National Institute for Health and Care Excellence

Final

Lyme disease: diagnosis and management

[I] Evidence review for the management of Lyme carditis

NICE guideline 95

Evidence review

April 2018

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: What is the most clinically and cost-effective treatment for people with carditis related to Lyme disease?

1.2 Introduction

Carditis related to Lyme disease describes inflammation of the tissue of the heart caused by the Lyme bacteria *Borrelia burgdorferi sensu lato*. It typically presents weeks to months after the bite of an infected tick, which may not be remembered. The most common presentations are due to inflammation of the conduction pathway (electrical pathway) of the heart. This can lead to arrhythmias (abnormal rhythms) and heart block, which can be mild to severe. Symptoms may include dizziness, chest pain and collapse. Inflammation may also occur at other sites such as the pericardium (lining of the heart) and myocardium (heart muscle). In rare cases, carditis can be severe or even fatal. Antibiotic treatment is effective and usually resolves symptoms within 1–4 weeks; however, people with severe Lyme disease will require specialist hospital input until the symptoms recover.

There are currently no national guidelines on the management of carditis caused by Lyme disease. Practice may vary between sites, but it would normally include 14–21 days of antibiotic treatment with specialist input where appropriate. Carditis caused by Lyme disease responds well to antibiotic therapy, but if it is left untreated, it can be potentially harmful.

Recommendations on this topic will standardise the management of carditis caused by Lyme disease in line with the best available evidence, increase awareness and highlight areas that may be targeted for further research.

1.3 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 symptoms consistent with carditis related to Lyme disease

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) Steroids (corticosteroids; oral, IV)
Comparisons	• Any type of intervention compared to each other ○ If data are available, consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment or steroids compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme carditis) 3. Reduction of clinical symptoms related to Lyme carditis 4. Relapse of symptoms related to Lyme carditis **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

1.4 Clinical evidence

1.4.1 Included studies

No relevant RCTs and cohort studies comparing the effectiveness of antibiotics and steroids versus each other or placebo as treatment for people with carditis related to Lyme disease were identified.

See also the study selection flow chart in appendix C.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.4.4 Quality assessment of clinical studies included in the evidence review

No relevant clinical studies were identified.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

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

1.5.2 Excluded studies

No relevant health economic studies were identified and excluded.

1.5.3 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	7 days-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
		>5 years	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	>3 months	tablets	250	1.27	4	14–28 (g)	70.88–141.76
Macrolide	Clarithromycin	>1 month	tablets	500	0.16	2	14–21	4.42–6.63
Macrolide	Azithromycin	<12 years	40 mg/1ml 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 ECM: 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 <50 kg) 50-80 mg/kg once daily for 14-21 days. BNF for children January 2017.[21]

(e) Administration can vary in adults and children >1 month: IV infusion over 30 mins or IV injection over 5 mins or deep muscular injection (doses over 1 g divided between more than 1 site): 2 g 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 weighted average unit cost of non-elective inpatient stays and day cases for infectious disease in adults and children are summarised estimated 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.

1.6 Resource impact

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

1.7 Evidence statements

1.7.1 Clinical evidence statements

No relevant clinical evidence was identified.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The guideline committee considered quality of life, cure or the resolution of symptoms related to Lyme carditis, reduction in clinical symptoms related to Lyme carditis and the reoccurrence of symptoms related to Lyme carditis to be critical outcomes to decision-making. They also considered adverse events to be an important outcome.

No evidence was found for any of the outcomes listed.

1.8.1.2 The quality of the evidence

No evidence was found.

1.8.1.3 Benefits and harms

No evidence was found.

1.8.2 Cost effectiveness and resource use

No relevant 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 for 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.

For people who are not haemodynamically compromised or systemically unwell, for example people with first- or second-degree heart block, the committee considered that oral doxycycline (or amoxicillin where doxycycline is contraindicated) should be offered. This was based on committee consideration of evidence for other presentations of Lyme and consensus.

For people who are haemodynamically compromised or systemically unwell, the committee noted that they would likely be inpatients and, based on consideration of evidence for other Lyme presentations and consensus, the committee recommended intravenous ceftriaxone.

Currently, the BNF recommends intravenous ceftriaxone for those with disseminated Lyme borreliosis at a dose of 2 grams per day for 14-21 days. The committee agreed that providing a range of treatment durations is not useful for generalists as it is unclear when to use the shorter or longer course. The committee decided to recommend the longer course as a standard to be cautious due to concern at low cure rates in some studies of other presentations and the lack of clear evidence for shorter courses.

Finally, ceftriaxone was chosen over cefotaxime as ceftriaxone can be given once daily. More frequent dosing would increase costs, as demonstrated in a costing analysis conducted for the NICE CG102 (Meningitis [bacterial] and meningococcal septicaemia in under 16s) and may require inpatient stay rather than home administration by a district nurse.

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. 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 number of people diagnosed with carditis symptoms related to Lyme disease.

1.8.3 Other factors the committee took into account

The guideline committee was aware that the majority of people who present with arrhythmias in UK practice will have causes other than Lyme disease and that patients with significant arrhythmias may also require specific cardiac treatment such as pacing or haemodynamic support, but the details of these treatments are outside the scope of the guideline. No recommendations were made for treatment options that go beyond the management of Lyme disease as an infectious disease directly.

The guideline committee was informed by evidence reviews for the antibiotic management of other Lyme disease presentations, particularly the management of erythema migrans, neuroborreliosis and Lyme arthritis. The committee considered it important to standardise dose and duration of treatments for people with Lyme disease to ensure consistency and clarity for treatment.

They acknowledged that cardiac problems associated with Lyme disease can vary and people may have, for example first- or second-degree heart block but may not be symptomatic or haemodynamically compromised, or they could have an arrhythmia that compromises their circulation. The committee recommended doxycycline 200 milligrams daily for 21 days for other presentations due to concern at low cure rates in some studies, the lack of clear evidence for shorter courses, evidence suggesting no increase in adverse events with longer courses and reassurance for patients that they have had the longer course if they continue to have symptoms. It was agreed that this was appropriate for people who were not acutely unwell.

The committee were aware that people who were haemodynamically compromised were likely to be inpatients and treatment with intravenous ceftriaxone 2 grams daily for 21 days is appropriate, as treating unstable people with oral antibiotics might be contraindicated. Physicians might decide to switch to an oral treatment regimen once the person's condition has improved.

No direct evidence was found for the care of children. The guideline recommends that the care of children and young people younger than 18 years be discussed with a specialist and expected that the care of this group would be delivered by a specialist. The guideline committee was aware that specialists do offer doxycycline in children aged 9 years and older 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 and international practice is moving to recommend use above 2 years. 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.

The committee made a research recommendation for the development of a core outcome set for treatments of Lyme disease and a research recommendation for antibiotic management of Lyme disease. The details of these are in appendix J of evidence report D.

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Appendices

Appendix A: Review protocols

Table 4: Review protocol for the management of Lyme carditis

Question number: 4.5

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for people with carditis 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 carditis related to Lyme disease. This review is only concerned with the treatment of Lyme disease as the underlying cause of cardiac symptoms and not with the treatment or management of cardiac symptoms directly.
Eligibility criteria – population / disease / condition	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with symptoms consistent with carditis related to Lyme disease

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
	  ○ Cefotaxime (IV)
	  ○ Ceftriaxone (IV)
	  ○ Cefuroxime axetil (oral)
	• Macrolides
	  ○ Azithromycin (oral)
	  ○ Clarithromycin (oral, IV)
	• Fluoroquinolones
	  ○ Ciprofloxacin (oral, IV)
	  ○ Levofloxacin (oral, IV)
	  ○ Moxifloxacin (oral, IV)

Field	Content
	○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) • Rifampicin (oral, IV) Steroids (corticosteroids; oral, IV)
Eligibility criteria – comparator(s)	• Any type of intervention compared to each other ○ If data are available, consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment or steroids compared to no treatment / placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme carditis) 3. Reduction of clinical symptoms related to Lyme carditis 4. Relapse of symptoms related to Lyme carditis **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 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 or steroid treatment has failed
Selection process – duplicate screening / selection / analysis	Studies will be sifted by title and abstract. Potentially significant publications obtained in full text will then be assessed against the inclusion criteria specified in this protocol.
Data management (software)	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

Field	Content
	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 individual studies critically. 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.
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 /	The NGC is funded by NICE and hosted by the Royal College of

Field	Content
support	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

Table 5: 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	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • 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). • 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.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • 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** • 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. • 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. • 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:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • 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:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • 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'. • 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:* • 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.

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 6: 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

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

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 7: 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

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/

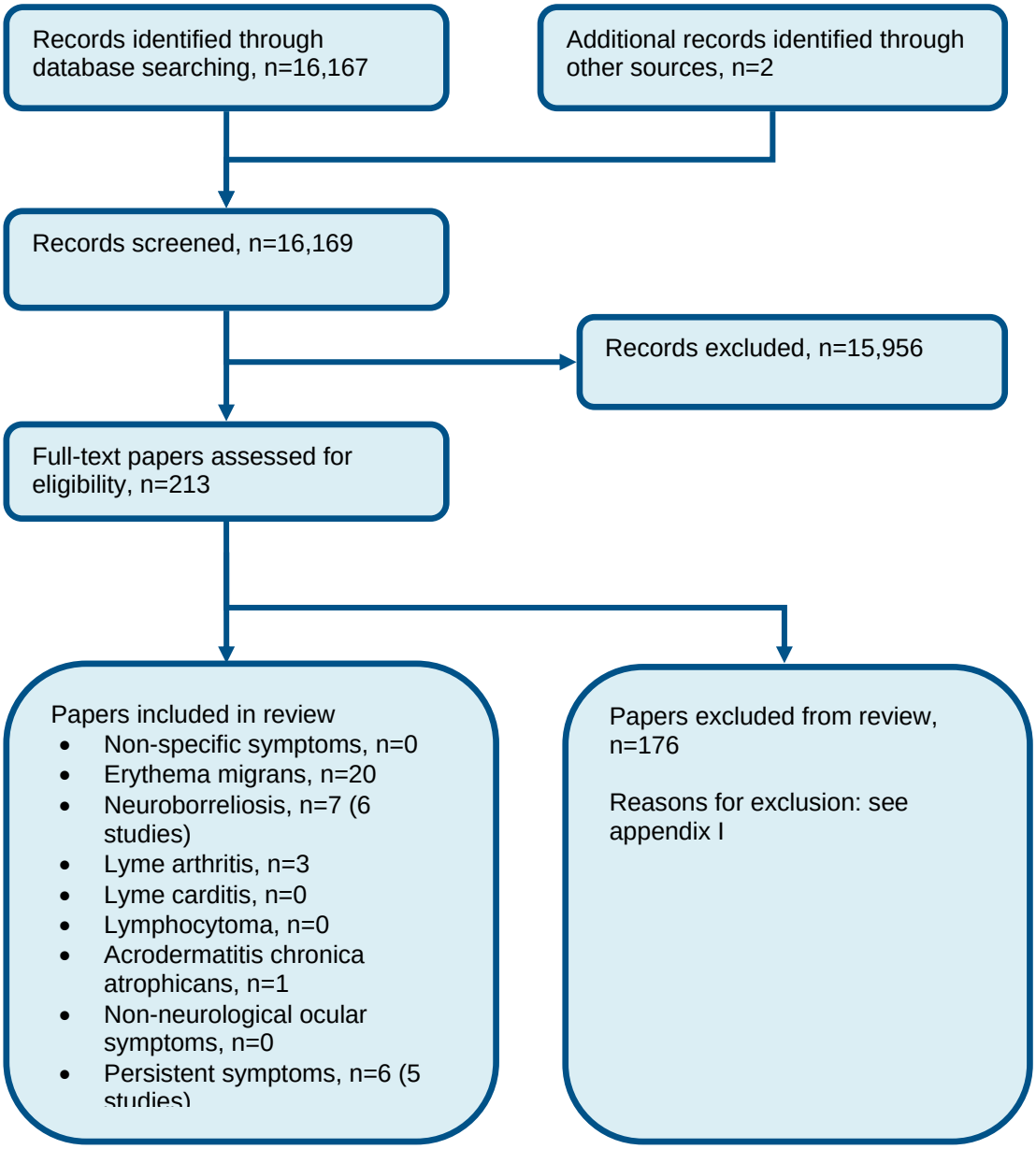
61.	(quality adj2 (wellbeing or well being)).ti,ab.
62.	sickness impact profile.ti,ab.
63.	disability adjusted life.ti,ab.
64.	(qal* or qtime* or qwb* or daly*).ti,ab.
65.	(euroqol* or eq5d* or eq 5*).ti,ab.
66.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
67.	(health utility* or utility 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

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

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

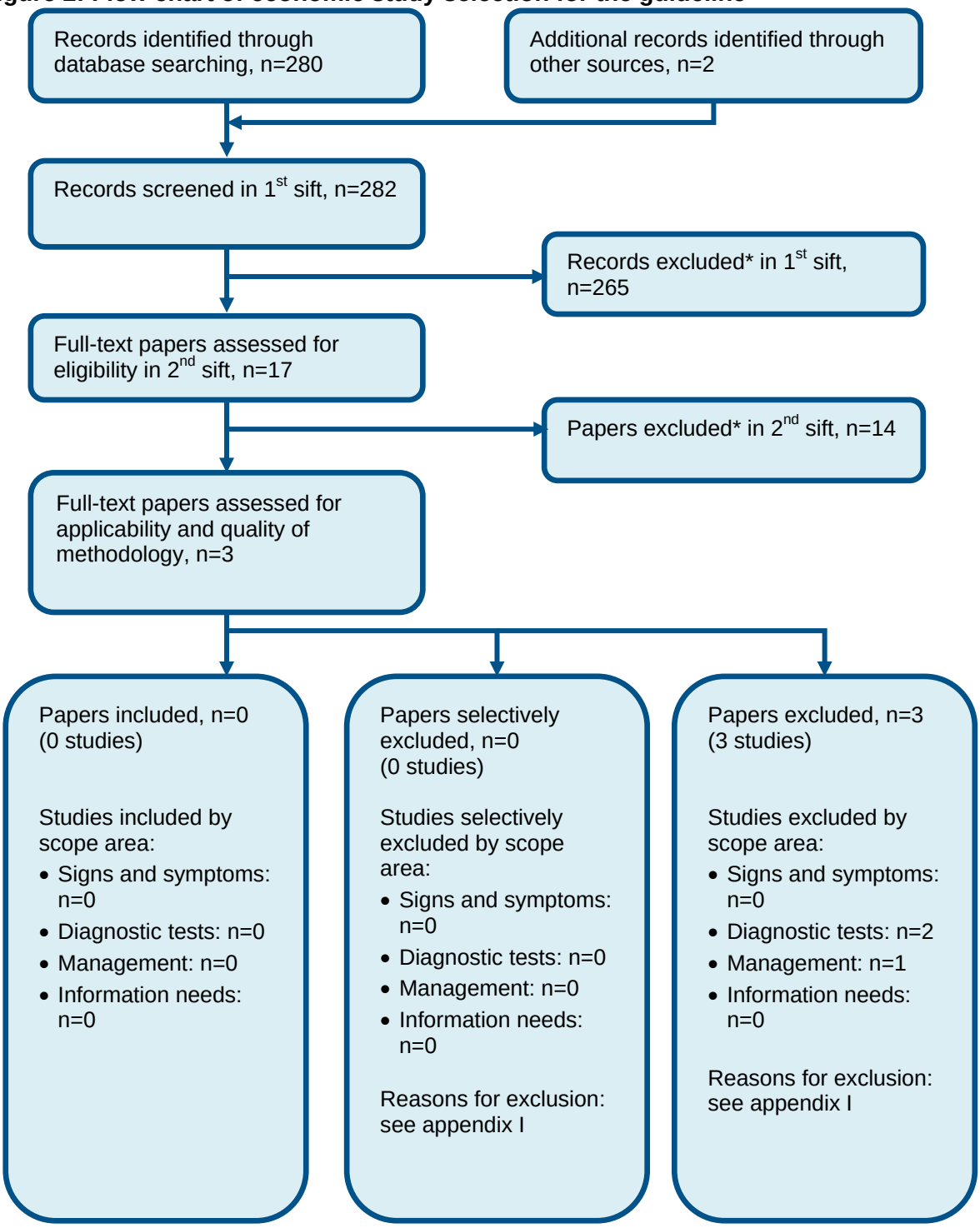
None.

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 8: 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
Galev 2005[59]	Excluded due to an incorrect study design
Garkowski 2017[60]	Systematic review
Gasser 1996[62]	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
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
Loewen 1999[91]	Excluded due to an incorrect study design
Loewen 2000[92]	Excluded due to an incorrect study design

Reference	Reason for exclusion
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
Rose 1996[141]	Excluded due to an incorrect intervention
Rubin 1992[142]	Excluded due to an incorrect study design

Reference	Reason for exclusion
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
Weber 1987[187]	Excluded due to an incorrect population
Weissenbacher 2005[189]	Excluded due to an incorrect intervention

Reference	Reason for exclusion
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 9: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None