National Institute for Health and Care Excellence

Draft for Consultation

Lyme disease: diagnosis and management

[F] Evidence review for the management of neuroborreliosis

NICE guideline

Evidence review

September 2017

Draft for Consultation

This evidence review was developed by the National Guideline Centre

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1 Management (Neuroborreliosis)

1.1 Review question: What is the most clinically and cost-effective treatment for people with symptoms consistent with neuroborreliosis?

1.2 Introduction

Lyme neuroborreliosis refers to Lyme disease infection of the nervous system, which includes the nerves, spinal cord and brain. There are a number of different presentations of neuroborreliosis including facial nerve palsy (weakness), meningitis and painful radiculopathy (inflammation of a nerve root).

Neuroborreliosis can lead to significant ongoing symptoms. Prompt, effective treatment is therefore important. Current practice depends on the type of neuroborreliosis diagnosed with a number of different treatment regimens ranging from a 14–21 day course of oral doxycycline for facial nerve palsy to 14–28 days of intravenous ceftriaxone for more complex disease. This evidence report includes the evidence reviewed to make recommendations in this area and the committee discussions.

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 clinical presentations consistent with neuroborreliosis, such as:
	• peripheral nervous system
	  ○ radiculopathy
	  ○ mononeuritis multiplex
	  ○ peripheral neuropathy or polyneuropathy
	  ○ myopathy (for example, myositis)
	• central nervous system
	  ○ white matter lesions
	  ○ cranial nerve lesions including facial nerve (VII) palsy
	  ○ autonomic nerve dysfunction
	  ○ meningitis
	  ○ encephalitis
	  ○ seizures
	  ○ optic neuritis
	  ○ transverse myelitis
	  ○ movement disorders (for example, chorea, ataxia)
	• psychiatric
	  ○ psychosis
	  ○ depression
	  ○ cognitive decline including dementia

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)
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 neuroborreliosis) 3. Reduction of clinical symptoms related to neuroborreliosis 4. Relapse of neuroborreliosis symptoms **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

1.4 Clinical evidence

1.4.1 Included studies

Six studies (7 papers) were included in the review;[73,76,82,95,96,135,136] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

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

A search was conducted for randomised controlled trials (RCTs) comparing the effectiveness of antibiotics versus each other or placebo as treatment for people with symptoms consistent

with neuroborreliosis. In the absence of sufficient evidence from RCTs, a search was conducted for observational studies.

Five RCTs were included in the review. All 5 RCTs were in adults. One retrospective cohort study comparing antibiotics with antibiotics plus corticosteroids was included in the review.[73] This study had an indirect population as it included children and adults.

One cohort study was in people with facial palsy,[73] 4 RCTs where in people with symptoms associated with neuroborreliosis[76,82,94,136] and 1 RCT was in people with acute radiculitis or meningitis with a history of a tick bite.[135]

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

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Jowett 2016[73]	Antibiotics alone (n=18) duration not reported Antibiotics plus Corticosteroids (n=17) duration not reported	n=51 (other treatment arm included antivirals, n=16) Diagnosis: Lyme disease-associated facial palsy meeting CDC definition for confirmed Lyme disease (facial palsy in addition to EM with known tick exposure, or facial palsy in addition to laboratory evidence of infection consisting of a positive CSF antibody test or positive 2-tier serology testing)	Reduction of clinical symptoms (eFACE composite score)	Retrospective cohort study. Indirect population - included children and adults.
Karlsson 1994[76]	Doxycycline 200 mg orally every 24 hours for 14 days (n=38) Benzylpenicillin sodium 3 g intravenously every 6 hours for 14 days (n=32)	n=70 Diagnosis: Clinical signs and symptoms compatible with Lyme neuroborreliosis and pleocytosis	Cure (resolution of symptoms) Adverse events	RCT
Kohlhepp	Doxycycline 200	n=75	Reduction of	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
1989[82]	mg orally on the first 2 days, 100 mg orally on each of the following 8 days (n=39) Benzylpenicillin sodium 20 mega units/day intravenously for 10 days (n=36)	Diagnosis: Elevated antibody titre specific to *B. burgdorferi* in the serum plus at least 3 of the following: radiculitis pain, meningitis symptoms, cranial neuritis, sensory or motor radiculitis, arthritis or carditis, tick bite or EM, specific antibody titre (serum or CSF), lymphocytic pleocytosis, elevated protein (>50mg/dl), elevated IgM/IgG/IgA index	clinical symptoms	Indirect outcome – full or partial remission (unclear how many people had full remission and how many had partial remission) 7 people had received previous antibiotics and 5 had received previous corticosteroids 20 received ancillary treatment with corticosteroids
Ljostad 2008[96] Ljostad 2010[95]	Doxycycline 200 mg orally per day for 14 days (n=59) Ceftriaxone 2 g intravenously per day for 14 days (n=59)	n=118 Diagnosis: Neurological symptoms suggestive of Lyme neuroborreliosis plus 1 or more of the following: CSF white-cell count of >5/mL, intrathecal production of Bb antibodies, verified acrodermatitis chronica atrophicans	Cure (resolution of symptoms) Reduction of clinical symptoms Adverse events	RCT
Pfister 1989[135]	Cefotaxime 2 g 3 times per day intravenously for 10 days (n=11) Benzylpenicillin sodium 5 million U 4 times per day intravenously for 10 days (n=10)	n=21 Diagnosis: Clinical signs of acute neuroborreliosis radiculitis (Bannwarth's syndrome) with severe radicular pain and lymphocytic pleocytosis in the CSF, elevated antibody titres	Cure (resolution of symptoms)	RCT

Study	Intervention and comparison	Population	Outcomes	Comments
		against *B. burgdorferi* or history of arthropod bite or erythema migrans; neuroborreliosis meningitis with history of tick bite or erythema migrans and elevated titres against *B. burgdorferi*		
Pfister 1991[136]	Cefotaxime 2 g every 8 hours intravenously for 10 days (n=16) Ceftriaxone 2 g every 24 hours intravenously for 10 days (n=17)	n=33 Diagnosis: Lyme neuroborreliosis (28 had typical Bannwarth's syndrome with intense radicular pain and lymphocytic pleocytosis in the CSF)	Cure (resolution of symptoms) Reduction of clinical symptoms Adverse events	RCT Indirect outcome – mild residual symptoms – unclear whether symptoms were reduced from baseline

1 See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Doxycycline (PO) versus Benzylpenicillin (IV)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with benzylpenicillin	Risk difference with doxycycline (95% CI)
Cure (resolution of symptoms at 4 weeks) no residual symptoms	54 (1 study) 4 weeks	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.89 (0.47 to 1.69)	435 per 1,000	48 fewer per 1,000 (from 230 fewer to 300 more)
Cure (resolution of symptoms at 3 months) no residual symptoms	53 (1 study) 3 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.98 (0.62 to 1.55)	591 per 1,000	12 fewer per 1,000 (from 225 fewer to 325 more)
Cure (resolution of symptoms at 6 months) no residual symptoms	52 (1 study) 6 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 1 (0.76 to 1.3)	810 per 1,000	0 fewer per 1,000 (from 194 fewer to 243 more)
Cure (resolution of symptoms at 12 months) no residual symptoms	51 (1 study) 12 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.85 to 1.3)	857 per 1,000	43 more per 1,000 (from 129 fewer to 257 more)
Adverse events at 2 weeks adverse events	70 (1 study) 2 weeks	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.12 (0.27 to 4.65)	94 per 1,000	11 more per 1,000 (from 68 fewer to 342 more)
Reduction of clinical symptoms (full/partial remission at 2 weeks) full or partial remission	75 (1 study) 2 weeks	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.05 (0.85 to 1.29)	806 per 1,000	40 more per 1,000 (from 121 fewer to 234 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] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 4: Clinical evidence summary: Doxycycline (PO) versus Ceftriaxone (IV)

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with ceftriaxone	Risk difference with doxycycline (95% CI)
Cure (clinical score=0 at 4 months) clinical score=0	102 (1 study) 4 months	LOW[1,2] due to risk of bias, imprecision	RR 1.44 (0.89 to 2.35)	333 per 1,000	147 more per 1,000 (from 37 fewer to 450 more)
Cure (complete recovery at 1 year) complete recovery	85 (1 study) 1 years	LOW[2] due to imprecision	RR 0.93 (0.62 to 1.4)	537 per 1,000	38 fewer per 1,000 (from 204 fewer to 215 more)
Reduction of clinical symptoms at 13 days improvement in clinical score; 0-64, lower values are beneficial	102 (1 study) 13 days	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean reduction of clinical symptoms at 13 days in the control group was 3.6 (SD 3.4)	The mean reduction of clinical symptoms at 13 days in the intervention group was 0.6 lower (1.98 lower to 0.78 higher)
Reduction of clinical symptoms at 4 months improvement in clinical score; 0-64, lower values are beneficial	102 (1 study) 4 months	MODERATE[1] due to risk of bias	Not applicable	The mean reduction of clinical symptoms at 4 months in the control group was 4.4 (SD 3.44)	The mean reduction of clinical symptoms at 4 months in the intervention group was 0.1 higher (1.21 lower to 1.41 higher)
Adverse events any adverse events	113 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.79 (0.51 to 1.23)	464 per 1,000	97 fewer per 1,000 (from 227 fewer to 107 more)
Adverse events serious adverse events	113 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	OR 0.13 (0.01 to 1.26)[3]	54 per 1,000	46 fewer per 1,000 (from 53 fewer to 13 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] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] The Peto odds ratio method was used because of a zero event rate in the intervention arm

Table 5: Clinical evidence summary: Cefotaxime (IV) versus Benzylpenicillin (IV)

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with benzylpenicillin	Risk difference with cefotaxime (95% CI)
Cure (normal neurologic findings at mean 7.7 months) normal neurologic findings	21 (1 study) 7.7 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.02 (0.67 to 1.55)	800 per 1,000	16 more per 1,000 (from 264 fewer to 440 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] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 6: Clinical evidence summary: Cefotaxime (IV) versus Ceftriaxone (IV)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with cefotaxime (95% CI)
Cure (normal neurologic findings at mean 8.1 months) normal neurologic findings	27 (1 study) 8.1 months	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.9 (0.51 to 1.6)	667 per 1,000	67 fewer per 1,000 (from 327 fewer to 400 more)
Reduction of symptoms (mild residual symptoms at mean 8.1 months) mild residual symptoms	27 (1 study) 8.1 months	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.33 (0.4 to 4.49)	250 per 1,000	83 more per 1,000 (from 150 fewer to 872 more)
Adverse events during treatment adverse reactions	30 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.62 (0.31 to 22.46)	71 per 1,000	116 more per 1,000 (from 49 fewer 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
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 7: Clinical evidence summary: Antibiotics versus Antibiotics plus Corticosteroids

Outcomes	No of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with antibiotics plus steroids	Risk difference with antibiotics (95% CI)
Reduction of symptoms (eFACE composite score at 3 months) eFACE composite score; 0-100, higher values are beneficial	35 (1 study)[1] 3 months	VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	Not applicable	Not applicable	The mean reduction of symptoms (eFace composite score at 3 months) in the intervention groups was 9.62 higher (0.19 to 19.05 higher)
Reduction of symptoms (eFACE composite score at 6 months) eFACE composite score; 0-100, higher values are beneficial	35 (1 study)[1] 6 months	VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	Not applicable	Not applicable	The mean reduction of symptoms (eFace composite score at 6 months) in the intervention groups was 11.4 higher (1.61 to 21.19 higher)
Reduction of symptoms (eFACE composite score at 12 months) eFACE composite score; 0-100, higher values are beneficial	35 (1 study)[1] 12 months	VERY LOW[2,3,4] due to risk of bias, indirectness, imprecision	Not applicable	Not applicable	The mean reduction of symptoms (eFace composite score at 12 months) in the intervention groups was 13.7 higher (2.16 lower to 29.56 higher)

[1] Observational study
[2] 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
[3] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by 1 increment) or a very indirect population (downgrade by 2 increments)
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

1 See appendix F for full GRADE tables.

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

One economic study relating to this review question was identified but was excluded due to limited applicability.[127] This is listed in appendix I, with reasons for exclusion given.

1.5.3 Unit costs

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

Table 8: 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/1.25ml oral suspension paediatric	125	0.20	3	14–28	8.35–16.70
		1-4 years	250 mg/5ml 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)	2000	3.75	3	10	112.50
Cephalosporins	Ceftriaxone	>9 years (c)(d)	2 g powder for solution for injection vials (IV) (e)	2000	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: intravenous.

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,[123] 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,[170] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[135] and Pfister 1991,[136] 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:[169] 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).[120] 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 9: 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 9, 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 (aged 12 and over):

- Very Low quality evidence from 1 RCT showed there was no clinically important difference between oral doxycycline and intravenous benzylpenicillin.
- Low quality evidence from 1 RCT showed a higher cure rate at 4 months for oral doxycycline over intravenous ceftriaxone, but no difference in cure rates at 12 months between the treatment arms. Moderate to Low quality evidence from 1 RCT showed no clinical difference between oral doxycycline and intravenous ceftriaxone in terms of a reduction of symptoms. Low to Very Low quality evidence from 1 RCT also found no difference in adverse events.
- Very Low quality evidence from 1 RCT showed there was no clinically important difference between intravenous cefotaxime and intravenous benzylpenicillin.
- Very Low quality evidence from 1 RCT found that people taking intravenous cefotaxime were more likely to experience adverse events compared to people taking intravenous ceftriaxone. Very Low quality evidence from 1 RCT found no difference in cure rates or reduction of symptoms.
- Very Low quality evidence from 1 cohort study showed that in people with a facial palsy associated with Lyme disease antibiotics alone resulted in a greater reduction of symptoms compared to antibiotics plus steroids.

Children (under 12 years):

- No relevant evidence in children was identified.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 Recommendations

F1. For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in Table 10.

F2. For children (under 12) diagnosed with Lyme disease, consider antibiotic treatment according to their symptoms as described in Table 11.

F3. Ask women whether they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation M1 on treatment in pregnancy).

F4. If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction.

Table 10: Antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) according to symptoms[a]

Symptoms	Treatment	First alternative	Second alternative

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

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

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

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

Table 11: 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]

Symptoms	Treatment	Alternative
Lyme disease affecting the cranial nerves or peripheral nervous system	Amoxicillin 30 mg/kg 3 times per day for 21 days up to a maximum of 1 g/dose	
Lyme disease affecting the central nervous system	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Arthritis	Amoxicillin 30 mg/kg 3 times per day 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Acrodermatitis chronica atrophicans	Amoxicillin 30 mg/kg 3 times per day 28 days up to a maximum of 1 g/dose	Intravenous ceftriaxone 80 mg/kg once per day for 28 days
Carditis[b]	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	
Carditis and haemodynamically unstable	Intravenous ceftriaxone 80 mg/kg once per day for 21 days	

[a] *Specialist practice may include use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult practice. At the time of consultation (September 2017), doxycycline did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.*

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

1.8.1 Research recommendations

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

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

See also rationales in appendix J of evidence report D.

1.9 Rationale and impact

1.9.1 Why the committee made the recommendations

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

Lyme disease can affect the nervous system and cause a number of different problems including meningitis, encephalitis, cranial nerve palsies and radiculopathies.

A study comparing oral doxycycline with intravenous ceftriaxone showed a greater benefit with oral doxycycline. However, both treatments showed low rates of cure (full resolution of

neurological symptoms). The committee noted that the study used a short, 14-day course of antibiotics and felt that a longer course could be beneficial.

The committee considered that people presenting with meningitis or encephalitis (prior to a diagnosis of Lyme disease) would receive treatment with intravenous ceftriaxone, and that intravenous treatment would achieve adequate concentrations in the central nervous system more rapidly than oral treatment.

The committee discussed the management of neurosyphilis, which has similar central nervous system involvement. The committee considered that, although the evidence was limited, central nervous system symptoms in Lyme disease should be treated with a similar antibiotic dose to that recommended for neurosyphilis.

Once-daily ceftriaxone has the advantage of being given more easily as an outpatient treatment than other intravenous options, which allows completion of the course as an outpatient.

Taking these factors into account, the committee agreed that a 21-day course of intravenous ceftriaxone 4 g daily was recommended as initial treatment for adults and young people (aged 12 and over) with Lyme disease affecting the central nervous system, with a 21-day course of doxycycline 400 mg daily recommended as an alternative treatment. A 21-day course of doxycycline 200 mg daily should be offered as initial treatment for adults and young people (aged 12 and over) with Lyme disease affecting the cranial nerves or the peripheral nervous system, with a 21-day course of amoxicillin recommended as an alternative treatment.

No studies were identified for nervous system symptoms in children. The guideline recommends that care of children and young people less than 18 years should be discussed with a specialist for advice about diagnosis and management and provides recommendations for children under 12 based on those for adults, with the same duration of treatment but using appropriate antibiotics for children and doses adjusted by weight.

1.9.2 Impact of the recommendations on practice

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

The recommendations should standardise treatment for neuroborreliosis in the NHS as practice may vary between centres.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

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

This review did not identify any evidence for quality of life.

1.10.1.2 The quality of the evidence

The evidence came from six studies with small sample sizes and was of Moderate to Very Low quality due to risk of bias, imprecision and indirectness. There were particular concerns about a lack of blinding of study participants, healthcare professionals who administered the treatment, and outcome assessors. Blinding is of particular importance for subjective outcomes, which are reported by a person with the disease and that cannot be objectively measured. Many studies did not fully report on the method of randomisation that had been used. Pre-treatment durations and the cohort of people also varied in studies. Some of the people included had peripheral neuroborreliosis, while others had neuroborreliosis affecting the central nervous system.

Outcomes and the time point at which they were assessed were poorly defined in the included studies. In particular, it was not clear whether cure or reduction of symptoms referred to the resolution or improvement of the neurological symptoms or of any Lyme disease symptoms. Similar ambiguity existed for the outcomes of reoccurrence of symptoms. Studies also varied in the outcomes they reported. In some studies cure, defined as no residual symptoms after a given time, was the primary outcome. However, the committee agreed that the treatment of neuroborreliosis may eliminate the bacteria, but the person may continue to have residual neurological symptoms as neurological damage may take time to resolve and full recovery may not occur. The committee acknowledged that there is currently no test of cure.

1.10.1.3 Benefits and harms

1.10.1.3.1 Treatment of neuroborreliosis affecting the peripheral nervous system (including the cranial nerves)

The committee agreed to recommend 100 mg of oral doxycycline twice daily for 21 days. In cases where doxycycline is contraindicated, the committee recommended 1 g of oral amoxicillin 3 times per day for 21 days.

Only 1 study in people with facial palsy related to Lyme disease was identified. The study compared a combination of antibiotics and steroids with antibiotics alone but did not specify which antibiotics people had received. The evidence showed that antibiotics alone were more effective in reducing symptoms than antibiotics with steroids combined. The committee were aware that steroids are recommended treatment for Bell's palsy. On the limited evidence available, the use of steroids when facial palsy is clearly caused by Lyme does not add additional benefit.

The committee used the evidence on the effectiveness of doxycycline in people with meningitis, radiculitis, pleocytosis and other signs and symptoms suggestive of neuroborreliosis to inform their decision as well as their clinical experience and current clinical practice.

Evidence from 1 study showed a clinical benefit of a 14-day treatment of oral doxycycline 200 mg over a 14-day treatment of intravenous ceftriaxone 2 g, although overall cure rates were low in both treatment arms. The committee also noted that only subclinical dosages and durations were used in the study and therefore decided to recommend a 21-day course of oral doxycycline 100mg twice daily.

Evidence from 1 small study found no difference between oral doxycycline (200 mg once on the first day followed by 100 mg once daily for 8 days) and intravenous benzylpenicillin (20 million units per day for 10 days) for any of the outcomes reported. There was also no difference between intravenous benzylpenicillin (5 million units 4 times per day for 10 days) and intravenous cefotaxime (2 g 3 times per day for 10 days) in another small study. The committee therefore decided not to recommend intravenous benzylpenicillin for neuroborreliosis affecting the peripheral nervous system.

1.10.1.3.2 Treatment of neuroborreliosis affecting the central nervous system

The committee agreed to recommend 4 g of intravenous ceftriaxone daily for 21 days.

The evidence showed a clinical benefit of high-dose cefotaxime (2 g every 8 hours for 10 days) over low-dose ceftriaxone (2 g every 24 hours for 10 days). Although there were less adverse events for ceftriaxone, the committee agreed that the evidence did not provide a clear benefit of cefotaxime over ceftriaxone, probably because of differences in dosages. The committee also agreed based on their clinical knowledge that there is no scientific basis for differences between the 2 drugs if equivalent dosages are used.

Ceftriaxone was also recommended over cefotaxime for practical and economic reasons. The committee acknowledged that cefotaxime was not as easily available as ceftriaxone, which can be administered via outpatient parenteral antibiotic therapy (OPAT) in the community nearer to the person's home on a once daily basis while cefotaxime requires a 3-times-per-day dosage. For people with CNS disease, the committee acknowledged the potentially serious negative outcome of inadequate levels of antibiotics. Intravenous treatment was considered to be helpful for ensuring that the treatment had been completed, as it is easier to monitor.

1.10.2 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 £43.26 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 presentations of neuroborreliosis affecting the cranial nerves or the peripheral nervous system, such as radiculopathy, the committee considered that oral doxycycline or amoxicillin (where doxycycline is contraindicated) should be offered, as there is no evidence that intravenous antibiotics are more effective; therefore, the additional cost and risks associated with the administration of intravenous antibiotics are not justifiable. Although the evidence showed a clinical benefit of a 14-day treatment of oral doxycycline, the committee agreed to recommend a 21-day course based on their clinical experience and to reduce any ambiguity around treatment duration. This is discussed in greater detail below in the section entitled 'Other factors the committee took into account'. The committee recommended a higher dose of amoxicillin (1 g 3 times per day versus 500 mg 3 times per day in BNF). The rationale for this higher dose is based on the fact that evidence in other presentations of Lyme disease (for example, EM) used probenecid to increase the concentration of amoxicillin with improved outcome; therefore, the committee decided to recommend 1 g amoxicillin 3 times per day as the preferred dose of amoxicillin.

For presentations of neuroborreliosis affecting the central nervous system, the committee noted that people who present with meningitis (prior to a diagnosis of Lyme disease being confirmed) would be likely to receive ceftriaxone intravenously. Based on the clinical evidence and their expert opinion, the committee agreed that in some circumstances it would be possible for clinicians to switch people from intravenous to oral antibacterials (doxycycline) when the person was clinically stable and when there is good bioavailability of the oral agent. This reduces the risk of line infection and allows people to be discharged thereby reducing costs of treatment to the NHS. However, there is no direct evidence for this in Lyme disease and it may increase the risk of non-compliance.

Currently, the BNF recommends intravenous ceftriaxone for those with disseminated Lyme borreliosis at a dose of 2 g per day for 14–21 days for adults and children 9 to 18 years with

body weight over 50 kg. For children 1 month to 12 years with a body weight below 50 kg, the BNF recommends a dose of 50–80 mg/kg once daily for 14–21 days to a maximum of 4 g daily. The higher dose of ceftriaxone was chosen for adults based on the evidence of a high equivalent effective dose of cefotaxime. Also, the committee discussed the doses used in the management of neurosyphilis (see section below for further detail) and the committee considered that this upper dose of 4 g is also required for neuroborreliosis affecting the central nervous system).

Finally, ceftriaxone was chosen over cefotaxime due to the impracticality of 3 daily infusions required for cefotaxime versus once daily infusion for ceftriaxone. This 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 an inpatient stay rather than a 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 person 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 for some individuals would not result in a significant resource impact given the number of people affected.

1.10.3 Other factors the committee took into account

The committee agreed that neurological symptoms and conditions, such as nerve damage, take an extended period of time to improve or resolve. Minimising delay in treatment is therefore important and would hopefully minimise nerve damage and result in better outcomes. The committee discussed extensively the choice of antibiotic for various clinical presentations of neuroborreliosis, including clinical scenarios that could lead to a switch from 1 type of antibiotic to another.

The limited evidence did not show a clear superiority of intravenous antibiotics over oral antibiotics for neuroborreliosis. Central nervous system neurological infections have the potential to be catastrophic and result in permanent or long-term damage or disability, which influenced the committee's recommendation for intravenous treatment for people presenting with symptoms consistent with central nervous system infection.

People with a more severe CNS involvement, such as encephalitis, are likely to have already received an initial dose, or doses, of intravenous ceftriaxone treatment prior to a diagnosis of Lyme disease. The committee, however, agreed that a switch from intravenous ceftriaxone to oral doxycycline might be indicated for people with Lyme disease who are clinically stable, as doxycycline is known to have good central nervous system bioavailability (see below). People who develop an allergic reaction to intravenous ceftriaxone should also be given oral doxycycline instead. The committee agreed that a switch from intravenous to oral antibiotics is part of current clinical practice and frequently done for other infectious diseases; the same would apply to Lyme disease.

Non-compliance or intolerance with doxycycline may be a justification for switching to intravenous ceftriaxone

The committee was informed by an expert witness and by the BASHH (British Association for Sexual Health and HIV) guideline for syphilis. The management of neurosyphilis was considered relevant for the development of borreliosis affecting the central nervous system. BASHH guidelines recommend intramuscular procaine penicillin (1.8–2.4 million units once daily) plus 500 mg probenecid for 14 days or intravenous benzylpenicillin (10.8–14.4 g given as 1.8–2.4 g every 4 hours) for 14 days. Alternatively, oral doxycycline (200 mg twice daily for 28 days), oral amoxicillin (2 g 3 times daily for 28 days) plus probenecid (500 mg 4 times per day for 28 days) or intramuscular or intravenous ceftriaxone (2 g for 10–14 days) can be given. The evidence underpinning these recommendations was, however, limited and of very poor quality. There was only 1 small study from 1985 each for doxycycline, amoxicillin and procaine penicillin. The evidence informing the recommendations of intramuscular or intravenous ceftriaxone included case reports, people with an HIV co-infection and animal studies. The committee considered that the potentially catastrophic effects of neuroborreliosis made it difficult to recommend more limited treatment despite the lack of good evidence.

The committee acknowledged the recommendations for Lyme disease developed by the European Federation of Neurological Societies (EFNS; now European Academy of Neurology, EAN). That guideline recommends 200 mg oral doxycycline per day or 2 g intravenous ceftriaxone per day for 14 days for symptoms confined to the meninges, cranial nerves, nerve roots or peripheral nerves. The guideline also recommends 2 g intravenous ceftriaxone per day for 14–21 days for CNS manifestations, such as myelitis, encephalitis or vasculitis. Treatment duration is dependent on the duration of symptoms, with a 3-week course of intravenous ceftriaxone being recommended for CNS manifestations for longer than 6 months. The committee acknowledged that the EFNS guideline was supported by very limited evidence and agreed to recommend a longer treatment duration of 21 days to reduce any ambiguity around treatment duration. The committee also agreed that oral doxycycline should be the treatment of choice for Lyme disease affecting the peripheral nervous system. Amoxicillin should be offered in cases where doxycycline is contraindicated.

The committee also discussed the penetration of oral doxycycline into the CSF. Research showed that CSF penetration 2–3 hours after 200 mg of oral doxycycline had been given was 15% with a concentration of 1.1 microgram per millilitre. With a doxycycline dose of 100 mg every 12 hours, the CSF concentration was only 0.6 microgram per millilitre 2-3 hours after administration.[53] The committee considered this provided additional justification for higher dose of doxycycline.

The guideline recommends that care of children and young people less than 18 years should be discussed with a specialist for advice about diagnosis and management. For children under the age of 12 amoxicillin is recommended as the antibiotic of choice. However the guideline committee was aware that specialists do offer doxycycline in children aged 9 years and above as a result of indirect evidence from the United States and Scandinavia despite no licence or BNFC dose. There is also increasing indirect evidence from use in other conditions in the United States and Canada that doxycycline does not cause teeth staining when used for short course (less than 4 weeks) in children aged 2 years and older. UK specialist clinicians may choose to use doxycycline as second line where a CSF-penetrating oral antibiotic is required, although the lack of direct evidence, lack of licence and lack of BNFC dose regimen has so far limited UK use in children aged 8 and under. Where used, in the United States and Canada, 1 dose regimen of doxycycline for children under 45 kilograms is: 5 milligram/kilogram in 2 divided doses on day 1 followed by 2.5 milligram/kilogram daily in 1 or 2 divided doses with a maximum for severe infections, up to 5 milligram/kilogram daily.

Azithromycin should otherwise be offered in cases where amoxicillin is contraindicated.

The committee made a general research recommendation for development of core outcome set and 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 12: Review protocol for the management of neuroborreliosis

Question number: 4.3

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for people with symptoms consistent with neuroborreliosis?
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 symptoms consistent with neuroborreliosis.

Eligibility criteria – population / disease / condition / issue / domain	People with clinical presentations consistent with neuroborreliosis, such as:
	• peripheral nervous system
	  ○ radiculopathy
	  ○ mononeuritis multiplex
	  ○ peripheral neuropathy or polyneuropathy
	  ○ myopathy (for example, myositis)
	• central nervous system
	  ○ white matter lesions
	  ○ cranial nerve lesions including facial nerve (VII) palsy
	  ○ autonomic nerve dysfunction
	  ○ meningitis
	  ○ encephalitis
	  ○ seizures
	  ○ optic neuritis
	  ○ transverse myelitis
	  ○ movement disorders (for example, chorea, ataxia)
	• psychiatric
	  ○ psychosis
	  ○ depression
	• cognitive decline including dementia

Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(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)

Field	Content
	○ 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)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• 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 neuroborreliosis) 3. Reduction of clinical symptoms related to neuroborreliosis 4. Relapse of neuroborreliosis symptoms **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

Field	Content
	Subgroups (to be investigated if heterogeneity is identified): • Pregnant women • People who are immunocompromised • People in whom a previous course of antimicrobial 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 and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library all years Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise critically individual studies. For details, please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual. Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) In the absence of clinically established MIDs, standard MIDs for dichotomous (25% risk reduction or risk increase) and continuous outcomes (+/-0.5 standard deviation) will be used If heterogeneity is found, the influence of subgroups will be examined
Methods for quantitative analysis – combining studies and exploring	For details, please see the separate Methods report for this guideline.

Field	Content
(in)consistency	
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 / 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

Table 13: 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).[121] **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.

1

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 14: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

1 **Embase (Ovid) search terms**

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

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

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

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

B.2 Health Economics literature search strategy

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

Table 15: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

1 **Embase (Ovid) search terms**

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

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

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

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

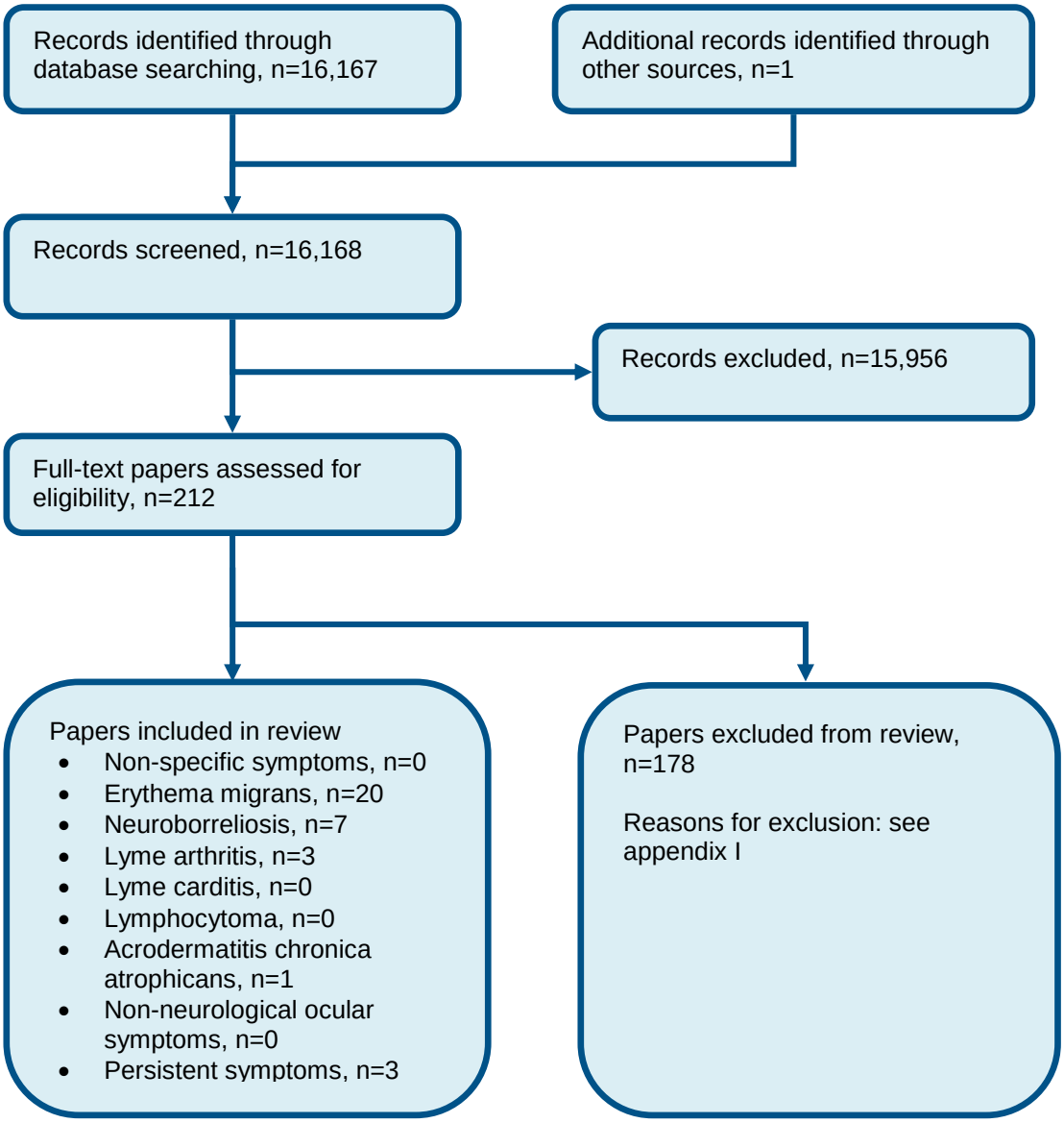
#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis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

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

1

Appendix C: Clinical evidence selection

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



Appendix D: Clinical evidence tables

Study	Jowett 2016[73]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=51)
Countries and setting	Conducted in USA; Setting: Specialist hospital
Line of therapy	first line
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	CDC definition for confirmed Lyme disease (facial palsy in addition to EM with known tick exposure, or facial palsy in addition to laboratory evidence of infection consisting of a positive CSF antibody test or positive 2-tier serology testing)
Exclusion criteria	Prior episode of facial palsy, inappropriate documentation of initial treatment, inappropriate antibiotic therapy (that is, onset delayed by 14 days or more following onset of facial palsy, or agent/route/duration of therapy inconsistent with treatment guidelines), recent botulinum toxin administration, absent video documentation of facial function, bilateral involvement
Recruitment or selection of people	People with Lyme disease facial palsy presenting at hospital between January 2002 and August 2015
Age, gender and family origin	Age - Mean (range): 39.6 years (6-72). Gender (M:F): 26:25. Family origin: Not reported
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	Serious indirectness: Includes children
Interventions	(n=17) Intervention 1: Polytherapy. Antibiotics plus corticosteroids. Duration Not reported. Concurrent medication/care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=18) Intervention 2: Monotherapy. Antibiotics only. Duration Not reported. Concurrent medication/care: Not reported Further details: 1. Previous treatment failure: Not applicable

Study	Jowett 2016[73]
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY versus POLYTHERAPY Protocol outcome 1: Reduction of clinical symptoms - Actual outcome: eFACE composite score at 6 months; MD: 11.40 (95% CI 1.61-21.19), p=0.021 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: eFACE composite score at 12 months; MD: 13.70 (95% CI -2.16 to 29.58) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: eFACE composite score at 3 months; MD: 9.62 (95% CI 0.19-19.04) Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Cure (resolution of symptoms); Symptom relapse; Adverse events

Study	Karlsson 1994[76]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in Sweden; Setting: Dual-centre study
Line of therapy	first line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis plus exocytosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Clinical signs and symptoms compatible with Lyme neuroborreliosis and pleocytosis
Exclusion criteria	Aged below 12 years, pregnancy, breast feeding, allergy to treatment compounds, antibiotic treatment within preceding 4 weeks
Recruitment or selection of people	Consecutive participants
Age, gender and family origin	Age - Median (range): Penicillin G group: 55 years (16-88); doxycycline group: 49 years (18-74). Gender

Study	Karlsson 1994[76]
	(M:F): 19:35. Family origin: Not reported
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=32) Intervention 1: Antibiotics - Benzylpenicillin sodium or Penicillin G. 3 g intravenous every 6 hours. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=38) Intervention 2: Antibiotics - Doxycycline. 200 mg oral every 24 hours. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BENZYLPENICILLIN SODIUM / PENICILLIN G versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No residual symptoms at 4 weeks; Group 1: 10/23, Group 2: 12/31 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9; Group 2 Number missing: 7 - Actual outcome: No residual symptoms at 3 months; Group 1: 13/22, Group 2: 18/31 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10; Group 2 Number missing: 7 - Actual outcome: No residual symptoms at 6 months; Group 1: 17/21, Group 2: 25/31 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11; Group 2 Number missing: 7 - Actual outcome: No residual symptoms at 12 months; Group 1: 18/21, Group 2: 27/30 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 11; Group 2 Number missing: 8 Protocol outcome 2: Adverse events - Actual outcome: Adverse events at 14 days; Group 1: 3/32, Group 2: 4/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Reduction of clinical symptoms; Symptom relapse

Study	Kohlhepp 1989[82]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in Germany; Setting: Department of neurology
Line of therapy	first line
Duration of study	Follow up (post intervention): 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Elevated antibody titre specific to *B. burgdorferi* in the serum plus at least 3 of the following: radiculitis pain, meningitis symptoms, cranial neuritis, sensory or motor radiculitis, arthritis or carditis, tick bite or EM, specific antibody titre (serum or CSF), lymphocytic pleocytosis, elevated protein (> 50 mg/dl), elevated IgM/IgG/IgA index
Exclusion criteria	Not reported
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Penicillin group: men 55.0 years (12.6), women 54.1 years (16.3); doxycycline group: men 49.6 years (14.0), women 55.7 years (14.3). Gender (M:F): 36:39. Family origin: Not reported
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=39) Intervention 1: Antibiotics - Doxycycline. 200 mg on the first 2 days, 100 mg on each of 8 days. Duration 10 days. Concurrent medication/care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=36) Intervention 2: Antibiotics - Benzylpenicillin sodium / Penicillin G. 20 mega units/day. Duration 10 days. Concurrent medication/care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus BENZYLPENICILLIN SODIUM / PENICILLIN G Protocol outcome 1: Reduction of clinical symptoms - Actual outcome: Full or partial remission at 2 weeks; Group 1: 33/39, Group 2: 29/36 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - High, Measurement -	

Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear how many people had a full remission and how many had a partial remission; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Symptom relapse; Adverse events

Study (subsidiary papers)	**Ljostad 2008[96] (Ljostad 2010[95])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=118)
Countries and setting	Conducted in Norway; Setting: Multi-centre study
Line of therapy	first line
Duration of study	Follow up (post intervention): 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Neurological symptoms suggestive of Lyme neuroborreliosis plus 1 or more of the following: CSF white-cell count of more than 5 per mL, intrathecal production of Bb antibodies, verified acrodermatitis chronica atrophicans.
Exclusion criteria	Allergy to interventions, previous type 1 reaction to penicillin, treatment with cephalosporin or penicillin or tetracycline in the past 14 days, under 18 years old, pregnancy or breast feeding
Recruitment or selection of people	Consecutive participants
Age, gender and family origin	Age - Mean (SD): Doxycycline group: 54 years (13); ceftriaxone group: 52 years (13). Gender (M:F): Doxycycline group: 28:26; ceftriaxone group: 31:17. Family origin: Not reported
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Extra comments	Mean symptom duration: doxycycline group (10 weeks, SD 19), ceftriaxone group (8 weeks, SD 13)
Indirectness of population	No indirectness
Interventions	(n=59) Intervention 1: Antibiotics - Doxycycline. Oral. 200 mg per day. Duration 14 days. Concurrent medication/care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=59) Intervention 2: Antibiotics - Ceftriaxone. Intravenous. 2 g per day. Duration 14 days. Concurrent medication/care: Not reported

Study (subsidiary papers)	Ljostad 2008[96] (Ljostad 2010[95])
	Further details: 1. Previous treatment failure: Not applicable
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus CEFTRIAXONE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Clinical score=0 at 4 months; Group 1: 26/54, Group 2: 16/48 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 11 - Actual outcome: Complete recovery at 1 year; Group 1: 22/44, Group 2: 22/41 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 18 Protocol outcome 2: Reduction of clinical symptoms - Actual outcome: Improvement in clinical score at 4 months; Group 1 Mean; 4.5 (95% CI 3.6-5.5) n=54, Group 2 Mean: 4.4 (95% CI 3.4-5.4) n=48 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 11 - Actual outcome: Improvement in clinical score at 13 days; Group 1 Mean; 3 (95% CI 2-4) n=54, Group 2 Mean; 3.6 (95% CI 2.6-4.7) n=48 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 5; Group 2 Number missing: 11 Protocol outcome 3: Adverse events - Actual outcome: Any adverse events at Unclear; Group 1: 21/57, Group 2: 26/56 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 3 - Actual outcome: Severe adverse events (cholecystitis, stomatitis, proctitis, allergy) at Unclear; Group 1: 0/57, Group 2: 3/56 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life; Symptom relapse

Study	Pfister 1989[135]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=21)
Countries and setting	Conducted in Germany; Setting: not reported

Line of therapy	first line
Duration of study	Intervention and follow up: 10 days plus mean 7.7 (2.4 SD)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical diagnosis
Stratum	Adults:
Subgroup analysis within study	Not applicable
Inclusion criteria	clinical signs of acute neuroborreliosis radiculitis (Bannwarth's syndrome) with severe radicular pain and lymphocytic pleocytosis in the CSF, elevated antibody titres against *B. burgdorferi* or history of arthropod bite or erythema migrans; neuroborreliosis meningitis with history of tick bite or erythema migrans and elevated titres against *B. burgdorferi*
Exclusion criteria	not reported
Recruitment/selection of people	not reported
Age, gender and family origin	Age - Mean (SD): penicillin group 56.7 (15) years; cefotaxime group 55.4 (10.8) years. Gender (M:F): 12/9. Family origin: not reported
Further population details	1. Immunocompromised people: Not stated or unclear 2. Pregnant women: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=10) Intervention 1: Antibiotics - Benzylpenicillin sodium or Penicillin G. 4 x 5million U/d for intravenously. Duration 10 days. Concurrent medication/care: people were not treated with corticosteroids during antibiotic treatment Further details: 1. Previous treatment failure: Not stated / Unclear (n=11) Intervention 2: Antibiotics - Cefotaxime. 3 x 2g/d intravenously. Duration 10 days. Concurrent medication/care: people were not treated with corticosteroids during antibiotic treatment Further details: 1. Previous treatment failure: Not stated / Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: BENZYLPENICILLIN SODIUM / PENICILLIN G versus CEFOTAXIME Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome for Adults: normal neurologic findings at mean 7.7 months (2.4 SD); Group 1: 8/10, Group 2: 9/11 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; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Reduction of clinical symptoms; Symptom relapse; Adverse events

Study	Pfister 1991[136]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=33)
Countries and setting	Conducted in Germany; Setting: not reported
Line of therapy	first line
Duration of study	Intervention and follow up: 10 days plus mean 8.1 (1.9 SD) months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: clinical diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Lyme neuroborreliosis
Exclusion criteria	seronegative people with painful radiculoneuritis or lymphocytic meningitis who had no history of arthropod bites or erythema migrans within 3 months before disease onset
Recruitment or selection of people	not reported
Age, gender and family origin	Age - Range: 12-84 years. Gender (M:F): 16/14. Family origin: not reported
Further population details	1. Immunocompromised people: Not stated / Unclear 2. Pregnant women: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=16) Intervention 1: Antibiotics - Cefotaxime. 2 g every 8 hours intravenously. Duration 10 days. Concurrent medication/care: not reported Further details: 1. Previous treatment failure: Not stated / Unclear (n=17) Intervention 2: Antibiotics - Ceftriaxone. 2 g every 24 hours intravenously . Duration 10 days . Concurrent medication/care: not reported Further details: 1. Previous treatment failure: Not stated / Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFOTAXIME versus CEFTRIAXONE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome for Adults: normal neurologic findings at mean 8.1 (SD 1.9) months; Group 1: 9/15, Group 2: 8/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 1, Reason: 1 excluded due to allergic reaction; Group 2 Number missing: 5, Reason: 3 excluded due to being asymptomatic at beginning of study, other 2 unclear	

Study	Pfister 1991[136]
Protocol outcome 2: Reduction of clinical symptoms - Actual outcome for Adults: mild residual symptoms at mean 8.1 (SD 1.9) months; Group 1: 5/15, Group 2: 3/12 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: doesn't take in to account baseline symptoms - unclear whether symptoms were reduced; Group 1 Number missing: 1, Reason: 1 excluded due to allergic reaction; Group 2 Number missing: 5, Reason: 3 excluded due to being asymptomatic at beginning of study, other 2 unclear Protocol outcome 3: Adverse events - Actual outcome for Adults: adverse reactions at during treatment; Group 1: 3/16, Group 2: 1/14 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: 0; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life; Symptom relapse

Appendix E: Forest plots

E.1 Doxycycline (PO) versus Benzylpenicillin (IV)

E.1.1 Neuroborreliosis (unspecified)

Figure 2: Cure (resolution of symptoms at 4 weeks)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karlsson 1994	12	31	10	23	100.0%	0.89 [0.47, 1.69]
Total (95% CI)		**31**		**23**	**100.0%**	**0.89 [0.47, 1.69]**
Total events	12		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)

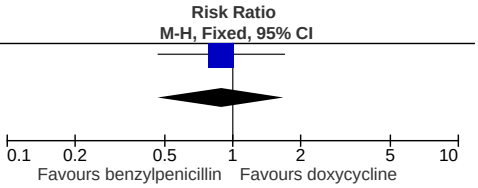


Figure 3: Cure (resolution of symptoms at 3 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karlsson 1994	18	31	13	22	100.0%	0.98 [0.62, 1.55]
Total (95% CI)		**31**		**22**	**100.0%**	**0.98 [0.62, 1.55]**
Total events	18		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)

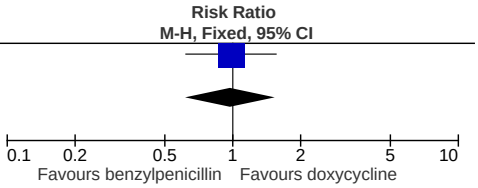


Figure 4: Cure (resolution of symptoms at 6 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karlsson 1994	25	31	17	21	100.0%	1.00 [0.76, 1.30]
Total (95% CI)		**31**		**21**	**100.0%**	**1.00 [0.76, 1.30]**
Total events	25		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)

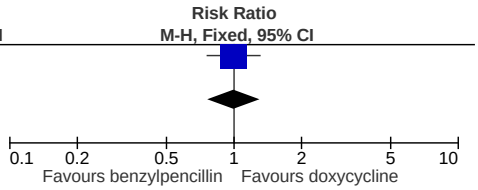


Figure 5: Cure (resolution of symptoms at 12 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karlsson 1994	27	30	18	21	100.0%	1.05 [0.85, 1.30]
Total (95% CI)		**30**		**21**	**100.0%**	**1.05 [0.85, 1.30]**
Total events	27		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.45 (P = 0.65)

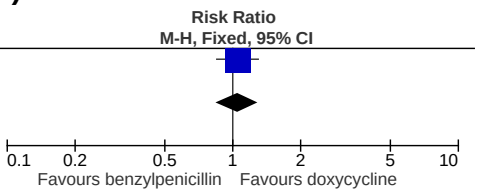


Figure 6: Adverse events at 2 weeks

Study or Subgroup	Doxycycline Events	Doxycycline Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Karlsson 1994	4	38	3	32	100.0%	1.12 [0.27, 4.65]
Total (95% CI)		**38**		**32**	**100.0%**	**1.12 [0.27, 4.65]**
Total events	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)

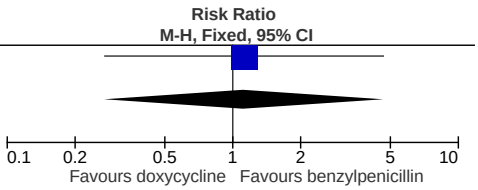
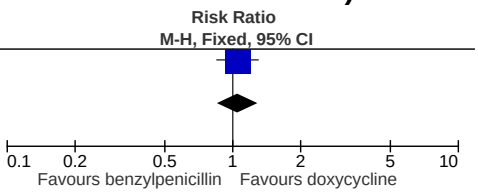


Figure 7: Reduction of clinical symptoms (full or partial remission at 2 weeks)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Benzylpenicillin Events	Benzylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kohlhepp 1989	33	39	29	36	100.0%	1.05 [0.85, 1.29]
Total (95% CI)		**39**		**36**	**100.0%**	**1.05 [0.85, 1.29]**
Total events	33		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)



E.2 Doxycycline (PO) versus Ceftriaxone (IV)

E.2.1 Neuroborreliosis (unspecified)

Figure 8: Cure (resolution of symptoms at 4 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ljostad 2008	26	54	16	48	100.0%	1.44 [0.89, 2.35]
Total (95% CI)		**54**		**48**	**100.0%**	**1.44 [0.89, 2.35]**
Total events	26		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)

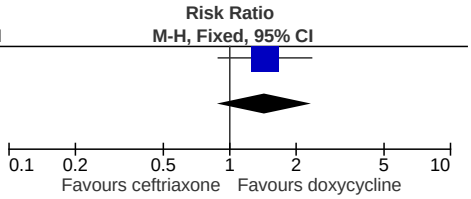


Figure 9: Cure (resolution of symptoms at 12 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ljostad 2008	22	44	22	41	100.0%	0.93 [0.62, 1.40]
Total (95% CI)		**44**		**41**	**100.0%**	**0.93 [0.62, 1.40]**
Total events	22		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)

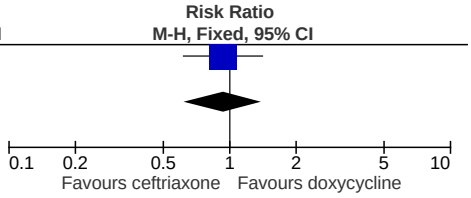


Figure 10: Reduction of symptoms (improvement in clinical score at 13 days)

Study or Subgroup	Doxycycline Mean	Doxycycline SD	Doxycycline Total	Ceftriaxone Mean	Ceftriaxone SD	Ceftriaxone Total	Weight	Mean Difference IV, Fixed, 95% CI
Ljostad 2008	3	3.6637	54	3.6	3.4439	48	100.0%	-0.60 [-1.98, 0.78]
Total (95% CI)			**54**			**48**	**100.0%**	**-0.60 [-1.98, 0.78]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.85 (P = 0.39)

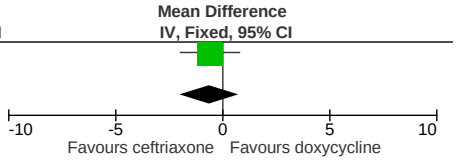


Figure 11: Reduction of symptoms (improvement in clinical score at 4 months)

Study or Subgroup	Doxycycline Mean	Doxycycline SD	Doxycycline Total	Ceftriaxone Mean	Ceftriaxone SD	Ceftriaxone Total	Weight	Mean Difference IV, Fixed, 95% CI
Ljostad 2008	4.5	3.2973	54	4.4	3.4439	48	100.0%	0.10 [-1.21, 1.41]
Total (95% CI)			**54**			**48**	**100.0%**	**0.10 [-1.21, 1.41]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.15 (P = 0.88)

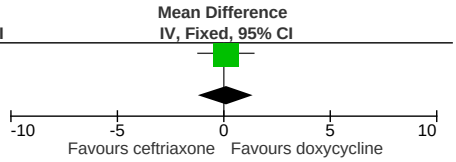


Figure 12: Adverse events (any adverse events)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ljostad 2008	21	57	26	56	100.0%	0.79 [0.51, 1.23]
Total (95% CI)		**57**		**56**	**100.0%**	**0.79 [0.51, 1.23]**
Total events	21		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)

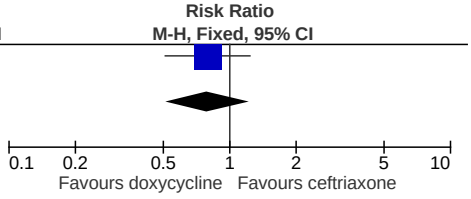
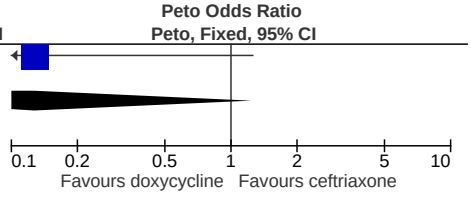


Figure 13: Adverse events (serious adverse events)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ljostad 2008	0	57	3	56	100.0%	0.13 [0.01, 1.26]
Total (95% CI)		**57**		**56**	**100.0%**	**0.13 [0.01, 1.26]**
Total events	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)



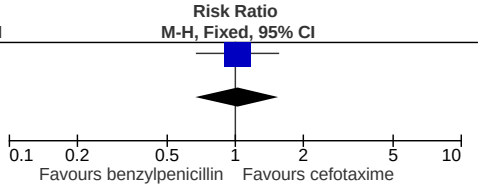
1 E.3 Cefotaxime (IV) versus Benzylpenicillin (IV)

2 E.3.1 Acute radiculitis or meningitis after tick-bite

Figure 14: Cure (resolution of symptoms at mean 7.7 months)

Study or Subgroup	Cefotaxime Events	Total	Benzylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfister 1989	9	11	8	10	100.0%	1.02 [0.67, 1.55]
Total (95% CI)		**11**		**10**	**100.0%**	**1.02 [0.67, 1.55]**
Total events	9		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.92)



3 E.4 Cefotaxime (IV) versus Ceftriaxone (IV)

4 E.4.1 Neuroborreliosis (unspecified)

Figure 15: Cure (resolution of symptoms at mean 8.1 months)

Study or Subgroup	Cefotaxime Events	Total	Ceftriaxone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfister 1991	9	15	8	12	100.0%	0.90 [0.51, 1.60]
Total (95% CI)		**15**		**12**	**100.0%**	**0.90 [0.51, 1.60]**
Total events	9		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)

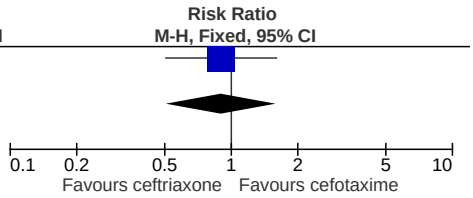


Figure 16: Reduction of symptoms (mild residual symptoms at mean 8.1 months)

Study or Subgroup	Cefotaxime Events	Total	Ceftriaxone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfister 1991	5	15	3	12	100.0%	1.33 [0.40, 4.49]
Total (95% CI)		**15**		**12**	**100.0%**	**1.33 [0.40, 4.49]**
Total events	5		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.64)

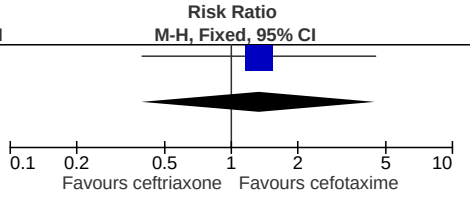
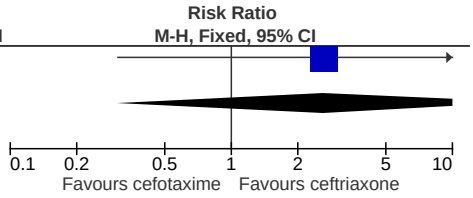


Figure 17: Adverse events (adverse reactions during treatment)

Study or Subgroup	Cefotaxime Events	Total	Ceftriaxone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Pfister 1991	3	16	1	14	100.0%	2.63 [0.31, 22.46]
Total (95% CI)		**16**		**14**	**100.0%**	**2.63 [0.31, 22.46]**
Total events	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)



5 E.5 Antibiotics versus Antibiotics plus Corticosteroids

6 E.5.1 Facial palsy

Figure 18: Reduction of symptoms (eFACE composite score at 3 months)

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Jowett 2016	9.62	4.8113	100.0%	9.62 [0.19, 19.05]
Total (95% CI)			**100.0%**	**9.62 [0.19, 19.05]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)

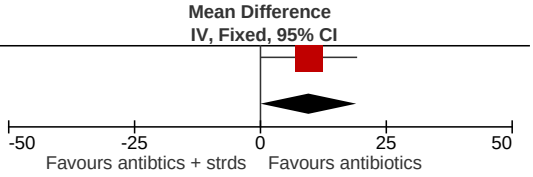


Figure 19: Reduction of symptoms (eFACE composite score at 6 months)

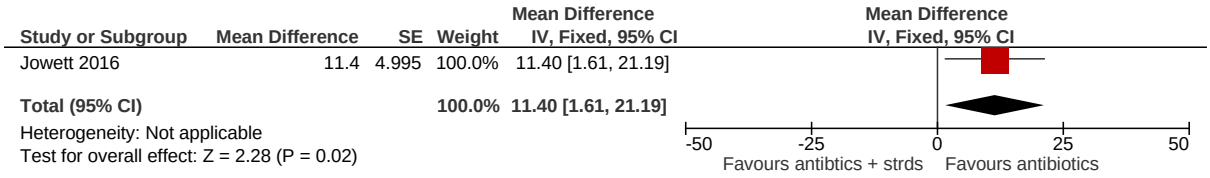
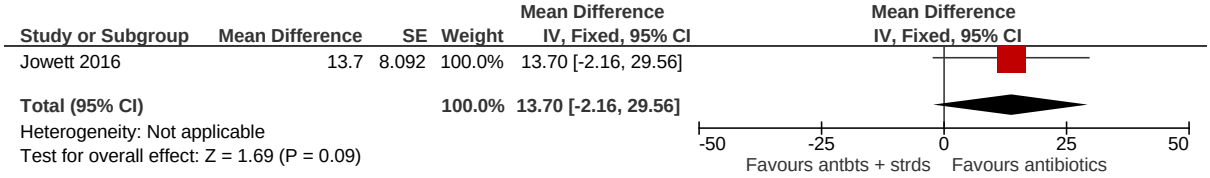


Figure 20: Reduction of symptoms (eFACE composite score at 12 months)



1

Appendix F:GRADE tables

Table 16: Clinical evidence profile: Doxycycline (PO) versus Benzylpenicillin (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Benzylpenicillin	Relative (95% CI)	Absolute		
Cure (resolution of symptoms at 4 weeks – follow-up 4 weeks; assessed with: no residual symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/31 (38.7%)	10/23 (43.5%)	RR 0.89 (0.47 to 1.69)	48 fewer per 1000 (from 230 fewer to 300 more)	⊕OOO VERY LOW	CRITICAL
Cure (resolution of symptoms at 3 months – follow-up 3 months; assessed with: no residual symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/31 (58.1%)	13/22 (59.1%)	RR 0.98 (0.62 to 1.55)	12 fewer per 1000 (from 225 fewer to 325 more)	⊕OOO VERY LOW	CRITICAL
Cure (resolution of symptoms at 6 months – follow-up 6 months; assessed with: no residual symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25/31 (80.6%)	17/21 (81%)	RR 1 (0.76 to 1.3)	0 fewer per 1000 (from 194 fewer to 243 more)	⊕OOO VERY LOW	CRITICAL
Cure (resolution of symptoms at 12 months – follow-up 12 months; assessed with: no residual symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27/30 (90%)	18/21 (85.7%)	RR 1.05 (0.85 to 1.3)	43 more per 1000 (from 129 fewer to 257 more)	⊕OOO VERY LOW	CRITICAL
Adverse events at 2 weeks (follow-up 2 weeks; assessed with: adverse events)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/38 (10.5%)	3/32 (9.4%)	RR 1.12 (0.27 to 4.65)	11 more per 1000 (from 68 fewer to 342 more)	⊕OOO VERY LOW	IMPORTANT

Reduction of clinical symptoms (full/partial remission at 2 weeks – follow-up 2 weeks; assessed with: full or partial remission)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	serious[2]	none	33/39 (84.6%)	29/36 (80.6%)	RR 1.05 (0.85 to 1.29)	40 more per 1000 (from 121 fewer to 234 more)	⊕OOO VERY 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] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 17: Clinical evidence profile: Doxycycline (PO) versus ceftriaxone (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Doxycycline**	**Ceftriaxone**	**Relative (95% CI)**	**Absolute**		
Cure (clinical score=0 at 4 months – follow-up 4 months; assessed with: clinical score=0)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26/54 (48.1%)	16/48 (33.3%)	RR 1.44 (0.89 to 2.35)	147 more per 1000 (from 37 fewer to 450 more)	⊕⊕OO LOW	CRITICAL
Cure (complete recovery at 1 year – follow-up 1 years; assessed with: complete recovery)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	22/44 (50%)	22/41 (53.7%)	RR 0.93 (0.62 to 1.4)	38 fewer per 1000 (from 204 fewer to 215 more)	⊕⊕OO LOW	CRITICAL
Reduction of clinical symptoms at 13 days (measured with: improvement in clinical score; 0-64, lower values are beneficial)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	54	48	Not applicable	MD 0.6 lower (1.98 lower to 0.78 higher)	⊕⊕OO LOW	CRITICAL
Reduction of clinical symptoms at 4 months (measured with: improvement in clinical score; 0-64, lower values are beneficial)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	54	48	Not applicable	MD 0.1 higher (1.21 lower to 1.41 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (assessed with: any adverse events)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/57 (36.8%)	26/56 (46.4%)	RR 0.79 (0.51 to 1.23)	97 fewer per 1000 (from 227 fewer to 107 more)	⊕⊕OO LOW	IMPORTANT
Adverse events (assessed with: serious adverse events)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/57 (0%)	3/56 (5.4%)	OR 0.13 (0.01 to 1.26)	46 fewer per 1000 (from 53 fewer to 13 more)	⊕OOO 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 if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] The Peto odds ratio method was used because of a zero event rate in the intervention arm

Table 18: Clinical evidence profile: Cefotaxime (IV) versus Benzylpenicillin (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cefotaxime**	**Benzylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure (normal neurologic findings at mean 7.7 months – follow-up mean 7.7 months; assessed with: normal neurologic findings)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/11 (81.8%)	8/10 (80%)	RR 1.02 (0.67 to 1.55)	16 more per 1000 (from 264 fewer to 440 more)	⊕OOO VERY 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] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 19: Clinical evidence profile: Cefotaxime (IV) versus ceftriaxone (IV)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cefotaxime**	**Ceftriaxone**	**Relative (95% CI)**	**Absolute**		

Cure (normal neurologic findings at mean 8.1 months – follow-up mean 8.1 months; assessed with: normal neurologic findings)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/15 (60%)	8/12 (66.7%)	RR 0.9 (0.51 to 1.6)	67 fewer per 1000 (from 327 fewer to 400 more)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (mild residual symptoms at mean 8.1 months – follow-up mean 8.1 months; assessed with: mild residual symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	5/15 (33.3%)	3/12 (25%)	RR 1.33 (0.4 to 4.49)	83 more per 1000 (from 150 fewer to 872 more)	⊕OOO VERY LOW	CRITICAL
Adverse events during treatment (assessed with: adverse reactions)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/16 (18.8%)	1/14 (7.1%)	RR 2.62 (0.31 to 22.46)	116 more per 1000 (from 49 fewer to 1000 more)	⊕OOO 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 if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[3] Downgraded by 1 or 2 increments because the majority of the evidence had indirect outcomes

Table 20: Clinical evidence profile: Antibiotics versus antibiotics plus corticosteroids

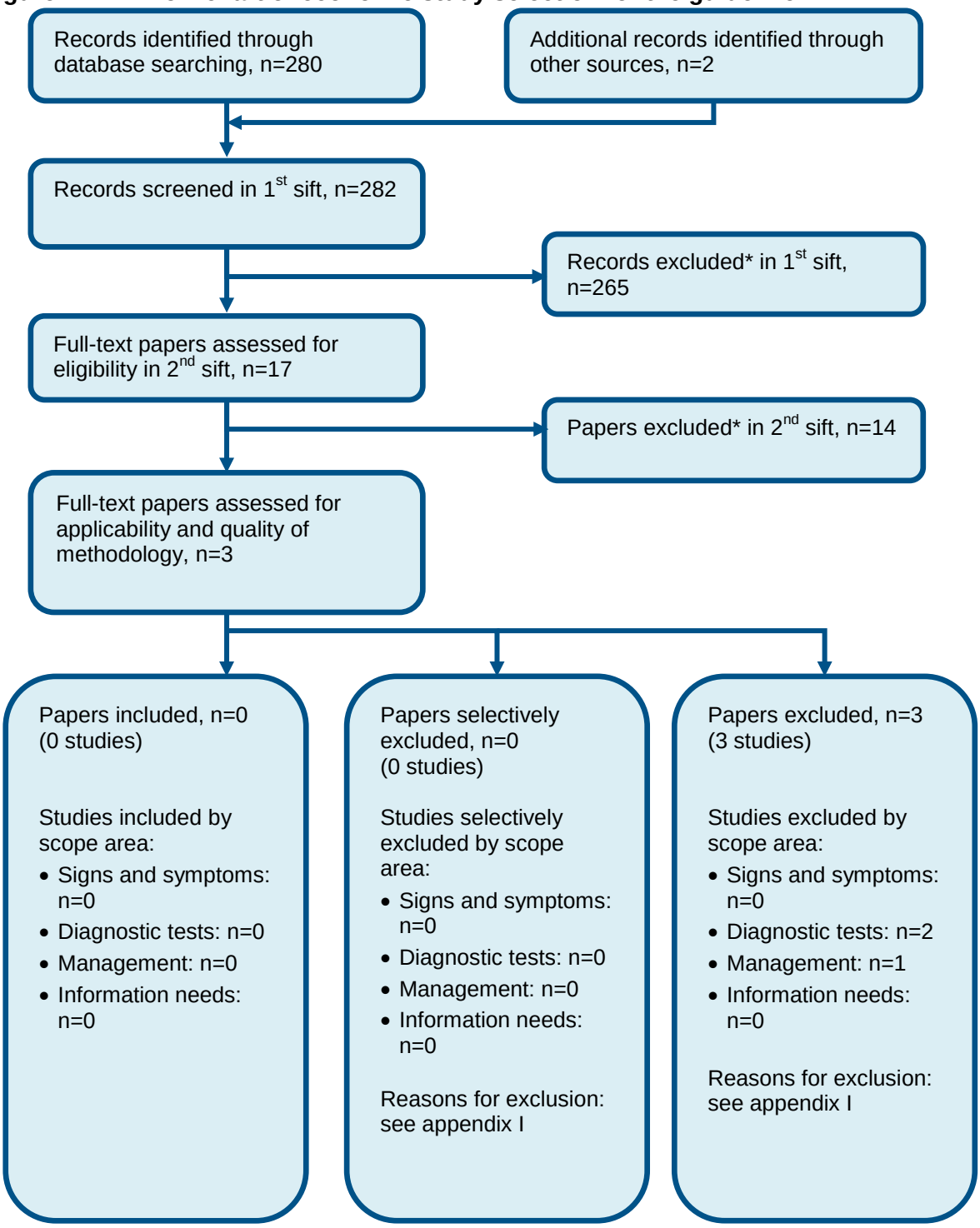
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Antibiotics**	**Antibiotics plus steroids**	**Relative (95% CI)**	**Absolute**		
Reduction of symptoms (eFACE composite score at 3 months); 0-100, higher values are beneficial												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18	17	Not applicable	MD 9.62 higher (0.19 to 19.05 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (eFACE composite score at 6 months); 0-100, higher values are beneficial												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18	17	Not applicable	MD 11.4 higher (1.61 to 21.19 higher)	⊕OOO VERY LOW	CRITICAL

Reduction of symptoms (eFACE composite score at 12 months); 0-100, higher values are beneficial												
1	observational studies	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	18	17	Not applicable	MD 13.7 higher (2.16 lower to 29.56 higher)	⊕OOO VERY 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] Downgraded by 1 or 2 increments because the majority of the evidence included an indirect population (downgrade by 1 increment) or a very indirect population (downgrade by 2 increments)
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

Appendix G: Health economic evidence selection

Figure 21: 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 21: 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
Dersch 2015[46]	Excluded due to an incorrect study design

Reference	Reason for exclusion
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[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[74]	Excluded due to an incorrect population
Karkkonen 2001[75]	Excluded due to an incorrect study design
Karlsson 1996[77]	Excluded due to an incorrect outcome
Kersten 1995[78]	Excluded due to an incorrect study design
Kilic Muftuoglu 2016[79]	Excluded due to an incorrect study design
Klempner 2013[81]	Excluded due to an incorrect study design
Korenberg 1996[83]	Excluded due to an incorrect intervention
Kowalski 2010[85]	Excluded due to an incorrect outcome
Kowalski 2011[84]	Excluded due to an incorrect study design
Krbkova 1996[86]	Excluded due to an incorrect comparison
Kuhn 2012[87]	Excluded due to an incorrect study design
Laasila 2003[88]	Excluded due to an incorrect population
Lantos 2013[89]	Excluded due to an incorrect study design
Lauhio 1994[90]	Excluded due to an incorrect population
Lauhio 1991[91]	Excluded due to an incorrect population
Lempner 2002[80]	Excluded due to an incorrect study design
Liegner 1992[92]	Excluded due to an incorrect study design
Lipsker 2002[93]	Excluded due to an incorrect study design
Ljostad 2008[94]	Study abstract
Loewen 1999[97]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Loewen 2000[98]	Excluded due to an incorrect study design
Luft 1988[100]	Excluded due to an incorrect outcome
Luft 1989[99]	Excluded due to an incorrect population
Maraspin 1995[106]	Excluded due to an incorrect study design
Maraspin 1996[101]	Excluded due to an incorrect study design
Maraspin 1999[102]	Excluded due to an incorrect study design
Maraspin 2002[103]	Excluded due to an incorrect study design
Maraspin 1999[104]	Excluded due to an incorrect study design
Maraspin 2002[105]	Excluded due to an incorrect population
Marks 2016[107]	Excluded due to an incorrect study design
McGill 1965[108]	Excluded due to an incorrect population
Meyerhoff 2002[109]	Excluded due to an incorrect study design
Meyerhoff 2016[110]	Excluded due to an incorrect study design
Millner 1996[111]	Excluded due to an incorrect outcome
Millner 1996[112]	Excluded due to an incorrect outcome
Morales 2000[113]	Excluded due to an incorrect study design
Muellegger 1995[115]	Excluded due to an incorrect study design
Muellegger 1996[114]	Excluded due to an incorrect comparison
Mullegger 1991[116]	Excluded due to an incorrect outcome
Nadelman 1993[118]	Excluded due to an incorrect study design
Nadelman 2001[117]	Excluded due to an incorrect population
Naglo 1989[119]	Excluded due to an incorrect study design
Neumann 1987[122]	Excluded due to an incorrect study design
Nimmrich 2014[124]	Excluded due to an incorrect study design
Nowakowski 2000[125]	Excluded due to an incorrect study design
Nowakowski 1995[126]	Excluded due to an incorrect study design
Ogrinc 2006[127]	Excluded due to an incorrect population
Oksi 1999[128]	Excluded due to an incorrect study design
Oksi 2007[129]	Excluded due to an incorrect population
Oksi 1998[130]	Excluded due to an incorrect population
Peltomaa 1998[131]	Excluded due to an incorrect comparison
Pena 1999[132]	Excluded due to an incorrect study design
Perronne 2015[133]	Not available
Pfister 1988[134]	Excluded due to an incorrect outcome
Pirila 1951[137]	Excluded due to an incorrect study design
Plorer 1993[138]	Excluded due to an incorrect study design
Plotkin 1991[139]	Excluded due to an incorrect study design
Puchalska 1996[140]	Excluded due to an incorrect study design
Puri 2015[141]	Excluded due to an incorrect comparison
Puri 2015[142]	Excluded due to an incorrect study design
Rebman 2015[143]	Excluded due to an incorrect study design
Renaud 2004[144]	Excluded due to an incorrect study design
Rohacova 1996[145]	Excluded due to an incorrect comparison
Rose 1994[146]	Excluded due to an incorrect study design
Rose 1996[147]	Excluded due to an incorrect intervention

Reference	Reason for exclusion
Rubin 1992[148]	Excluded due to an incorrect study design
Salazar 2005[149]	Excluded due to an incorrect intervention
Salazar 1993[150]	Excluded due to an incorrect study design
Sanchez 2016[151]	Excluded due to an incorrect study design
Sandstrom 1989[152]	Excluded due to an incorrect study design
Schmidt 1995[153]	Excluded due to an incorrect study design
Selby 2008[154]	Excluded due to an incorrect study design
Shadick 1994[155]	Excluded due to an incorrect study design
Shadick 1999[156]	Excluded due to an incorrect study design
Shemenski 2016[157]	Excluded due to an incorrect study design
Shoemaker 2006[158]	Excluded due to an incorrect intervention
Sjowall 2012[160]	Excluded due to an incorrect intervention
Sjowall 2011[159]	Excluded due to an incorrect study design
Skogman 2003[162]	Excluded due to an incorrect intervention
Skogman 2008[161]	Excluded due to an incorrect study design
Skoldenberg 1988[163]	Excluded due to an incorrect study design
Smith 2002[164]	Excluded due to an incorrect study design
Solomon 1998[165]	Excluded due to an incorrect intervention
Spathling 1992[166]	Article not in English
Stanek 1999[167]	Excluded due to an incorrect study design
Steere 1980[171]	Excluded due to an incorrect study design
Steere 1983[172]	Excluded due to an incorrect study design
Steere 1987[168]	Excluded due to an incorrect study design
Steurer 2016[173]	Article not in English
Stricker 2011[174]	Excluded due to an incorrect study design
Stricker 2010[175]	Excluded due to an incorrect study design
Strle 1996[176]	Excluded due to an incorrect outcome
Strle 1996[177]	Excluded due to an incorrect outcome
Strle 1992[178]	Excluded due to an incorrect study design
Strle 1993[179]	Excluded due to an incorrect outcome
Stupica 2015[181]	Excluded due to an incorrect comparison
Stupica 2011[180]	Excluded due to an incorrect comparison
Suarez-Magdalena 2017[182]	Not available
Thompson 2012[183]	Excluded due to an incorrect study design
Thorstrand 2002[184]	Excluded due to an incorrect study design
Thyresson 1949[185]	Excluded due to an incorrect study design
Torbahn 2016[186]	Excluded due to an incorrect study design
Tory 2010[187]	Excluded due to an incorrect comparison
Tseng 2017[188]	Excluded due to an incorrect outcome
Valesova 1996[189]	Excluded due to an incorrect comparison
Vazquez 2003[191]	Excluded due to an incorrect study design
Vazquez-Lopez 2016[190]	Excluded due to an incorrect study design
Wahlberg 1994[192]	Excluded due to an incorrect intervention
Weber 1988[194]	Excluded due to an incorrect study design
Weber 1987[193]	Excluded due to an incorrect population

Reference	Reason for exclusion
Weissenbacher 2005[195]	Excluded due to an incorrect intervention
White 2013[196]	Excluded due to an incorrect study design
Zochling 1996[197]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Table 22: Studies excluded from the health economic review

Reference	Reason for exclusion
Ogrinc 2006[127]	This study was assessed as not applicable. This cost consequence analysis included non-NHS and personal and social services related costs: sick pay. This cost was included in the total costs and no breakdown was presented, therefore it did not report the health-related costs only.