National Institute for Health and Care Excellence

Draft for Consultation

Lyme disease: diagnosis and management

[E] Evidence review for the management of non-specific symptoms related to Lyme disease

NICE guideline

Intervention evidence review

September 2017

Draft for Consultation

This evidence review was developed by the National Guideline Centre

1

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ISBN:

Contents

1

1 Management (non-specific symptoms)

1.1 Review question: What is the most clinically and cost-effective treatment for seropositive people, who have non-specific symptoms that may be related to Lyme disease?

1.2 Introduction

People with Lyme disease may present with non-specific or non-focal symptoms such as headache, fatigue, dizziness and muscle pain, which can be distressing and impact their quality of life. This review question is important to understand the most appropriate antibiotic and duration of treatment for these presentations.

These people might not have the typical erythema migrans (EM) rash at the site of the tick bite and there is currently no standardised management approach for these people.

PICO table

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

Table 1: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with Lyme disease determined by a diagnostic test or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia

Interventions	Antimicrobials, including but not limited to:
	• Penicillins
	  ○ Amoxicillin (oral, IV)
	  ○ Ampicillin (oral, IV)
	  ○ Benzylpenicillin sodium / Penicillin G (IV)
	  - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines
	  ○ Doxycycline (oral)
	  ○ Minocycline (oral)
	• Cephalosporins
	  ○ Cefotaxime (IV)
	  ○ Ceftriaxone (IV)
	  ○ Cefuroxime axetil (oral)
	• Macrolides
	  ○ Azithromycin (oral)

	○ Clarithromycin (oral, IV) • Fluoroquinolones ○ Ciprofloxacin (oral, IV) ○ Levofloxacin (oral, IV) ○ Moxifloxacin (oral, IV) ○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) • Rifampicin (oral, IV)
• Comparisons	• Antimicrobial agents compared with each other ○ If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Study design	Randomised control studies (RCT) Cohort studies (if no RCT evidence is found)

1.3 Clinical evidence

1.3.1 Included studies

No relevant RCTs and cohort studies assessing the effectiveness of antimicrobial therapy in people with solely non-specific symptoms in the early stages of Lyme disease were identified.

Studies in people with Lyme disease, who had persistent, non-specific symptoms despite having undergone antibiotic treatment, were included in the chapter on the management of persistent symptoms related to Lyme disease.

See also the study selection flow chart in appendix C.

1.3.2 Excluded studies

See the excluded studies list in appendix I.

1.3.3 Summary of clinical studies included in the evidence review

No evidence was identified.

1.3.4 Quality assessment of clinical studies included in the evidence review

No evidence was identified.

1.4 Economic evidence

1.4.1 Included studies

No relevant health economic studies were identified.

1.4.2 Excluded studies

No relevant health economic studies were identified and excluded.

See also the health economic study selection flow chart in appendix G.

1.4.3 Unit costs

The following unit costs were presented to the committee to aid consideration of cost-effectiveness.

Table 2: UK costs of antimicrobials

Class	Drug	Age	Preparation	Mg/unit	Cost/unit (£)	Units/day	Course duration (days)	Cost per course (£)
Penicillins	Amoxicillin	7days-11 months	125 mg/1.25 ml oral suspension paediatric	125	0.20	3	14–28	8.35–16.70
		1-4 years	250 mg/5 ml oral suspension	250	0.06	3	14–28	2.37–4.75
		>5years	capsules	500	0.06	3	14–28 (g)	2.54–5.08
Penicillins	Phenoxymethylpenicillin	Adults (a)	tablets	250	0.04	4	10	1.49
Tetracyclines	Doxycycline	>12 years	capsules	100	0.11	2	10–28 (h)	2.18–6.09
Cephalosporins	Cefuroxime axetil	>3months	tablets	250	1.27	4	14–28 (g)	70.88–141.76
Macrolide	Clarithromycin	>1month	tablets	500	0.16	2	14–21	4.42–6.63
Macrolide	Azithromycin	<12 years	40 mg/1 ml oral suspension	40	0.27	10 mg/kg	9 (i)	Weight dependent
		Adults	tablets	500	0.42	1	9 (i)	3.75
Cephalosporins	Cefotaxime	Adults (b)	2 g powder for solution for injection vials (IV)	2,000	3.75	3	10	112.50
Cephalosporins	Ceftriaxone	>9 years (c)(d)	2 g powder for solution for injection vials (IV) (e)	2,000	1.03	1	14–21	14.42–21.63
Penicillins	Benzylpenicillin sodium	Adults (f)	600 mg powder for solution for injection vials (IM)	600	2.73	2	3	16.38

Abbreviations: IM: intramuscular; IV: intravenously.

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,[117] except cefotaxime from BNF, January 2017[20] and ceftriaxone from EMIT March 2017;[37] dosage from BNF and BNF for Children January 2017,[20,21] exceptions below:

(a) Source of dosage from RCT in adults with EM: Steere 1983,[164] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[129] and Pfister 1991,[130] dosage for Lyme disease not available from BNF or BNF for children. [20,21]

(c) For disseminated Lyme borreliosis.

(d) Dose for neonate and child up to 11 years (body weight <50kg) 50-80 mg/kg once daily for 14-21 days. BNF for children January 2017[21].

(e) Administration can vary in adults and children >1month: IV infusion over 30 mins or IV injection over 5 mins or deep muscular injection (doses over 1g divided between more than 1 site): 2g per day for 14-21 days BNF January 2017.[20]

(f) Source of dosage from RCT in adults with Lyme arthritis: Steere 1985:[163] 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Dosage for Lyme disease not available from BNF or BNF for children. [20,21]

(g) Course duration for early Lyme 14-21 days; 28 days for Lyme arthritis. BNF January 2017.[20]

(h) Course duration for early Lyme 10-14 days; 28 days for Lyme arthritis. BNF January 2017.[20]

(i) Course dose and duration for adults: 500 mg once daily for 3 days for 3 weeks. For children under 12 years, 10 mg/kg once daily for 3 days for 3 weeks. Committee expert opinion.

The cost of intravenous antibiotics will vary depending on where these are administered and by whom. These costs will include some of the following cost components:

- antibiotic
- nursing time (for example, Band 6 nurse, £44 per hour, PSSRU 2016[40])
- clinic space and clerical time (for outpatient administration)
- travel time (for home administration)
- hospital bed (for inpatient administration)
- consumables (for example, cannula, needles, syringes, dressing, IV giving set and glucose or sodium chloride solution).

A large proportion of the total cost of intravenous antibiotics is likely to be the cost of administration rather than the drug itself. As a result, intravenous drugs that have multiple doses administered per day will be more costly than those administered once daily. This was explored in a detailed costing analysis conducted for the NICE CG102 (Meningitis [bacterial] and meningococcal septicaemia in under 16s).[114] In this analysis, they found that ceftriaxone was the cheapest antibiotic when compared to cefotaxime and benzylpenicillin. This was due to savings in staff time associated with once daily dosing, which offset the higher cost of the drug itself.

Inpatient administration

Intravenous antibiotics administered in an inpatient setting will incur the cost of an inpatient stay, which is assumed to include intravenous antibiotics treatment as part of the unit cost. The estimated weighted average unit cost of non-elective inpatient stays and day cases for infectious disease in adults and children are summarised in the table below using the NHS reference costs 2015/2016.[45]

Table 3: Unit costs of inpatient administration

Schedule	Currency description	Currency codes	Weighted average unit costs (per day)
Day-case adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01B, WJ01D, WJ01E, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£352
Day-case paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£448
Non-elective inpatient short-stay adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01A, WJ01B, WJ01C, WJ01D, WJ01E, WJ02A, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£432
Non-elective inpatient short-stay paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£521
Non-elective inpatient long-stay adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01A, WJ01B, WJ01C, WJ01D, WJ01E, WJ02A, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£473
Non-elective inpatient long-stay paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£699

Source: NHS reference costs 2015/2016[45]

Outpatient administration

Intravenous antibiotics may also be administered as part of an outpatient parenteral antibiotic therapy (OPAT) service, which is available in some hospitals. This allows for administration in an outpatient clinic or in a home setting by a district nurse and is for people who require parenteral treatment but are otherwise stable and well enough not to be in hospital. There is currently no NHS reference cost for this service.

A UK study by Chapman 2009[29] reports that this type of service costs between 41% and 61% of the equivalent inpatient costs. Based on these estimates from Chapman 2009 and the unit cost for an adult day case in Table 3, the cost of OPAT would be approximately £144 to £215 per day. These costs would include the cost of the drug as well as the administration.

1.5 Resource impact

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

1.6 Evidence statements

1.6.1 Clinical evidence statements

No relevant published evidence was identified.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 Recommendations

E1. For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in Table 4.

E2. For children (under 12) diagnosed with Lyme disease, consider antibiotic treatment according to their symptoms as described in Table 5.

E3. Ask women whether they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation M1 on treatment in pregnancy).

E4. If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction.

Table 4: Antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) according to symptoms[a]

Symptoms	Treatment	First alternative	Second alternative
Erythema migrans	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	Azithromycin 500 mg on 3 consecutive days each week for 3 consecutive weeks[c]
Non-focal symptoms	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	Azithromycin 500 mg on 3 consecutive days each week for 3 consecutive weeks[c]
Lyme disease affecting the cranial nerves or peripheral nervous system	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Amoxicillin 1 g 3 times per day for 21 days	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 2 g twice per day or 4 g once per day for 21 days (consider switching to oral doxycycline when no longer acutely unwell)	Doxycycline 200 mg twice per day or 400 mg once per day for 21 days	
Arthritis	Doxycycline 100 mg twice per day or 200 mg once per day for 28 days	Amoxicillin 1 g 3 times per day for 28 days	Intravenous ceftriaxone 2 g once per day for 28 days

Symptoms	Treatment	First alternative	Second alternative
Acrodermatitis chronica atrophicans	Doxycycline 100 mg twice per day or 200 mg once per day for 28 days	Amoxicillin 1 g 3 times per day for 28 days	Intravenous ceftriaxone 2 g once per day for 28 days
Carditis[b]	Doxycycline 100 mg twice per day or 200 mg once per day for 21 days	Intravenous ceftriaxone 2 g once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 2 g once per day for 21 days (consider switching to oral doxycycline when no longer acutely unwell)		

[a] *For Lyme disease suspected during pregnancy, use appropriate antibiotics for stage of pregnancy.*

[b] *Do not use azithromycin to treat adults with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.*

[c] *At the time of consultation (September 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.*

Table 5: Antibiotic treatment for Lyme disease in children (aged under 12) according to symptoms[a]

Symptoms	Treatment	Alternative
Erythema migrans	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	Azithromycin 10 mg/kg on 3 consecutive days each week for 3 weeks[b]
Non-focal symptoms	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	Azithromycin 10 mg/kg on 3 consecutive days each week for 3 weeks[b]
Lyme disease affecting the cranial nerves or peripheral nervous system	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Arthritis	Amoxicillin 30 mg/kg 3 times per day 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Acrodermatitis chronica atrophicans	Amoxicillin 30 mg/kg 3 times per day 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Carditis[b]	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	

[a] *Specialist practice may include use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult* practice. *At the time of consultation (September 2017), doxycycline*

Symptoms	Treatment	Alternative
did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information. [b] *At the time of consultation (September 2017), azithromycin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.*		

1.8 Rationale and impact

1.8.1 Why the committee made the recommendations

The committee considered it important to standardise dose and duration of treatments for people with Lyme disease to ensure consistency and clarity for treatment across different presentations.

People diagnosed with Lyme disease often have symptoms that are not specific to an organ system (such as fever, sweats, muscle pain), which are referred to here as 'non-focal' symptoms.

No studies were identified comparing different antibiotics for management of Lyme disease in people with non-focal symptoms. However, the committee reviewed the evidence available for treating other symptoms and agreed that people with non-focal symptoms should be given the same treatment as people with erythema migrans.

1.8.2 Impact of the recommendations on practice

The recommendations aim to standardise antibiotic treatment, providing a consistent framework for good practice in managing Lyme disease. Overall, there may be changes to prescribing practices, but the impact is likely to be small.

1.9 The committee's discussion of the evidence

1.9.1 Interpreting the evidence

1.9.1.1 The outcomes that matter most

The guideline committee considered quality of life, cure or the resolution of non-specific Lyme disease symptoms, the reduction of non-specific Lyme disease symptoms, and the relapse of non-specific Lyme disease symptoms to be critical outcomes. Adverse events as a result of treatment were considered to be an important outcome.

No evidence on non-specific symptoms associated with Lyme disease was identified.

1.9.1.2 The quality of the evidence

No evidence on non-specific symptoms associated with Lyme disease was identified in this review.

1.9.1.3 Benefits and harms

No evidence on non-specific symptoms associated with Lyme disease was identified in this review.

1.9.2 Cost effectiveness and resource use

No health economic evidence was identified. The unit costs of different oral and intravenous antimicrobials were presented to the committee. The cost of oral doxycycline and amoxicillin is much lower than that of intravenous ceftriaxone (£4.57 and £7.62 versus £21.63 in adults). The committee also considered the cost of intravenous administration, which would include the cost of nurse time, clinic space and clerical time (if administered in an outpatient setting), nurse travel time (if administered at home) and disposables required for administration. These costs would likely be greater than the cost of the antibiotics themselves.

The committee recommended oral doxycycline or amoxicillin for people with non-specific Lyme disease. The dose and duration is based on committee consideration of evidence for other presentations of Lyme disease and consensus. For those in whom both doxycycline and amoxicillin are contraindicated, azithromycin is recommended. The unit cost of azithromycin is low at £3.75 for 500 mg, once daily for 3 days for 3 weeks.

The recommendations for children closely reflect those for adults, unless drugs are contraindicated. For younger children, oral suspension formulations may be required rather than tablets. The unit costs of the recommended antimicrobials for children are not dissimilar to those for adults.

The committee considered the different adverse event profiles of different antimicrobials and whether these may impact the costs of managing Lyme disease as well as their impact on the patient's quality of life. Doxycycline adverse events, for example, include photosensitivity, nausea and vomiting. It was also noted that a rare side effect of azithromycin is QT prolongation. In practice, if a patient experiences any of these adverse events, these would be managed by switching to another antimicrobial; therefore, the cost to the NHS would be a consultation with a GP and additional antimicrobials. These costs are considered to be low and would be offset by the cure and reduction of symptoms after successful treatment of Lyme disease.

The committee agreed that this potential change in practice in terms of a longer course of antimicrobials would not result in a significant resource impact given the relatively small number of people diagnosed with Lyme disease.

1.9.3 Other factors the committee took into account

Non-specific symptoms could be an indication of an acute infection without the involvement of specific organ systems. The committee agreed that people with a positive test result for Lyme disease and non-specific symptoms should be treated in the same way as people with an erythema migrans rash.

The evidence identified through the evidence review on the management of erythema migrans influenced the recommendations made for the management of non-specific symptoms. There was evidence that doxycycline was more effective than some other antibiotics, but there was no clear evidence that doxycycline was more effective than an amoxicillin/probenecid combination or azithromycin. The committee noted that doxycycline and amoxicillin can penetrate the blood-cerebrospinal fluid barrier and pass into the central nervous system, whereas azithromycin cannot. Doxycycline can also be taken as a single daily dose.

Therefore, the committee recommended doxycycline as the antibiotic of choice. In cases where doxycycline is contraindication, amoxicillin should be offered to the patient. Azithromycin can be offered if doxycycline and amoxicillin are contraindicated. The guideline recommends that care of children and young people less than 18 years should be discussed with a specialist for advice about diagnosis and management. In children under the age of 12, amoxicillin is recommended as the antibiotic of choice.

The guideline committee was aware that specialists do offer doxycycline in children aged 9 years and above as a result of indirect evidence from the United States and Scandinavia despite no licence or BNFC dose., There is also increasing indirect evidence from use in other conditions in the United States and Canada that doxycycline does not cause teeth staining when used for short course (less than 4 weeks) in children aged 2 years and older. UK specialist clinicians may choose to use doxycycline as second line where a CSF-penetrating oral antibiotic is required, although the lack of direct evidence, lack of licence and lack of BNFC dose regimen has so far limited UK use in children aged 8 and under. Where used, in the United States and Canada, 1 dose regimen of doxycycline for children under 45 kilograms is: 5 milligram/kilogram in 2 divided doses on day 1 followed by 2.5 milligram/kilogram daily in 1 or 2 divided doses with a maximum for severe infections, up to 5 milligram/kilogram daily.

Azithromycin should be otherwise be offered in cases where amoxicillin is contraindicated. The committee made research recommendations for the development of a core outcome set for use in studies of Lyme disease and a research recommendation for antibiotic management. These are outlines in detail in appendix J of evidence report D.

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Appendices

Appendix A: Review protocols

Table 6: Review protocol for the management of non-specific symptoms

Question number: 4.1

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for seropositive people, who have non-specific symptoms that may be related to Lyme disease?
Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	The review questions on the condition-specific management of Lyme disease aim to identify the most effective treatment in different clinical scenarios. The questions have been developed in a way to identify the evidence for all potential populations and scenarios, even if clinical presentations are more diverse. The population for this review consists of people with a seropositive test result for Lyme disease, who have non-specific symptoms that may be related to Lyme disease.
Eligibility criteria – population / disease / condition	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with Lyme disease determined by a diagnostic tests or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia

Eligibility criteria – intervention(s)	Antimicrobials, including but not limited to:
	• Penicillins
	  ○ Amoxicillin (oral, IV)
	  ○ Ampicillin (oral, IV)
	  ○ Benzylpenicillin sodium / Penicillin G (IV)
	  - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines
	  ○ Doxycycline (oral)
	  ○ Minocycline (oral)
	• Cephalosporins

Field	Content
	○ Cefotaxime (IV) ○ Ceftriaxone (IV) ○ Cefuroxime axetil (oral) • Macrolides ○ Azithromycin (oral) ○ Clarithromycin (oral, IV) • Fluoroquinolones ○ Ciprofloxacin (oral, IV) ○ Levofloxacin (oral, IV) ○ Moxifloxacin (oral, IV) ○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) • Rifampicin (oral, IV)
Eligibility criteria – comparator(s)	• Antimicrobial agents compared with each other ○ If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Eligibility criteria – study design	RCTs Cohort studies (if no RCT evidence is found)
Other inclusion exclusion criteria	Date limits for search: none Language: English only Setting: all settings in which NHS is care is provided or commissioned The following interventions will not be considered for inclusion: • Metronidazole • Trimethoprim
Proposed sensitivity / subgroup analysis, or meta-regression	The following groups will be considered separately if data are available (strata): • Children (under 12 years); young people and adults (12 years and over) • Onset of specific symptoms less than 6 weeks; 6 weeks to 6 months; over 6 months Subgroups (to be investigated if heterogeneity is identified): • Pregnant women • People who are immunocompromised • People in whom a previous course of antimicrobial treatment has failed
Selection process – duplicate screening /	Studies will be sifted by title and abstract. Potentially significant publications obtained in full text will then be assessed against the

Field	Content
selection / analysis	inclusion criteria specified in this protocol.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome Bibliographies, citations, study sifting and reference management will be managed using EndNote. Data extractions will be performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library all years Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise critically individual studies. For details, please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual. Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) In the absence of clinically established MIDs, standard MIDs for dichotomous (25% risk reduction or risk increase) and continuous outcomes (+/-0.5 standard deviation) will be used If heterogeneity is found, the influence of subgroups will be examined
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.

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

1 **Table 7: Health economic review protocol**

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	1. Populations, interventions and comparators must be as specified in the clinical review protocol above. 2. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). 3. Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) 4. Unpublished reports will not be considered unless submitted as part of a call for evidence. 5. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the US will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[115] **Inclusion and exclusion criteria** 6.If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. 7.If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. 8.If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. **Where there is discretion**

	The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude the remaining studies selectively. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* 9.UK NHS (most applicable). 10. OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). 11. OECD countries with predominantly private health insurance systems (for example, Switzerland). 12. Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* 13. Cost–utility analysis (most applicable). 14. Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). 15. Comparative cost analysis. 16. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* 17. The more recent the study, the more applicable it will be. 18. Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly before 2001 will be rated as 'Not applicable'. 19. Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* 20. The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

1

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 8: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

1 **Embase (Ovid) search terms**

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

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

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

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

B.2 Health Economics literature search strategy

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

Table 9: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

1 **Embase (Ovid) search terms**

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

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

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

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

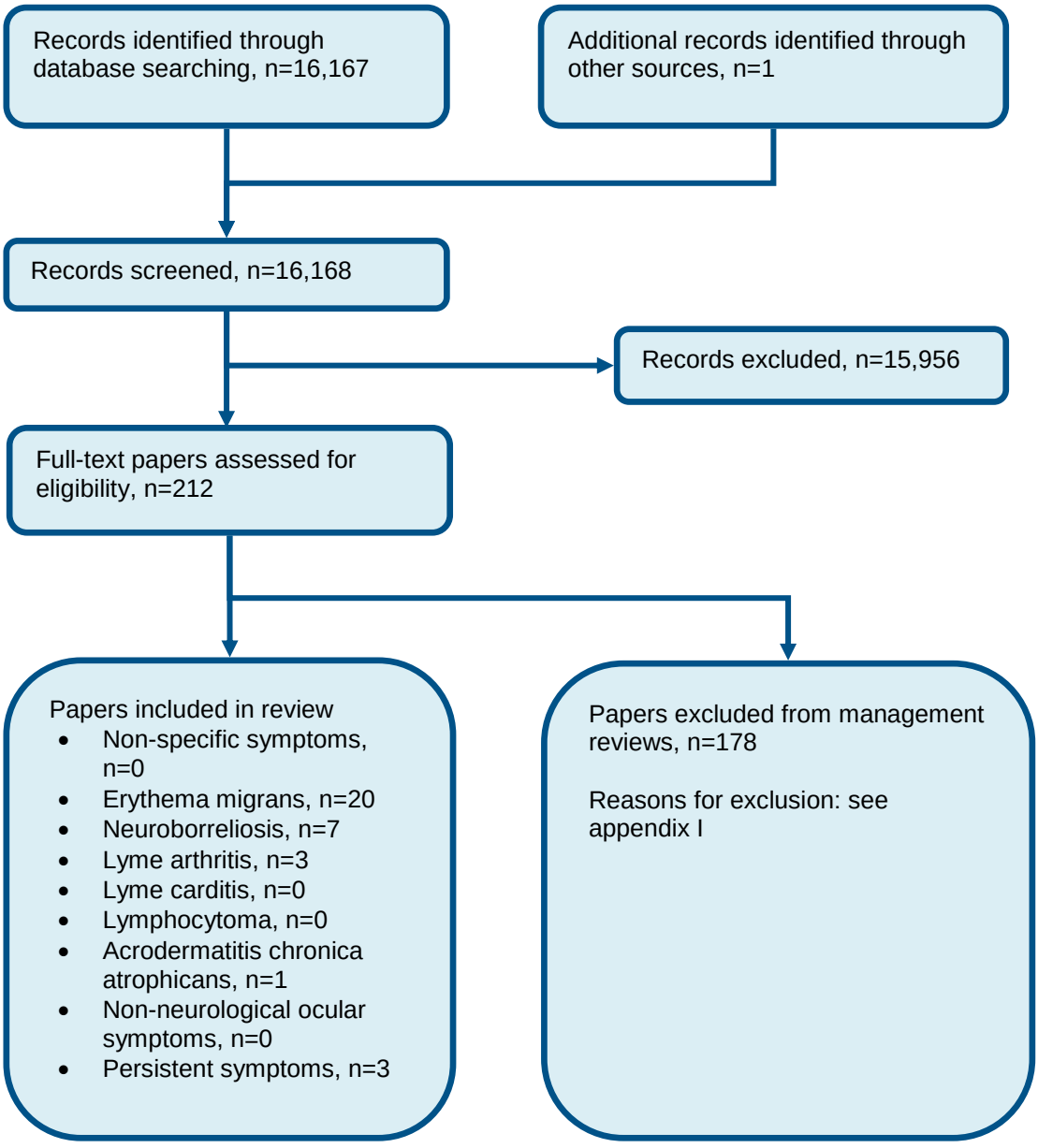
#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis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

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

1

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the reviews of the management of specific clinical scenarios for Lyme disease



Appendix D: Clinical evidence tables

None.

Appendix E: Forest plots

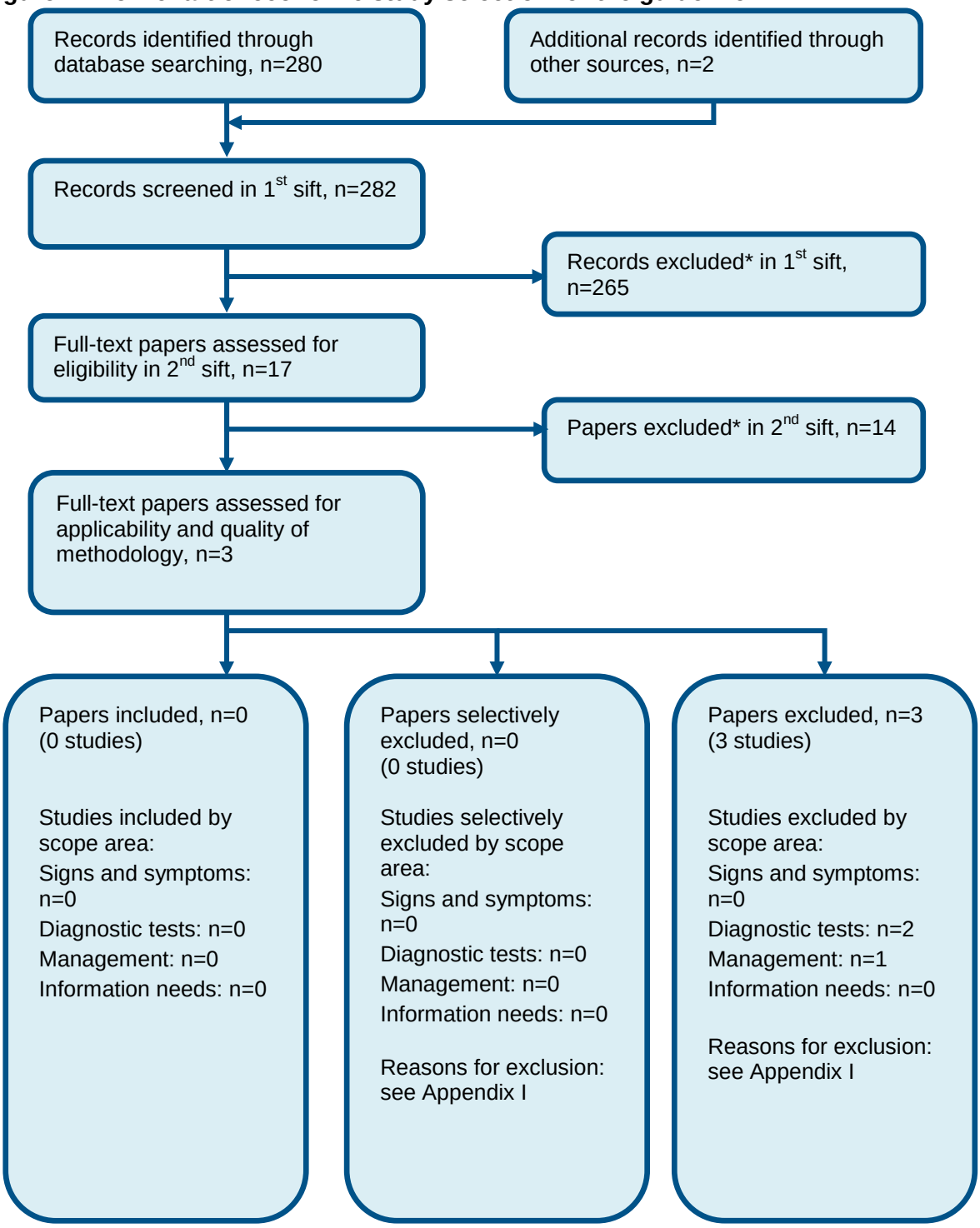
None.

Appendix F: GRADE tables

None.

Appendix G: Health economic evidence selection

Figure 2: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical management reviews

Reference	Reason for exclusion
Aberer 2006[1]	Excluded due to an incorrect intervention
Abrutyn 1989[2]	Excluded due to an incorrect study design
Agger 1992[3]	Excluded due to an incorrect study design
Agus 1995[4]	Excluded due to an incorrect study design
Agwuh 2006[5]	Excluded due to an incorrect study design
Ahmed 2005[6]	Excluded due to an incorrect study design
Ahmed 2013[7]	Excluded due to an incorrect study design
Alarcon 1994[8]	Excluded due to an incorrect study design
Andiman 1986[9]	Excluded due to an incorrect study design
Anonymous 1991[10]	Excluded due to an incorrect study design
Arvikar 2015[11]	Excluded due to an incorrect study design
Auwaerter 2004[12]	Excluded due to an incorrect study design
Bennet 2003[13]	Excluded due to an incorrect study design
Berende 2014[14]	Excluded due to an incorrect study design
Berger 1988[16]	Excluded due to an incorrect study design
Berger 1986[15]	Excluded due to an incorrect study design
Bernardino 2009[17]	Excluded due to an incorrect study design
Bhate 2011[18]	Excluded due to an incorrect study design
Bjark 2016[19]	Not available
Borg 2005[22]	Excluded due to an incorrect study design
Bratton 2008[23]	Excluded due to an incorrect study design
Bremell 2014[24]	Excluded due to an incorrect study design
British Infection Association 2011[25]	Excluded due to an incorrect study design
Butler 1978[26]	Excluded due to an incorrect population
Cadavid 2016[27]	Excluded due to an incorrect study design
Canadian Paediatric Society 1992[28]	Excluded due to an incorrect study design
Chen 1999[30]	Excluded due to an incorrect outcome
Choo-Kang 2010[31]	Excluded due to an incorrect study design
Christian 1992[32]	Excluded due to an incorrect study design
Cimmino 1992[34]	Excluded due to an incorrect study design
Cimmino 1997[33]	Excluded due to an incorrect study design
Cimperman 1999[35]	Excluded due to an incorrect study design
Coblyn 1981[36]	Excluded due to an incorrect study design
Committee on Infectious Diseases 1991[38]	Excluded due to an incorrect study design
Cuisset 2008[39]	Excluded due to an incorrect study design
Dattwyler 1996[41]	Excluded due to an incorrect comparison
Dattwyler 1987[42]	Excluded due to an incorrect study design
Dattwyler 1988[43]	Excluded due to an incorrect population
Dattwyler 2005[44]	Excluded due to an incorrect population

Reference	Reason for exclusion
Dersch 2015[46]	Excluded due to an incorrect study design
Dersch 2016[49]	Excluded due to an incorrect study design
Dersch 2014[47]	Excluded due to an incorrect study design
Dersch 2017[48]	Not available
Dhoot 2011[50]	Excluded due to an incorrect study design
Dinser 2005[51]	Excluded due to an incorrect study design
Dotevall 1988[52]	Excluded due to an incorrect study design
Eliassen 2017[53]	Excluded due to an incorrect study design
Eliassen 2017[54]	Excluded due to an incorrect intervention
Eppes 2003[55]	Excluded due to an incorrect study design
Esposito 2013[56]	Excluded due to an incorrect study design
Fallon 1999[58]	Excluded due to an incorrect intervention
Fallon 2008[57]	Excluded due to an incorrect outcome
Galev 2005[59]	Excluded due to an incorrect study design
Garkowski 2017[60]	Systematic review
Gasser 1996[62]	Excluded due to an incorrect not available
Gasser 1995[63]	Excluded due to an incorrect study design
Gasser 1995[61]	Excluded due to an incorrect study design
Gerber 1996[64]	Excluded due to an incorrect intervention
Gillies 2015[65]	Excluded due to an incorrect study design
Goodwin 1990[66]	Excluded due to an incorrect study design
Hansen 1992[67]	Excluded due to an incorrect intervention
Hassler 1990[68]	Excluded due to an incorrect population
Horton 2017[69]	Conference abstract
Hu 2001[70]	Excluded due to an incorrect study design
Inboriboon 2010[71]	Excluded due to an incorrect study design
Kaplan 2003[72]	Excluded due to an incorrect population
Karkkonen 2001[73]	Excluded due to an incorrect study design
Karlsson 1996[74]	Excluded due to an incorrect outcome
Kersten 1995[75]	Excluded due to an incorrect study design
Kilic Muftuoglu 2016[76]	Excluded due to an incorrect study design
Klempner 2013[78]	Excluded due to an incorrect study design
Korenberg 1996[79]	Excluded due to an incorrect intervention
Kowalski 2010[81]	Excluded due to an incorrect outcome
Kowalski 2011[80]	Excluded due to an incorrect study design
Krbkova 1996[82]	Excluded due to an incorrect comparison
Kuhn 2012[83]	Excluded due to an incorrect study design
Laasila 2003[84]	Excluded due to an incorrect population
Lantos 2013[85]	Excluded due to an incorrect study design
Lauhio 1994[86]	Excluded due to an incorrect population
Lauhio 1991[87]	Excluded due to an incorrect population
Lempner 2002[77]	Excluded due to an incorrect study design
Liegner 1992[88]	Excluded due to an incorrect study design
Lipsker 2002[89]	Excluded due to an incorrect study design
Ljostad 2008[90]	Study abstract

Reference	Reason for exclusion
Loewen 1999[91]	Excluded due to an incorrect study design
Loewen 2000[92]	Excluded due to an incorrect study design
Luft 1988[94]	Excluded due to an incorrect outcome
Luft 1989[93]	Excluded due to an incorrect population
Maraspin 1995[100]	Excluded due to an incorrect study design
Maraspin 1996[95]	Excluded due to an incorrect study design
Maraspin 1999[96]	Excluded due to an incorrect study design
Maraspin 2002[97]	Excluded due to an incorrect study design
Maraspin 1999[98]	Excluded due to an incorrect study design
Maraspin 2002[99]	Excluded due to an incorrect population
Marks 2016[101]	Excluded due to an incorrect study design
McGill 1965[102]	Excluded due to an incorrect population
Meyerhoff 2002[103]	Excluded due to an incorrect study design
Meyerhoff 2016[104]	Excluded due to an incorrect study design
Millner 1996[105]	Excluded due to an incorrect outcome
Millner 1996[106]	Excluded due to an incorrect outcome
Morales 2000[107]	Excluded due to an incorrect study design
Muellegger 1995[109]	Excluded due to an incorrect study design
Muellegger 1996[108]	Excluded due to an incorrect comparison
Mullegger 1991[110]	Excluded due to an incorrect outcome
Nadelman 1993[112]	Excluded due to an incorrect study design
Nadelman 2001[111]	Excluded due to an incorrect population
Naglo 1989[113]	Excluded due to an incorrect study design
Neumann 1987[116]	Excluded due to an incorrect study design
Nimmrich 2014[118]	Excluded due to an incorrect study design
Nowakowski 2000[119]	Excluded due to an incorrect study design
Nowakowski 1995[120]	Excluded due to an incorrect study design
Ogrinc 2006[121]	Excluded due to an incorrect population
Oksi 1999[122]	Excluded due to an incorrect study design
Oksi 2007[123]	Excluded due to an incorrect population
Oksi 1998[124]	Excluded due to an incorrect population
Peltomaa 1998[125]	Excluded due to an incorrect comparison
Pena 1999[126]	Excluded due to an incorrect study design
Perronne 2015[127]	Not available
Pfister 1988[128]	Excluded due to an incorrect outcome
Pirila 1951[131]	Excluded due to an incorrect study design
Plorer 1993[132]	Excluded due to an incorrect study design
Plotkin 1991[133]	Excluded due to an incorrect study design
Puchalska 1996[134]	Excluded due to an incorrect study design
Puri 2015[135]	Excluded due to an incorrect comparison
Puri 2015[136]	Excluded due to an incorrect study design
Rebman 2015[137]	Excluded due to an incorrect study design
Renaud 2004[138]	Excluded due to an incorrect study design
Rohacova 1996[139]	Excluded due to an incorrect comparison
Rose 1994[140]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Rose 1996[141]	Excluded due to an incorrect intervention
Rubin 1992[142]	Excluded due to an incorrect study design
Salazar 2005[143]	Excluded due to an incorrect intervention
Salazar 1993[144]	Excluded due to an incorrect study design
Sanchez 2016[145]	Excluded due to an incorrect study design
Sandstrom 1989[146]	Excluded due to an incorrect study design
Schmidt 1995[147]	Excluded due to an incorrect study design
Selby 2008[148]	Excluded due to an incorrect study design
Shadick 1994[149]	Excluded due to an incorrect study design
Shadick 1999[150]	Excluded due to an incorrect study design
Shemenski 2016[151]	Excluded due to an incorrect study design
Shoemaker 2006[152]	Excluded due to an incorrect intervention
Sjowall 2012[154]	Excluded due to an incorrect intervention
Sjowall 2011[153]	Excluded due to an incorrect study design
Skogman 2003[156]	Excluded due to an incorrect intervention
Skogman 2008[155]	Excluded due to an incorrect study design
Skoldenberg 1988[157]	Excluded due to an incorrect study design
Smith 2002[158]	Excluded due to an incorrect study design
Solomon 1998[159]	Excluded due to an incorrect intervention
Spathling 1992[160]	Article not in English
Stanek 1999[161]	Excluded due to an incorrect study design
Steere 1980[165]	Excluded due to an incorrect study design
Steere 1983[166]	Excluded due to an incorrect study design
Steere 1987[162]	Excluded due to an incorrect study design
Steurer 2016[167]	Article not in English
Stricker 2011[168]	Excluded due to an incorrect study design
Stricker 2010[169]	Excluded due to an incorrect study design
Strle 1996[170]	Excluded due to an incorrect outcome
Strle 1996[171]	Excluded due to an incorrect outcome
Strle 1992[172]	Excluded due to an incorrect study design
Strle 1993[173]	Excluded due to an incorrect outcome
Stupica 2015[175]	Excluded due to an incorrect comparison
Stupica 2011[174]	Excluded due to an incorrect comparison
Suarez-Magdalena 2017[176]	Not available
Thompson 2012[177]	Excluded due to an incorrect study design
Thorstrand 2002[178]	Excluded due to an incorrect study design
Thyresson 1949[179]	Excluded due to an incorrect study design
Torbahn 2016[180]	Excluded due to an incorrect study design
Tory 2010[181]	Excluded due to an incorrect comparison
Tseng 2017[182]	Excluded due to an incorrect outcome
Valesova 1996[183]	Excluded due to an incorrect comparison
Vazquez 2003[185]	Excluded due to an incorrect study design
Vazquez-Lopez 2016[184]	Excluded due to an incorrect study design
Wahlberg 1994[186]	Excluded due to an incorrect intervention
Weber 1988[188]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Weber 1987[187]	Excluded due to an incorrect population
Weissenbacher 2005[189]	Excluded due to an incorrect intervention
White 2013[190]	Excluded due to an incorrect study design
Zochling 1996[191]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Table 11: Studies excluded from the health economic review

Reference	Reason for exclusion
None	