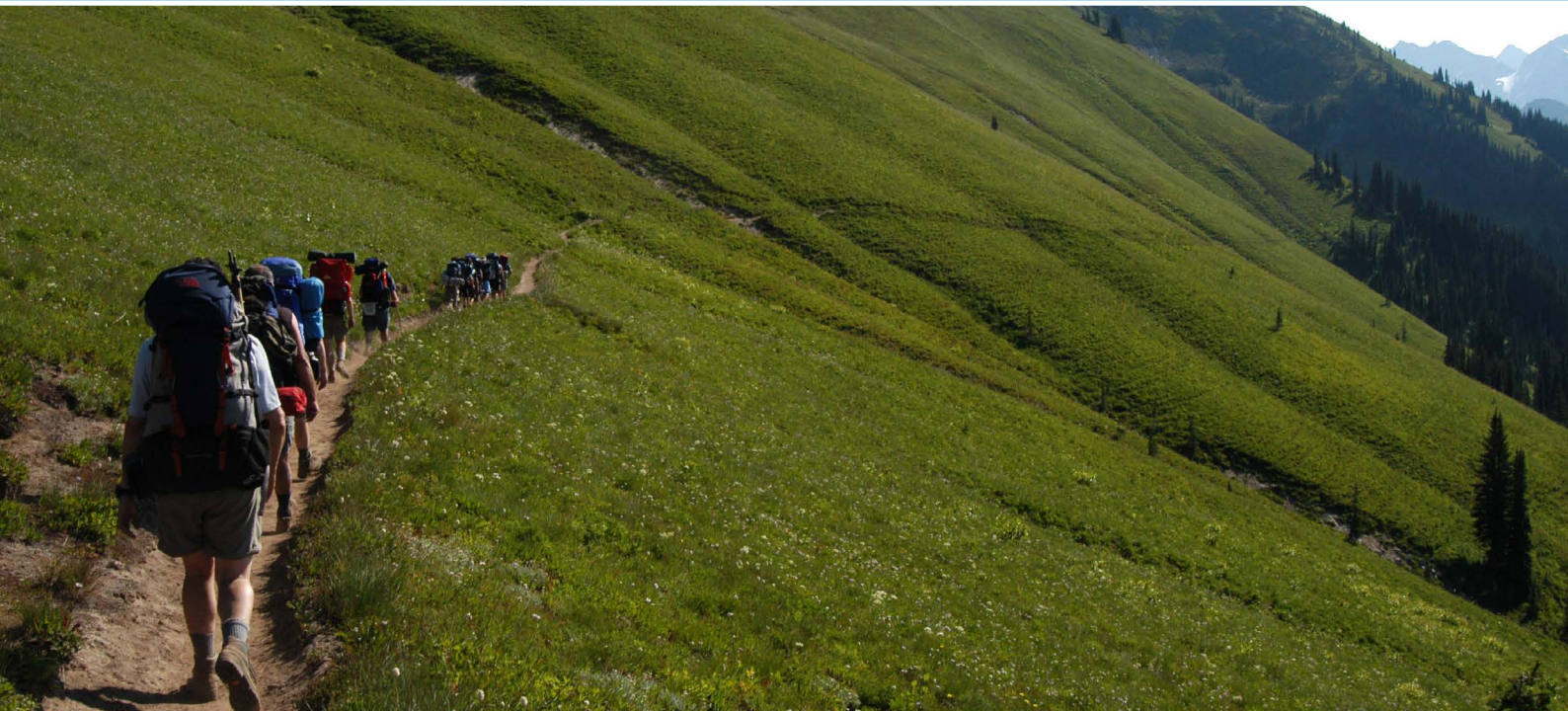


# Stakeholder experiences of the diagnosis of Lyme disease

## A systematic review



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

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## List of Abbreviations

AG	scientific advisory group
DTA	diagnostic test accuracy
IDSA	Infectious Diseases Society of America
ILADS	International Lyme and Associated Diseases Society

# 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 bitten by an infected tick. This report describes one of a series of evidence reviews on Lyme disease commissioned by the Department of Health (England) Policy Research Programme and undertaken by the Department of Health Reviews Facility. This evidence review focuses on the diagnosis of Lyme disease. Its aim is to bring together evidence from patients, clinicians and researchers about their perspectives on, and experiences of, receiving or delivering Lyme disease diagnoses, or evaluating diagnostic tests. As well as being of value in themselves, we aim for these syntheses to assist interpretations of evidence about the accuracy of different diagnostic approaches.

## Review questions and methods

The review aimed to address the following questions:-

- *What are patients', clinicians' and researchers' perspectives and experiences of diagnosis of Lyme disease?*
- *How do these perspectives and experiences help us to understand and implement findings about the accuracy of different diagnostic approaches?*

Evidence for this systematic review is drawn from a systematic evidence map which covers the range of available research evidence on Lyme disease in humans (Stokes et al. 2017a). The evidence map was produced from searches of 17 electronic databases and additional web-based searching for unpublished and grey literature. The map includes empirical research published from 2002 onwards on Lyme disease in humans.

For this in-depth review focusing on experiences of Lyme disease diagnosis, studies needed to be one of three kinds. One type consisted of diagnostic test accuracy (DTA) studies from which we extracted researchers' comments about barriers and facilitators to the use of diagnostic tests in the rationale for their study. The second type were studies that reported the views, experiences or behaviours of clinicians with respect to Lyme disease diagnosis. The third type were studies that reported the views and experiences of patients with regards to Lyme disease diagnosis. All studies needed to describe their methods of data collection and analysis.

Each type of study was synthesised separately to explore different stakeholders' perspectives on Lyme disease diagnosis. The findings of each synthesis were then pulled together to examine cross-cutting themes.

To understand whether our emerging analyses resonated with UK experiences we conducted consultation meetings in which we shared our initial findings with eight UK patient advocacy groups. Following completion of our analyses we sought comment on the key findings from these eight groups via an online survey.

## Findings

- Researcher arguments from 33 DTA studies suggest that they perceive that:-
  - Laboratory tests for Lyme disease have significant limitations relating to the accuracy of the tests, the timing of tests, a lack of consistency in interpretation of test results and the expense and time associated with conducting tests.
  - There are challenges for diagnosing Lyme disease arising from variation in presenting symptoms.
  - Precise and timely diagnosis is important.
  - There are gaps in the existing evidence base including a lack of good evidence for diagnostic tests generally, a lack of evidence for diagnosing Lyme in children, a lack of evidence comparing test use in different regions and a lack of evidence about tests for specific stages or manifestations of Lyme disease.
- Nine studies that examined clinicians' experiences of diagnosing Lyme revealed that:-
  - Clinicians develop diagnostic expertise through exposure to cases of Lyme and familiarity with the disease, as such their knowledge of the disease varies considerably across regions, types of practitioner and in relation to the manifestations presented.
  - Clinicians find it challenging to diagnose Lyme disease accurately due to the wide variation in symptoms, the infrequency with which they see the disease in practice, their level of confidence about being able to diagnose correctly, the ambiguity they experience about diagnostic tools and their beliefs and behaviour relating to atypical or persistent symptoms.
  - Clinicians access a wide range of sources to help them diagnose Lyme disease; sometimes they draw on the patient's own knowledge.
- Nine studies on the experiences of patients with persistent symptoms revealed that they experienced:-
  - A difficult journey to obtaining a diagnosis and treatment.
  - Ambivalence or scepticism from clinicians.
  - Negative practical consequences such as personal financial burden and costs to society.
  - Negative emotional consequences for themselves and their families.
  - Needing to inform themselves about Lyme disease in order to challenge clinicians who contested the validity of their symptoms.
- Feedback from UK patient advocacy groups indicated that these findings largely resonated with their experiences.
- Researchers, clinicians and patients all appear to share a concern that the currently available diagnostic tests are not always accurate.
- Patients and clinicians appear to agree that clinicians lack sufficient knowledge about Lyme disease and that uncertainties surrounding Lyme disease can lead to tensions in patient-clinician relationships as well as unproductive health care use and other costs to society.
- The evidence base would be strengthened by further qualitative research to explore clinicians' experiences of diagnosing Lyme disease and research with patients who

experience a more straightforward diagnosis of Lyme disease. Patient advocacy groups noted a need for evidence from the UK.

### **Conclusions**

Similar themes were identified between researchers who evaluate diagnostic tests, clinicians asked about their experiences of Lyme diagnosis, and people whose diagnosis was not straightforward or who identify as having chronic Lyme disease. Future research could focus on gaining the perspectives of UK clinicians and patients. Such studies should seek out and analyse separately the range of symptoms and/or diagnoses with which patients present, in order to understand differences in experiences.



# 1. Background

This report is one of a series on Lyme disease commissioned by the Department of Health (England) Policy Research Programme and conducted 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 diagnosis of Lyme disease
- 3) patient, clinician and researcher experiences of treatment and management of Lyme disease
- 4) prevention of Lyme disease

This report contains the findings from review 2) on experiences of diagnosis.

The primary objective of this review is to examine evidence from various stakeholders about their experiences of seeking or making a diagnosis of Lyme disease. The aim is to assemble evidence of stakeholder views and experiences to assist in the interpretation and implementation of evidence about the accuracy of tests for diagnosing Lyme disease.

## 1.1 Lyme disease

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

In many cases, an early sign of the infection is an erythema migrans or ‘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, p535).

## 1.2 Diagnosis of Lyme disease

Current UK guidance (Public Health England 2017) recommends diagnosing Lyme disease from patient symptoms when they present with an erythema migrans rash. Laboratory testing for Lyme disease is also recommended in cases where an erythema migrans rash is

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<sup>1</sup> We refer here to ‘*Borrelia Burgdoferi Sensu Lato*’ which includes all sub-species (including *afzelii*, *garinii*, *mayonii*, *bissettii*, *lusitaniae* and *spielmanii*). We have used the abbreviated phrase in the text for improved accessibility.

absent or unclear, but only if patients have both a history of tick bite and other symptoms suggestive of Lyme disease such as facial palsy, headache and fever.

Several international organisations have also produced guidelines and knowledge summaries (British Infection Association 2017, Centres for Disease Control 2017, European Centre for Disease Prevention and Control 2017, Mygland et al. 2010, NICE 2017d) (NICE 2017a, 2017b, 2017c), which vary in terms of the symptoms indicating Lyme disease and the interpretation of laboratory test values.

### **1.3 Using experiential evidence to help interpret and implement evidence of diagnostic test accuracy**

Diagnostic test accuracy studies evaluate how well a test is able to correctly identify or rule out a disease (Mallett et al. 2012). However, many factors may affect whether and how appropriately these tests are used in clinical practice. For example, clinicians may not be aware of the circumstances in which testing is appropriate or they may not be aware of the significance of the timing of tests. Similarly, patients may have experiences and symptoms that differ from typical cases, which makes diagnosis challenging.

Bringing together evidence from researchers, patients and clinicians about their experiences of diagnosis can help to understand the issues that may serve to help or hinder successful diagnosis in clinical practice. For example, qualitative evidence syntheses have sought to examine patients' experiences of cancer diagnosis as a result of an emergency presentation (Black et al. 2015), the barriers and facilitators to implementing diagnostic guidelines in the area of Tuberculosis (Ochodo et al. 2016) and general practitioners' experiences of managing diagnostic uncertainty (Alam 2017).

### **1.4 Research on Lyme disease diagnosis**

In 2012 a priority setting exercise was conducted in the UK by The James Lind Alliance involving patients, carers and medical professionals who identified 10 priorities for future research. Of the ten research priorities identified, the first two focused on the effectiveness of laboratory tests currently being used in the UK and the key questions clinicians should ask to help make a diagnosis of Lyme disease. Recent systematic reviews have examined evidence on the accuracy of laboratory diagnostic tests (Leeftang et al. 2016). The National Institute for Health and Care Excellence (NICE) is also currently undertaking a series of evidence reviews on the accuracy of both clinical and laboratory approaches for diagnosing Lyme disease.

However, to our knowledge, no previous evidence synthesis has attempted to systematically identify and assess evidence of patients' and clinicians' experiences of diagnosis.

## 2 Aims and methods

This section provides a brief overview of the methods used to conduct the review. A detailed account of the methods is provided in Section 5.

The primary objective of this review is to bring together evidence from researchers, patients and clinicians about their experiences of receiving, delivering and evaluating diagnoses for Lyme disease. The aim of the work is to help to understand the issues that may help or hinder the diagnosis of Lyme disease in real-world clinical settings; in particular to help interpret and implement *evidence about the accuracy of diagnostic tests for Lyme disease*.

### 2.1.1 Review questions

The review aimed to address the following overarching questions:-

- *What are patients', clinicians' and researchers' perspectives and experiences of diagnosis of Lyme disease?*
- *How do these perspectives and experiences help us to understand and implement findings about the accuracy of different diagnostic approaches?*

## 2.2 Methods

### 2.2.1 Study identification

The first phase of the project involved producing a systematic evidence map covering the whole range of research evidence on Lyme disease in humans published in or since 2002. We sought relevant studies from within the map for this systematic review.

Full details of the systematic map are available elsewhere (Stokes et al. 2017b).

### 2.2.2 Inclusion criteria

To be included in this evidence review, studies had to be one of the following types:

- A qualitative or quantitative study published in or since 2002 that reports *patient views* relating to the diagnosis of Lyme disease and which reports methods for data collection and analysis.
- A qualitative study published in or since 2002 or a quantitative study published in or since 2008 that reports *clinician views, experiences, knowledge or behaviours* relating to the diagnosis of Lyme disease and which reports methods for data collection and analysis.
- An evaluation of a diagnostic test for Lyme disease included in one or more of the NICE evidence syntheses published in or since 2008 that includes *informal researcher views (i.e. not collected using formal research methods) about factors that help or hinder the use of diagnostic tests*.

### 2.2.3 Data extraction, quality appraisal and synthesis

For the synthesis of researcher arguments, no suitable theoretical framework existed; thus thematic analysis, rather than framework synthesis, was used to synthesise findings by coding data in individual studies and then iteratively developing themes through

examination of commonalities and differences (Thomas and Harden 2008). For the syntheses on patient experiences and clinician experiences, framework synthesis was used to inductively code and thematically analyse data from qualitative studies and to narratively synthesise evidence from surveys (Brunton 2017). In each case, an a priori framework was developed based on research team's expertise and from issues arising in background scoping literature. Data were coded into these frameworks and new codes added where new concepts arose. For the synthesis of patient experiences, themes were iteratively developed from examination of common patterns. For the studies of clinician experiences, higher order concepts were drawn out of the data within codes and narratively summarised.

Findings from all three types of evidence were then compared and contrasted, to identify where common themes arose and where differences existed. While we had planned to use framework synthesis for all three types of evidence, the nature of the literature meant that we were unable to do so. We used pre-existing tools as appropriate for appraising qualitative evidence (Garside 2014), (Wong 2008). EPPI-Reviewer software was used for all stages of data extraction and synthesis (Thomas 2010).

#### *2.2.4 Quality assurance*

All studies considered for inclusion in the systematic review were screened by two reviewers, who first screened and agreed a subset of references to establish standardised screening. Once agreement was reached, pairs of reviewers screened references independently. Duplicate data extraction was used initially to standardize reviewers. Once standardisation was reached, studies were extracted by one researcher and checked by a second. During synthesis, reviewers discussed and resolved any discrepancies and worked together to refine emergent themes.

#### *2.2.5 Consultation with patient advocacy groups and scientific advisory group*

In July 2017 we conducted a series of face-to-face consultations with eight UK-based patient advocacy groups. This was done in order to understand how our draft emerging findings from international studies of patient views and clinician experiences resonated with UK experiences. Participants included both patients and clinicians. Findings from consultations were distilled into themes, which were compared to findings arising from studies of patients' views and clinician experiences. Findings were shared with all stakeholders who attended consultations to ensure accuracy.

In October 2017, following the completion of our analyses, we shared the key review findings with the patient stakeholder groups. The findings were presented as a series of bullet points via an online survey and stakeholder groups were invited to comment.

We also convened a scientific advisory group (AG) of academics and clinicians with expertise in Lyme disease. This group was expected to provide 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.

## 3 Findings

### 3.1 Overview of included studies

A total of 310 studies related to diagnosis were identified from the map as potentially relevant to our review questions. A total of 61 studies (described in 62 papers) met the criteria for inclusion in the review. Our analysis was based on 33 DTA studies, nine studies of clinician experiences, and nine studies of patient views. Nine DTA researcher arguments studies were not synthesised because thematic saturation had been reached, described below. The findings from all three groups of studies are presented below.

### 3.2 Findings from researchers' arguments presented in DTA studies

#### 3.2.1 Overview of findings from researcher arguments

- Researcher arguments about diagnosis of Lyme disease were extracted from 33 DTA studies; most of the studies were about laboratory diagnosis (n=27), and the remainder (n=6) were about clinical or symptom-based diagnosis
- Arguments about the limitations of laboratory tests for Lyme disease were put forward in most studies (n=31); these arguments related to the accuracy of the tests, the timing of tests, a lack of consistency in interpretation of test results and the expense and time associated with conducting tests
- Challenges for diagnosing Lyme arising from variation in presenting symptoms were noted in 19 studies
- The importance of a precise and timely diagnosis was recognised in 11 studies
- Gaps in the existing evidence base were noted in 11 studies, including a lack of good evidence for diagnostic tests generally, a lack of evidence for diagnosing Lyme in children, a lack of evidence comparing test use in different regions and a lack of evidence about tests for specific stages or manifestations of Lyme disease

#### 3.2.2 Nature of studies included in researcher arguments synthesis

A total of 42 papers met our inclusion criteria. We extracted data from 33 of these before thematic saturation was achieved (i.e. no new patterns or themes were expected to emerge from the remaining nine studies; none of which were UK-based). The majority of the 33 studies focused on laboratory diagnosis; six focused on clinical diagnosis (see Appendix 3 for a list of the studies). Clinical diagnosis studies were published between 2008 and 2016; five were conducted in Europe and one was from North America. Laboratory diagnosis studies were published between 2009 and 2016. Sixteen were conducted in Europe, ten in North America and one in Asia. None were conducted in the UK.

Four broad themes were identified:

- The limitations of laboratory diagnostic tests
- The importance of precise and timely diagnosis
- Lyme disease symptoms made diagnosis a challenge
- Gaps in the current evidence base.

Themes appeared across studies as illustrated in Appendix 2. These four themes are discussed in more detail below.

### 3.2.3 Theme 1: Limitations of laboratory diagnostic tests

Authors in almost all studies (n=31) argued that there were limitations to the diagnostic accuracy of laboratory tests for Lyme disease, as part of their justification for their study. There were four main reasons why laboratory diagnostic testing was considered to be problematic. First, there were concerns about the sensitivity and specificity of the tests, mentioned by four of the six clinical diagnosis studies and 22 of the 27 laboratory studies. For example, one study noted:

*“The diagnosis of LNB poses a challenge to clinicians. Detecting B. burgdorferi directly by culture or by PCR from cerebrospinal fluid (CSF) yields a maximum sensitivity of only about 50%. The sensitivity and specificity of the C6-peptide ELISA in serum have been reported to be equal, if not superior, to those of two-tier testing. [However]...data on the performance of the C6-peptide ELISA performed on CSF for the diagnosis of LNB remain limited and conflicting” (van Burgel et al. 2011).*

Limitations raised by authors about the sensitivity and specificity of the tests focused on low test sensitivity, with **false negatives** (i.e. the result wrongly indicates a person *is not* infected) identified as a particular problem in the early stages of the disease but also recognised as a problem in the late stage (Branda et al. 2010, von Baehr et al. 2012). Specificity was another challenge, with **false positives** (i.e. the result wrongly indicates a person *is* infected) resulting from cross-reactivity from antibodies caused by other bacteria or viruses, or the persistence of antibodies after the treatment of Lyme disease (Senel et al. 2010, Seifert et al. 2016, Tjernberg et al. 2011, von Baehr et al. 2012) and past infections (Cerar et al. 2010), or when there are no longer symptoms (Ang et al. 2015).

Second, linked to the issue of sensitivity and specificity was the problem that existing tests were not reliable for early or late-stage Lyme disease. One clinical study and 17 laboratory studies noted the challenge of lab-based diagnostic tests either during the early stages of the disease, or for late-stage Lyme disease, using the study authors’ definitions (which varied between studies, or in some cases was lacking). For example:

*“standard 2-tiered immunoglobulin G (IgG) testing has performed well in late Lyme disease (LD), but IgM testing early in the illness has been problematic” (Branda et al. 2010 p.20).*

Third, concerns relating to the **variability in the interpretation or reproducibility** of laboratory diagnostic results were discussed in 12 laboratory studies. These related particularly to the Western Blot test and the subjective nature of the interpretation of results, variation in criteria and the lack of standardisation between laboratories. For example, authors of one study wrote, ‘the difficulty of Western blotting has led to inter-laboratory and intra-laboratory variation and to false-positive results caused by over-interpretation, a particular problem with IgM blots’ q (Branda et al. 2010:p.546). Porwancher et al. (2011) also state:

*“when first introduced for LD diagnosis, whole-cell enzyme immunoassays (EIAs) and indirect immunofluorescence assays (IFAs) for serum antibodies to Borrelia burgdorferi suffered from a lack of standardization, poor reproducibility, and high false-positive rates” (p.851).*

Fourth, two clinical and eight laboratory studies referred to the fact that laboratory tests, particularly Western Blot, were **expensive, labour-intensive, time-consuming** (leading to delays in treatment) or, for lumbar puncture, **painful and invasive**.

#### *3.2.4 Theme 2: The importance of precise and timely diagnosis to inform treatment decisions*

Two clinical diagnosis studies (Aucott et al. 2009, Skogman et al. 2015) and nine laboratory diagnosis studies cited the importance of precise and timely diagnosis. Authors linked this need for ‘early’ detection in children (Lipsett et al. 2016, Skogman et al. 2015) and adults (Aucott et al. 2009, Molins et al. 2015, Weiner et al. 2015) with accurate and timely treatment decisions overall and made specific reference to the appropriate use of antibiotics (Henningsson et al. 2014, Lahey et al. 2015, Skogman et al. 2015, von Baehr et al. 2012, Wutte et al. 2011). Henningsson et al. (2014) wrote, for example:

*“a rapid and reliable diagnosis of LNB is essential for patients, since delayed antibiotic treatment is associated with slower recovery and persistent symptoms” (p.797).*

#### *3.2.5 Theme 3: Wide variety of symptoms makes diagnosis challenging*

Fifteen studies, all six of the clinical studies and 13 of the 27 laboratory studies, raised the issue of variation in Lyme symptomology and the challenge it poses for diagnosis. Both clinical and laboratory studies, for example, found diagnosis of Lyme disease problematic in the absence of, or after the resolution of, erythema migrans (Aucott et al. 2009, Lahey et al. 2015, Pomelova et al. 2015, von Baehr et al. 2012, Weiner et al. 2015) when rashes are atypical (Aucott et al. 2009, Lahey et al. 2015, Tjernberg et al. 2011); when presenting symptoms are nonspecific in adults (Molins et al. 2015), (Senel et al. 2010) (Bil-Lula et al. 2015, Fallon et al. 2014, Lahey et al. 2015, Ogrinc et al. 2008, von Baehr et al. 2012, Wutte et al. 2011) or in children (Skogman et al. 2008, Skogman et al. 2015, Sundin et al. 2012) and when symptoms are difficult to distinguish from other causes of illness, in either children (Waespe et al. 2010) or adults (Molins et al. 2015). For example, one group of authors wrote:

*“many patients who are referred to our Outpatients’ Clinic for suspected LB report unspecific symptoms that can be attributed to LB or any other disease” (Ogrinc et al. 2008 p.358).*

#### *3.2.6 Theme 4: Gaps in the evidence base*

In eleven studies authors argued that their current study could fill a gap in the evidence base. Two studies cite a lack of evidence for diagnostic tests generally (Molins et al. 2015) (Ang et al. 2015), or specifically for the C6 Elisa test (Tjernberg et al. 2009). Ang et al. (2015) write, for example:

*“there are few studies that use well-defined patient cohorts and compare tests head to head” (Ang et al. 2015 p.222).*

The general lack of comparative studies of diagnostic specificity is noted by Krbkova et al. (2016). In addition, three studies were found to argue explicitly that there is a lack of evidence on satisfactory tests, either to identify the infection (Lahey et al. 2015, Porwancher et al. 2011) or to confirm ‘early’ Lyme disease in the absence of erythema migrans (Aucott et al. 2009). Two studies reported a lack of evidence comparing tests from different geographical areas (Ang et al. 2015, Branda et al. 2010). Five studies argued there was a lack of evidence on the detection of Lyme in children (Lipsett et al. 2016, Skogman et al. 2015, Sundin et al. 2012, Tveitnes et al. 2012, Waespe et al. 2010). The point was made that, although there is evidence for adults, there is a lack specifically for children, for either the C6 EIA test (Lipsett et al. 2016) or the occurrence of long-term neurological deficits caused by tick-borne CNS infections (Sundin et al. 2012). Similarly, Tveitnes et al. (2012) explained that although

*“Research has aimed to develop models for the prediction of LM [Lyme meningitis] in these children, no such studies have been performed in a fully population based setting in an endemic area for LB” (p.215).*

### *3.2.7 Patient advocacy group views on these findings*

Four main arguments were used by researchers to justify the need for a study on diagnosis: that laboratory tests for Lyme disease are limited, that precise and timely diagnosis is important, that Lyme disease symptoms make diagnosis a challenge and that there are gaps in the evidence base around Lyme disease diagnosis. Few responses to our survey of key findings in October 2017 were specifically about the findings from researcher arguments. However, during our face-to-face consultations with groups in July 2017 several of the issues raised by patient advocacy groups corresponded with these findings.

First, several groups discussed the limitations of existing laboratory tests for Lyme disease and the overreliance of clinicians on these tests for both supporting and excluding a diagnosis of Lyme disease. In two consultations, the limitations of testing for antibodies as opposed to the *Borrelia* organism itself was raised. In several consultations variability in interpretation of test results was raised, and two stakeholders raised concerns about a lack of knowledge or consistent practice in storing and transporting blood samples. Also in line with the researcher arguments synthesis was a concern for many participants around the timeliness of testing and diagnosis. Participants also had concerns about the barriers to conducting useful research (discussed further below) which appear to mirror researchers’ concerns about gaps in the research; in particular several stakeholders described a need for rigorous evaluations of alternative tests (i.e. not those used as standard by the NHS).

## **3.3 Findings from studies of clinician experiences**

### *3.3.1 Overview of findings from studies of clinician experiences*

- Nine studies of non-UK origin were identified that examined clinicians’ experiences of diagnosing Lyme: eight of these were surveys of knowledge, attitudes and behaviour and one was a qualitative study of clinicians’ views about learning to diagnose Lyme disease



- Findings suggest that clinicians develop familiarity and expertise with Lyme disease in order to diagnose it, but that their knowledge of the disease varies considerably across regions, types of practitioner and in relation to the manifestations presented
- Clinicians find it challenging to diagnose Lyme disease accurately due to the wide variation in symptoms, the infrequency with which they see the disease in practice, their level of confidence about being able to diagnose correctly, the ambiguity they experience about diagnostic tools and their beliefs and behaviour relating to atypical or recurring symptoms
- Despite these challenges, clinicians access a wide range of sources to help with diagnosis; sometimes involving the patient

### 3.3.2 *Nature of included studies*

Nine studies examining clinicians' experiences with diagnosing Lyme disease were included in the review (see Appendix 4 for a list of the studies). Study aims varied. Most explored practitioners' knowledge and practices so as to understand adherence to recommended guidelines for Lyme diagnosis and treatment (Brett et al. 2014, Esposito et al. 2013, Henry et al. 2012, Hill and Holmes 2015, Johnson et al. 2010, Singh et al. 2016). Four studies sought to understand the frequency with which practitioners encountered Lyme disease and the impact on knowledge and skills (Brett et al. 2014, Ferrouillet et al. 2015, Johnson et al. 2010, Singh et al. 2016). Only one qualitative study was identified (Bakken 2002). Here authors aimed to understand how practitioners learned to diagnose Lyme disease in order to provide a theoretical framework for designing future medical practitioner education. Finally, one study examined the impact of different serological test thresholds on the clinical practice of infectious disease specialists (Hansmann et al. 2014). Studies were conducted in the US (n=5), Canada (n=2), France (n=1) and Italy (n=1). No UK studies of clinician experiences were located. Two studies sought the experiences of infectious disease specialists only and one surveyed general practitioners only; the remaining included studies included practitioners from a range of specialisms.

Four studies were considered to be of high quality (Bakken 2002, Brett et al. 2014, Henry et al. 2012, Hill and Holmes 2015), with the remaining five studies of low quality (Esposito et al. 2013, Ferrouillet et al. 2015, Hansmann et al. 2014, Johnson et al. 2010, Singh et al. 2016). Lower quality ratings in the quantitative studies were largely due to non-probability sampling (n=5 studies), a response rate below 70% (n=7 studies), and no description of control for confounding factors (n=6 studies). Detailed quality assessment ratings for each of these studies is provided in Appendix 5.

Data from the nine studies were captured under four categories: knowledge, attitudes, behaviours, and other issues. The issues seen within each of these categories gave rise to several sub-categories, which resulted in the development of three overarching themes: (1) familiarity and expertise; (2) diagnostic uncertainty; and (3) navigating uncertainty. These are discussed below.

### 3.3.3 *Theme 1: Familiarity and Expertise*

Bakken (2002) reports that clinicians undergo a process of learning to diagnose Lyme disease that is built upon gaining familiarity with the disease presentation, observing a range of cases in order to get familiar and then putting it together using a patient's history and

background. However the extent to which clinicians see patients with Lyme disease varies by location and the type of practitioner. Knowledge of Lyme disease etiology, epidemiology, signs and symptoms and diagnostic test processes were assessed across studies. Findings across this set of studies suggested clinician knowledge of all of these dimensions was incomplete and varied considerably within each dimension. While three studies reported overall high knowledge scores (between 72% and 75%) about Lyme disease, it was suggested the clinicians had knowledge gaps because clinicians did not answer all questions correctly (Ferrouillet et al. 2015, Henry et al. 2012, Hill and Holmes 2015). For example, while two studies reported very high levels of knowledge that Lyme disease was caused by *Borrelia burgdorferi* (96%-99%), generally only moderate levels of knowledge were reported with respect to the incubation period and knowledge of when to test and to follow-up (50%-84%) (Henry et al. 2012, Singh et al. 2016). While studies used the terms 'prevalence' (number of individuals with a disease at one given time), 'incidence' (the number of individuals who contract a disease over a period of time) and 'endemic' (the regular presence of disease in a given area) interchangeably, clinician knowledge about whether Lyme disease was endemic or highly prevalent in their region varied from 51% to 78% across studies, and appeared linked to whether clinicians were from a high or low prevalence area (Ferrouillet et al. 2015, Henry et al. 2012, Hill and Holmes 2015). Further, in regional studies of areas of high and low prevalence, fewer clinicians reported knowing their region was of high prevalence, with scores between 25% and 28% (Henry et al. 2012, Hill and Holmes 2015).

Knowledge scores ranged from 10% to 66% in studies where clinicians were asked to identify endemic regions in areas adjacent to or in other countries (Ferrouillet et al. 2015, Henry et al. 2012). Where clinicians had this knowledge, Bakken (2002) noted that they used this information to their advantage when establishing a differential diagnosis:

*"If somebody comes in with, since we're talking about Lyme disease, a funny rash... erythema marginatum. If you see that, you know that this is a family who has a cabin up north... You know some of those things. While that family probably would be acquainted with Lyme disease,... then you could say, 'Well, couldn't you have had a tick bite?' ... 'Oh, sure.'"* (p.135)

Knowledge of common symptoms of Lyme disease (i.e. erythema migrans) appeared to be moderate. This varied across the studies according to whether the region of practice had a high prevalence of tick bites. For example, in one study set in an area of high prevalence, only 56% of respondents reported knowing that erythema migrans alone was diagnostic for Lyme disease (Singh et al. 2016). For recognition of more uncommon symptoms of Lyme disease, such as arthritis, fever, radiculoneuropathy, meningitis and heart block, participant responses also varied according to the type of clinician. It appears that 63% to 99% of specialists were more likely to demonstrate knowledge of uncommon symptoms (Henry et al. 2012), with only 5% to 14% of general practitioners reporting similar knowledge (Ferrouillet et al. 2015).

Bakken (2002) noted that clinicians needed to encounter many patients with Lyme disease symptoms in order to experience the wide variability in symptoms. However, clinicians across the surveys reported seeing Lyme disease fairly infrequently. Those in areas of high prevalence reported more experience (Brett et al. 2014, Ferrouillet et al. 2015). In one

study, only 61% of infectious disease specialists reported seeing patients suspected of having Lyme disease less than once per month (Hansmann et al. 2014). While some authors suggested that the number of patients seen and the prevalence rates in the area of practice were not associated with higher knowledge scores, data were not presented to support this finding (Singh et al. 2016).

These factors were all suggested to influence overdiagnosis, underdiagnosis and incorrect treatment in relation to recommended guidelines. Many of the studies sought to assess clinician knowledge of correct management of diagnosis and treatment of Lyme disease. Across the studies, authors reported very low levels of knowledge of correct management. For example, two studies reported that only between 5% and 18% of clinicians would correctly prescribe antibiotics without a blood test for a patient presenting with a bull's eye rash and tick removal (Brett et al. 2014, Ferrouillet et al. 2015). Other studies suggested that knowledge of correct management differed by type of clinician; however, some claimed that general practitioners demonstrated higher correct management (Singh et al. 2016), while others asserted that rates were roughly similar, with specialists having slightly greater knowledge (Henry et al. 2012). These findings may have been due to geographic differences in the studies' samples: Henry et al. (2012) sampled across a Canadian province, suggesting a potentially more representative sample, while Singh et al. (2016) sampled from one regional medical centre. Years of practice may also influence correct management: one study found that clinicians who had been practising longer were more likely to incorrectly perform additional diagnostic tests if the first test for Lyme disease was positive (Hill and Holmes 2015).

The lack of exposure to patients presenting with Lyme symptoms appeared to lead clinicians to overdiagnose or overtreat patients. Studies noted examples of this, including 75% incorrectly ordering screening tests for patients with erythema migrans rash (Brett et al. 2014, Esposito et al. 2013); incorrect ordering of repeat serology for children presenting with Lyme arthritis in non-endemic areas and inappropriate use of Polymerase Chain Reaction (PCR) testing for children presenting with either Lyme arthritis or neuroborreliosis symptoms (Esposito et al. 2013). Studies also described 33% of clinicians treating patients inappropriately for Lyme disease in a region with low prevalence (Brett et al. 2014); 31% ordering post-tick bite prophylaxis in the absence of symptoms (Brett et al. 2014); and moderate use of appropriate antibiotic treatment in children with erythema migrans rash (Esposito et al. 2013). In another study, almost 40% of respondents in one study reported initiating treatment for Lyme disease, despite a belief that the patient may not have the condition (Hill and Holmes 2015).

### *3.3.4 Theme 2: Diagnostic Uncertainty*

As clinicians gain experience in diagnosing Lyme disease, they report encountering considerable clinical, personal and practice uncertainties. Clinically, the symptoms appear to vary widely, from those that occur in the majority of cases (i.e. erythema migrans), to those which occur less frequently (i.e. cardiac, neurological and arthritic involvement), to those which are atypical or may mimic other conditions (i.e. atypical rash, fatigue, joint pain, fever, weakness), to those which persist after treatment has occurred.

Clinicians need to have confidence in their abilities to detect Lyme disease. However, across the studies clinicians appeared to vary in their belief about their ability to correctly diagnose

the condition. Almost 70% of responding clinicians in one state-wide study agreed or strongly agreed that they were knowledgeable about Lyme disease (Brett et al. 2014). In another, high proportions of infectious disease specialists in one clinic saw their role as ‘experts’ who should

*“put an end to long series of investigations, specialized consultations and...useless or deleterious antibiotic therapies” (Hansmann et al. 2014 p.202 - 203).*

In contrast to these findings, authors elsewhere noted that over 84% of general practitioners expressed a need for further information about symptoms, lab tests and treatment (Ferrouillet et al. 2015).

In terms of practice uncertainties, the screening tests themselves created uncertainty for some clinicians. Some studies indicated that uncertainties existed amongst some clinicians around the reliability and validity of the diagnostic tests themselves. Hill and Holmes (2015) reported that 51.8% of clinicians considered the diagnostic tests currently in use to be unreliable. Hansmann et al. (2014) studied the impact of one private laboratory’s lower diagnostic thresholds and ‘subjective’ interpretation for Lyme disease on infectious disease specialists’ practice. Here, patients with both positive and negative lab results presented with symptoms, some of whom had been treated but were still consulting infectious disease specialists because symptoms had not resolved. Authors suggested that seeking out positive lab results from a private lab with lower diagnostic thresholds resulted in ‘useless antibiotic therapies...that failed to solve the patients’ problems, since they continued consulting specialists for an effective treatment.’ (p.203).

Patients’ symptoms also created uncertainty. Five of the studies reported or suggested a belief amongst some clinicians that the patients’ symptoms were caused by something other than Lyme disease (Bakken 2002, Hansmann et al. 2014, Henry et al. 2012, Johnson et al. 2010, Singh et al. 2016). Bakken (2002) describes this most clearly:

*“...but Lyme disease in practice appears to include such a high degree of variability, even to the point where there are hundreds, thousands of folks who believe they have Lyme disease, who have almost no findings at all. (Dr. NE)” (p.136)*

Another study assessed clinicians’ diagnostic and treatment behaviours based on their belief in the existence of ‘chronic’ Lyme disease, defined as persistent *Borrelia burgdorferi* infection requiring long term oral and/or intravenous antibiotic therapy (Johnson et al. 2010). Only 2% of responding clinicians reported a belief in chronic Lyme disease, with 48% undecided and 50% reporting they did not believe it was a condition.

Reluctance to attribute presenting symptoms to Lyme disease or scepticism about the existence of ‘chronic’ Lyme disease appeared to lead to differences in management. In one study, a small proportion of clinicians (30% of general practitioners and 12% of specialists) still treated patients, despite believing the person did not have the disease (Henry et al. 2012). In contrast, authors in another study suggested that the end result of patient consultations based on inaccurate lab tests was ‘useless antibiotic treatment’ and the ‘continued consultation of specialists’ (Hansmann et al. 2014). Others claimed that patients

who presented with what they termed ‘chronic’ Lyme disease ‘were not helped by the oral and intravenous antibiotics, and sometimes underlying diagnoses, such as depression and in one case leukaemia, were missed.’ (Johnson et al. 2010 p.1028).

### 3.3.5 Theme 3: Navigating Uncertainty

In order to navigate the uncertainty presented by the setting in which they practice, their previous experience with the disease, the wide variety of symptoms presented by patients and the challenges to diagnostic tests and consultation processes, clinicians reported using a variety of methods to help them diagnose Lyme disease.

Bakken (2002) described clinicians needing some time to consider a patient’s case before making a diagnosis. Respondents described using strategies such as looking farther back in a patient’s history in order to decide on the most appropriate specialist for referral, reviewing a patient’s notes, discussing the case with a colleague or consulting a research article. A wide variety of sources of information were also described across two studies (Brett et al. 2014, Ferrouillet et al. 2015), with websites commonly cited across all types of clinicians in one state-wide survey, but most likely to be utilised by clinicians who encountered Lyme disease infrequently (Brett et al. 2014). Professional meetings were preferred by older clinicians and dermatologists, and in those who saw more than 100 patients per week (Brett et al. 2014). Another study noted that general practitioners preferred continuing medical education (73%) and medical literature (63%)(Ferrouillet et al. 2015).

Patients themselves could also be a source of learning, reportedly bringing information about Lyme disease to the clinical encounter (Bakken 2002, Hill and Holmes 2015). In one study, 52% of participants reported that patients had brought up Lyme disease as a possible diagnosis (Hill and Holmes 2015). Elsewhere, clinicians reported co-investigation by patients and clinicians, with patients raising the possibility of Lyme disease themselves:

*“...I said, ‘I’ll tell you what, I’m going to have to do some more research on this, but this bugs me that I can’t remember what it is’, so I sent him out and said I want to see you back in a week. And he was . . . other than the rash, he had no problem. He called me back in 2 days and he said, ‘I think I may know what I have.’ And I said, ‘You have Lyme disease.’ And he said, ‘Yes.’ (Dr. GS)”* (Bakken 2002) p.137

### 3.3.6 Patient advocacy group views on these findings

Patient advocacy group feedback on these findings from both the face-to-face consultations and the online survey is reported below.

#### **Feedback on clinician experiences theme 1: Familiarity and expertise**

Many of the stakeholders felt patients often encountered a lack of knowledge among clinicians. This was particularly emphasised in relation to the recognition of signs and symptoms, in particular a ‘staggering ignorance’ about erythema migrans, for example in terms of recognising atypical rashes or knowing some infected patients do not have a rash. Stakeholders also reported experiences indicating a lack of awareness among clinicians about areas in which Lyme is endemic, or current guidance for diagnosis and treatment. For example, several groups raised the issue of clinicians ordering unnecessary blood tests for

patients presenting with erythema migrans or ordering tests too early, before antibodies have a chance to develop. Others raised the issue of a lack of awareness among clinicians that Lyme disease can be acquired throughout the UK.

### **Feedback on clinician experiences theme 2: Diagnostic uncertainty**

Several of the patient stakeholders and all of the clinicians recognised the challenges placed on clinicians by the varied nature of signs and symptoms of Lyme disease. One patient advocacy group member described trying to convey this to group members:-

*“I say try to imagine you’re doctor that has only seen three Lyme disease patients before, with symptoms that could be caused by a hundred different things, would you be confident making a clinical diagnosis of Lyme disease?”*

Nevertheless, many of the groups also indicated a view that clinicians needed to acknowledge and communicate their uncertainty to patients. For example, several stakeholders were of the view that clinicians were over-reliant on test results, for example ‘So many doctors are sure that NHS testing or other tests should not be questioned. That is not how we do science.’

Another stakeholder noted that:-

*“We need to remember we’re dealing with a complicated illness - there wouldn’t be all of this politics around it if we knew exactly how to test for the bacteria and we knew how to treat with success across the board.”*

### **Feedback on clinician experiences theme 3: Navigating uncertainty**

Whilst many stakeholders recognised the challenges faced by clinicians in obtaining sufficient knowledge, they also felt that the political climate surrounding Lyme disease in the UK was not conducive to learning as it hampered both clinical practice and research. For example:-

*“Until we become more open-minded nothing will change, but no one wants to step out of line.”*

In relation to research, several stakeholders indicated that researchers are reluctant to address important questions for patients, with one referring to the lack of relevant research as ‘institutional denial’. One stakeholder noted that there was only one registered medical practitioner from the UK at a global conference where current treatments and new research were being discussed. A key perceived impediment to research was possible harm to researchers’ and clinicians’ careers:-

*“There are very few papers that look at harm to patients from misdiagnosis - why is that? It’s because nobody is going to enhance their career if they publish a paper that illustrates that their profession is failing patients.”*

Both patients and clinicians involved in the July 2017 consultations recognised that similar constraints hindered practice. Many described clinicians feeling anxious about losing their licence to treat, being vilified by their profession or being ‘chased’ by authorities.

*“There are doctors who have been chased by GMC for trying to do a bit more. You’re really putting things on the line by trying to push the limits of what you can give a patient.”*

Some indicated that another barrier to increased knowledge was the loss of both clinicians and patients to other countries. For example:-

*“I think we are missing valuable information in the UK with so many seeking diagnosis, testing and treatment overseas because they aren’t getting answers here in the UK.”*

Stakeholders from four groups specifically contested the finding that clinicians’ welcome information about Lyme disease from patients. One described this finding as being ‘at odds with UK patient experience’ and another noted that ‘clinicians tend to be defensive in the face of patient knowledge, often advising patients not to educate themselves on the internet.’

One stakeholder, in describing the range of clinician attitudes and knowledge, summed up the consequences for patients of constraints to knowledge and practice:-

*“There’s an arrogance amongst some, a limited knowledge amongst others or there are those who are more open-minded but feel their hands are tied.”*

### **3.4 Findings from studies of patient views and experiences**

#### **3.4.1 Overview of findings**

- Nine studies which discussed the patient experience of Lyme disease were identified; all of these focused on experiences of patients for whom diagnosis was not straightforward or who had persistent symptoms
- The patients described a range of consequences of living with a condition that is contested and controversial including:-
  - Their concern to obtain a diagnosis and the difficulties of achieving this
  - Ambivalence from medical practitioners
  - Negative practical consequences such as financial burden
  - Negative emotional consequences for them and their families
  - Ways in which they challenged the contested nature of their condition

#### **3.4.2 Nature of the included studies**

We found nine studies reported in ten papers which discussed the patient experience of Lyme disease; Appendix 6 provides an overview of the included studies. Critical assessment of the studies was undertaken using the tool presented in Appendix 7. Studies were of low to moderate quality overall, with gaps noted most often in reporting of epistemological and theoretical underpinnings. Quality ratings are summarised in Appendix 8.

All of the studies focused on patients who had experienced persistent symptoms. Thus, the literature contained in this synthesis relates to the experiences of a particular group of Lyme patients whose journey was not straightforward. The experiences of those who were

diagnosed and treated promptly and who experienced no ongoing problems are notably absent from this research evidence.

In understanding the context of these findings, it is also important to understand the position of the study authors, given the divergent views about the existence of legitimacy of persistent Lyme disease symptoms. Eight of the studies indicated that they ascribed to a heterodox perspective (Ali et al. 2014, Bloor and Hale 2013, Chaudhury 2016, Dankyi 2016, Drew and Hewitt 2006, Johnson et al. 2014, Johnson et al. 2010, Rebman et al. 2015). In other words, the authors described Lyme disease, in contrast to many medical guidelines, as a complex condition with various symptoms, which has the potential for long-term complications and which is often misdiagnosed or under-diagnosed. Only one study took an orthodox perspective (Csallner et al. 2013) viewing Lyme disease as a straightforward, acute infection which is easily diagnosed and successfully treated.

In terms of participants, seven of the papers (all categorised as heterodox) were unclear as to the diagnostic status of their sample, with some stating that it was not a matter of concern for their paper, since their focus was on the lived experience of the disease (Ali et al. 2014, Chaudhury 2016, Dankyi 2016). Patients in six of these studies were recruited from patient support groups and the other via a ‘home infusion company’ treating patients with persistent symptoms. Rebman et al. (2015) was the only study classified as heterodox to focus on patients with verified clinical and serological diagnosis. The one paper classified as orthodox (Csallner et al. 2013) recruited patients referred to a Lyme clinic and compared the views of those with a positive Lyme disease test result to those with a negative one; therefore, the orthodox diagnosis of Lyme disease became the central explanatory variable for their results.

### 3.4.3 *Theme 1: The difficult path to diagnosis: “It’s not this invisible thing anymore.” (Drew and Hewitt 2006 p.24).*

- The process of obtaining a diagnosis of Lyme disease when clinical markers are unclear or atypical can be a highly charged experience, leaving the patients fraught with uncertainty and frustration.
- The legitimacy ascribed by an official diagnosis leads to relief from uncertainty and opened up access to treatment and care.

The first key theme arising from the research with patients was that they were keen to receive a correct diagnosis so that they could access appropriate treatment and have their symptoms resolved. However, the research also indicated that the process of obtaining a diagnosis was often difficult and lengthy. Patients emphasised the emotional impact of seeking and receiving a diagnosis. Respondents expressed relief if they did receive a diagnosis, since it put an end to uncertainty and validated their experience of the illness:

*“He tested me for it and it came back positive. I was pleased. I can hold this now. I can deal with it. We’re gonna treat it. It’s not this invisible thing anymore [...] I just felt like, oh my God, someone believes me.” (Drew and Hewitt 2006 p.24).*

For many patients however, diagnosis was not so straightforward. The tell-tale rash erythema migrans, a key marker for a clinical diagnosis, was missing (43%) or not typical (17%) for patients in a UK survey (Bloor and Hale 2013). In this survey, less than half (48%)



of the respondents remembered the bite, whilst the remaining 52% couldn't remember, weren't sure they had been bitten or thought they may have caught the disease in another way (Bloor and Hale 2013). Respondents in the Chaudhury (2016) study also described unclear memories of tick bites.

Uncertainty about infection or untypical symptoms could lead to frustration as it could be a factor in a delayed diagnosis (Drew and Hewitt 2006). Delays were attributed to visiting multiple centres where specialists conducted their own tests to rule out other diseases, such as multiple sclerosis (Chaudhury 2016, Dankyi 2016):

*“Like many chronic Lyme disease patients, I was launched into a medical maze, searching for answers as things worsened. I told my husband that something in my body had broken. It was falling apart. I went to specialist after specialist, and each one found some possible cause within his or her specialty.”(Chaudhury 2016 p.29)*

The multiple tests used to verify infection and disease were described as leading to long delays in receiving treatment (Bloor and Hale 2013, Chaudhury 2016, Dankyi 2016, Drew and Hewitt 2006, Johnson et al. 2014, Johnson et al. 2010). Johnson et al. (2014) reported that for 61.7% of respondents there was a wait of at least two years. Some respondents described difficulty in persuading doctors to do the testing for Lyme disease (Dankyi 2016). As a result, some ambivalence about the testing process was expressed:

*“They kept doing all this blood work over and over and over and everything, liver, kidneys, immune, everything they could do and everything is coming back negative....extremely frustrating.” (Drew and Hewitt 2006 p.23)*

#### 3.4.4 Theme 2: Ambivalence from clinicians - *“The thing that upset me the most about the whole thing was what a political football it is.” (Rebman et al. 2015 p.8)*

- Many patients indicated that they felt they were denied a diagnosis by clinicians who questioned the legitimacy of persistent symptoms of Lyme disease.
- As a result patients indicated that doctor-patient relationships could be strained.
- Many patients perceived that clinicians often undermined the legitimacy of their illness by implying that their problems were psychosomatic, therefore leading to further uncertainties and potentially more misdiagnosis.

The second key theme from the patient views research was that many clinicians were perceived as ambivalent, sceptical or even hostile to the idea of persistent symptoms of Lyme disease. Whilst patients in one study described attributes of helpful doctors as 'open-minded', 'supportive' and willing to 'acknowledge patient concerns' (Ali et al. 2014), patients in several studies described experiencing doctors to be 'dismissive', 'condescending' or 'patronizing' (Ali et al. 2014, Bloor and Hale 2013, Dankyi 2016).

In the study by Rebman et al. (2015) one patient described chronic Lyme as a ‘political football’, while another recalled an instance where their therapy was questioned by a doctor in an encounter at a dinner party:

*“We were having dinner [...] I said you know I have chronic Lyme disease, and his immediate reaction was just sort of to pull back from the table and he said well, who told you that? And I explained you know, what had been going on and all this time and he said well, I don’t think that evidence supports what you’re doing.” (Rebman et al. 2015 p.8)*

Patients were wary of the imputation of a psychological cause to their suffering since it seemed to suggest that their illness was illegitimate (Chaudhury 2016). A parent in one study expressed frustration at the constant uncertainty expressed by clinicians describing it as:-

*“...this shadow disease where people are constantly questioning you and questioning your child.” (Dankyi 2016 p.67)*

Published in the journal ‘Psychosomatics’, the article by Csallner et al. (2013) underscores these patients’ perceptions that some see their illness as illegitimate. The authors suggest that patients ‘claim to suffer from “chronic Lyme disease”’ and that this leads to:-

*“Inappropriate use of health services, avoidable treatment-related illness, and substantial disability and distress”. It has been repeatedly suggested that “Chronic Lyme Disease” is just another unwarranted label for “organically unexplained symptoms (OUS).” (Csallner et al. 2013 p.360)*

### 3.4.5 Theme 3: Practical consequences of ‘living in limbo’ - “I have already reached my out-of-pocket max” (Ali et al. 2014 p.4)

- Patients whose symptoms remained undiagnosed and unresolved could suffer long term negative financial consequences such as: ongoing medical bills, travelling long distances for care, prolonged absences from work.
- The negative consequences were not only borne by the patients themselves, studies indicated societal impacts including increased use of healthcare resources and patients turning to higher usage of complementary alternative therapies, which can also be expensive.

The third theme arising from the patient views research was that patients with persistent symptoms, and particularly those without an official diagnosis, could experience negative consequences with regards to their livelihoods. All of the papers from the USA, where healthcare is paid for by insurance, commented on the financial burden of the disease for patients (Ali et al. 2014, Dankyi 2016, Drew and Hewitt 2006, Johnson et al. 2014, Johnson et al. 2010). Johnson et al. (2014) reported higher out-of-pocket expenses than the general population for medicines and treatments, with 69% spending more than USD\$2,000 a year, compared to 20% of the general population spending that amount. For example:-

*“Even though insurance pays for this ... I have already reached my out-of-pocket max and it’s August. I met it last month and that’s \$2500. That*

*doesn't include other prescriptions or co-pays for August visits.” (Ali et al. 2014 p.4)*

Costs were also incurred in travelling for care. Many respondents found it difficult to obtain care at their local hospital and some described travelling some distance to find doctors willing to treat them (Johnson et al. 2010). The seeking out of diagnosis or treatment that was not officially recognised could have further financial consequences; one study reported that patients were either not covered by insurance because their doctors were outside state borders or the treatment was considered experimental (Drew and Hewitt 2006).

These costs were particularly problematic since many could no longer work (Drew and Hewitt 2006, Johnson et al. 2010); and others reported that their retirement savings had been spent (Dankyi 2016). Johnson et al. (2014) reported that 42% of respondents had stopped working as a result of illness, while 25% had reduced their hours or changed the type of job they were doing. A quarter of survey respondents indicated that they had received benefits at some point, and more than half had had disability benefits for over two years (Johnson et al. 2010). This impact on ability to work and productivity thus has consequences for employers and for the state.

Another consequence of being left ‘in limbo’ (Rebman et al. 2015) in terms of societal costs was that patients were more likely to use health services more (Csallner et al. 2013, Johnson et al. 2014). Johnson et al. (2014) found that chronic Lyme disease patients were five times more likely than the general population to visit doctors and healthcare professionals and twice as likely to visit the emergency department of a hospital. They also spent more time in hospital (15.2% vs. 7.9%) and had six times more homecare visits (12.8% vs. 2%).

#### *3.4.6 Theme 4: The emotional consequences of living with a contested condition: “People do not believe me about how bad I feel.” (Rebman et al. 2015 p.7)*

- Patients reported poor mental health, and negative emotional and social impacts

The personal costs of living with a contested illness were not purely limited to financial costs. Csallner et al. (2013) found scores on a scale measuring ‘excessive health worry’ were higher among those without a diagnosis than those whose test results were positive; they also had much lower scores on measures looking at quality of life. These findings reflect the experiences of the patients from other studies, who report higher than average physical and mental illness events, such as days lost to pain and mental distress (Johnson et al. 2014) or anxiety and depression (Ali et al. 2014, Chaudhury 2016, Rebman et al. 2015).

Patients attest to the psychological aspects of living with persistent symptoms; in their accounts of dealing with the chronic nature of the disease, they acknowledge the emotional toll it can take and experiencing a sense of loss for the life before their illness (Chaudhury 2016, Rebman et al. 2015):

*“I’ll say, ‘oh, I know I’m accepting it much more’ but I realize that when I hit a wall again and I get really disappointed all over again, I realize you weren’t accepting this as much as you said you were. I mean, I think we can kid ourselves.” (Rebman et al. 2015 p.6)*

In these accounts, the patients do not discuss tick bites, the results of serological tests or erythema migrans. Their concerns are about the problems of living with the illness, compounded by a sense of uncertainty about the prognosis and the moral ambiguity related to its contested diagnosis.

Living with a chronic condition was life changing not only for the patient but for their family and friends. Although patients shared views of support from families and friends, some reported their illness was not recognised as real, which resulted in feeling unsupported by those closest to them. As one female patient described:

*“I mean, even the supportive people like my husband and my mother were sort of like, you just kind of need to buck up and you know, try a little harder [...] you just need to quit whining and put your happy face on and act like everything’s going to be okay and it will be okay and I was like, you don’t understand what kind of tired I’m talking about”. (Rebman et al. 2015 p.7)*

The invisible nature of the illness and the lack of legitimacy from being without a diagnosis made relations with friends and family difficult for some patients. Patients described responses to their condition as isolating and upsetting:

*“It’s hard enough when you’re declining and you get everybody’s love and support. But to do it without anyone believing you is I think one of the most difficult things to deal with, as far as the psychology of the illness.” (Rebman et al. 2015 p.7)*

Patients were also affected by uncertainty about the trajectory of their unrecognised condition; general uncertainty about the course of the condition could be compounded by a lack of support and recognition from the medical community:

*“I live in fear, am I going to be a cripple? Am I going to go nuts?” (Rebman et al. 2015 p.8)*

3.4.7 *Theme 5: Contesting the contested - “So you really have to educate yourself and everyone around you...” (Drew and Hewitt 2006 p.24)*

- Patients challenge their lack of official diagnosis by seeking alternative solutions, education or by joining or forming self-advocacy groups.
- Patients sought diagnoses from alternative sources to achieve some legitimacy for their experiences.

Patients discussed the importance of self-advocacy to educate themselves and others (Drew and Hewitt 2006).

*“So you really have to be your own advocate... and educate yourself and educate everyone around you so that people are aware. In fact, all along I had to be my own advocate.” (Drew and Hewitt 2006 p.24)*

Additionally, patients questioned the knowledge of the doctors, as reported in Bloor and Hale (2013); 62% of survey respondents did not think their general practitioners were fully

informed about infections from ticks and 63% believed NHS consultants did not have the required expertise to deal with the infection.

*"I was tested early and it came back negative. They spent the next one and a half years trying to say I had MS, until a consultant suggested retesting for Lyme. That test was positive. Now if the doctors who saw me (and there were many) had any knowledge about Lyme they should have realized tests come back negative if tested early in the infection, because the body has not yet produced antibodies." (Bloor and Hale 2013 p.6).*

Patients also expressed uncertainty about the accuracy of serological tests (Bloor and Hale 2013, Dankyi 2016, Drew and Hewitt 2006, Johnson et al. 2014). For example, Johnson et al. (2014) mentioned that most patients had co-infections with other types of tick-borne infections, which made test results difficult to analyse. This mistrust of diagnostic tests led patients to challenge test negative test results:-

*"What do you mean, she doesn't have Lyme? I see something on here that says positive." (Dankyi 2016 p.66)*

From Bloor and Hale (2013)'s survey, 56% of respondents reported negative officially recognised test results; though by responding to the survey they indicate that they still identify as having Lyme. Both Bloor and Hale (2013) and (Drew and Hewitt 2006) discussed patients who had a diagnosis of Lyme disease but, initially, had negative test results. Likewise, the majority of respondents (58.7%) in Johnson et al. (2010) derived their diagnosis from tests that were not the medically recognised diagnostic tests for the disease.

These difficult relations led patients to seek other providers. Some sought out providers who adhered to different medical guidelines than those developed by the Infectious Diseases Society of America (IDSA) (Johnson et al. 2010). These doctors were described by study authors as 'Lyme literate medical doctors' (LLMD) and were willing to diagnose and prescribe long courses of antibiotics, if necessary, according to the guidelines set out by ILADS (International Lyme and Associated Diseases Society), seen as an alternative at the time of the included study (Johnson et al. 2010). Complementary and alternative medicine was taken up by others, since these therapies enabled patients to manage their symptoms (Ali et al. 2014).

Thus, the patients describe a range of strategies to counter their experience of denial and dismissal by clinicians based on contested guidelines and their efforts to reinforce the concept of chronic Lyme disease as a legitimate condition.

#### *3.4.8 Patient advocacy group views on these findings*

Patient advocacy group feedback on these findings from both the face-to-face consultations and the online survey is reported below. For many of the stakeholders who attended the face-to-face consultations the overall findings from the research on patient views were felt to resemble their own experiences. Some stakeholders explicitly noted that the themes from the research covered many key issues, for example, 'there's a lot of it covered there'. Given the lack of research from the UK, the similarity of the research findings with UK experiences was unexpected for one stakeholder, 'I was wondering how well it would

correspond with the British experience and it does. It's highlighted all of the main problems.'

In addition, the stakeholder feedback also indicated that the five main themes from the patient views research were appropriate; in many cases they provided additional insights about these themes.

**Feedback on patient views Theme 1: The difficult journey to obtaining a diagnosis**

Many stakeholders recognised the often fraught and emotionally charged nature of obtaining a diagnosis for Lyme disease. Some described the relief of receiving a diagnosis. However, many stakeholders described the 'frustration', 'fear' and 'trauma' of uncertainties surrounding diagnosis. Stakeholders strongly expressed a view that diagnosis is delayed as all symptoms are not considered together; all eight patient groups commented on this. For example, one clinician described multi-disciplinary working as 'key' and several patients described being '*pushed from pillar to post*' around different specialist departments and that '*no one is in charge*'. One stakeholder described frustration with this experience:-

*"When you go to the cardiologist you're just a heart, and when you go to the dermatologist you're just a piece of skin. You're not going to twig Lyme disease like that. It's like the fairy tale of the wise men and the elephant, nobody will look at the whole patient."*

A related issue, highlighted by several stakeholders as missing from the analysis of research, was the issue of misdiagnosis. Receiving an incorrect diagnosis for an alternative illness was noted as further delaying the diagnosis of Lyme and therefore appropriate treatment. One group shared findings from their survey of UK patients self-identifying as having Lyme, which indicated that many of their respondents had initially been diagnosed with one of 37 alternative conditions. One stakeholder pointed out that many of the alternative conditions, such as Chronic Fatigue Syndrome and Fibromyalgia, are labels which describe people's symptoms and leave patients feeling deflated as the root cause of the problem is not being established.

**Feedback on patient views Theme 2: Ambivalence from clinicians**

Participants from all eight patient advocacy groups described a view that patients were denied diagnosis by sceptical clinicians. These clinicians were described as explicitly denying the existence of persistent symptoms of Lyme disease or informing patients that they '*don't deal with Lyme*'. Some stakeholders indicated this theme as particularly relevant, for example '*What has hurt me just as much [as my illness] is the way we are treated*'. Others stressed the fact that the consequences of doctors' scepticism were severe for patients, i.e. little or no support and treatment. Some felt clinician scepticism arose because their symptoms were not immediately visible; many indicated parallels to other contested illnesses with few visible symptoms such as Chronic Fatigue Syndrome. Some also contrasted their experiences against those with very visible symptoms such as acne '*We're giving people with acne a longer course of doxycycline than we are Lyme patients at the moment*'. Stakeholders also indicated that relations with clinicians were fraught as a result. This was not only because patients experience '*a system of disbelief*' but because they also experience clinicians as condescending and dismissive.

*“Infectious diseases laughed down phone when given my private test results. Not just not believed, but laughed at and ridiculed.”*

The research indicated that patients felt clinicians who regarded persistent symptoms of Lyme to be a psychological problem undermined them by suggesting their problems were not a genuine physical illness; many stakeholders agreed with this. For example, *‘The attitude is “Things that I can’t explain or things that I haven’t got a test for just call it psychological.” And that happens over and over.’* A related theme which was not described in the research was a questioning of parents’ sanity when they believed their child to be suffering from symptoms of Lyme disease; several stakeholder groups noted that some mothers were being diagnosed as having Munchausen syndrome by proxy (MSBP).

It should be noted that whilst many of the participating clinicians recognised themselves as more ‘open-minded’ in relation to persistent Lyme disease symptoms, many also recognised the difficulties clinicians face in diagnosing and managing those with complicated symptoms and unclear laboratory findings.

### **Feedback on patient views theme 3: Practical consequences of living in limbo**

The third theme arising from the patient views research was that patients with persistent symptoms, and particularly those without an official diagnosis, could experience negative consequences with regards to their livelihoods.

Emotive descriptions were given of the very real impacts on the lives of those living with disabling symptoms. Stakeholders described patients having to sell or re-mortgage their homes in order to pay for private treatment. Others described the impact on their careers *‘when you fall off the career ladder... you can’t get those years back!’* The significance of this issue for patients was emphasised by one stakeholder:-

*“That’s probably the single biggest factor that is ruining lives, is that they can’t function and they can’t remain financially independent, and they’re not given support. They’re just cut loose by the state.”*

Beyond financial and employment consequences identified in the research, the life-changing impact of patients’ unresolved symptoms was indicated by several stakeholders. For example, some described families breaking up under the strain of caring responsibilities and others expressed concerns about being able to have children *‘I’ve lost the right to have children and everything - because of a disease that’s not being treated.’*

Many groups also agreed with the findings about negative impacts for society because of delays to diagnosis and the consequent lack of treatment. For some this weighed heavily:-

*“We’re going to cost the NHS more money if nothing is done. Last year I went to hospital 36 times. I’ve got surgery on Thursday because of the damage that has been done. I’ve been out of work, I can’t give anything back to the country.”*

Others pointed out that there are likely to be hidden costs related to misdiagnosed and undiagnosed cases with countless visits to clinicians, consultants and numerous tests to eliminate other diseases.

#### **Feedback on patient views theme 4: Emotional consequences of living with a contested condition**

The fourth key theme arising from the research for patient group stakeholders was the emotional costs for patients of living with a condition that they feel is poorly understood, not recognised and even contested by many clinicians.

Most of the groups agreed that in addition to living with persistent disabling symptoms, living with a contested condition has emotional consequences, for example:-

*“I can’t put into words the level of suffering you experience, and at the same time as having to navigate all this judgement about your treatment choices. It’s a really desperate situation.”*

In common with the research findings there was a recognition among stakeholders of the negative impact of this on families - ‘When you have doctors calling patients into question families don’t know what to do’ - and the knock-on impact on patients of family members’ uncertainties. However, several stakeholders noted a related mental-health issue that was not clearly identified in the research. They described how patients’ mental health could be affected both by not being believed and by the infection itself. For example:-

*“The psychological component, people are really upset by it. But a lot of people start completely mentally healthy but end up with problems; it could be due to neurological complications but the trauma of whole thing could possibly contribute.”*

Many stakeholders referred to serious cases of mental ill-health among patients with ongoing symptoms; several referred to cases of suicide.

#### **Feedback on patient views theme 5: The challenges inherent in self-advocacy**

The final key theme from the patient views research was that many patients felt compelled to inform themselves and others in order to challenge the views of clinicians who were sceptical about persistent symptoms of Lyme disease.

Many stakeholders discussed their view that evidence does not support the accuracy of diagnostic tests. In some consultations these issues were discussed at length. Unsurprisingly, the patient stakeholders also agreed with the need for self-advocacy. However, they further illuminated how the need to advocate could have negative consequences. For example:-

*“I agree with the literature, people find themselves in position where they have to push, argue or confront. But this makes them appear in a certain way.”*

This dilemma was also alluded to in another consultation in which it was noted that coming armed with information was not always welcomed by clinicians, ‘You’re dismissed as going to doctor Google.’ Some advocacy groups described advising their members on how to advocate successfully, for example by printing out PHE guidelines and taking them to the clinic to illustrate that, in the instance of an erythema migrans rash, further tests are not required for a diagnosis.



Several stakeholders described a view that marginalised groups would be more easily dismissed and therefore far less successful at self-advocacy. One stakeholder described being aware of only two patients who had successfully negotiated access to benefits, and noted that both of these patients were highly educated. This same stakeholder was also of the view that those with autism or mental health problems were likely to be the most disadvantaged in terms of accessing support or benefits. Another stakeholder described a view that women are more likely to be dismissed by clinicians than men.

### **3.5 Comparing these findings**

The themes arising from each of these different types of research study (researcher arguments, clinician experiences and patient views research) were compared and contrasted, in order to discover where experiences converged or diverged. This is illustrated by Table 1 below:

**Table 1: Comparison of themes from each type of study**

Themes arising/ Study type	Themes arising from Researcher arguments in DTA studies				Themes arising from studies of Clinician experiences			Themes arising from studies of Patient views				
	Lab tests inaccurate	Precise/ timely diagnosis important	Varied symptoms	Gaps in tests re: geography, children, uncommon symptoms	Varied familiarity and expertise	Differences in dealing with Uncertainty	Varying ways to navigate uncertainty	The difficult path to diagnosis	Ambivalence from clinicians	Emotional consequences of living with a contested diagnosis	Practical consequences of 'living in limbo'	Contesting the contested
Researcher arguments in DTA studies	✓	✓	✓	✓	--	--	--	--	--	--	--	--
Studies of Clinician experiences	✓	--	✓	--	✓	✓	✓	✓	✓	✓	✓	✓
Studies of Patient views	✓	--	✓	--	✓	✓	✓	✓	✓	✓	✓	✓

✓ convergent theme -- theme not addressed by study type

### *3.5.1 Themes arising from studies of researcher arguments*

Four themes were identified in the set of studies examining researcher arguments for DTA studies. These are described below.

#### **Gaps in the evidence base**

This theme was only identified in this type of study, focusing on addressing gaps in tests related to geographic differences and a need for tests focused specifically on children.

The remaining three themes were addressed within findings across all three types of study.

#### **Lab tests inaccurate**

There was agreement across all three types of research that current serological tests for diagnosing Lyme disease have limitations. Researchers conducting DTA studies most often argued that evaluations of the clinical or serological tests were needed because of a high prevalence of either false positives or false negatives in the current standard tests, as well as difficulties in subjective interpretation of lab results. This ambiguity was echoed in the studies of clinician experiences, where clinicians expressed doubts about the validity of test results, and infectious disease specialists in one study expressing concerns about high rates of false positive results due to a lower threshold for the serological test in use. The studies of patient views of diagnosis suggested that patients were concerned about false negatives and there was a belief that serological tests may not be capturing everyone who might be infected.

#### **Test interpretation and Timing**

Findings from all three types of research also suggested that both the timing of serological testing and the interpretation of those tests created difficulties. Researchers argued that current lab tests could be ambiguously interpreted, and that outcomes were affected by the length of time between tick bite and administration of the serologic test to detect antibodies. Studies examining clinician experiences reported concerns about private laboratory testing because the labs set a lowered threshold for positive diagnosis of Lyme disease, resulting in more consultations for patients who they believed did not have Lyme disease. The timing and interpretation of tests were also raised as a concern in the patient views studies and by the patient stakeholder groups.

#### **Varied symptoms**

The wide variation in symptoms of Lyme disease was identified in all three types of research. For example, researchers cited a need for new or improved serological tests to accurately detect the varied manifestations of Lyme disease. Studies of clinician experiences noted that common manifestations of Lyme disease such as erythema migrans were correctly recognised by clinicians, but only where they frequently encountered it. These studies reported that clinicians' knowledge and adherence to recommended management of Lyme disease with less common symptoms was lower. Studies of patient views indicated that the variation in symptoms could be a problem for patients in gaining access to Lyme disease tests and treatment.

### *3.5.2 Themes arising from studies of clinician experiences*

Three themes were identified from the studies of clinician experiences: familiarity and expertise, dealing with diagnostic uncertainty, and navigating uncertainty. Aspects of each of these themes were also addressed in the patient views studies but were not located in researcher arguments.

#### **Familiarity and Expertise**

Familiarity with Lyme disease varied across the studies of clinician experiences. Most studies suggested that clinicians who see more cases of Lyme disease have higher knowledge scores and diagnose according to recommended guidelines more than those who see Lyme disease less often. However overall knowledge of Lyme disease etiology, epidemiology and diagnostic processes were still well below 100% in any group under study. Studies of patient views suggested that patients picked up on this, and clinicians were often described by patients as having low levels of knowledge.

#### **Dealing with Diagnostic Uncertainty**

Within this theme, findings in several studies suggested concerns about overdiagnosis. Clinicians in some studies appeared to attribute patients' presenting symptoms to conditions other than Lyme disease and some sought to put an end to multiple consultations and delivery of treatment they deemed unnecessary. By contrast, studies of patient views reported that they were concerned about underdiagnosis and gaps in clinicians' knowledge concerning uncommon symptoms.

#### **Navigating Uncertainty**

In order to navigate these uncertainties, clinicians reported using a range of sources to help them diagnose. These included external sources such as websites, other professionals, and continuing education opportunities. Some clinicians also report co-investigation with patients, who bring information with them to the clinical encounter. Whilst patients in the views studies did describe the need to do independent research on Lyme disease, feedback on these findings from UK patient advocacy groups suggested that they experienced clinicians as being defensive in the face of patient knowledge and advised them not to educate themselves on the internet.

### *3.5.3 Themes arising from studies of patient views*

#### **The difficult path to diagnosis**

Studies of patient views suggested that obtaining an accurate diagnosis was often a frustrating and lengthy process. The studies of clinician experiences noted that some clinicians were uncertain of what to do with patients who had a negative test result.

#### **Ambivalence from clinicians**

Studies of patient views described clinicians' responses as ranging from helpful and supportive to dismissive or even hostile. Patients also suggested that they felt undermined by clinicians who ascribed a psychological cause to their suffering. Some clinician studies noted that when patients presented with symptoms or markers outside of current understanding of the disease they would treat them despite not believing that their symptoms were due to Lyme. Others described trying to convince patients that they did not

have Lyme disease because they did not meet the established criteria. Some described taking the latter approach in order to alleviate the suffering they perceived their patients to be experiencing due to multiple consultations for a diagnosis of Lyme disease.

#### **Emotional consequences of living with a contested diagnosis**

Living with a chronic condition created uncertainty, worry and lower quality of life for patients. Authors and patients in the views studies called for the value of patient experience to be recognised. In contrast, studies of clinician experiences focused on doctors' knowledge of and adherence to the correct diagnosis procedures, rather than their ability to meet patients' emotional needs. Nevertheless, since some clinicians described prescribing antibiotics to patients who they believed did not have Lyme, there is an indication that they may have had an awareness of patients' frustration.

#### **Practical consequences of 'living in limbo'**

Patient views studies described considerable personal financial difficulties resulting from multiple visits to different specialists without achieving diagnosis or treatment or paying for private treatment not covered by health insurance. Patient advocacy groups also described concern about the costs to society because of unproductive healthcare use. These themes were also expressed in the clinician studies, where specialists expressed frustration at the increased number of referrals of patients with non-accredited tests. Some also acted to stop treatment that they considered unhelpful and possibly harmful to the patient.

#### **Contesting the contested**

Studies of patient views highlighted the self-advocacy role that patients adopted in order to challenge sceptical clinicians or inform those lacking knowledge. However, studies of clinician experiences reported a somewhat more positive relationship, noting examples of clinicians working with patients to arrive at a diagnosis.

## 4 Discussion and conclusions

### 4.1 Summary of findings

Below we summarise the findings in order to address the two review questions:

#### ***1. What are patients', clinicians and researchers' views and experiences of Lyme disease diagnosis?***

This review sought to understand the perspectives and experiences of three types of stakeholder with respect to Lyme disease diagnosis. Several common themes emerged across the diverse evidence-base of different stakeholders' experiences. The themes largely resonated with UK-based patient advocacy groups.

Many of the emergent themes indicate that there are significant uncertainties among stakeholders surrounding the two key approaches for diagnosing Lyme disease: (1) laboratory testing and (2) diagnosis via signs and symptoms.

Evidence from each of the different stakeholder groups indicates a widely-held view that laboratory tests for Lyme disease are inaccurate. All three types of stakeholders described issues with false positives (overdiagnosis) and/or false negatives (underdiagnosis). The stakeholders' perceptions appear to be in line with findings from systematic reviews examining the accuracy of diagnostic tests (Leeflang 2016, NICE 2017). Related to this, difficulties with the interpretation and timing of tests were noted in all three types of research. Uncertainties surrounding diagnosis via signs and symptoms were also recognised by all three types of stakeholder. Researchers, clinicians and patients noted that the wide range of symptoms and varied progression of the disease pose challenges for diagnosing and treating Lyme disease.

The syntheses also suggested that the uncertainties surrounding Lyme disease diagnosis approaches were compounded by low-levels of knowledge among clinicians. This also raised questions for participants about the competency of the clinicians with whom they consulted. Inevitably these uncertainties were experienced as having significant negative impacts.

One key impact was that these uncertainties appeared to undermine clinician-patient relationships, which has been noted elsewhere (Netherlands 2013):-

*'In the event of persistent symptoms or uncharacteristic complaints, the picture becomes more complex and both patients and physicians are occasionally affected by increasing uncertainty. This uncertainty may then, in turn, cause some awkwardness in the consulting room, with both parties being keenly aware of a lack of common viewpoints.'* (Health Council of the Netherlands 2013 p.81)

The quality of the provider-client relationship is often highly variable. However, it can play an important role in accessing appropriate diagnosis and treatment (Stevenson et al. 2004). Our synthesis of patient views suggests that patients with uncommon or persistent symptoms, especially in the absence of positive laboratory tests, experience difficulties and

delays in obtaining a diagnosis and treatment. Findings from the studies of clinician experiences indicate that the underlying uncertainties impact on their ability manage these cases sensitively and productively.

An awareness of a 'lack of common viewpoints' was clearly evident in both the patient studies and from patients and clinicians who participated in our advocacy group consultations. Consultation participants suggested that, in addition to the breakdown in clinician-patient relationships, the awareness of a lack of common viewpoints has wider impacts. They reported that this awareness of polarised opinion surrounding Lyme disease hampers knowledge about Lyme disease as it deters researchers and clinicians from conducting investigations in this area. Controversy over research in the area of Chronic Fatigue, also a highly contentious condition, perhaps illustrates these challenges (Geraghty 2016).

A second negative impact of the uncertainties surrounding Lyme disease diagnosis that was reported in both the clinician and the patient views studies was the costs associated with unproductive healthcare use and costs to society. Despite a lack of common viewpoints about Lyme disease itself, the different stakeholders appeared to concur that uncertainties led to increased healthcare use and knock-on costs for individuals and society. Multiple consultations and the associated fragmentation of care are recognized to result in increased costs to patients, increased burden on health and laboratory services and increased risk of medical errors and adverse events (Bourgeois et al. 2010, Frandsen et al. 2015).

The review findings thus suggest that researchers, clinicians and patients all recognize that there are significant uncertainties surrounding the diagnosis of Lyme disease. Both patients and clinicians also recognize that these uncertainties can result in significant negative impacts.

## ***2. How do these perspectives and experiences help us to understand and implement findings about the accuracy of different diagnostic approaches?***

This review was designed to help interpret the findings of the reviews undertaken by NICE on the accuracy of diagnostic tests, in order to aid the use of these tests in practice. Findings from our review suggested some possible approaches for mitigating the problems different stakeholders experience around Lyme disease diagnosis. For example, our review suggests that patients and clinicians could acknowledge diagnostic test inaccuracies and consider together the limitations of tests. Co-investigation/shared decision-making may help patients and clinicians work together to tolerate uncertainties in diagnosis. This will help both stakeholders to establish a plan for proceeding with further observation, testing, treatment or referral (Politi 2011). Similarly, NICE guidance recommended (NICE 2017c) to:

- Discuss with the person the accuracy and limitations of the different tests for diagnosing Lyme disease.
- Explain to people being tested that most tests for Lyme disease assess for the presence of an immune response (antibodies) to borreliosis infection, and that the accuracy of blood tests may be reduced if:
  - testing is carried out too early (before antibodies have developed)
  - the person has reduced immunity which might affect the development of antibodies.

- Advise people that tests available privately (including from overseas) may not have been fully evaluated or meet the standards needed to diagnose Lyme disease.

Findings from our review and from the NICE reviews highlight multiple uncertainties surrounding Lyme disease diagnosis. This suggests a need for a considerable depth of clinician knowledge. The constantly evolving understanding of the etiology and epidemiology of Lyme disease in the UK and worldwide also suggests that clinicians must update their knowledge regularly. While understanding of UK clinicians' knowledge is unknown, training opportunities for medical students and continuing professional development exist. For example, the Royal College of General Practitioners has developed an e-learning package on Lyme disease, in collaboration with Lyme Disease UK (Royal College of General Practitioners and UK 2014). Such resources are thus available for wide integration into medical education. These could be developed in collaboration with patient groups and modelled on training efforts in countries where Lyme disease is more frequently diagnosed. Related to this, the uncertainty created by the wide variation of symptoms experienced by patients, the lack of consistent clinician knowledge and the lack of accurate tests could perhaps be acknowledged more openly when discussing options for managing a patient's symptoms.

The findings around strained patient-clinician relationships suggest that maintaining a good relationship is key to addressing patient symptoms and the impact these have on people's lives (Conboy 2010). In the absence of evidence from those who are infected with Lyme disease and recover, it may be assumed by providers that for many patients, current practice is effective in managing this presentation of Lyme disease. However, those people who present with a more complex set of symptoms, or whose symptoms are not recognised and managed appropriately, must also be given consideration to ensure their needs are also met. Rather than multiple referrals to specialists for specific symptoms, a more holistic approach to care is suggested. This could be take the form of care provided by a multidisciplinary team, with one professional designated as the lead provider for the patient.

## **4.2 Strengths and limitations**

While this review is the first we are aware of that draws together findings from a range of stakeholders to present a broader picture of Lyme disease diagnosis, we note that there are gaps and limitations in the evidence base underpinning our findings on patient, clinician and researcher views. The available studies were of low to moderate methodological quality. With regards to gaps, most notably, there is a lack of UK-based research across the three types of study. Only one included study of patient views was UK-based (Bloor and Hale 2013), raising questions about the experiences of patients in the UK context.

The UK evidence base on patient experiences of Lyme disease appears to be in the early stages of development. Several online surveys of UK patient experience were identified by the research team and more were provided by several public advocacy groups (Caudwell Lyme Disease 2016, Newton and et al. 2017, Tick Talk 2016, Viras 2014, 2015). However, we were unable to include most of them in the review because of limitations in reporting methods of sampling, data collection and analysis, which made it difficult to understand how the surveys were conducted and raised questions about potential sampling, selection and recall bias. The limitations in these studies demonstrate the challenges in building



capacity in citizen science, particularly around fostering public understanding about science communication (Bonney 2009, Research Council UK 2014, Selin 2016).

It is unclear whether the experiences reported in the included patient views studies are generalisable to a wider population of patients with Lyme disease. All of the included patient views studies focused on people with persistent symptoms. However, despite both the non-UK settings and a focus on only part of the population affected by Lyme disease, patient advocacy groups described very similar experiences. Very few of the public advocacy group members we consulted reported a straightforward diagnosis of Lyme disease.

With regards to clinician experiences of diagnosing Lyme, there were no UK studies and very limited qualitative evidence; only one of the nine studies used a qualitative research design. Studies of clinician experiences focused almost exclusively on measuring knowledge, attitudes, and behaviour related to the diagnosis and management of Lyme disease, often comparing against recommended guidelines to determine clinician adherence. While this provides insight into how well clinicians are able to diagnose Lyme disease in its common and uncommon presentations, a gap in understanding exists with respect to clinician experiences of managing atypical symptoms. Analysis of findings by type of clinician proved difficult. However, though we noted that a meta-regression of factors associated with knowledge/behaviours would be possible from this review, timelines did not allow us to conduct this analysis. This could add more information about how to appropriately target such a strategy.

Consulting with UK patient advocacy groups helped to mitigate some of these weaknesses as it enabled us to assess the validity of our findings and their relevance to the UK context (Rees and Oliver 2017). In addition, inclusion of evidence from multiple stakeholders and multiple types of research study allowed a broad consideration of evidence that is suited to helping policymakers, clinicians and the public gain a holistic understanding of the complex issues involved in Lyme disease diagnosis (Rees and Oliver 2017, Thomas et al. 2017). Working closely with patient groups has helped to disseminate the findings in ‘real time’ and created relationships that will help us to explore future dissemination.

Additionally, there were challenges due to working on a highly sensitive and hotly debated issue. Our concern was with reflecting the experiences and perspectives of each stakeholder group as equally as possible in order to foster understanding of the issues and try to build common ground for addressing the issues in future. We hope that this approach has allowed a balanced and equitable synthesis of the different stakeholders’ views, as far as the literature allows.

Despite employing a systematic approach to reviewing this literature, to ensure the methods and findings are transparent and robust (Gough et al. 2017), there were some possible limitations to our review processes. The timelines for completion of this review meant that we had to have separate teams of researchers undertaking each of the four syntheses, each with different perspectives on the issue. This could have influenced our results but as a team we discussed emerging findings as each synthesis progressed. However, this may also have served to strengthen the findings by bringing a multidisciplinary perspective.

The inclusion of ‘informal evidence’ (Sutcliffe 2015) for the researcher arguments synthesis is another possible limitation. Researcher arguments were extracted from the introduction

section of included DTA studies. We were motivated to conduct this additional analysis due to a limited amount of robust, synthesizable evidence from stakeholders (a limitation which is discussed above). However, they remain indirect representations of this group of stakeholders' experiences and are thus a less robust form of evidence than research evidence that is potentially subject to bias (Enkin and Jadad 1998, Moore and Stilgoe 2009). Nevertheless, this innovative approach to understanding the issues from the perspective of researchers helped to increase the diversity and richness of the evidence-base. The triangulation of these perspectives against those of patients and clinicians also support the robustness of the findings. They can serve as a starting point to consider the perspectives of researchers well-versed in the issues surrounding Lyme disease diagnostic test accuracy.

### 4.3 Implications

Bringing together the research literature on patient, clinician and researcher experiences of Lyme disease diagnosis provides a starting point to understand the complex challenges in diagnosing this complex condition. The themes arising demonstrate that each group identifies similar issues with diagnosis, but that their perspectives differ.

Several implications for future research arise from this synthesis. To inform our understanding of the full range of experiences of patients within the UK, **a mixed-methods study comprising a survey of patient symptoms, their progress through diagnosis and a qualitative study of their perspectives of those experiences could be conducted.** To ensure that the full range of patient experiences are explored, research should focus both on patients with uncommon or persistent symptoms and patients who present with erythema migrans rash, are treated and have symptoms resolve. This could be achieved by conducting **qualitative research of the full range of patient experiences, and by including nested process evaluations in future trials of Lyme disease diagnosis.** Qualitative research in particular would be strengthened by careful description of its epistemological stance, theoretical integration into the wider literature, and methodological considerations. Survey designs should include descriptions of sampling, facilitate higher response rates, and ensure control for confounders in analysis. Analyses should include examining differences in patients grouped according to: (1) the type of diagnostic method and (2) the clustering of symptoms.

Similarly, research is needed on the perspectives of UK-based clinicians who diagnose Lyme disease. **A mixed method study of UK clinician experiences of diagnosing Lyme disease** could provide insight into knowledge gaps amongst clinicians from different specialties and with different exposures to Lyme disease cases using survey methodology. This should include qualitative exploration of **clinicians' experiences of diagnosing atypical symptoms of Lyme disease and chronic Lyme disease.**

This literature also suggests that there is room for clinicians and patients to work together in resolving the issues identified. This suggests **a need for research methods to facilitate co-investigation of Lyme disease by patients and clinicians.** This would help to identify the barriers and facilitators to effective co-investigation. Because each has considerable expertise in respective situational and differential diagnostic skills to bring to the situation, more effort could be made to make use of these strengths. This could also help to inform medical training and practice.

In the absence of evidence from those who are infected with Lyme disease and recover, it is unclear, but appears to be assumed by providers, that current practice is effective in managing this presentation of Lyme disease in the majority of these patients. However, those people who present with a more complex set of symptoms, or whose symptoms are not recognised and managed appropriately, must also be given consideration to ensure their needs are also met. Future medical education intervention development could draw on these findings and develop them further. We noted that **a meta-regression of factors associated with knowledge/behaviours** would be possible from this review, but timelines did not allow us to conduct this analysis. This could add more information about how to appropriately target such a strategy.

## 5 Detailed methods

### 5.1 Aims

The aim of this review was to understand the perspectives of those people involved in the diagnosis of Lyme disease within the UK context.

#### 5.1.1 *User involvement*

We worked closely with the review's 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 leading experts, seeking to obtain a balance of specialist expertise and a range of perspectives. The group was comprised of UK and national academics who have published on a range of issues relating to Lyme as well as representatives from Public Health England. The AG were expected to provide 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. Their main contribution was to advise on a cut-off date for searching. Lastly, we ran a series of consultations with patient and practitioner groups to help interpret our emerging findings in relation to current UK experience.

#### 5.1.2 *Review questions*

- *What are patients', clinicians' and researchers' perspectives and experiences of diagnosis of Lyme disease?*
- *How do these perspectives and experiences help us to understand and implement findings about different diagnostic approaches?*

### 5.2 Methods

To understand the research evidence on stakeholder experiences of diagnosis, we conducted a systematic review. This included several stages of searching, inclusion screening, data extraction, synthesis, and interpretation and communication of findings (Gough et al. 2017).

#### 5.2.1 *Study identification and inclusion in the map*

The first phase of the project involved producing a systematic evidence map covering the whole range of research evidence on Lyme disease in humans (Stokes et al. 2017). The findings of the map were then used to populate the subsequent, more focused systematic evidence reviews, including this review on experiences of diagnosis.

Given the broad scope of focus of the systematic map, the search strategy was sensitive, consisting in effect of a single cluster of terms for Lyme disease. Further details of the strategy and databases searched are provided in section 5, and an example search strategy is shown in Appendix 1.

To be included in the evidence map, studies had to meet the criteria set out in Table 6.2 below.

**Table 6.2: 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 the capacity to search for and examine evidence in all languages we will include only those available in English Language.
Health condition	Be about Lyme disease.	Studies may focus on more than one condition but must include at least some focus on Lyme.
Evidence	Be an empirical research study OR systematic review.	In addition to empirical studies, systematic reviews (i.e. reviews for which $\geq 2$ databases were searched and inclusion criteria applied) will be included. Non-empirical evidence, commentary pieces, editorials and non-systematic reviews will be excluded.
Population	Be about Lyme in humans.	Whilst studies of Lyme in animals may provide some information with implications for human populations, the priority is to focus in on those studies directly addressing Lyme in humans.
Focus	Not be a biomedical study focusing purely on markers or mechanisms of Lyme disease within blood samples, tissue samples, or cells.	The aim of the evidence reviews is to understand patient and clinician experiences of Lyme, rather than the underpinning biomedical processes and causative mechanisms, in order to support DH in future policy development.

### 5.2.2 Screening for inclusion in the review

To be included in this evidence review, studies had to be one of the following types:

- A qualitative or quantitative study published in or since 2002 that reports *patient views* relating to the diagnosis of Lyme disease and which reports methods for data collection and analysis.
- A qualitative study published in or since 2002 or quantitative study published in or since 2008 that reports *clinician views, experiences, knowledge or behaviours*

relating to the diagnosis of Lyme disease and which reports methods for data collection and analysis.

- An evaluation of a diagnostic test for Lyme disease included in one or more of the NICE evidence syntheses published in or since 2008 that includes *informal researcher views (i.e. not collected using formal research methods) about factors that help or hinder the use of diagnostic tests.*

Because the diagnostic test studies and the quantitative clinician studies focused on understanding of diagnostic tests in relation to guidance we required them to be published in or since 2008 to ensure the findings reflect current guidance. For qualitative studies of either clinician or patient views, as these experiences were more wide-ranging we employed a cut-off date of 2002, reflecting the advice from the scientific advisory group, as noted in Table 6.2 above.

Screening criteria were applied hierarchically: each study had to meet a criterion before the next criterion was applied. Screening of all titles and abstracts for the evidence reviews was followed by retrieval and screening of potentially relevant full-text reports by two reviewers working independently, with differences resolved by discussion.

### *5.2.3 Data extraction and quality appraisal*

Standardised tools were used to assess the quality of qualitative (Garside 2014) and quantitative (Wong et al. 2008) studies in the patient views and clinician experiences syntheses. Studies were judged to be of 'high' or 'low' quality depending on the number of criteria met. Researcher arguments studies were not quality assessed as they evidence used was authors' arguments and informal observations rather than formal research.

### *5.2.4 Synthesis*

#### *Researcher arguments for rationale of DTA studies*

It was hypothesised that researchers' reflections on the need for DTA studies may suggest barriers and facilitators to the use of these diagnostic tests. To understand these reflections, thematic synthesis was undertaken of relatively informal data in these studies, for example the hypotheses or insights reported in their introduction or discussion sections. This synthesis used a grounded, iterative approach, translating themes between studies (Thomas et al. 2017).

#### *Studies of clinician experiences*

Using framework synthesis methods, data from the findings of the studies on clinician experiences were coded into an analytic framework of knowledge, attitudes and behaviour, as these were determined to be the themes most likely to be examined in this set of studies. New themes were generated into this framework as they emerged from the data. Higher order themes were then derived from patterns in the data (Brunton 2017, Carroll et al. 2011).

#### *Patient views studies*

To synthesise studies of patient views, we inductively coded patient views and experiences as expressed in direct quotes and study authors' descriptions of participants' views using

thematic analysis (Thomas et al. 2017). To understand the context of the studies we collected information about how the authors presented arguments about chronic Lyme disease; whether they mentioned clinical guidelines; whether and how they problematized clinical and serological diagnosis; and whether there was any potential for a conflict of interest among authors. We also focused on the diagnostic status of their sample, including who had diagnosed and the recruitment source of their participants.

#### Synthesising across study types

Findings were then integrated across the three types of research (i.e. DTA researcher arguments, clinician experience and patient views studies). This was done by comparing and contrasting themes arising from the analysis of each type of research. This mixed methods synthesis balanced the systematic consideration of each type of study on its own terms with the need for iteration and flexibility (Sandelowski and Barroso 2006).

#### *5.2.5 Quality assurance*

Screening, data extraction and synthesis of studies were conducted by two or more reviewers. Two reviewers either extracted data independently or a second reviewer checked the extraction of a first. Reviewers discussed and resolved any discrepancies and worked together to refine emergent themes.

#### *5.2.6 Consultations patient advocacy groups*

In July 2017 we ran a series of face-to-face or telephone consultations with eight UK-based patient advocacy groups. Participants included both patients and clinicians. Through these consultations we sought to understand whether our initial draft findings resonated with UK patient experiences, and would therefore be useful in informing policy and practice in the UK. Participants were provided with information about the purpose and methods of the consultations. They were informed that individuals would not be named but that groups would be acknowledged in the report if they agreed. They were also informed that quotes would be used in the write-up but that they would not be attributed to any individual or group. Before taking part all participants were asked to sign a consent form acknowledging their agreement to take part. Consultations were scheduled to last approximately 90 minutes, although some were shorter and some longer than this. The sessions involved a presentation of themes arising from our initial analyses from patient and clinician studies and participants were asked to then comment on whether or not these findings resonated with their experiences. Participants were also asked to identify any areas or themes that they felt were missing from our analyses. The sessions were recorded and notes taken. The write-up of the consultations was shared with the stakeholder groups to allow them to check for factual errors or missing details.

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

patient groups own experiences. Comments relating to the findings of this exercise are reported in section 3.



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## 7 Appendices

### Appendix 1: Sample 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)

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 database (HTA)
- International Bibliography of the Social Sciences (IBSS)
- MEDLINE
- PsycINFO
- PubMed
- Social Policy and Practice



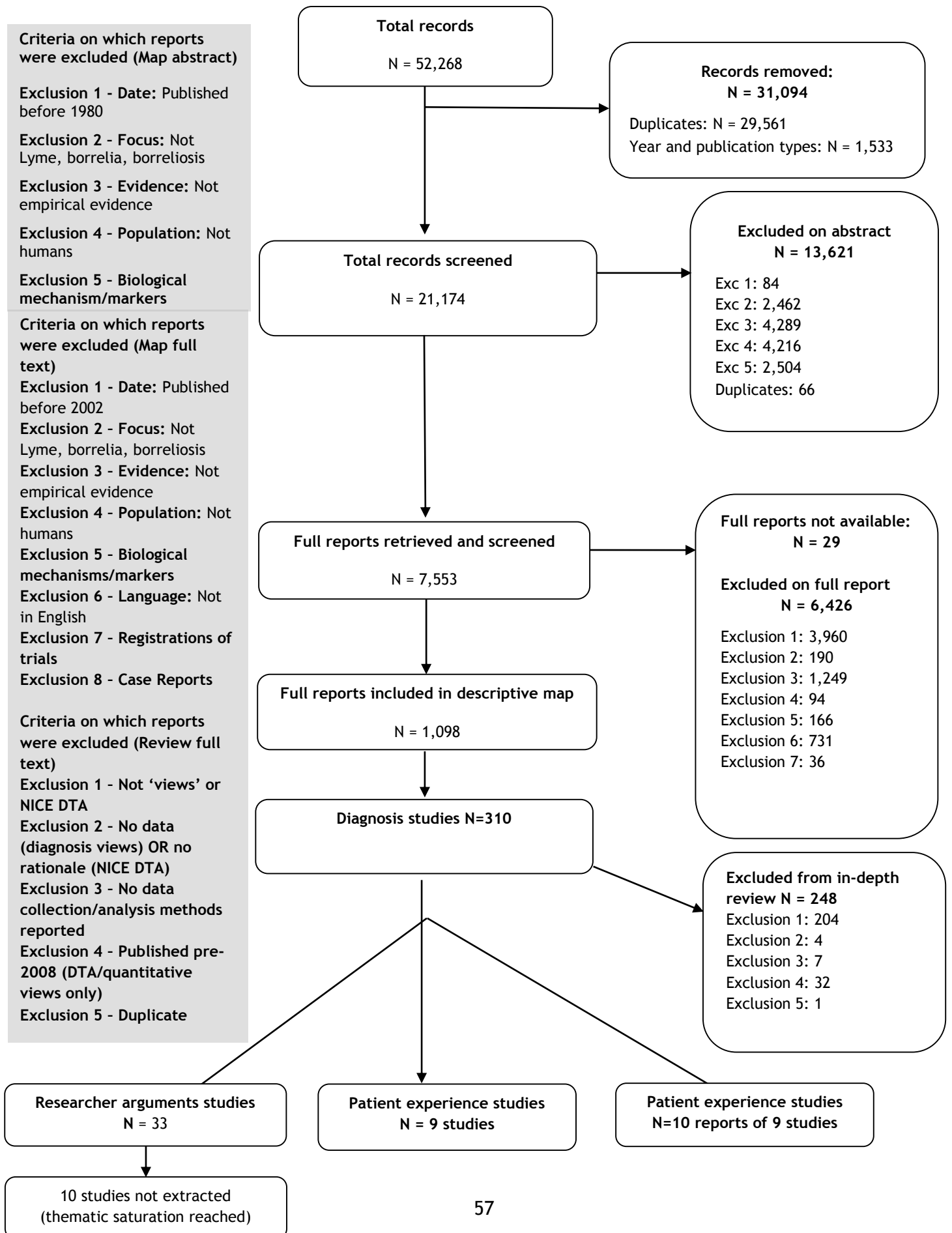
- Social Science Citation Index
- Sociological Abstracts

In addition, the following resources were searched for on-going studies, 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.

## Appendix 2: Flow of literature through the review process



### Appendix 3: Researcher arguments in DTA studies: Review arguments by study

Studies	Population focus <i>i.e. children or all ages/ adults</i>	Limitations of Laboratory Tests for Lyme Disease				Importance of precise and timely diagnosis	Lyme symptoms make diagnosis a challenge	Disease make	Gaps in the current evidence base
		Sensitivity & Specificity	Timeliness	Variation in interpretation	Logistics				
<b>Clinical diagnosis</b>									
<a href="#">Aucott et al. 2009</a> USA	Non-specific population	x	x			x	x		x
<a href="#">Ogrinc et al. 2008</a> Slovenia	Non-specific population	x					x		
<a href="#">Skogman et al. 2008</a> Sweden	Children <18y old	x					x		
<a href="#">Skogman et al. 2008</a> Sweden	Children <18y old				x	x	x		x
<a href="#">Sundin et al. 2012</a> Sweden	Children <18y old				x		x		x
<a href="#">Waespe et al. 2010</a> Switzerland	Children <18y old	x					x		x
<b>Laboratory diagnosis</b>									
<a href="#">Ang et al. 2015</a> Netherlands	Non-specific population	x	x	x					x
<a href="#">Bil-Lula et al. 2015</a> Poland	High risk occupation	x	x			x	x		
<a href="#">Branda et al. 2010</a> USA	Non-specific population	x	x	x					
<a href="#">Branda et al. 2011</a> USA	Non-specific population	x		x	x				
<a href="#">Branda et al. 2013</a> Slovenia	Non-specific population								x
<a href="#">Cerar et al. 2010</a> Slovenia	Non-specific population	x	x		x				
<a href="#">Dessau et al. 2010</a> Denmark	Non-specific population	x	x	x					
<a href="#">Fallon et al. 2014</a> USA	Non-specific population			x		x	x		
<a href="#">Henningsson et al. 2014</a> Sweden	Non-specific population	x							
<a href="#">Krbkova et al. 2016</a> Czech Republic	Children <18y old	x	x	x	x				x

<b>Lahey et al. 2014</b> <i>USA</i>	Non-specific population	x	x	x		x	x	
<b>Lipsett et al. 2016</b> <i>USA</i>	Children <18y old				x			x
<b>Liu et al. 2013</b> <i>China</i>	Non-specific population	x	x	x				
<b>Molins et al. 2015</b> <i>USA</i>	Non-specific population	x	x			x	x	
<b>Nordberg et al. 2012</b> <i>Sweden</i>	Non-specific population	x	x		x		x	
<b>Pomelova et al. 2015</b> <i>Russia</i>	Non-specific population	x		x	x		x	
<b>Porwancher et al. 2011</b> <i>USA</i>	Non-specific population	x	x	x	x			
<b>Sapi et al. 2013</b> <i>USA</i>	Non-specific population	x				x	x	
<b>Senel et al. 2010</b> <i>Germany</i>	Non-specific population							
<b>Tjernberg et al. 2009</b> <i>Sweden</i>	Non-specific population	x	x				x	x
<b>Tjernberg et al. 2011</b> <i>Sweden</i>	Non-specific population	x	x					
<b>Tveitnes et al. 2012</b> <i>Norway</i>	Children <18y old							x
<b>Van Burgel et al. 2011</b> <i>Netherlands</i>	Non-specific population	x						
<b>Von Baehr et al. 2012</b> <i>Germany</i>	Non-specific population	x	x			x	x	
<b>Weiner et al. 2015</b> <i>USA</i>	Non-specific population	x	x	x		x	x	
<b>Wutte et al. 2011</b> <i>Austria</i>	Non-specific population	x	x		x	x	x	

Appendix 4: Characteristics of included studies: Clinician experiences (n=9)

Study (Location)	Aim	Population sample	Prevalence of Lyme in study region
Bakken 2002 (Wisconsin, USA)	'the purpose of this study was to explore how physicians learn to diagnose Lyme disease so that a theory could be developed to identify variables that can be used to design educational programs that facilitate the accurate diagnosis of this disease...This study is based in a conceptual framework of experiential learning, situated cognition, and reciprocal determinism.'	Physicians practising within a range of settings N=9 physicians  Reported characteristics: practice setting, years of experience, gender, specialty	Mixed regions 'endemic and non-endemic for Lyme disease'
Brett et al. 2014 (nationwide, USA)	'to characterize the frequency of tick-borne diseases in clinical practice and the knowledge of healthcare providers regarding their management'	Nationwide survey of physicians and nurse practitioners N=2261 respondents  Reported characteristics: Range of specialities, years of practice, region of practice (South, Northeast, Midwest, West)	Defined high- and low incidence states
Esposito et al. 2013 (nationwide, Italy)	'to verify the adherence of specialists in paediatric infectious diseases (PIDs) to diagnostic and therapeutic recommendations by comparing their approaches in non-endemic and endemic areas of Italy'	Paediatric infectious disease specialists participating in the Italian Society for Paediatric Infectious Disease Registry of Lyme Disease - includes all hospital PID specialists in Italy N=162 respondents  No description of characteristics of practitioners related to years of practice, gender, location of practice	'Endemic and non-endemic areas'
Ferrouillet et al. 2015 (two communities, Québec, Canada)	'A descriptive study of Quebec family physicians was performed to describe their clinical experience related to Lyme disease, their knowledge of the disease, and their	General practitioners N=201 respondents	'Two areas, one with known infected tick

Study (Location)	Aim	Population sample	Prevalence of Lyme in study region
	familiarity with practices regarding the diagnosis and management of cases to validate whether these practices are compliant with the most recent guidelines'	Reported characteristics: range of years in practice, first-line or second-line practice, average number of patients seen per week	populations and one without'
Hansmann et al. 2014 (unspecified locations, France)	'i) to evaluate the accuracy of serologic testing for Lyme borreliosis performed in a private medical laboratory (PML); ii) to evaluate the impact of these tests on the practices of infectious diseases specialists (IDS)'	Infectious disease specialists subscribed to the French 'infection-flash' mailing list N=93 respondents answered first stage survey N=49 respondents answered second stage survey  Reported characteristics: Both male and female practitioners, range of ages, practice settings, frequency of consultation	Unclear
Henry et al. 2012 (province-wide, British Columbia, Canada)	'to determine physicians' level of awareness and knowledge of Lyme disease (LD) in a low-prevalence area and whether physicians' practices align with current guidelines for treatment of LD'	Paediatricians, general practitioners and internal medicine specialists licensed to practice in the province N= 2040 respondents  Reported characteristics: years in practice, location of practice, number of patients seen per week	Areas of high and low prevalence of tick bites
Hill and Holms 2015 (state-wide, Arkansas, USA)	'to compare the knowledge and attitudes to the practice for diagnosing and reporting LD for primary care providers in Arkansas'	Paediatricians, internal medicine, general practitioners licensed to practice in the state N=984 respondents  Reported characteristics: region of practice, practice specialty, years of practice	Unclear
Johnson and Feder 2010	'to survey a random sample of Connecticut primary care physicians to determine	Random sample of 33% of all primary care physicians in the state	High

Study (Location)	Aim	Population sample	Prevalence of Lyme in study region
(state-wide, Connecticut, USA)	whether they diagnose and treat patients with what they believe is chronic Lyme disease'	N=285 respondents  Reported characteristics: type of physician, number of cases diagnosed	
Singh et al. 2016 (regional, West Virginia, USA)	'to determine the distribution of reported cases of Lyme disease in the state of West Virginia and assess clinicians' knowledge of Lyme disease symptoms, diagnosis, and surveillance'	Clinicians from departments of Emergency Medicine, Internal Medicine, Family Medicine at an academic medical centre in northern central West Virginia N=91 respondents  Reported characteristics: specialty, number of patients per week, number of LD cases seen	High

Appendix 5: Quality assessment: studies of clinician experiences (n=9)

Study, Year	Appropriate sampling method/representative of population?	Reliable/ valid measurement independent variable?	Reliable/ valid measurement dependent variable?	Reasonable response rate?	Control for confounding factors in analysis?	Any concerns about the statistical methods?
Brett et al., 2014 Low Risk of Bias 4/6	Non-probability sampling (score 0)  -Convenience sample of providers registered with a national professional database -no random sampling from this database reported	Yes (score 1)  -type of provider, age, sex, location - drawn from register which was described as verified by the AMA	Yes (score 1)  -diagnosing LD - treating LD - hypothetical diagnosis and treatment of LD - same questionnaire applied to all respondents -but no description of pre-testing these new four questions within the full questionnaire	No (score 0)  -response rate 48.5%	Yes (score 1)  -multivariate regression done factoring in type of provider, age, sex, high- or low-incidence setting	No (score 1)
Esposito et al., 2013 High risk of bias 3/6	Not applicable (score 1)  Whole population of paediatric infectious	Yes (score 1)  -practitioner behaviour Authors used a piloted survey questionnaire. Some	No (score 0)  children with LD; but their diagnosis was established by the same practitioners who were being	Yes (score 1)  N=176 PIDs sent emails n=52 replied that they had treated child with LD n=110 replied that	No (score 0)  Comparison for endemic and non-endemic regions only; no	Yes (score 0)  No report of how missing data were dealt with. No



Study, Year	Appropriate sampling method/representative of population?	Reliable/ valid measurement independent variable?	Reliable/ valid measurement dependent variable?	Reasonable response rate?	Control for confounding factors in analysis?	Any concerns about the statistical methods?
Overall Quality Rating	disease specialists (PIDs) surveyed	risk of recall bias possible.	surveyed about those diagnoses. So no, not reliable.	they didn't treat a child with LD n=14 missing data; 92% response rate questionably high	consideration of other confounders such as age, years of practice, number of cases seen	controlling for confounders reported.
Ferrouillet et al., 2015  High risk of bias 3/6	Non-probability sampling (score 0)  Recruited during educational sessions, so non-random sampling from a specific and potentially biased segment of the population under study	Yes (score 1)  Authors describe development of questionnaire based on previous tools and pre-testing of instrument on a sample of five experts and 10 Family Practitioners (FPs) before applying -questionnaire is reasonably described in terms of content - method of	Yes (score 1)  Authors describe development of questionnaire based on previous tools and pre-testing of instrument on a sample of five experts and 10 FPs before applying - questionnaire is reasonably described in terms of content - method of establishing endemic	No (score 0)  (p.153) 'In total, 201 general practitioners answered the questionnaire, for a participation rate of 59% (ranging from 28% to 100%)' -but not sure what this latter phrase means as the eligible number of participants	No (score 0)  Not reported	No (score 1)

Study, Year	Appropriate sampling method/representative of population?	Reliable/ valid measurement independent variable?	Reliable/ valid measurement dependent variable?	Reasonable response rate?	Control for confounding factors in analysis?	Any concerns about the statistical methods?
		establishing endemic and non-endemic regions clearly described on p.151	and non-endemic regions clearly described on p.151			
Hansmann et al., 2014 High risk of bias 0/7	Non-probability sampling (score 0) Population was subscribers to infectious disease specialists' newsletter	No (score 0) Development and testing of questionnaire is not described -authors appear to have designed a questionnaire that acts to confirm, rather than test, their hypothesis	No (score 0) Poorly described	No (score 0) Response rate 19% for Survey 1 8% for Survey 2	No (score 0) Not reported	Yes (score 0) Not reported
Henry et al., 2012 Low risk of bias 4/6	Not applicable (score 1) All physicians registered to practice in province were eligible and contacted=whole	Yes (score 1) Self-identified type of physician	Yes (score 1) Somewhat; authors described modifying a previously developed and validated questionnaire,	No (score 0) Response rate 32.2%	No (score 0) Not reported	No (score 1)

Study, Year	Appropriate sampling method/representative of population?	Reliable/ valid measurement independent variable?	Reliable/ valid measurement dependent variable?	Reasonable response rate?	Control for confounding factors in analysis?	Any concerns about the statistical methods?
	population of interest		although they don't report testing it themselves once it was modified			
Hill and Holms, 2015  Low risk of bias 4/6	Non-probability sampling (score 0)  Authors describe using a 'convenience sample'	Yes (score 1)  Type and location of provider likely to be reliable and valid, since drawn from state practice register	Yes (score 1)  Previously developed and validated data collection tool -pilot tested on subsample	No (score 0)  Response rate 24.5%	Yes (score 1)  (p.343) 'Confounders were also noted for speciality of practice, years in practice and years of practice as determined by logistic regression analysis.'	No (score 1)
Johnson et al., 2010	Probability sampling (score 1)  Random sample of licensed	No (score 0)  Independent variable: belief in the existence of	No (score 0)  No reporting of reliability or validity checks on how	No (score 0)  Response rate 39.1%	No (score 0)  No description of measuring, or controlling	No (score 1)

Study, Year Overall Quality Rating	Appropriate sampling method/representative of population?	Reliable/ valid measurement independent variable?	Reliable/ valid measurement dependent variable?	Reasonable response rate?	Control for confounding factors in analysis?	Any concerns about the statistical methods?
High Risk of Bias 2/6	practitioners in one state	chronic Lyme disease -measure was not validated nor was any reliability testing reported	doctors made the diagnosis of Lyme disease, or chronic Lyme disease, in their patients - just that they were 'diagnosed'.		for, potential confounders provided	
Singh et al., 2016 High risk of bias 3/6	Non-probability sampling (score 0)  No description of random sampling within medical centre	Yes (score 1)  Previous questionnaire used	Yes (score 1)  Previous questionnaire used	No (score 0)  Can't tell; authors don't report how many were eligible to participate, just how many surveys they received	No (score 0)  Questionable - some, like age and gender, were not reported; also authors state that they measured participants' belief that most pts suspicious of LD actually have it but no data reported	No (score 1)

Study, Year Overall Rating	Quality Appropriate sampling method/representative of population?	Reliable/ measurement independent variable? valid	Reliable/ measurement dependent variable? valid	Reasonable response rate?	Control for confounding factors in analysis?	Any concerns about the statistical methods?
					on this, nor is it used in the regression analysis	

**Appendix 6: Characteristics of patient views studies (n=9)**

Study Country (location)	Focus	Author description of chronic Lyme disease	Diagnostic status of participants	Data collection/ number of participants	Recruitment
Ali et al. 2014 USA (Connecticut)	'Experiences of patients who identify themselves as having chronic Lyme disease'	'A constellation of persistent symptoms in patients with or without evidence of previous BB infection'	Self-report - diagnosed by a clinician or self-diagnosed	In-depth interviews. (n=12)	Patient-oriented Lyme disease email lists and website
Bloor and Hale 2013 UK/Eire (Unclear location)	'Lived experience of access to care of patients with a Lyme disease diagnosis'	'The range of potential symptoms can be considerable (particularly at an advanced stage), and can include fatigue, musculoskeletal pain, and neurocognitive difficulties'	Self-report - diagnosis by a clinician - some had positive and some had negative NHS (official UK) tests	Internet based survey. (n=152)	Lyme support networks and social media
Chaudhury 2016 Canada (Unclear location)	'Social, cultural and environmental implications of the illness'	'Lyme patients, especially those with "chronic" Lyme may experience random resurfacing of symptoms, so do not ever consider themselves "cured"'	Unclear	Web-based patient accounts. (unclear)	Non-profit patient advocacy website
Csallner et al. 2013 Germany (Munich)	'Clinical and psychobehavioral characteristics and health-related quality of life of patients with "organically unexplained symptoms"'	'There is no evidence for ongoing infection with <i>Borrelia burgdorferi</i> in patients with prolonged subjective symptoms after adequate antibiotic therapy ... "Chronic Lyme Disease" is just another unwarranted label for "organically unexplained symptoms"'	Patients symptoms rated as "organically unexplained" or "organically explained" based on clinical and laboratory findings	Self-rating questionnaires. (n=125)	Outpatients who presented to a borreliosis clinic

Study Country (location)	Focus	Author description of chronic Lyme disease	Diagnostic status of participants	Data collection/ number of participants	Recruitment
Dankyi 2016 USA (Maryland, Virginia & Washington DC)	'Lived experiences of families with children under 26 years diagnosed with Lyme disease'	'Currently, there are two treatment guidelines for Lyme disease published by the Infectious Diseases Society of America (IDSA) and International Lyme and Associated Diseases Society (ILADS) ... Patients and their families find themselves caught between this silent war'	Self-report - children with a diagnosis of Lyme disease and under the care of a physician	Structured face-to-face interviews (n=10)	Lyme disease organizations
Drew and Hewitt 2006 USA (Unclear location)	'Lived experience of becoming diagnosed with Lyme disease'	'The chronic form of Lyme disease is supported by epidemiological studies showing that 30–50% of patients, even if treated, later develop multisymptom disorders of fibromyalgia' and/or chronic fatigue syndrome	Unclear - 'a home infusion company's database of patients with the diagnosis of chronic Lyme disease'	In-depth interviews (n=10)	A home infusion company's database
Johnson et al. 2011 USA (Unclear location)	'Challenges faced by Lyme disease patients in obtaining adequate healthcare'	'The controversy between IDSA and ILADS over the diagnosis and treatment of Lyme disease has been uneven in terms of power and resources ... the consequences of IDSA's influence from the patient perspective have	Self-report - clinically diagnosed Lyme disease	Web-based survey	A non-profit Lyme disease association website

Study Country (location)	Focus	Author description of chronic Lyme disease	Diagnostic status of participants	Data collection/ number of participants	Recruitment
		not been studied on a national level in the United States'			
Johnson et al. 2014 USA (Unclear location)	'Severity of chronic Lyme disease compared to other chronic conditions'	'A proportion of patients with Lyme disease develop debilitating symptoms that persist in the absence of initial treatment or following short-course antibiotic therapy'	Self-report - EM rash and/or laboratory diagnosis	Survey. (n=3090)	A grassroots Lyme disease education and research organisation
Rebman et al. 2015 USA (Maryland)	'Patient experience of this medically contested condition'	'A subset of patients (an estimated 10%-50% in prior studies) reports a range of largely subjective symptoms after antibiotic treatment ... When these symptoms persist for 6 months or longer in otherwise healthy individuals, they meet a proposed case definition for post-treatment Lyme disease syndrome (PTLDS)'	Patients at the clinical practice of one of the authors who met the case definition for PTLDS	Semi-structured interviews. (n=29)	The clinical practice of one of the authors



## Appendix 7: Quality assessment tool: studies of patient views and experiences

Q1. What are the **epistemological underpinnings** of the study?

*(i.e. if the study is trustworthy, judged by whether or not the voices of participants come through)*

Are the design and execution appropriate to the research question?

What evidence of reflexivity is there?

Do the voices of the participants come through?

Are alternative interpretations, theories, etc. explored?

How well supported by the data are the conclusions?

Are ethical considerations given appropriate thought?

Q2. What **theoretical aspects** are considered by the authors?

*(i.e. whether an explicit framework shapes the design of the study, thus enhancing claims for generalisability)*

Does the report connect to a wider body of knowledge or existing theoretical framework?

Does the paper develop explanatory concepts for the findings?

Q3. What **technical considerations** do the authors make?

*(i.e. the methods of the study, full and appropriate description of the stages of search, background to the project, etc.)*

Is the research question clear?

Is the research question suited to qualitative enquiry?

Is the context clearly described?

Are data collection methods and tools clearly described?

Are data analysis methods clearly described?

Does this study usefully contribute to the review?

**Reviewer Comments:**

## Appendix 8: Quality ratings of patient views studies (n=9)

### Qualitative studies

Study	Epistemological underpinning met? Yes/Partial/No	Theoretical Aspects Considered? Yes/Partial/No	Technical considerations Yes/Partial/No
Ali et al. (2014)	NO	PARTIAL	YES
Bloor and Hale (2013)	NO	NO	NO
Chaudhury (2016)	PARTIAL	YES	NO
Dankyi (2016)	PARTIAL	PARTIAL	YES
Drew and Hewitt (2006)	NO	PARTIAL	YES
Rebman et al. (2015)	YES	PARTIAL	YES

### Quantitative studies

Study, Year	Appropriate sampling method/ representative of population? (Score)	Reliable/ valid measurement independent variable? (Score)	Reliable/ valid measurement dependent variable? (Score)	Reasonable response rate? (Score)	Control for confounding factors in analysis? (Score)	Any concerns about the statistical methods? (Score)	Overall Risk of Bias High/Low (Score)
Csallner et al. (2013)	Not applicable (1)	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (1)	Low risk (6)
Johnson et al. (2011)	No (0)	No (0)	No (0)	Yes (0)	No (0)	No (1)	High risk (1)
Johnson et al. (2013)	No (0)	Yes (1)	Yes (1)	Yes (0)	No (0)	No (1)	High risk (3)

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