

Department of Health Reviews Facility

To support national policy development and implementation

A systematic evidence map of research on Lyme disease in humans



Gillian Stokes, Laurence Blanchard, Katy Sutcliffe, Kelly Dickson, Ginny Brunton, Helen Burchett, Julie Jones-Diette, Kate Hinds, Meena Khatwa, Theo Lorenc, Claire Khouja, Ruth Walker, Antonio Rojas-Garcia, Rebecca Rees, Melissa Harden, Claire Stansfield, Amanda Sowden, James Thomas

December 2017

The Department of Health Reviews Facility is a collaboration between the following centres of excellence

The authors of this report are: G Stokes¹, L Blanchard², K Sutcliffe¹, K Dickson¹, G Brunton¹, H Burchett², J Jones-Diette³, K Hinds¹, M Khatwa¹, T Lorenc³, C Khouja³, R Walker³, A Rojas-Garcia⁴, R Rees¹, M Harden³, C Stansfield¹, A Sowden³, J Thomas¹

¹ Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre), Social Science Research Unit, UCL Institute of Education, University College London, UK

² London School of Hygiene & Tropical Medicine, London, UK

³ Centre for Reviews and Dissemination, University of York, York, UK

⁴ Department of Applied Health Research, University College London, UK

Acknowledgements

We would like to acknowledge and give thanks for the valuable contribution of patient advocacy group members who attended our consultation sessions and who provided feedback to our survey on the key findings. Participating groups included:- About Time for Lyme, Caudwell LymeCo Charity, Fight Lyme Now, Lyme Disease Action, Lyme Disease UK, VIRAS and Vis-a-Vis Symposiums.

Thanks also go to the members of our scientific advisory group, Public Health England (PHE) and the Department of Health team who provided guidance on the direction of the reviews. We would also like to thank the team undertaking the NICE reviews with whom we worked to ensure synergy between our concurrent programmes of work.

Funding

This is an independent report commissioned and funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the Department.

Funder involvement

This work is part of an ongoing programme of work funded by the Department of Health (DH) England. Throughout the review, the DH policy team members were consulted to understand the context of the issue under study, collaborated on the development of the research question(s), and informed the focus of the review findings.

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.

Guarantor of the review

James Thomas, Professor of Social Research and Policy, EPPI-Centre, Social Science Research Unit, UCL Institute of Education University College London.

This report should be cited as:

Stokes G, Blanchard L, Sutcliffe K, Dickson K, Brunton G, Burchett H, Jones-Diette J, Hinds K, Khatwa M, Lorenc T, Khouja C, Walker R, Rojas-Garcia A, Rees R, Harden M, Stansfield C, Sowden A, Thomas J (2017) *A Systematic Evidence Map of Research on Lyme disease in Humans*. London: EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London.

ISBN: 978-1-907345-98-2

© Copyright 2017

Authors of the systematic reviews on the EPPI-Centre website (<http://eppi.ioe.ac.uk/>) hold the copyright for the text of their reviews. The authors give permission for users of the review to display and print the contents of the review for their own non-commercial use, provided that the materials are not modified, copyright and other proprietary notices contained in the materials are retained, and the source of the material is cited clearly, following the citation details provided. Otherwise, users are not permitted to duplicate, reproduce, republish, distribute, or store the review without written permission.

Contents

Executive Summary	1
Background	1
Review questions and methods	1
Findings	1
Conclusions	3
1 Background	4
1.1 Lyme disease	4
1.2 What is known about the evidence base relating to Lyme disease in humans?	4
1.3 The purpose and value of evidence mapping	5
2 Aims and methods	6
2.1 Aims	6
2.2 Methods	6
3 Findings	8
3.1 Flow of literature through the review	8
3.2 Overview of all included papers	9
3.3 Papers on diagnosis of Lyme disease	12
3.4 Papers on symptoms and co-occurring conditions of Lyme disease	14
3.5 Papers on incidence and prevalence of Lyme disease	16
3.6 Papers on prevention of Lyme disease	19
3.7 Papers on treatment for Lyme disease	22
3.8 Papers on the risk factors for Lyme disease	24
3.9 Papers on the cost assessment of Lyme disease	26
3.10 Papers on multiple aspects of Lyme disease	28
3.11 Systematic reviews on Lyme disease	30
3.12 Media scan on Lyme disease	35

4	Discussion and conclusions	37
5	Detailed methods	41
5.1	Aims	41
5.2	Methods	41
6	References*	46
	Appendices	49
	Appendix 1: Example search strategy	49
	Appendix 2: Flow of literature through the review	50
	Appendix 3: Number of papers by country*	51
Figures		
	Figure 3.2.1 Number of papers by year of publication (n=1,098)	9
	Figure 3.2.2 Number of papers by continent* (n=1,098)	10
	Figure 3.2.3 Population focus of included papers* (n=1,098)	10
	Figure 3.2.4 Aspect of Lyme disease (n=1,098)	11
	Figure 3.2.5 Aspect of Lyme disease by continent* (n=1,079)	11
	Figure 3.2.6 Aspect of Lyme disease by year* (n=1,098)	12
	Figure 3.3.1 Diagnosis papers by research aims and diagnostic approach (n=310)*	13
	Figure 3.4.1 Research aims of papers on symptoms and co-occurring conditions (n=283)	15
	Figure 3.5.1 Research aims of papers on the incidence and prevalence of Lyme disease (n=189)	17
	Figure 3.5.2 Population focus of papers which examine the incidence and prevalence of Lyme disease (n=189)	18
	Figure 3.6.1 Research aims of papers on prevention knowledge and behaviour (n=42)*	20
	Figure 3.6.2 Research aims of papers on prevention interventions (n=40)	20
	Figure 3.7.1 Research aims of papers on the treatment of Lyme disease (n=78)	23
	Figure 3.8.1 Research aims of papers on risk factors of Lyme disease (n=46)	25

How to read this report

This report commences with a brief summary which focuses on gaps in the evidence base and implications for future research. This is followed by a brief background chapter (one) and the aims and methods in chapter two. The findings chapter (three) starts with an overview of the results from the search and a descriptive overview of all the papers included in the map. The findings are then presented, in turn, for each sub-set of papers determined by the topic focus (e.g., diagnosis, symptoms and co-occurring conditions, treatment, etc.). In chapter five, a discussion of the map's overall findings and its conclusions are presented. This is followed by a detailed methods chapter (five), which presents the handling of the reports identified, screened, and otherwise examined, during the mapping process. An example search strategy is provided in the appendix. A catalogue of the included papers by sub-set is provided in supplementary files.

Executive 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 is part 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 contains a systematic evidence map; it provides a descriptive overview of the available research on Lyme disease in humans.

Review questions and methods

The systematic map aimed to address the following question:

- *What is the nature and extent of empirical research evidence on Lyme disease in humans?*

We searched 17 electronic databases and conducted additional web-based searching for unpublished and grey literature. Papers were included in the map if they reported empirical research, published in or since 2002, on Lyme disease in humans. All papers were coded in relation to their topic focus and key characteristics. Papers were categorised into one of nine groups; seven groups reflect the aspect of Lyme that the paper primarily focused on: i.e. diagnosis; symptoms and co-occurring conditions; incidence and prevalence; prevention; treatment; risk factors; and costs. The remaining two groups cover systematic reviews and papers which focus on more than one of the above categories, for example, papers focusing on both diagnosis and treatment. In addition to mapping the research literature, we also undertook a brief scan of the most popular websites to understand the sources of information that are available to the public through online searches.

Findings

A large, diverse and growing body of literature on Lyme disease was identified. In total, 1,098 papers were included, with publications in the field of Lyme disease increasing steadily since 2002. The majority of papers were from Europe (n=631); approximately five percent (n=47) were from the UK. There was a particularly predominant evidence base from the USA (n=404 papers).

Almost three quarters of papers focused on just three aspects of Lyme disease; diagnosis (n=310), symptoms and co-occurring conditions (n=283), and incidence and prevalence of Lyme disease (n=189). Far fewer papers focused on Lyme disease prevention (n=82), treatment (n=78), risk factors (n=46), or costs (n=10). Eighty-one papers focused on more than one of the above aspects of Lyme disease, and 19 were systematic reviews.

Most of the diagnosis papers focused on the accuracy of diagnostic tests (n=253). Of the remainder, 19 focused on patient experiences of diagnosis, 18 focused on clinician knowledge and behaviours in relation to diagnosis, and 21 focused on other diagnosis-

related issues. One paper reported both clinician views and the accuracy of diagnostic tests.

Papers on symptoms, co-infections and co-occurring conditions (n=283), focused either on symptoms or manifestations of Lyme, such as Lyme neuroborreliosis or Lyme arthritis (n=73), on the association between Lyme disease and other tick-borne infections (n=41), or on the association between Lyme disease and other conditions, such as Parkinson's disease (n=156). A small number focused on other symptom-related issues (n=13).

The incidence and prevalence papers (n=189) predominantly focused on incidence (i.e. new cases of Lyme disease in a population) (n=126), with fewer measuring prevalence (i.e. the total number of cases within a population) (n=60). A very small number of papers focused on both incidence and prevalence (n=3).

Papers on the prevention of Lyme disease (n=82) focused either on people's knowledge and behaviour (n=42) or on the effectiveness or cost-effectiveness of interventions to prevent Lyme disease (n=40).

Approximately one third of treatment papers examined the safety or effectiveness of one specific type of antibiotic (n=24) or other specific treatment (n=2). Other papers examined multiple antibiotic treatments (n=23), either used together as combination therapies, or to compare the effectiveness of one treatment versus another. The remainder (n=29), focused on specific patients, rather than specific treatments; that is, they examined whether symptoms had resolved in a cohort of patients who received antibiotic treatment of any kind.

Papers on risk factors (n=46) examined whether the risk of Lyme disease infection was affected by season/climate (n=10), landscape factors (n=6), residential location (n=4), contact with animals (n=3), or other factors (n=3). Four papers examined the risk of human-to-human transmission (n=4). Sixteen papers examined more than one of the above risk factors.

Of the few cost assessments identified (n=10), the majority (n=7) provided information on costs or resource use relating to the diagnosis and treatment of Lyme disease; the remainder (n=3) evaluated the relative costs and outcomes of different diagnostic and/or treatment approaches.

Of the papers that explicitly aimed to examine more than one of the above aspects of Lyme disease (n=81), almost half focused on both symptoms and treatment (n=35). Other common combinations included incidence and prevalence and risk factors (n=12), diagnosis, symptoms and treatment (n=7) or symptoms, treatment and incidence and prevalence (n=7).

We identified 19 systematic reviews; these focused on diagnosis (n=4), symptoms and co-occurring conditions (n=2), incidence and prevalence (n=1), prevention (n=4), treatment (n=6), and risk factors (n=1).

In the media scan, we found that the majority of webpages (n=9), on the first page of a Google search, gave factual information about the condition, with NHS Choices being the most consulted page.

As part of the broader project on Lyme disease, studies were identified from within this map to populate four in-depth systematic reviews. These reviews focus on: 1) the incidence and surveillance of Lyme disease (Lorenc et al. 2017); 2) experiences of Lyme disease diagnosis (Brunton et al. 2017); 3) experiences of treatment for Lyme disease (Sutcliffe et al. 2017a); and 4) prevention of Lyme disease (Richardson et al. 2017).

Conclusions

There is little research that focuses on specific vulnerable populations other than children, for example, older people and pregnant women. There is limited research into the diagnosis of Lyme disease via signs and symptoms, as opposed to via laboratory tests. There are relatively few papers on treatment and prevention; in particular, more controlled-design studies might prove beneficial for these topics. There is limited research on the risk factors and the costs associated with Lyme disease. Research into Lyme disease might also benefit from papers that focus on more clearly defined populations, interventions or outcomes, and are clearly reported.

1 Background

This report is part of a series of reports on Lyme disease, commissioned by the Department of Health (England) (DH) 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) patient, clinician and researcher experiences of the diagnosis of Lyme disease
- 3) patient, clinician and researcher experiences of treatment for Lyme disease
- 4) prevention of Lyme disease

This report contains the findings from the systematic evidence map.

The objective of this map is to provide a comprehensive overview of available research evidence relating to Lyme disease in humans. Our aim was to produce a descriptive account of the key characteristics of papers and identify any gaps in the research evidence base.

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 (PHE 2015).

In many cases, an early sign of the infection is an erythema-migrans or ‘bull’s-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 What is known about the evidence base relating to Lyme disease in humans?

There exist a number of recent systematic reviews on Lyme disease that have focused on: the existence of chronic Lyme disease (Lantos and Wormser 2014; Lantos et al. 2015), the effectiveness of preventative efforts (Mowbray et al. 2012, Beaujean et al. 2016a and b), diagnostic test accuracy for Lyme disease (Leeflang et al. 2016) and on the treatment of Lyme disease (Dersch 2015a and b). The National Institute for Health and Care Excellence

¹ We refer here to ‘*Borrelia burgdorferi sensu lato*’ which includes all sub-species (including *burgdorferi sensu stricto*, *afzelii*, *garinii*, *mayonii*, *bissettii*, *lusitaniae* and *spielmanii*). We have used the abbreviated phrase in the text for improved accessibility.

(NICE) is also, presently, undertaking a series of evidence reviews which aim to inform the development of a clinical guideline on the diagnosis and management of Lyme disease. This work will include reviews of the evidence on the accuracy of diagnosis techniques and on the effectiveness of treatment. However, these systematic reviews each examine a single aspect of Lyme disease, to our knowledge, there have been no previous attempts to systematically identify and map the full range of existing literature on Lyme disease.

1.3 The purpose and value of evidence mapping

This report takes the form of a systematic evidence map (Gough et al. 2017). Systematic evidence maps describe and characterise research evidence, for example, in terms of the countries, research designs or populations focused on, or the methodologies used. Maps are distinct from systematic reviews as they do not involve assessment of research quality or synthesis of research findings, they are purely descriptive in nature. The benefits of systematic evidence maps lie in their ability to provide a broad overview of a particular research field, to identify gaps in the evidence base or help to prioritise the research questions that are appropriate for systematic review (Snilstveit et al. 2013; Sutcliffe et al. 2017b). To enable readers to understand the landscape of research on a particular topic, maps should consist of a systematic search of a broad topic area, with the results presented in an easily navigable and user-friendly format (Miake-Lye et al. 2016).

The purpose of this systematic evidence map, therefore, is to comprehensively describe the research field relating to Lyme disease in humans. The aim is to facilitate a greater understanding of what has been investigated and to identify areas which require further investigation.

2 Aims and methods

This section provides a brief overview of the methods used to conduct this systematic evidence map. A more detailed account of the methods is provided in Chapter 5.

2.1 Aims

The primary aim of the systematic evidence map is to describe the nature and range of available research evidence pertaining to Lyme disease in humans. To achieve this, this map describes the key characteristics of research papers and identifies gaps in the research evidence base.

A secondary, or minor, aim of the project was to undertake a ‘media scan’ to identify the most popular websites relating to Lyme disease to understand the sources of information available to the public through online searches.

2.1.1 Review questions

The evidence map aimed to address the following question:

- *What is the nature and extent of empirical research evidence on Lyme disease in humans?*

2.2 Methods

2.2.1 Study identification

The systematic evidence map aimed to cover the breadth of research evidence on Lyme disease in humans. As such, a maximally sensitive search strategy was employed consisting of a single cluster of terms for Lyme disease. Details of the search strategy and databases used are provided in Chapter 5; an example search is shown in Appendix 1.

2.2.2 Inclusion criteria

To be included in the map papers needed to:

- Be published in or after 2002.
- Be published in the English Language.
- Be about Lyme disease.
- Be an empirical research study OR systematic review.
- Be about Lyme disease in humans.
- Not focus purely on markers or mechanisms of Lyme disease within blood samples, tissue samples, or cells.

Further detail on the rationale for these criteria is provided in section 5.2.2.

2.2.3 Data extraction and quality appraisal

Reviewers extracted descriptive data from the included papers, using coding tools developed specifically for the map. The following information was extracted from all papers:

- **Bibliographic details:** e.g., publication details, date.
- **Geographical location:** continent and individual country.
- **Population:** e.g., children, adults, high-risk groups.
- **Aspect of Lyme:** e.g., diagnosis, treatment, prevention.

Coding tools, specific to each aspect of Lyme, focused on capturing more detailed information. Where relevant, this included research design (e.g., aim, research method); focus of investigation (e.g., type of diagnostic test, treatment or prevention programme); outcomes; and other contextual details.

The figures reported denote individual publications, referred to as papers. There are potentially numerous linked papers, i.e. single studies reported in multiple papers or single papers that report on multiple studies. However, the large volume of included papers precluded the identification of all linked studies.

2.2.4 Quality assurance

Papers for the map were initially screened independently by two reviewers at both the title and abstract and full-text screening stages, in order to identify potential differences in interpretation of the criteria and refine the guidance for reviewers. Screening was conducted by single reviewers, once an agreement rate of 90% was achieved. Papers were then coded by two reviewers, due to the complex nature of the identified papers, in order to ensure that the appropriate information was identified and extracted. To ensure consistency and accuracy in reporting, data cleaning steps were taken, such as checking that papers were not double coded, or coded and subsequently excluded.

2.2.5 Media Scan

We carried out a simple search on the internet, on the 31st July, 2017, and investigated the first page of results, in order to assess the source and content of the most popular pages relating to Lyme disease.

3 Findings

Summary of findings

- 1,098 research papers met the criteria for inclusion in the map.
- Research interest in Lyme disease appears to have steadily increased since 2002.
- Most of the research comes from Europe and North America.
- The majority of papers focus on three aspects of Lyme disease: diagnosis; symptoms and co-occurring conditions; and incidence and prevalence.
- Far fewer papers focus on Lyme disease treatment, prevention, risk factors or costs.
- Some papers focus on more than one of the above aspects of Lyme disease and some report systematic reviews.

The first section of this chapter (3.1) reports on the flow of literature through the review. The next section provides an overview of all of the included papers (3.2). The following sections provide additional detail on the papers that focus on specific aspects of Lyme disease, including: diagnosis (3.3), symptoms and co-occurring conditions (3.4), incidence and prevalence (3.5), prevention (3.6), treatment (3.7), risk factors (3.8), and costs (3.9). Further, we present information on the papers that investigated multiple aspects of Lyme disease (3.10) and systematic reviews that focused on Lyme disease (3.11). Due to the high number of papers included in this map, references are not included within the write-up; instead a comprehensive table of papers is provided for each aspect of Lyme disease (see Appendices 4 to 12).

3.1 Flow of literature through the review

52,268 references were identified from the bibliographic database searches conducted in August 2016. Searching of other sources resulted in a further 5,206 references and patient advocacy groups provided us with 62 more. Of these, 29,541 were duplicates and 1,533 were removed because of publication year (published before 1980²) or type (notes, letters, editorials and book reviews). This resulted in 21,174 references being screened on title and abstract; 13,621 were excluded at this stage. Of the remaining 7,553 potential includes, we were able to obtain and re-screen 7,524 full-text papers. At this second stage of screening 6,440 reports were excluded, of which more than half were published before 2002. This resulted in 1,098 papers that met all inclusion criteria (see Supplementary File 1 for the references of included papers). A diagram illustrating the flow of literature through the review is provided in Appendix 2.

² This initial cut-off was used before 2002 was selected with the scientific advisory group; the initial rationale being that since the causal organism and transmission vector of Lyme disease was first identified in 1982, searching for papers published prior to that time would not be fruitful.

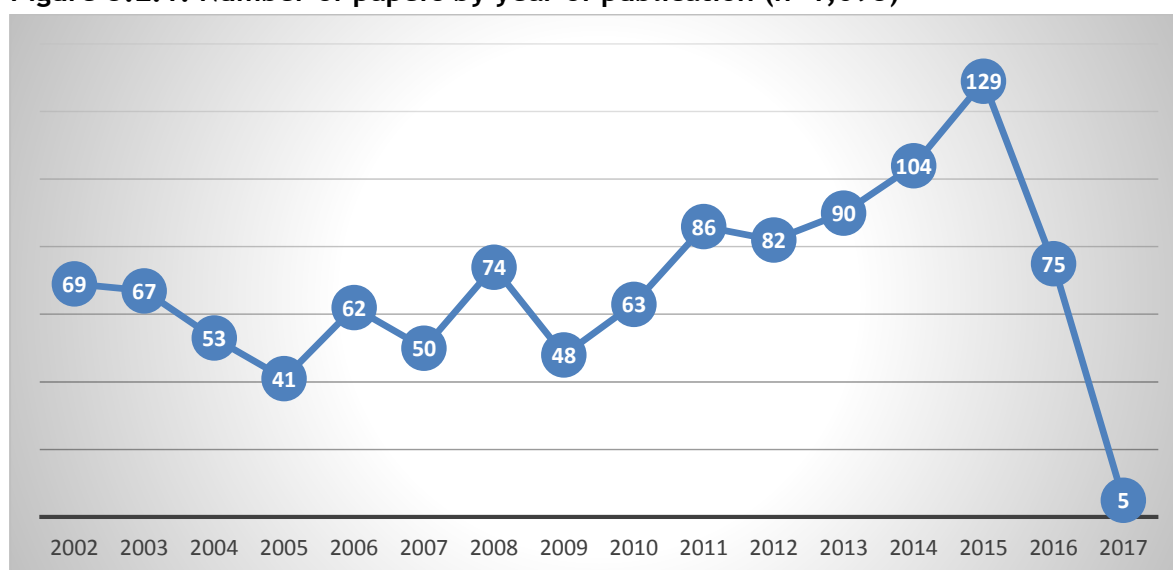
3.2 Overview of all included papers

An overview of the 1,098 included papers and their key characteristics is provided below. We document the number of papers by year of publication, geographical location, population and aspect of Lyme disease focused on.

3.2.1 When were the papers published?

The number of published papers on Lyme disease remained relatively stable between 2002 and 2010, when it started to increase (Figure 3.2.1). The number for 2016 does not include figures for the latter part of August, and September to December, as database searches were completed in August 2016. The small number of papers from 2017 were provided by stakeholders during consultation, and are, therefore, not representative of the literature published in the whole year.

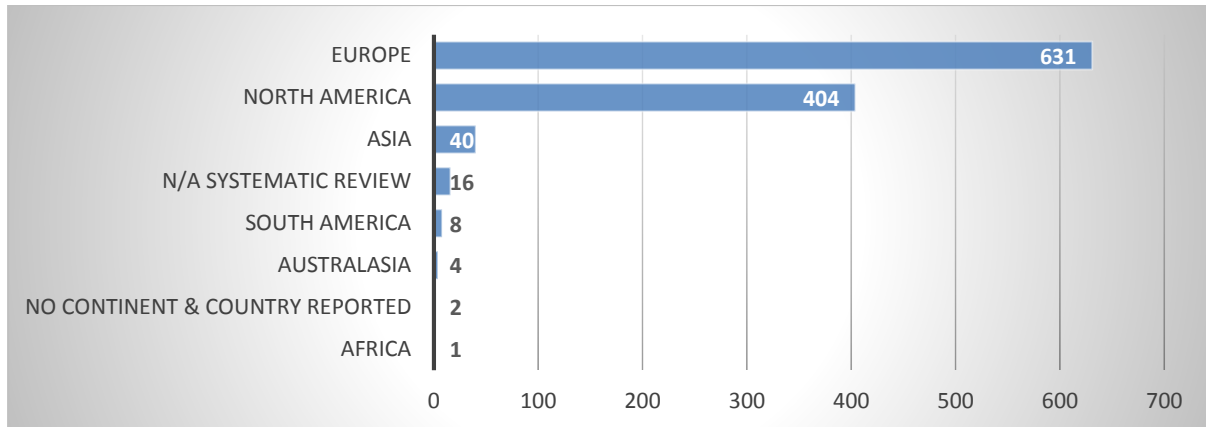
Figure 3.2.1: Number of papers by year of publication (n=1,098)



3.2.2 Which countries were the papers from?

More than half of papers originated from Europe (n=631), and over a third from North America (n=404) (see figure 3.2.2). This is consistent with the wide recognition of the presence of the disease in these two continents. Few papers focused on studies from other continents, including only one in Africa. Germany (n=80), Poland (n=58), Sweden (n=52) and the UK (n=46) were the European countries that accounted for the most papers on Lyme disease. In North America, most publications were from the USA (n=371). Some papers focused on more than one country or continent. The 19 systematic reviews (SR) included papers from multiple countries and were, therefore, grouped separately. Appendix 3 lists the number of publications by continent and country.

Figure 3.2.2: Number of papers by continent* (n=1,098)

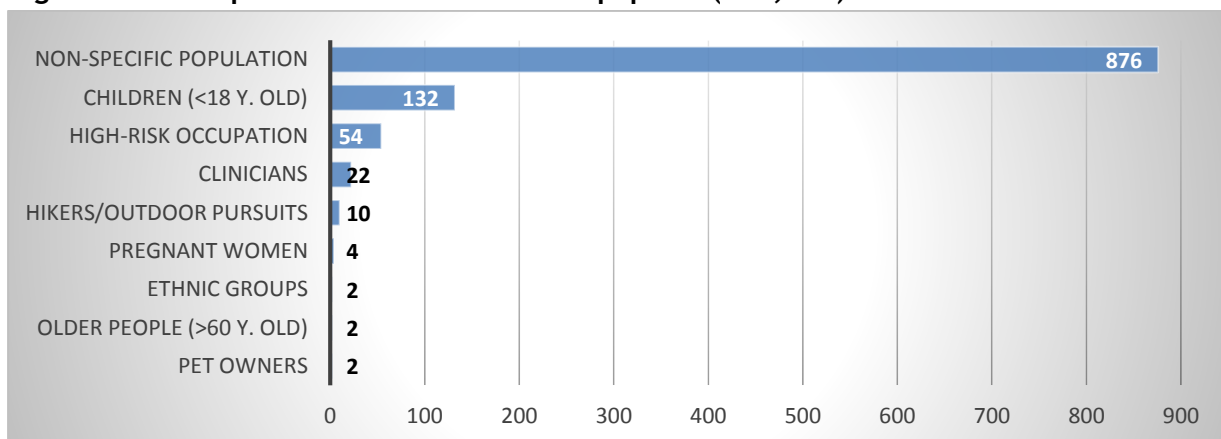


* Categories are not mutually exclusive

3.2.3 Which populations did the papers focus on?

We coded the population focus of the papers as either a) groups with specific characteristics, including sociodemographic characteristics (age, ethnicity, or pregnant women), or people who carry out activities associated with an increased risk of Lyme disease (hiking, occupation, or pet owners) or clinicians; or b) as “nonspecific”, i.e. the paper does not focus on one of the above. As shown in Figure 3.2.3, the majority of papers reported on non-specific populations (n=876). This is followed by papers that focused on children (under 18 years old) (n=132) and those in high-risk occupations, such as forestry workers (n=54). Twenty-two papers focused on clinicians and only a handful focused on pregnant women (n=4) or ethnic groups, older people (>60 y. old) and pet owners (n=2 each).

Figure 3.2.3: Population focus of included papers* (n=1,098)



* Categories are not mutually exclusive

3.2.4 Which aspect of Lyme disease did the papers focus on?

We classified the included papers into one of nine mutually exclusive topic groups based on the aspect of Lyme disease that they focused on or if they were systematic reviews (Fig. 3.2.4). The most common aspects of Lyme disease studied were diagnosis (n=310), symptoms and co-occurring conditions (n=283) and incidence/prevalence (n=189). Substantially fewer papers focused on Lyme disease prevention (n=82), treatment for

Lyme disease (n=78), risk factors for Lyme disease (n=46) and economic factors (n=10). Further, we identified 19 systematic reviews and 81 papers which explicitly aimed to investigate more than one of the above Lyme disease topics.

Figure 3.2.4: Aspect of Lyme disease (n=1,098)

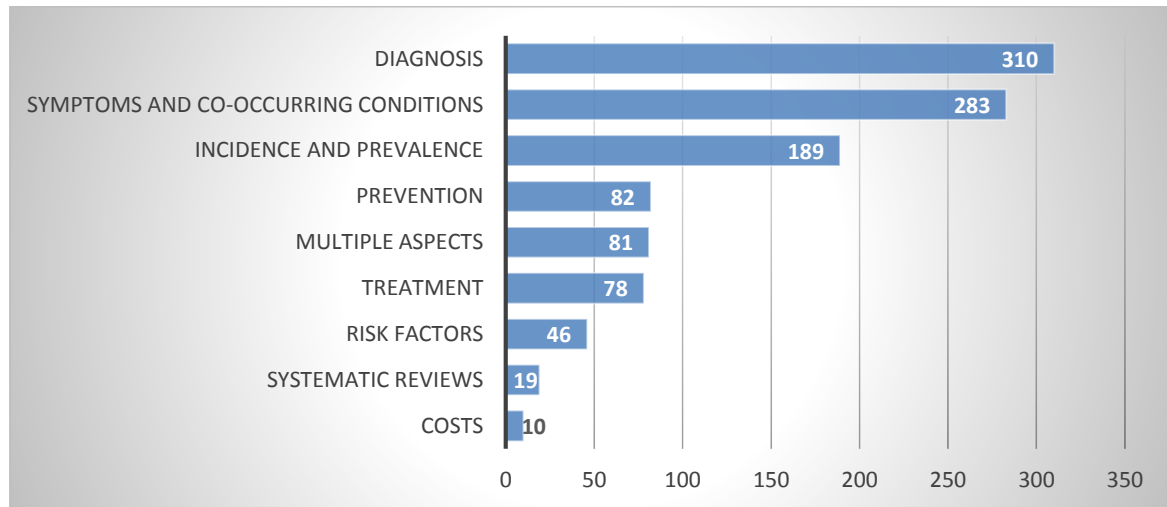
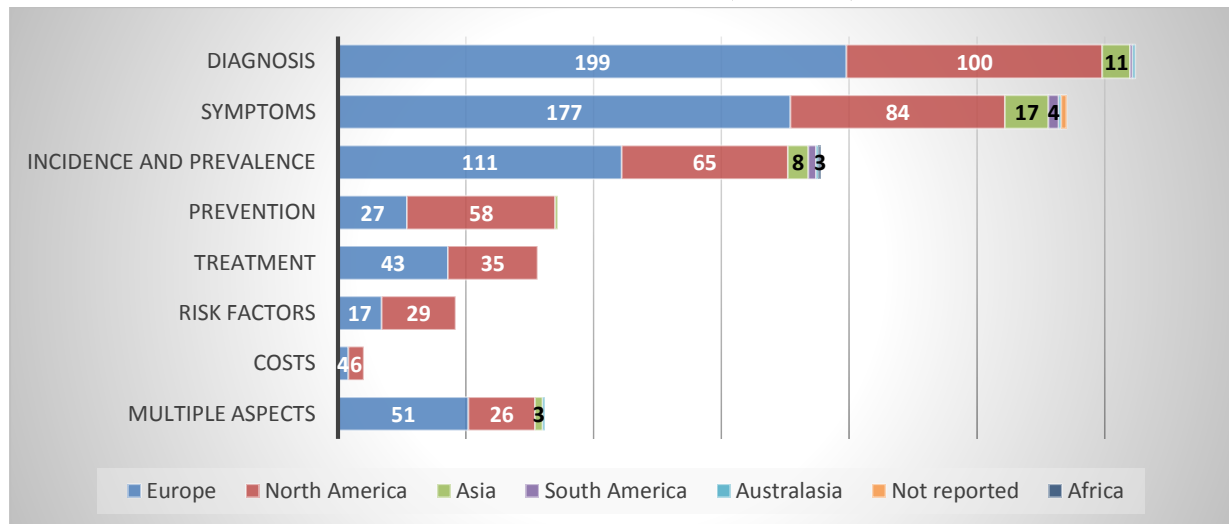


Figure 3.2.5, below, illustrates that for most aspects of Lyme disease, European papers accounted for the largest proportion, followed by papers from North America. However, among the papers on prevention and risk factors and costs, the largest proportion came from North America.

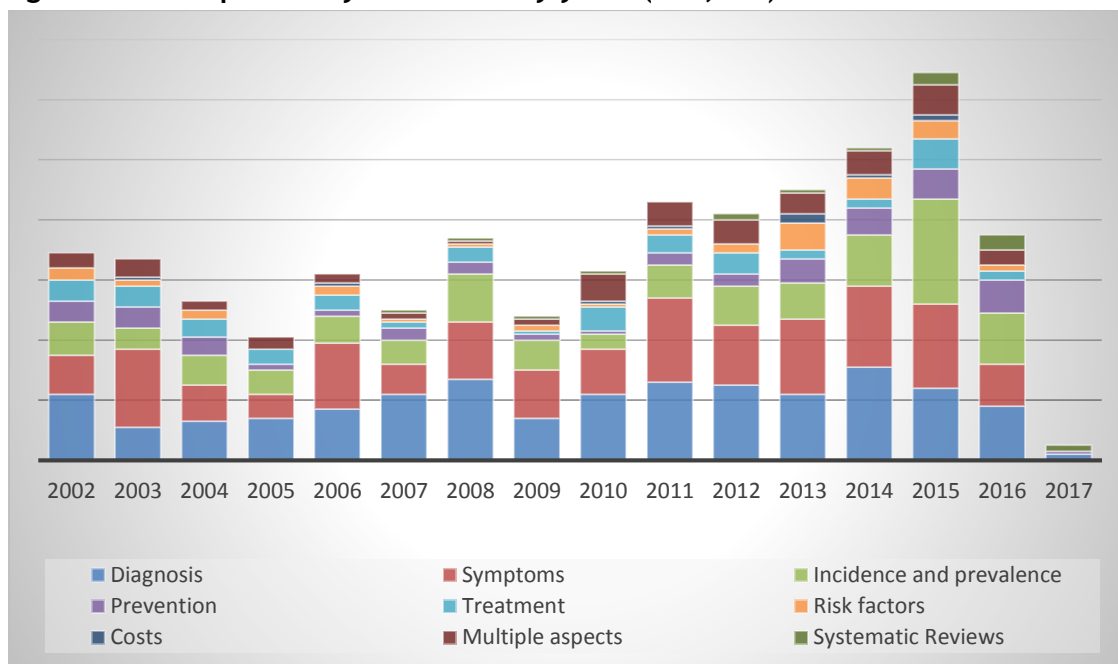
Figure 3.2.5: Aspect of Lyme disease by continent* (n=1,079)



*All papers except the 19 systematic reviews are included in this figure. Data labels for continents with two papers or fewer are not displayed.

Figure 3.2.6, below, illustrates the focus on different aspects of Lyme disease for each year; as noted above, the figures for 2016 and 2017 are incomplete. For most years the largest proportion of papers focused on diagnosis, but this was not the case for 2003, 2006, 2011 or 2013 when there were more papers on symptoms and co-occurring conditions. The most recent year for which we have complete data (2015) is the first year in which papers on incidence and prevalence accounted for the largest proportion.

Figure 3.2.6: Aspect of Lyme disease by year* (n=1,098)



These findings illustrate that the body of research on Lyme disease in humans, published since 2002, is large, diverse and growing. The following sections provide more detail on the nature of the papers focusing on each of the different aspects of Lyme disease.

3.3 Papers on diagnosis of Lyme disease

Nature of the evidence: Papers on the diagnosis of Lyme disease in humans.

Extent of evidence: 310 papers.

Research aims: The majority of papers assessed the accuracy of tests for diagnosing Lyme disease (n=253). The remainder explored patient views of diagnosis (n=19), clinician knowledge and/or behaviours relating to Lyme disease diagnosis (n=18), or other diagnosis-related issues (n=21). One paper focused on both test accuracy and clinician knowledge/behaviours.

Diagnostic focus: The majority of papers focused on laboratory tests for diagnosing Lyme (n=234); a minority focused on symptom-based diagnosis (n=48) and nine investigated both. The diagnosis method was not coded for papers on patient views (n=19).

Context of evidence: 197 papers originated from Europe, 15 of which were from the UK. Ninety-eight papers originated from North America. Two papers focused on both Europe and North America. There were 13 papers from other continents.

3.3.1 Introduction

This section describes the 310 papers that focused on the diagnosis of Lyme disease. A table, with details of each diagnosis paper, can be found in Supplementary File 2,

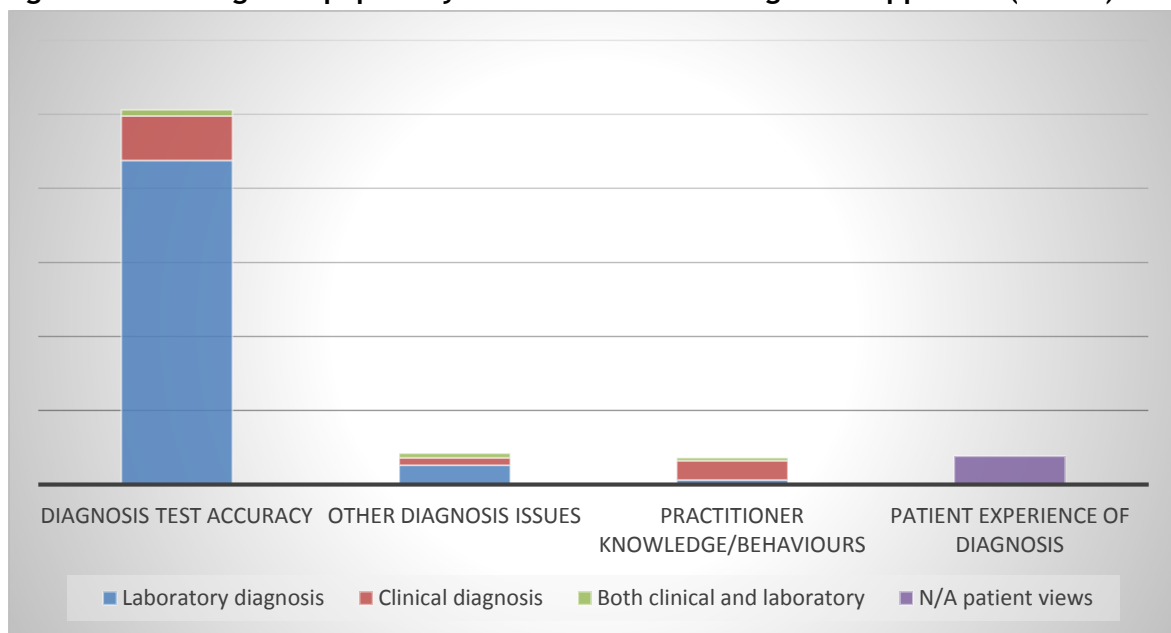
Appendix 4. A further 14 papers that focused on diagnosis, alongside other aspects of Lyme disease, are described in section 3.10 on papers with multiple foci.

3.3.2 What were the aims of the included papers?

The majority of papers (n=253) explored diagnostic test accuracy (see figure 3.3.1). Among the remainder (n=57), 19 explored patient experiences of diagnosis, 18 focused on clinician knowledge and/or behaviours, and 21 looked at other aspects of diagnosis. These other papers focused on the misdiagnosis of Lyme disease (n=9), methods for reading and interpreting Western blot test results (n=4), the impact of sample preparation and storage on test outcomes (n=3), diagnosis among Lyme vaccine recipients (n=2), the challenges for laboratories in diagnosing Lyme disease (n=1), the usefulness of testing for Lyme among those with arthritis (n=1), and the association between positive tests and various Lyme disease symptoms (n=1).

Laboratory diagnostic tests were the focus of 234 papers, the remaining papers focused on clinical diagnosis (n=48) or both clinical and laboratory diagnosis (n=9). The diagnosis method was not coded for papers on patient views (n=19).

Figure 3.3.1: Diagnosis papers by research aims and diagnostic approach (n=310)*



*One included paper had two foci.

3.3.3 What research designs were used?

The papers on accuracy of diagnostic tests compared the tests they were studying with a reference standard, such as a clinician diagnosed erythema migrans rash or two-stage ELISA and Western-blot testing. Of the patient views papers, twelve were quantitative surveys and seven were qualitative interview studies. Of the clinician knowledge and behaviours papers, 16 were quantitative surveys, one was a qualitative interview study and one was a retrospective case review to assess clinician adherence to guidelines. A variety of methods were used in the papers on other diagnostic issues.

3.3.4 Who were the research participants?

Most of the papers (n=254) did not focus on a specific population. Of the remainder, 32 focused on children, 18 on clinicians and six on those in high-risk occupations.

3.3.5 Where were the papers from?

Table 3.3.1, below, shows the number of papers by continent. Within the 195 papers that were from Europe, 15 papers focused on the UK. Of these, seven explored patients' views, four examined diagnostic test accuracy, one looked at clinician knowledge/behaviours and three examined other diagnosis issues. Other European papers most commonly came from Germany (n=31), Sweden (n=21), Finland (n=12), Poland (n=12) and Slovenia (n=12).

Table 3.3.1: Diagnosis papers by continent (n=310)

Continent	Number of included papers*
Europe	197
North America	98
Asia	11
South America	1
Australasia	1

*Two papers focused on both Europe and North America

3.4 Papers on symptoms and co-occurring conditions of Lyme disease

Nature of the evidence: Papers that focused on symptoms and co-occurring conditions relating to Lyme disease in humans.

Extent of evidence: 283 papers.

Research aims: Seventy-three papers investigated the characteristics of Lyme disease symptoms or manifestations. The majority of papers examined associations between Lyme disease and other conditions (n=156). Forty-one investigated the association of Lyme disease with other tick-borne infections, and 13 examined other issues.

Context of evidence: Most studies were from Europe (n=177) including 5 from the UK. Others were from North America (n=84), Asia (n=17), South America (n=4), and Australasia (n=1). Two studies did not report the continent/country. Two studies compared evidence from North America and Europe.

3.4.1 Introduction

This section describes the 283 papers that examined Lyme disease symptoms or co-occurring conditions. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 5. A further 61 papers that focused on symptoms, coinfections or co-occurring conditions, alongside other aspects of Lyme disease are described in section 3.10 on papers with multiple foci.

3.4.2 What were the aims of the included papers?

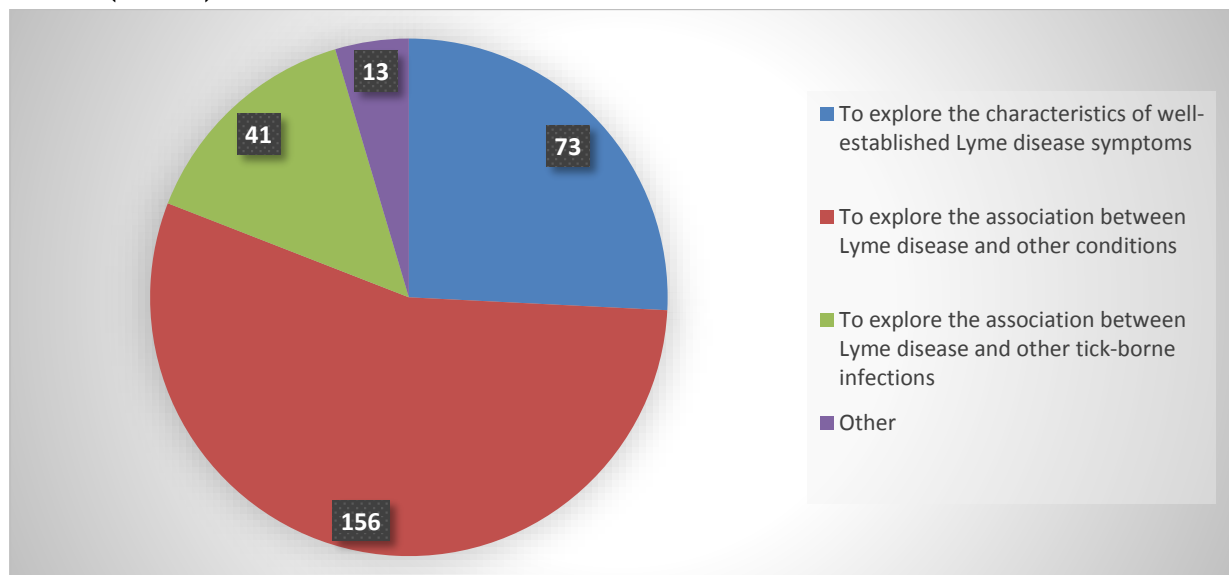
Seventy-three papers investigated the characteristics of well-established Lyme disease symptoms including Lyme neuroborreliosis (n=41), erythema migrans (n=13), Lyme arthritis (n=12), Lyme carditis (n=8) and acrodermatitis chronica atrophicans (n=2). One paper focused on several of the above symptoms.

The majority of papers (n=156) examined whether Lyme disease is associated with other symptoms and conditions (i.e. not those listed above). The conditions examined included Parkinson's disease, dementia, autism and many others. Of the 156 papers, 92 examined the presence of Lyme among populations with another condition, 60 examined the presence of other conditions among populations with Lyme, and four examined the correlation of Lyme with another condition.

Forty-one papers investigated the association of Lyme disease with other tick-borne infections, such as Babesia or Anaplasmosis Rickettsia. Of these, 15 papers examined the presence of tick-borne infections among populations with Lyme, and 16 examined the presence of Lyme disease among those with other tick-borne infections. Seven examined the correlation between Lyme disease and other tick-borne infections in 'healthy' populations - e.g., blood donors. Three papers examined the clinical characteristics of co-infection.

Lastly, 13 papers examined other issues, including the clinical features of early Lyme and the clinical features of those with different strains of infection. See Table 5 in the appendices for details. Figure 3.4.1, below, illustrates the number of papers focusing on each of the different research aims.

Figure 3.4.1: Research aims of papers on symptoms and co-occurring conditions (n=283)



N.B. Figures in pie sections denote numbers of papers and not percentages.

3.4.3 What research designs were used?

The majority of included papers reported that a single-group design was used (n=179); in the remainder (n=104) a controlled/comparative design was used.

3.4.4 Who were the research participants?

Approximately one fifth of the papers focused on children (n=54). Older people, pregnant women and forestry workers were the focus of one paper each. The remainder (n=226) focused on non-specific or general adult populations.

3.4.5 Where were the papers from?

The majority of papers were European (n=177), including five from the UK; European papers were most commonly from Germany (n=26), Poland (n=22), Czech Republic (n=16), Slovenia (n=16), Sweden (n=15), Austria (n=13) and Norway (n=10). Of the remainder, 84 were from North America, 16 were from Asia, four were from South America, and one was from Australasia. Two papers did not report the continent/country. One paper compared evidence from North America and Europe.

3.4.6 Which outcomes were measured?

The most common symptoms studied were neurological (brain) symptoms (n=89), followed by symptoms of the skin (n=44), joints (n=19), heart (n=17), eyes (n=13), immune system (n=4), ears (n=4), and urinary tract (n=2). Two papers examined functioning, three examined fatigue, one examined endocrinal symptoms and one examined flu-like symptoms. Sixteen papers examined other symptoms and 27 examined a range of symptoms. Forty-one focused on co-infections rather than symptoms. Some papers examined more than one symptom.

3.5 Papers on incidence and prevalence of Lyme disease

Nature of the evidence: Papers that focused on the incidence or prevalence of Lyme disease in human populations.

Extent of evidence: 189 papers.

Research aims: Most papers examined Lyme disease incidence (n=126), fewer measured prevalence (n=60), and a very small number measured both (n=3).

Context of evidence: More than half of publications (n=111) examined European populations. In Europe, the UK and Poland were the countries most studied.

3.5.1 Introduction

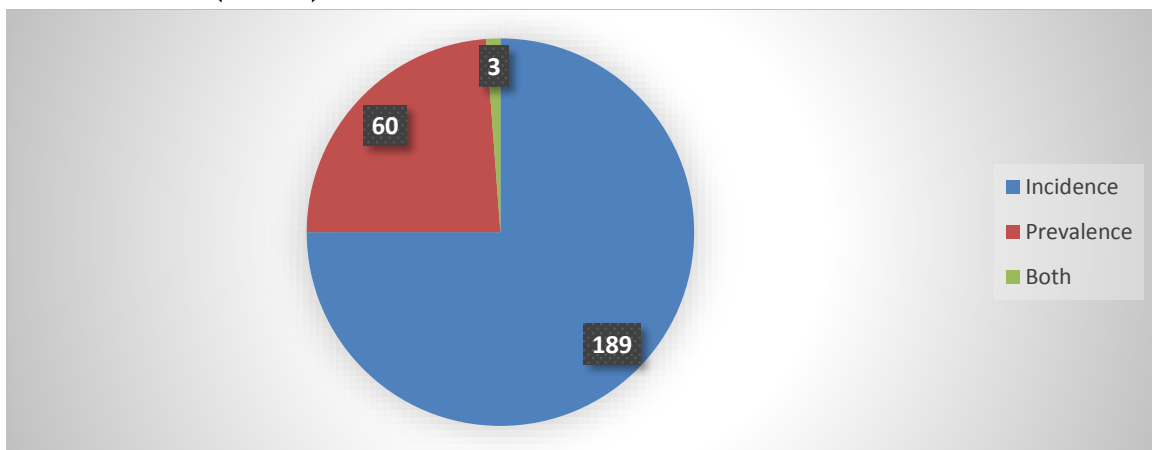
This section describes 189 papers that investigated the incidence and prevalence of Lyme disease in humans. Incidence refers to the measurement of new cases of Lyme disease, while prevalence refers to the total number of existing or seroprevalent cases in the population at a given time. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 6. A further 31 papers that focused on incidence and

prevalence, alongside other aspects of Lyme disease are described in section 3.10 on papers with multiple foci.

3.5.2 What were the aims of the included papers?

Approximately two-thirds of papers focused on incidence (i.e. new cases of Lyme disease in a population) (n=126) with fewer measuring prevalence (i.e. the total number of cases within a population) (n=60). A small number of papers focused on both incidence and prevalence (n=3).

Figure 3.5.1: Research aims of papers on the incidence and prevalence of Lyme disease (n=189)



N.B. Figures in pie sections denote numbers of papers and not percentages.

3.5.3 What sources of data were used?

Most commonly, papers analysed the existing data, including surveillance data (the figures collected by governmental authorities to track Lyme disease) (n=96), medical records (n=28), insurance claims (n=6), and laboratory data (n=6). The remaining papers used data collected as part of a research project (n=82); this includes research in general practices, and hospitals, as well as investigation of blood donors. We identified five further papers that used other sources, in one case the log book from a camp nursery, to estimate incidence and prevalence. In three papers, the data sources were unclear. Some papers used more than one data source.

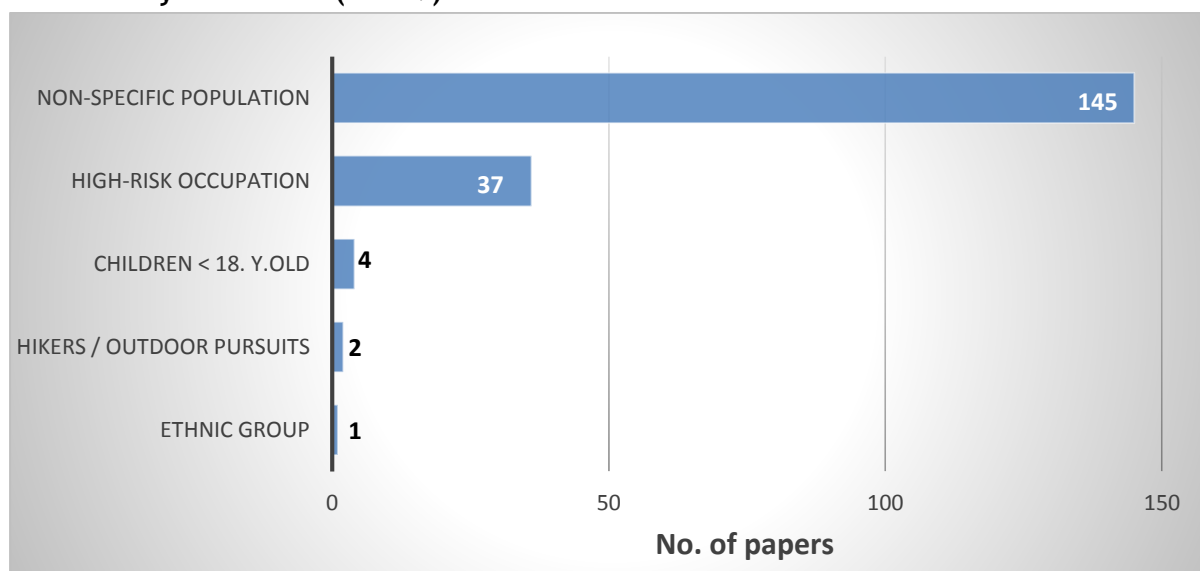
3.5.4 How were the incidence and prevalence of Lyme disease measured?

Most commonly, papers used a combination of laboratory and clinical assessment (n=72) to measure cases of Lyme disease. This is followed by the use of blood serum (n=55) or laboratory diagnosis alone (n=26). The use of clinical measures alone was less common, either via the International Classification of Disease (ICD) system (n=12) or via clinical manifestations (n=6). Patient self-reporting was used in a small number of papers (n=6). Many papers used more than one method. The measurement methods were unclear in 31 papers.

3.5.5 Who were the research participants?

The majority of papers did not focus on a specific population (n=145). “High-risk occupation” is the group which was most examined (n=37). A few papers focused on children (n=4), people who did outdoor activities (n=2), and ethnic groups (n=1).

Figure 3.5.2: Population focus of papers which examine the incidence and prevalence of Lyme disease (n=189)



3.5.6 Where were the papers from?

More than half of papers focused on European populations (n=111), followed by North America (n=65). Table 3.4.1 below shows the number of included papers by continent.

Seventeen papers described the incidence and prevalence of Lyme disease in UK populations, which, along with Poland (n=18), were the most evaluated countries in Europe, followed by Germany (n=12) and Italy (n=8).

Table 3.4.1: Incidence and prevalence papers by continent (n=189)

Continent	Number of included papers
Europe	111
North America and the Caribbean	65
Asia	8
South America	3
Africa	1
Australasia	1

3.6 Papers on prevention of Lyme disease

Nature of the evidence: Papers that focus on Lyme disease prevention.

Extent of evidence: 82 papers.

Research aims: 42 papers examined people's knowledge of and behaviours for preventing Lyme disease and 40 evaluated whether interventions to prevent Lyme disease are effective.

Prevention focus: The knowledge and behaviour surveys (n=42) focused on one or more of: knowledge about Lyme prevention (n=29), preventive behaviours (n=26) or attitudes about prevention (n=6). The interventions evaluated (n=40) include: education (n=14), vaccines (n=10), personal protective measures (n=6), domestic protective measures (n=4), deer-targeted programmes (n=4), preventive antibiotics following a tick-bite (n=3) and habitat restoration (n=1).

Context of evidence: 27 papers were from Europe of which 5 were from the UK. Fifty-eight papers were from North America. Four papers were from both Europe and North America. One paper was from Asia.

3.6.1 Introduction

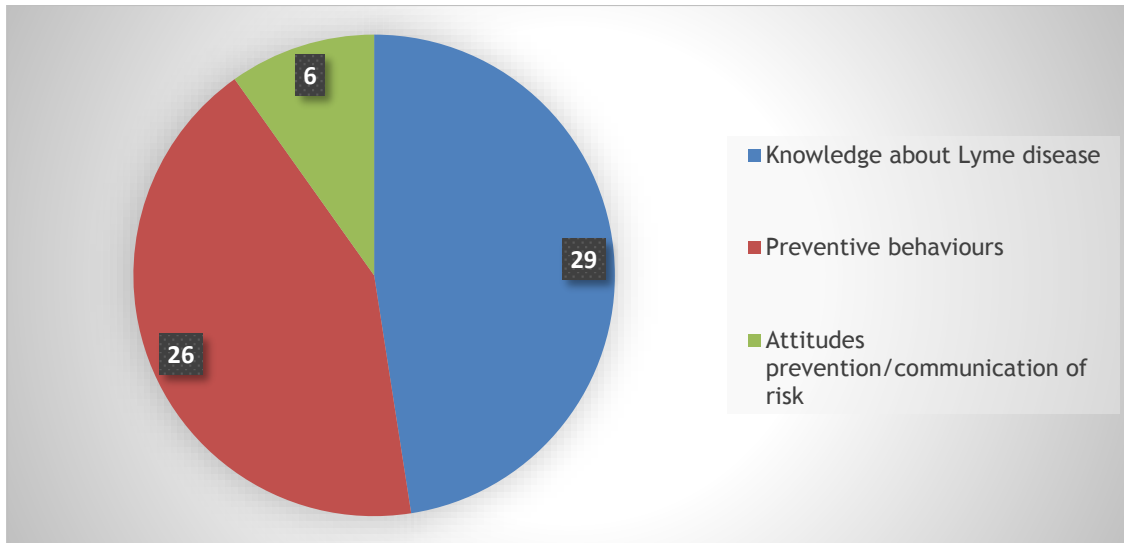
This section describes the 82 papers on Lyme disease prevention. Two additional papers that focused on prevention alongside other aspects of Lyme disease are described in section 3.10 on papers with multiple foci. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 7.

3.6.2 What were the aims of the included papers?

Of the 82 papers on Lyme disease prevention, just over half (n=42) were surveys measuring Lyme disease prevention knowledge and behaviours; the remainder (n=40) evaluated the effectiveness or cost-effectiveness of Lyme disease prevention interventions.

Among the 42 knowledge and behaviour papers, 29 surveyed knowledge about Lyme disease prevention, 26 surveyed preventive behaviours, and six surveyed attitudes about Lyme prevention approaches or the communication of risks about Lyme disease. Twenty papers surveyed both knowledge and behaviours and one surveyed both Lyme knowledge and views on Lyme prevention interventions.

Figure 3.6.1: Research aims of papers on prevention knowledge and behaviour (n=42)*

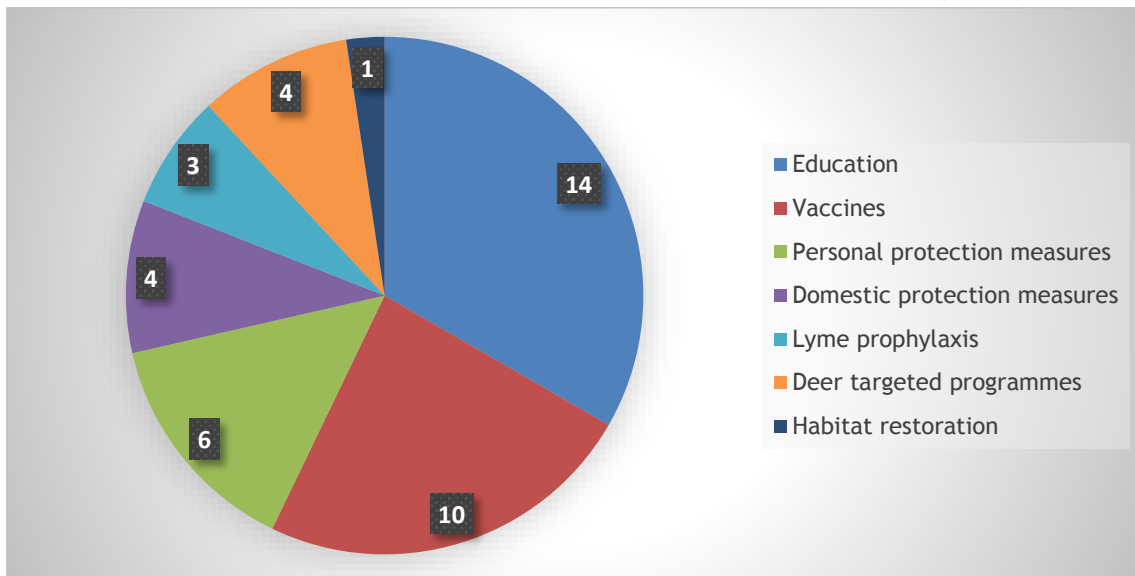


N.B. Figures in pie sections denote numbers of papers and not percentages.

* papers may have multiple aims.

Across the 40 papers on Lyme disease prevention interventions, a range of different interventions were examined, including: education (n=14), vaccines (n=10), personal protection measures, such as repellents or protective clothing (n=6), domestic protective measures, such as using chemical sprays in the garden (n=4), Lyme disease prophylaxis i.e. preventative antibiotic therapy following a tick bite (n=3), deer-targeted programmes (n=4), and habitat restoration (n=1). Two papers examined both personal protection and domestic protection measures.

Figure 3.6.2: Research aims of papers on prevention interventions (n=40)



N.B. Figures in pie sections denote numbers of papers and not percentages.

* papers may have multiple aims.

3.6.3 What research designs were used?

Of the papers that examined knowledge and behaviours, 30 employed a quantitative survey design, six employed a qualitative design and six employed a mixed-methods design. Among the evaluations of Lyme prevention interventions, just over half employ a controlled/comparative design (n=21), of which nine were randomised controlled trials (RCTs), nine were controlled trials and three were case-control studies. Seventeen papers employed a single-group design; of these, nine employed a pre/post evaluation design, five conducted a retrospective review of medical records, two collected data following intervention implementation only and one was a case study. The remaining two papers provided a cost analysis; one examined the cost-effectiveness of a Lyme disease vaccine and the other estimated the cost-benefit of habitat restoration as a result of a reduction in Lyme-disease risk. See section 3.9 for further details.

3.6.4 Who were the research participants?

Among the 42 papers examining knowledge and behaviours, most focused on the general public (n=31). The others focused on Lyme-prevention experts or professionals (n=6), both the public and Lyme professionals (n=4), and forestry workers (n=1).

Among the 40 intervention papers, 30 interventions were delivered to non-specific populations, six were delivered to children, three to those working in high-risk occupations, and one to immigrants living in endemic areas of the United States.

3.6.5 Where were the papers from?

This is one of only two categories of papers for which there were more North American papers (n=58) than European ones (n=27). Five papers were from the UK. Other European papers were from the Netherlands (n=8), Germany (n=4), Switzerland (n=4), Austria (n=2), Poland (n=2), and 1 from each from Czech Republic, Russia, Slovenia and Sweden. The North American papers were from USA (n=50) and Canada (n=8). One paper was from Asia (China). The total is greater than 82 as the data in four papers came from both Europe (Switzerland) and North America (Canada). Table 3.6.1 below provides a breakdown of the papers by research aim and continent.

Table 3.6.1: Prevention papers by continent (n=82)

Continent	Knowledge and behaviour survey	Evaluation of Lyme disease prevention interventions
North America	28	30
Europe	17	10
Asia	1	0

3.6.6 Which outcomes were measured?

Papers that examined knowledge and behaviours measured a range of outcomes. Those that focused on knowledge and awareness measured factors such as awareness of various risk factors and perception of risk, knowledge of Lyme symptoms and knowledge of prevention practices, such as tick removal. Papers that focused on prevention behaviours

measured factors such as wearing protective clothing, checking for ticks, and the use of insect repellents.

Among the papers that evaluated the effectiveness of interventions, the outcomes measured include: increase in knowledge (n=15), efficacy and safety of clinical interventions (vaccine, prophylaxis) (n=12), incidence of Lyme infection (n=10), change in self-protective behaviour (n=7), acceptability of intervention (n=7), evidence of ticks/tick bites (n=4), and costs (n=1). Many papers focused on studies that employed multiple outcome measures.

3.7 Papers on treatment for Lyme disease

Nature of the evidence: Papers that focused on pharmacological or non-pharmacological treatments for Lyme disease.

Extent of evidence: 78 papers.

Research aims: The majority of papers examined the effectiveness and safety of a single treatment for Lyme disease (n=53); others compared the effectiveness of different treatments (n=13) or different lengths of treatment (n=10). One paper described the nature of antibiotic treatments used in a large cohort of patients and one explored views about treatment for Lyme disease.

Treatment focus: Most papers (n=76) focused on antibiotic drug interventions. Two studies focused on non-pharmacological treatments.

Context of evidence: Most studies were conducted in European countries (n=43), of which only two were conducted in the UK. The remainder (n=35) were conducted in the USA.

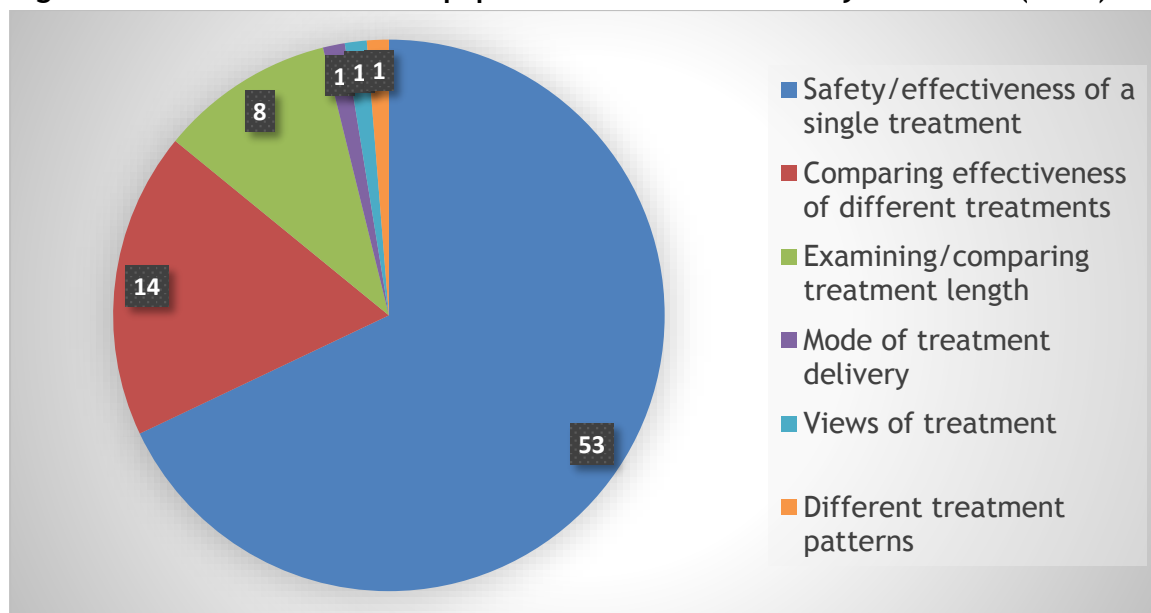
3.7.1 Introduction

This section describes the 78 papers which focused on the treatment of Lyme disease. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 8. A further 56 papers that focused on treatment alongside other aspects of Lyme disease are described in section 3.10 on papers with multiple foci.

3.7.2 What were the aims of the included papers?

The majority of papers examined the effectiveness and/or safety of a single treatment (n=53), mainly a single antibiotic. Others compared the effectiveness of different treatments (n=14) or different lengths of treatment (n=8). Of the remainder, one paper compared different modes of delivery, one paper described antibiotic treatment patterns in over 10,000 patients with newly-diagnosed Lyme disease, and one paper explored beliefs about long-term antibiotic therapy among the general public.

Figure 3.7.1: Research aims of papers on the treatment of Lyme disease (n=78)



N.B. Figures in pie sections denote numbers of papers and not percentages.

3.7.3 What types of treatment were studied?

Most papers (n=76) focused on antibiotic therapy. Approximately one third of these papers examined the safety or effectiveness of one specific type of treatment only (n=26). Others examined multiple antibiotic treatments (n=23) either used together as combination therapies, or to compare the effectiveness of one treatment versus another. The remainder (n=29) did not focus on specific treatments, rather they focused on outcomes in a cohort of patients who had received a range of treatments.

Of the two papers that did not focus on antibiotics, one examined the effects of exercise for patients with persistent symptoms and the other examined peripheral nerve stimulation for Lyme disease patients with intractable headaches.

3.7.4 What research designs were used?

Half of the papers reported controlled or comparative design studies (n=39). Of these 14 were RCTs, 13 were controlled trials, four were case-control studies and eight were comparative rather than controlled studies. The remaining papers (n=39) employed a single-group design.

3.7.5 Who were the research participants?

Eight papers focused specifically on children and one on pregnant women; the remainder (n=69) did not have a specific population focus.

Many papers focused on patients with specific Lyme disease symptoms, including Lyme neuroborreliosis (n=22), erythema migrans (n=17), cardiovascular involvement (n=4), Lyme arthritis (n=4), and facial palsy (n=3). Others focused on Lyme disease populations in general (n=20). One paper focused on treatment for Lyme patients co-infected with Babesia. The paper examining views about treatments collected evidence from the general public.

3.7.6 Where were the papers from?

The majority of papers were from Europe (n=43), of which only two were from the UK. Both UK papers were non-comparative studies that monitored the treatment effectiveness of antibiotics. The remaining papers were all North American (n=35).

Table 3.7.1: Treatment papers by continent (n=78)

Continent	Number of included papers
Europe	43
North America	35

3.7.7 Which outcomes were measured?

Of those papers assessing treatment effects (n=76), most measured changes in, or resolution of, physical symptoms (n=69). Some studies measured changes in biological markers, such as the presence of antibodies (n=36). Some focused on the adverse effects of treatment (n=20) and some on other outcomes, such as quality of life or cognitive function (n=6). Many papers measured more than one outcome.

Over half of the papers focused on long-term outcomes, where patient outcomes were measured more than six months after receiving treatment (n=47); 19 papers measured short-term outcomes (i.e. outcomes were measured within six months of treatment). The remaining papers either did not specify when outcomes were measured (n=10) or the timing of outcome measurement was not relevant due to the type of paper (n=2).

3.8 Papers on the risk factors for Lyme disease

Nature of the evidence: Papers that focused on potential risk factors for Lyme disease.

Extent of evidence: 46 papers.

Research aims: The papers focused on a range of potential risk factors and their association with Lyme disease infection. Sixteen papers focused on multiple risk factors, and 30 focused on single risk factors, including season/climate (n=10), landscape factors (n=6), human-to-human transmission (n=4), residential location (n=4), contact with animals (n=3), or other factors (n=3).

Context of evidence: No studies were conducted in the UK; 17 papers were from Europe and 29 from North America.

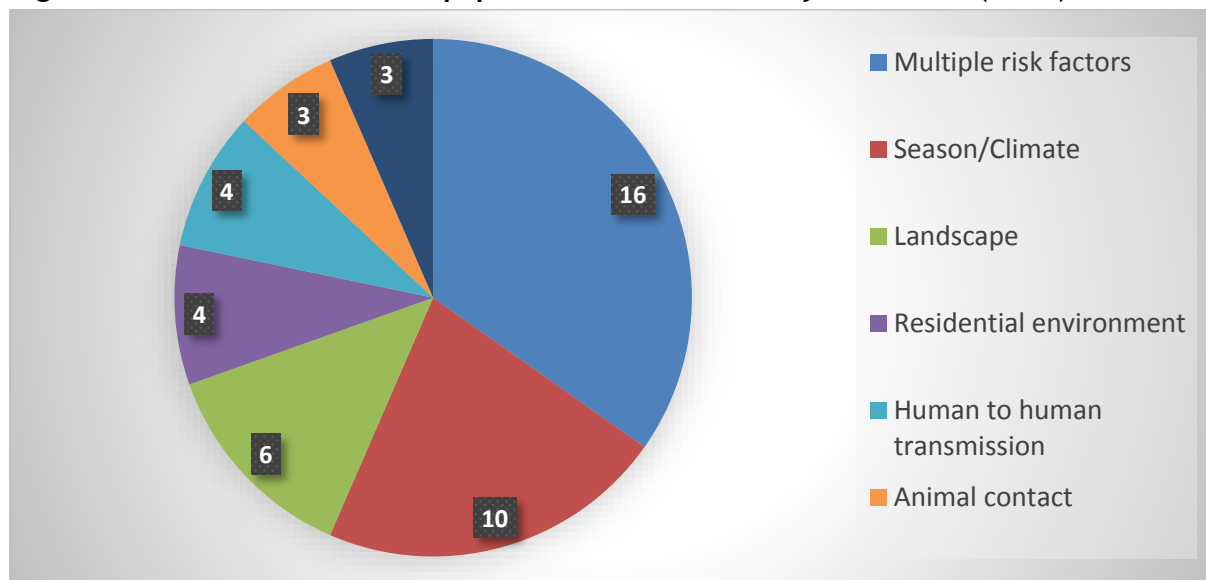
3.8.1 Introduction

We identified 46 papers which examined the association of Lyme disease with different potential risk factors. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 9. A further 15 papers that focused on risk factors alongside other aspects of Lyme disease are described in section 3.10 on papers with multiple foci.

3.8.2 What were the aims of the included papers?

The papers examined whether the risk of Lyme disease infection is affected by a range of factors including season/climate (n=10), landscape factors (n=6), residential location (n=4) or contact with animals (n=3); sixteen papers examined more than one of the above risk factors. Four papers examined the risk of human-to-human transmission (n=4). One paper examined the risk of re-infection and one the level of risk following a tick-bite, in a highly endemic area of Switzerland. The remaining paper did not examine Lyme disease risk factors, but examined the influence of Lyme disease risk on the decision to settle in a high-prevalence area.

Figure 3.8.1: Research aims of papers on risk factors of Lyme disease (n=46)



N.B. Figures in pie sections denote numbers of papers and not percentages.

3.8.3 What research designs were used?

The majority of papers employed an ecological design (n=33), for example, looking for correlations between Lyme disease incidence and geographical variation in the prevalence of risk factors, such as the climate or environment. Other designs include: survey (n=5), case series (n=3), case control (n=2), longitudinal serological survey (n=2), review of medical records (n=1), and risk behaviour simulation (n=1). One study employed both survey and serological testing.

3.8.4 Who were the research participants?

Forty-one of the papers focused on a non-specific or general adult population. Of the remaining five papers, two focused on walkers/hikers, two focused on pregnant women and one focused on people in high-risk occupations.

3.8.5 Where were the papers from?

None of the papers on risk factors were from the UK. Seventeen reported studies conducted in Europe; Czech Republic (n=5), Hungary (n=5), Belgium (n=2), Germany (n=2), France (n=1), Sweden (n=1) and Switzerland (n=1). Twenty-nine were from North America,

of which 28 were from the USA and one did not specify which North American country it was conducted in.

3.8.6 Which outcomes were measured?

The papers on ecological studies, a simulation study and two of the case-series, estimated or hypothesised the association of risk factors with Lyme disease (n=34). The level of association between Lyme disease and risk factors was directly measured in ten papers, for example, via survey. The remaining two papers examined clinical evidence of human-to-human transmission.

3.9 Papers on the cost assessment of Lyme disease

Nature of the evidence: Papers that focused on economic or cost issues of healthcare relating to Lyme disease.

Extent of evidence: 10 papers.

Research aims: The majority of included papers focused on the costs of treating and caring for patients with Lyme disease (n=7); others focused on the costs of testing for Lyme disease (n=4). One paper focused on both therapeutic and diagnosis costs.

Economic focus: All papers focused on health-related costs; they assessed the cost of laboratory testing, diagnosis, treatment and management. Four of these also assessed social costs, such as time and productivity lost due to Lyme disease (n=4).

Context of evidence: Only one paper was from the UK. The majority of papers focused on the USA (n=6), followed by Germany (n=2) and Sweden (n=1). The majority of the papers focused on studies set in hospitals (n=4), with the remaining studies being set in unspecified clinics (n=1), other environments (n=3) or not explicit about where they were set (n=3).

3.9.1 Introduction

This section focuses on cost assessments of various aspects of the management, treatment, impact, diagnosis, and other health care and health-related aspects of Lyme disease. Cost assessments are studies that examine either the cost-benefit, cost-effectiveness, cost-utility, or cost savings of interventions or services.

This section comprises ten papers that focused on cost assessments of services and impacts related to Lyme disease. An additional six papers were identified that briefly mention cost data within the context of a study that focused on another aspect of Lyme disease. These are summarised at the end of the section. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 10.

3.9.2 What were the aims of the included papers?

The majority of included papers focused on the cost of service organisation and service delivery for Lyme disease (n=7), such as therapeutic costs and disease management, but also the costs to those impacted by Lyme disease, such as loss of time and productivity. Four papers focused on the cost of diagnosis or laboratory testing (n=4). One paper focused on both therapeutic and diagnosis costs.

3.9.3 What research designs were used?

The majority of the included papers (n=7) reported cost and utilisation data, or cost-of-illness information; these papers did not compare the cost and outcomes of alternative services or interventions. Two papers reported cost-effectiveness; that is they evaluated the effectiveness of an intervention, compared with alternative interventions, in terms of “cost per unit of effect”. One paper looked at length of stay in hospital for children with Lyme disease, comparing those who had laboratory tests with those who did not.

3.9.4 What setting was the focus for the papers?

The papers focused on costs in hospital settings (n=4) or commercial laboratories (n=3). The setting in three papers was unclear.

3.9.5 Where were the papers from?

The majority of papers were from the USA (n=6), with remainder being from Germany (n=2), the UK (n=1) and Sweden (n=1). The UK paper was from Scotland and provided a partial cost evaluation of a broad spectrum of health and social costs of Lyme disease.

Table 3.9.1: Continent of focus for papers that describe cost assessments of Lyme disease in healthcare (n=10)

Continent	Number of included papers
North America	6
Europe	4

3.9.6 Which outcomes were measured?

All papers focused on healthcare costs, i.e. the costs of clinical treatment, diagnosis, testing or consultation. However, four also looked at social costs, such as time and productivity lost due to Lyme disease.

3.9.7 Are there other papers that mention economic data?

We located six further papers that provided brief sections on economic data within studies that primarily focused on another aspect of Lyme disease. The main focus of these papers was: prevention (n=2), prevalence (n=1), multiple aims (n=1), symptoms (n=1), or treatment (n=1). The economic perspective was varied; three papers provided partial evaluations, the others looked at cost-effectiveness (n=1), cost-benefit (n=1)) and resource utilisation data (n=1). All papers focused on health outcomes only. Further details about these papers can be found in the relevant sections. See Supplementary File 7.

3.10 Papers on multiple aspects of Lyme disease

Nature of the evidence: Papers that explicitly aimed to investigate multiple aspects of Lyme disease within a single patient population.

Extent of evidence: 81 papers.

Research aims: Most of the included papers (n=48) focused on the clinical characteristics, the course of specific symptoms and co-occurring conditions associated with Lyme disease (n=28), and/or examined the clinical characteristics of Lyme disease within a specific population (n=21). Papers mainly focused on Lyme disease in general (n=39), Lyme neuroborreliosis (n=11), erythema migrans (n=11) and/or Lyme arthritis (n=9).

Research design: A variety of research designs was employed. Most papers used a single-group design (n=46), with a smaller number of papers using a controlled design (n=15), none of which was a RCT.

Context of evidence: The majority of papers were from Europe (n=51). The country with the largest number of papers was the USA (n=25).

3.10.1 Introduction

This section focuses on papers that had the explicit aim of investigating multiple clinical characteristics of Lyme disease; that is, they had a clear aim to examine two or more of a range of aspects of Lyme disease, within a single patient population. We identified 81 papers for this category. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 11.

3.10.2 What were the aims of the included papers?

The majority of papers (n=48) focused on the clinical characteristics or course of specific symptoms and co-occurring conditions associated with Lyme disease (n=28), and/or examined the clinical characteristics of Lyme disease within a specific population (n=21). Some papers had multiple clearly defined research aims (n=16), in that the authors were explicit that they would address two or more different aims in the paper. The remainder evaluated the clinical or microbiological findings of Lyme disease (n=6), investigated susceptibility to Lyme disease (n=5), evaluated clinician practices or adherence to recommendations (n=3), or defined the clinical characteristics of ongoing symptoms (n=2). The clinical aspects examined include symptoms (n=62), treatment (n=57), incidence and prevalence (n=31), risk factors (n=15), diagnosis (n=14), and prevention (n=2), with each paper examining more than one of these topics.

3.10.3 What research designs were used?

The majority of included papers employed a single-group design (n=46), that is they did not employ a control or comparison group. There are a smaller number of papers that used controlled designs (n=15), none of which was a RCT. The remainder (n=23) employed various other designs: retrospective chart reviews (n=11), database analysis or surveillance

data (n=7), interviews or questionnaires (n=4), and one observational cohort study. Three papers employed more than one research design.

3.10.4 Who were the participants?

Several papers focused on more than one population. Generally, papers focused on non-specific populations (n=56). Those papers, in which the population was specified, mainly focused on children (n=19). There were also papers with a focus on a high-risk occupation (n=4), clinicians (n=2), hikers/outdoor pursuits (n=1) and older people (n=1). Papers mainly focused on post-treatment patients (n=49) or the general population (n=26). The remainder focused on patients currently undergoing treatment (n=5) and pre-treatment populations (n=4). Most commonly, papers focused on Lyme disease in general (n=39), in that they did not specify a particular manifestation. Some focused on Lyme neuroborreliosis (n=11), Lyme arthritis (n=11) and erythema migrans (n=11). The remainder focused on facial palsy (n=3), Post Lyme Disease Syndrome (PLDS) (n=3), Lyme carditis (n=2) and other systemic conditions: lymphocytoma in children (n=2), Lyme meningitis (n=1), and acute polyradiculoneuritis syndrome (n=1). Papers that focused on Lyme arthritis specifically focused on the child population.

3.10.5 Where were the papers from?

The majority of papers were European (n=51); most commonly from Slovenia (n=8), Poland (n=6), Sweden (n=5), France (n=4), Norway (n=4), Germany (n=3) and Romania (n=3). The remaining thirteen European countries were the source for two or fewer papers per country; details can be found in Supplementary File 8. Only one UK paper was identified, which was a retrospective case note review study, focused on clinician practices in a referral clinic. North America accounted for 26 papers, and the remainder were from China (n=2), Turkey (n=1) and Australia (n=1). The country with the largest number of papers was the USA (n=25). Table 3.10.1 below details papers by continent.

Table 3.10.1: Continent of focus for papers that examined multiple aspects of Lyme disease (n=81)

Continent	Number of included papers
Europe	51
North America	26
Asia	3
Australasia	1

3.10.6 Which outcomes were measured?

The outcomes that were reported centred on the clinical characteristics being researched and included physical symptoms (n=61), biological characteristics (n=57) and non-physiological measures (n=9).

Physical symptoms that were reported were skin changes (n=32), neurological changes (n=25), clinician-identified symptoms (n=19), pain (n=14), inflammation (n=13), fever or flu-like symptoms (n=8), cardiac symptoms (n=7), and patient self-reported symptoms (n=6).

Biological characteristics that were reported mainly examined immunoblot for immunoglobulin M (IgM) and/or for immunoglobulin G (IgG) (n=29), blood serum (n=26), general antibodies (n=21) and polymerase chain reaction (PCR) positivity (n=9). The remainder were: cerebral spinal fluid (CSF) (n=7), magnetic resonance imaging (MRI) scan (n=2), biopsy results of particular cells or organs (n=2), and synovial fluid effusion (n=1).

Non-physiological outcomes that were reported were incidence (n=6), prevalence (n=2) and service use (n=1).

3.11 Systematic reviews on Lyme disease

Nature of the evidence: Systematic reviews on Lyme disease in humans.

Extent of evidence: 19 systematic reviews.

Review aims: The reviews aimed to examine: treatment (n=5), prevention (n=4), diagnosis (n=4), symptoms (n=2), incidence and prevalence (n=1), risk factors (n=1) and chronic Lyme (n=1).

Context of evidence: Two reviews included studies from Europe only. The remaining reviews did not apply a geographical filter.

Gaps in research: There is a lack of systematic reviews on the prevalence of Lyme disease in the general population and the effectiveness of prevention interventions.

3.11.1 Introduction

Nineteen systematic reviews were identified. One review was an update of a previous systematic review, and therefore, eighteen reviews were coded and analysed. The review-level evidence base on Lyme disease in humans is relatively new, with over half published between 2015 and 2017 (n=11). The majority of reviews focused on treatment (n=5), prevention (n=4), and diagnosis (n=4) of Lyme disease, with fewer reviews on symptoms (n=2), incidence/prevalence (n=1), or risk factors (n=1). One review focused on chronic Lyme disease. A comprehensive table of the included papers can be found in Supplementary File 2, Appendix 12.

3.11.2 Systematic reviews on diagnosis (n=4)

The diagnostic test accuracy (DTA) of serological assays (e.g., ELISA, or Western Blot) was investigated in four systematic reviews. Meta-analysis was undertaken in two reviews, one of which conducted a critical appraisal of studies from Europe. The scale of the evidence-base varied from 75 to 12 studies.

Table 3.11.1: Systematic reviews on diagnosis

Authors	Inclusion criteria		Details of the review		
	Population	Study focus	No. of studies	Quality appraisal	Type of synthesis
Bakker et al. (2012)	Adults	DTA: ELISA or Western blot, using cerebrospinal fluid	n=12	Risk of bias	Narrative synthesis
Cook & Puri (2016)	Adults	DTA: PCR assay; ELISA, Western Blot	n=18	None	Meta-analysis
Leeflang et al. (2016)	Adults	DTA: ELISA or an immunoblot assay	n=75	Risk of bias	Meta-analyses
Stanek & Strle (2009)	Adults Children	DTA: Diagnostic assays or procedures	Not reported	None	No synthesis

DTA = diagnostic test accuracy; ELISA = enzyme-linked immunosorbent assay; PCR = polymerase chain reaction

3.11.3 Systematic reviews on symptoms and co-occurring conditions (n=2)

Two systematic reviews considered the symptoms and manifestations of Lyme disease. One meta-analysis investigated the presence of residual symptoms in a cohort of adults after they had received pharmacological treatment for Lyme neuroborreliosis. A second review narratively explored the symptoms of Lyme disease in patients presenting with sudden deafness.

Table 3.11.2: Systematic reviews on symptoms and co-occurring conditions

Authors	Inclusion criteria		Details of the review		
	Population	Lyme diagnosis	No. of included studies	Quality appraisal	Type of synthesis
Dersch et al. (2016)	Adults	Patients with Lyme neuroborreliosis after pharmacological treatment	n=44	None	Meta-analysis
Peeters et al. (2013)	Adults	Patients presenting with sudden deafness	n=9	None	Narrative synthesis

Table 3.11.3: Systematic reviews on incidence and prevalence

Authors	Inclusion criteria		Details of the review		
	Population	Lyme diagnosis	No. of included studies	Quality appraisal	Type of Synthesis
Sykes and Makiello (2016)	Adults Children	Confirmed cases of Lyme infection	n=11	None	Narrative synthesis

3.11.4 Systematic reviews on prevention (n=4)

Three systematic reviews focused on the effectiveness of a single clinical treatment, such as vaccines (n=1) or antibiotics (n=1) in preventing Lyme disease, one of which conducted a meta-analysis. One systematic review focused solely on communication-based public health messages to encourage the use of protective behaviours. The scale of the evidence identified on prevention interventions is quite small, ranging from three to nine studies. The quality of the evidence base is unassessed.

Table 3.11.4: Systematic reviews on prevention of Lyme disease

Authors	Inclusion criteria		Details of the review		
	Population	Intervention type	No. of studies	Quality appraisal	Type of synthesis
Badawi et al. (2017)	Adults	Vaccine	n=7	None	Narrative synthesis
Mowbray and Rubin (2012)	Adults Children	Communications-based public health interventions	n=9	None	No synthesis
Warshafsky et al. (2010)	Adults Children	Antibiotic prophylaxis	n=4	None	Meta-analysis
Zhao et al. (2017)	Adults	Vaccine	n=3	None	Meta-analysis

3.11.5 Systematic reviews on treatment (n=5)

All five reviews on treatment investigated the effectiveness of antibiotics for treating Lyme disease. Four reviews included studies that focused on children or adults, where a clinical diagnosis of definite, possible or probable Lyme neuroborreliosis had been

established. One review focused specifically on children, and another on adults or children with any symptom of Lyme disease. A review, conducted to inform treatment guidelines, also included trials that investigated antibiotic therapy for patients who had received an initial course of antibiotics, but continued to experience symptoms associated with Lyme. The scale of the evidence base, identified in each review, ranged from six to 37 studies, with smaller reviews limiting their eligibility criteria to RCTs. Four reviews critically appraised trials using a risk of bias tool, two of which conducted a meta-analysis.

Table 3.11.5: Systematic reviews on treatment

Authors	Inclusion criteria		Details of the review		
	Population	Lyme diagnosis	No. of studies	Quality appraisal	Type of synthesis
Cadavid et al. (2016) update of Cadavid (2008)	Adults Children	Clinical diagnosis	n=7	Risk of bias	Narrative synthesis
Carris & Shaer (2015)	Adults Children	Symptoms of Lyme disease	n=6	Risk of bias	Narrative synthesis
Dersch et al. (2015a)	Adults Children	Clinical diagnosis	n=16	Risk of bias	Meta-analysis
Dersch et al. (2015b)	Children	Clinical diagnosis	n=6	Risk of bias	Meta-analysis
Halperin et al. (2007)	Adults Children	Clinical diagnosis / post-Lyme symptoms	n=37	None	Narrative synthesis

3.11.6 Systematic reviews on incidence and prevalence of Lyme disease (n=1)

One systematic review narratively reported on the incidence of Lyme disease in adults or children in Western Europe.

3.11.7 Systematic reviews on risk factors (n=1)

One review narratively synthesised evidence from geographic information system (GIS) studies. Studies contain data on spatiotemporal patterns and interactions between populations of reservoir hosts, clusters of infected ticks and humans to better understand the spread of Lyme disease transmission. Populations of interest included adults and children living in high-risk endemic areas or having high-risk occupations.

Table 3.11.6: Systematic reviews on risk factors

Authors	Inclusion criteria		Details of the review		
	Population	Study focus	No. of studies	Quality appraisal	Type of synthesis
Ozdenerol et al. 2015	Adults Children	Spatiotemporal patterns of Lyme disease	n=22	None	Narrative synthesis

3.11.8 Systematic reviews on chronic Lyme disease (n=1)

One review, provided a descriptive overview of 89 studies on the complexity of chronic Lyme disease. Complexity was understood in relation to the patients' care needs, such as difficulty in diagnosing and treating Lyme disease when symptoms persist.

Table 3.11.7: Systematic reviews on chronic Lyme disease

Authors	Inclusion criteria		Details of the review		
	Population	Study focus	No. of studies	Quality appraisal	Type of synthesis
Borgermans et al. 2014	Adults Children	Complexity of CLD as a multidimensional chronic disease construct	n=89	None	No synthesis

CLD = chronic Lyme disease

3.12 Media scan on Lyme disease

Our simple search to identify the sources of information about Lyme disease that are accessible to the general public, in the UK, resulted in identifying nine webpages on the first page of the Google search. The details of these nine sources can be found in table 3.12 below.

Table 3.12: results of media scan

Name of Page	Source	Nature of source	Link
Lyme Disease	NHS choices	Government	https://www.nhs.uk/conditions/lyme-disease/
FAQ Lyme Disease Action	Lyme Disease Action	Patient Group	http://www.lymediseaseaction.org.uk/about-lyme/faq/
Home page - Lyme Disease Action	Lyme Disease Action	Patient Group	http://www.lymediseaseaction.org.uk/
Lyme Disease	Wikipedia	Non commercial, factual	https://en.wikipedia.org/wiki/Lyme_disease
Lyme Disease (Borreliosis)	BADA UK	Patient Group	Page no longer available
Home page - Lyme Disease UK	Lyme Disease UK	Patient Group	http://lymediseaseuk.com/about-us/
Lyme Disease	NHS - Fit for Travel	Government	http://www.fitfortravel.nhs.uk/advice/disease-prevention-advice/lyme-disease.aspx
Lyme Disease: symptoms, causes and treatment	Netdoctor	Commerical, medical	http://www.netdoctor.co.uk/conditions/infections/a5681/lyme-disease/
The controversy over the chronic form of Lyme Disease	BBC News	Media	http://www.bbc.co.uk/news/magazine-34579423

The resources were produced by a range of institutions, most commonly patient advocacy groups (n=4), followed by the NHS (n=2). We identified one media article, a news story produced by the BBC, which was over two years old. One of the pages we found is no

longer available, Lyme Disease/BADA UK was associated with Lyme Disease UK. The majority of these pages presented factual information about the illness, for example, there were pictures showing the distinctive bullseye rash.

In addition to providing information about acute Lyme disease, most pages also made reference to chronic Lyme disease. Lyme Disease Action and Net Doctor presented medical information, without mentioning the controversy surrounding this issue; by contrast, the NHS choices and Lyme Disease UK pages both explicitly referred to the controversy. We conclude that simple web searches, such as those likely to be conducted by the general public, largely yield useful information and advice for those concerned about the illness.

4 Discussion and conclusions

This systematic evidence map aimed to investigate the *nature and extent of empirical research evidence on Lyme disease in humans*. This exercise identified a diverse and growing body of literature on Lyme disease, resulting in the inclusion of 1,098 papers. The scope and breadth of the identified literature on Lyme disease is broad, revealing a wide variety of study foci.

4.1.1 Summary of the evidence

Generally, research in the field of Lyme disease is increasing globally, with a particularly predominant evidence base from the USA. However, despite many papers being identified from Europe, only 7 percent of European studies were from the UK. Of the 47 UK papers, most focused on incidence and prevalence (n=17) and diagnosis (n=15). Far fewer focused on symptoms (n=5), prevention (n=5), treatment (n=2), multiple aspects (n=2) or costs (n=1). We identified no UK papers that focused on risk factors.

In addition to research papers, we identified 19 systematic reviews, the majority of which were conducted in the last three years.

Most commonly, research populations for Lyme disease proved to be general, with most of the papers having no specific study population (n=868). Children were also commonly researched (n=133). There were few papers on high-risk populations (n=52) or other vulnerable populations, such as pregnant women (n=4) or older people (n=2).

The nature of research evaluating aspects of Lyme disease is broad. Papers were grouped into seven domains: 1) diagnosis; 2) symptoms and co-occurring conditions; 3) incidence and prevalence; 4) prevention; 5) treatment; 6) risk factors; and 7) cost assessments. The largest body of research evidence focused on diagnosis (n=310), in particular, on diagnosis testing accuracy. This is followed by symptoms and co-occurring conditions (n=283), most noticeably on the association between Lyme disease and other conditions, such as Parkinson's disease. Also, a high percentage of papers focused on incidence and prevalence of Lyme disease (n=189); two thirds of these focused on incidence. Far fewer papers focused on prevention (n=82), those included were surveys or effectiveness evaluations. Papers that focused on treatment are also relatively few in number (n=78) and predominately focused on antibiotic therapy. Research evidence on risk factors (n=46) was limited and focused on factors such as season and climate, human-to-human transmission, and contact with animals. It should be noted that studies on environmental risk factors were included only when outcome measures had been calculated for resultant disease in humans; a wider literature exists on the Lyme disease hazard to humans, based on field surveillance of tick-infection prevalence, but this was beyond this map's scope. The few cost assessments identified (n=10) were partial economic evaluations that provided cost and utilisation data or cost-of-illness information. We located eighty-one papers that focused on more than one aspect of Lyme disease, almost half of which focused on both symptoms and treatment. Further, we identified systematic reviews (n=19), which focused on all seven domains.

In 2012 a priority setting exercise on Lyme disease was conducted, in the UK, by The James Lind Alliance (JLA), an NIHR funded non-government organisation (NGO), which involves patients, carers and medical professionals in identifying priorities for future research. The ten research priorities identified in the JLA exercise appear to reflect the current availability of research on different aspects of Lyme. Whilst only seven percent of studies in the map focused on treatment for Lyme disease (n=78) the majority of the ten JLA identified research priorities (n=7) focused on the efficacy and consequences of treatments for Lyme disease at different stages. By contrast, while almost one third of the studies in the map focused on diagnosis (n=310) just two of the ten JLA priorities focused on diagnosis (JLA, 2012).

A variety of different research designs was described in the included papers. Research design is dependent upon its appropriateness for the research aims. Research that aims to test or evaluate the effectiveness of treatments should employ a comparative design. RCTs are widely accepted as being the gold standard for evaluating the effectiveness of interventions, however, we identified very few RCTs (n=23); these were for treatment (n=14) and prevention (n=9). Few qualitative research papers were identified that gathered patient and clinician experiences, in particular with regard to diagnosis and treatment.

4.1.2 Gaps in the evidence

Whilst a high proportion of papers focused on Europe, just under five percent of included papers (n=47) were from the UK.

A noticeable lack of research was identified on specific populations, such as older people, hikers, dog walkers and pregnant women, for all aspects of Lyme disease. Further, research is limited for Lyme disease manifestations other than Lyme neuroborreliosis, erythema migrans, Lyme arthritis and Lyme carditis.

The reporting of the costs for interventions, such as treatment, diagnosis and vaccines, is limited. Only ten cost assessments were identified; 16 papers reported any level of costs.

Lyme disease research evidence might benefit from a greater number of experimental studies, in the form of RCTs that evaluate the effectiveness of treatment and prevention interventions. It might also benefit from more evidence of patient and clinician experiences, in order to highlight real-world issues that impact the effectiveness of diagnosis, treatments and prevention.

Few papers focused on the clinical or symptom-led diagnosis of Lyme disease (n=68), compared with the laboratory diagnosis of Lyme disease.

Certain aspects of Lyme disease appear to be relatively limited. Papers focusing on the treatment of Lyme disease (n=78) account for less than seven percent of all the identified papers. Only four percent (n=46) focused on the potential risk factors associated with Lyme disease.

4.1.3 Strengths and limitations

The characteristics of the search strategy and inclusion criteria of this map must be considered. Systematic evidence mapping provides a means to understand the landscape

of research that has been conducted, however, the included papers are not critically assessed for their methodological quality. Therefore, it is not possible for the review team to make judgements about the relevance or robustness of the findings reported in the papers.

Despite the review team's efforts to be inclusive, with no constraints placed on the type of intervention, country, or methodological design, the review did have language limitations. Only papers that were indexed in English-language databases, and reported in the English language, were included. Therefore, the extent of evidence is potentially greater than is reflected in this report.

Despite identifying several hundred case reports, these are not included in this map. This is both a limitation of the review and of the research field, as these studies do not qualify as rigorous research and, therefore, do not comply with the inclusion criteria.

It must be noted that whilst this systematic evidence map categorises papers within specific foci, the papers within these categories are often more complex than the group headings indicate. In addition, the aims and objectives of the identified papers were often difficult to discern and, therefore, categorise. Further, issues with the reporting of studies were encountered. Initially, the review team aimed to categorise papers by the nature or stage of Lyme disease under study, but this proved impossible due to the lack of detailed or explicit definitions and the variability in the terminology used. The observed lack of clarity in reporting may mean that relevant papers may have been missed. Researchers in this field should publish research that follows reporting guidelines, such as CONSORT or the EQUATOR Network, as a matter of course.

The methods used in the production of this map follow the rigorous standard procedure of conducting systematic reviews developed at the Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre). This systematic map benefits from user involvement, in the form of a scientific advisory group, as well as patient and professional stakeholders.

To locate relevant research papers, the review team conducted a very comprehensive systematic search of electronic databases in the clinical sciences, social sciences, psychology, economics, and governmental and non-governmental organisations. This was supplemented by searching relevant websites and grey literature, checking the references of systematic reviews, and suggested papers from the involved stakeholders. The search strategy for this map was designed to be both sensitive and exhaustive, in order to gain insight into the range and variety of aspects of Lyme disease that have been investigated. However, as with any systematic review, there is a possibility that the searches may have missed some papers.

To ensure consistency and quality of screening, all reviewers performed a moderation exercise on title and abstract screening and again for full-text screening. Due to the nature and diversity of the papers, identified by the search, approximately three quarters of the papers were double screened. Although samples of papers were screened independently, by two reviewers, at various stages of the screening process, there is the possibility that some papers may have been excluded, which should have been included within the map.

Papers included in each research topic were assigned to at least two reviewers to be double coded. While initial quality assurances were put into place regarding the testing of the coding tools for single-coder use, after coding a random sample of papers, agreement between reviewers, for certain research areas, was not high and, therefore, papers were double coded, which reduced the risk of variations in coding strategies.

4.1.4 Implications for research

This is the first systematic evidence map of research focused on Lyme disease in humans. This map provides a unique resource for investigating the content of Lyme disease research and demonstrates the scope and diversity of research conducted in formal empirical studies. This map provides a valuable tool for stakeholders to understand and navigate the research evidence in the field, and for researchers, commissioners and clinicians to develop an evidence-informed approach to identify potential areas in which to conduct or commission further research, and to impact on policy and practice in the field of Lyme disease research.

4.1.5 Conclusion

Despite identifying a large number of papers, there are many gaps in the research evidence base. Whilst a relatively high proportion of papers emanated from Europe (n=631), the 47 papers from the UK accounted for less than five percent of the total number of papers. In addition, we located little research that focused on specific populations other than children, for example, older people or pregnant women. Research into the diagnosis and treatment of Lyme disease might also benefit from an increase in papers that focus on patient and clinician experiences, as highlighted by our evidence reviews (Brunton et al, 2017 and Sutcliffe et al, 2017). There are relatively few papers on treatment and prevention; in particular more robust evaluations to test the effectiveness of treatments or prevention approaches (i.e. controlled design studies) might prove to be beneficial. Further research on the risk factors associated with Lyme disease might also help to further understanding in this area. Future research on interventions should report the costs for intervention set-up and cost per patient, as a matter of course, to inform commissioners and providers of healthcare services. Finally, research into Lyme disease would benefit from papers that focus on more clearly defined populations, interventions or outcomes, and are clearly reported. This would facilitate greater access to knowledge and help progress in research in this area.

5 Detailed methods

5.1 Aims

5.1.1 *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.

5.1.2 *Review questions*

The primary aim of this evidence map is to provide a comprehensive overview of available research evidence pertaining to Lyme disease in humans. To achieve this, we systematically identified and described the available research evidence to address the following question:

- *What is the nature and extent of empirical research evidence on Lyme disease in humans?*

A secondary, or minor, aim of the project was to understand the sources of information available to the public through online searches. To address this aim, we undertook a brief ‘media scan’ to identify the most popular websites relating to Lyme disease.

5.2 Methods

5.2.1 *Searching for studies for the systematic evidence map*

Searching for studies to populate the systematic evidence map involved a broad and sensitive search strategy, consisting in effect of a single cluster of terms for Lyme disease. An example strategy is shown in Appendix 1. The following databases were searched:

ASSIA

British Nursing Index (BNI)

Cochrane Central Register of Controlled Trials (CENTRAL)

Cochrane Database of Systematic Reviews (CDSR)

Cumulative Index for Nursing and Allied Health Literature (CINAHL)

Database of Abstracts of Reviews of Effects (DARE)

Embase

Global Health

Health Management and Information Consortium (HMIC)

Health Technology Assessment (HTA) database

International Bibliography of the Social Sciences (IBSS)

MEDLINE

PsycINFO

PubMed

Social Policy and Practice

Social Science Citation Index

Sociological Abstracts

In addition, the following resources were searched for on-going studies, and unpublished or grey literature:

ClinicalTrials.gov

Conference Proceedings Citation Index: Science

Conference Proceedings Citation Index: Social Science

EU Clinical Trials Register

ProQuest Dissertations & Theses: UK and Ireland

PROSPERO

WHO International Clinical Trials Registry Platform portal

A search for guidelines on Lyme disease was carried out via the following websites: Health Protection Scotland, Public Health England, Public Health Wales, National Guideline Clearinghouse, NHS Evidence, NICE Clinical Knowledge Summaries (CKS), NICE website and the Trip database.

5.2.2 Including studies in the systematic evidence map

To be included in this systematic evidence map, studies had to meet the criteria set out in Table 5.1 below. The table also provides details of the rationale underpinning each of the map inclusion criteria.

Table 5.1: 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 disease.
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 were excluded.
Population	Be about Lyme disease in humans.	Whilst studies of Lyme disease in animals and ticks may provide some information with implications for human populations, the priority is to focus in on those studies directly addressing Lyme disease 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. For example, this criterion was used to exclude studies on novel diagnosis methods that were not compared against a reference standard as these were considered to be exploratory bio-mechanism studies.

5.2.3 Screening for inclusion in the review

Inclusion criteria were applied to the title and abstract of each study. Full reports were then obtained for those references that were judged to meet our inclusion criteria, based on the title and abstract, or where there was insufficient information within the title and abstract to judge eligibility for inclusion. References that met the inclusion criteria for title and abstract screening were subject to a second round of screening using the same approach, based on the full reports of potential studies to determine a final set of papers for inclusion in the review.

5.2.4 *Data extraction and quality appraisal*

Reviewers extracted descriptive data from papers using coding tools developed specifically for the evidence map. An iterative and inductive approach to develop the coding tools was undertaken. Initially a generic tool applicable to all papers was developed. However, when testing this tool, it proved difficult to use, as it was not fit for purpose and in alignment with key aspects of studies according to their substantive topic focus. Instead, smaller teams took a subset of papers specific to each topic focus (e.g., diagnosis, prevalence, treatment, prevention, or symptoms) and developed individual coding tools to capture key characteristics of those studies relevant to their aim. The coding tools were refined, and guidance provided, for questions, where required. Coding for each paper was agreed by two reviewers.

The following information was extracted from all papers:

- **Bibliographic details:** e.g., publication details, and date
- **Geographical location:** continent and individual country
- **Population:** e.g., children, adults, high-risk groups

Coding tools specific to each topic focused on capturing more detailed information. Where relevant, this included research design (e.g., aim, or research method); focus of investigation (e.g., type of diagnostic test, or treatment or prevention programme); outcomes and other contextual details.

As this is a map, the key features of papers were descriptively analysed and written-up. The empirical findings from studies have been appraised for their quality and synthesised in separate reviews.

5.2.5 *Quality assurance*

At each stage of dealing with records for the evidence map (screening titles and abstracts, screening full reports, and coding records), an initial sample of records was screened or coded by two reviewers, independently, and differences were resolved by discussion. Where it was not possible to get agreement, a third reviewer was consulted before a final decision on eligibility was made. Once an adequate level of agreement was reached (90% agreement rate), the remaining papers were screened and coded by a single reviewer.

To ensure consistency and accuracy in reporting, several data cleaning steps were taken. Firstly, we ensured that papers were not double coded either across or within screening tools (e.g., with two or more codes within one screening tool, or in more than one coding tool, such as diagnosis and prevention). Secondly, we ensured that papers which had been excluded had no map codes. Thirdly, we ensured that all relevant questions in the coding tool were applied to each paper. Where errors appeared, groups of reviewers were asked to check and update their coding set and/or coding was removed.

5.2.6 *Consultation with patient advocacy groups*

In October 2017, we shared the key findings of the four evidence reviews that are derived from this map (Brunton et al. 2017, Lorenc et al. 2017, Richardson et al. 2017 and Sutcliffe et al. 2017a) with eight patient stakeholder groups; the feedback received is reported within each of the reviews. Prior to sharing the review 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 these consultations see Brunton et al. (2017). Whilst this consultation work informed the project as a whole, we did not consult with patient groups on the map findings specifically.

5.2.7 Media Scan

To understand the nature of the most accessible information about Lyme disease for the general public on the internet we conducted a simple search, on 31 July 2017, using the phrase 'Lyme disease' on the most popular search engine (Google). We gathered together details of the source and content of the most popular pages, i.e. those resources listed on the first page of the returned search.

6 References*

* The following is the list of references cited in this report. A complete list of references of included papers can be found in Supplementary File 2.

Beaujean D J, Crutzen R, Gassner F, Ameling C, Wong A, van Steenberg J E, and Ruwaard D. (2016a). Comparing the effect of a leaflet and a movie in preventing tick bites and Lyme disease in The Netherlands. *BMC Public Health*, 16, pp.495.

Beaujean D J, Gassner F, Wong A, Steenberg J E, Crutzen R, and Ruwaard D. (2016b). Education on tick bite and Lyme borreliosis prevention, aimed at schoolchildren in the Netherlands: comparing the effects of an online educational video game versus a leaflet or no intervention. *BMC Public Health*; 16: 1163.

Bingham P M, Galetta S L, Athreya B, and Sladky J. (1995). Neurologic manifestations in children with Lyme disease. *Pediatrics*; 96: 1053-1056.

Borgermans L, Goderis G, Vandevoorde J, Devroey D. (2014). Relevance of chronic Lyme disease to family medicine as a complex multidimensional chronic disease construct: a systematic review. *International Journal of Family Medicine* 2014: 1-10.

Brunton G, Sutcliffe K, Hinds, K, Khatwa M, Burchett H, Dickson K, Rees R, Rojas-Garcia A, Stokes G, Sowden A, and Thomas J. (2017). Patient, clinician and researcher experiences of the diagnosis of Lyme disease: a systematic review. London: EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London.

Christen HJ, Hanefeld F, Eiffert H, Thomssen R. Epidemiology and clinical manifestations of Lyme borreliosis in childhood. A prospective multicentre study with special regard to neuroborreliosis. *Acta Paediatr Suppl.* (1993); 386: 1-75.

Dersch R, Freitag MH, Schmidt S, Sommer H, Rauer S, Meerpohl JJ (2015a). Efficacy and safety of pharmacological treatments for acute Lyme neuroborreliosis - a systematic review. *European Journal of Neurology*; 22: 1249-1259.

Dersch R, Hottenrott T, Schmidt S, Sommer H, Huppertz HI, Rauer S, Meerpohl JJ (2015b). Efficacy and safety of pharmacological treatments for Lyme neuroborreliosis in children: a systematic review. *BMC Neurology*; 16: 189.

Gough D, Oliver S, Thomas, J (2017). *An introduction to systematic reviews*, (2nd ed.), London: Sage Publishing.

JLA (2012). Lyme disease top 10 [Online]. Available from <http://www.jla.nihr.ac.uk/priority-setting-partnerships/lyme-disease/top-10-priorities>. London: James Lynd Alliance. Updated: 2017.

Lantos PM, Nigrovic LE, Auwaerter PG, Fowler VG, Jr., Ruffin F, Brinkerhoff RJ, Reber J, Williams C, Broyhill J, Pan WK, Gaines DN (2015) Geographic Expansion of Lyme Disease in the Southeastern United States, 2000-2014. *Open Forum Infectious Diseases*; 2: 1-6.

Lantos P M, and Wormser G P. (2014). Chronic coinfections in patients diagnosed with chronic Lyme disease: a systematic review. *American Journal of Medicine*; 127: 1105-1110.

Leeflang MM, Ang CW, Berkhout J, Bijlmer HA, Van Bortel W, Brandenburg AH, Van Burgel ND, Van Dam AP, Dessau RB, Fingerle V, Hovius JW, Jaulhac B, Meijer B, Van Pelt W, Schellekens JF, Spijker R, Stelma FF, Stanek G, Verduyn-Lunel F, Zeller H, Sprong H (2016) The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. *BMC Infectious Diseases*; 16: 140.

Lorenc T, Jones-Diette J, Blanchard L, Sutcliffe K, Sowden A, and Thomas J. (2017) Incidence and surveillance of Lyme disease: Systematic review and policy mapping. London: EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London.

Miake-Lye I, Hempel S, Shanman R, Shekelle PG (2016) What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. *Systematic Reviews*; 5: 1-21.

Mowbray F, Amlot R, Rubin GJ (2012) Ticking All the Boxes? A Systematic Review of Education and Communication Interventions to Prevent Tick-Borne Disease. *Vector-Borne and Zoonotic Diseases*; 12: 817-825.

PHE (2015). Lyme disease: Signs and symptoms. Online. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/463701/LymeDisease_SignsAndSymptoms.pdf Accessed on: 02/11/2017.

Rebman A W, Aucott J N, Weinstein E R, Bechtold K T, Smith K C, and Leonard L. (2017). Living in Limbo: Contested Narratives of Patients with Chronic Symptoms Following Lyme Disease. *Qualitative Health Research*; 27(4): 534-546.

Richardson M, Khouja C, Walker R, Sutcliffe K, Stansfield C, Sowden A and Thomas, J. (2017) Prevention interventions for Lyme disease: A systematic review. London: EPPI-Centre, Social Science Research Unit, Institute of Education, University of London.

Snilstveit B, Vojtkova M, Bhavsar A and Gaarder M. (2013) Evidence Gap Maps – A Tool for Promoting Evidence-Informed Policy and Prioritizing Future Research. *Policy Research Working Papers*; 6725: 1-32.

Stanek G, Fingerle V, Hunfeld KP, Jaulhac B, Kaiser R, Krause A, et al. (2011) Lyme borreliosis: clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect*; 17(1): 69-79.

Stanek G, Strle F. (2003) Lyme borreliosis. *Lancet*; 362(9396): 1639-47.

Stanek G, Wormser GP, Gray J, Strle F. (2012) Lyme borreliosis. *Lancet*; 379(9814): 461-73.

Sutcliffe K, Sowden A, Burchett H and Thomas J. (2017a). Patient, clinician and researcher experiences of the treatment and management of Lyme disease: a systematic review. London: EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London.

Sutcliffe K, Oliver S and Richardson M. (2017b). Describing and analysing studies, In Gough D, Oliver S and Thomas J. An introduction to systematic reviews, (2nd ed.) London: Sage Publishing.

United Nations (2017) Methodology: Standard country or area codes for statistical use (M49) - Geographic Regions <https://unstats.un.org/unsd/methodology/m49/> (accessed 31-10-2017).

Wormser G P, Dattwyler R J, Shapiro E D, Halperin J J, Steere A C, Klempner M S, Krause P J, Bakken J S, Strle F, Stanek G, Bockenstedt L, Fish D, Dumler J S, and Nadelman R B. (2006). The clinical assessment, treatment, and prevention of lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America; 43: 1089-1134.

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)

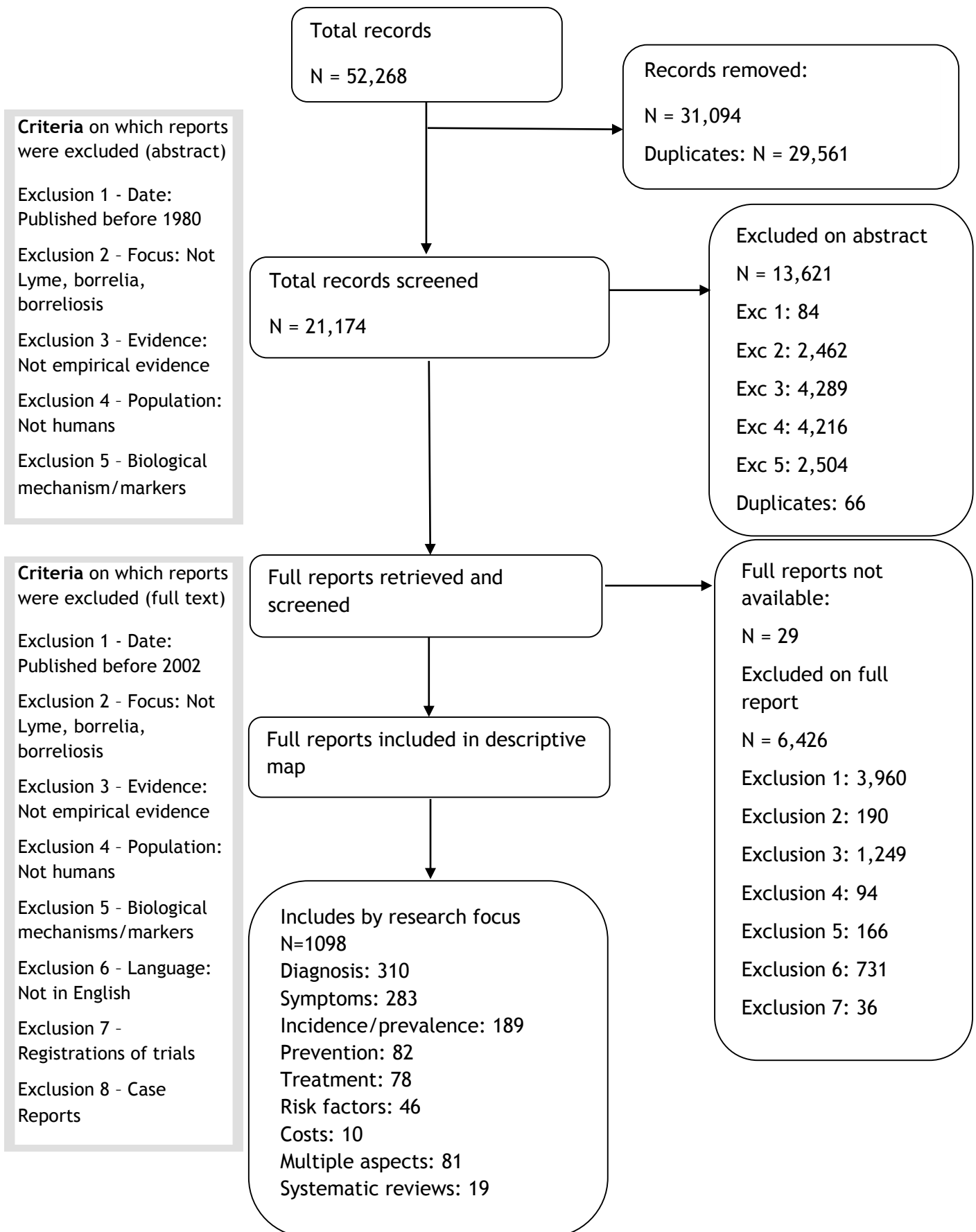
11 8 or 9 or 10 (8983)

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: Number of papers by country*

Africa (n=1)		Europe (continued)	
Egypt	1	Luxemburg	1
Asia (n=40)		Macedonia	1
China	14	Montenegro	2
Turkey	14	Netherlands	31
Iran	1	Norway	30
Japan	3	Poland	61
Korea	2	Portugal	2
India	2	Romania	11
Malaysia	1	Russia	17
Mongolia	1	Serbia	5
Taiwan	2	Slovakia	16
Australasia (n=4)		Slovenia	47
Australia	3	Spain	9
New Zealand	1	Sweden	52
Europe (n=631)		Switzerland	14
Austria	32	Turkey	14
Belarus	3	United Kingdom	47
Belgium	13	Ukraine	2
Bosnia and Herzegovina	1	Multi-country (SR + EU)	3
Bulgaria	7	Not reported	4
Croatia	5	North America (n=404)	
Czech Republic	40	Canada	26
Denmark	11	Mexico	2
Estonia	2	USA	374
Finland	22	Cuba	1
France	28	No country reported	1
Germany	84	South America (n=8)	
Greece	1	Brazil	7
Hungary	8	Venezuela	1
Ireland	4	No geographical country limit (n=16)	
Italy	28		
Latvia	3		

* numbers are not mutually exclusive

The Department of Health Reviews Facility aims to put the evidence into development and implementation of health policy through:

- Undertaking policy-relevant systematic reviews of health and social care research
- Developing capacity for undertaking and using reviews
- Producing new and improved methods for undertaking reviews
- Promoting global awareness and use of systematic reviews in decision-making

The Reviews Facility is a collaboration between three centres of excellence: EPPI-Centre (Evidence for Policy and Practice Information and Co-ordinating Centre), UCL Institute of Education, University College London; CRD (Centre for Reviews and Dissemination), University of York; and PIRU (Policy Innovation Research Unit), London School of Hygiene and Tropical Medicine.

The Department of Health Reviews Facility collaboration has grown out of a previous 'reviews facility' in Health Promotion and Public Health based at the EPPI-Centre, and has been funded by the Department since 1995.

The views expressed in this work are those of the authors and do not necessarily reflect the views of the collaborating centres or the funder. All errors and omissions remain those of the authors.

First produced in 2017 by:

Evidence for Policy and Practice Information and Co-ordinating Centre (EPPI-Centre)
Social Science Research Unit
UCL Institute of Education, University College London
18 Woburn Square
London WC1H 0NR

Tel: +44 (0)20 7612 6397

<http://eppi.ioe.ac.uk/>
<http://www.ucl.ac.uk/ioe>

ISBN: 978-1-907345-98-2

Cover image © Flickr user Franck Michel Attribution 2.0 Generic (CC BY 2.0)

This document is available in a range of accessible formats including large print.

Please contact the UCL Institute of Education for assistance:
telephone: +44 (0)20 7947 9556 email: info@ioe.ac.uk