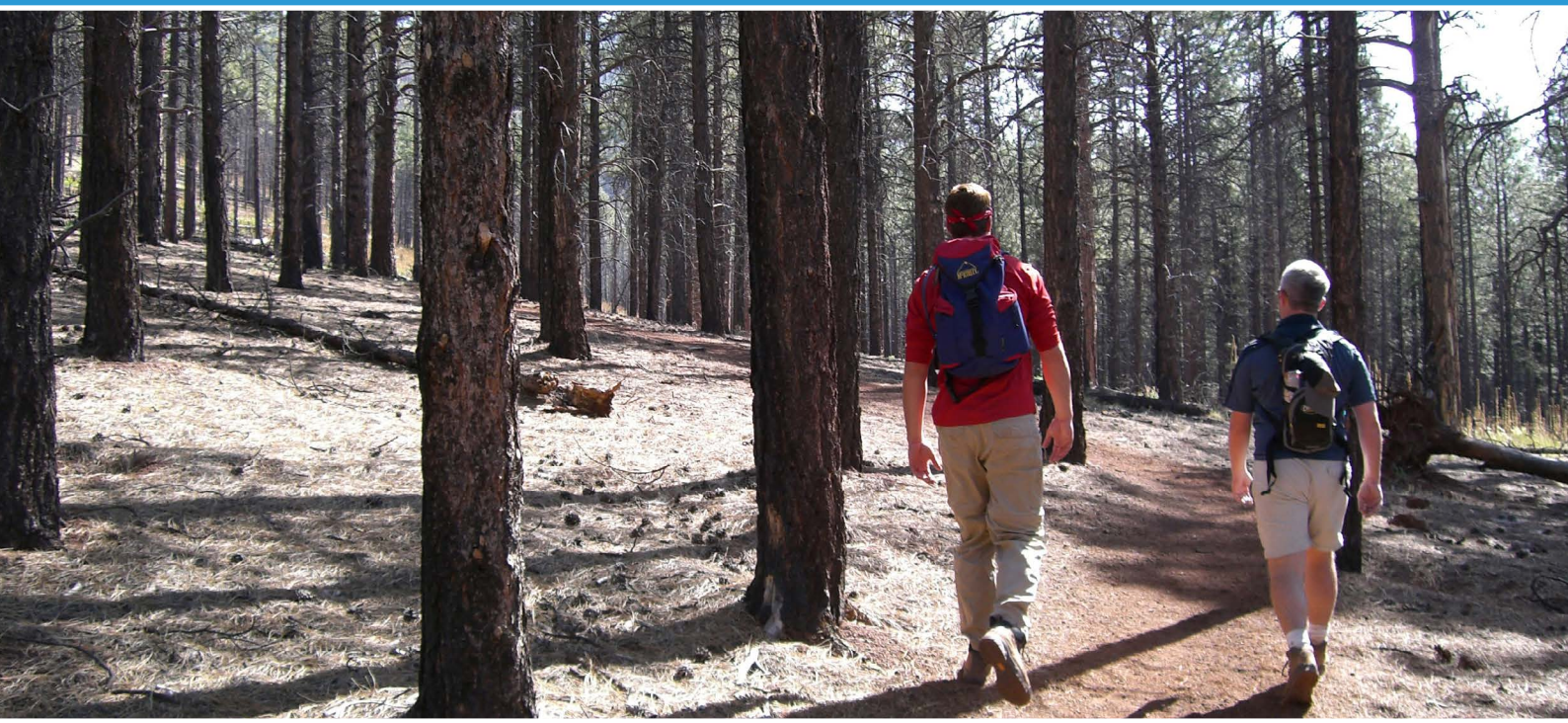
Department of Health Reviews Facility
To support national policy development and implementation

Patient, clinician and researcher experiences of the treatment and management of Lyme disease

A systematic review



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Conflicts of interest

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

Contributions

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

Guarantor of the review

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CONTENTS

Summary

Background

Lyme disease is the result of an infection, caused by the Borrelia burgdorferi bacterium, which is common in ticks; people can develop Lyme disease after being bitten by an infected tick. This report describes one of a series of evidence reviews on Lyme disease commissioned by the Department of Health (England) Policy Research Programme and undertaken by the Department of Health Reviews Facility. This evidence review focuses on treatment for Lyme disease. Its aim is to bring together evidence from patients, clinicians and researchers about their experiences of receiving, delivering or evaluating interventions for Lyme disease in order to identify factors that might impact on successful treatment.

Review questions and methods

The review aimed to address the following questions:-

- *What are patients', clinicians' and researchers' perspectives and experiences of treatments for Lyme disease?*
- *How do these perspectives and experiences help us to understand and implement treatments at different stages of Lyme disease?*

Before starting work on the evidence reviews we produced a systematic map which covered the whole range of research evidence on Lyme disease in humans (Stokes et al., 2017). We searched 17 electronic databases and conducted additional web-based searching for unpublished and grey literature. We included empirical research published from 2002 on Lyme disease in humans. Studies were coded in relation to their topic focus and characteristics.

For this in-depth review focusing on treatment, studies had to report patient or clinician views or experiences relating to the treatment of Lyme disease or, in order to gather researcher's insights, an evaluation of a Lyme treatment intervention. Studies could use a qualitative or quantitative design. Following assessment of the evidence to answer these questions we sought feedback on the findings from eight UK patient advocacy groups.

Findings

We found insufficient evidence from patient and clinician studies to undertake a meaningful synthesis on treatment experiences. Whilst a few studies had a partial focus on experiences, the evidence overall is extremely limited. One qualitative and one quantitative study provided some evidence on patient experiences of treatment and five quantitative studies on clinician experiences. Researcher insights from evaluation studies were deemed to be too insubstantial to be informative. Patient advocacy groups lamented the lack of evidence on treatment experiences for this review, and the lack of evidence on treatment for Lyme disease in general.

Conclusions

Insufficient evidence was available to produce a useful or meaningful synthesis on experiences of treatments for Lyme disease. Research is urgently needed to fill this gap as patient and clinician experiences are important for understanding ‘real world’ factors that might impact on the implementation of effective treatment.

1 Background

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

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

1) the incidence and surveillance of Lyme disease
2) patient, clinician and researcher experiences of 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 3) where the objective was to examine evidence from patients, clinicians and researchers about their experiences of receiving, delivering or evaluating treatments for Lyme disease. The aim is to use this research evidence to assist in the interpretation and implementation of evidence about the efficacy and safety of different treatments for Lyme disease patients.

1.1 Lyme disease

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

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

1.2 Treatment for Lyme disease

Treatment with antibiotics is the standard care approach for people with Lyme disease. In the UK a two-week course of oral antibiotics (Doxycycline, amoxicillin or cefuroxime) is recommended for patients with a typical acute presentation of Lyme involving an erythema-migrans rash. Longer courses of antibiotics, or intravenous administration, may

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

be considered for those with neurological or arthritic complications (https://www.gov.uk/government/publications/lyme-disease-diagnosis-and-treatment/lyme-disease-diagnosis-and-treatment). As the existence of chronic Lyme disease is contested, efforts to treat those with longer term or wide-ranging symptoms is controversial (Berende et al., 2016).

1.3 Using experiential evidence to help interpret and implement evidence of effectiveness and safety

Systematic reviews of randomized controlled trials (RCTs) are considered the 'gold standard' for assessing the effectiveness and safety of medical treatments (Sullivan, 2011). However, as the strength of an RCT for evaluating treatment effectiveness comes from adopting carefully controlled experimental conditions, other research is needed to translate and interpret that evidence for real-world situations. For example, patients often have characteristics and experiences that differ from the strict inclusion criteria that apply to those participating in RCTs, and therefore the information gained from an RCT may be less applicable to a broader group of patients (Sullivan, 2011).

Bringing together evidence from patients and clinicians about their experiences of receiving and delivering treatment can highlight issues that impact on the effectiveness of treatments in real-world settings. For example, qualitative evidence syntheses have identified patient factors leading to discontinuation of treatment (Rashid et al., 2014), clinician factors which hinder appropriate prescribing (Cullinan et al., 2015) and clinician and parent views about prescribing antibiotics for children (Lucas et al., 2015).

1.4 Previous research on the treatment and management of Lyme disease

In 2012 a priority setting exercise on Lyme disease was conducted in the UK by The James Lind Alliance, an NGO which involves patients, carers and medical professionals in identifying priorities for future research. Of the ten research priorities identified, seven focused on the efficacy and consequences of treatments for Lyme disease at different stages (JLA, 2012). Recent systematic reviews have examined evidence on the efficacy and safety of treatments for Lyme patients with neurological symptoms (Lyme neuroborreliosis) (Cadavid et al., 2016, Dersch et al., 2015). NICE is currently undertaking a series of evidence reviews on treatment efficacy in relation to a range of Lyme-related conditions to inform the development of a clinical guideline.

However, to our knowledge, no previous systematic review has attempted to identify, assess and synthesise evidence of patients' and clinicians' experiences of treatment of Lyme disease.

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.

2.1 Aims

The primary objective of this review is to bring together evidence from patients, clinicians and researchers about their experiences of receiving, delivering and evaluating treatments for Lyme disease. The aim of the work is to help to understand the issues that may help or hinder the prescription and use of effective treatments in real-world settings; in particular to help interpret evidence about the efficacy and safety of different treatments for Lyme disease patients.

2.1.1 Review questions

The review aimed to address the following overarching questions:-

- *What are patients', clinicians' and researchers' perspectives and experiences of treatment/management of Lyme disease?*
- *How do these perspectives and experiences help us to understand and implement findings about effective treatment at different stages of Lyme disease?*

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., 2017).

2.2.2 Inclusion criteria

To be included in this evidence review, studies had to meet the following criteria:

- A qualitative or quantitative study that reports *patient views* relating to the treatment of Lyme disease and which reports methods for data collection and analysis.
- A qualitative or quantitative study that reports *clinician views, experiences, knowledge or behaviours* relating to the treatment or management of Lyme disease and which reports methods for data collection and analysis.
- An evaluation of a Lyme disease treatment included in one or more of the NICE evidence reviews that includes *informal researcher views* about factors that help or hinder treatments in real world settings.

2.2.3 Data extraction, quality appraisal and synthesis

We planned to use thematic analysis (Thomas and Harden, 2008) to inductively code and analyse data from qualitative studies and to narratively synthesise evidence from surveys.

We planned to assess quality using pre-existing tools as appropriate for appraising qualitative evidence (Shepherd et al., 2010) or survey evidence (Wong et al., 2008).

2.2.4 Quality assurance

All studies considered for inclusion in the systematic review were screened independently by two reviewers using the full text.

2.2.5 Consultation with patient advocacy groups

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

Prior to sharing findings, we conducted a series of face-to-face consultations with the advocacy groups in July 2017 for our review on experiences of diagnosing Lyme disease (Brunton et al. 2017). In these face-to-face consultations, we did not ask participants to comment on treatment issues directly, however several participants raised issues relating to treatment, which we summarise in this report. Comments relating to Lyme disease treatment from both consultation exercises are reported in section 3.1.5.

3 Findings

We found insufficient evidence from patient and clinician studies to undertake a meaningful synthesis on treatment experiences. Some studies we identified had a partial focus on treatment experiences but data were too limited in extent and relevance to warrant synthesising. Below we provide an overview of the evidence considered for inclusion, but excluded because of these limitations.

3.1 Overview of available evidence on patient, clinician and researcher experiences of treatment for Lyme disease

3.1.1 Evidence on patient experiences of treatment for Lyme disease

Nineteen research studies identified from the evidence map focus on the views of patients with Lyme disease. However, seventeen of these did not focus on treatment experiences and two had only a partial focus.

Both of these studies, conducted in the USA, provided very limited information: one study included *qualitative* data (Ali et al., 2014) and one *quantitative* data (Johnson et al., 2014). From the qualitative study a theme emerged around the use of 'Unconventional therapies to treat chronic Lyme Disease'. The authors described how some patients sought out providers who offered long-term antibiotic therapy or complementary and alternative therapies (Ali et al., 2014) (p. 5 of 8). The quantitative study reported the reasons why some participants were not currently taking antibiotics; for example because they were using other treatments, were currently well or in remission, or because of financial constraints (Johnson et al., 2014) (p.5 of 21).

Thus whilst two patient views studies *partially* meet the criteria for inclusion, the limitations of the available data, in terms of a) the extent and/or b) the lack of depth or richness, precluded undertaking a meaningful synthesis of evidence on patient experiences.

3.1.2 Evidence on clinician experiences of treating/managing Lyme disease

Nine research studies identified from the evidence map focus on the knowledge, attitudes and behaviours of clinicians with regards to Lyme disease. Whilst five quantitative studies included some data relating to clinicians' treatment practices none focused in-depth on treating or managing the condition. The limited data precluded meaningful synthesis.

3.1.3 Evidence on researcher insights about treatment for Lyme disease

We examined studies included in the 2017 NICE evidence reviews on efficacy of treatments for Lyme disease to explore whether researcher insights and or reflections reported in the introduction or discussion sections of the research reports would provide a useful lens through which to further understand experiences of treatment. However, this source of evidence was deemed too 'thin' to produce a useful synthesis.

3.1.4 Other qualitative evidence on treatment for Lyme disease

We identified one qualitative study which focuses specifically on treatment for Lyme disease but from the perspective of the general public rather than from patients,

clinicians or researchers (Macauda et al., 2011). This US-based study explored public perceptions about the need for long-term treatment of Lyme disease following persistent symptoms.

3.1.5 Patient advocacy groups views on these findings

When we asked patient advocacy groups, in October 2017, to comment on the key findings of this review, two of the eight groups provided feedback. Both indicated the need for future research to focus on patients' and clinicians' experiences of Lyme disease treatment.

Similarly, during our face-to-face consultations with eight groups in July 2017, a number commented on, and lamented, the lack of evidence on treatment experiences for this review, and the lack of evidence on treatment for Lyme disease in general. One noted the predominance of evidence from the USA and its limited relevance to the UK because the strains of Borrelia commonly found in the UK are different to those found in the USA.

4 Discussion and conclusions

4.1 Gaps and limitations in the evidence base on Lyme disease treatment

4.1.1 Limited evidence on stakeholder experiences of treatment

The initial aim of this review was to draw together evidence on the experiences and insights of patients, clinicians and researchers with regard to treatment for Lyme disease. By doing so, we hoped to aid understanding of factors which might impact on treatment effectiveness. However, due to limitations of the evidence this has not been possible. This is in contrast with stakeholder experiences of the diagnosis of Lyme disease (Brunton et al., 2017).

4.2 Conclusions

The current evidence base precludes drawing any conclusions about stakeholder views on treatment/management of Lyme disease. The implications below address future research needs only.

4.2.1 Implications for future research

Qualitative and quantitative research which focuses on patient and clinician experiences of treatments for Lyme disease is needed. Qualitative research, and in particular embedded qualitative process evaluations of effectiveness studies, would enable understanding of the issues and complexities faced by patients and clinicians around treatment for Lyme disease. Quantitative survey research would enable understanding of how widespread any issues and problems are and how they vary in different populations. As such, this research would provide insight into why interventions might or might not be effective for particular patient groups.

5 Detailed methods

5.1.1 Review questions

The review aimed to address the following overarching questions in relation to stakeholder experiences of Lyme disease treatment:-

- *What are patients', clinicians' and researchers' perspectives and experiences of treatment/management of Lyme disease?*
- *How do these perspectives and experiences help us to understand and implement findings about treatment effectiveness at different stages of Lyme disease?*

5.1.2 User involvement

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

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

5.1.3 Study identification

As noted above, the first phase of the project involved producing a systematic evidence map covering the whole range of research evidence on Lyme disease in humans. We searched 17 electronic databases and conducted additional web-based searching for unpublished and grey literature. We included empirical research published in or since 2002 on Lyme disease in humans. Studies were coded in relation to their topic focus and characteristics. The findings of the map coding were then used to identify studies for this review. Full details of the methods and findings of the systematic map are available in the map report (Stokes et al., 2017).

5.1.4 Inclusion criteria

To be included in this review studies from the systematic evidence map needed to meet the criteria set out in table 5.1.4 below.

Table 5.1.4: Criteria for inclusion in the in-depth review

To be included in the evidence review on experiences of Lyme treatment studies needed to be either of the following:-
• A qualitative or quantitative that reports a) research methods and b) findings about patient views relating to the treatment or care of Lyme disease.
• A qualitative or quantitative study that reports a) research methods and b) findings on practitioner views, experiences, knowledge or behaviours relating to the treatment or care of Lyme disease.
• An evaluation of a Lyme treatment intervention that is a) included in one or more of the NICE evidence syntheses relating to treatment and b) provides the authors' informal views about factors which may enhance or hinder delivery of treatments in real world settings.

5.1.5 Data extraction and quality appraisal

Since no studies met the inclusion criteria for this evidence review quality appraisal and data extraction were not undertaken.

However, we had planned to employ an inductive approach for extracting and coding qualitative data using line-by-line coding. For quality appraisal we planned to assess any included qualitative patient and clinician studies using a modified set of criteria that were developed for examining the findings of evaluations of intervention processes in a review of behavioural interventions for sexually transmitted diseases in young people (Shepherd et al., 2010). The criteria were based on previous work at the EPPI-Centre on assessing the quality of qualitative research and process evaluations (Harden, 2007b, Harden, 2007a) and the work of others in the field (Popay et al., 2003). For included quantitative data we planned to use the quality assessment tool for systematic reviews of observational studies (QATSO) (Wong et al., 2008).

5.1.6 Synthesis methods

We planned to use thematic analysis (Thomas and Harden, 2008) to inductively analyse data from the studies. In this method initial descriptive themes are organised into higher-order analytical themes that move 'beyond' the original findings of the studies in order to directly address the review questions.

5.1.7 Quality assurance

Screening of full-text of studies of patient views and practitioner experiences was undertaken by two reviewers working independently with differences resolved by discussion. For assessment of the researcher insights from treatment evaluations, a single reviewer conducted initial assessments which were then verified by a second reviewer.

5.1.8 Consultation on key findings with patient advocacy groups

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

group were then assessed to check whether the key findings resonated or not with patient groups' own experiences.

Prior to sharing findings, we conducted a series of face-to-face consultations with the groups in July 2017. The consultations focused on experiences of diagnosis; for further details on the methods for these consultations see Brunton et al. (2017). Whilst we did not directly ask participants to comment on treatment issues, several participants did raise issues relating to treatment.

Comments relating to Lyme disease treatment from both of these consultation exercises are reported in section 3.1.5.

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Appendices

Appendix 1: Example search strategy

MEDLINE (via Ovid) search strategy

1 exp Lyme Disease/ (9589)

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

3 borreliosis.ti,ab. (3230)

4 neuroborreliosis.ti,ab. (1024)

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

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

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

8 exp Borrelia burgdorferi Group/ (6501)

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

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

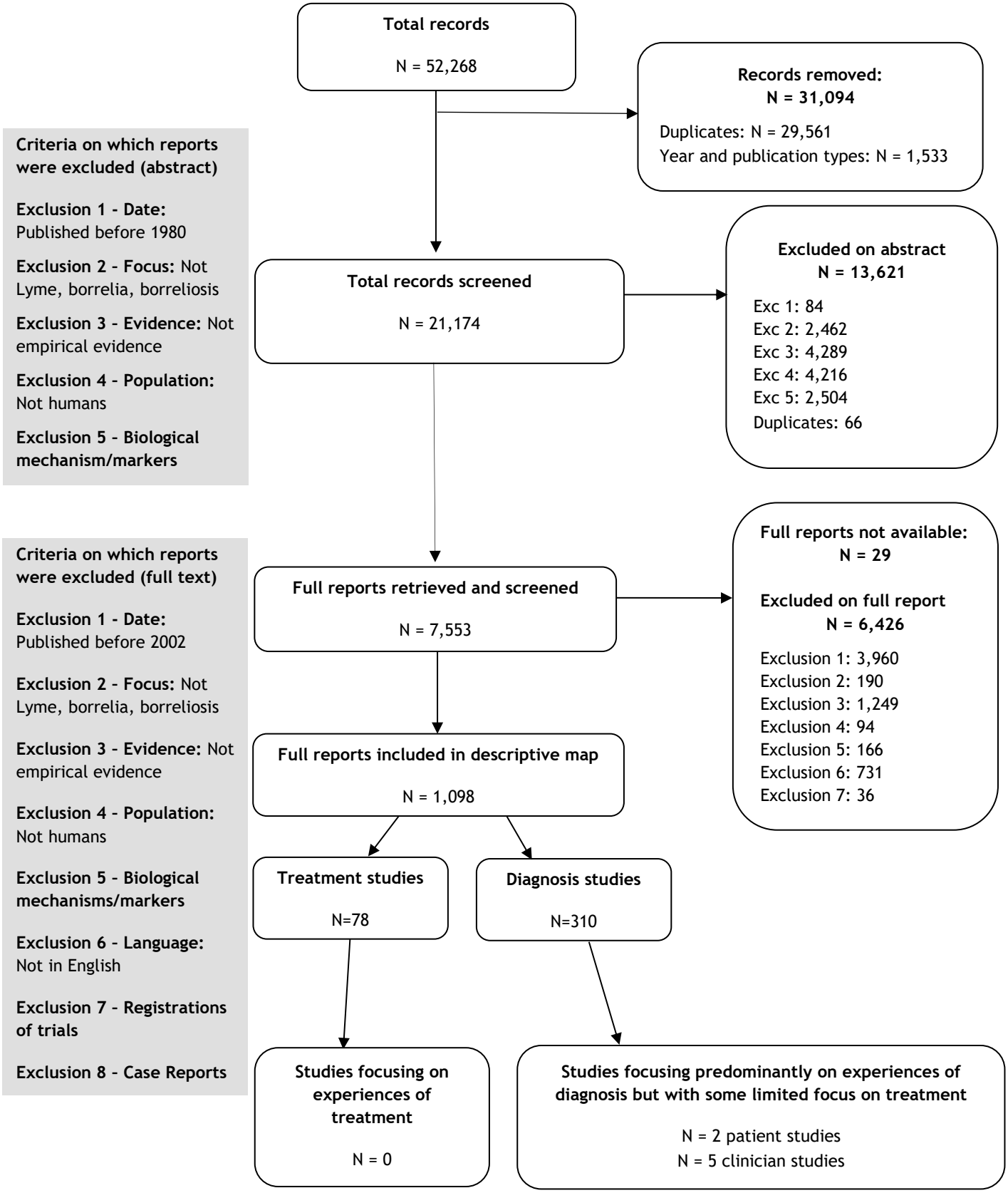
11 8 or 9 or 10 (8983)

12 7 or 11 (14245)

13 exp animals/ not humans/ (4279323)

14 12 not 13 (11450)

Appendix 2: Flow of literature through the review



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