

Lyme disease: diagnosis and management

[G] Evidence review for the management of Lyme arthritis

NICE guideline

Evidence review

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Draft for Consultation

*This evidence review was developed by
the National Guideline Centre*

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1 Management (arthritis)

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

1.2 Introduction

Arthritis related to Lyme disease can be a painful and disabling condition. The choice and duration of antibiotic treatment to resolve the condition is therefore important. It can present as arthritis of one joint or can affect many joints. It is often not recognised without a good history and until other causes of mono- or poly-arthritis are excluded.

The current treatment of Lyme arthritis is inconsistent in terms of both choice of antibiotic and duration of treatment. Presently the BNF states that 'doxycycline, amoxicillin [unlicensed indication] or cefuroxime (as cefuroxime axetil) are the antibacterials of choice for early Lyme disease or Lyme arthritis'. Current treatment is often determined by advice from the local or reference laboratory microbiologist and may differ from region to region.

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 arthritis related to Lyme disease
Interventions	Antimicrobials, including but not limited to: <ul style="list-style-type: none">• Penicillins<ul style="list-style-type: none">○ Amoxicillin (oral, IV)○ Ampicillin (oral, IV)○ Benzylpenicillin sodium / Penicillin G (IV)<ul style="list-style-type: none">- Including Augmentin (Amoxicillin + clavulanic acid; oral, IV)○ Phenoxymethylpenicillin / Penicillin V (oral)• Tetracyclines<ul style="list-style-type: none">○ Doxycycline (oral)○ Minocycline (oral)• Cephalosporins<ul style="list-style-type: none">○ Cefotaxime (IV)○ Ceftriaxone (IV)○ Cefuroxime axetil (oral)• Macrolides<ul style="list-style-type: none">○ Azithromycin (oral)○ Clarithromycin (oral, IV)• Fluoroquinolones<ul style="list-style-type: none">○ Ciprofloxacin (oral, IV)○ Levofloxacin (oral, IV)○ Moxifloxacin (oral, IV)○ Nalidixic acid (oral)○ Norfloxacin (oral)○ Ofloxacin (oral, IV)• Rifampicin (oral, IV)

	<p>Steroids (corticosteroids; systemic, local injections)</p> <ul style="list-style-type: none"> • Dexamethasone (local injection, IV) • Hydrocortisone (local injection, IV) • Methylprednisolone (local injection, IV) • Prednisolone (local injection, IV) <p>Non-steroidal anti-inflammatory drugs (NSAIDs)</p> <p>Hydroxychloroquine sulfate (Plaquenil, Quinoric; oral)</p>
Comparisons	<ul style="list-style-type: none"> • Any type of intervention compared to each other <ul style="list-style-type: none"> ○ If data are available consider: <ul style="list-style-type: none"> - 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, steroids or NSAIDs compared to no treatment / placebo
Outcomes	<p>Critical:</p> <ol style="list-style-type: none"> 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme arthritis) 3. Reduction of clinical symptoms related to Lyme arthritis 4. Relapse of symptoms related to Lyme arthritis <p>Important:</p> <ol style="list-style-type: none"> 5. Adverse events
Study design	<ul style="list-style-type: none"> • RCTs • Cohort studies (if no RCT evidence is found)

1 1.4 Clinical evidence

2 1.4.1 Included studies

3 Three RCTs were included in the review;^{29,164,166} these are summarised in Table 2 below.
 4 One study included children, young people and adults above the age of 8 years,¹⁶⁴ 1 study
 5 included young people and adults 13 years or older¹⁶⁶ and 1 study was in adults only.²⁹ The
 6 diagnosis of Lyme arthritis was based on recurrent or chronic inflammatory arthritis and a
 7 positive blood test *B. burgdorferi* titre or a history of other Lyme disease-related symptoms,
 8 such as an erythema migrans or facial palsy. Evidence from these studies is summarised in
 9 the clinical evidence summary below (Table 3).

10 See also the study selection flow chart in appendix C, study evidence tables in appendix D,
 11 forest plots in appendix E and GRADE tables in appendix F.

12 A search was conducted for randomised trials comparing the effectiveness of antibiotics
 13 compared to each other, versus steroids or non-steroidal anti-inflammatory drugs, versus
 14 hydroxychloroquine sulfate or versus placebo as treatment for people with arthritis-related
 15 Lyme disease.

16 One RCT¹⁶⁶ included an indirect intervention as people in the amoxicillin group had also
 17 received probenecid.

18 1.4.2 Excluded studies

19 See the excluded studies list in appendix I.

1 **1.4.3 Summary of clinical studies included in the evidence review**

2 **Table 2: Summary of studies in adults and young people included in the evidence**
3 **review**

Study	Intervention and comparison	Population	Outcomes	Comments
Caperton 1990 ²⁹	(n=40) Ceftriaxone. 2 g intravenously in a 30-minute infusion daily. Vitamin preparation added to prevent people from detecting their treatment group by appearance or taste of solution. Duration 14 days. Concurrent medication or care: Not reported (n=20) Placebo. Duration 14 days. Concurrent medication or care: Not reported	n=60 Diagnosis: chronic inflammatory arthritis, 2 reactive antibody titres to <i>B. burgdorferi</i> in a titre at 1:64 or greater within 6 months of enrolment including a positive test within 2 weeks of starting therapy	Reduction in symptoms	29 people had been treated with at least 1 course of oral antibiotic for 2 to 10 weeks before entering the study
Steere 1985 ¹⁶⁴	(n=20) Benzylpenicillin sodium or Penicillin G. 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Concurrent medication or care: other anti-inflammatory medications continued according to clinical indications (n=20) Placebo. 2 ml saline injected in each buttock weekly. Duration 3 weeks. Concurrent medication or care: other anti-inflammatory medications continued according to clinical indications	n=40 Diagnosis: living in an area endemic for Lyme disease; history of EM, meningitis, or Bell's palsy during the summer followed within 1 year by arthritis; or to have short recurrent attacks of oligoarticular arthritis not due to other known causes; onset of infection >1 year earlier; at least 1 actively inflamed joint	Cure	5 people in each group had previously received antibiotic therapy Most people received ancillary therapy (NSAIDs, hydroxychloroquine, intraarticular steroids) during treatment Serious indirectness: intramuscular route of administration
Steere 1994 ¹⁶⁶	(n=23) Amoxicillin. 500 mg plus probenecid 500 mg	n=40 Diagnosis: initial	Cure Symptom relapse	Serious indirectness: people in the amoxicillin group

Study	Intervention and comparison	Population	Outcomes	Comments
	<p>4 times per day. Duration 30 days. Concurrent medication or care: NSAIDs taken by people with marked joint inflammation, steroid infections were not allowed during antibiotic therapy</p> <p>(n=25) Doxycycline. 100 mg twice per day. Duration 30 days. Concurrent medication or care: NSAIDs taken by people with marked joint inflammation, steroid infections not allowed during antibiotic treatment</p>	<p>attack or intermittent episodes of arthritis in 1 or a few joints; at least 1 actively inflamed joint at the time of study entry; positive antibody response to <i>B. burgdorferi</i> determined by ELISA</p>	<p>Adverse events</p>	<p>also received probenecid</p> <p>5 people in the amoxicillin group and 3 in the doxycycline group had received prior treatment with oral antibiotics <30 days and intraarticular steroids</p>

1 See appendix D for full evidence tables.

2

1 **1.4.4 Quality assessment of clinical studies included in the evidence review**

2 **Table 3: Clinical evidence summary: doxycycline (PO) versus amoxicillin (PO) plus probenecid**

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amoxicillin plus probenecid	Risk difference with doxycycline (95% CI)
Cure (resolution of arthritis at 3 months)	38 (1 study)	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 1.01 (0.81 to 1.26)	889 per 1,000	9 more per 1,000 (from 169 fewer to 231 more)
Symptom relapse (subsequent complications at mean 3.3 years)	34 (1 study)	VERY LOW ^{1,2,3} due to risk of bias, indirectness, imprecision	RR 0.36 (0.08 to 1.59)	312 per 1,000	200 fewer per 1,000 (from 287 fewer to 184 more)
Adverse events (side effects during treatment)	40 (1 study)	VERY LOW ^{1,2} due to risk of bias, indirectness	OR 0.09 (0.02 to 0.47) ⁴	350 per 1,000	304 fewer per 1,000 (from 148 fewer to 339 fewer)

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
² Downgraded by 1 increment because of a serious intervention indirectness
³ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
⁴ The Peto odds ratio method was used because of a zero event rate in the intervention arm

3 **Table 4: Clinical evidence summary: ceftriaxone (IV) versus placebo**

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ceftriaxone (95% CI)
Reduction of symptoms (improvement at 1 month)	59 (1 study)	LOW ¹ due to risk of bias	RR 4.87 (1.26 to 18.86)	100 per 1,000	387 more per 1,000 (from 26 more to 1,000 more)

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 5: Clinical evidence summary: benzylpenicillin (IM) versus placebo

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with benzylpenicillin (95% CI)
Cure (complete resolution at mean 33 months)	40 (1 study)	LOW ¹ due to risk of bias	OR 10.63 (2.12 to 53.21) ²	0 per 1,000	350 more per 1,000 (from 141 more to 559 more)
¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias ² The Peto odds ratio method was used because of a zero event rate in the control arm					

See appendix F for full GRADE tables.

1 **1.5 Economic evidence**

2 **1.5.1 Included studies**

3 No relevant health economic studies were identified.

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

5 **1.5.2 Excluded studies**

6 No relevant health economic studies were identified and excluded.

7

1 **1.5.3 Unit costs**

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

3 **Table 6: 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	Phenoxy-methylpenicillin	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/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

4 *Abbreviations: IM: intramuscular; IV: intravenous.*

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,¹¹⁸ except cefotaxime from BNF, January 2017²⁰ and ceftriaxone from EMIT March 2017,³⁸ dosage from BNF and BNF for Children January 2017,^{20,21} exceptions below:

- (a) Source of dosage from RCT in adults with EM: Steere 1983,¹⁶⁵ dosage for Lyme disease not available from BNF or BNF for children.
- (b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989¹³⁰ and Pfister 1991,¹³¹ 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 >1month: 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 1985:¹⁶⁴ 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 2016⁴¹)
- 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).¹¹⁵ 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 2015/2016.⁴⁶

Table 7: 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 2015/2016⁴⁶

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 for example, 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 2009³⁰ 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 7, 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

Adults and young people:

- Very Low quality evidence from 1 RCT showed a clinical benefit of oral doxycycline over oral amoxicillin with oral probenecid in terms of symptom relapse and adverse events. Very Low quality evidence from 1 RCT did not find any difference between the two treatment arms for cure rates.
- Low quality evidence from 1 RCT showed a clinical benefit of intravenous ceftriaxone over placebo for the reduction of symptoms.
- Low quality evidence from 1 RCT showed a clinical benefit of intramuscular phenoxymethylpenicillin over placebo for cure.

Children:

- No evidence in children was identified.

1.7.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.8 Recommendations

G1. For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in Table 8.

G2. For children (under 12) diagnosed with Lyme disease, consider antibiotic treatment according to their symptoms as described in Table 9.

G3. Ask women whether they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation M1 on treatment in pregnancy).

G4. If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction.

Table 8: 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

Symptoms	Treatment	First alternative	Second alternative
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
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.

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Table 9: Antibiotic treatment for Lyme disease in children (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

Symptoms	Treatment	Alternative
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 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 1.8.1 Research recommendations

2 RR1. Can a core outcome set be developed for clinical trials in management of Lyme
3 disease?

4 RR2. What are the most clinically and cost-effective treatment options for different clinical
5 presentations of Lyme disease in the UK?

6 See also rationales in appendix J of evidence report D.

7 1.9 Rationale and impact

8 1.9.1 Why the committee made the recommendations

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

12 Lyme disease can cause inflammation affecting one or more joints.

13 The studies identified looked at antibiotic treatment in children, young people and adults.
14 One study found that a 30-day course of doxycycline resulted in fewer symptom relapses
15 and adverse events than 30 days of amoxicillin plus probenecid.

16 The committee agreed that longer courses of treatment are appropriate when treating
17 arthritis associated with Lyme disease because it is difficult for antibiotics to penetrate to the
18 synovium and synovial fluid.

19 Taking these factors into account, the committee decided that a 28-day course of
20 doxycycline 200 mg daily should be offered to adults and young people (aged 12 and over)
21 as initial treatment, with a 28-day course of amoxicillin recommended as an alternative
22 treatment. A 28-day course was recommended, as the committee was aware that antibiotics
23 are available in weekly packs. The committee also agreed that if oral doxycycline and
24 amoxicillin are contraindicated or unsuitable, 28 days of intravenous ceftriaxone should be
25 offered.

1 The committee agreed that the evidence supported similar treatment to adults for children
2 under 12, with the same duration of treatment but using appropriate antibiotics for children
3 and doses adjusted by weight.

4 **1.9.2 Impact of the recommendations on practice**

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

8 **1.10 The committee's discussion of the evidence**

9 **1.10.1 Interpreting the evidence**

10 **1.10.1.1 The outcomes that matter most**

11 The guideline committee considered quality of life, the resolution of symptoms associated
12 with arthritis, the reduction in symptoms related to arthritis and the reoccurrence of
13 symptoms related to arthritis to be critical outcomes for decision-making. Adverse events
14 were also considered to be important outcomes.

15 Resolution of symptoms, reduction in symptoms, symptom relapse and adverse events were
16 the only outcomes for which data were available. No evidence for quality of life was found.

17 **1.10.1.2 The quality of the evidence**

18 The evidence came from 3 RCTs comprising 140 people and was of Low to Very Low quality
19 due to risk of bias, imprecision and indirectness. There were particular concerns regarding
20 the lack of blinding, which could have had a confounding effect on subjective outcomes, such
21 as signs and symptoms that could not be measured by objective tests.

22 Many outcomes and the time point at which they were assessed were poorly defined in the
23 included studies. In particular, it was not clear whether cure or reduction of symptoms
24 referred to the resolution or improvement of the arthritic symptoms or of any Lyme disease
25 symptoms. Similar ambiguity existed for the outcomes of reoccurrence of symptoms. Studies
26 also varied in the outcomes they reported.

27 One of the studies included an indirect intervention. People in the amoxicillin group also
28 received 500 mg probenecid, which was used to increase the effective body concentration of
29 amoxicillin. Meta-analysis was not possible due to the different treatments regimens given in
30 the studies.

31 **1.10.1.3 Benefits and harms**

32 We identified 3 RCTs assessing the effectiveness of antibiotics in people with Lyme arthritis.
33 One study included children, young people and adults above the age of 8 years, 1 study
34 included young people and adults 13 years or older and 1 study was in adults only. The
35 diagnosis of Lyme arthritis was based on recurrent or chronic inflammatory arthritis and a
36 positive blood test *B. burgdorferi* titre or a history of other Lyme disease-related symptoms,
37 such as an erythema migrans or facial palsy.

38 The evidence showed that there was no difference in cure rates, but people had fewer
39 symptom relapses and adverse events when taking 100 mg of oral doxycycline twice daily for
40 30 days compared to 500mg of oral amoxicillin plus 500 mg oral probenecid 4 times per day
41 for 30 days. Therefore the committee determined that there was an overall clinical benefit of
42 doxycycline.

1 People who received a daily intravenous infusion of 2 g ceftriaxone for 14 days showed
2 better symptom improvement after 1 month than people who received placebo. Similarly, the
3 cure rate, defined as a complete resolution of symptoms, was considerably higher in people
4 who had received an intramuscular injection of 2.4 million IU (1.2 million IU in each buttock)
5 of benzylpenicillin or penicillin G every week for 3 weeks compared to people who had
6 received placebo. No person in the placebo group experienced a complete resolution of
7 symptoms. People in both treatment arms had continued to take anti-inflammatory
8 medications according to clinical indications during the trial.

9 The committee acknowledged that a 30-day course of doxycycline was more effective than a
10 combination of amoxicillin plus probenecid for reducing symptom relapse. People in the
11 doxycycline group also experienced fewer adverse events. The committee did not judge the
12 evidence alone to be strong enough upon which to base a recommendation, but considered
13 it in conjunction with current clinical practice and their own clinical experience and decided to
14 recommend 100 mg of oral doxycycline twice per day for 28 days due to available pack
15 sizes. In cases where doxycycline is contraindicated, 1 g of amoxicillin 3 times per day for
16 28-days should be given. The rationale for recommending 1 g amoxicillin 3 times per day,
17 which is higher than the current practice dosage of 500 mg 3 times per day, is due to the
18 included study using probenecid to increase the concentration of amoxicillin and the
19 evidence identified for the reviews on the management of erythema migrans and arthritis
20 related to Lyme disease.

21 **1.10.2 Cost effectiveness and resource use**

22 No relevant health economic evidence was identified. The unit costs of different
23 antimicrobials were presented to the committee. Both doxycycline and amoxicillin are low
24 cost generic antimicrobials (£6.09 and £10.16 respectively for adults).

25 The BNF recommends doxycycline, amoxicillin or cefuroxime axetil as the antibacterials of
26 choice for Lyme arthritis. The dose and duration of treatment for doxycycline the committee
27 recommended is the same as that listed in the BNF. The committee recommended a higher
28 dose of amoxicillin (1 g 3 times per day versus 500 mg 3 times per day in BNF). As noted
29 above, the rationale for this higher dose is because the included study used probenecid to
30 increase the concentration of amoxicillin; therefore, the committee decided to recommend 1
31 g amoxicillin 3 times per day as the preferred dose of amoxicillin. The committee considered
32 that the additional minimal cost of treatment for a higher dose of amoxicillin would be offset
33 by the improved quality of life as a result of a reduction in symptoms and associated costs in
34 the management of symptoms.

35 The BNF recommended cefuroxime axetil as one of their first choices for Lyme arthritis. The
36 committee did not consider that there was clinical evidence to support such a
37 recommendation. Furthermore, cefuroxime axetil is much more expensive than the other oral
38 antimicrobials (£141.76 for 500 mg 2 times per day for 28 days).

39 The committee considered that where both doxycycline and amoxicillin are contraindicated
40 intravenous ceftriaxone should be considered. The committee considered that the number of
41 people for whom the drugs would be contraindicated would be small. The unit cost of 2 g
42 once daily for 21 days is £21.63. The committee also considered the cost of intravenous
43 administration, which would include the cost of nurse time, clinic space and clerical time (if
44 administered in an outpatient setting), nurse travel time (if administered at home) and
45 disposables required for administration. These costs would likely be greater than the cost of
46 the antibiotics themselves.

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

1 The committee considered the adverse event profiles of different antimicrobials and whether
2 these may impact the costs of managing Lyme disease as well as their impact on the
3 patient's quality of life. Doxycycline adverse events, for example, include photosensitivity,
4 nausea and vomiting. In practice, if a person experiences any of these adverse events, these
5 would be managed by switching to another antimicrobial; therefore, the cost to the NHS
6 would be a consultation with a GP and additional antimicrobials. These costs are considered
7 to be low and would be offset by the cure and reduction of symptoms after successful
8 treatment of Lyme disease.

9 The committee agreed that this potential change in practice in terms of a higher dose of
10 amoxicillin would not result in a significant resource impact given the relatively small number
11 of people diagnosed with Lyme disease.

12 **1.10.3 Other factors the committee took into account**

13 The committee agreed that a longer course of treatment, for example 28 days, is justified, as
14 it is harder for antibiotics to penetrate to the synovium and synovial fluid than other body
15 compartments.

16 Although both intramuscular benzylpenicillin and intravenous ceftriaxone showed a clinical
17 benefit over placebo, the committee agreed to recommend intravenous ceftriaxone for
18 people with Lyme arthritis. Intramuscular administration is painful for the person. The
19 intravenous route of administration for benzylpenicillin is likely to be effective for the
20 treatment of Lyme-associated arthritis but requires multiple daily doses as opposed to
21 intravenous ceftriaxone, which can be given once daily. Treatment with intravenous
22 benzylpenicillin requires inpatient care for the duration of treatment; the committee therefore
23 recommended ceftriaxone.

24 No evidence was found was treatment of children. Recommendations for children are based
25 on those for adults with adjustment for current licensing. The committee was aware that was
26 aware that specialists do offer doxycycline in children aged 9 years and above as a result of
27 indirect evidence from the United States and Scandinavia despite no licence or BNFC dose.
28 There is also increasing indirect evidence from use in other conditions in the United States
29 and Canada that doxycycline does not cause teeth staining when used for short course (less
30 than 4 weeks) in children aged 2 years and older. UK specialist clinicians may choose to use
31 doxycycline as second line where a CSF-penetrating oral antibiotic is required although the
32 lack of direct evidence, lack of licence and lack of BNFC dose regimen has so far limited UK
33 use in children aged 8 and under. Where used, in the United States and Canada, 1 dose
34 regimen of doxycycline for children under 45 kilograms is: 5 milligram/kilogram in 2 divided
35 doses on day 1 followed by 2.5 milligram/kilogram daily in 1 or 2 divided doses with a
36 maximum for severe infections, up to 5 milligram/kilogram daily. The guideline includes a
37 recommendation that care of people under 18 years be discussed with a specialist and it
38 would be expected that a person less than 18 years with mono- or poly-arthritis would be
39 under the care of a specialist.

40 The committee made a research recommendation for the development of core outcome set
41 for studies of Lyme disease treatment and a research recommendation for antibiotic
42 management of Lyme disease. The details of the research recommendations are in appendix
43 J of evidence report D.

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Appendices

Appendix A: Review protocols

Table 10: Review protocol for the management of Lyme arthritis

Question number: 4.4

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for people with arthritis 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 arthritis related to Lyme disease. This review is only concerned with the treatment of Lyme disease as the underlying cause of arthritic symptoms and not with the treatment or management of arthritic symptoms directly.
Eligibility criteria – population / disease / condition / issue / domain	People with symptoms consistent with arthritis related to Lyme disease
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	<ul style="list-style-type: none"> • Antimicrobials, including but not limited to: <ul style="list-style-type: none"> ○ Penicillins <ul style="list-style-type: none"> - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) <ul style="list-style-type: none"> -Including Augmentin (Amoxicillin + clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines <ul style="list-style-type: none"> ○ Doxycycline (oral) ○ Minocycline (oral) • Cephalosporins <ul style="list-style-type: none"> ○ Cefotaxime (IV) ○ Ceftriaxone (IV) ○ Cefuroxime axetil (oral) • Macrolides <ul style="list-style-type: none"> ○ Azithromycin (oral) ○ Clarithromycin (oral, IV) • Fluoroquinolones <ul style="list-style-type: none"> ○ Ciprofloxacin (oral, IV) ○ Levofloxacin (oral, IV) • Moxifloxacin (oral, IV)

Field	Content
	<ul style="list-style-type: none"> ○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) ● Rifampicin (oral, IV) ● Steroids (corticosteroids; systemic, local injections) <ul style="list-style-type: none"> ○ Dexamethasone (local injection, IV) ○ Hydrocortisone (local injection, IV) ○ Methylprednisolone (local injection, IV) ○ Prednisolone (local injection, IV) ● Non-steroidal anti-inflammatory drugs (NSAIDs) ● Hydroxychloroquine sulfate (Plaquenil, Quinoric; oral)
Eligibility criteria – comparator(s) / control or reference (gold) standard	<ul style="list-style-type: none"> ● Any type of intervention compared to each other <ul style="list-style-type: none"> ○ If data are available consider: <ul style="list-style-type: none"> - 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, steroids or NSAIDs compared to no treatment/placebo
Outcomes and prioritisation	<p>Critical:</p> <ol style="list-style-type: none"> 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme arthritis) 3. Reduction of clinical symptoms related to Lyme arthritis 4. Relapse of symptoms related to Lyme arthritis <p>Important:</p> <ol style="list-style-type: none"> 5. Adverse events
Eligibility criteria – study design	<p>RCTs</p> <p>Cohort studies (if no RCT evidence is found)</p>
Other inclusion exclusion criteria	<p>Date limits for search: none</p> <p>Language: English only</p> <p>Setting: all settings in which NHS care is provided or commissioned</p> <p>The following interventions will not be considered for inclusion:</p> <ul style="list-style-type: none"> ● Metronidazole ● Trimethoprim
Proposed sensitivity / subgroup analysis, or meta-regression	<p>The following groups will be considered separately if data are available (strata):</p> <ul style="list-style-type: none"> ● 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 <p>Subgroups (to be investigated if heterogeneity is identified):</p> <ul style="list-style-type: none"> ● Pregnant women ● People who are immunocompromised ● People in whom a previous course of antimicrobial treatment, steroid or NSAID treatment has failed
Selection process – duplicate screening / selection / analysis	<p>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.</p>
Data management (software)	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).</p>

Field	Content
	<p>GRADEpro will be used to assess the quality of evidence for each outcome</p> <p>Bibliographies, citations, study sifting and reference management will be managed using EndNote.</p> <p>Data extractions will be performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)</p>
Information sources – databases and dates	<p>Clinical searches Medline, Embase, The Cochrane Library all years</p> <p>Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years</p>
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	<p>Standard study checklists were used to critically appraise individual studies. For details, please see section 6.2 of Developing NICE guidelines: the manual</p> <p>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/</p>
Criteria for quantitative synthesis	<p>For details, please see section 6.4 of Developing NICE guidelines: the manual.</p> <p>Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)</p> <p>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</p> <p>If heterogeneity is found, the influence of subgroups will be examined</p>
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.

Field	Content
	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 11: 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	<ul style="list-style-type: none"> • 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	<p>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.</p> <p>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).¹¹⁶</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • 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. <p>Where there is discretion</p> <p>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</p>

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 selectively exclude the remaining studies. All studies excluded on the basis of 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 from 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 12: 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.	(granulocytic 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 bissetii or b valaisiana or b microti).ti,ab.
10.	(granulocytic 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.	(granulocytic 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

1 B.2 Health Economics literature search strategy

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

8 **Table 13: 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

9 **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.	(granulocytic 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 bissetii or b valaisiana or b microti).ti,ab.
10.	(granulocytic 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 bissetii or b valaisiana or b microti)) IN NHSEED, HTA
#9.	((granulocytic anaplasmosis or babesia or babesiosis)) IN NHSEED, HTA
#10.	MeSH DESCRIPTOR Lyme Disease EXPLODE ALL TREES IN NHSEED,HTA

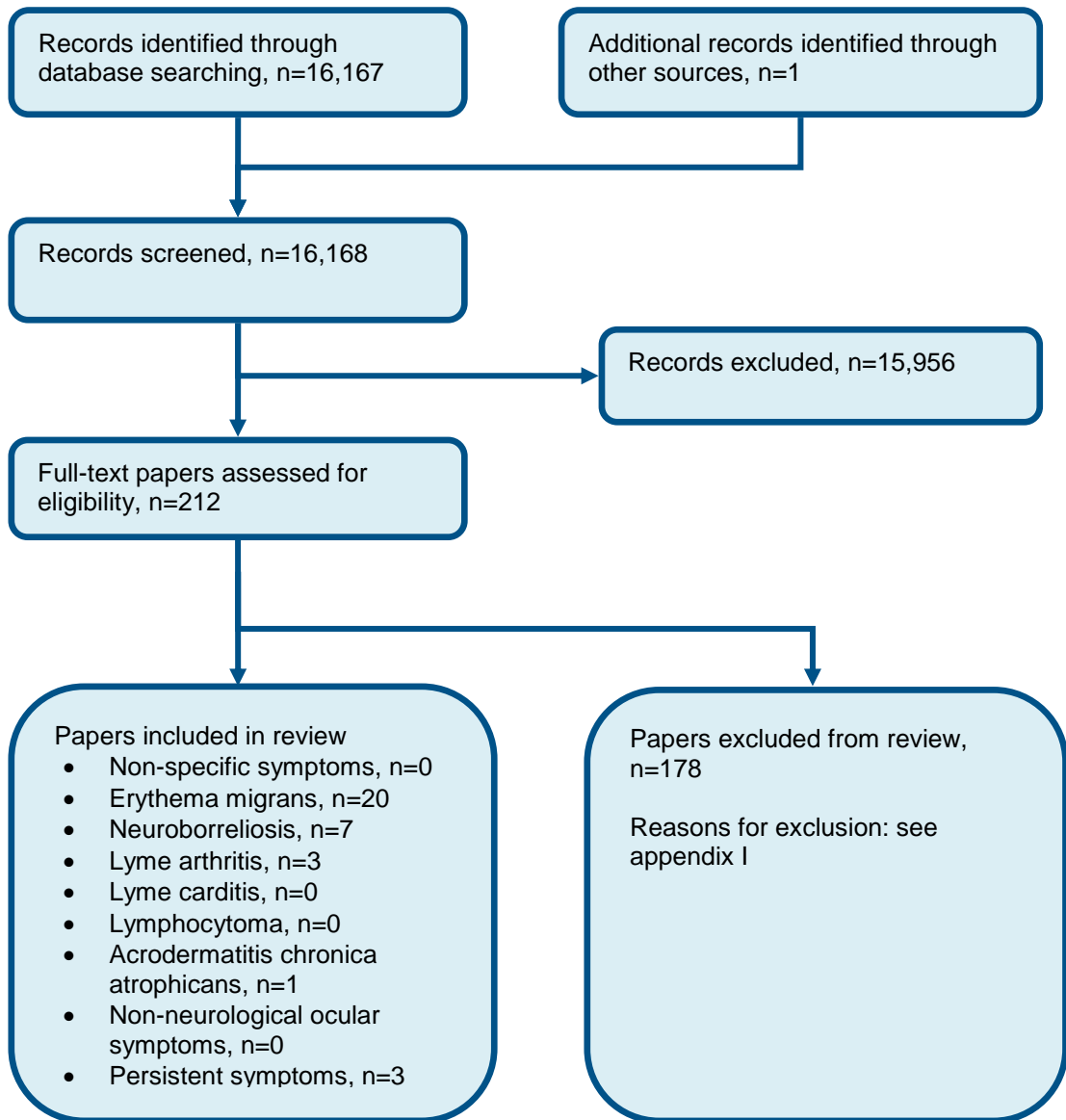
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
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2

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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



2

Appendix D: Clinical evidence tables

Study	Caperton 1990 ²⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	first line
Duration of study	
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults, chronic inflammatory arthritis, 2 reactive antibody titres to <i>B. burgdorferi</i> in a titre at 1:64 or greater within 6 months of enrolment including a positive test within 2 weeks of starting therapy
Exclusion criteria	Not reported
Recruitment or selection of patients	Not reported
Age, gender and family origin	Age - Mean (SD): Ceftriaxone group: 46.7 years (13.9); placebo group: 42.7 years (13.7). Gender (M:F): 22:37. Family origin: Not reported
Further population details	1. Immunosuppression: Not applicable 2. Pregnancy: Not applicable 3. Previous treatment failure: Not applicable
Indirectness of population	Very serious indirectness: Rheumatoid arthritis, psoriatic arthritis, vasculitis (with arthritis) and atypical arthritis with a <i>B. burgdorferi</i> titre; most people had been treated with antibiotics before
Interventions	(n=40) Intervention 1: Antibiotics - Ceftriaxone. 2 g intravenously in a 30-minute infusion daily. Vitamin preparation added to prevent people from detecting their treatment group by appearance or taste of solution. Duration 14 days. Concurrent medication or care: Not reported (n=20) Intervention 2: Placebo. Placebo. Duration 14 days. Concurrent medication or care: Not reported
Funding	Study funded by industry (Grant from Hoffmann-LaRoche Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PLACEBO	

Study	Caperton 1990 ²⁹
Protocol outcome 1: Reduction of symptoms - Actual outcome: Improvement at 1 month; Group 1: 19/39, Group 2: 2/20 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Symptom relapse; Adverse events

Study	Steere 1985 ¹⁶⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in USA; Setting: Lyme disease clinic, Yale University, USA
Line of therapy	Unclear
Duration of study	Intervention + follow up: 3 weeks + 3-12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	living in an area endemic for Lyme disease; history of EM, meningitis, or Bell's palsy during the summer followed within 1 year by arthritis; or to have short recurrent attacks of oligoarticular arthritis not due to other known causes; onset of infection >1 year earlier; at least 1 actively inflamed joint
Exclusion criteria	history of penicillin allergy or atopy; children younger than 8 years
Recruitment/selection of patients	consecutive people meeting the inclusion criteria during the recruitment period
Age, gender and family origin	Age - Mean (SD): penicillin group 30 (17); placebo group 31 (15) years. Gender (M:F): 28/12. Family origin: not reported
Further population details	1. Immunosuppression: Not stated or unclear 2. Pregnancy: Not stated or unclear 3. Previous treatment failure: Not stated or unclear
Indirectness of population	No indirectness: NA
Interventions	(n=20) Intervention 1: Antibiotics - Benzylpenicillin sodium or Penicillin G. 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Concurrent medication or care: other anti-inflammatory medications continued according to clinical indications

Study	Steere 1985 ¹⁶⁴
	(n=20) Intervention 2: Placebo. 2 ml saline injected in each buttock weekly. Duration 3 weeks. Concurrent medication/care: other anti-inflammatory medications continued according to clinical indications
Funding	Academic or government funding (grants from the National Institutes of Health and the Arthritis Foundation and its Connecticut Chapter)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BENZYL PENICILLIN SODIUM / PENICILLIN G versus PLACEBO	
Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome for Adults: complete resolution of arthritis at mean 33 months ; Group 1: 7/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: more people in the placebo group used intraarticular steroids; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Symptom relapse; Adverse events

Study	Steere 1994 ¹⁶⁶
Study type	RCT (randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in USA; Setting: 3 study sites (private practices or Lyme disease clinics)
Line of therapy	first line
Duration of study	Intervention + follow up: 30 days + up to 12 months
Method of assessment of guideline condition	Partially adequate method of assessment or diagnosis: arthritis, inflamed joint and positive response to <i>B. burgdorferi</i> by ELISA
Stratum	Adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	13 years or older; initial attack or intermittent episodes of arthritis in 1 or a few joints; at least 1 actively inflamed joint at the time of study entry; positive antibody response to <i>B. burgdorferi</i> determined by ELISA
Exclusion criteria	12 years or younger; pregnant or nursing; active neuroborreliosis; allergic to study medications; already failed to respond to a 30-day course of oral doxycycline or amoxicillin for Lyme arthritis
Recruitment/selection of patients	unclear
Age, gender and family origin	Age - Median (range): doxycycline group 40 (13-72); amoxicillin + probenecid group 45.5 (14-67) years.

Study	Steere 1994 ¹⁶⁶
	Gender (M:F): 28/12. Family origin: not reported
Further population details	1. Immunosuppression: Not stated or unclear 2. Pregnancy: No pregnancy 3. Previous treatment failure: No previous treatment
Indirectness of population	No indirectness: NA
Interventions	(n=23) Intervention 1: Antibiotics - Amoxicillin. 500 mg + probenecid 500 mg 4 times per day. Duration 30 days. Concurrent medication/care: NSAIDs taken by people with marked joint inflammation, steroid infections were not allowed during antibiotic therapy (n=25) Intervention 2: Antibiotics - Doxycycline. 100 mg twice per day. Duration 30 days. Concurrent medication/care: NSAIDs taken by people with marked joint inflammation, steroid infections not allowed during antibiotic treatment
Funding	Academic or government funding (supported by NIH grants and by the Eshe fund)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus DOXYCYCLINE	
<p>Protocol outcome 1: Cure (resolution of symptoms)</p> <p>- Actual outcome: resolution of arthritis at 3 months; Group 1: 16/18, Group 2: 18/20</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: 23 originally randomised, 3 excluded from analysis, 2 switched to doxycycline due to drug eruption; Group 2 Number missing: 0, Reason: 25 originally randomised, 5 excluded from analysis</p>	
<p>Protocol outcome 2: Symptom relapse</p> <p>- Actual outcome: subsequent complications at mean 3.3 years; Group 1: 5/16, Group 2: 2/18</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: 23 originally randomised, 3 excluded from analysis, 2 switched to doxycycline due to drug eruption; Group 2 Number missing: 0, Reason: 25 originally randomised, 5 excluded from analysis</p>	
<p>Protocol outcome 3: Adverse events</p> <p>- Actual outcome: side effects at during antibiotic treatment ; Group 1: 7/20, Group 2: 0/20</p> <p>Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 3, Reason: 23 originally randomised, 3 excluded from analysis; Group 2 Number missing: 5, Reason: 25 originally randomised, 5 excluded from analysis</p>	

Study	Steere 1994¹⁶⁶
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms

1 Appendix E: Forest plots

2 E.1 Doxycycline (PO) versus amoxicillin (PO) plus probenecid

3 E.1.1 Lyme arthritis

Figure 2: Cure (at 3 months)

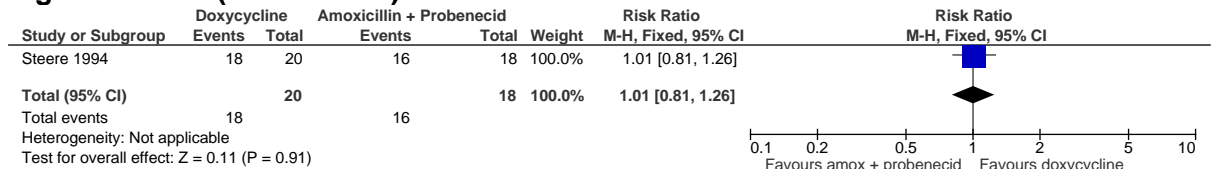
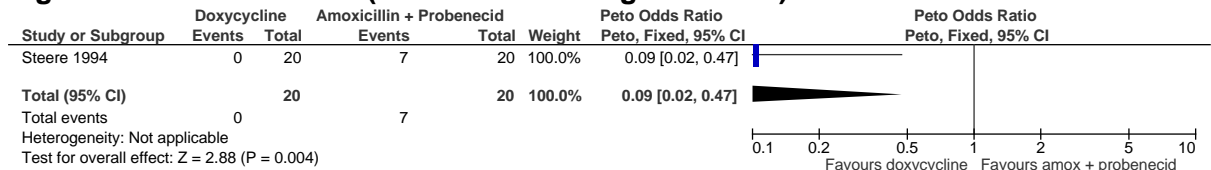


Figure 3: Symptom relapse (subsequent complications at a mean of 3.3 years)



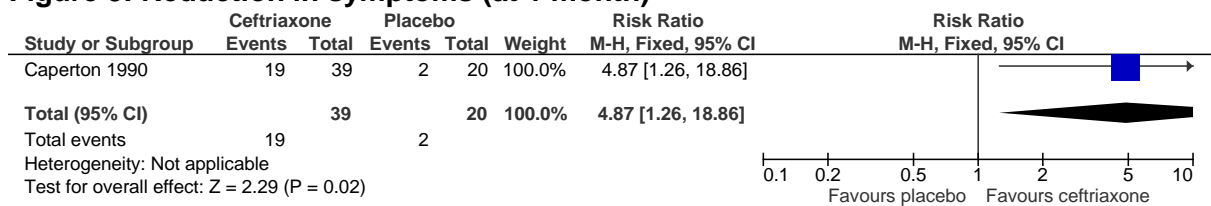
Figure 4: Adverse events (side effects during treatment)



4 E.2 Ceftriaxone (IV) versus placebo

5 E.2.1 Lyme arthritis

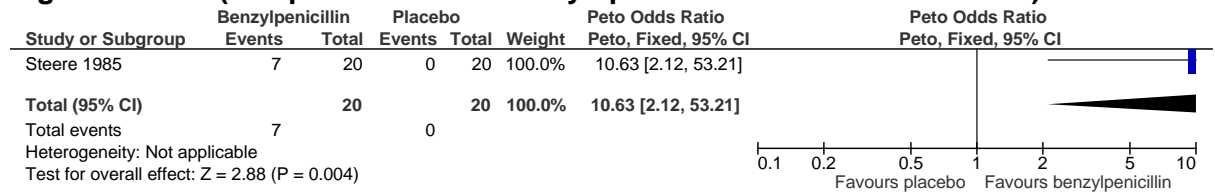
Figure 5: Reduction in symptoms (at 1 month)



1 E.3 Benzylpenicillin (IM) versus placebo

2 E.3.1 Lyme arthritis

Figure 6: Cure (complete resolution of symptoms at a mean of 33 months)



3

Appendix F: GRADE tables

Table 14: Clinical evidence profile: doxycycline (PO) versus amoxicillin (PO) plus probenecid

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Amoxicillin plus probenecid	Relative (95% CI)	Absolute		
Cure (resolution of arthritis at 3 months)												
1	randomised trials	very serious ¹	no serious inconsistency	serious ²	serious ³	none	18/20 (90%)	16/18 (88.9%)	RR 1.01 (0.81 to 1.26)	9 more per 1,000 (from 169 fewer to 231 more)	⊕○○○ VERY LOW	CRITICAL
Symptom relapse (subsequent complications at mean 3.3 years)												
1	randomised trials	very serious ¹	no serious inconsistency	serious ²	very serious ³	none	2/18 (11.1%)	5/16 (31.3%)	RR 0.36 (0.08 to 1.59)	200 fewer per 1,000 (from 287 fewer to 184 more)	⊕○○○ VERY LOW	CRITICAL
Adverse events (side effects during treatment)												
1	randomised trials	very serious ¹	no serious inconsistency	serious ²	no serious imprecision	none	0/20 (0%)	7/20 (35%)	OR 0.09 (0.02 to 0.47) ⁴	304 fewer per 1,000 (from 148 fewer to 339 fewer)	⊕○○○ VERY LOW	IMPORTANT

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

² Downgraded by 1 increment because of a serious intervention indirectness

³ Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

⁴ The Peto odds ratio method was used due to a zero event rate in the intervention arm

Table 15: Clinical evidence profile: ceftriaxone (IV) versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Placebo	Relative (95% CI)	Absolute		
Reduction of symptoms (improvement at 1 month)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/39 (48.7%)	2/20 (10%)	RR 4.87 (1.26 to 18.86)	387 more per 1,000 (from 26 more to 1,000 more)	⊕⊕○○ LOW	CRITICAL

¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Table 16: Clinical evidence profile: benzylpenicillin (IM) versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzylpenicillin	Placebo	Relative (95% CI)	Absolute		
Cure (complete resolution at mean 33 months)												
1	randomised trials	very serious ¹	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/20 (35%)	0/20 (0%)	OR 10.63 (2.12 to 53.21) ²	350 more per 1,000 (from 141 more to 559 more)	⊕⊕○○ LOW	CRITICAL

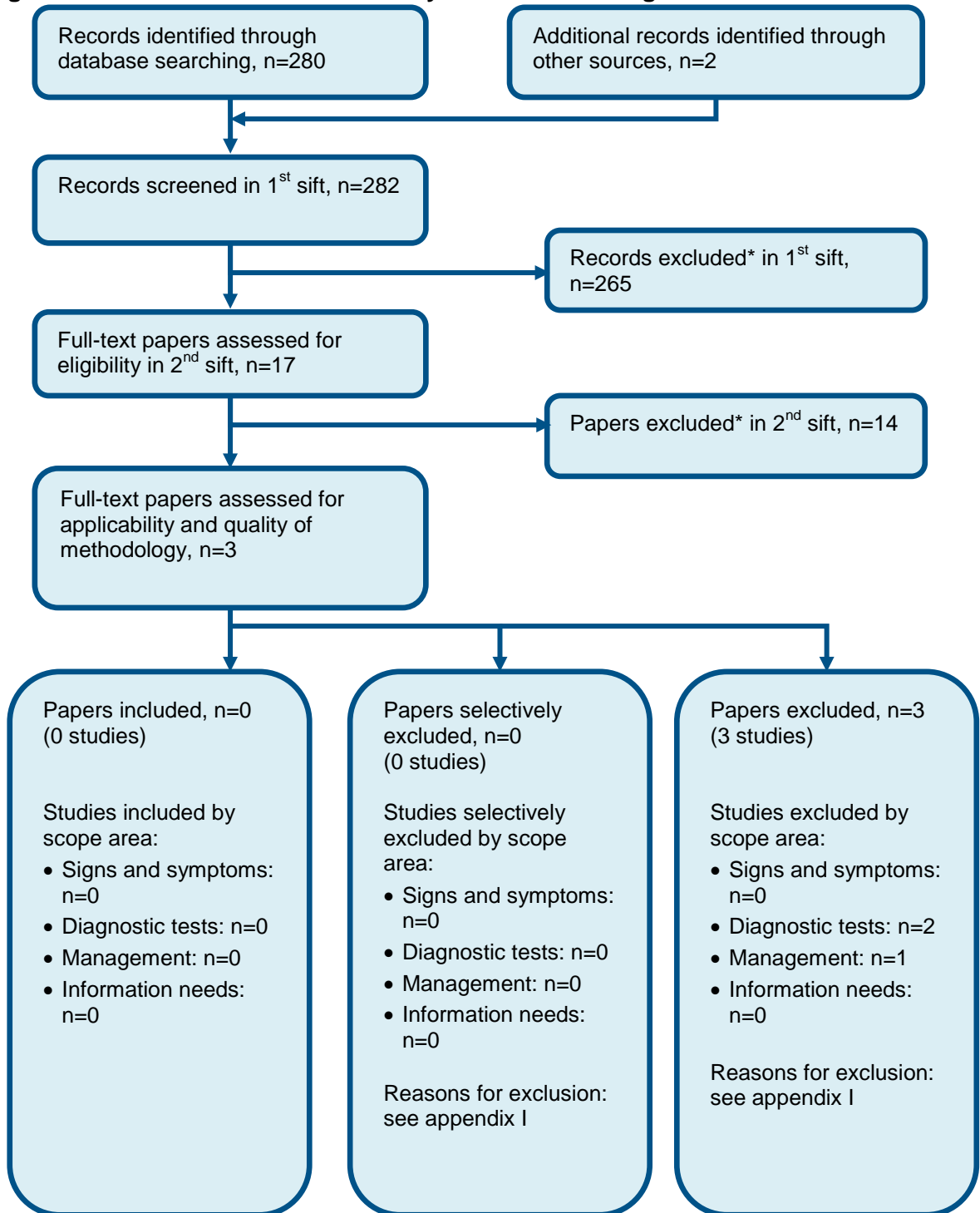
¹ Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

² The Peto odds ratio method was used due to a zero event rate in one of the treatment arms

1
2

Appendix G: Health economic evidence selection

Figure 7: Flow chart of economic study selection for the guideline



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

3

1 **Appendix H: Health economic evidence**
2 **tables**

3 None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 17: 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 ³¹	Excluded due to an incorrect outcome
Choo-Kang 2010 ³²	Excluded due to an incorrect study design
Christian 1992 ³³	Excluded due to an incorrect study design
Cimmino 1992 ³⁵	Excluded due to an incorrect study design
Cimmino 1997 ³⁴	Excluded due to an incorrect study design
Cimperman 1999 ³⁶	Excluded due to an incorrect study design
Coblyn 1981 ³⁷	Excluded due to an incorrect study design
Committee on Infectious Diseases 1991 ³⁹	Excluded due to an incorrect study design
Cuisset 2008 ⁴⁰	Excluded due to an incorrect study design
Dattwyler 1996 ⁴²	Excluded due to an incorrect comparison
Dattwyler 1987 ⁴³	Excluded due to an incorrect study design
Dattwyler 1988 ⁴⁴	Excluded due to an incorrect population
Dattwyler 2005 ⁴⁵	Excluded due to an incorrect population
Dersch 2015 ⁴⁷	Excluded due to an incorrect study design

Reference	Reason for exclusion
Dersch 2016 ⁵⁰	Excluded due to an incorrect study design
Dersch 2014 ⁴⁸	Excluded due to an incorrect study design
Dersch 2017 ⁴⁹	Not available
Dhoot 2011 ⁵¹	Excluded due to an incorrect study design
Dinser 2005 ⁵²	Excluded due to an incorrect study design
Dotevall 1988 ⁵³	Excluded due to an incorrect study design
Eliassen 2017 ⁵⁴	Excluded due to an incorrect study design
Eliassen 2017 ⁵⁵	Excluded due to an incorrect intervention
Eppes 2003 ⁵⁶	Excluded due to an incorrect study design
Esposito 2013 ⁵⁷	Excluded due to an incorrect study design
Fallon 1999 ⁵⁹	Excluded due to an incorrect intervention
Fallon 2008 ⁵⁸	Excluded due to an incorrect outcome
Galev 2005 ⁶⁰	Excluded due to an incorrect study design
Garkowski 2017 ⁶¹	Systematic review
Gasser 1996 ⁶³	Excluded due to an incorrect not available
Gasser 1995 ⁶⁴	Excluded due to an incorrect study design
Gasser 1995 ⁶²	Excluded due to an incorrect study design
Gerber 1996 ⁶⁵	Excluded due to an incorrect intervention
Gillies 2015 ⁶⁶	Excluded due to an incorrect study design
Goodwin 1990 ⁶⁷	Excluded due to an incorrect study design
Hansen 1992 ⁶⁸	Excluded due to an incorrect intervention
Hassler 1990 ⁶⁹	Excluded due to an incorrect population
Horton 2017 ⁷⁰	Conference abstract
Hu 2001 ⁷¹	Excluded due to an incorrect study design
Inboriboon 2010 ⁷²	Excluded due to an incorrect study design
Kaplan 2003 ⁷³	Excluded due to an incorrect population
Karkkonen 2001 ⁷⁴	Excluded due to an incorrect study design
Karlsson 1996 ⁷⁵	Excluded due to an incorrect outcome
Kersten 1995 ⁷⁶	Excluded due to an incorrect study design
Kilic Muftuoglu 2016 ⁷⁷	Excluded due to an incorrect study design
Klempner 2013 ⁷⁹	Excluded due to an incorrect study design
Korenberg 1996 ⁸⁰	Excluded due to an incorrect intervention
Kowalski 2010 ⁸²	Excluded due to an incorrect outcome
Kowalski 2011 ⁸¹	Excluded due to an incorrect study design
Krbkova 1996 ⁸³	Excluded due to an incorrect comparison
Kuhn 2012 ⁸⁴	Excluded due to an incorrect study design
Laasila 2003 ⁸⁵	Excluded due to an incorrect population
Lantos 2013 ⁸⁶	Excluded due to an incorrect study design
Lauhio 1994 ⁸⁷	Excluded due to an incorrect population
Lauhio 1991 ⁸⁸	Excluded due to an incorrect population
Lempner 2002 ⁷⁸	Excluded due to an incorrect study design
Liegner 1992 ⁸⁹	Excluded due to an incorrect study design
Lipsker 2002 ⁹⁰	Excluded due to an incorrect study design
Ljostad 2008 ⁹¹	Study abstract
Loewen 1999 ⁹²	Excluded due to an incorrect study design

Reference	Reason for exclusion
Loewen 2000 ⁹³	Excluded due to an incorrect study design
Luft 1988 ⁹⁵	Excluded due to an incorrect outcome
Luft 1989 ⁹⁴	Excluded due to an incorrect population
Maraspin 1995 ¹⁰¹	Excluded due to an incorrect study design
Maraspin 1996 ⁹⁶	Excluded due to an incorrect study design
Maraspin 1999 ⁹⁷	Excluded due to an incorrect study design
Maraspin 2002 ⁹⁸	Excluded due to an incorrect study design
Maraspin 1999 ⁹⁹	Excluded due to an incorrect study design
Maraspin 2002 ¹⁰⁰	Excluded due to an incorrect population
Marks 2016 ¹⁰²	Excluded due to an incorrect study design
McGill 1965 ¹⁰³	Excluded due to an incorrect population
Meyerhoff 2002 ¹⁰⁴	Excluded due to an incorrect study design
Meyerhoff 2016 ¹⁰⁵	Excluded due to an incorrect study design
Millner 1996 ¹⁰⁶	Excluded due to an incorrect outcome
Millner 1996 ¹⁰⁷	Excluded due to an incorrect outcome
Morales 2000 ¹⁰⁸	Excluded due to an incorrect study design
Muellegger 1995 ¹¹⁰	Excluded due to an incorrect study design
Muellegger 1996 ¹⁰⁹	Excluded due to an incorrect comparison
Mullegger 1991 ¹¹¹	Excluded due to an incorrect outcome
Nadelman 1993 ¹¹³	Excluded due to an incorrect study design
Nadelman 2001 ¹¹²	Excluded due to an incorrect population
Naglo 1989 ¹¹⁴	Excluded due to an incorrect study design
Neumann 1987 ¹¹⁷	Excluded due to an incorrect study design
Nimmrich 2014 ¹¹⁹	Excluded due to an incorrect study design
Nowakowski 2000 ¹²⁰	Excluded due to an incorrect study design
Nowakowski 1995 ¹²¹	Excluded due to an incorrect study design
Ogrinc 2006 ¹²²	Excluded due to an incorrect population
Oksi 1999 ¹²³	Excluded due to an incorrect study design
Oksi 2007 ¹²⁴	Excluded due to an incorrect population
Oksi 1998 ¹²⁵	Excluded due to an incorrect population
Peltomaa 1998 ¹²⁶	Excluded due to an incorrect comparison
Pena 1999 ¹²⁷	Excluded due to an incorrect study design
Perronne 2015 ¹²⁸	Not available
Pfister 1988 ¹²⁹	Excluded due to an incorrect outcome
Pirila 1951 ¹³²	Excluded due to an incorrect study design
Plorer 1993 ¹³³	Excluded due to an incorrect study design
Plotkin 1991 ¹³⁴	Excluded due to an incorrect study design
Puchalska 1996 ¹³⁵	Excluded due to an incorrect study design
Puri 2015 ¹³⁶	Excluded due to an incorrect comparison
Puri 2015 ¹³⁷	Excluded due to an incorrect study design
Rebman 2015 ¹³⁸	Excluded due to an incorrect study design
Renaud 2004 ¹³⁹	Excluded due to an incorrect study design
Rohacova 1996 ¹⁴⁰	Excluded due to an incorrect comparison
Rose 1994 ¹⁴¹	Excluded due to an incorrect study design
Rose 1996 ¹⁴²	Excluded due to an incorrect intervention

Reference	Reason for exclusion
Rubin 1992 ¹⁴³	Excluded due to an incorrect study design
Salazar 2005 ¹⁴⁴	Excluded due to an incorrect intervention
Salazar 1993 ¹⁴⁵	Excluded due to an incorrect study design
Sanchez 2016 ¹⁴⁶	Excluded due to an incorrect study design
Sandstrom 1989 ¹⁴⁷	Excluded due to an incorrect study design
Schmidt 1995 ¹⁴⁸	Excluded due to an incorrect study design
Selby 2008 ¹⁴⁹	Excluded due to an incorrect study design
Shadick 1994 ¹⁵⁰	Excluded due to an incorrect study design
Shadick 1999 ¹⁵¹	Excluded due to an incorrect study design
Shemenski 2016 ¹⁵²	Excluded due to an incorrect study design
Shoemaker 2006 ¹⁵³	Excluded due to an incorrect intervention
Sjowall 2012 ¹⁵⁵	Excluded due to an incorrect intervention
Sjowall 2011 ¹⁵⁴	Excluded due to an incorrect study design
Skogman 2003 ¹⁵⁷	Excluded due to an incorrect intervention
Skogman 2008 ¹⁵⁶	Excluded due to an incorrect study design
Skoldenberg 1988 ¹⁵⁸	Excluded due to an incorrect study design
Smith 2002 ¹⁵⁹	Excluded due to an incorrect study design
Solomon 1998 ¹⁶⁰	Excluded due to an incorrect intervention
Spathling 1992 ¹⁶¹	Article not in English
Stanek 1999 ¹⁶²	Excluded due to an incorrect study design
Steere 1980 ¹⁶⁷	Excluded due to an incorrect study design
Steere 1983 ¹⁶⁸	Excluded due to an incorrect study design
Steere 1987 ¹⁶³	Excluded due to an incorrect study design
Steurer 2016 ¹⁶⁹	Article not in English
Stricker 2011 ¹⁷⁰	Excluded due to an incorrect study design
Stricker 2010 ¹⁷¹	Excluded due to an incorrect study design
Strle 1996 ¹⁷²	Excluded due to an incorrect outcome
Strle 1996 ¹⁷³	Excluded due to an incorrect outcome
Strle 1992 ¹⁷⁴	Excluded due to an incorrect study design
Strle 1993 ¹⁷⁵	Excluded due to an incorrect outcome
Stupica 2015 ¹⁷⁷	Excluded due to an incorrect comparison
Stupica 2011 ¹⁷⁶	Excluded due to an incorrect comparison
Suarez-Magdalena 2017 ¹⁷⁸	Not available
Thompson 2012 ¹⁷⁹	Excluded due to an incorrect study design
Thorstrand 2002 ¹⁸⁰	Excluded due to an incorrect study design
Thyresson 1949 ¹⁸¹	Excluded due to an incorrect study design
Torbahn 2016 ¹⁸²	Excluded due to an incorrect study design
Tory 2010 ¹⁸³	Excluded due to an incorrect comparison
Tseng 2017 ¹⁸⁴	Excluded due to an incorrect outcome
Valesova 1996 ¹⁸⁵	Excluded due to an incorrect comparison
Vazquez 2003 ¹⁸⁷	Excluded due to an incorrect study design
Vazquez-Lopez 2016 ¹⁸⁶	Excluded due to an incorrect study design
Wahlberg 1994 ¹⁸⁸	Excluded due to an incorrect intervention
Weber 1988 ¹⁹⁰	Excluded due to an incorrect study design
Weber 1987 ¹⁸⁹	Excluded due to an incorrect population

Reference	Reason for exclusion
Weissenbacher 2005 ¹⁹¹	Excluded due to an incorrect intervention
White 2013 ¹⁹²	Excluded due to an incorrect study design
Zochling 1996 ¹⁹³	Excluded due to an incorrect study design

1 I.2 Excluded health economic studies

2 **Table 18: Studies excluded from the health economic review**

Reference	Reason for exclusion
None	None

3