clinician questionnaire	Any clinician report of diagnosing or treating	1	96.33
Clayton et al. (2015)	USA	2011-2013	Mandatory clinician reporting with follow-up	(EM or disseminated) + lab test + exposure	Insurance records	With ≥3 codes (ICD-9) (initial analysis); as surveillance (final analysis)	5	1.19

Henry et al. (2011)	Canada	1997-2008	Mandatory clinician reporting (passive / active)	Any diagnosed (initial analysis); (appropriate diagnosis + exposure) or lab test (final analysis)	Laboratory records	Lab test (initial analysis); as surveillance (final analysis)	6	1.41 (cases reported) 1.53 (estimated from model)*
Jones et al. (2012); Jones et al. (2013)	USA	2000-2009	Mandatory clinician reporting with follow-up	Any diagnosed + lab test	Insurance records	Any coded (ICD-9) + ≥3 corroborating events	2	3.09 (cases reported) 7.76 (estimated from model)
MacDonald et al. (2016)	Norway	2008-2012	Mandatory clinician and lab reporting	Diagnosed disseminated or chronic	Medical records	Any coded (ICD-10)	1	3.97
Müller et al. (2012)	Germany	2006-2008	Mandatory clinician reporting	NR	Insurance records	Any coded (ICD-10) + serologic test ordered	1	7.68
Naleway et al. (2002)	USA	1992-1998	Mandatory clinician reporting with follow-up	EM or (disseminated + lab test)	Medical records	Any coded (ICD-9) or lab test (initial analysis); as surveillance (final analysis)	7	1.12

Nelson et al. (2015)	USA	2005-2010	Mandatory clinician reporting with follow-up	EM or (late manifestation + lab test) (pre-2008) EM + (exposure or lab test), or late manifestation + lab test (2008 on)	Insurance records	Coded (ICD-9) as principal diagnosis or coded as secondary + consistent principal	3	4.76 (cases reported) 11.34 (estimated from model)
Robinson (2014)	USA	2008-2011	Mandatory clinician reporting with follow-up	EM + (exposure or lab test), or late manifestation + lab test	Medical records	Any coded (ICD-9)	1	2.61
Schiffman et al. (2016)	USA	2009	Mandatory clinician reporting with follow-up	EM + (exposure or lab test), or late manifestation + lab test	Medical records	Any coded (ICD-9) or related codes (initial analysis); as surveillance (final analysis)	6	2.16
Tseng et al. (2015)	USA	2004-2006; 2010-2012	Mandatory clinician reporting	EM or (late manifestation + lab test) (pre-2008)	Insurance records	Any coded (ICD-9) + serologic test ordered +	1	≈2.38

			with follow-up	EM + (exposure or lab test), or late manifestation + lab test (2008 on)		treatment ≥14 days		

* First ratio for Henry et al. (2011) is ratio of total deduplicated cases to cases from clinician reporting; second ratio for Henry 2011 is ratio of estimated total rate (using capture-recapture methodology) to total number of cases identified through all sources (in best-fitting model; other models give different rates)

'Initial analysis' refers to the initial coding of cases, 'final analysis' to the final coding on which the calculation of a reporting multiplier is based

Table 6: Studies comparing data within surveillance systems (N=3)

	Country	Years	1st data source	2nd data source	3rd data source	QA score
Centers for Disease Control and Prevention (2008)	USA	2001-2006	Electronic laboratory reports	Clinician reports + paper-based laboratory reports	N/A	5
Dessau et al. (2015)	Denmark	2010-2012	Clinician reports	Electronic laboratory reports	N/A	2
Ertel et al. (2012)	USA	1996-2007	Clinician reports	Clinician active surveillance network	Laboratory reports (2 systems)	5

In the following synthesis we first discuss the studies comparing surveillance with non-surveillance sources, and then the studies comparing sources within a surveillance system. Within the groups studies are divided into higher-quality (QA score >4) and lower-quality (QA score ≤4). The results of lower-quality studies are only briefly summarised; synthesis focuses on the higher-quality studies.

5.3 Findings: studies comparing surveillance with non-surveillance sources

5.3.1 Higher-quality studies

Four studies received a QA score higher than 4 (Clayton et al., 2015, Henry et al., 2011, Naleway et al., 2002, Schiffman et al., 2016). Three were conducted in the USA and one in Canada. In all four studies, mandatory clinician reporting was in force during the study period.

All four higher-quality studies used secondary data analysis comparing the number of cases reported to the surveillance system with another source of data (clinical records, insurance records, laboratory records or enhanced surveillance databases). In all these studies the comparison data source was reviewed and validated by the study authors, either for all the cases included (Henry et al., 2011, Naleway et al., 2002, Schiffman et al., 2016) or for a random sample (Clayton et al., 2015), and a consistent case definition was applied (based on the surveillance case definition in force in the jurisdiction where the study was conducted). In three studies data analysis consisted of directly comparing the different sources, with a view to identifying cases from the comparison source which had not been reported to the surveillance system, and hence calculating a reporting multiplier (Clayton et al., 2015, Naleway et al., 2002, Schiffman et al., 2016). The other study combined three sources of data and analysed them using capture-recapture analysis, which estimates the true number of cases in a population based on the overlap between distinct data sources, to arrive at an estimate of the total number of cases unreported to any source (Henry et al., 2011).

Reporting multipliers calculated from these studies ranged between 1.1 to 2.2, with an unweighted median of 1.3, when comparing incidence rates from surveillance systems with mandatory clinician reporting to other data sources. The capture-recapture study indicated a reporting multiplier of between 1 and 1.5, depending on model specification, for a system including both mandatory clinician notification and mandatory laboratory notification.

Two of these studies also investigated whether there was any difference in the demographics of cases between the different data sources, both of which found no significant difference with respect to age or gender (Clayton et al., 2015, Naleway et al., 2002).

5.3.2 Lower-quality studies

Nine studies (ten study reports) received a QA score of 4 or lower (Bleyenheuft et al., 2015, Bochničková et al., 2012, Boltri et al., 2002, Jones et al., 2013, MacDonald et al., 2016, Müller et al., 2012, Nelson et al., 2015, Robinson, 2014, Tseng et al., 2015). Five were conducted in the USA and four in continental Europe. In most cases (N=7) mandatory clinician reporting was in force.

Most of these studies use secondary data analysis to compare surveillance data with other data sources (medical records, insurance records, hospital episode data); one study reports the findings of a questionnaire survey of clinicians and compares this to surveillance data (Boltri et al., 2002). In none of these studies were the case definitions consistent between sources, which limits the validity of the resulting data. The methods used to analyse data from the comparison data sets varied considerably: some included any cases coded with a Lyme disease diagnosis in the data set, while others used more inclusive and others more exclusive definitions. In most cases (N=7) the analysis consisted in directly comparing rates between the two sources; one study used generalised linear mixed modelling (Jones et al., 2013), and one applied a correction factor to account for under-diagnosis (Nelson et al., 2015).

The results of these studies vary widely, with calculable reporting multipliers ranging between just over 1 and more than 10, or almost 100 in one outlying case (Boltri et al., 2002). The unweighted median multiplier was 3.1 on the basis of direct comparisons, or 4.0 if the 'corrected' findings in the two studies using more complex analyses are included.

5.4 Findings: studies comparing data sources within a surveillance system

5.4.1 Higher-quality studies

Two studies in this group, both conducted in the USA, received a QA score higher than 4 (Centers for Disease Control and Prevention, 2016, Ertel et al., 2012). One found that the combination of clinician and paper-based laboratory reporting identified approximately 2.8 times as many cases as electronic laboratory reporting (Centers for Disease Control and Prevention, 2016). The other found that mandatory laboratory reporting found a substantial number of cases over and above those found by the combination of passive and active clinician reporting (Ertel et al., 2012). Results on case demographics were mixed: one study finds differences in the age and presentation of cases, with clinician-reported

cases more likely to be younger and to present with early Lyme disease than those reported by laboratories (Ertel et al., 2012); the other study shows no difference in age but did find some differences in geographical location and seasonality (Centers for Disease Control and Prevention, 2016).

5.4.2 Lower-quality studies

One study in this group received a QA score of 4 or lower. This study was conducted in Denmark and compared clinician reporting to electronic laboratory reporting (Dessau et al., 2015). Laboratory reporting found approximately 2.5 times as many cases as clinician reporting. More clinician-reported cases than laboratory-reported cases were children; there was no significant difference by gender, but there was some variation in geographical region.

5.5 Discussion

5.5.1 Summary of findings

The findings from higher-quality studies that compare surveillance data with other sources (N=4), all of which relate to systems which require mandatory clinician notification, show that at least some cases identifiable from other sources are not reported to surveillance authorities, and hence that there is some under-reporting of cases. Estimates of the under-reporting multiplier (i.e. the ratio of cases in the comparison source to cases in the surveillance source) in these studies range from 1.1 to 2.2 (or, in other words, between 10% and 120% additional cases); the unweighted median is 1.3. One study, using capture-recapture methods, indicates that a system which includes both mandatory clinician notification and mandatory laboratory notification under-reports cases by a factor of between 1 and 1.5 (Henry et al., 2011). Estimated multipliers from lower-quality studies are considerably higher, but the validity of these findings is limited.

Fewer reliable data are available on the performance of laboratory reporting relative to clinician reporting. However, some evidence suggests that electronic laboratory reporting may identify more cases than mandatory clinician reporting alone (Dessau et al., 2015, Henry et al., 2011).

There is little data on active surveillance systems or sentinel networks, and what there is is hampered by limited information on the nature of the system.

5.5.2 Transferability of the findings to the UK context

We located no comparative studies from the UK. The context of most of the studies diverges from the UK in several respects, which may present barriers to the transferability of the findings. Firstly, almost all the studies were conducted in countries where Lyme disease is notifiable by clinicians, which is not the case in the UK. Findings regarding the rate of under-reporting in these systems are thus not immediately applicable in the UK context.

Most of the studies were conducted in countries and regions which have a higher incidence of Lyme disease than the UK. This may translate into higher awareness of Lyme disease among both clinicians and the general population. This may in turn affect clinician practices in ways which impact on reporting behaviour and on the data recorded in

administrative datasets (for example, it may make clinicians more likely to recognise Lyme disease, but also to treat it without ordering serologic tests).

Most of the studies were conducted in countries with insurance-based health systems (private or public). Several studies use health insurance providers as a comparison data source, and these data have no direct analogue in the UK context. Differences in the health system (for example, with respect to whether testing and treatment for Lyme disease are reimbursed) may also affect the behaviour of clinicians and people seeking healthcare.

Current UK surveillance operates on the basis of tracking positive laboratory tests alone; there is no case definition distinct from this, since Lyme disease as distinct from *B. burgdorferi* is not notifiable. The studies in this review are based upon official case definitions for Lyme disease which include clinical symptoms and/or exposure to ticks in addition to laboratory tests (or even without laboratory tests in some cases; see section 0 and Appendix 4). This may limit the applicability of the findings to the UK context.

5.5.3 Strengths and limitations of the review

In this phase we used full systematic review methods, with systematic screening, quality assessment and data extraction. However, while all records were double-screened, quality assessment and data extraction were checked rather than redone independently by the second reviewer. Studies were identified from a comprehensive map of Lyme disease research (Stokes et al. 2017).

Interpretation of the findings depends to some extent on contextual information, particularly relating to the surveillance system in force. This was frequently not reported in the studies and has been added from other policy documents where appropriate for the analysis.

As the results show, much of the literature has severe limitations, mainly relating to the comparability of data sources and case definitions, and the results of lower-quality studies cannot be regarded as reliable. The body of studies using comparable data from both a surveillance system and an independent data source is small, although the findings across studies are reasonably consistent.

5.5.4 Implications for policy and practice

The findings imply that even in countries where Lyme disease is mandatorily notifiable by clinicians, there is some under-reporting of cases. While estimates of the reporting multiplier vary considerably – with higher-quality studies suggesting multipliers between 1.1 and 2.2 - the data do suggest that at least some cases go unreported in all systems. There is more limited data on laboratory surveillance systems, but the data available do not suggest that they perform worse than mandatory clinician reporting, and they may perform better. This is probably due to the automated nature of electronic laboratory reporting systems, although it may to some extent reflect differences in case definitions (Dessau et al., 2015).

Most studies do not indicate major differences between reported and unreported cases in terms of demographics or location, in either clinician or laboratory systems, although the data are not fully consistent. There are fewer data comparing demographics between

clinician-reported and laboratory-reported cases, but there are some divergences, with clinician-reported cases more likely to be younger and to have an early form of Lyme disease than laboratory-reported cases. This aside, the findings do not suggest that the performance of either clinician or laboratory systems are inadequate in terms of tracking the overall trends in incidence of Lyme disease. However, we identified some variability in the geographical distribution of cases between different data sources (but, again, no clear implication in terms of the superiority of one type of system over another). This may raise concerns as to how accurately surveillance data captures local variation in incidence rates, particularly at smaller spatial scales.

The findings suggest that a combination of methods gives more complete coverage in terms of the identification of cases than any single method alone, but also that no combination can guarantee full coverage of all cases. Whether such a combination of systems gives a better representation of overall trends cannot be determined from the available data.

Our findings do not suggest that administrative datasets would be a valuable addition to the surveillance system, due to limited reliability of these data; plus such datasets are largely unavailable for the UK.

6. Patient advocacy groups views on these findings

Six patient advocacy groups provided feedback on these findings in our October 2017 survey. Responses largely focused on the incidence of Lyme disease in the UK.

All groups were concerned that the evidence does not reflect the true extent of Lyme incidence in the UK. Stakeholders indicated that several problems undermine an accurate picture of both absolute figures and regional comparisons of Lyme disease incidence. These included a) the fact that clinically diagnosed cases are not accounted for in the figures (noted by six groups), b) the unreliability of laboratory tests (noted by four groups) and c) the variability of Lyme disease knowledge among clinicians, for example about the need for and appropriate timing of serology testing (noted by two groups).

Three groups suggested that the true scale of UK Lyme disease incidence should be monitored and two groups expressed a need for more comprehensive evidence about regional differences.

Similar issues were raised in the consultation meetings in July 2017. Stakeholders raised concerns about the lack of evidence on endemic areas or Lyme 'hot-spots' in the UK and about the likelihood of underestimation of Lyme disease incidence given the limitations of diagnosis procedures and testing.

7. Conclusions

7.1 Incidence of Lyme disease in the UK

Our findings do not permit us to estimate a 'true' incidence rate for the UK, given the limitations in transferability of the evidence on under-reporting. They also do not give any reason to challenge PHE's pragmatic estimate of 2,000 to 3,000 cases a year for England and Wales, implying a value of 2 to 3 for the reporting multiplier and an incidence of approximately 3.5 to 5 per 100,000 (Public Health England, 2013).

7.2 Context and goals of Lyme disease surveillance

The aspects of a surveillance system which are most important depend on the overarching goal of the system and on the ways in which data will be used by practitioners and policy-makers (German et al., 2001). In the case of Lyme disease, one potential concern is how well surveillance data identifies 'hotspots' of higher incidence within an overall context of relatively low incidence. The UK data suggest that most cases may be accounted for by a small number of geographically limited areas; however, information on the geographical distribution of cases in England and Wales is sparse and somewhat inconsistent, so we cannot identify these areas with any confidence. Information on national incidence rates does not provide an accurate measure of local risk, and so may be of limited value to clinicians or local policy-makers. In addition, rates may vary between very small areas and over time, so even a relatively fine-grained breakdown by areas might not give a full picture of the local situation.

Laboratory tests can only provide evidence of *B. burgdorferi* infection. This in itself is not evidence of Lyme disease as patients can be infected but not develop the disease. Lyme disease can only be confirmed clinically. In addition, laboratory tests cannot distinguish between active and past infection. Therefore, some patients that are seropositive may be incorrectly labelled as having Lyme disease. By contrast, clinical surveillance schemes provide a direct indication of the burden of Lyme disease. However, if strict case definitions have to be adhered to it is likely that some real cases of Lyme disease will not be labelled as such.

7.3 Policy options

Our findings, along with the broader literature, suggest several potential policy directions for England and Wales.

a) Maintain the existing system with no change. The current laboratory-based system has some advantages. It minimises the burden on both clinicians and public health authorities. The evidence does not suggest that other systems, such as mandatory clinician reporting, are superior in terms of the ability to track trends and estimate approximate overall incidence (although the data are not fully conclusive). However, the current system does not provide contextual information - for example, on the location, demographics and clinical presentation of cases - which could give a more complete picture of disease trends.

b) Introduce mandatory clinician reporting for all Lyme disease cases. Our findings suggest that the introduction of mandatory clinician reporting for Lyme disease in England and

Wales would probably locate more cases than the current system. However, they also suggest that it would not eliminate under-reporting (and might introduce some over-reporting). The issues with mandatory clinician reporting are well known and suggest that such a move in England and Wales would probably not lead to substantively more reliable information, or mitigate the challenges which currently beset the interpretation of surveillance data. Mandatory reporting requirements could include a requirement to report contextual data about cases, although again, there would be limitations to the reliability of these data overall.

c) Introduce mandatory clinician reporting for late or disseminated Lyme disease cases alone. If late manifestations of Lyme disease are a particular policy concern, these could be made notifiable without adding notification of all manifestations of Lyme disease. The data suggest that the overall numbers are likely to be fairly low, which could make the system harder to implement. Other options (see (d) and (e) below) could also provide information on late Lyme disease without the need to introduce mandatory notification.

d) Include Lyme disease in clinician sentinel networks. Some primary care sentinel networks already exist in the UK, such as the Royal College of General Practitioners' Research and Surveillance Centre (Correa et al., 2016), which could in theory be utilised to collect data on Lyme disease. Sentinel networks could collect data on EM, which, as van den Wijngaard et al. (2017) suggest, might complement data on other forms of Lyme disease. Other primary care datasets, such as the Clinical Practice Research Datalink (CPRD) or The Health Improvement Network (THIN) database, might also be usable to supplement existing data. However, given the low overall incidence in England and geographical variation in rates, it is likely that many GPs encounter very few or no cases of Lyme disease. This may limit the usefulness of data from sentinel GP networks or datasets.

e) Introduce enhanced surveillance using clinician questionnaires. Questionnaires were used to collect further data on cases in conjunction with laboratory reporting in England and Wales between 1997 and 2003 (Public Health England, 2013), and are still used in Scotland. Such systems appear to attain reasonable response rates, and can give substantially more information on cases than is currently available, which could help to illuminate disease dynamics and identify hotspots. This research, for example, has relied extensively on the data from Scotland to address questions about the situation in England and Wales which would otherwise remain obscure. (This move would of course not address under-reporting in the current system, but all systems suffer from under-reporting to some degree.) However, this move would obviously require some additional resources to collect and manage data.

8. Detailed methods

8.1 Research questions

The research questions for this project were as follows:

- What is the incidence of Lyme disease in the UK, and how does this vary between areas and population groups?
- What surveillance systems and policies are in place internationally to monitor the incidence of Lyme disease?
- What is known about the completeness of prevalence data drawn from surveillance systems?

Correspondingly, this report has three sections, relating to the three phases of the project. The data for phases 1 and 3 were extracted from the overall map of Lyme disease research; detailed methods for the map as a whole are reported elsewhere. The data for phase 2 were mostly collected specifically for this project.

1. Systematic review of Lyme incidence data for the UK
2. Map of national surveillance systems and policies for Lyme in Europe and North America
3. Systematic review of comparative studies using more than one method to estimate incidence

The methods and findings for each phase are set out below.

8.2 User involvement

We worked closely with the review commissioners throughout in order to ensure that the review is closely aligned with their needs and emerging programme. In particular we sought to identify research avenues that would support and complement the evidence being assembled by NICE in 2017 to produce a guideline for Lyme disease.

We also convened a Scientific Advisory Group (AG) of UK and international academics and UK policy-makers to obtain specialist expertise and input. The AG provided advice on an as-needed basis with regard to technical issues relating to the research questions, concepts and definitions as well as strategies for dissemination and impact. Lastly, we ran a series of consultations with patient and practitioner groups to help interpret our emerging findings in relation to current UK experiences.

8.3 Study identification

As noted above, the first phase of the overarching project involved producing a systematic evidence map covering the whole range of research evidence on Lyme disease in humans. The findings of the map coding were then used to populate the subsequent, more focused systematic evidence reviews.

Full details of the methods and findings of the systematic map are available (Stokes et al., 2017). Given the broad scope of focus of the systematic map, the search strategy was sensitive, consisting in effect of a single cluster of terms for Lyme disease.

To be included in the evidence map studies had to meet the criteria set out in Table 7 below.

Table 7: Inclusion criteria for the systematic evidence map

Criterion	To be included in the map a study must:-	Rationale
Date	Be published in or after 2002.	*Guidance from members of the scientific advisory group was to focus on recent research from the last 15 years in order to reflect current experiences and practices relating to Lyme disease.*
Language	Be published in English Language.	*Since the team does not have capacity to search for and examine evidence in all languages, we will include only those available in English Language.*
Health condition	Be about Lyme disease.	*Studies may focus on more than one condition but must include at least some focus on Lyme.*
Evidence	Be an empirical research study OR systematic review.	*In addition to empirical studies, systematic reviews (i.e. reviews for which ≥ 2 databases were searched and inclusion criteria applied) will be included. Non-empirical evidence, commentary pieces, editorials and non-systematic reviews will be excluded.*
Population	Be about Lyme in humans.	*Whilst studies of Lyme in animals may provide some information with implications for human populations, the priority is to focus in on those studies directly addressing Lyme in humans.*
Focus	Not be a biomedical study focusing purely on markers or mechanisms of Lyme disease within blood samples, tissue samples, or cells.	*The aim of the evidence reviews is to understand patient and clinician experiences of Lyme, rather than the underpinning biomedical processes and causative mechanisms, in order to support DH in future policy development.*

8.4 Inclusion criteria

8.4.1 Systematic review of UK Lyme disease incidence data

For the review, we screened the records from the overall evidence map which were coded both as 'incidence or prevalence' and as 'UK' (N=17). The following criterion was used:

- Does the study report either newly collected data, or new analyses of routine data (i.e. not just the number of cases available from routine data)?

8.4.2 Map of international Lyme disease surveillance systems and policies

The map of policies included information from 34 countries in Europe (EU member states plus Norway and Switzerland) and North America (USA and Canada). We focused on these countries as they are broadly comparable to the UK in socioeconomic and policy terms, and most are known or suspected to have Lyme disease in their territory. The UK was considered as three separate systems (England and Wales, Scotland and Northern Ireland).

The methods for this phase were pragmatic and non-systematic in nature, with a focus on collating publicly available data. Thus, formal inclusion criteria were not used for this phase. Searching was conducted by focused web searches, using Google Translate where necessary. Sources of information mainly consisted of websites of relevant agencies, legal or regulatory documents on the notification of communicable diseases and surveillance reports published by national health authorities. We also scanned studies in the section on incidence and prevalence of the overall Lyme disease map to locate further information.

We aimed to include information on any governmental system or policy designed to collect information about the incidence of Lyme disease in humans. For pragmatic reasons, where the surveillance system was organised at a sub-national (e.g. state or province) level, and/or systems or policies varied between sub-national regions, we aimed to characterise the system overall at national level and note the variations, rather than characterising every sub-national system separately in detail (with the exception of the UK).

8.4.3 Systematic review of comparative studies of Lyme disease incidence

For this phase, we re-screened all the studies coded as 'incidence or prevalence' in the overall evidence map (N=187) against the following criteria:

- Does the study compare data on incidence from more than one source?
- Do the sources cover the same geographical area at the same time point?
- Do the sources use comparable disease definitions?
    - *Include* comparisons of clinically diagnosed disease with laboratory findings ordered by clinicians as part of the diagnosis process (i.e. which represent confirmation of possible or suspected clinical Lyme disease). *Exclude* comparisons of clinically diagnosed Lyme disease with population-level seropositivity (i.e. rates of positive laboratory findings across the population as a whole). *Exclude* comparisons of different stages of Lyme disease (e.g. erythema migrans and disseminated disease or hospitalisation) within a single dataset, or different methods for analysing a single dataset to estimate incidence. *Exclude* comparisons of different laboratory methodologies.

8.5 Data extraction and quality appraisal

8.5.1 Systematic review of UK Lyme disease incidence data

For the systematic review, data were extracted on the data collection methods, the context of the study, the findings on incidence, and any other analyses. We did not carry

out quality assessment as the main purpose of the literature review was to supplement what is available from routine data, that is, we did not seek to base conclusions on the literature alone.

8.5.2 Map of international Lyme disease surveillance systems and policies

The themes used for data extraction are shown in Table 8 and were based on the characteristics suggested by van den Wijngaard et al. (2017). The authors of that study described five characteristics of surveillance systems on Lyme disease:

1. Key indicators: a) the surveillance of EM and disseminated infections (selected to document different stages and manifestations of Lyme disease); b) the determination of groups of humans that are in areas susceptible to tick bites; and c) the determination of the dynamics between the infected wildlife and tick populations.
2. Reporting entity: a) GP, other physicians and laboratories; b) research groups; and c) general public.
3. Coverage, defined as comprehensive or sentinels.
4. Type of reporting, defined as mandatory or voluntary notification.
5. Surveillance administrative level, defined as national or regional.

We have changed the first characteristic to "Case definitions" and have focused on category (a) since we were interested in the general population and in Lyme disease in humans only. Furthermore, in order to document the variety of definitions used to notify Lyme disease, we have differentiated systems that assess the number of diagnosis, the number of consultations and the number of positive laboratory tests. Regarding the reporting entity, since British systems are based on laboratory reporting, we were interested in the difference between laboratory- and clinician-based systems, and therefore separated the two for data extraction. Research projects were not considered unless they were conducted by a governmental entity as part of a surveillance system. The general public was kept as a secondary reporting entity of interest. "Type of reporting" was renamed "Obligation". In addition to these five characteristics, information was collected on the bodies responsible for the systems, reports, laws and case definitions. Further information about data sources is presented in Appendix 4.

Table 8: Data extracted for the map of surveillance systems and policies

Characteristics	Definitions
Administrative level	National (same system across the country) or sub-national (the responsibility to define and implement the system lies with regional authorities)
Reporting entity	Refers to the unit responsible for reporting a positive case: • Clinician-based: the GP or clinician treating a patient with the disease is responsible for notifying the health authority. • Laboratory-based: the laboratory notifies the health authority. • Both clinician and laboratory have responsibility for notifying the health authority.

	• Other reporting entities; these were not systematically searched but noted.
Obligations	Mandatory (e.g. by law) or voluntary
Coverage	Comprehensive (covers the whole country; or region for sub-national systems) or samples in a country or region (e.g. sentinels)
Case definitions	Information that, for the system in place, describes a positive case or diagnosis of Lyme disease such that it is notifiable according to the definition of Lyme disease in the country: • Erythema migrans (EM; clinical signs only, or confirmed with a laboratory test), neuroborreliosis (NB) and other late or disseminated conditions (e.g. Lyme carditis and arthritis). In systems where case definitions include options according to the level of confidence in the diagnosis (e.g. probable, confirmed), the definition for confirmed cases was extracted. • Number of consultations (e.g. for EM or tick bites) • Positive lab tests alone
Body responsible for maintaining and reporting the data	Name in original language
Main surveillance report	Title, reference and the most recent year for which annual data is available. We focused on yearly reports on Lyme disease. If not available, yearly general surveillance reports that include data on Lyme disease, monthly reports or data portals allowing user-defined queries were used.
Surveillance laws/regulations	Name and reference to laws or regulations governing surveillance of Lyme disease

8.5.3 Systematic review of comparative studies of Lyme disease incidence

We assessed quality using a tool based on the QATSO tool developed by Wong et al. (2008), with some modifications to suit the specific purpose of this review. The full tool is set out in Appendix 5. As our overall aim was to estimate the extent of under-reporting in surveillance data, the main purpose of the tool was to establish how far the comparison reported in the study could be reliably used to do this. Where there are discrepancies between the different data sources in a study, this is likely to bias the findings and make the study less useful for answering our review question.

We extracted data on: the data sources used; the findings from the different data sources; any comparative data on demographics, seasonality and trends over time; and the study authors' conclusions or explanations of the findings. All quality assessment and data extraction were conducted by a single reviewer and checked in detail by a second reviewer. The full results are included in Appendices 6 and 7.

8.6 Synthesis methods

8.6.1 Systematic review of UK Lyme disease incidence data

For the routine data, synthesis focused on calculating incidence rates from available data, by dividing the number of cases reported by the surveillance agencies by ONS population estimates (Office for National Statistics, 2017), and presenting trends over time. For the research studies, a descriptive narrative synthesis was undertaken.

8.6.2 Map of international Lyme disease surveillance systems and policies

Data synthesis involved the collation of descriptive statistics about the most salient differences between national systems and policies and the description of a limited number of systems in greater detail to provide examples of different policies utilised internationally.

8.6.3 Systematic review of comparative studies of Lyme disease incidence

A descriptive narrative synthesis was undertaken, with studies separated into high-quality and low-quality. We calculated reporting multipliers by dividing the total number of cases in the comparison source by the number of cases reported in the surveillance source; where both 'raw' numbers and model results were presented, multipliers were calculated for both.

8.7 Quality assurance

8.7.1 Systematic review of UK Lyme disease incidence data

For the systematic review, screening was carried out by a single reviewer. All data were extracted by a single reviewer and checked in detail by a second reviewer.

8.7.2 Map of international Lyme disease surveillance systems and policies

Data for each country were extracted by one reviewer and checked in detail by a second reviewer. Disagreements were discussed and, if required, a third reviewer was consulted.

8.7.3 Systematic review of comparative studies of Lyme disease incidence

All studies were screened by two reviewers independently and differences resolved by discussion. All data were extracted by a single reviewer and checked in detail by a second.

8.8 Consultation on key findings with patient advocacy groups

In October 2017, following the completion of our analyses, we shared the key findings with eight patient stakeholder groups. The findings were presented as a series of bullet points via an online survey and stakeholder groups were invited to comment. We requested that each group provide a single collated response for their group. As one group was unable to meet this request we had a member of the research team who was not involved in writing up the consultation findings collate the response for this group. The collated responses for each group were then assessed to check whether the key findings resonated or not with patient groups' own experiences.

Prior to sharing findings, we conducted a series of face-to-face consultations with the advocacy groups in July 2017 for our review on experiences of diagnosis; for further details

on the methods for these consultations see Brunton et al. (2017). Whilst we did not directly ask participants to comment on incidence and surveillance issues during the face-to-face consultations, several participants did raise issues relating to UK incidence.

Comments relating to Lyme disease incidence and surveillance from both of these consultation exercises are reported in chapter 6.

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Appendices

Appendix 1: Example search strategy

MEDLINE (via Ovid) search strategy

1 exp Lyme Disease/ (9589)

2 (lyme or lymes or lyme's).ti,ab. (9797)

3 borreliosis.ti,ab. (3230)

4 neuroborreliosis.ti,ab. (1024)

5 (borrelia$ adj2 arthritis).ti,ab. (38)

6 (erythema adj2 migrans).ti,ab. (1471)

7 1 or 2 or 3 or 4 or 5 or 6 (12593)

8 exp Borrelia burgdorferi Group/ (6501)

9 (borrelia adj (burgdorferi or afzelii or garinii)).ti,ab. (7347)

10 (b adj (burgdorferi or afzelii or garinii)).ti,ab. (4289)

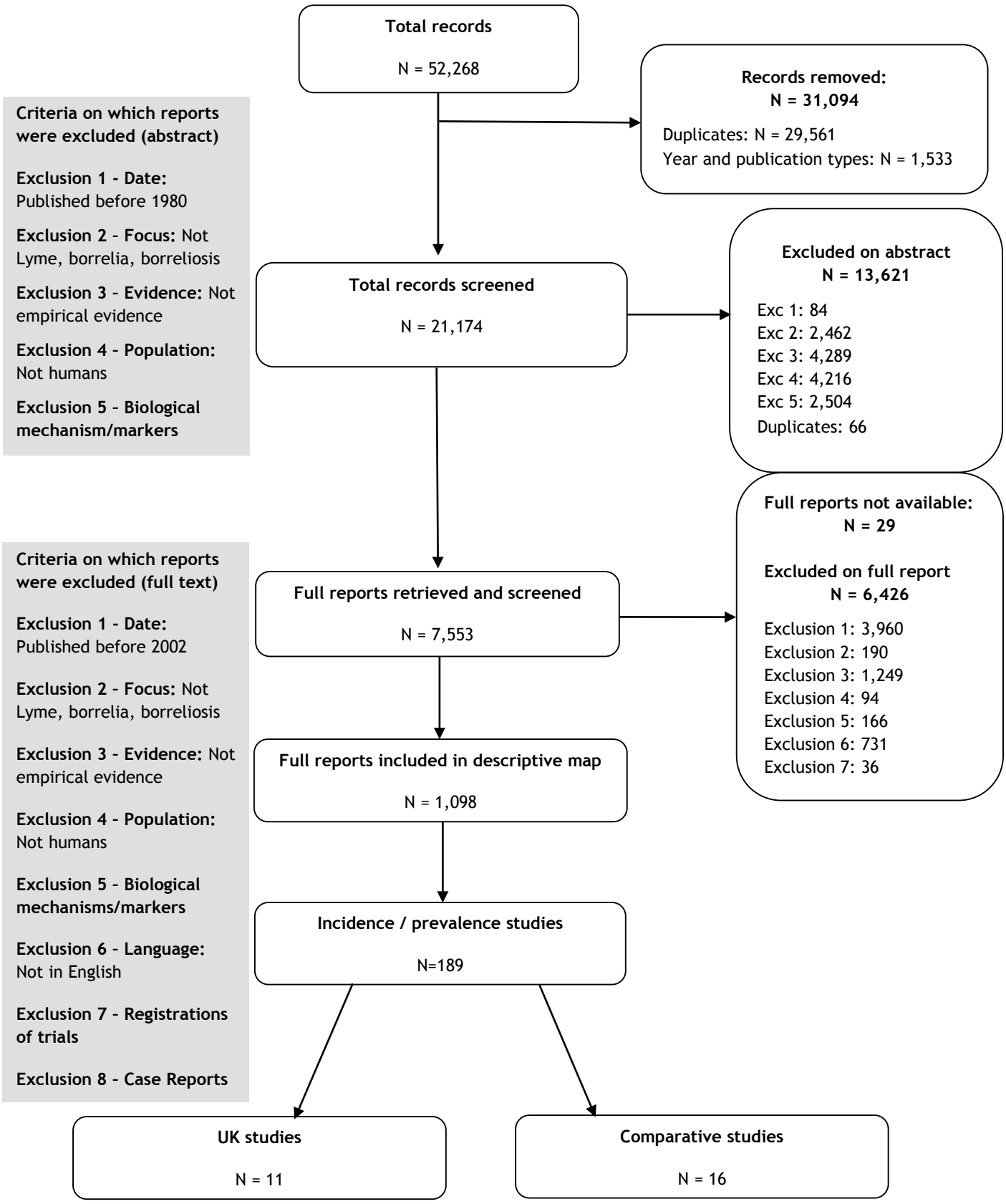
11 8 or 9 or 10 (8983)

12 7 or 11 (14245)

13 exp animals/ not humans/ (4279323)

14 12 not 13 (11450)

Appendix 2: Flow of literature through the review



Appendix 3: Further details of UK studies

Table 9: UK incidence studies based on surveillance data (N=5)

Reference	Country (area)	Data years	Dimension analysed	Findings
Ho-Yen et al. (2008)	Scotland	2004-2006	Gender	Male 55% cases ($p<0.01$)
			Age	Highest rate 60-64 years
			Disease stage	75% possible early Lyme disease 20% possible late Lyme disease 4% no data
			Area	Scotland 2.08 per 100,000 Highlands 28.0 per 100,000
Lawrence and Jones (2007)	England, Wales, NI	2002-2005	Seasonality	Third quarter 45%-70% cases
		2005	Clinical presentation	Tick bites / exposure 55% cases Erythema migrans (EM) 42% cases Neuroborreliosis 10% cases Arthritis 1% cases
		2002-2005	Travel- vs UK-acquired	Foreign travel-associated 12%-21% cases
	Scotland (Highlands)	2004-2006	Urban v rural	Urban (incl. small towns) 5.1% positive test; rural 7.1% ($p<0.0001$)

Mavin et al. (2009)				Highest rates in category 7 (remote rural areas) and category 3 (settlements of 10,000 to 125,000 people)
			Distance from woodland	Higher risk with residence near woodland (141% of general population if ≤700m, 174% if ≤200m)
Mavin et al. (2015)	Scotland	2008-2013	Gender	Male 55% cases
			Age	Highest rate 50-54 years
			Area	Ayrshire & Arran 1.9 per 100,000 annual incidence Tayside 9.2 Dumfries & Galloway 6.3 Lothian 3.3 Fife 2.1 Greater Glasgow & Clyde 4.5 Highland 44.1 Lanarkshire 1.7 Borders 3.1 Western Isles 13.8
			Clinical presentation	EM 48% cases Tick bite recalled 61% cases Joint symptoms 25% cases Neurological symptoms 15% cases Cardiac symptoms 1% cases
Milner et al. (2009)	Scotland	2007-2008	Gender	Male 53.7% cases
			Age	Highest rates 40-44 and 50-54 years

			Area	All Scotland 5.9 per 100,000 Highlands 43.4 per 100,000
			Disease stage	early Lyme disease 83.9% cases
			Clinical presentation	EM 57.1% cases Arthritis 21.7% cases Neurological symptoms 7.5% cases Cardiac symptoms 25% cases

Table 10: UK incidence studies reporting new data (N=6)

Reference	Data collected from	Case definition	Geographical area	Years	Overall incidence in study (annual, per 100,000)	Comparison incidence from routine data (annual, per 100,000)	Other findings
Dryden et al. (2015)	Hospital laboratory; programme of awareness-raising among GPs	Laboratory confirmed	Hampshire	1992-2012	9.68	1.7 (England, 2011)	508 cases over 10 years; rise to peak of 18.4 in 2009, then stabilised at ~14-16 in 2010-12 47% cases male Highest rate 50-59 years Tick bite recalled 38% cases Acquired abroad 5.1% cases

Lashley et al. (2014)	Hospital laboratory / hospital records	Laboratory confirmed / hospitalisations	Devon	2006-2011	NR	1.5 (England)	206 positive laboratory tests over study period 21 attended hospital (of whom 72% had neurological symptoms) Hospitalisations similar rate to 2000-2005
Lovett et al. (2008)	Hospital laboratory	Laboratory confirmed	Devon	2000-2004	NR	0.38-1.46 (England + Wales)	98 of 2,825 confirmed cases over study period Male 58% cases Tick bite recalled 64% cases EM 65% cases Arthralgia / myalgia 27% cases Arthritis 0% cases Carditis 0% cases
Munro et al. (2011); Munro et al. (2015)	Blood donations (random stratified sample)	Seropositivity only	Scotland	2010-2011	NR	NR	4.2% seropositive (IgG Western blot) 4.0% male, 4.4% female (ns) 3.7% urban, 5.5% rural (ns) Highest rates 36-45 years (ns) 8.6% in Inverness postcode area, 6.1% Perth, 4.8% Glasgow, 4.3% Outer Hebrides, 4.2% Paisley, 3.6% Aberdeen, 3.6% Dundee, 0 Dumfries, Falkirk, Kilmarnock, Kirkwall,

							Motherwell, Galashiels and Lerwick
Roberts and Lever (2003)	Hospital records; only travel-related cases	Clinical	Cambridge	1998-2002	NR	NR	2 cases over 5 years
Slack et al. (2011)	Hospital laboratory	Laboratory confirmed	Tayside	2001-2010 (2006-2010 for demo-graphics)	2.57 (2001-2002) 16.76 (2009-2010)	25.43 (2006-2007, Highland) 56.35 (2009-2010, Highland) 0.78 (2005-2006, Scotland) 5.53 (2009-2010, Scotland)	Male 50%-57% cases Most cases 'working age' Early Lyme disease 57%-83% cases

Appendix 4: Further details for the map of surveillance policies

Table 11: Surveillance bodies and reports

Country	Body/ies responsible for maintaining / collating surveillance data (original language)	Title of main surveillance report or data source (original language)	URL / reference for most recent report
UK - England/Wales	Public Health England	Zoonoses Report UK	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/621094/UK_Zoonoses_report_2015.pdf
UK - Scotland	Health Protection Scotland	"	"
UK - Northern Ireland	Public Health Agency Northern Ireland	"	"
Austria	None	N/A	
Belgium	Wetenschappelijk Instituut Volskgezondheid / Institut Scientifique de Santé Publique	Zoonoses et maladies à transmission vectorielle	https://epidemio.wiv-isp.be/ID/reports/Zoonoses%20et%20maladies%20%c3%a0%20transmission%20vectorielle.%20Synth%c3%a8se%20annuelle%202015.pdf
Bulgaria	Националният център по заразни и паразитни болести	N/A	http://www.ncipd.org/index.php?option=com_biuletin&view=view&month=31&year=2017&lang=en
Croatia	Službe za epidemiologiju Hrvatskog zavoda za javno zdravstvo	Zarazne bolesti u Hrvatskoj	https://www.hzjz.hr/novosti/hrvatski-zdravstveno-statisticki-ljetopis-za-2016-tablicni-podaci/
Cyprus	None	N/A	

Country	**Body/ies responsible for maintaining / collating surveillance data (original language)**	**Title of main surveillance report or data source (original language)**	**URL / reference for most recent report**
Czech Rep.	Státní zdravotní ústav	Infekce v ČR	http://www.szu.cz/publikace/data/kumulativni-nemocnost-vybranych-hlasenych-infekci-v-ceske-republice
Denmark	Statens Serum Institut	Neuroborreliose, laboratorieanmeldelsespligtige sygdomme	http://miba.ssi.dk/Home/Smitteberedskab/Sygdomsovervaagning/Sygdomsdata.aspx?sygdomskode=NEBOM&aar=2010|2017&kon=&aldersgruppe=&landsdelkode=&maaned=&xaxis=Aar&yaxis=Total&show=Table&datatype=Laboratory&extendedfilters=False#HeaderText
Estonia	Terviseamet	Nakkushaiguste esinemine, immunoprofülaktika ja järelevalve tulemused Eestis 2016. aastal	http://www.terviseamet.ee/fileadmin/dok/Nakkushaigused/statistika/2016/Epid_ulevaade_2016.pdf
Finland	Terveyden ja Hyvinvoinnin Laitos	Borrelian esiintyvyys 2016	https://www.thl.fi/fi/web/infektiotaudit/seuranta-ja-epidemiat/tartuntatautirekisteri/tartuntataudit-suomessa-vuosiraportit/tautien-esiintyvyys-2016/borrelian-esiintyvyys-2016
France	Réseau Sentinelles (partnership of Santé publique France, INSERM and universities)	Reseau sentinelle, Bilan annuel	https://websenti.u707.jussieu.fr/sentiweb/?page=bilan
Germany	Robert Koch Institut	No regular report*	N/A
Greece	None	N/A	

Country	**Body/ies responsible for maintaining / collating surveillance data (original language)**	**Title of main surveillance report or data source (original language)**	**URL / reference for most recent report**
Hungary	Állami Népegészségügyi és Tisztiorvosi Szolgálat	OEK, Bejelentett fertőző megbetegedések Magyarországon	http://www.oek.hu/oek.web?to=,2475,2465&nid=509&pid=1&lang=hun
Ireland (Rep)	Health Protection Surveillance Centre	HPSC Annual Epidemiological Report	http://www.hpsc.ie/abouthpsc/annualreports/
Italy	None	N/A	
Latvia	Slimību profilakses un kontroles centrs	Pārskats Par Atsevišķām Infekcijas Un Parazitārajām Slimībām 2016. Gadā	https://spkc.gov.lv/upload/Infekcijas_lim_statistika/Statistikas%20parskati/statistikas_parskats_par_2016_gadu.pdf
Lithuania	Užkrečiamųjų ligų ir AIDS centro	Užregistruotų susirgimų skaičius iš viso	http://www.ulac.lt/uploads/downloads/Ataskaitos/2016/forma4_pagal_16ligu_2016.pdf
Luxembourg	Direction de la Santé	Système des maladies à déclaration obligatoire: Bulletin mensuel	http://www.sante.public.lu/fr/publications/b/bulletin-maladies-transmissibles-2011-07-05/bulletin-maladies-transmissibles-2011-07-05.pdf
Malta	None	N/A	N/A
Netherlands	Rijksinstituut voor Volksgezondheid en Milieu	No regular report*	N/A
Norway	Folkehelseinstituttet	Meldingssystem for smittsomme sykdommer (web portal)	www.msis.no
Poland	Narodowy Instytut Zdrowia Publicznego – Państwowy Zakład Higieny	Choroby zakaźne i zatrucia w Polsce	http://wwwold.pzh.gov.pl/oldpage/epimeld/2016/Ch_2016.pdf

Country	**Body/ies responsible for maintaining / collating surveillance data (original language)**	**Title of main surveillance report or data source (original language)**	**URL / reference for most recent report**
Portugal	Instituto Nacional de Saúde	Doenças de Declaração Obrigatória, 2011-2014	https://www.dgs.pt/estatisticas-de-saude/estatisticas-de-saude/publicacoes/doencas-de-declaracao-obrigatoria-2011-2014-volume-i-pdf.aspx
Romania	Centrul National de Supraveghere si Control al Bolilor Transmisibile, Institutul National de Sanatate Publica	Analiza epidemiologica descriptiva a cazurilor de Boala Lyme intrate in sistemul national de supraveghere	http://cnscbt.ro/index.php/analiza-date-supraveghere/boala-lyme-1/659-boala-lyme-2016-analiza/file
Slovakia	Úrad verejného zdravotníctva Slovenskej republiky	Analýza epidemiologickej situácie a činnosti odborov epidemiológie v Slovenskej Republike	http://www.epis.sk/InformacnaCast/Publikacie/VyrocneSpravy.aspx
Slovenia	Nacionalni inštitut za javno zdravje	Epidemiološko spremljanje nalezljivih bolezni v Sloveniji	http://www.nijz.si/sites/www.nijz.si/files/datoteke/epidemiolosko_spremljanje_nb_v_letu_2015.pdf
Spain	Ministerio de Sanidad, Servicios Sociales e Igualdad	Informe anual del Sistema de Información Microbiológica 2015	http://gesdoc.isciii.es/gesdoccontroller?action=download&id=31/03/2017-766cfe4967
Sweden	None	N/A	

Country	**Body/ies responsible for maintaining / collating surveillance data (original language)**	**Title of main surveillance report or data source (original language)**	**URL / reference for most recent report**
Switzerland	Office fédéral de santé publique / Bundesamt für Gesundheit / Ufficio federale della sanità pubblica	Maladies transmises par les tiques – Situation en Suisse	https://www.bag.admin.ch/bag/fr/home/themen/mensch-gesundheit/uebertragbare-krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/zeckenuebertragene-krankheiten.html
USA	Centers for Disease Control and Prevention	Summary of Notifiable Infectious Diseases and Conditions — United States	https://www.cdc.gov/mmwr/mmwr_nd/index.html
Canada	Public Health Agency of Canada	Surveillance of Lyme disease	https://www.canada.ca/en/public-health/services/diseases/lyme-disease/surveillance-lyme-disease.html

* For countries without a regular report, the following data sources are available:
Germany (Bayern): Meldepflicht für Lyme-Borreliose in Bayern – eine erste Bilanz, in *Epidemiologisches Bulletin* 8/2015, available at: http://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2015/Ausgaben/08_15.pdf
Germany (eastern Länder): Wilking H, Stark K. Trends in surveillance data of human Lyme borreliosis from six federal states in eastern Germany, 2009–2012. *Ticks and Tick-Borne Diseases 5*(3):219-224
Netherlands: Hofhuis A et al. Decrease in tick bite consultations and stabilization of early Lyme borreliosis in the Netherlands in 2014 after 15 years of continuous increase. *BMC Public Health 16*(425).

Table 12: Laws and regulations on surveillance and case definitions

Country	Laws / regulations relating to surveillance	URL / reference	Case definition (summary)
UK - England/Wales	Health Protection (Notification) Regulations 2010	http://www.legislation.gov.uk/uksi/2010/659/contents/made	Lab test
UK - Scotland	Public Health etc. (Scotland) Act 2008	http://www.legislation.gov.uk/asp/2008/5/pdfs/asp_20080005_en.pdf	Lab test
UK - Northern Ireland	N/A	N/A	Lab test
Austria	N/A	N/A	N/A
Belgium	N/A	N/A	[For clinical system] Unclear
Bulgaria	Ordinance 21 / 18th July 2005	http://www.mh.government.bg/media/filer_public/2015/04/17/naredba-21-ot-2005g-spisak-zarazni-bolesti-red-registratsia.pdf	[Confirmed case] (EM or late manifestation) + lab test
Cyprus	N/A	N/A	N/A
Czech Rep.	Law on Epidemiological surveillance 473/2008	https://www.zakonyprolidi.cz/cs/2008-473	(EM or disseminated LD) + lab test + exposure
Croatia	Law 79/2007 on protection from infectious diseases	http://narodne-novine.nn.hr/clanci/sluzbeni/2007_07_79_2486.html	[Confirmed case] (EM or late) + lab test
Denmark	Executive Order on Medical Review of Infectious Diseases (no. 2777 of 14 April 2000)	https://www.retsinformation.dk/Forms/R0710.aspx?id=21406	[For clinical system] Neuroborreliosis + lab test

Country	**Laws / regulations relating to surveillance**	**URL / reference**	**Case definition (summary)**
Estonia	Communicable Diseases Prevention and Control Act (RT I 2003, 26, 160)	https://www.riigiteataja.ee/akt/104122015003	EM + lab test
Finland	N/A	N/A	Lab test
France	N/A	N/A	EM or (other symptoms + lab test)
Germany	Various at region (Bundesland) level; governed by 2001 Infection Protection Act	Various	EM or (neuroborreliosis + lab test) or (Lyme arthritis + lab test)
Greece	N/A	N/A	N/A
Hungary	Decree 18/1998 (VI.3) on epidemiological measures	https://net.jogtar.hu/jr/gen/hjegy_doc.cgi?docid=99800018.nm	[Confirmed case] (EM or (neuroborreliosis + tick bite)) + lab test
Ireland	Infectious Diseases (Amendment) Regulations 2016 (S.I. No. 276 of 2016)	http://www.irishstatutebook.ie/eli/2016/si/276/made/en/print	Neuroborreliosis + lab test
Italy	N/A	N/A	N/A
Latvia	Infectious diseases registration procedure 1999	https://likumi.lv/doc.php?id=20667	Unclear
Lithuania	Communicable Diseases Prevention and Control Act 1996	https://www.e-tar.lt/portal/lt/legalAct/TAR.EE245B47423C	Unclear

Country	**Laws / regulations relating to surveillance**	**URL / reference**	**Case definition (summary)**
Luxembourg	Grand-ducal ruling of 10 sept 2004 on notification of infectious diseases	http://www.securite-alimentaire.public.lu/organisme/administrations-competentes/insa/maladies_trans/reglement_grand_ducal.pdf	EM or neuroborreliosis or (late symptoms + lab test)
Malta	N/A	N/A	N/A
Netherlands	N/A	N/A	EM
Norway	2003 Regulation on Communicable Disease	https://lovdata.no/dokument/SF/forskrift/2003-06-20-740	(Disseminated or late symptoms) + lab test
Poland	Law on prevention and control of infectious diseases 2008 nr 234 poz. 1570 (5 December 2008)	http://isap.sejm.gov.pl/DetailsServlet?id=WDU20082341570	EM or (late + lab test)
Portugal	Decree no. 15385-A / 2016 on mandatory notification of diseases	https://dre.pt/home/-/dre/105574339/details/maximized?serie=II&dreId=105574337	[Confirmed case] (EM or disseminated or late) + lab test
Romania	Law 589/2007 on the reporting of communicable diseases	http://legislatie.just.ro/Public/DetaliiDocument/82975	[Confirmed case] (EM or disseminated or late) + lab test

Country	**Laws / regulations relating to surveillance**	**URL / reference**	**Case definition (summary)**
Slovakia	Act 355/2007 on protection and promotion of public health	https://www.slov-lex.sk/pravne-predpisy/SK/ZZ/2007/355/20170301	Lab test
Slovenia	Law on Infectious Diseases no.69/95	https://www.uradni-list.si/glasilo-uradni-list-rs/vsebina/72546	EM or late
Spain	Various at region (autonomous community) level	Various	Varies
Sweden	N/A	N/A	N/A
Switzerland	N/A	N/A	Unclear
USA	Various at state level	Various	[Confirmed case] (EM + exposure in high incidence area) or (EM + lab test + exposure in low incidence area) or (late + lab test)
Canada	Various at province level	Various	[Confirmed case] (any symptom + lab test [+ exposure if only serologic test])

Appendix 5: Quality assessment tool for review of comparative studies

1. Did the two data sources cover the same population?
    - Yes = 2
    - No / unclear, but the datasets are similar due to mode of collection (e.g. both derive from national statutory systems which cover the population as a whole; or overlap in populations is <100% but is measured and found to be sufficiently high) = 1
    - No / unclear = 0

2. Were the data validated or reviewed?
    - At least one source validated by study authors = 2
    - No validation by study authors, but all sources had previously been validated by data collectors (e.g. clinician follow-up) = 1
    - No / unclear = 0

3. Was the same case definition used for the different sources?
    - Yes = 2
    - No, but corroborating information was used to address the discrepancy = 1
    - No / unclear = 0

4. (If answer to 2 is (b) or (c)) Did the analysis use modelling or capture-recapture analysis to estimate the rate of under-reporting?
    - Yes / not applicable (answer to 3 is (a)) = 1
    - No / unclear = 0

5. Did the analysis report comparisons of general trends in the two sources, e.g. w.r.t. demographics, seasonality or time trends, with significance tests?
    - Yes = 1
    - No = 0

Appendix 6: Quality assessment tables for review of comparative studies

Bleyenheuft 2015	Score	Notes
1. Population	1	i) Sentinel laboratory network covering 50% of population ii) Data from every general hospital in Belgium Populations are not explicitly compared but both national statutory datasets. (Authors mention (i) is not geographically fully representative (p7).)
2. Data validation	0	
3. Case definition	0	i) Positive laboratory tests ii) Hospitalisations
4. Analysis	0	
5. Comparisons	0	Reported but sig NR
TOTAL	1	

Bochničková 2012	Score	Notes
1. Population	0	Unclear whether patients using hospital are similar to population included in surveillance data (e.g. whether they cover same geographical area, whether patients seek care at other facilities)
2. Data validation	0	
3. Case definition	0	Notifiable cases (exact case definition NR) vs hospitalisations
4. Analysis	0	
5. Comparisons	0	Reported for one source only (hospital data but not surveillance data)
TOTAL	0	

Boltri 2002	Score	Notes
1. Population	1	Questionnaire attempts to sample all family physicians in study area (Georgia state). Response rate 54.3%
2. Data validation	0	
3. Case definition	0	Case definition for questionnaire data appears to be broader as includes clinician-diagnosed cases without serologic testing
4. Analysis	0	
5. Comparisons	0	
TOTAL	1	

CDC 2008	Score	Notes
1. Population	1	Both from surveillance sources but unclear if there was divergence between populations

2. Data validation	1	Not by study authors, but cases for both sources were followed up within surveillance system
3. Case definition	2	Both used national (US pre-2008) case definition
4. Analysis	0	
5. Comparisons	1	Geography, age, season; sig tests reported
TOTAL	5	

Clayton 2015	Score	Notes
1. Population	0	Insurance dataset covers ≈50% of state population. Population divergences not discussed by study authors (e.g. uninsured people).
2. Data validation	2	Random sample of cases from insurance data source reviewed by study authors
3. Case definition	2	Not in original source, but data review carried out using surveillance case definition
4. Analysis	1	
5. Comparisons	0	Reported no sig diff by age and gender, but full data NR
TOTAL	5	

Dessau 2015	Score	Notes
1. Population	1	i) Cases reported through clinician notification ii) Cases reported through electronic laboratory reporting Not explicitly discussed, but both data sources are national statutory surveillance systems
2. Data validation	0	All reported cases considered as cases
3. Case definition	0	i) Neuroborreliosis only ii) All positive laboratory tests (AI) Appears to be divergent – authors assume all tests are for neuroborreliosis but unclear that this assumption is justified
4. Analysis	0	
5. Comparisons	1	Gender, age, geography; sig tests and 95% CIs reported
TOTAL	2	

Ertel 2012	Score	Notes
1. Population	1	i) Cases reported to surveillance system (passive) ii) Active surveillance network iii) Enhanced laboratory surveillance iv) Mandatory laboratory surveillance Not explicitly discussed, but at least (i), (iii) and (iv) are statewide statutory surveillance systems (unclear for (ii))
2. Data validation	1	Not by study authors, but cases for both sources were followed up within surveillance system
3. Case definition	2	All sources used standard (US 1996) case definition

4. Analysis	0	
5. Comparisons	1	Age, gender, ethnicity; sig tests reported
TOTAL	5	

Henry 2011	Score	Notes
1. Population	1	i) Cases reported to surveillance system ii) Laboratory tests (from sole laboratory conducting tests in state) iii) Enhanced surveillance database Not explicitly discussed, but at least (i) and (ii) are from statewide statutory systems.
2. Data validation	2	Cases from (ii) reviewed by study authors
3. Case definition	2	Consistent case definition applied to all cases as part of data validation
4. Analysis	1	Capture-recapture analysis to estimate unreported cases over and above combination of all methods
5. Comparisons	0	
TOTAL	6	

Jones 2012, 2013	Score	Notes
1. Population	0	Data from MCO covers ≈50% of state population. Divergences in population not discussed
2. Data validation	0	
3. Case definition	1	i) Surveillance data uses standard US case definition ii) MCO data uses any case with ICD-9 code and ≥3 corroborating events
4. Analysis	1	Generalized linear mixed model
5. Comparisons	0	Sig only reported for cluster analysis (in 2012 paper)
TOTAL	2	

MacDonald 2016	Score	Notes
1. Population	1	i) Cases reported to surveillance system (clinician and laboratory) ii) Medical record data (nationwide; hospitals and specialists only) Both sources are from national statutory systems, but populations not compared explicitly
2. Data validation	0	
3. Case definition	0	i) Disseminated / chronic LD (excl EM) ii) Any case with ICD-10 code Authors recognise that definitions diverge (e.g. (ii) includes EM only)

4. Analysis	0	
5. Comparisons	0	Findings on age mentioned but sig NR
TOTAL	1	

Müller 2012	Score	Notes
1. Population	0	i) Cases reported to surveillance system ii) People covered by statutory health insurance company Authors report some divergences (e.g. (ii) covers more women than men, p2) but full information NR
2. Data validation	0	
3. Case definition	1	i) Cases reported to surveillance system ii) Diagnosis code + serologic test ordered
4. Analysis	0	
5. Comparisons	0	
TOTAL	1	

Naleway 2002	Score	Notes
1. Population	1	i) Residents in 8-county area surrounding area (ii) ii) Residents in 24 zip codes around study clinic (≈95% of whom utilise the clinic)
2. Data validation	2	Data from (ii) reviewed and validated by study authors
3. Case definition	2	National case definition applied as part of data validation
4. Analysis	1	
5. Comparisons	1	Gender, age, disease stage; sig reported
TOTAL	7	

Nelson 2015	Score	Notes
1. Population	0	i) Cases reported to surveillance system ii) Insurance claims database Authors mention that (ii) only contains <65-year-olds and correct for this in analysis, but do not consider other limitations e.g. uninsured people
2. Data validation	0	
3. Case definition	1	i) All notifiable cases ii) Any diagnosis code plus (for outpatients) prescription for antimicrobial drug recommended for LD treatment (note: correction factor applied for undercoding, but this is a generic multiplier and is not based on further analysis of the data)
4. Analysis	1	Correction factor applied to estimate rates
5. Comparisons	1	Age, gender, geography; sig reported
TOTAL	3	

Robinson 2014	Score	Notes
1. Population	1	i) Cases reported to surveillance system ii) Statewide medical records database Not explicitly discussed but both systems are statewide statutory systems
2. Data validation	0	
3. Case definition	0	Clinical data includes any patient with ICD code
4. Analysis	0	
5. Comparisons	0	Authors mention sig (for time trend and gender) but full data NR
TOTAL	1	

Schiffman 2016	Score	Notes
1. Population	1	i) Cases reported in study county ii) Medical records for all acute care facilities in study county (n=51); response rate 92% Populations not explicitly compared, and unclear if county residents could seek care elsewhere, but seems sufficiently similar
2. Data validation	2	Cases reviewed by study authors
3. Case definition	2	National case definition applied as part of data validation
4. Analysis	1	
5. Comparisons	0	
TOTAL	6	

Tseng 2015	Score	Notes
1. Population	0	i) Cases reported to CDC ii) Medical insurance claims data Population divergences not discussed
2. Data validation	0	
3. Case definition	1	Cases defined for insurance data as recorded diagnosis (ICD-9) + serologic test ordered + antibiotic treatment ≥14 days
4. Analysis	0	
5. Comparisons	0	Only time trends; sig NR
TOTAL	1	

Appendix 7: Evidence tables for review of comparative studies

First author, year	Bleyenheuft 2015
Country (location)	Belgium
Years for which comparison reported	2003-2010
First data source (use surveillance source if appl.)	Positive tests from voluntary sentinel laboratory network co-ordinated by Institute of Public Health (WIV-ISP)
N of cases from first source	N=1,200.5 per year (median)
Incidence rate per 100,000 per year from first source	NR for whole sample; three highest-incidence provinces had cumulative incidence rates over whole study period (8 years) of 508.5, 301.2 and 172.0 per 100,000 (but other provinces appear to be much lower)
Further info re first source	"The laboratories participate in this network on a voluntary basis. The absolute number of participating laboratories decreased over time due to fusions between laboratories, but the proportion of tests covered by the network remained globally stable. The network covers around 50 % of all laboratory tests carried out in Belgium." Data to 2008 represent ELISA results, post-2008 only positive immunoblot assays are reported.
Comparison data source	Hospital episode data (Belgian Ministry of Health)
N of cases from comparison source	N=1,132.5 per year (median)
Incidence rate per 100,000 per year from comparison source	NR for whole sample; three highest-incidence provinces had cumulative incidence rates over whole study period (8 years) rates of 228.8, 221.1 and 153.5 per 100,000 based on 2010 population figures (but other provinces appear to be much lower).
Further info re comparison source	"[T]he Belgian Ministry of Health (federal public service Health, Food chain safety and Environment) collects compulsorily registered data (registration of minimal clinical data, RMC) from every general hospital in Belgium. For each patient discharged, the physician has to fill in a standardized form summarizing medical records, and specifying all diagnosis. Data are then encoded following the International Classification of Diseases (ICD-9).... At the time of this study, data were available until 2010. We therefore used RMC data (for all hospitalization wards) from 2003 to 2010, with Lyme borreliosis as principal and secondary diagnosis."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A

Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	Mostly similar with respect to (wrt) region with some discrepancies. Males 58% of hospital data, 52% of laboratory data; age similar in both sources (peaks at 5-9/14 and 45/50-69) (sig NR).
Findings on time trends / seasonality	Similar wrt seasonality (sig NR; interquartile ranges reported). Time trends broadly stable over study period; hospital data peak in 2006-7 and laboratory data in 2004-5 (sig reported for trends within sources, but not for comparison).
Any other findings / analyses	NR
Authors' conclusions / explanations	"Both data sources converge to the same result". Recorded rates may depend on systems / policies (e.g. regarding reimbursement). Hospital data is in principle comprehensive; includes secondary diagnoses. Laboratory data is incomplete and coverage varies by region. Neither source includes early manifestations e.g. EM.
Reviewer notes	Neither data source validated. Data sources not comparable wrt absolute numbers.

First author, year	Bochničková 2012
Country (location)	Slovakia (Liptovský Mikuláš and Ružomberok districts)
Years for which comparison reported	1989-2010
First data source (use surveillance source if appl.)	Cases reported to regional Public Health Office in Liptovský Mikuláš and Ružomberok districts
N of cases from first source	221
Incidence rate per 100,000 per year from first source	7.5
Further info re first source	NR
Comparison data source	Medical records from Infectious Department of The Central Military Hospital in Ružomberok, Department of Infectology at the hospital in Liptovský Mikuláš, and Infectology Clinic in Liptovský Mikuláš
N of cases from comparison source	476
Incidence rate per 100,000 per year from comparison source	16.24

Further info re comparison source	"The diagnosis of Lyme borreliosis was established on the basis of the comprehensive assessment of epidemiological history, clinical symptoms of disease, and serological tests for antibodies against antigen Borrelia burgdorferi by using the immunofluorescent method (1989-2005) and later by using the method ELISA." But unclear if this is a general description of practice, or a consistent case definition.
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	NR (reported for hospital data but not surveillance data)
Findings on time trends / seasonality	NR (reported for hospital data but not surveillance data)
Any other findings / analyses	NR
Authors' conclusions / explanations	"The real incidence of disease (all diagnosed cases) is two times higher than the number of reported cases." No further information relevant to data comparison.
Reviewer notes	Neither data source validated. No information re surveillance system. Data sources not directly comparable wrt absolute numbers (and unclear if population coverage was exactly the same, i.e. who used hospitals which provided data).

First author, year	Boltri 2002
Country (location)	USA (Georgia)
Years for which comparison reported	Dec 1999 – Dec 2000
First data source (use surveillance source if appl.)	Cases reported to Georgia Division of Public Health
N of cases from first source	6
Incidence rate per 100,000 per year from first source	NR
Further info re first source	"Lyme disease was designated a reportable disease in 1991 … Current CDC reporting guidelines define confirmed Lyme disease as 'either: (a) physician-diagnosed erythema migrans ≥5 cm in diameter or (b) at least one disseminated manifestation (e.g., musculoskeletal, neurologic, or cardiac) plus laboratory confirmation of

	infection.' … In Georgia, confirmed surveillance case definition of Lyme disease requires laboratory confirmation for all cases."
Comparison data source	Survey of family physicians
N of cases from comparison source	927 suspected, of which 316 treated without firm diagnosis; 262 diagnosed, of which 132 confirmed by serologic test. Authors regard all cases treated and/or diagnosed as cases, for a total of 578.
Incidence rate per 100,000 per year from comparison source	NR
Further info re comparison source	"A confidential survey was developed to determine the frequency and distribution of Lyme disease cases suspected, diagnosed, and treated by Family Physicians in Georgia during the twelve month period beginning December 1999. The survey also included questions about the criteria used to establish a diagnosis of Lyme disease. The survey did not inquire about the specific type of serologic testing utilized for diagnosis. Prior to the administration of the final survey instrument to the target physicians, a preliminary survey instrument was administered to physicians within our department. The survey instrument was refined and administered to a second group of 20 physicians from across Georgia. After a final revision, the survey was re-administered to another 20 physicians for validation. The survey was mailed to 1,331 family physicians in Georgia in late November 2000. The mailing list was comprised of the active membership of the Georgia Academy of Family Physicians, as provided by the Academy." Response rate 54.3%
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	NR
Findings on time trends / seasonality	NR
Any other findings / analyses	NR
Authors' conclusions / explanations	Probable response bias in survey and other clinician specialities not included, so rate could be underestimated. Many cases from clinician questionnaire

	likely to not be LD, either misdiagnosed southern tick-associated rash illness based on EM, diagnoses based on musculoskeletal symptoms alone, or based on unreliable one-step serologic tests. "Because the Georgia reporting requirements were more stringent than the CDC guidelines, the reported rate of Lyme disease in Georgia during this study period was most likely inaccurately low."
Reviewer notes	Neither data source validated. No further information on surveillance data.

First author, year	Centers for Disease Control and Prevention 2008
Country (location)	USA (New Jersey)
Years for which comparison reported	2001-2006
First data source (use surveillance source if appl.)	Cases reported through electronic laboratory reporting to New Jersey Communicable Disease Reporting and Surveillance System (NJCDRSS)
N of cases from first source	3,609 (confirmed); total reported cases ranged from 1,142 to 6,799 annually
Incidence rate per 100,000 per year from first source	38.6 (2005)
Further info re first source	"Since 1980, New Jersey has mandated that health-care providers and clinical laboratories report all LD cases to local health departments, which investigate these reports to confirm that they meet the national surveillance case definition. … reports from laboratories do not contain exposure and clinical information, and local health departments must follow up with health-care providers to obtain the missing information needed to confirm a case for surveillance purposes. In 2002, New Jersey expanded its paper-based laboratory reporting system to include electronic laboratory-reporting (ELR) for all laboratory-reportable diseases."
Comparison data source	Cases reported through other means (i.e. both paper-based laboratory reports and clinician diagnoses) to NJCDRSS.
N of cases from comparison source	9,958 (confirmed)
Incidence rate per 100,000 per year from comparison source	NR
Further info re comparison source	"Since 1980, New Jersey has mandated that health-care providers and clinical laboratories report all LD cases to local health departments, which investigate these reports to confirm that they meet the national surveillance case definition. Reports from health-care providers typically

	include exposure and clinical information needed for case confirmation."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	Non-ELR cases more likely to be in northern NJ (higher-prevalence region) ($p<0.05$). No difference by age
Findings on time trends / seasonality	Non-ELR cases more likely to be in April-September ($p<0.05$)
Any other findings / analyses	A lower proportion of ELR reports were confirmed ("ELR reports accounted for 31%-71% of total annual reports but only 5%-33% of confirmed cases per year"), representing a substantial volume of staff time in following up cases.
Authors' conclusions / explanations	Data reflect pre-2008 US case definitions which did not distinguish confirmed, probable and suspect cases; system has now changed so that not all laboratory reports are followed up. Increased reporting in ELR system "likely reflected technological improvements in data acquisition and not an actual increase in the number of laboratory reports received." Seasonal difference probably reflects clinician diagnosis of early LD without serologic testing. "Laboratory reports are useful to identify LD cases that otherwise might not have been reported by health-care providers and are an important component of LD surveillance in New Jersey." Study did not examine test accuracy or clinicians' willingness to report cases. Non-ELR category conflates both laboratory and clinician reports, so comparison of electronic and paper-based laboratory reports was not possible.
Reviewer notes	Study compares two sources within a single system and main purpose is to audit the system as a whole. Some unclarities about the relation of the two procedures (e.g. there is presumably considerable overlap, but this is not analysed). Because study does not investigate test accuracy, unclear what accounts for the high rate of laboratory reports which are subsequently not confirmed.

First author, year	Clayton 2015
Country (location)	USA (Tennessee)
Years for which comparison reported	Jan 2011 – Jun 2013

First data source (use surveillance source if appl.)	Cases reported to Tennessee Department of Health
N of cases from first source	74 (9 confirmed, 65 probable)
Incidence rate per 100,000 per year from first source	NR
Further info re first source	"TDH cases met the national surveillance case definition for Lyme disease (2), consisting of the following criteria: clinical (erythema migrans [EM] rash or late manifestation of disease), laboratory (positive results by immunoassay followed by positive western blot results), and exposure and endemicity (possible exposure to infected ticks <30 days before rash onset). A person with physician-diagnosed disease who met laboratory criteria was considered to have a probable case. A person with a confirmed case had an EM rash and either met laboratory criteria, had possible exposure to ticks, or had a late manifestation of disease and positive laboratory results."
Comparison data source	Insurance claims data from Blue Cross Blue Shield of Tennessee (BCBST)
N of cases from comparison source	1,367 with any code; 391 with ≥3 codes, of which 5 were reported to TDH and 386 were not; of the latter 106 records were reviewed, of which 4 met the surveillance case definition (2 confirmed, 2 probable) and 102 did not. Authors estimate that insurance data represents approximately a further 14 cases which are not recorded in the surveillance data.
Incidence rate per 100,000 per year from comparison source	NR
Further info re comparison source	"BCBST is a health insurance provider covering ≈50% of Tennessee's population. … We defined Lyme disease diagnosis for a BCBST-insured person as assignment of >3 primary or secondary codes for Lyme disease (088.81, International Classification of Diseases, Ninth Revision [ICD-9]), recorded in the claims data."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	No differences by age and sex, similar by location (full data and sig NR)

Findings on time trends / seasonality	NR
Any other findings / analyses	Diagnoses not meeting case definitions "were made by a limited number of clinicians". Many of the excluded reports had history of LD (i.e. were not incident cases).
Authors' conclusions / explanations	"By supplementing passive surveillance with BCBST claims data, we identified 20% more Lyme disease cases than were reported to TDH." Most people with diagnosis in insurance dataset did not meet case definitions; using these data for surveillance purposes "would be unsustainable".
Reviewer notes	None

First author, year	Dessau 2015
Country (location)	Denmark
Years for which comparison reported	Jan 2010 – Dec 2012
First data source (use surveillance source if appl.)	Cases reported to statutory Danish notification system for infectious diseases (DNSID)
N of cases from first source	217
Incidence rate per 100,000 per year from first source	1.3
Further info re first source	"The current statutory Danish notification system for infectious diseases (DNSID) is based on collection of paper forms completed by the physician treating the patient; the forms are sent by mail to the Department of Infectious Disease Epidemiology at SSI and the Regional Medical Officer of Health. SSI sends reminders to the clinicians if intrathecal antibody production has been detected by the SSI laboratory and no notification has been received within a certain timeframe. From 2011 to 2012, 44% of the notifications was received only after a reminder had been sent. Due to increased testing at the regional microbiological laboratories, SSI is responsible for a decreasing fraction of the AI tests in Denmark … Both confirmed and probable cases … were included in the DNSID dataset extracted for the present study, as both, so far, have been included in the national surveillance." Statutory system only covers Lyme neuroborreliosis and not other late manifestations (or early LD, although this is not explicitly stated).
Comparison data source	Electronic laboratory reports from Danish microbiology database (MiBa)
N of cases from comparison source	533

Incidence rate per 100,000 per year from comparison source	3.2
Further info re comparison source	"MiBa receives real-time electronic copies of all reports from all Danish departments of clinical microbiology. … Within MiBa local codes are automatically mapped to national shared codes before data extraction. … In Denmark a total 11 laboratories performed AI tests. At the time of the study, nine of these reported to MiBa through their microbiology laboratory information systems [and two did not] … To obtain complete nationwide data, data on AI test results were acquired directly from the two latter laboratories and merged with the MiBa data." Data were deduplicated where patients had >1 test in the study period. "For this study, with the purpose of surveillance, the conclusion by the laboratory in the report was considered valid regardless of the type of assay and method of index calculation. All laboratories except one used an assay based on native purified flagella antigen."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	DSNID cases significantly more likely to be children (0-15 years; 29% vs 19%). Gender no sig diff. Significantly more DSNID cases in Capital and Northern Jutland regions, fewer in other regions.
Findings on time trends / seasonality	Time trends appear broadly similar
Any other findings / analyses	N=182 cases were in both datasets; of those in DSNID but not MiBa, 29 tested negative and 6 were not tested. Median time lag from sampling date to data availability was 58 days for DSNID and 5 days for MiBa.
Authors' conclusions / explanations	"The present study demonstrated underreporting as only 34% of the 533 AI positive LNB were notified. This probably reflects both the workload associated with filling in and sending paper forms and uncertainty on whether LNB is notifiable or not." Danish clinical guideline recommends lumbar puncture with leucocytosis for diagnosis of Lyme neuroborreliosis, but these data were unavailable. Some positive tests may thus represent earlier infections rather than active LD (authors estimate

	≈6%). Notification system includes probable cases as well as laboratory-confirmed. MiBa data was not fully complete for study period. Electronic laboratory reporting is more efficient in terms of clinician and laboratory staff time. A large number of LD tests were carried out (N=13,923 over study period) and 96% were negative. Tests were more commonly conducted for the 30-79 age groups, but positive tests were more common for children and older ages (55-79).
Reviewer notes	Neither data source validated (although appears that laboratory tests were reliable). Authors assume that all positive laboratory tests represent LNB (and e.g. tests are not being ordered for early LD); this assumption is discussed but arguably not fully justified.

First author, year	Ertel 2012
Country (location)	USA (Connecticut)
Years for which comparison reported	1996-2007 (for clinician sources)
First data source (use surveillance source if appl.)	Cases reported through passive surveillance to Connecticut Department of Public Health
N of cases from first source	12,185 cases (19,350 total reports) in addition to cases identified through active surveillance
Incidence rate per 100,000 per year from first source	NR
Further info re first source	For all data sources: "Lyme disease reports were categorized by using the national surveillance case definition issued in 1996 (6). A case was defined as 1) physician report of erythema migrans of >5 cm in diameter or 2) at least 1 objective late manifestation (i.e., musculoskeletal, neurologic, or cardiovascular) with laboratory confirmation of infection with B. burgdorferi by enzyme immunoassay, immunofluorescent assay, or Western immunoblot. CDPH classified reports that did not meet the case definition as not a case. Because clinical information is required for case classification, when supplemental follow-up reports were not returned, they were considered lost to follow-up."
Comparison data source	Active clinician surveillance system
N of cases from comparison source	8,666 (13,040 total reports)
Incidence rate per 100,000 per year from comparison source	NR
Further info re comparison source	"Active surveillance comprised a voluntary network of health care providers who reported cases 1× per month"; no further information

Second comparison data source (if appl.)	Enhanced laboratory surveillance (1996-1997) and mandatory laboratory surveillance (1998-2002 and 2007)
N of cases from second comparison source	Enhanced 1,949 cases (3,739 total reports) in addition to clinician reported cases; mandatory 10,657 cases (43,767 total reports) in addition to clinician reported cases
Incidence rate per 100,000 per year from second comparison source	NR
Further info re second comparison source	"Enhanced laboratory surveillance, conducted during 1996-1997, required participating Connecticut laboratories to send supplemental case report forms with each positive B. burgdorferi result to the ordering physician. In January 1998, to study the effectiveness of a newly released Lyme disease vaccine, mandatory laboratory surveillance was implemented that required all laboratories to report positive and equivocal results to CDPH. Follow-up, conducted by CDPH staff, involved sending a letter and supplemental report form to the ordering physician. To assist the physician, demographic and patient-identifying information from the laboratory report was incorporated into the form. Mandatory laboratory surveillance ended after 2002 when the Lyme disease vaccine was removed from the market. In 2007, mandatory reporting of positive Lyme disease results was reinstated for laboratories with electronic reporting capability. Two large commercial laboratories provided electronic reports. Follow-up was reestablished by using the previous method, i.e., CDPH staff sent a letter and supplemental report form to the ordering physician."
Findings on demographics	Clinician-reported cases more likely to be younger ($p<0.001$); no sig diff by gender or ethnicity
Findings on time trends / seasonality	Time trends and seasonality broadly similar
Any other findings / analyses	Cases with EM only more likely to be reported by clinicians ($p<0.001$), late manifestations by laboratories ($p<0.001$). More cases (mean 16.0% more) were reported by clinicians in years with mandatory laboratory reporting. Percentage of confirmed cases was much higher for clinician reporting than for mandatory laboratory reporting where it was <25%.
Authors' conclusions / explanations	Changes over time more likely to due to changes in surveillance methods than underlying disease rate. Increase in clinician-reported cases in years with mandatory laboratory reporting suggests that follow-up for laboratory surveillance helps to reduce clinician under-reporting. Combination of methods performed substantially better wrt identifying cases than either on

	its own. "Of all reported cases, nearly one third (31.9%) originated through laboratory-based surveillance. However, use of laboratory-based surveillance is inefficient: only 24.3% were classified as cases." Clinicians participating in active surveillance probably more likely to report cases in the passive system. Intensive surveillance in endemic regions may not be best use of resources.
Reviewer notes	Limited information on either the active or passive clinician surveillance systems

First author, year	Henry 2011
Country (location)	Canada (British Columbia)
Years for which comparison reported	Jan 1997 – Dec 2008
First data source (use surveillance source if appl.)	Cases reported to surveillance system (Integrated Public Health Information System)
N of cases from first source	64 confirmed (66 total cases)
Incidence rate per 100,000 per year from first source	NR
Further info re first source	"Both clinical (physician-diagnosed erythema migrans with or without laboratory confirmation) and laboratory-confirmed cases of LD have been reportable to public health authorities in BC since 1994." No further information
Comparison data source	Laboratory test results (from sole site where tests conducted)
N of cases from comparison source	74 confirmed (1,144 total tests)
Incidence rate per 100,000 per year from comparison source	NR
Further info re comparison source	"We reviewed the provincial Laboratory database to identify all individuals with a positive enzyme immunoassay (EIA) test for B. burgdorferi antibodies and subsequent confirmatory Western blot (WB) testing. … Standard diagnostic criteria set out by the Canadian Public Health Agency (Canadian Public Health Laboratory Network 2007) were then applied … resulting in the exclusion of individuals without (1) an appropriate clinical diagnosis (e.g., erythema migrans) or (2) positive two-step serological testing including a positive EIA and confirmatory positive WB test."
Second comparison data source (if appl.)	Enhanced surveillance database
N of cases from second comparison source	48 confirmed (51 total cases)

Incidence rate per 100,000 per year from second comparison source	NR
Further info re second comparison source	"[A] repository of detailed epidemiological information (e.g., exposure location) captured during public health interviews of probable or confirmed cases"; no further information
Findings on demographics	NR
Findings on time trends / seasonality	NR
Any other findings / analyses	Total of N=93 cases after deduplication between 3 sources. Authors use capture-recapture methodology to estimate the true rate and arrive at an estimate of N=142 (95% CI 111-224) in the best-fitting model (although this seems to be an outlier relative to other models which give substantially lower numbers, between N=95 and N=111), leading them to estimate that the system as a whole (i.e. all 3 sources combined) under-reports cases by approximately 40%. Total of N=27 cases not in the surveillance database but in one of the other sources (i.e. surveillance database found N=66 of N=93)
Authors' conclusions / explanations	Low sample size means estimate of under-reporting should be interpreted with caution. Unclear whether unreported cases are treated without testing or never diagnosed. A large number of people were tested for LD and received negative confirmatory (Western blot) tests.
Reviewer notes	Limited information on surveillance system or enhanced system.

First author, year	Jones 2012, Jones 2013
Country (location)	USA (Tennessee)
Years for which comparison reported	2000-2009
First data source (use surveillance source if appl.)	Cases reported to Tennessee Department of Health Center for Environmental and Communicable Diseases
N of cases from first source	292
Incidence rate per 100,000 per year from first source	0.49 (estimated from generalized linear mixed model)
Further info re first source	Analysis includes 'confirmed' and 'probable' cases according to CDC definitions
Comparison data source	Administrative records from managed care organisation (MCO), BlueCross BlueShield of Tennessee
N of cases from comparison source	903

Incidence rate per 100,000 per year from comparison source	3.8 (estimated from generalized linear mixed model)
Further info re comparison source	"The participating MCO insures approximately 50% of the entire state's population. For the purposes of this study, cases are defined as all medical claims filed to the MCO having a primary or secondary arthropod-borne disease diagnosis code of interest [ICD-9] with at least three separate corroborating events, using the member's first recorded occurrence." Only first diagnosis for each individual patient retained in analysis.
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	"Significant spatial variation," not defined further
Findings on time trends / seasonality	Some discrepancies over time (MCO data peaks in 2000, 2002, 2008 and these are not visible in surveillance data).
Any other findings / analyses	NR
Authors' conclusions / explanations	Incidence estimated from MCO data 7.7 times higher than reported rate. Study did not analyse how many cases appeared in both data sources. MCO data does not distinguish confirmed and probable cases (although not all reported cases are necessarily laboratory confirmed, as per CDC guidelines). Reported data may be subject to both under- and over-reporting. Claims data were not validated and could be mis-coded in some cases. Analysis of spatio-temporal clusters showed 2 clusters in the surveillance data and 1 in the MCO data which did not overlap.
Reviewer notes	Neither data source validated (authors argue that MCO data should reflect only confirmed cases since clinicians would not code with specific ICD codes without laboratory confirmation).

First author, year	MacDonald 2016
Country (location)	Norway
Years for which comparison reported	Jan 2008 – Dec 2012

First data source (use surveillance source if appl.)	Cases reported to MSIS system (Norwegian Institute of Public Health) by both clinicians and laboratories
N of cases from first source	1,410
Incidence rate per 100,000 per year from first source	NR
Further info re first source	Mandatory clinician and laboratory notification. "Group A diseases, which includes LB, are notifiable to the Department of Infectious Disease Surveillance at the NIPH by clinicians and medical microbiological laboratories with complete patient information. … Since 1991, LB has been nominally notifiable. … only disseminated and chronic manifestations [are] notifiable (specifically excluding cases with only erythema migrans)."
Comparison data source	Medical record data from Norwegian Patient Registry
N of cases from comparison source	5,596 coded as LD (and an additional 7,430 with related codes which authors define as 'possible' LD)
Incidence rate per 100,000 per year from comparison source	NR
Further info re comparison source	"NPR is administered by the Norwegian Directorate of Health and contains information on all referrals or treatments of patients to tertiary care facilities and specialists only. The diagnosis registered in NPR is based on ICD-10 codes." Study reports on both cases coded as LD (A69.2 or M01.2) and also on 'possible' cases coded with a wide range of other symptoms.
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	Cases in both sources more likely to be <19 years than those in only one source (sig NR).
Findings on time trends / seasonality	NR
Any other findings / analyses	N=1,047 cases were in both data sets. Cases in both sets more likely to be registered as neuroborreliosis than those in MSIS only.
Authors' conclusions / explanations	ICD codes in NPR data may not reflect final diagnosis. Diagnosis by ICD code includes EM only, which is not notifiable (but source included hospitals and specialists only so unlikely that many had EM only). NPR data may be

	miscoded and cannot be directly compared to surveillance data. Variability between laboratory case definitions affects MSIS data. Results might support case for changing notification criteria e.g. including only neuroborreliosis.
Reviewer notes	Neither data source validated. Definition of 'possible' cases is very broad, although these are reported separately and can be ignored.

First author, year	Müller 2012
Country (location)	Germany (six eastern *Länder*: Berlin, Brandenburg, Mecklenburg-Vorpommern, Saxony, Saxony-Anhalt, Thuringia)
Years for which comparison reported	2007-2008
First data source (use surveillance source if appl.)	Cases reported to surveillance system (Robert Koch Institute)
N of cases from first source	5,624
Incidence rate per 100,000 per year from first source	34
Further info re first source	Mandatory reporting; no further information
Comparison data source	Health insurance records (Deutsche Angestellten-Krankenkasse)
N of cases from comparison source	31,483 incident diagnoses
Incidence rate per 100,000 per year from comparison source	261
Further info re comparison source	"The basic dataset consists of health insurance data from a German statutory health insurance company (Deutsche Angestellten-Krankenkasse, DAK) which covers approx. 6.04 million individuals all over Germany. In a first step, relevant international classification of diseases (ICD 10-GM, 2004) diagnoses for Lyme borreliosis were defined as follows: ICD A69.2 for Lyme-specific erythema chronicum migrans, GO1∗ for LB-related meningitis, G63.0 for LB-related polyneuropathy, and M01.2 for LB-related Arthritis. Claims' data of the years 2007 and 2008 were derived from the underlying datasets (patient data, ambulatory treatment data, and medication data)… Individuals insured at least since January 1, 2006, or January 1, 2007, respectively, in whom at least one laboratory diagnostic procedure performed for LB in either year 2007 or 2008, were included in our analyses. The diagnostic procedures according to the general laboratory health insurance claim code … included laboratory claim numbers 32586 (B. burgdorferi antibody/ enzyme-linked

	immune assay, ELISA), 32662 (B. burgdorferi antibody/ western blot), and/or 32743 (culture of B. burgdorferi). Individuals already having a coded diagnosis of Lyme borreliosis in 2006 were excluded from the analysis."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	NR
Findings on time trends / seasonality	NR
Any other findings / analyses	NR
Authors' conclusions / explanations	Comparison "strongly suggests significant underreporting". Possible misdiagnosis and/or miscoding.
Reviewer notes	Neither data source validated. Limited info on surveillance data (comparison of prevalence data not main purpose of study). Definition of LD in insurance data wrt ICD codes is fairly generous.

First author, year	Naleway 2002
Country (location)	USA (Wisconsin)
Years for which comparison reported	1992-1998
First data source (use surveillance source if appl.)	Cases reported to Wisconsin Division of Public Health in 8 counties surrounding area covered by comparison source
N of cases from first source	375
Incidence rate per 100,000 per year from first source	17.0
Further info re first source	"Lyme disease has been a reportable disease in Wisconsin since 1980. Written case report forms, including information about patient demographics (name, race, gender, and date of birth), dates of onset and diagnosis, and clinical and laboratory information pertinent to the national Lyme disease case criteria, are completed by health care providers and mailed to local county health departments. These reports are then forwarded to the Wisconsin Division of Public Health where each form is reviewed, and those patients that have been determined to meet the national case criteria based on the

	information provided by the reporting form are included in the state database."
Comparison data source	Medical records from Marshfield Epidemiologic Study Area, covering residents receiving care at Marshfield Clinic
N of cases from comparison source	189 (102 probable, 87 possible)
Incidence rate per 100,000 per year from comparison source	19.1
Further info re comparison source	"The Marshfield Epidemiologic Study Area was established in 1991 to facilitate population-based research using the integrated health care network of the Marshfield Clinic. … Data pertaining to MESA residents are extracted on a daily basis from the administrative and clinical files of the Marshfield Clinic computer systems to track when persons enter and leave the selected population as a result of birth, death, or migration. … Computerized International Classification of Diseases, Ninth Revision, codes from the Marshfield Clinic database were used to identify potential cases of Lyme disease that occurred in 1992–1998 in the MESA population. The specific codes identified were codes 088.81, 695.90, and 066.90. The Marshfield Clinic laboratory database was also searched for positive Lyme serologic tests (indirect fluorescent antibody or enzyme immunoassay, with or without Western immunoblot) to identify potential cases. Persons with a history of Lyme disease diagnosis prior to 1992 were excluded from study. To validate these diagnostic codes and laboratory results, we abstracted data from patients' medical records. Potential cases were grouped into three categories (probable cases, possible cases, and noncases) based on the chart abstraction findings. Probable Lyme disease cases were defined as those patients who met the national case definition The criteria for a probable case included physician-diagnosed erythema migrans of ≥5 cm in diameter or at least one late, noncutaneous manifestation with laboratory confirmation of infection. … Possible cases included patients with erythema migrans but no documented size information and patients with positive serology and recurrent joint pain or neurologic symptoms that did not meet the criteria for a probable case."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A

Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	No sig diff by gender or age
Findings on time trends / seasonality	Broadly similar time trends
Any other findings / analyses	N=52 of 189 cases in medical record data had been reported (along with 23 classified as noncases in medical record data); comparisons are based on this subset. Reported cases less likely to be early LD (sig NR). Many cases identified as potential LD from records were excluded as they did not meet the case definitions (n=354 of 543).
Authors' conclusions / explanations	"In this study, approximately one third of probable Lyme disease cases were captured by the state surveillance system … despite a degree of both underreporting and overreporting, the surveillance data provide a reasonable surrogate for characterizing the age, gender, and temporal distribution of Lyme disease cases detected in a general population." Some residents in 8-county area were not in medical records sample and there may be differences which bias the analysis.
Reviewer notes	None

First author, year	Nelson 2015
Country (location)	USA
Years for which comparison reported	2005-2010
First data source (use surveillance source if appl.)	Cases reported to CDC
N of cases from first source	NR
Incidence rate per 100,000 per year from first source	9.4
Further info re first source	"State and local health officials report LD cases to the Centers for Disease Control and Prevention (CDC) through the National Notifiable Diseases Surveillance System according to standardized case definitions. For comparison with MarketScan findings, we analyzed surveillance cases reported during 2005–2010. Cases reported during 2005–2007 reflected a surveillance case definition comprising confirmed cases only. Beginning in 2008, a revised case definition was in place that altered the laboratory criteria and distinguished between confirmed and probable cases;

	cases reported during 2008–2010 included both categories."
Comparison data source	Nationwide insurance claims database (Truven Health MarketScan Commercial Claims and Encounters Database)
N of cases from comparison source	45,430 (clinician-diagnosed events); 329,000 (95% credible interval 296,000–376,000) (estimated with correction for under-coding)
Incidence rate per 100,000 per year from comparison source	44.8 (actual coded events); 106.6 (estimated with correction for under-coding)
Further info re comparison source	"During 2013–2014, we retrospectively analyzed the 2005–2010 Truven Health MarketScan Commercial Claims and Encounters Database, which contains health insurance claims information for a median of 27 million persons each year. The database contains records for persons 0–64 years of age with employer-provided health insurance and includes information about employees and their spouses and dependents from all 50 states. … Each patient encounter record is assigned >1 diagnostic code from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), by a clinician or billing specialist. Inpatient admissions in the database include 1 principal diagnosis and up to 14 secondary diagnoses. Outpatient encounters include up to 4 associated ICD-9-CM codes but do not distinguish between principal and secondary diagnoses. … The study population comprised persons enrolled in a participating health plan for the entirety of any year during 2005–2010 and for whom prescription drug information was available. For this analysis, we defined an inpatient event as a hospital admission with the ICD-9-CM code for LD (088.81) as the principal diagnosis or the 088.81 code as a secondary diagnosis plus a principal diagnosis consistent with an established manifestation of LD or plausible co-infection … We defined an outpatient event as any outpatient or emergency department visit with the 088.81 code plus a prescription filled for an antimicrobial drug recommended by the Infectious Diseases Society of America for LD treatment. … To estimate the total number of patients with clinician-diagnosed LD in the United States, we calculated age- and county-specific rates derived from the MarketScan database and applied them to the 2010 population of each corresponding county. Counts for all US counties were then summed. Because the MarketScan database is limited to persons <65 years of age, these calculations do not include clinician-diagnosed cases among persons >65 years. To adjust for this exclusion, we

	multiplied by a correction factor of 1.17. This correction factor was inferred from the age distribution of LD patients reported through national surveillance. During 2005–2010, persons <65 years of age accounted for 85.8% of LD cases reported through national surveillance. Therefore, we multiplied the estimated number of cases among persons <65 years by 1.00/0.858, or 1.17, to arrive at an estimate of cases in all age groups. The estimated number of patients with clinician-diagnosed LD was based on extraction of a single ICD-9-CM code. Research has shown, however, that clinician diagnosis of a medical condition does not necessarily correlate with existence of the ICD-9-CM code in the chart (17,18). The primary reasons are coding errors and inclusion of codes for accompanying symptoms but not the specific disease (e.g., coding for joint pain but not LD) (17,19). … to account for patients in whom LD was diagnosed but whose charts were not coded with 088.81, we multiplied the estimated number of cases with 088.81 by a correction factor calculated as follows: 313/655 = 1/x, where x = 2.09."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	Not sig diff wrt age or gender except that insurance data showed higher rates among women age 15-44. High-incidence states were the same in both data sets, but ordering was sig diff.
Findings on time trends / seasonality	Higher seasonal peak for June-Aug in surveillance data (65.0% of cases) than for insurance data (61.9% inpatient, 50.0% outpatient) "though this is likely an artifact of the large sample sizes." No difference wrt time trends: "Interannual fluctuation in incidence in MarketScan data was similar to that in surveillance data (x^2 test, p = 0.81; Cramer's V = 0.037)."
Any other findings / analyses	NR
Authors' conclusions / explanations	Possible overdiagnosis in insurance data and codes may not reflect ultimate diagnosis. Finding on higher incidence among younger adult women may reflect differences in health-seeking behaviour or clinical presentation. Findings

	indicate under-reporting of LD. Insurance database is not precisely representative of general population.
Reviewer notes	Data not validated. The method for estimating the population figure from the insurance database involves some assumptions which are discussed but arguably not fully justified (and is different to the methods of other studies).

First author, year	Robinson 2014
Country (location)	USA (Maine)
Years for which comparison reported	2008-2011
First data source (use surveillance source if appl.)	Cases reported to Maine CDDC
N of cases from first source	3,648 (cases); 160 (hospitalisations)
Incidence rate per 100,000 per year from first source	NR for whole sample
Further info re first source	"Maine's Lyme disease surveillance system is a passive system … Surveillance data was extracted from Maine's NBS for the years 2008-2011. Only confirmed and probable cases were included in data analysis. This data source includes patients who were seen by a provider for Lyme disease and met the federal case definition."
Comparison data source	Hospital records (Maine Health Data Organization)
N of cases from comparison source	9,043 (outpatient visits); 461 (inpatient visits)
Incidence rate per 100,000 per year from comparison source	NR for whole sample
Further info re comparison source	"The Maine Health Data Organization (MHDO) … collects information on inpatient and outpatient hospital encounters which are available annually. This reporting is required in Maine Rules and the definitions of who must submit data and what data must be submitted are clearly spelled out. … MHDO inpatient and outpatient hospital encounters with a diagnosis of 08881 in any diagnosis field were extracted from the full dataset from 2008-2011. Data were de-duplicated using hospital ID, medical record number, date of service, and sequential visit number. Data for inpatient visits and outpatient visits were analyzed separately. This data includes provider visits for Lyme disease, but no case classification is applied."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A

Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	Surveillance data shows highest rates in 5-14 and 45-64 age groups, hospital data in 45-64 and >65. Surveillance data shows no sig diff by gender; hospital inpatient data shows no sig diff, but outpatient data shows higher rate for females (sig NR). Geographical distribution: surveillance data shows higher rates in southern and mid-coast area, hospital data in mid-coast area and Franklin county (western Maine).
Findings on time trends / seasonality	Similar seasonal patterns. Surveillance data shows rise 2010-2011 which is less marked in the hospital data
Any other findings / analyses	For inpatient data, LD was primary diagnosis for 27%-40% of all cases, for outpatients 52%-71%
Authors' conclusions / explanations	Hospital data is events rather than individuals, so individuals can be counted more than once. Surveillance case definition stricter than clinical diagnosis. Children may have lower outpatient rates because they would not go to a hospital-associated clinic; older adults higher because of comorbidities. Gender differences may reflect differences in healthcare-seeking behaviour. Geographical distribution reflects hospital location and possibly patterns of healthcare utilisation. Hospital data is only a partial picture of healthcare utilisation overall. ICD-9 does not distinguish new diagnoses from old.
Reviewer notes	Data not validated (and hospital data uses only raw diagnosis figures).

First author, year	Schiffman 2016
Country (location)	USA (Crow Wing County, Minnesota)
Years for which comparison reported	2009
First data source (use surveillance source if appl.)	Cases reported to Minnesota Department of Health
N of cases from first source	Only reported as proportion of cases identified from chart review: of 163 of the latter, 66 were reported and 97 not reported (an additional 29 cases were reported but were regarded as misclassified on chart review)
Incidence rate per 100,000 per year from first source	81.3 (confirmed) plus 60.6 (probable)
Further info re first source	"Minnesota's communicable disease reporting rules require physicians and healthcare facilities to report cases of LD, anaplasmosis and babesiosis to MDH, which

	performs centralized TBD surveillance ... In addition, reference laboratories must report positive laboratory results. Minnesota Department of Health staff conduct routine case surveillance by contacting health providers to obtain information about each reported case's clinical presentation. To be considered confirmed according to the national surveillance case definition, a case must have laboratory evidence of infection with either a late manifestation of disease or a physician-diagnosed erythema migrans (EM) rash ≥5 cm in diameter. If there is no laboratory evidence of infection, in addition to the EM rash, a case must have exposure to tick habitat in an endemic county within 30 days of the rash onset … To increase the accuracy of case classification, MDH staff interview LD EM case patients for missing rash size or exposure information."
Comparison data source	Medical chart review (acute care facilities)
N of cases from comparison source	163 (confirmed or probable); 299 (all reportable events) (209 clinician diagnosis only, 23 laboratory result only, 67 both)
Incidence rate per 100,000 per year from comparison source	227.6 (confirmed) plus 78.8 (probable) (estimated)
Further info re comparison source	"[W]e contacted all 51 acute care medical facilities located in either Crow Wing or one of four adjacent counties … for lists of patient encounters assigned medical billing codes suggestive of LD, anaplasmosis and babesiosis. Only facilities that provided data on Crow Wing County were included in the final study. For billing codes, we used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9- CM) and Current Procedural Terminology (CPT). … Disease-specific codes of closely related diseases were also included to capture possible instances of miscoding or misdiagnosis. To further increase capture of possible LD diagnoses, we included symptomspecific ICD-9-CM codes consistent with localized LD (rash), disseminated LD (joint, cardiac or other manifestations) or tick bite in conjunction with CPT codes for LD laboratory tests ... After confirming that identified patients were residents of Crow Wing County who met study criteria for ICD-9- CM and CPT coding, we conducted chart reviews. … All reviewed events were assigned a case status (confirmed, probable, suspect or not a case) and assessed for reportability. An event was considered to be 'reportable' if it met the criteria defined in Minnesota's communicable disease reporting rule … Disease-specific ICD- 9-CM codes

	were not used as a proxy for physician diagnosis. Chart review data were compared to MDH's 2009 TBD surveillance data set using patient name and date of birth to establish whether patients had been reported independent of this study and classified correctly according to the CSTE [Council of State and Territorial Epidemiologists] case definition."
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	NR
Findings on time trends / seasonality	NR
Any other findings / analyses	NR
Authors' conclusions / explanations	Authors calculate 'reporting multiplier' of 2.8 for the confirmed cases [142/50], i.e. total confirmed cases = 2.8× reported cases. A total of 1,301 LD events were reviewed, but only 299 met definition for reportable events; this was partly due to the use of ICD symptom codes and Current Procedural Terminology codes. Study area is endemic and clinicians are likely familiar with LD, so may be more likely to treat empirically without using diagnostic tests. Healthcare data may be incomplete.
Reviewer notes	Surveillance data only partly reported.

First author, year	Tseng 2015
Country (location)	USA (Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Vermont, Virginia, Wisconsin)
Years for which comparison reported	2004-2006 and 2010-2012
First data source (use surveillance source if appl.)	Cases reported to CDC
N of cases from first source	NR
Incidence rate per 100,000 per year from first source	≈25 (2004-2006); ≈28 (2010-2012) (reviewer estimated from graph)
Further info re first source	NR
Comparison data source	Nationwide insurance claims database

N of cases from comparison source	1,965 (2004-2006); 3,474 (2010-2012) using full inclusion criteria, i.e. LD ICD code + serologic test + antibiotic treatment ≥14 days 7,213 (2004-2006); 10,512 (2010-2012) with any primary LD diagnosis code
Incidence rate per 100,000 per year from comparison source	50.25 (2004-2006); 75.67 (2010-2012)
Further info re comparison source	"We conducted a population-based retrospective cohort study using medical insurance claims data from a nationwide health insurance plan in the United States… The database covers records of outpatient and inpatient visits, drug prescriptions, and laboratory orders. Every outpatient or inpatient visit was coded with one principal and up to three secondary International Classification of Diseases, Ninth Revision (ICD-9) codes and one zip code associated with the provider's address. Prescription-filling data include the date, National Drug Code, and quantity dispensed (in days). Laboratory orders were coded with the Current Procedural Terminology (CPT) code." Cases were defined as patients having at least one occurrence of the ICD-9 code for LD in the study period, antibiotic treatment for LD for at least 14 days, and a serologic test order.
Second comparison data source (if appl.)	N/A
N of cases from second comparison source	N/A
Incidence rate per 100,000 per year from second comparison source	N/A
Further info re second comparison source	N/A
Findings on demographics	NR
Findings on time trends / seasonality	Larger difference in insurance claims in later time period (i.e. increasing incidence over time compared to surveillance data)
Any other findings / analyses	NR
Authors' conclusions / explanations	Codes may not reflect ultimate diagnosis. Database only includes people using that health plan. Claims data do not include serologic test results. Findings suggest under-reporting is becoming more common, "perhaps due to 'reporting fatigue.'"
Reviewer notes	Data not validated. Surveillance data not discussed in any detail or reported numerically.

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