National Institute for Health and Care Excellence

Draft for Consultation

Lyme disease: diagnosis and management

[A] Evidence review for the awareness of Lyme disease

NICE guideline

Evidence review

September 2017

Draft for Consultation

This evidence review was developed by the National Guideline Centre

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1 Awareness of Lyme disease

1.1 Introduction

The true incidence of Lyme disease in England is unknown. In England and Wales, cases of laboratory-confirmed Lyme disease have increased. This is thought to be a result of better reporting, increased diagnostic testing and increased awareness by the public and healthcare professionals but may also be a result of increased spread of disease. There is a need to increase awareness of Lyme disease as there are assumptions about where infected ticks may be found and hence the risk of Lyme disease to an individual.

Lyme disease can occur anywhere although there are geographical locations with higher reported incidence. The distribution of laboratory confirmed cases varies by region, with approximately 50% diagnosed in the Southeast and Southwest of England and other reported high areas of incidence in Scotland. Travellers to specific areas of Europe and North America may also be at risk.[31]

1.2 Review question: In whom should Lyme disease be suspected?

No specific evidence review was conducted to inform recommendations on the awareness of Lyme disease because it was agreed that such information was unlikely to be found in evidence review. The committee used their expert opinion and the review on incidence of Lyme disease (see review below) to inform recommendations.

1.3 Review question: What is the incidence of Lyme disease in the UK?

1.4 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with confirmed Lyme disease
Target condition	Lyme disease Specifically, conditions caused by *Borrelia burgdorferi sensu lato*
Setting	UK only
Statistical measures	Incidence of Lyme disease (any clinical presentation related to Lyme disease), defined as the number of new cases within a specified time period divided by the size of the population initially at risk. In the absence of reliable incidence data, prevalence data will be included in the review. The prevalence of Lyme disease (any clinical presentation related to Lyme disease) is defined as the number of individuals with the disease divided by the number of individuals tested in the population at risk.
Study design	All studies that report an incidence estimate of Lyme disease in the UK

1.5 Evidence of the incidence of Lyme disease in the UK

1.5.1 Included studies

A search was conducted for studies reporting incidence estimates of Lyme disease in the UK. Studies that reported an estimate of the prevalence of Lyme disease in the UK were also considered for inclusion.

Eight studies were included in the review;[9,17,21-23,26,36,37] evidence from these studies is summarised in Table 2 below.

Study limitations are listed in Table 4.

See also the study selection flow chart in appendix C and study evidence tables in appendix D.

One study[9] provided hospital episode statistics (HES) data on Lyme disease, Bell's palsy and the combination of both for England in the form of finished consultant episodes (FCE). The study interrogated HES data for the ICD-10 codes for Lyme disease (A69.2) and Bell's palsy (G51.0); there is no separate code for facial palsy. It is not possible to calculate incidence or prevalence estimates based on FCE and therefore the data are provided in this review as reported in the article. Furthermore, HES data only covers secondary care and the possibility that people might have been duplicated over the years cannot be ignored.

1.5.2 Excluded studies

See the excluded studies list in appendix I.

1.5.3 Summary of studies included in the evidence review

Table 2: Summary of studies on incidence included in the evidence review

Study	Incidence	Geographic area	Time period	How were data collected?	How was Lyme disease defined?	Comments
Hubalek 2009[17]	England and Wales: 0.59 per 100,000 (range 0.3-1.1) Scotland: 1.72 per 100,000 (range 1.6-1.9)	England and Wales, Scotland	England and Wales: 1997-2005 Scotland: 2002-2005	Data for England and Wales provided by Health Protection Agency Data for Scotland provided by Eurosurveillance Editorial Advisors Number tested or positive not reported	Unclear	Primary data source not identifiable
Lovett 2008[21]	28 per 100,000	RDEH catchment area (population 350,000), Southwest England	2000-2004	Royal Devon and Exeter Hospital n=2,825 samples (98 confirmed cases)	Positive antibody test using the internationally recommended 2-stage procedure Initial test performed at RDEH; confirmatory immunoblotting performed at Health Protection Agency Lyme Borreliosis Unit, Southampton General Hospital	
Mavin 2009[22]	46 per 100,000	Highland, Scotland	April 2004 to March 2006	Highland samples tested at Raigmore	Positive/equivocal EIA plus positive	More people from rural areas (n=1,113) than

Study	Incidence	Geographic area	Time period	How were data collected?	How was Lyme disease defined?	Comments
	Urban: 23 per 100,000 Rural: 68 per 100,000			Hospital[a] n=1,602 (104 were positive)	IgG western blot Negative samples with strong clinical suspicion of Lyme disease also tested using the western blot	from urban areas (n=489) tested
Mavin 2015[23]	6.8 per 100,000 (average annual incidence from 2008-2013) Regional differences: 1.7 per 100,000 (Lanarkshire) 44.1 per 100,000 (NHS Highland) 9.2 per 100,000 (Tayside) 2.1 per 100,000 (Fife)	Scotland	January 1996 to December 2014 (data only reported for 2008-2013)	Serum samples sent to Raigmore Hospital[a] Number tested (year): n=869 (1996) n=5,366 (2011) n=4,630 (2013) Number positive (year): n=27 (1996) n=52 (2003) n=339 (2008) n=393 (2009) n=440 (2010) n=308 (2011) n=210 (2012) n=175 (2013)	Positive/equivocal EIA plus positive in-house western blot From July 2012 onwards: Positive/equivocal EIA plus positive commercial IgG western blot; following BIA[b] guidance samples from people with a clear recent history of tick bite and EM, tick bite only, or no clinical symptoms were no longer tested	Steady rise in samples tested over the study period: from 869 in 1996 to 5,366 in 2011 Confirmed Lyme disease cases: 27 in 1996, 52 in 2003, 339 in 2008, 292 in 2009, 440 in 2010, 308 in 2011, 210 in 2012, 175 in 2013
Milner 2009[26]	Scotland (annual): 5.9 per 100,000 Scotland (July-	Scotland	2007-2008	Samples from across Scotland tested at Raigmore Hospital[a]	Positive/equivocal EIA plus positive IgG western blot Negative samples	Significantly more people tested in July to September 2008 than in the same period of the previous year (1,330

Study	Incidence	Geographic area	Time period	How were data collected?	How was Lyme disease defined?	Comments
	September): 10.6 per 100,000 Highlands (annual): 43.4 per 100,000 Highlands (July – September): 81 per 100,000			Number tested or positive not reported	with strong clinical suspicion of Lyme disease also tested using the western blot	versus 1,097, p<0.001)
Slack 2011[36]	Tayside: 2.51 per 100,000 (2001/02) 16.8 per 100,000 (2009/10) Highland: 25.4 per 100,000 (2006/07) 56.4 per 100,000 (2009/10) Rest of Scotland: 0.8 per 100,000 (2005/06) 5.5 per 100,000 (2009/10)	Scotland	April 2001 to March 2010 (Tayside) April 2004 to March 2010 (rest of Scotland)	Samples tested at Medical Microbiology Department at Ninewells Hospital & Medical School in Dundee Samples tested at Raigmore Hospital[a] Number tested in Tayside (year): n=505 (2001/02) n=547 (2002/03) n=691 (2003/04) n=630 (2004/05) n=606 (2005/06) n=736 (2006/07) n=749 (2007/08) n=780 (2008/09) n=881 (2009/10)	Positive/equivocal EIA plus positive IgG western blot Negative samples with strong clinical suspicion of Lyme disease also tested using the western blot	Steady rise in samples tested over the study period Test interpretation criteria revised in April 2004, June 2007 and October 2008 Tayside: Early Lyme disease (EM, rash, tick-bite, flu-like illness): 39 (2006/08) versus 70 (2008/10) Neurological symptoms: 5 (2006/08) versus 31 (2008/10) Joint symptoms: 0 (2006/08) versus 6 (2008/10)

Study	Incidence	Geographic area	Time period	How were data collected?	How was Lyme disease defined?	Comments
				Number tested in Highland (year): n=1,072 (2005/06) n=1,165 (2006/07) n=1,052 (2007/08) n=1,069 (2008/09) n=1,202 (2009/10)		
Smith 2000[37]	0.06 per 100,000 (average annual rate from 1986-1992) 0.11 per 100,000 (average annual rate from 1992-1996) 0.32 per 100,000 (average annual rate from 1996-1998)	England and Wales Reports from 68 counties (only 14 counties had more than 10 cases each); 219 from Hampshire, 72 from Wiltshire, 61 from Dorset, 47 from Devon, 32 from Somerset, 29 from Norfolk 118 acquired abroad (mainly USA, France, Germany, Austria and Scandinavia)	1986-1992 and 1992-1996 Enhanced surveillance from 1996-1998	Questionnaires sent to laboratories by the Public Health Laboratory Services reference lab n=227 (1986-1992) n=235 (1992-1996) n=334 (1996-1998)	Two-tier testing: antibody screening test followed by immunoblot of reactive or equivocal samples	Seasonal pattern: 48% of cases reported in the third quarter of each year EM (n=325), EM plus tick bite (n=140), Neuroborreliosis (n=118), other neurological symptoms (n=82), cardiac involvement (n=5), arthritis (n=32) tick bite (n=255)

(a) National Lyme Borreliosis Testing Laboratory at Raigmore Hospital
(b) British Infection Association

Table 3: Study reporting HES data on Lyme disease and Bell's palsy

Study	Finished consultant episodes (FCE)	Geographic area	Time period	How are data collected?	How is Lyme disease defined?	Comments
Cooper 2017[9]	Lyme disease: 260 FCE (2011/12)[a] 336 FCE (2012/13) 316 FCE (2013/14) 370 FCE (2014/15) Bell's palsy and Lyme disease: 20 FCE (2011/12) 5 FCE (2012/13) 11 FCE (2013/14) 11 FCE (2014/15)	England	April 2011 to March 2015	Hospital Episode Statistics (HES) data in England from the Health and Social Care Information Centre (HSCIC)	No definition ICD-10 codes: A69.2 (Lyme disease) and G51.0 (Bell's palsy)	No ICD-10 code for facial palsy. People with both a code for Lyme disease and Bell's palsy assumed to have Lyme disease-associated facial palsy.

(a) FCE = finished consultant (hospital) episode

1.5.4 Quality assessment of studies included in the evidence review

Table 4: Study limitations [adapted from the Joanna Briggs Institute[29]]

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
Cooper 2017[9]	Yes	Yes	No	Yes	No – Hospital episode statistics (HES), finished consultant episodes (FCE)	Unclear	No	Does not account for those people who did not present to secondary care. HES data relies on inputs by non-clinical coders. No separate code for facial palsy. People might have been duplicated over years.
Hubalek 2009[17]	Yes	Yes	No	Yes	Unclear – Data provided by Eurosurveillance (for Scotland) and Health Protection	Unclear	Unclear	N/A

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					Agency (for England and Wales). No further details provided.			
Lovett 2008[21]	Yes	Yes	No	Yes	Yes - Samples tested at Royal Devon and Exeter Hospital	Yes – 2-tier serological testing	Yes - Based on Royal Devon and Exeter Hospital catchment area (population 350,000) and positive samples	N/A
Mavin 2009[22]	Yes	Yes	No	Yes	Yes - Serum samples sent to Scottish reference laboratory	Yes – 2-tier serological testing; negative samples with strong clinical suspicion of Lyme disease also tested using the western blot	Yes - Based on population of Scottish Highland and positive samples	More people from rural areas than from urban areas tested
Mavin 2015[23]	Yes	Yes	No	Yes	Yes - Serum samples sent	Yes – 2-tier serological	Yes - Based on population	Significant change in

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					to Scottish reference laboratory	testing	of Scotland and positive samples	testing protocols in July 2012: in-house western blot replaced by CE marked commercial assays People with an EM and a clear recent history of Lyme were not included in the testing regimen; not included in incidence calculations
Milner 2009[26]	Yes	Yes	No	Yes	Yes - Serum samples sent to Scottish reference laboratory	Yes – 2-tier serological testing; negative samples with strong clinical suspicion of Lyme disease also tested	Yes - Based on population of Scotland and positive samples	Significantly more people tested in July to September 2008 than in the same period of the previous year

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
						using the western blot		
Slack 2011[36]	Yes	Yes	No	Yes	Yes - Samples tested at Medical Microbiology Department at Ninewells Hospital & Medical School in Dundee	Yes – 2-tier serological testing; negative samples with strong clinical suspicion of Lyme disease also tested using the western blot	Yes - Based on population of Scotland and positive samples	Test interpretation criteria revised in April 2004, June 2007 and October 2008
Smith 2000[37]	Yes	No	No	Yes	Unclear - Questionnaires sent to laboratories by the Public Health Laboratory Services reference lab	Yes – 2-tier serological testing	Yes - Based on population of England and positive samples	N/A

1.6 Economic evidence

Health economic evidence was not relevant to this question; therefore, a health economic evidence review was not conducted.

1.7 Resource impact

We do not expect recommendations resulting from this review area to have a significant impact on resources.

1.8 Evidence statements

1.8.1 Clinical evidence statements

The majority of the identified studies provided annual incidence estimates for Scotland, which ranged from 1.72 to 6.8 cases of Lyme disease per 100,000 people. Limited evidence for England and Wales showed significantly lower annual incidence of 0.06 to 0.59 Lyme disease cases per 100,000 people. There were significant regional differences in incidence, with rural areas and the Scottish Highlands, for example, showing higher rates. The evidence also indicated a significant rise in incidence over the past 2 decades although the increases could at least partially be attributed to an increase in Lyme disease testing and changes in diagnostic testing protocols. It is unclear if the increases in incidence over time were statistically significant. There were concerns about the patient population, changes in testing practice over time and the lack of a clear description of the clinical presentations of Lyme disease. In some studies, people with an erythema migrans were excluded, which most likely resulted in an underestimate of the true incidence.

No review on the awareness of Lyme disease was conducted.

1.8.2 Health economic evidence statements

Not applicable.

1.9 Recommendations

A1. Be aware that:

- Lyme disease is transmitted by the bite of an infected tick
- ticks are mainly found in grassy and wooded areas, particularly areas that are overgrown, including gardens and parks
- tick bites may not always be noticed
- infected ticks are found throughout the UK and Ireland, and although some areas appear to have a higher prevalence of infected ticks, prevalence data are incomplete
- particularly high-risk areas are the South of England and Scottish Highlands but infection can occur in many areas
- Lyme disease may be more prevalent in parts of central, eastern and northern Europe (including Scandinavia) and parts of Asia, the US and Canada.

A2. Be aware that most tick bites do not transmit Lyme disease and that prompt removal of the tick reduces the risk of transmission.

A3. Give people advice about:

- where ticks are commonly found (such as grassy, wooded and overgrown areas, including gardens and parks)

- the importance of prompt tick removal and how to do this
- covering exposed skin and using insect repellents
- how to check themselves and their children for ticks on the skin
- sources of information on Lyme disease, such as NHS Choices and Public Health England, and organisations providing information and support, such as patient charities.

1.9.1 Research recommendations

RR1. What are the incidence, presenting features, management and outcome of Lyme disease, including in women with Lyme disease who are pregnant, in the UK?

See also the rationale in appendix J.

1.10 Rationale and impact

1.10.1 Why the committee made the recommendations

The committee agreed that raising awareness is of great importance to improve diagnosis and management of Lyme disease. The recommendations highlight how infection occurs, typical tick habitats and areas of higher prevalence, based on evidence of incidence and the committee's knowledge and experience. This may be helpful to guide healthcare professionals, for example, in recognising the possibility of Lyme disease when a person is unaware that they have been bitten by a tick, or in areas where ticks are found but where Lyme disease is not highly prevalent.

1.10.2 Impact of the recommendations on practice

These recommendations aim to improve awareness of Lyme disease, to promote early investigation and treatment, and to optimise outcomes in people with Lyme disease. They will change current practice by prompting healthcare professionals to think about the possibility of Lyme disease. These recommendations are not considered to have a significant resource impact because considering Lyme disease as a differential diagnosis does not necessarily result in any testing for Lyme disease. Furthermore, the number of people with Lyme disease is generally low.

1.11 The committee's discussion of the evidence

1.11.1 Interpreting the evidence

1.11.1.1 The outcomes that matter most

No specific evidence review was conducted to inform recommendations on the awareness of Lyme disease because it was agreed that such information would generally not be available. The recommendations were informed by what is known about the microbiology and epidemiology of Lyme disease, as well as by the review on the incidence of Lyme disease. The recommendations were reached by consensus and draw on expertise of the guideline committee.

The review on the incidence of Lyme disease aimed to identify studies reporting incidence or prevalence estimates of Lyme disease in the UK. Incidence of Lyme disease, that is, any clinical presentation related to Lyme disease, was defined as the number of new cases within a specified time period divided by the size of the total population in a given area. The prevalence of Lyme disease was defined as the number of individuals with the disease

divided by the number of individuals tested or assessed in the population at risk. Incidence was considered as a critical outcome. In the absence of incidence data, prevalence figures would have been considered for inclusion. Only UK data were considered for inclusion because this review was intended to provide supporting evidence for clinical recommendations and health economic analyses in the UK.

1.11.1.2 The quality of the evidence

Quality assessment of the individual studies was carried out according to an adapted version of The Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data.[16] Generally, the included studies used an appropriate sample to calculate an incidence estimate of Lyme disease because of the way samples were tested. There was a general lack of details on the clinical presentations of Lyme disease. The majority of studies used 2-tier serological testing to determine whether Lyme disease was present. Four of the 8 included studies were on data from the reference laboratories in England and Scotland, which resulted in a more accurate national incidence estimate than regional sampling used by 2 studies. One study provided HES data that were difficult to interpret due to the way HES data are collected and finished consultant episodes are defined and calculated.

There were particular concerns around changes in testing practices and the lack of inclusion of people who did not undergo 2-tier testing, for example, people who presented with an erythema migrans rash and were treated without having undergone serological testing. In 1 study, the test interpretation criteria were revised during the study period and in another study, the in-house western blot was replaced with a CE marked commercial assay. It is, however, not clear if the CE marked assay was more accurate in identifying Lyme disease than the in-house western blot. These issues could have had a significant impact on the annual average incidence although the extent of any such impact could not be determined by the evidence provided.

There were no concerns regarding the applicability of the population.

1.11.1.3 Benefits and harms

The committee discussed Lyme disease awareness in the absence of an evidence review and agreed that raising awareness was of the utmost importance. Raising awareness of Lyme disease reduces the possibility that people with Lyme disease are overlooked or not adequately assessed and diagnosed for Lyme disease. Receiving appropriate treatment provides the best chance of reducing morbidity.

No English Lyme disease incidence estimates were identified. The majority of the identified studies provide annual incidence estimates for Scotland, which ranged from 1.72 to 6.8 cases of Lyme disease per 100,000 people. Limited evidence for England and Wales showed significantly lower annual incidence figures of 0.06 to 0.59 Lyme disease cases per 100,000 people.

There were significant regional differences in incidence, which were based on laboratory confirmed cases of Lyme disease. Higher incidence figures than overall English or Scottish averages were found in the Scottish Highlands and Southwest England. The incidence of Lyme disease in the Scottish Highlands increased from 25.4 per 100,000 in 2006/07 to 56.4 per 100,000 in 2009/10. Based on samples tested at the Royal Devon and Exeter Hospital in Southwest England, there was an average annual Lyme disease incidence of 28 per 100,000 from 2000 to 2004 for the hospital catchment area; far higher than the annual average of 0.59 per 100,000 from 1997 to 2005 for England and Wales.

Of note is that the incidence figures reported in the studies increased over the past 2 decades for Scotland, England and Wales. In part, this may be due to changes in testing protocols and practices, such as the switch to CE marked assays, revised test criteria and significant increases in the number of samples tested, although the extent of the impact on

overall Lyme disease incidence cannot be determined. It should also be noted that data were only available for the past 15-20 years.

1.11.2 Cost effectiveness and resource use

A specific economic evidence review was not conducted to inform these recommendations. The committee considered that raising awareness of Lyme disease would allow for appropriate consideration of Lyme disease as a diagnosis. This would ideally minimise the number of people with Lyme disease being overlooked and avoid referring too many people inappropriately for Lyme disease testing and treatment, thus allowing for appropriate allocation of NHS resources. As a result, these recommendations are not anticipated to have a significant resource impact.

1.11.3 Other factors the committee took into account

The committee developed the recommendations using informal consensus. The committee considered that one of the most important issues in the diagnosis and management of Lyme disease is that the healthcare professional considers Lyme disease as a possible diagnosis. This is a particular issue in areas where Lyme disease is less prevalent. One of the difficulties for healthcare professionals and for their patients is that people often do not recollect having been bitten by a tick and people with Lyme disease may present with non-specific symptoms. Furthermore, not every tick carries *Borrelia* and the majority of tick bites do not lead to an infection.

It is therefore important that healthcare professionals assess people who are likely to have contracted Lyme disease adequately, while also considering other possible diagnoses. A balance needs to be struck between ensuring that people with Lyme disease are not overlooked and avoiding referring too many people for Lyme disease testing.

Although there are areas in the UK with higher incidence than the national average, infected ticks are found throughout the country, including urban parks. Some people may also have contracted Lyme disease abroad. Northeastern areas and upper Midwestern areas of the United States; southern parts of British Columbia, Manitoba, Ontario, Quebec and New Brunswick in Canada; Central Europe and Scandinavia show a particularly high prevalence of Lyme disease.

The committee considered that the majority of people with Lyme disease would be seen by general practitioners. Experienced general practitioners assess people with infectious diseases on a daily basis and refer them to specialists if needed.

The committee considered it important that people who may have been exposed to ticks are informed about how to manage future exposure and where to get further information and support. The recommendation includes reference to NHS sources of information and Lyme disease charities.

The committee developed a research recommendation to improve clinical epidemiology of Lyme disease in the UK, which would provide information to inform both health care professionals and the public about presentation and outcomes for Lyme disease. Identifying the incidence, presenting features, management and outcome of Lyme disease in the UK was considered to be a research priority. The committee were aware of research using GP databases to estimate incidence of Lyme disease but such research is clearly dependent on accurate and comprehensive coding. The committee also agreed that an additional focus should be on pregnant women with Lyme disease when undertaking this research.

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Appendices

Appendix A: Review protocol

Table 5: Review protocol for the awareness of Lyme disease

Question number: 1

Relevant section of Scope: assessment and information needs

Field	Content
Review question	In whom should Lyme disease be suspected?
Type of review question	No formal review will be undertaken
Objective of the review	The question aims to identify key information about Lyme disease that should be highlighted in order to raise awareness and support healthcare professionals in offering an appropriate assessment to people who are likely to have contracted Lyme disease.
Eligibility criteria – population / disease / condition	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with suspected (or under investigation for) Lyme disease.
Eligibility criteria – exposure(s) / prognostic factor(s)	Not applicable
Eligibility criteria – comparator(s) /reference (gold) standard	Not applicable
Outcomes and prioritisation	Identify people who may have Lyme disease and should undergo further investigation
Eligibility criteria – study design	Not applicable
Other inclusion exclusion criteria	Not applicable
Proposed sensitivity / subgroup analysis, or meta-regression	Not applicable
Selection process – duplicate screening / selection / analysis	No formal evidence review will be undertaken for this question. Recommendations will be informed by findings from other reviews in the guideline where relevant and informal consensus of the guideline committee.
Data management (software)	Not applicable
Information sources – databases and dates	Not applicable
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	Not applicable
Data collection process – forms / duplicate	Not applicable
Data items – define all variables to be collected	Not applicable

Field	Content
Methods for assessing bias at outcome / study level	Not applicable
Criteria for quantitative synthesis	Not applicable
Methods for quantitative analysis – combining studies and exploring (in)consistency	Not applicable
Meta-bias assessment – publication bias, selective reporting bias	Not applicable
Confidence in cumulative evidence	Not applicable
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 6: Review protocol for the incidence of Lyme disease

Question number: 5

Relevant section of Scope: assessment and information needs

Field	Content
Review question	What is the incidence of Lyme disease in the UK?
Type of review question	Epidemiological Health economic evidence was not relevant for this review question.
Objective of the review	To assess the incidence of Lyme disease in the UK.
Eligibility criteria – population / disease / condition / issue / domain	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with confirmed Lyme disease. Lyme disease (specifically, conditions caused by *Borrelia burgdorferi sensu lato*)
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Not applicable
Eligibility criteria –	Not applicable

Field	Content
comparator(s) / control or reference (gold) standard	
Outcomes and prioritisation	Incidence of Lyme disease (any clinical presentation related to Lyme disease), defined as the number of new cases within a specified time period divided by the size of the population initially at risk. In the absence of reliable incidence data, prevalence data will be included in the review. The prevalence of Lyme disease (any clinical presentation related to Lyme disease) is defined as the number of individuals with the disease divided by the number of individuals tested in the population at risk.
Eligibility criteria – study design	All studies that report an incidence estimate of Lyme disease in the UK.
Other inclusion exclusion criteria	Date limits for search: none Language: English only Setting: UK only
Proposed sensitivity / subgroup analysis, or meta-regression	Stratum: Clinical presentation of Lyme disease (for example, erythema migrans, neuroborreliosis) Geographic region
Selection process – duplicate screening / selection / analysis	Studies will be sifted by title and abstract. Potentially significant publications obtained in full text will then be assessed against the inclusion criteria specified in this protocol.
Data management (software)	Bibliographies, citations and study sifting will be managed using EndNote
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	Identified evidence for this review question will be presented in a table in the evidence report.
Data items – define all variables to be collected	Not applicable
Methods for assessing bias at outcome / study level	Study limitations for each study will be assessed using an adaptation of a checklist for prevalence studies published by the Joanna Briggs Institute.
Criteria for quantitative synthesis	No quantitative synthesis will be performed. The evidence will be presented as a list or, if applicable, range of values.
Methods for quantitative analysis – combining studies and exploring (in)consistency	No quantitative synthesis will be performed. The evidence will be presented as a list or, if applicable, range of values.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	No quantitative synthesis will be performed.
Rationale / context – what is known	For details, please see the introduction to the evidence review.

Field	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

The search for this review was constructed using population terms. An excluded studies filter was applied where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 03 July 2017	Exclusions
Embase (OVID)	1974 – 03 July 2017	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 7 of 12 CENTRAL to 2017 Issue 6 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	(letter or comment*).ti.
19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20

22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	11 not 28
30.	limit 29 to English language

1 **Embase (Ovid) search terms**

1.	exp Borrelia Infection/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	(letter or comment*).ti.
16.	or/12-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	11 not 26
28.	limit 27 to English language

2 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Borrelia Infections] explode all trees
#2.	MeSH descriptor: [Lyme Disease] explode all trees
#3.	MeSH descriptor: [Erythema Chronicum Migrans] explode all trees
#4.	(erythema near/3 migrans):ti,ab

#5.	lyme*:ti,ab
#6.	(tick* near/2 (bite* or bitten or biting or borne)):ti,ab
#7.	acrodermatitis chronica atrophicans:ti,ab
#8.	MeSH descriptor: [Ixodidae] explode all trees
#9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or ixodid or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti):ti,ab
#10.	(granulocyctic anaplasmosis or babesia or babesiosis):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Lyme disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 03 July 2017	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 03 July 2017	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 03 July 2017 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/

13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	(letter or comment*).ti.
19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	11 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	exp models, economic/
49.	*Models, Theoretical/
50.	*Models, Organizational/
51.	markov chains/
52.	monte carlo method/

53.	exp Decision Theory/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/48-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.
68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	30 and 47
79.	30 and 57
80.	30 and 77

1 **Embase (Ovid) search terms**

1.	exp Borrelia Infection/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.

11.	or/1-10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	Case report/ or Case study/
16.	(letter or comment*).ti.
17.	or/12-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animal/ not human/
21.	Nonhuman/
22.	exp Animal Experiment/
23.	exp Experimental animal/
24.	Animal model/
25.	exp Rodent/
26.	(rat or rats or mouse or mice).ti.
27.	or/19-26
28.	11 not 27
29.	limit 28 to English language
30.	health economics/
31.	exp economic evaluation/
32.	exp health care cost/
33.	exp fee/
34.	budget/
35.	funding/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/30-42
44.	statistical model/
45.	exp economic aspect/
46.	44 and 45
47.	*theoretical model/
48.	*nonbiological model/
49.	stochastic model/
50.	decision theory/

51.	decision tree/
52.	monte carlo method/
53.	(markov* or monte carlo).ti,ab.
54.	econom* model*.ti,ab.
55.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
56.	or/46-55
57.	quality adjusted life year/
58.	"quality of life index"/
59.	short form 12/ or short form 20/ or short form 36/ or short form 8/
60.	sickness impact profile/
61.	(quality adj2 (wellbeing or well being)).ti,ab.
62.	sickness impact profile.ti,ab.
63.	disability adjusted life.ti,ab.
64.	(qal* or qtime* or qwb* or daly*).ti,ab.
65.	(euroqol* or eq5d* or eq 5*).ti,ab.
66.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
67.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
68.	(hui or hui1 or hui2 or hui3).ti,ab.
69.	(health* year* equivalent* or hye or hyes).ti,ab.
70.	discrete choice*.ti,ab.
71.	rosser.ti,ab.
72.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
73.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
74.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
75.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
76.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
77.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
78.	or/57-77
79.	29 and 43
80.	29 and 56
81.	29 and 78

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis chronica atrophicans) IN NHSEED, HTA
#7.	MeSH DESCRIPTOR Ixodidae EXPLODE ALL TREES IN NHSEED,HTA
#8.	((borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti)) IN NHSEED, HTA
#9.	((granulocyctic anaplasmosis or babesia or babesiosis)) IN NHSEED, HTA
#10.	MeSH DESCRIPTOR Lyme Disease EXPLODE ALL TREES IN NHSEED,HTA

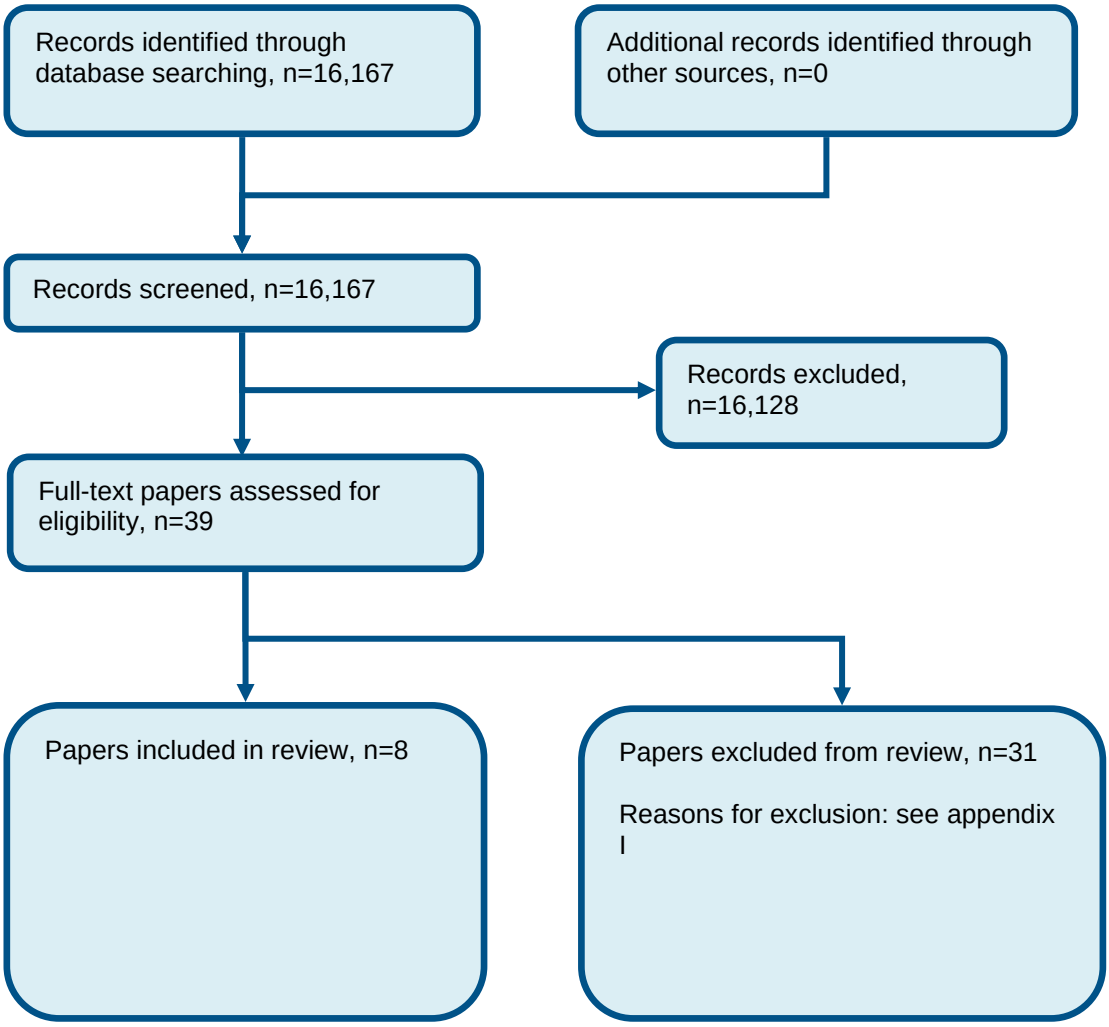
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

1

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of the incidence of Lyme disease



Appendix D: Clinical evidence tables

D.1 Awareness of Lyme disease

None.

D.2 Incidence of Lyme disease

Reference	Cooper 2017[9]
Data source	Hospital Episode Statistics (HES) data in England from the Health and Social Care Information Centre (HSCIC)
Region or catchment area	England
Time period	April 2011 to March 2015
Case definition	No definition ICD-10 codes: A69.2 (Lyme disease) and G51.0 (Bell's palsy)
Incidence	Lyme disease: 260 FCE (2011/12) 336 FCE (2012/13) 316 FCE (2013/14) 370 FCE (2014/15) Bell's palsy and Lyme disease: 20 FCE (2011/12) 5 FCE (2012/13) 11 FCE (2013/14) 11 FCE (2014/15)
Quality assessment	Subjects and setting not described in detail; unclear if valid methods used for identification of the condition; unclear if condition measured in a standard, reliable way for all people; appropriate statistical analysis not used; does not account for those who did not

Reference	Cooper 2017[9]
	present to secondary care; HES data relies on inputs by non-clinical coders; no separate code for facial palsy; people might have been duplicated

Reference	Hubalek 2009[17]
Data source	Health Protection Agency (England and Wales) Eurosurveillance Editorial Advisors (Scotland)
Region or catchment area	England and Wales, Scotland
Time period	England and Wales: 1997-2005 Scotland: 2002-2005
Case definition	Not reported
Incidence	England and Wales: 0.59 per 100,000 (range 0.3-1.1) Scotland: 1.72 per 100,000 (range 1.6-1.9)
Quality assessment	Subjects and setting not described in detail; unclear if valid methods used for identification of the condition; unclear if condition measured in a standard, reliable way for all people; unclear if there was appropriate statistical analysis

Reference	Lovett 2008[21]
Data source	Royal Devon and Exeter Hospital n=2,825 samples (98 confirmed cases)
Region or catchment area	RDEH catchment area (population 350,000), Southwest England
Time period	2000-2004
Case definition	Positive antibody test using the internationally recommended 2-stage procedure Initial test performed at RDEH; confirmatory IB performed at Health Protection Agency Lyme Borreliosis Unit, Southampton General Hospital
Incidence	28 per 100,000
Quality assessment	Subjects and setting not described in detail

Reference	Mavin 2009[22]
Data source	Highland samples tested at Raigmore Hospital n=1,602 (104 were positive)
Region or catchment area	Highland, Scotland
Time period	April 2004 to March 2006
Case definition	Positive/equivocal EIA plus positive IgG WB Negative samples with strong clinical suspicion of Lyme disease also tested using the WB
Incidence	46 per 100,000 Urban: 23 per 100,000 Rural: 68 per 100,000
Quality assessment	Subjects and setting not described in detail; more people from rural areas than urban areas tested

Reference	Mavin 2015[23]
Data source	Serum samples sent to Raigmore Hospital
Region or catchment area	Scotland
Time period	January 1996 to December 2014 (data only reported for 2008-2013)
Case definition	Positive/equivocal EIA plus positive in-house WB From July 2012 onwards: Positive/equivocal EIA plus positive commercial IgG WB; following BIA guidance samples from people with a clear recent history of tick bite and EM, tick bite only, or no clinical symptoms were no longer tested
Incidence	6.8 per 100,000 (average annual incidence from 2008-2013) Regional differences: 1.7 per 100,000 (Lanarkshire) 44.1 per 100,000 (NHS Highland) 9.2 per 100,000 (Tayside) 2.1 per 100,000 (Fife)
Quality assessment	Subjects and setting not described in detail; change in testing protocols during study period; people with EM and clear recent Lyme history not included in incidence calculation

Reference	Milner 2009[26,36]
Data source	Samples from across Scotland tested at Raigmore Hospital
Region or catchment area	Scotland
Time period	2007-2008
Case definition	Positive/equivocal EIA plus positive IgG WB Negative samples with strong clinical suspicion of Lyme disease also tested using the WB
Incidence	Scotland (annual): 5.9 per 100,000 Scotland (July-September): 10.6 per 100,000 Highlands (annual): 43.4 per 100,000 Highlands (July – September): 81 per 100,000
Quality assessment	Subjects and setting not described in detail; more people tested later on in the study period

Reference	Slack 2011[36]
Data source	Samples tested at Medical Microbiology Department at Ninewells Hospital & Medical School in Dundee Samples tested at Raigmore Hospital
Region or catchment area	Scotland
Time period	April 2001 to March 2010 (Tayside) April 2004 to March 2010 (rest of Scotland)
Case definition	Positive/equivocal EIA plus positive IgG WB Negative samples with strong clinical suspicion of Lyme disease also tested using the WB
Incidence	Tayside: 2.51 per 100,000 (2001/02) 16.8 per 100,000 (2009/10) Highland: 25.4 per 100,000 (2006/07) 56.4 per 100,000 (2009/10) Rest of Scotland: 0.8 per 100,000 (2005/06) 5.5 per 100,000 (2009/10)
Quality assessment	Subjects and setting not described in detail; test interpretation criteria revised during study period

Reference	Smith 2000[37]
Data source	Questionnaires sent to laboratories by the Public Health Laboratory Services reference lab n=227 (1986-1992) n=235 (1992-1996) n=334 (1996-1998)
Region or catchment area	England and Wales Reports from 68 counties (only 14 counties had more than 10 cases each); 219 from Hampshire, 72 from Wiltshire, 61 from Dorset, 47 from Devon, 32 from Somerset, 29 from Norfolk 118 acquired abroad (mainly USA, France, Germany, Austria and Scandinavia)
Time period	1986-1992 and 1992-1996 Enhanced surveillance from 1996-1998
Case definition	Two-tier testing: antibody screening test followed by immunoblot of reactive or equivocal samples
Incidence	0.06 per 100,000 (average annual rate from 1986-1992) 0.11 per 100,000 (average annual rate from 1992-1996) 0.32 per 100,000 (average annual rate from 1996-1998)
Quality assessment	Study participants not sampled in an appropriate way; subjects and setting not described in detail; unclear if valid methods used for identification of the condition

Appendix E: Forest plots

None.

Appendix F:GRADE tables

None.

Appendix G: Health economic evidence selection

None.

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 9: Studies excluded from the clinical review

Study	Reason for exclusion
Ai 1994[1]	Not conducted in the UK
Alpert 1992[2]	Not reliable incidence data
Asbrink 1993[3]	Literature review
Bennet 2006[4]	Not conducted in the UK
Beytout 2007[5]	Not conducted in the UK
Bleyenheuft 2015[6]	Not conducted in the UK
Christen 1993[7]	Not conducted in the UK
Cisak 2014[8]	Not conducted in the UK; analysis of ticks
Cutler 2001[10]	Literature review
Dressler 1994[11]	Literature review
Fahrer 1991[12]	Not conducted in the UK
Garro 2011[13]	Not conducted in the UK
Guy 1989[14]	No incidence or prevalence data
Ho-Yen 1990[15]	Case series of Lyme disease patients
Joss 2003[18]	No incidence or prevalence data
Kazmierczak 1992[19]	Literature review
Li 2016[20]	No incidence or prevalence data
McGarry 2001[24]	No incidence or prevalence data
Medlock 2015[25]	Literature review
Muhlemann 1984[27]	Case series of Lyme disease patients
Muhlemann 1987[28]	No incidence or prevalence data
O'Connell 1995[30]	Literature review
Rees 1994[32]	No incidence or prevalence data
Roberts 2003[33]	No incidence or prevalence data
Robertson 2000[34]	No incidence or prevalence data
Santino 1997[35]	Literature review
Sodermark 2017[38]	Not conducted in the UK
Sykes 2016[39]	Systematic review; references screened
Thomas 1998[40]	No reliable national or regional incidence or prevalence data
Waindok 2017[41]	Not conducted in the UK
Zintl 2017[42]	Literature review

I.2 Excluded health economic studies

None.

Appendix J: Research recommendations

J.1 Clinical epidemiology of Lyme disease in the UK

Research question: What are the incidence, presenting features, management and outcome of Lyme disease, including in women with Lyme disease who are pregnant, in the UK?

Why this is important:

There is a lack of robust epidemiological data on Lyme disease in the UK population, particularly in those who are immunocompromised or pregnant. A large clinico-epidemiological study to collect data on incidence, presenting clinical features, management and outcome of Lyme disease in community and hospital settings in the UK would generate population-based statistics. These statistics would enable interventions such as antibiotic treatment and service improvements to be assessed properly and for services to be tailored so they best serve people with Lyme disease; this was felt to be of high priority. There is no current requirement to notify cases of Lyme disease, therefore, current data are likely to under-estimate the number of people who are seen and treated in the community without serological testing. The morbidity of those who are not rapidly diagnosed and those who seek and receive non-standardised care outside the NHS would justify the costs of this large study.

Criteria for selecting high-priority research recommendations:

PICO question	The questions that should be answered are: • What is the epidemiology of Lyme disease UK? • How and where is Lyme disease treated? • What are the clinical presentations of Lyme disease? • What are short- and long-term outcomes of Lyme disease? • What are short- and long-term outcomes of Lyme disease in pregnant women and in children of mothers who had Lyme disease during pregnancy?
Importance to patients or the population	Information on the epidemiology and the clinical features of Lyme disease can help shape services so they best serve patients. Patients will benefit from improved and tailored services.
Relevance to NICE guidance	This research will provide baseline data on the impact of Lyme disease in the UK population and help inform future guidance on effective service improvement methodologies.
Relevance to the NHS	Information on the epidemiology of Lyme disease will help assess interventions and service improvements. It can also assist in shaping services so they best serve patients with Lyme disease. This research can also provide assurance of guideline implementation, which will further drive service improvement.
National priorities	No
Current evidence base	There is a lack of current national statistics for Lyme disease with poor coding of episodes of Lyme disease and limited knowledge of UK Lyme disease epidemiology. There is also a general lack of evidence for mother-to-child transmission and outcomes related to Lyme disease during pregnancy.
Equality	None relevant
Study design	Prospective cohort study. A long study duration is crucial as it can provide more detailed and reliable data on the clinic-epidemiological features of Lyme disease, especially for relatively rare situations, such as Lyme disease during pregnancy.

Feasibility	The cost of this research will be offset by a reduction in cost for the NHS due to improved, tailored and more efficient services, as well as improved patient outcomes.
Other comments	
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

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