National Institute for Health and Care Excellence

Final

Lyme disease: diagnosis and management

[D] Evidence review for the management of erythema migrans

NICE guideline 95

Evidence review

April 2018

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

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Update information
July 2018: A minor correction was made to section 2.7.1. on oral doxycycline effectiveness.

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Contents

1 Management

This evidence report includes evidence examined for antibiotic management of erythema migrans and the discussions and decision-making of the committee. Antibiotic management for other presentations are outlined in reports E, F, G, H, I and L.

2 Management (erythema migrans)

2.1 Review question: What is the most clinically and cost-effective treatment for people with an erythema migrans?

2.2 Introduction

Erythema migrans (EM) is an early skin manifestation of Lyme disease. It normally occurs at the site of a tick bite (which may not have been noticed) as a gradually spreading area of erythema, which may or may not have an area of central clearing. EM is the most common presentation of Lyme disease. EM is generally treated following recognition without further testing, and serological blood tests may be negative at the time EM occurs, so blood tests may not be useful for diagnosis.

2.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People with erythema migrans

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

Comparisons	• Antimicrobial agents compared with each other
	  ○ If data are available consider:
	  - Type of antimicrobial agent (within class or between class)
	  - Route of administration
	  - Duration of treatment: 1 month versus longer

	• Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of EM) 3. Reduction of EM symptoms 4. EM relapse **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

2.4 Clinical evidence

2.4.1 Included studies

Twenty studies were included in the review; 18 RCTs[11,12,16,29,35,52,53,66,104,107,115,125,134,180,190,209,210,213] and 2 non-randomised comparative studies.[13,193] The non-randomised studies comparing different doses of doxycycline in adults and azithromycin with amoxicillin in children were included in this review as no RCT evidence could be found for these comparisons. Fifteen studies were in adults[16,29,35,52,53,104,107,115,125,180,190,193,209,210,213] and 5 studies in children.[11-13,66,134] No studies in young people were identified for this review. The studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 4).

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.

Two studies[53,115] showed serious intervention indirectness as people in the amoxicillin arm also received probenecid. Two studies[52,115] included an indirect population because the inclusion criteria allowed for an early-disseminated Lyme disease presentation.

2.4.2 Excluded studies

See the excluded studies list in appendix I.

2.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies in adults included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Barsic 2000[16]	(n=48) Azithromycin. 500 mg bid on the first day, followed by 500 mg once daily for the next 4 days. Duration 5 days. Concurrent medication or care: Not reported (n=40) Doxycycline. 100 mg bid. Duration 14 days.	n=88 Diagnosis: diagnosed with early Lyme disease confirmed by the presence of EM with or without systemic manifestations of infection	Cure Reduction in symptoms Symptom relapse Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	Concurrent medication or care: Not reported			
Breier 1996[29]	(n=30) Phenoxymethylpenicillin. 1.5 million IU 3 times per day. Duration 21 days. Concurrent medication or care: Not reported (n=30) Minocycline. 100 mg twice daily. Duration 21 days. Concurrent medication or care: Not reported	n=60 Diagnosis: EM	Cure Adverse events	
Cerar 2010[35]	(n=145) Doxycycline. 100 mg oral twice daily. Duration 15 days. Concurrent medication or care: Not reported (n=140) Cefuroxime axetil. 500 mg oral twice daily. Duration 15 days. Concurrent medication or care: Not reported	n=285 Diagnosis: typical solitary EM as defined by the CDC; or people with a skin lesion <5cm in diameter if they recalled a tick bite at the site of the skin lesion, had a symptom-free interval between the bite and the onset of the lesion, and reported an expanding skin lesion before diagnosis	Cure Reduction in symptoms Symptom relapse Adverse events	
Dattwyler 1990[53]	(n=38) Amoxicillin. 500 mg 3 times per day. Duration 21 days. Concurrent medication or care: 500 mg probenecid 3 times per day (n=38) Doxycycline. 100 mg twice per day. Duration 21 days. Concurrent medication or care: Not reported	n=75 Diagnosis: EM	Cure Symptom relapse	Serious indirectness: people in the amoxicillin arm also received probenecid
Dattwyler 1997[52]	(n=68) Ceftriaxone. 2 g once daily (50 mg per kg body weight for children), intravenously or	n=140 Diagnosis: acute disseminated	Cure Adverse events	Serious indirectness: people with acute disseminated Lyme disease

Study	Intervention and comparison	Population	Outcomes	Comments
	intramuscular at the discretion of the physician. Duration 14 days. Concurrent medication or care: Not reported (n=72) Doxycycline. 100 mg twice daily (4.4 mg per kg body weight for children), orally. Duration 21 days. Concurrent medication or care: Not reported	Lyme disease		
Luft 1996[104]	(n=122) Amoxicillin. 500 mg 3 times daily. Duration 20 days. Concurrent medication or care: Not reported (n=124) Azithromycin. 500 mg once daily and placebo doses twice daily for 7 days, then placebo doses 3 times daily until day 20. Duration 20 days. Concurrent medication or care: Not reported	n=246 Diagnosis: physician-documented EM	Cure Reduction in symptoms Symptom relapse Adverse events	
Luger 1995[107]	(n=119) Cefuroxime axetil. 500 mg twice daily, Ceftin (Glaxo Inc.). Duration 12 days. Concurrent medication or care: Not reported (n=113) Doxycycline. 100 mg 3 times per day, doxycycline hyclate (E R Squibb & Sons). Duration 12 days. Concurrent medication or care: Not reported	n=232 Diagnosis: physician-documented EM	Cure Reduction in symptoms Symptom relapse Adverse events	
Massarotti 1992[115]	(n=26) Azithromycin. 500 mg orally on the	n=81 Diagnosis:	Cure Symptom relapse	Serious indirectness: includes people with disseminated Lyme

Study	Intervention and comparison	Population	Outcomes	Comments
	first day followed by 250 mg once per day for 4 days. Duration 5 days. Concurrent medication or care: Not reported (n=29) Amoxicillin. 500 mg orally 3 times per day. Duration 10 days. Concurrent medication or care: 500 mg probenecid (n=26) Doxycycline. 100 mg orally twice per day. Duration 10 days. Concurrent medication or care: Not reported	erythema migrans or flu-like symptoms; if only flu-like symptoms then an elevated IgM or IgG antibody response to *B. burgdorferi* was required		disease Serious indirectness: people in the amoxicillin group also received probenecid
Nadelman 1992[125]	(n=63) Cefuroxime axetil. 500 mg twice daily, Ceftin (Glaxo Inc.). Duration 12 days. Concurrent medication or care: Not reported (n=60) Doxycycline. 100 mg 3 times per day, Doxycycline hyclate (E R Squibb). Duration 12 days. Concurrent medication or care: Not reported	n=123 Diagnosis: diagnosis of early Lyme disease confirmed by the presence of physician-documented EM	Cure Reduction in symptoms	
Steere 1983[180]	(n=40) Phenoxymethylpenicillin. 250 mg orally 4 times per day. Duration 10 days. Concurrent medication or care: Not reported (n=29) Erythromycin. 250 mg 4 times per day, orally. Duration 10 days. Concurrent medication or care: Not reported	n=184 Diagnosis: EM	Cure Symptom relapse	Symptom relapse measured with minor or major late disease. Minor late disease: facial palsy, supraventricular tachycardia, brief arthritis (<2 weeks), musculoskeletal pain Major late disease: myocarditis, meningoencephalitis, recurrent arthritis

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=39) Tetracycline. 250 mg 4 times per day, orally. Duration 10 days. Concurrent medication or care: Not reported (n=24) Tetracycline. 250 mg 4 times per day, orally. Duration 20 days. Concurrent medication or care: Not reported (n=25) Tetracycline. 250 mg 4 times per day, orally. Duration 10 days. Concurrent medication or care: Not reported			
Strle 1002[190]	(n=23) Doxycycline. 100 mg twice daily orally. Duration 14 days. Concurrent medication or care: not reported (n=22) Azithromycin. 250 mg twice daily for 2 days, 250 mg once daily for 8 days orally. Duration 10 days. Concurrent medication or care: not reported (n=23) Phenoxymethylpenicillin. 1 million IU 3 times daily orally. Duration 14 days. Concurrent medication or care: not reported	n=68 Diagnosis: typical EM	Adverse events	
Stupica 2012[193]	(n=117) High dosage. Oral doxycycline 100 mg twice daily. Duration 15 days. Concurrent medication or care: not reported	n=225 Diagnosis: typical solitary erythema migrans as defined by CDC; lesions <5cm in diameter also included if people	Cure	Non-randomised comparative study

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=108) Low dosage. Oral doxycycline 100 mg twice daily. Duration 10 days. Concurrent medication or care: not reported	recalled a recent tick bite at the site of a later skin lesion, had a symptom-free interval between the bite and onset of the lesion and reported an expanding skin lesion prior to diagnosis		
Weber 1990[209]	(n=40) Ceftriaxone. 1 g intramuscularly daily. Duration 5 days. Concurrent medication or care: not reported (n=33) Phenoxymethylpenicillin. 1 million units 3 times daily orally. Duration 12 days. Concurrent medication or care: not reported	n=73 Diagnosis: erythema migrans defined as expanding homogenous or ring-like erythema of the skin, with or without a history of a tick bite in the centre of the lesion	Adverse events	
Weber 1993[210]	(n=32) Azithromycin. 500 mg once daily orally. Duration 10 days. Concurrent medication or care: not reported (n=33) Phenoxymethylpenicillin. 1 million U (0.6g) 3 times daily orally. Duration 10 days. Concurrent medication or care: not reported	n=65 Diagnosis: EM	Cure Adverse events	
Wormser 2003[213]	(n=60) Polytherapy. Single 2 g dose of intravenous ceftriaxone followed by 10 days of oral doxycycline capsules twice daily, then 10 days of oral placebo. Duration 20 days. Concurrent medication or care: not reported Further details: 1.	n=180 Diagnosis: with EM; satisfying the US Centers for Disease Control and prevention's surveillance definition of Lyme disease (annular erythematous skin lesion >5cm in diameter)	Cure Reduction in symptoms Adverse events	Stratified then randomised: randomisation was stratified by whether people were symptomatic (any systemic symptoms or multiple EM lesions) or asymptomatic (single EM and no systemic symptoms) See clinical evidence

Study	Intervention and comparison	Population	Outcomes	Comments
	Previous treatment failure: No previous treatment (n=61) Monotherapy. Placebo injection followed by 10 days of oral doxycycline 100 mg twice daily, then 10 days of oral placebo twice daily. Duration 20 days. Concurrent medication or care: not reported (n=59) High dosage. Placebo injection followed by 20 days of oral doxycycline 100 mg twice daily. Duration 20 days. Concurrent medication or care: not reported			tables for full definitions of early and late complete and partial treatment response

Table 3: Summary of studies in children included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Arnez 1999[12]	(n=47) Cefuroxime axetil. 30 mg/kg/d (maximum 1,000 mg per day) divided into 2 equal doses every 12 hours. Duration 14 days. Concurrent medication or care: Not reported (n=47) Phenoxymethylpenicillin. 100,000 IU/kg/d (maximum 3 million IU/d) divided into 3 equal doses given every 8 hours. Duration 14 days. Concurrent medication or care: Not reported	n=94 Diagnosis: solitary EM	Adverse events	
Arnez 2002[11]	(n=42) Azithromycin. 20 mg/kg/d (maximum 1,000 mg/d) for the first day followed by 10 mg/kg/d (maximum 500 mg/d) for a further 4 days. Duration 5 days. Concurrent medication or care: Not reported (n=42) Phenoxymethylpenicillin. 100,000 IU/kg/d (maximum 3 million IU/d) divided into 3 equal doses given every 8 hours. Duration 14 days. Concurrent medication or care: Not reported	n=84 Diagnosis: solitary EM	Adverse events	
Arnez 2015[13]	(n=84) Azithromycin. 20 mg/kg/d (maximum 1,000 mg/d) for the first day followed by 10 mg/kg/d (maximum 500 mg/d) once per day for 4 days. Duration	n=168 Diagnosis: solitary EM	Cure (resolution of symptoms) Adverse events	Non-randomised study Cure measured with duration of symptoms

Study	Intervention and comparison	Population	Outcomes	Comments
	5 days. Concurrent medication/care: Not reported. (n=84) Amoxicillin. 50 mg/kg/d (maximum 1,500 mg/d) every 8 hours. Duration 14 days. Concurrent medication/care: Not reported.			
Eppes 2002[66]	(n=13) Amoxicillin. 50 mg/kg/d (maximum dose: 1,500 mg/d) divided every 8 hours. Duration 20 days. Concurrent medication or care: Not reported (n=15) High dosage. Cefuroxime axetil: 30 mg/kg/d (maximum dose: 1,000 mg/d) divided every 12 hours. Duration 20 days. Concurrent medication or care: 7 people received not further specified additional treatment (n=15) Low dosage. Cefuroxime axetil: 20 mg/kg/d (maximum dose: 750 mg/d) divided every 12 hours. Duration 20 days. Concurrent medication or care: Not reported	n=43 Diagnosis: physician-diagnosed EM	Cure Adverse events	
Nizič 2012[134]	(n=69) Amoxicillin. 50 mg/kg per day divided into 3 equal doses every 8 hours (max. 500mg/8h) orally. Duration 14 days. Concurrent medication or care: not reported	n=135 Diagnosis: untreated solitary EM established by modified CDC criteria; EM <5cm in diameter if they recalled a recent tick bite at the site	Adverse events	

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=66) Clarithromycin. 15 mg/kg per day divided into 2 equal doses every 12 hours (max. 500 mg/12 h) orally. Duration 14 days. Concurrent medication or care: not reported	of EM, had a symptom-free interval between the bite and onset of EM, or reported an expanding skin lesion prior to diagnosis		

See appendix D for full evidence tables.

2.4.4 Quality assessment of clinical studies in adults included in the evidence review

Table 4: Clinical evidence summary: doxycycline (PO) versus azithromycin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with azithromycin	Risk difference with doxycycline (95% CI)
Cure	126 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.83 (0.69 to 1)	859 per 1,000	146 fewer per 1,000 (from 266 fewer to 0 more)
Reduction in symptoms	88 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.2 (0.32 to 4.5)	83 per 1,000	17 more per 1,000 (from 57 fewer to 292 more)
Symptom relapse	126 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.85 (0.82 to 9.87)	47 per 1,000	87 more per 1,000 (from 8 fewer to 416 more)
Adverse events	125 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.21 (0.8 to 6.11)	75 per 1,000	90 more per 1,000 (from 15 fewer to 381 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 5: Clinical evidence summary: doxycycline (PO) versus cefuroxime axetil (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cefuroxime axetil	Risk difference with doxycycline (95% CI)
Cure (at 14 days)	285 (1 study)	LOW[1] due to risk of bias	RR 0.97 (0.85 to 1.12)	750 per 1,000	22 fewer per 1,000 (from 112 fewer to 90 more)
Cure (at 1 month)	300	LOW[1]	RR 1.01	690 per 1,000	7 more per 1,000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cefuroxime axetil	Risk difference with doxycycline (95% CI)
	(2 studies)	due to risk of bias	(0.87 to 1.17)		(from 90 fewer to 117 more)
Cure (at 2 months)	270 (1 study)	LOW[1] due to risk of bias	RR 0.96 (0.88 to 1.05)	896 per 1,000	36 fewer per 1,000 (from 107 fewer to 45 more)
Cure (at 6 months)	195 (1 study)	LOW[1] due to risk of bias	RR 1.02 (0.95 to 1.09)	935 per 1,000	19 more per 1,000 (from 47 fewer to 84 more)
Cure (at 1 year)	434 (3 studies)	LOW[1] due to risk of bias	RR 1.03 (0.97 to 1.09)	885 per 1,000	27 more per 1,000 (from 27 fewer to 80 more)
Reduction of symptoms (at 1 month)	300 (2 studies)	VERY LOW[1] due to risk of bias, imprecision	RR 1.13 (0.75 to 1.71)	219 per 1,000	29 more per 1,000 (from 55 fewer to 156 more)
Reduction of symptoms (at 1 year)	204 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.98 (0.47 to 2.04)	124 per 1,000	2 fewer per 1,000 (from 66 fewer to 129 more)
Symptom relapse (at 14 days)	285 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.71 to 1.56)	250 per 1,000	12 more per 1,000 (from 73 fewer to 140 more)
Symptom relapse (at 1 month)	300 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.54 (0.14 to 2.09)	39 per 1,000	18 fewer per 1,000 (from 33 fewer to 42 more)
Symptom relapse (at 2 months)	270 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.2 (0.61 to 2.33)	104 per 1,000	21 more per 1,000 (from 41 fewer to 139 more)
Symptom relapse (at 6 months)	195 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.46 (0.12 to 1.77)	65 per 1,000	35 fewer per 1,000 (from 57 fewer to 50 more)
Symptom relapse (at 1 year)	434 (3 studies)	LOW[1] due to risk of bias	RD -0.03 (-0.05 to 0.00)[3]	31 per 1,000	27 fewer per 1,000 (from 50 fewer to 0 more)
Adverse events	517 (2 studies)	VERY LOW[1,2,4] due to risk of bias, inconsistency,	RR 1.26 (0.7 to 2.27)	166 per 1,000	43 more per 1,000 (from 50 fewer to 211 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cefuroxime axetil	Risk difference with doxycycline (95% CI)
		imprecision			

[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] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms
[4] Downgraded by 1 increment because of heterogeneity, I^2=50-74%

Table 6: Clinical evidence summary: doxycycline (PO) versus amoxicillin (PO) plus probenecid

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amoxicillin plus probenecid	Risk difference with doxycycline (95% CI)
Cure	114 (2 studies)	VERY LOW[1,2,3,4] due to risk of bias, inconsistency, indirectness, imprecision	RR 0.91 (0.6 to 1.4)	945 per 1,000	85 fewer per 1,000 (from 378 fewer to 378 more)
Disease progression to late disease	73 (1 study)	VERY LOW[1,3,4] due to risk of bias, indirectness, imprecision	RR 1.62 (0.42 to 6.29)	83 per 1,000	52 more per 1,000 (from 48 fewer to 441 more)
Symptom relapse	111 (2 studies)	VERY LOW[1,5] due to risk of bias, indirectness	RD -0.01 (-0.07 to 0.06)[6]	19 per 1,000	6 fewer per 1,000 (from 70 fewer to 60 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 2 increments because of heterogeneity, I-squared >75%
[3] Downgraded by 1 increment because of intervention indirectness
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[5] Downgraded by 2 increments because of population indirectness and intervention indirectness

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amoxicillin plus probenecid	Risk difference with doxycycline (95% CI)

[6] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms

Table 7: Clinical evidence summary: doxycycline (PO) versus ceftriaxone (IV or IM)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with doxycycline (95% CI)
Cure (at 3 months)	123 (1 study)	VERY LOW[1,2] due to risk of bias, indirectness	RR 1.06 (0.98 to 1.14)	932 per 1,000	56 more per 1,000 (from 19 fewer to 131 more)
Cure (at 6 months)	123 (1 study)	VERY LOW[1,2] due to risk of bias, indirectness	RR 0.98 (0.84 to 1.13)	864 per 1,000	17 fewer per 1,000 (from 138 fewer to 112 more)
Cure (at 9 months)	123 (1 study)	VERY LOW[1,2] due to risk of bias, indirectness	RR 0.95 (0.87 to 1.05)	949 per 1,000	47 fewer per 1,000 (from 123 fewer to 47 more)
Adverse events	140 (1 study)	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.33 (0.95 to 1.86)	431 per 1,000	142 more per 1,000 (from 22 fewer to 370 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 because of population indirectness
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: doxycycline (PO) versus phenoxymethylpenicillin (PO)

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with phenoxymethylpenicillin	Risk difference with doxycycline (95% CI)
Adverse events	44 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 4.57 (0.58 to 35.96)	48 per 1,000	170 more per 1,000 (from 20 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

Table 9: Clinical evidence summary: 10-day doxycycline (PO) versus 15-day doxycycline (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 15-day doxycycline	Risk difference with 10-day doxycycline (95% CI)
Cure (at 14 days)	225 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision	RR 0.92 (0.73 to 1.14)	607 per 1,000	49 fewer per 1,000 (from 164 fewer to 85 more)
Cure (at 2 months)	217 (1 study)	VERY LOW[1,3] due to risk of bias	RR 0.98 (0.87 to 1.09)	867 per 1,000	17 fewer per 1,000 (from 113 fewer to 78 more)
Cure (at 6 months)	197 (1 study)	VERY LOW[1,3] due to risk of bias	RR 0.9 (0.81 to 0.99)	941 per 1,000	94 fewer per 1,000 (from 9 fewer to 179 fewer)
Cure (at 1 year)	177 (1 study)	VERY LOW[1,3] due to risk of bias	RR 0.98 (0.9 to 1.07)	934 per 1,000	19 fewer per 1,000 (from 93 fewer to 65 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] Non-randomised comparative study

Table 10: Clinical evidence summary: 10-day doxycycline (PO) versus 20-day doxycycline (PO)

Outcomes	Number of	Quality of the evidence	Relative	Anticipated absolute effects

	Participants (studies) Follow up	(GRADE)	effect (95% CI)	Risk with 20-day doxycycline	Risk difference with 10-day doxycycline (95% CI)
Cure (at 20 days)	93 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.1 (0.83 to 1.46)	644 per 1,000	64 more per 1,000 (from 110 fewer to 296 more)
Cure (at 3 months)	88 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.05 (0.82 to 1.34)	732 per 1,000	37 more per 1,000 (from 132 fewer to 249 more)
Cure (at 1 year)	83 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.12 (0.89 to 1.39)	750 per 1,000	90 more per 1,000 (from 83 fewer to 292 more)
Cure (at 30 months)	62 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.08 (0.89 to 1.31)	839 per 1,000	67 more per 1,000 (from 92 fewer to 260 more)
Reduction of symptoms (at 20 days; partial response)	93 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision, indirectness	RR 0.76 (0.41 to 1.4)	356 per 1,000	85 fewer per 1,000 (from 210 fewer to 142 more)
Reduction of symptoms (at 3 months; partial response)	88 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision, indirectness	RR 0.79 (0.38 to 1.67)	268 per 1,000	56 fewer per 1,000 (from 166 fewer to 180 more)
Reduction of symptoms (at 1 year; partial response)	83 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision, indirectness	RR 0.56 (0.22 to 1.39)	250 per 1,000	110 fewer per 1,000 (from 195 fewer to 97 more)
Reduction of symptoms (at 30 months; partial response)	62 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision, indirectness	RR 0.4 (0.08 to 1.91)	161 per 1,000	97 fewer per 1,000 (from 148 fewer to 147 more)
Adverse events	120 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.04 (0.69 to 1.57)	424 per 1,000	17 more per 1,000 (from 131 fewer to 242 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 increment if the majority of the evidence was based on an indirect outcome

Table 11: Clinical evidence summary: 10-day tetracycline (PO) versus 20-day tetracycline (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 20-day tetracycline	Risk difference with 10-day tetracycline (95% CI)
Cure	49 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.02 (0.69 to 1.51)	667 per 1,000	13 more per 1,000 (from 207 fewer to 340 more)
Minor late disease	49 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.96 (0.43 to 2.15)	333 per 1,000	13 fewer per 1,000 (from 190 fewer to 383 more)
Major late disease	49 (1 study)	LOW[1] due to risk of bias	RD 0.00 (-0.08 to 0.08)[3]	0 events in the control arm	0 events in the intervention arm

[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] Risk difference is given because of a zero event rate in both arms

Table 12: Clinical evidence summary: tetracycline (PO) versus phenoxymethylpenicillin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with tetracycline (95% CI)
Cure	79 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.41 (0.88 to 2.25)	400 per 1,000	164 more per 1,000 (from 48 fewer to 500 more)
Minor late disease	79 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.54 to 1.4)	500 per 1,000	65 fewer per 1,000 (from 230 fewer to 200 more)
Major late disease	79 (1 study)	VERY LOW[1,2] due to risk of bias,	OR 0.13 (0.01 to 1.3)[3]	75 per 1,000	65 fewer per 1,000 (from 74 fewer to 20 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with tetracycline (95% CI)
		imprecision			

[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 group

Table 13: Clinical evidence summary: amoxicillin (PO) versus azithromycin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with azithromycin	Risk difference with amoxicillin (95% CI)
Cure	217 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.16 (1.02 to 1.32)	757 per 1,000	121 more per 1,000 (from 15 more to 242 more)
Reduction of symptoms	217 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.57 (0.31 to 1.05)	216 per 1,000	93 fewer per 1,000 (from 149 fewer to 11 more)
Symptom relapse	209 (1 study)	MODERATE[1] due to risk of bias	RR 0.24 (0.08 to 0.7)	160 per 1,000	122 fewer per 1,000 (from 48 fewer to 148 fewer)
Adverse events	246 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.69 (0.46 to 1.02)	347 per 1,000	108 fewer per 1,000 (from 187 fewer to 7 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 14: Clinical evidence summary: amoxicillin (PO) plus probenecid versus azithromycin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with azithromycin	Risk difference with amoxicillin and probenecid (95% CI)
Cure	35 (1 study)	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 1.04 (0.76 to 1.41)	812 per 1,000	32 more per 1,000 (from 195 fewer to 333 more)
Symptom relapse	35 (1 study)	VERY LOW[1,2,3] due to risk of bias, indirectness, imprecision	RR 0.84 (0.06 to 12.42)	62 per 1,000	10 fewer per 1,000 (from 59 fewer to 714 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 because of intervention indirectness
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 15: Clinical evidence summary: ceftriaxone (IM) versus phenoxymethylpenicillin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with ceftriaxone (95% CI)
Jarisch-Herxheimer reaction	73 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.06 (0.44 to 2.54)	212 per 1,000	13 more per 1,000 (from 119 fewer to 327 more)
Major side effects	73 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	OR 6.36 (0.39 to 105.1)[3]	0 per 1,000	50 more per 1,000 (from 18 more to 118 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 control arm

Table 16: Clinical evidence summary: ceftriaxone (IV) plus doxycycline (PO) versus doxycycline (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with doxycycline	Risk difference with ceftriaxone and doxycycline (95% CI)
Cure (at 20 days)	100 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 0.92 (0.71 to 1.21)	708 per 1,000	57 fewer per 1,000 (from 205 fewer to 149 more)
Cure (at 3 months)	95 (1 study)	MODERATE[1] due to risk of bias	RR 0.98 (0.78 to 1.23)	766 per 1,000	15 fewer per 1,000 (from 169 fewer to 176 more)
Cure (at 1 year)	88 (1 study)	MODERATE[1] due to risk of bias	RR 0.98 (0.81 to 1.19)	837 per 1,000	17 fewer per 1,000 (from 159 fewer to 159 more)
Cure (at 30 months)	68 (1 study)	MODERATE[1] due to risk of bias	RR 0.96 (0.81 to 1.14)	903 per 1,000	36 fewer per 1,000 (from 172 fewer to 126 more)
Reduction of symptoms (at 20 days)	100 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.28 (0.7 to 2.32)	271 per 1,000	76 more per 1,000 (from 81 fewer to 357 more)
Reduction of symptoms (at 3 months)	95 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.17 (0.56 to 2.45)	213 per 1,000	36 more per 1,000 (from 94 fewer to 309 more)
Reduction of symptoms (at 1 year)	88 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.27 (0.48 to 3.37)	140 per 1,000	38 more per 1,000 (from 73 fewer to 331 more)
Reduction of symptoms (at 30 months)	68 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.09 (0.44 to 10.06)	65 per 1,000	70 more per 1,000 (from 36 fewer to 585 more)
Adverse events	121 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.39 (0.99 to 1.97)	443 per 1,000	173 more per 1,000 (from 4 fewer to 429 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 17: Clinical evidence summary: minocycline (PO) versus phenoxymethylpenicillin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with minocycline (95% CI)
Cure	39 (1 study)	LOW[1] due to risk of bias	RR 1 (0.91 to 1.1)	1,000 per 1,000	0 fewer per 1,000 (from 90 fewer to 100 more)
Adverse events	39 (1 study)	LOW[1] due to risk of bias	RR 3.5 (1.37 to 8.96)	190 per 1,000	476 more per 1,000 (from 70 more to 1,000 more)

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

Table 18: Clinical evidence summary: azithromycin (PO) versus phenoxymethylpenicillin (PO)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with azithromycin (95% CI)
Cure (at 10 days) number of people with signs and symptoms	65 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.64 (0.46 to 0.89)	879 per 1,000	316 fewer per 1,000 (from 97 fewer to 475 fewer)
Cure (at 1 month) number of people with signs and symptoms	65 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.44 to 1.37)	485 per 1,000	112 fewer per 1,000 (from 272 fewer to 179 more)
Cure (at 3 months) number of people with signs and symptoms	65 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.44 (0.51 to 4.08)	152 per 1,000	67 more per 1,000 (from 74 fewer to 467 more)
Cure (at 6 months) number of people with signs and symptoms	53 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.89 (0.25 to 3.2)	160 per 1,000	18 fewer per 1,000 (from 120 fewer to 352 more)
Adverse events	106 (2 studies)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.41 (1.02 to 5.69)	111 per 1,000	157 more per 1,000 (from 2 more to 521 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with azithromycin (95% CI)
[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 summary: erythromycin (PO) versus phenoxymethylpenicillin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with erythromycin (95% CI)
Cure	69 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.21 (0.71 to 2.06)	400 per 1,000	84 more per 1,000 (from 116 fewer to 424 more)
Minor late disease	69 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.76 (0.43 to 1.33)	500 per 1,000	120 fewer per 1,000 (from 285 fewer to 165 more)
Major late disease	69 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.84 (0.45 to 7.6)	75 per 1,000	63 more per 1,000 (from 41 fewer to 495 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 20: Clinical evidence summary: erythromycin (PO) versus tetracycline (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with tetracycline	Risk difference with erythromycin (95% CI)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with tetracycline	Risk difference with erythromycin (95% CI)
Cure	68 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.86 (0.54 to 1.37)	564 per 1,000	79 fewer per 1,000 (from 259 fewer to 209 more)
Minor late disease	68 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.87 (0.48 to 1.56)	436 per 1,000	57 fewer per 1,000 (from 227 fewer to 244 more)
Major late disease	68 (1 study)	LOW[1] due to risk of bias	OR 11.64 (1.53 to 88.43)[3]	0 per 1,000	138 more per 1,000 (from 12 more to 263 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 control arm

2.4.5 Quality assessment of clinical studies in children included in the evidence review

Table 21: Clinical evidence summary: amoxicillin (PO) versus high-dose cefuroxime axetil (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with high-dose cefuroxime axetil	Risk difference with amoxicillin (95% CI)
EM resolved	27 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.77 (0.49 to 1.2)	867 per 1,000	199 fewer per 1,000 (from 442 fewer to 173 more)
Lyme disease symptoms resolved (at 3 weeks)	27 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.14 (0.9 to 1.44)	867 per 1,000	121 more per 1,000 (from 87 fewer to 381 more)
Lyme disease symptoms resolved (at 6 months)	28 (1 study)	LOW[1] due to risk of bias	RR 1 (0.87 to 1.14)	1,000 per 1,000	0 fewer per 1,000 (from 130 fewer to 140 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with high-dose cefuroxime axetil	Risk difference with amoxicillin (95% CI)
Lyme disease symptoms resolved (at 1 year)	27 (1 study)	LOW[1] due to risk of bias	RR 1 (0.87 to 1.15)	1,000 per 1,000	0 fewer per 1,000 (from 130 fewer to 150 more)
Allergic reaction	27 (1 study)	LOW[1] due to risk of bias	RD 0.00 (-0.13 to 0.13)[3]	0 events in the control arm	0 events in the intervention arm
Vomiting	27 (1 study)	LOW[1] due to risk of bias	RD 0.00 (-0.13 to 0.13)[3]	0 events in the control arm	0 events in the intervention arm
Diarrhoea between 2-5 days	27 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.83 (0.16 to 4.21)	200 per 1,000	34 fewer per 1,000 (from 168 fewer to 642 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] Risk difference is given because of a zero event rate in both arms

Table 22: Clinical evidence summary: amoxicillin (PO) versus low-dose cefuroxime axetil (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low-dose cefuroxime axetil	Risk difference with amoxicillin (95% CI)
EM resolved	25 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.72 (0.47 to 1.11)	923 per 1,000	258 fewer per 1,000 (from 489 fewer to 102 more)
Lyme disease symptoms resolved (at 3 weeks)	25 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.42 (0.97 to 2.06)	692 per 1,000	291 more per 1,000 (from 21 fewer to 734 more)
Lyme disease symptoms	25	LOW[1]	RR 1	1,000 per	0 fewer per 1,000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low-dose cefuroxime axetil	Risk difference with amoxicillin (95% CI)
resolved (at 6 months)	(1 study)	due to risk of bias	(0.86 to 1.16)	1,000	(from 140 fewer to 160 more)
Lyme disease symptoms resolved (at 1 year)	25 (1 study)	LOW[1] due to risk of bias	RR 1 (0.86 to 1.16)	1,000 per 1,000	0 fewer per 1,000 (from 140 fewer to 160 more)
Allergic reaction	27 (1 study)	LOW[1] due to risk of bias	RD 0.00 (-0.13 to 0.13)[3]	0 events in the control arm	0 events in the intervention arm
Vomiting	27 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	OR 0.17 (0 to 8.54)[4]	67 per 1,000	55 fewer per 1,000 (from 67 fewer to 312 more)
Diarrhoea between 2-5 days	27 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 2.5 (0.26 to 24.38)	67 per 1,000	100 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] Risk difference is given because of a zero event rate in both arms
[4] The Peto odds ratio method was used because of a zero event rate in the intervention group

Table 23: Clinical evidence summary: amoxicillin (PO) versus clarithromycin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clarithromycin	Risk difference with amoxicillin (95% CI)
Jarisch-Herxheimer reaction	130 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.16 (0.65 to 2.07)	242 per 1,000	39 more per 1,000 (from 85 fewer to 259 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

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with clarithromycin	Risk difference with amoxicillin (95% CI)
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 24: Clinical evidence summary: cefuroxime axetil (PO) versus phenoxymethylpenicillin (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with cefuroxime axetil	Risk difference with cefuroxime axetil (95% CI)
Adverse events	90 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 3.83 (1.16 to 12.65)	68 per 1,000	193 more per 1,000 (from 11 more to 794 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 25: Clinical evidence summary: high-dose cefuroxime axetil (PO) versus low-dose cefuroxime axetil (PO)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low-dose cefuroxime axetil	Risk difference with high-dose cefuroxime axetil (95% CI)
EM resolved	28 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.94 (0.73 to 1.21)	923 per 1,000	55 fewer per 1,000 (from 249 fewer to 194 more)
Lyme disease symptoms resolved (at 3 weeks)	28 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.25 (0.83 to 1.89)	692 per 1,000	173 more per 1,000 (from 118 fewer to 616 more)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with low-dose cefuroxime axetil	Risk difference with high-dose cefuroxime axetil (95% CI)
Lyme disease symptoms resolved (at 6 months)	28 (1 study)	LOW[1] due to risk of bias	RR 1 (0.87 to 1.14)	1,000 per 1,000	0 fewer per 1,000 (from 130 fewer to 140 more)
Lyme disease symptoms resolved (at 12 months)	28 (1 study)	LOW[1] due to risk of bias	RR 1 (0.87 to 1.14)	1,000 per 1,000	0 fewer per 1,000 (from 130 fewer to 140 more)
Allergic reaction	30 (1 study)	LOW[1] due to risk of bias	RD 0.00 (-0.12 to 0.12)[3]	0 events in the control arm	0 events in the intervention arm
Vomiting	30 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	OR 0.14 (0 to 6.82)[4]	67 per 1,000	57 fewer per 1,000 (from 67 fewer to 261 more)
Diarrhoea between 2-5 days	30 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 3 (0.35 to 25.68)	67 per 1,000	133 more per 1,000 (from 43 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] Risk difference is given because of a zero event rate in both arms
[4] The Peto odds ratio method was used because of a zero event rate in the intervention group

Table 26: Clinical evidence summary: azithromycin (PO) versus phenoxymethylpenicillin (PO)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with azithromycin (95% CI)
Adverse events	81 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.17 (0.47 to 2.93)	171 per 1,000	29 more per 1,000 (from 90 fewer to 330 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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with phenoxymethylpenicillin	Risk difference with azithromycin (95% CI)
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 27: Clinical evidence summary: azithromycin (PO) versus amoxicillin (PO)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amoxicillin	Risk difference with azithromycin (95% CI)
Duration of EM symptoms	168 (1 study)	VERY LOW[1,2]	Not applicable	The mean duration of EM symptoms in the control group was 5.9 days (SD 8.8)	The mean duration of EM symptoms in the intervention group was 1.2 lower (3.35 lower to 0.95 higher)
Duration of systemic symptoms	15 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision	Not applicable	The mean duration of systemic symptoms in the control group was 6.3 days (SD 4.6)	The mean duration of systemic symptoms in the intervention group was 3.3 higher (7.18 lower to 13.78 higher)
Adverse events	168 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision	RR 1.38 (0.73 to 2.64)	155 per 1,000	59 more per 1,000 (from 42 fewer to 254 more)
Jarisch-Herxheimer reaction	168 (1 study)	VERY LOW[1,2,3] due to risk of bias, imprecision	RR 0.46 (0.18 to 1.16)	155 per 1,000	84 fewer per 1,000 (from 127 fewer to 25 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with amoxicillin	Risk difference with azithromycin (95% CI)

[1] Non-randomised 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 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

2.5 Economic evidence

2.5.1 Included studies

No relevant health economic studies were identified.

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

2.5.2 Excluded studies

No relevant health economic studies were identified and excluded.

2.5.3 Unit costs

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

Table 28: UK costs of antimicrobials

Class	Drug	Age	Preparation	Mg/unit	Cost/unit (£)	Units/day	Course duration (days)	Cost per course (£)
Penicillins	Amoxicillin	7 days-11 months	125 mg/1.25 ml oral suspension paediatric	125	0.20	3	14–28	8.35–16.70
		1-4 years	250 mg/5 ml oral suspension	250	0.06	3	14–28	2.37–4.75
		>5 years	capsules	500	0.06	3	14–28 (g)	2.54–5.08
Penicillins	Phenoxymethylpenicillin	Adults (a)	tablets	250	0.04	4	10	1.49
Tetracyclines	Doxycycline	>12 years	capsules	100	0.11	2	10–28 (h)	2.18–6.09
Cephalosporins	Cefuroxime axetil	>3 months	tablets	250	1.27	4	14–28(g)	70.88–141.76
Macrolide	Clarithromycin	>1 month	tablets	500	0.16	2	14–21	4.42–6.63
Macrolide	Azithromycin	<12 years	40 mg/1 ml oral suspension	40	0.27	10 mg/kg	9 (i)	Weight dependent.
		Adults	tablets	500	0.42	1	9 (i)	3.75
Cephalosporins	Cefotaxime	Adults (b)	2 g powder for solution for injection vials (IV)	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,[132] except cefotaxime from BNF, January 2017[25] and ceftriaxone from EMIT March 2017;[44] dosage from BNF and BNF for Children January 2017,[25,26] exceptions below:

(a) Source of dosage from RCT in adults with ECM: Steere 1983,[180] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[145] and Pfister 1991,[146] dosage for Lyme disease not available from BNF or BNF for children.[25,26]

(c) For disseminated Lyme borreliosis.

(d) Dose for neonate and child up to 11 years (body weight <50kg) 50-80 mg/kg once daily for 14-21 days. BNF for children January 2017.[26]

(e) Administration can vary in adults and children >1month: IV infusion over 30 mins or IV injection over 5 mins or deep muscular injection (doses over 1 g divided between more than 1 site): 2 g per day for 14-21 days BNF January 2017.[25]

(f) Source of dosage from RCT in adults with Lyme arthritis: Steere 1985[179]: 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.[25,26]

(g) Course duration for early Lyme 14-21 days; 28 days for Lyme arthritis. BNF January 2017.[25]

(h) Course duration for early Lyme 10-14 days; 28 days for Lyme arthritis. BNF January 2017.[25]

(i) Course dose and duration for adults: 500 mg once daily for 3 days, for 3 weeks. For children under 12 years: 10mg/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[48])
- 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)[129]. 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 that offset the higher cost of the drug itself. In addition, once daily administration of drug will be additionally cost effective due to reduced likelihood of drug administration error and the associated costs (personal health and financial).

Inpatient administration

Intravenous antibiotics administered in an inpatient setting will incur the cost of an inpatient stay that 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.[55]

Table 29: 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[55]

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[36] 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 29, 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.

2.6 Resource impact

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

2.7 Evidence statements

2.7.1 Clinical evidence statements

Adults:

- Very Low quality evidence from 2 RCTs showed that oral azithromycin resulted in higher cure rates than oral doxycycline. Very Low quality evidence from 1 RCT and Very Low quality from 2 RCTs did not find any clinically important difference in reduction of symptoms and symptom relapse, respectively, between oral doxycycline and oral azithromycin. Very Low quality evidence form 2 RCTs did not find any difference in adverse events between oral doxycycline and oral azithromycin.
- Low to Very Low quality evidence from 3 RCTs did not find any clinically important difference for any of the outcomes reported for the comparison of oral doxycycline versus oral cefuroxime axetil.
- Very Low quality evidence from 2 RCTs showed that oral doxycycline was equally as effective as oral amoxicillin plus probenecid for cure and symptom relapse. Very Low quality evidence from 1 RCT found oral doxycycline to be equally as effective as oral amoxicillin plus probenecid for the prevention of progression to late disease.
- Very Low quality evidence from 1 RCT found no difference between oral doxycycline and intravenous or intramuscular ceftriaxone for cure at 3, 6 or 9 months. Very Low quality evidence from 1 RCT found oral doxycycline to result in fewer adverse events than intravenous or intramuscular ceftriaxone.
- Very Low quality evidence from 1 RCT showed that oral doxycycline resulted in more adverse events than oral phenoxymethylpenicillin.
- Very Low quality from 1 cohort study did not find any clinically important difference in cure between a 10-day course of oral doxycycline and a 15-day course of oral doxycycline.
- Low quality evidence from 1 RCT did not find any difference in cure between a 10-day course and a 20-day course of oral doxycycline. Very Low quality evidence from 1 RCT did not find any difference in reduction of symptoms at 20 days, 3 months or 30 months. Very Low quality evidence from 1 RCT did not find any difference in adverse events between a 10-day course and a 20-day course of oral doxycycline.
- Low to Very Low quality evidence from 1 RCT did not find any difference in cure and minor and major late disease between a 10-day course and a 20-day course of oral tetracycline.
- Very Low quality evidence from 1 RCT found oral tetracycline to result in higher cure rates than oral phenoxymethylpenicilllin. Very Low quality evidence from 1 RCT did not find any difference between in oral tetracycline and oral phenoxymethylpenicillin for the outcomes minor and major late disease.
- Low quality evidence from 1 RCT found oral amoxicillin to be more effective than oral azithromycin for cure. Moderate quality evidence from 1 RCT showed that oral amoxicillin resulted less often in symptom relapse and Very Low quality evidence form 1 RCT found oral amoxicillin to result in fewer adverse events than oral azithromycin. Low quality evidence from 1 RCT did not find a difference in reduction of symptoms between oral amoxicillin and oral azithromycin.

July 2018: A minor correction was made to section 2.7.1. on oral doxycycline effectiveness.

- Very Low quality from 1 RCT did not find any difference in cure and symptom relapse between oral amoxicillin plus probenecid and oral azithromycin.
- Very Low quality from 1 RCT did not find any difference in the occurrence of Jarisch-Herxheimer reactions and major side effects between intramuscular ceftriaxone and oral phenoxymethylpencillin.
- Moderate to Low quality evidence from 1 RCT did not find any difference in cure between a 1-off dose of intravenous ceftriaxone followed by oral doxycycline and oral doxycycline alone. Very Low quality evidence from 1 RCT did not find any difference in the reduction of symptoms between a 1-off dose of intravenous ceftriaxone followed by oral doxycycline and oral doxycycline alone. Low quality evidence from 1 RCT found a 1-off dose of intravenous ceftriaxone followed by oral doxycycline to result in more adverse events than oral doxycycline alone.
- Low quality evidence from 1 RCT found oral minocycline to result in more adverse events than oral phenoxymethylpenicillin but there was no difference in cure.
- Very Low quality evidence from 1 RCT showed a clinical benefit of oral azithromycin over oral phenoxymethylpenicillin for cure at 10 days and 1 month. Very Low quality evidence from 1 RCT did not find any difference between oral azithromycin and oral phenoxymethylpencillin for cure at 3 months and 6 months. Very Low quality evidence from 1 RCT showed that oral azithromycin resulted in more adverse events than oral phenoxymethylpencillin.
- Very Low quality evidence form 1 RCT did not find any difference in cure or the chance of progression to major late disease between oral erythromycin and oral phenoxymethylpenicillin. Very Low quality from 1 RCT found a clinical benefit of oral erythromycin compared to oral phenoxymethylpenicillin for the chance of progression to minor late disease.
- Very Low quality evidence form 1 RCT did not find any difference in cure or the chance of progression to minor late disease between oral erythromycin and oral tetracycline. Low quality from 1 RCT found a clinical benefit of oral tetracycline compared to oral erythromycin for the chance of progression to major late disease.

Young people:

- No evidence was found.

Children:

- Very Low quality evidence from 1 RCT found a clinical benefit of oral amoxicillin over oral high-dose cefuroxime axetil for the resolution of Lyme disease symptoms at 3 weeks and a clinical benefit of oral high-dose cefuroxime axetil over oral amoxicillin for the resolution of EM. Low to Very Low quality evidence from 1 RCT did not find any difference between oral amoxicillin and oral high-dose cefuroxime axetil for the resolution of Lyme disease symptoms as 6 months and 1 year and adverse events.
- Very Low quality evidence from 1 RCT found a clinical benefit of oral amoxicillin over oral low-dose cefuroxime axetil for the resolution of Lyme disease symptoms at 3 weeks and a clinical benefit of oral low-dose cefuroxime axetil over oral amoxicillin for the resolution of EM. Low to Very Low quality evidence from 1 RCT did not find any difference between oral amoxicillin and oral low-dose cefuroxime axetil for the resolution of Lyme disease symptoms as 6 months and 1 year. Low to Very Low quality evidence from 1 RCT did not find any difference in adverse events, except for diarrhoea between 2-5 days, which occurred more often in the amoxicillin group.
- Very Low quality evidence from 1 RCT did not find any difference between oral amoxicillin and oral clarithromycin for the occurrence of a Jarisch-Herxheimer reaction.

- Very Low quality evidence from 1 RCT showed a clinical benefit of oral phenoxymethylpenicillin over oral cefuroxime axetil for adverse events.
- Very Low quality evidence from 1 RCT found a clinical benefit of oral high-dose cefuroxime axetil over oral low-dose cefuroxime axetil for the resolution of Lyme disease symptoms at 3 weeks. Low to Very Low quality evidence form 1 RCT did not find any difference between high-dose and low-dose cefuroxime axetil for the resolution of EM or the resolution of Lyme disease symptoms at 6 months and 12 months. Low to Very Low quality evidence from 1 RCT did not find any difference in adverse events, except for diarrhoea between 2-5 days, which occurred more often in the high-dose cefuroxime axetil group.
- Very Low quality evidence from 1 RCT did not find any difference between oral azithromycin and oral phenoxymethylpenicillin for adverse events.
- Very Low quality evidence from 1 cohort study found systemic symptoms to be on average of shorter duration when taking oral amoxicillin compared to oral azithromycin. Very Low quality evidence from 1 cohort study did not find any difference in the duration of EM symptoms between oral amoxicillin and oral azithromycin. Very Low quality evidence from 1 cohort study did not find any difference in adverse events or Jarisch-Herxheimer reactions between oral amoxicillin and oral azithromycin.

2.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

2.8 The committee's discussion of the evidence

2.8.1 Interpreting the evidence

2.8.1.1 The outcomes that matter most

The committee considered cure (resolution of symptoms), reduction in symptoms, symptom relapse, and quality of life to be critical outcomes to decision-making. Adverse events were also considered to be important to decision-making.

2.8.1.2 The quality of the evidence

The evidence was of Low to Very Low quality due to risk of bias, imprecision, inconsistency and indirectness. There were particular concerns about a lack of blinding of study participants, healthcare professionals who administered the treatment, and outcome assessors. There were also issues regarding randomisation with many studies not fully reporting on what method of randomisation had been used. Many outcomes and the time point at which they were assessed were poorly defined in the included studies making a clear interpretation of the evidence difficult. In particular, it was not clear whether cure or reduction of symptoms referred to the resolution or improvement of the erythema migrans rash or of any Lyme disease symptoms. Similar ambiguity existed for the outcomes of reoccurrence of symptoms. Studies also varied in the outcomes they reported.

Most of the included studies used low, probably sub-therapeutic, doses of antibiotics, which made the interpretation of their effectiveness difficult. Two studies included an indirect intervention as people received probenecid in addition to amoxicillin to increase the concentration of amoxicillin. There was no consistency in comparisons of dose or lengths of treatments used between included studies, or throughout the literature.

Two studies had an indirect population, that is, people had symptoms in addition to the erythema migrans rash. In 1 study, people had acute disseminated Lyme disease, which

included multiple erythema migrans lesions or flu-like symptoms, heart block, facial palsy or radiculitis of less than 3 months' duration, and acute large-joint arthritis. The second study was in people with an erythema migrans rash and flu-like symptoms.

The lack of evidence meant that, for most comparisons, no meta-analyses could be conducted. Ten of the 20 included studies were relatively small and included less than 100 participants. For some antibiotics listed in the review protocol, no evidence could be found.

2.8.1.3 Benefits and harms

Dosing, duration of antibiotic treatments and comparisons were extremely varied. For clarity, the benefits and harms of treatments for EM are discussed in 3 broad groups. There was a general lack of evidence for many of the antibiotics listed in the review protocol. Most of the evidence identified was of poor quality and based on single, small studies.

2.8.1.3.1 Benefits and harms of doxycycline compared with other antibiotics

The evidence on the effectiveness of a longer duration of oral doxycycline therapy over a shorter course of oral doxycycline showed no difference. Evidence from 1 study showed that a 20-day course of doxycycline 100 milligrams twice daily resulted in a better long-term reduction of symptoms compared to a 10-day course of doxycycline; however, the committee recognised that this outcome was indirect, as it did not include those who had had a complete recovery, and thus could not be considered a benefit. There was no clinically important difference for cure or in the number of adverse events between the 2 treatment durations.

There was no difference in clinical effectiveness between a 15-day and a 10-day course of oral doxycycline 100 milligrams twice daily.

Doxycycline was as effective as intravenous antibiotics or a combination of other types of antibiotics.

Oral doxycycline 100 milligrams twice and 3 times daily was equally as effective as oral cefuroxime axetil 500 milligrams twice daily at cure, preventing symptom relapse or the reduction in symptoms. The duration of treatment varied between 12 and 15 days.

Oral doxycycline was less effective than oral azithromycin for cure with a high absolute rate for cure for both interventions. The evidence did not show any clinical difference between oral azithromycin and oral doxycycline for the prevention of symptom relapse. The absolute chance of symptom relapse was low in both groups. The committee noted that people in the doxycycline group received 100 milligrams doxycycline twice daily for 10 days in 1 study and 14 days in the other. Azithromycin was given over a total of 5 days; people received 500 milligrams once on the first day followed by 250 milligrams once per day for 4 additional days in 1 study and 500 milligrams twice on the first day followed by 500 milligram once per day for 4 additional days in the other, thus receiving therapeutic treatment levels for 1 week compared to 10 or 14 days used for doxycycline. The committee agreed that these azithromycin regimens were not in line with standard prescribing practice, which requires azithromycin to be given once daily for 3 consecutive days to achieve a desired tissue concentration for a week.

Doxycycline 100 milligrams twice daily was equally as effective as amoxicillin 500 milligrams 3 times daily plus 500 milligrams probenecid 3 times daily for cure and preventing disease progression to late disease. There was also no difference between the groups in preventing symptoms relapse although the absolute chance of symptom relapse was very low in both groups.

The evidence review included comparisons between oral doxycycline and intravenous or intramuscular cephalosporins. There was no clear clinical benefit of intravenous or

intramuscular ceftriaxone 2 grams once daily for 14 days over oral doxycycline 100 milligrams twice daily for 21 days. Doxycycline resulted in fewer adverse events, however, than intravenous or intramuscular ceftriaxone. There was no benefit of a 1-off dose of 2 grams intravenous ceftriaxone followed by oral doxycycline 100 milligrams twice daily for 10 days over oral doxycycline 100 milligrams twice daily for 10 days alone for cure or the reduction of symptoms. The combination of intravenous ceftriaxone and oral doxycycline resulted in a higher number of adverse events than oral doxycycline alone. There was no difference in cure rates. The committee considered that the 10-day course of doxycycline given in the study was a shorter duration than that usually used in clinical practice.

Doxycycline was associated with more adverse events than the other antibiotics it was compared to. The committee acknowledged the common side effects associated with doxycycline such as photosensitivity, nausea and diarrhoea. The committee considered the clinical benefit of doxycycline to outweigh the risk of side effects, particularly considering the relatively low number of people experiencing side effects from doxycycline in the included studies.

The committee noted that doses and treatment durations in most of the included studies did not reflect current clinical practice. While 100 milligrams of doxycycline twice daily was in line with current prescribing practice, treatment durations tended to be significantly shorter than the committee was expecting. Treatment durations and doses of the other antibiotics were also significantly shorter and lower than what is currently used in clinical practice.

No evidence on the effectiveness of doxycycline in children was identified.

2.8.1.3.2 Benefits and harms of oral amoxicillin when compared with antibiotics other than doxycycline

In adults, oral amoxicillin 500 milligrams 3 times per day with probenecid for 10 days was equally as effective as a 1-off dose of 500 milligrams oral azithromycin followed by a 4-day course of 250 milligrams of oral azithromycin for cure and preventing symptom relapse. There was a benefit of azithromycin 500 milligrams once daily for 7 days over amoxicillin 500 milligrams 3 times per day for 20 days for cure, but a benefit of amoxicillin for preventing symptom relapse (developing late complications) and adverse events.

In children, evidence from 1 study showed that oral amoxicillin (50 milligrams per kilogram body weight per day given every 8 hours for 20 days) was more effective than high dose oral cefuroxime axetil (30 milligrams per kilogram body weight per day given every 12 hours for 20 days) for the resolution of Lyme disease symptoms at 3 weeks, while the reverse was true for the resolution of erythema migrans. There was no difference in the long-term resolution of Lyme disease symptoms, cure rates or adverse events. When compared with low dose oral cefuroxime axetil (20 milligrams per kilogram body weight per day given every 12 hours for 20 days), there was a benefit of cefuroxime axetil for resolution of erythema migrans, a benefit of amoxicillin for resolution of Lyme disease symptoms at 3 weeks, but no difference for resolution of Lyme disease symptoms at 6 months or 1 year. Diarrhoea events occurred more often in the amoxicillin group, while there was no difference between amoxicillin and cefuroxime axetil in the chance of allergic reactions and vomiting.

There was also no clear benefit of oral azithromycin (20 milligram per kilograms body weight on the first day followed by 10 milligram per kilogram body weight per day for 4 days) over oral amoxicillin (50 milligram per kilogram body weight per day given every 8 hours for 14 days) in children, although this comparison is equivalent to comparing 7 days azithromycin with 14 days amoxicillin. Evidence from 1 non-randomised study showed that amoxicillin was associated with a lower rate of adverse events than azithromycin. The duration of systemic symptoms was shorter in the amoxicillin group than in the azithromycin group, although only a very small proportion of the study population presented with systemic symptoms. There was no difference in duration of erythema migrans symptoms between the 2 treatment arms.

The usual dosage of oral amoxicillin in the included studies in adults was 500 milligram 3 times per day. The committee noted that 500 milligram probenecid was given 3 times per day in some studies to increase plasma concentration of amoxicillin. Despite a lack of evidence for a direct comparison, the committee considered that the evidence for oral amoxicillin was convincing and that oral amoxicillin was a potential alternative option to oral doxycycline. They recognised that the effect of probenecid would be to increase concentration of amoxicillin and therefore decided to recommend 1 gram amoxicillin 3 times per day as the preferred dose of amoxicillin.

Compared to oral clarithromycin, there was no clinical difference in the occurrence of Jarisch-Herxheimer reactions for oral amoxicillin in children.

2.8.1.3.3 Benefits and harms of other antibiotics

Studies that fitted the inclusion criteria of the protocol included other comparisons of other tetracyclines and penicillins.

There was no clinically important difference between different durations of oral tetracycline treatment. Oral tetracycline (250 milligram 4 times per day for 10 days) was more effective than oral phenoxymethylpenicillin (250 milligram 4 times per day for 10 days) for cure, but there was no difference in progression to minor or late disease. There was also no clear benefit of oral minocycline 100 milligram twice daily for 21 days over oral phenoxymethylpenicillin 1.5 million IU 3 times per day for 21 days, although minocycline resulted in more adverse events.

Evidence in adults showed that both phenoxymethylpenicillin 250 milligram 4 times daily for 10 days and tetracycline 250 milligram 4 times daily for 10 days were more effective than erythromycin 250 milligram 4 times daily for 10 days in the preventing progression to late disease. There were no differences for cure. The committee noted the relatively low cure rates for both antibiotics in this study, which was also limited by a small sample size.

There was no clear benefit of oral azithromycin 500 milligram once daily for 10 days over oral phenoxymethylpenicillin 1 million U (0.6 gram) 3 times daily for 10 days or vice versa. Oral azithromycin showed a clinical benefit for cure at 10 days and 1 month, but this effect was no longer evident at 3 and 6 months. Oral Azithromycin also resulted in higher adverse event rates than oral phenoxymethylpenicillin. A comparison between high dose (30 milligram per kilogram body weight per day given every 12 hours for 20 days) and low dose (20 milligram per kilogram body weight per day given every 12 hours for 20 days) oral cefuroxime axetil in children showed a benefit of the high dose for resolving Lyme disease symptoms at 3 weeks, but the symptoms of all people had resolved at 6 and 12 months in both groups. However, the committee noted the limitations of the small sample size in the study.

In adults, there was no clinically important difference in the occurrence of Jarisch-Herxheimer reactions between intramuscular ceftriaxone and oral phenoxymethylpenicillin. Adverse events occurred more often in children when given oral cefuroxime axetil compared to oral phenoxymethylpenicillin, but there was no difference in adverse events between oral azithromycin and oral phenoxymethylpenicillin.

2.8.2 Cost effectiveness and resource use

No relevant health economic evidence was identified. The unit costs of different antimicrobials were presented to the committee. Both doxycycline and amoxicillin are low cost generic antimicrobials (£4.57 and £7.62 respectively for adults).

The BNF currently recommends doxycycline, amoxicillin or cefuroxime axetil as the antibacterials of choice for ‘early Lyme’ disease. The dose quoted for adults for doxycycline is 100 milligram twice daily for 10–14 days and amoxicillin is 500 milligram 3 times per day

for 14–21 days. The committee recommended a longer duration of doxycycline than current practice in order to reduce ambiguity around the range of treatment time periods provided by current guidelines, which is not useful for generalists who may be unclear when to use the shorter or longer course. In the absence of good quality evidence for treatment duration, the committee opted for the longer duration to be cautious, as there was concern at the low cure rates in some of the studies and the clinical evidence showed no additional adverse events with a longer course (20 versus 10 days). The committee recommended a higher dose of amoxicillin compared to that listed in the BNF (1 gram 3 times per day versus 500 milligram 3 times per day). As noted above, the rationale for this higher dose is because the included studies used probenecid to increase the concentration of amoxicillin; therefore, the committee decided to recommend 1 gram amoxicillin 3 times per day as the preferred dose of amoxicillin. The committee considered that the additional minimal cost of treatment for a longer course of doxycycline or higher dose of amoxicillin would be offset by the improved quality of life as a result of a reduction in symptoms and associated costs in the management of symptoms.

The BNF recommends cefuroxime axetil as one of their first choices for 'early Lyme' disease. The committee did not consider that there was sufficient clinical evidence of effectiveness compared to other treatments to support such a recommendation. Furthermore, cefuroxime axetil is much more expensive than the other oral antimicrobials (£106.32 for 500 milligram 2 times per day for 21 days).

The committee considered that where both doxycycline and amoxicillin are contraindicated azithromycin should be considered because the evidence did not show any difference in effect between azithromycin and doxycycline or amoxicillin. A longer treatment duration than the 7-10 days recommended in the BNF was in keeping with the overall strategy of treating Lyme disease with higher doses. The committee was also persuaded that as beta lactams are bacteriolytic and macrolides are bacteriostatic, longer courses of macrolides are justified. The unit cost of azithromycin is low (£3.75 for 500 milligram, once daily for 3 days for 3 weeks).

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

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

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

2.8.3 Other factors the committee took into account

The committee used the evidence relating to management of people with erythema migrans as well as evidence relating to other presentations of Lyme disease to develop the recommendations.

The committee noted the low quality of the studies, the use of sub-therapeutic doses of antibiotics in some studies, the lack of clarity about outcomes and lack of detail in studies about how people presented clinically. No placebo-controlled trials were identified for this review.

The committee was aware that both doxycycline and beta-lactam antibiotics are able to penetrate the blood-cerebrospinal fluid barrier and penetrate into the central nervous system, which may be important for the prevention of later disseminated disease. Azithromycin is known not to penetrate the blood brain barrier.

The committee agreed that it was important to aim for clarity and reduction of ambiguity in the management of Lyme disease. Most current guidelines suggest treatments over a range of time periods, for example the BNF suggests doxycycline for 10 to 14 days and amoxicillin for 14 to 21 days. The committee considered that providing a range of times was not useful for generalists as it is unclear when to use the shorter or longer course. The evidence for length of treatment was weak and the committee decided to recommend longer courses of 21 days of treatment as standard because of their concern at low cure rates in some studies and the lack of clear evidence for shorter courses. They also considered it important that people being treated for Lyme could be reassured that they have had the longer course if they continue to have symptoms. The committee were reassured that adverse rates were not increased for longer courses.

The committee decided to recommend oral azithromycin for adults when doxycycline and amoxicillin are contra-indicated because the evidence did not show a clear benefit or harm between azithromycin and doxycycline or amoxicillin. Azithromycin is the alternative to amoxicillin for children although the committee noted that azithromycin does not cross the blood brain barrier and caution would be required if there was any suspicion of more disseminated disease. Due to the long half-life of azithromycin, the committee decided to recommend a treatment course of 17 days, 4 days less than doxycycline or beta lactam equivalents. This treatment regimen for provides 21 days of effective drug levels in vivo. A daily dosing strategy was agreed by the committee as has been routinely used for other slow-growing bacterial conditions such as atypical mycobacterial infection. For such conditions, azithromycin is used daily, reaching a higher steady level than if the 3 consecutive days per week strategy is used.

The committee discussed at length whether doxycycline and amoxicillin were equivalent choices and whether in view of possible adverse effects of doxycycline, amoxicillin should be suggested as the first choice of antibiotic. The majority view, however, was for doxycycline to be first line, in light of the lack of direct evidence between doxycycline and amoxicillin alone, the known better penetration of doxycycline to cerebrospinal fluid and the absence of longer-term outcomes for use of amoxicillin. Doxycycline can also be taken once daily, which is convenient and likely to help adherence.

The guideline committee was aware of a current re-appraisal in the literature of the risks of doxycycline in women who are pregnant and in children.[17,46,198,205] They recognised, however, that concerns still exists about the use of doxycycline in pregnancy and so included a recommendation to ensure women are asked about risk of pregnancy before antibiotics are prescribed.

The guideline committee was aware that specialists in the UK 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 and international practice is moving to recommend use above 2 years. 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.

The committee also wished to ensure that people being treated for Lyme disease did not stop antibiotics if they experienced a Jarisch-Herxheimer reaction. This reaction can occur within a few hours of starting treatment but is usually self-limiting and is not a reason to stop antibiotic treatment. The committee agreed that while a Jarisch-Herxheimer reaction is a possibility, it is an unusual reaction to antibiotic treatment.

In the light of the concerns around sub-clinical antibiotic dosages and the definition of outcomes, the committee decided to develop research recommendations for further research. Trials assessing the effectiveness of antibiotic treatment regimens for Lyme disease should include antibiotic dosages that reflect current prescribing practice. Research should also be conducted to determine a core outcome set to develop well-defined outcome for clinical trials and enable studies to be compared and included in meta-analyses.

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Appendices

Appendix A: Review protocols

Table 30: Review protocol for the management of erythema migrans (EM)

Question number: 4.2

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for people with an erythema migrans?
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 an erythema migrans (EM).
Eligibility criteria – population / disease / condition / issue / domain	People with an erythema migrans
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Antimicrobials, including but not limited to: • Penicillins o Amoxicillin (oral, IV) o Ampicillin (oral, IV) o Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) o Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines o Doxycycline (oral) o Minocycline (oral) • Cephalosporins o Cefotaxime (IV) o Ceftriaxone (IV) o Cefuroxime axetil (oral) • Macrolides o Azithromycin (oral) o Clarithromycin (oral, IV) • Fluoroquinolones o Ciprofloxacin (oral, IV) o Levofloxacin (oral, IV) o Moxifloxacin (oral, IV) o Nalidixic acid (oral) o Norfloxacin (oral)

Field	Content
	○ Ofloxacin (oral, IV) ○ Rifampicin (oral, IV)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Antimicrobial agents compared with each other ○ If data are available consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of EM) 3. Reduction of EM symptoms 4. EM relapse **Important:** 5. Adverse events
Eligibility criteria – study design	• RCTs • Cohort studies (if no RCT evidence is found)
Other inclusion exclusion criteria	Date limits for search: none Language: English only Setting: all settings in which NHS is care is provided or commissioned The following interventions will not be considered for inclusion: • Metronidazole • Trimethoprim
Proposed sensitivity / subgroup analysis, or meta-regression	The following groups will be considered separately if data are available (strata): • Children (under 12 years); young people and adults (12 years and over) • Onset of EM less than 6 weeks; 6 weeks to 6 months; over 6 months Subgroups (to be investigated if heterogeneity is identified): • Pregnant women • People who are immunocompromised • Single EM versus multiple EM • People in whom a previous course of antimicrobial 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

Field	Content
	Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual. Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) In the absence of clinically established MIDs, standard MIDs for dichotomous (25% risk reduction or risk increase) and continuous outcomes (+/-0.5 standard deviation) will be used If heterogeneity is found, the influence of subgroups will be examined
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NGC and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / 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.

Field	Content
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 31: 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).[130] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both, then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude the remaining studies selectively. All studies excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

	The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly before 2001 will be rated as 'Not applicable'. • Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 32: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

Embase (Ovid) search terms

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

Cochrane Library (Wiley) search terms

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

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

B.2 Health Economics literature search strategy

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

Table 33: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

Embase (Ovid) search terms

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

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

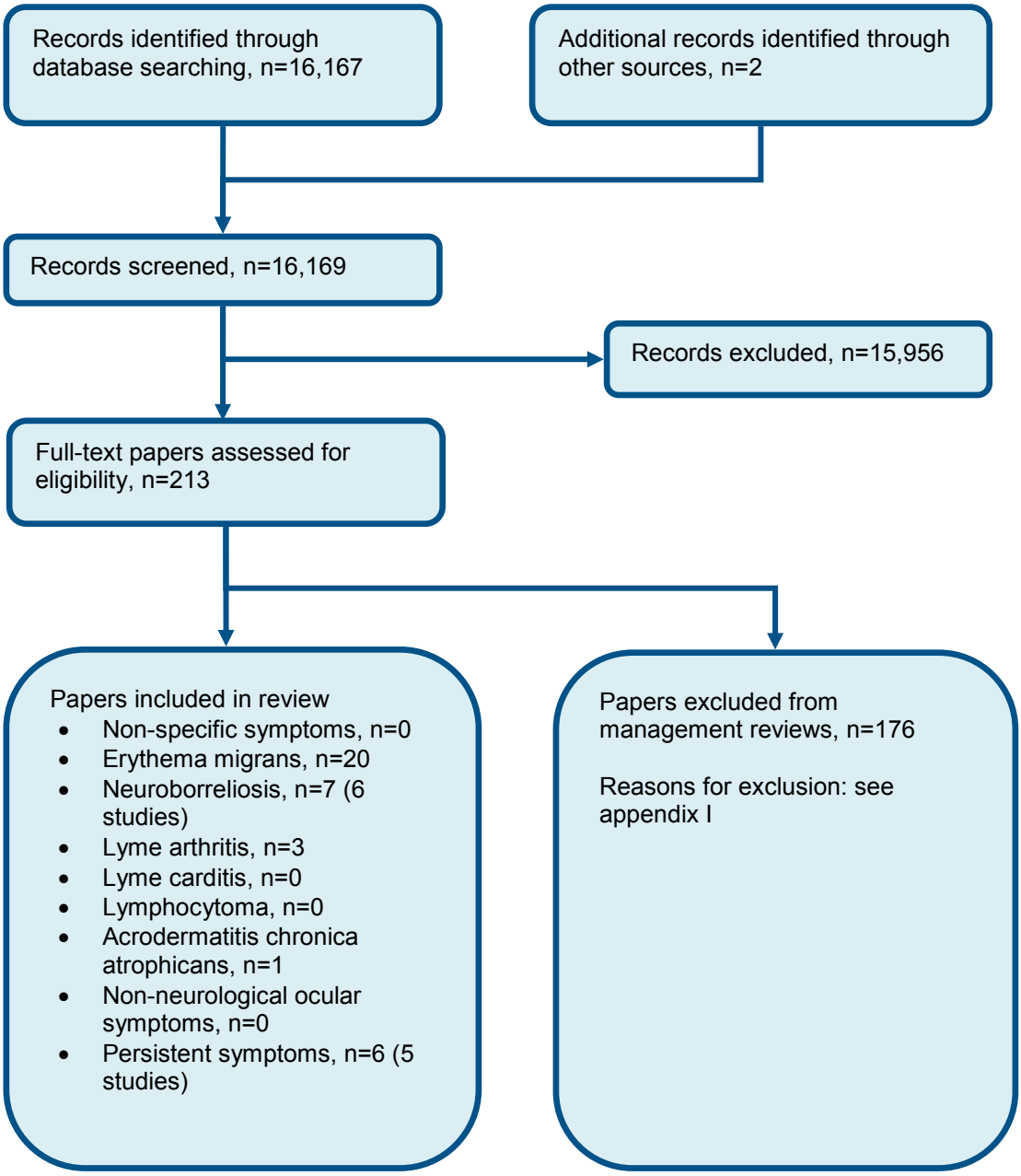
55.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
56.	or/46-55
57.	quality adjusted life year/
58.	"quality of life index"/
59.	short form 12/ or short form 20/ or short form 36/ or short form 8/
60.	sickness impact profile/
61.	(quality adj2 (wellbeing or well being)).ti,ab.
62.	sickness impact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

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis chronica atrophicans) IN NHSEED, HTA
#7.	MeSH DESCRIPTOR Ixodidae EXPLODE ALL TREES IN NHSEED,HTA
#8.	((borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti)) IN NHSEED, HTA
#9.	((granulocyctic anaplasmosis or babesia or babesiosis)) IN NHSEED, HTA
#10.	MeSH DESCRIPTOR Lyme Disease EXPLODE ALL TREES IN NHSEED,HTA
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

Appendix C: Clinical evidence selection

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



Appendix D: Clinical evidence tables

Study	Arnez 1999[12]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=94)
Countries and setting	Conducted in Slovenia; Setting: academic hospital
Line of therapy	first line
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Solitary EM, younger than 15 years, treated as outpatients or hospitalised at the department
Exclusion criteria	Not reported
Recruitment or selection of participants	Between 10 May 1996 and 27 November 1996
Age, gender and family origin	Age - Mean (SD): Cefuroxime Axetil group: 6.3 years (3.3); phenoxymethylpenicillin group: 7.8 years (3.6). Gender (M:F): 43:47. Family origin: Not reported
Further population details	1. EM presentation: Not applicable 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Antibiotics - Cefuroxime Axetil. 30 mg/kg/d (maximum 1,000 mg per day) divided into 2 equal doses every 12 hours. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=47) Intervention 2: Antibiotics - Phenoxymethylpenicillin. 100 000 IU/kg/d (maximum 3 million IU/d) divided into 3 equal doses given every 8 hours. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Funding not stated

Study	Arnez 1999[12]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFUROXIME AXETIL versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Adverse events - Actual outcome: Side effects at 14 days; Group 1: 12/46, Group 2: 3/44 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Baseline details: Differences in terms of age; Group 1 Number missing: 1; Group 2 Number missing: 3	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	Arnez 2002[11]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=84)
Countries and setting	Conducted in Slovenia; Setting: academic hospital
Line of therapy	first line
Duration of study	Intervention time: 14 days
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Solitary EM
Exclusion criteria	Previous treatment
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (SD): Azithromycin group: 5.9 years (3.5); phenoxymethylpenicillin group: 7.1 years (3.7). Gender (M:F): 40:44. Family origin: Not reported
Further population details	1. EM presentation: Not applicable 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=42) Intervention 1: Antibiotics - Azithromycin. 20 mg/kg/d (maximum 1,000 mg/d) for the first day followed by 10 mg/kg/d (maximum 500 mg/d) for a further 4 days. Duration 5 days. Concurrent medication or care:

Study	Arnez 2002[11]
	Not reported Further details: 1. Previous treatment failure: Not applicable (n=42) Intervention 2: Antibiotics - Phenoxymethylpenicillin. 100,000 IU/kg/d (maximum 3 million IU/d) divided into 3 equal doses given every 8 hours. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AZITHROMYCIN versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Adverse events - Actual outcome: Side effects at Not stated; Group 1: 8/40, Group 2: 7/41 Risk of bias: All domain - High, Selection - High, 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: 1	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	Arnez 2015[13]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=168)
Countries and setting	Conducted in Slovenia; Setting: Department of Infectious Diseases
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, EM
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with an EM referred to the department between 2002 and 2003
Exclusion criteria	Not reported
Recruitment/selection of patients	Not reported
Age, gender and family origin	Age - Other: Under 15 years. Gender (M:F): Not reported. Family origin: Not reported

Study	Arnez 2015[13]
Further population details	1. EM presentation: Single EM 2. Immunocompromised people: No immunosuppression 3. Pregnant women: No pregnancy
Indirectness of population	No indirectness
Interventions	(n=84) Intervention 1: Antibiotics - Azithromycin. 20mg/kg/d (maximum 1,000mg/d) for the first day followed by 10mg/kg/d (maximum 500 mg/d) once per day for 4 days. Duration 5 days. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Previous treatment failure: Not stated / Unclear (n=84) Intervention 2: Antibiotics - Amoxicillin. 50mg/kg/d (maximum 1500mg/d) every 8 hours. Duration 14 days. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. Previous treatment failure: Not stated / Unclear
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AZITHROMYCIN versus AMOXICILLIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Duration of EM symptoms at Unclear; Group 1: mean 4.7 Days (SD 4.9); n=84, Group 2: mean 5.9 Days (SD 8.8); n=84 Risk of bias: All domain - High, Selection - High, Blinding - Low, 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: Duration of systemic symptoms at Unclear; Group 1: mean 9.6 Days (SD 11.5); n=5, Group 2: mean 6.3 Days (SD 4.6); n=10 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Very high, Measurement - Very high, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 79, Reason: Only 5 people had systemic symptoms; Group 2 Number missing: 74, Reason: Only 10 people had systemic symptoms Protocol outcome 2: Adverse events - Actual outcome: Adverse events at Unclear; Group 1: 18/84, Group 2: 13/84 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Jarisch-Herxheimer reaction at 24 hours; Group 1: 6/84, Group 2: 13/84 Risk of bias: All domain - High, Selection - High, Blinding - Low, 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; Reduction of symptoms; Symptom relapse

Study	Barsic 2000[16]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=88)
Countries and setting	Conducted in Croatia; Setting: Dual-centre study
Line of therapy	first line
Duration of study	Intervention and follow up: Intervention time: 14 days and 12 month follow-up
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Outpatients, aged 12 years or older, weighting at least 45 kg, diagnosed with early Lyme disease confirmed by the presence of EM with or without systemic manifestations of infection
Exclusion criteria	Pregnancy or lactation, history of adverse reactions to tetracyclines or azithromycin, treatment with systemic antimicrobial agent with known activity against *Borrelia burgdorferi sensu lato* within 10 days before enrolment, antibiotic treatment of Lyme disease during the preceding 12 months, participants with gastrointestinal or hepatic disorders that would interfere with the pharmacokinetics of orally administered antimicrobial agents as well as those showing major manifestations of disseminated Lyme disease
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (SD): Azithromycin group: 41.5 years (17.8); doxycycline group: 48.7 years (11.9). Gender (M:F): 39:49. Family origin: Not reported
Further population details	1. EM presentation: Not applicable 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Antibiotics - Azithromycin. 500 mg bid on the first day, followed by 500 mg once daily for the next 4 days. Duration 5 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=40) Intervention 2: Antibiotics - Doxycycline. 100 mg bid. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AZITHROMYCIN versus DOXYCYCLINE	

Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Treatment success at 12 months; Group 1: 42/48, Group 2: 29/40 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, 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 outcome 2: Reduction of symptoms - Actual outcome: Improvement at 12 months; Group 1: 4/48, Group 2: 4/40 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 outcome 3: Symptom relapse - Actual outcome: Treatment failure at 12 months; Group 1: 2/48, Group 2: 7/40 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: Serious indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 4: Adverse events - Actual outcome: Adverse events at 14 days; Group 1: 3/47, Group 2: 5/35 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life

Study	**Breier 1996[29]**
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Austria; Setting: Outpatients' centre
Line of therapy	first line
Duration of study	Intervention time: 21 days
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Study	Breier 1996[29]
Inclusion criteria	Erythema chromium migrans
Exclusion criteria	History of allergy to penicillin or minocycline, antibiotic treatment since time of infection, pregnancy
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (range): 43 years (19-80). Gender (M:F): 25:35. Family origin: Not reported
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Antibiotics - Phenoxymethylpenicillin. 1.5 million IU 3 times per day. Duration 21 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=30) Intervention 2: Antibiotics - Minocycline. 100 mg twice daily. Duration 21 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus MINOCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Complete recovery from EM at 21 days; Group 1: 21/21, Group 2: 18/18 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: Did not finish treatment; Group 2 Number missing: 12, Reason: Did not finish treatment Protocol outcome 2: Adverse events - Actual outcome: Side effects at 21 days; Group 1: 4/21, Group 2: 12/18 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9, Reason: Did not finish treatment; Group 2 Number missing: 12, Reason: Did not finish treatment	
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Symptom relapse

Study	Cerar 2010[35]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=285)
Countries and setting	Conducted in Slovenia; Setting: academic hospital
Line of therapy	first line
Duration of study	Intervention and follow up: 15-day intervention time and 12 months follow-up
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Participants aged 15 years or more with a typical solitary EM as defined by the CDC; or participants with a skin lesion <5cm in diameter if they recalled a tick bite at the site of the skin lesion, had a symptom-free interval between the bite and the onset of the lesion, and reported an expanding skin lesion before diagnosis
Exclusion criteria	Previous Lyme disease, pregnancy, lactating, immunocompromised, serious adverse reaction to a beta-lactam or tetracycline drug, previous antibiotic treatment with known anti-Borrelia activity within 10 days, multiple EM, extracutaneous manifestation of Lyme disease
Recruitment or selection of participants	Presentation to clinic between June 2006 and September 2006
Age, gender and family origin	Age - Mean (range): Doxycycline group: 54 years (17-85); Cefuroxime Axetil group: 51.5 years (19-82). Gender (M:F): 124:161. Family origin: Not reported
Further population details	1. EM presentation: Not applicable 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=145) Intervention 1: Antibiotics - Doxycycline. 100mg oral twice daily. Duration 15 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=140) Intervention 2: Antibiotics - Cefuroxime Axetil. 500 mg oral twice daily. Duration 15 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Academic or government funding (Slovenian Research Agency)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus CEFUROXIME AXETIL Protocol outcome 1: Cure (resolution of symptoms)	

Study	Cerar 2010[35]
- Actual outcome: Complete response at 14 days; Group 1: 106/145, Group 2: 105/140 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, 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: Complete response at 2 months; Group 1: 117/136, Group 2: 120/134 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9; Group 2 Number missing: 6 - Actual outcome: Complete response at 6 months; Group 1: 97/102, Group 2: 87/93 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 43; Group 2 Number missing: 47 - Actual outcome: Complete response at 12 months; Group 1: 113/116, Group 2: 110/114 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 29; Group 2 Number missing: 26 Protocol outcome 2: Reduction of symptoms - Actual outcome: Partial response at 6 months; Group 1: 3/102, Group 2: 6/93 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 43; Group 2 Number missing: 47 - Actual outcome: Partial response at 12 months; Group 1: 1/116, Group 2: 4/114 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 29; Group 2 Number missing: 26 Protocol outcome 3: Symptom relapse - Actual outcome: Partial response at 14 days; Group 1: 38/145, Group 2: 35/140 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Incomplete resolution or presence of new or increased symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Partial response at 2 months; Group 1: 17/136, Group 2: 14/134 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 9; Group 2 Number missing: 6 Protocol outcome 4: Adverse events - Actual outcome: Any adverse events at 15 days; Group 1: 22/145, Group 2: 23/140 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Study	Cerar 2010[35]
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

Study	Dattwyler 1990[53]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=75)
Countries and setting	Conducted in USA; Setting: Single-centre, outpatients
Line of therapy	first line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	EM
Exclusion criteria	History of nervous system, cardiac or collagen vascular disease or arthritis; pregnancy; breastfeeding
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (SD): Amoxicillin group: 38.9 years; doxycycline group: 36.1 years. Gender (M:F): 39:33. Family origin: Not reported
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Antibiotics - Amoxicillin. 500 mg 3 times per day. Duration 21 days. Concurrent medication or care: 500 mg probenecid 3 times per day Further details: 1. Previous treatment failure: Not stated or unclear (n=38) Intervention 2: Antibiotics - Doxycycline. 100 mg twice per day. Duration 21 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not stated or unclear
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Resolution of symptoms at Unclear; Group 1: 37/37, Group 2: 36/36 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear when outcome was measured; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: Disease progression to late Lyme disease at Unclear; Group 1: 5/37, Group 2: 3/36 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear when outcome was measured; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 2: Symptom relapse - Actual outcome: Recurrence of EM at Unclear; Group 1: 0/37, Group 2: 0/36 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: Unclear when outcome was measured; Group 1 Number missing: 1; Group 2 Number missing: 2	
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Adverse events

Study	**Dattwyler 1997[52]**
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=140)
Countries and setting	Conducted in USA; Setting: Multi-centre study
Line of therapy	first line
Duration of study	Follow up (post intervention): 9 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	8 years or older, acute disseminated Lyme disease
Exclusion criteria	Pregnancy, breastfeeding, evidence of syphilis/meningitis/collagen vascular disease, current symptoms of

Study	Dattwyler 1997[52]
	Lyme disease for which they had previously received treatment, serious underlying condition, gallbladder disease, hypersensitivity to study drugs, treatment with anti-Borrelia antibiotics within 48 hours of study entry or treatment with investigational compound within 2 weeks before enrolment
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (SD): Ceftriaxone group: 42.1 years (17.8); doxycycline group: 43.1 years (18.1). Gender (M:F): Define. Family origin: Not reported
Further population details	1. EM presentation: Multiple EM (91% of ceftriaxone group and 99% of doxycycline group had multiple EM at study entry). 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Extra comments	91% of ceftriaxone group and 99% of doxycycline group had multiple EM at study entry
Indirectness of population	Serious indirectness: Acute disseminated Lyme disease
Interventions	(n=68) Intervention 1: Antibiotics - Ceftriaxone. 2 g once daily (50 mg per kg body weight for children), intravenously or intramuscular at the discretion of the physician. Duration 14 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=72) Intervention 2: Antibiotics - Doxycycline. 100 mg twice daily (4.4 mg per kg body weight for children), orally. Duration 21 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Study funded by industry (Grant from Hoffmann-La Roche)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Clinically cured at 3 months; Group 1: 55/59, Group 2: 63/64 Risk of bias: All domain - Very high, Selection - 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: 9; Group 2 Number missing: 8 - Actual outcome: Clinically cured at 6 months; Group 1: 51/59, Group 2: 54/64 Risk of bias: All domain - Very high, Selection - 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: 9; Group 2 Number missing: 8 - Actual outcome: Clinically cured at 9 months; Group 1: 56/59, Group 2: 58/64 Risk of bias: All domain - Very high, Selection - 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: 9; Group 2 Number missing: 8 Protocol outcome 2: Adverse events	

Study	Dattwyler 1997[52]
- Actual outcome: Drug-related adverse events at Unclear; Group 1: 39/68, Group 2: 31/72 Risk of bias: All domain - Very high, Selection - 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; Reduction of symptoms at Define; Symptom relapse at Define

Study	Eppes 2002[66]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in USA; Setting: Multi-centre, paediatric offices in Delaware region
Line of therapy	first line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	6 months to 12 years old, physician-diagnosed EM
Exclusion criteria	Allergic to penicillins or cephalosporins, significant past or current medical conditions, neurologic findings (other than isolated peripheral facial palsy)
Recruitment or selection of participants	Unclear
Age, gender and family origin	Age - Mean (SD): Amoxicillin group: 6.2 years; low-dose cefuroxime group: 6.3 years; high-dose cefuroxime group: 7.5 years. Gender (M:F): 24:19. Family origin: Not reported
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=13) Intervention 1: Antibiotics - Amoxicillin. 50 mg/kg/d (maximum dose: 1500 mg/d) divided every 8 hours. Duration 20 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=15) Intervention 2: Dosage - High dosage. Cefuroxime axetil: 30 mg/kg/d (maximum dose: 1,000 mg/d) divided every 12 hours. Duration 20 days. Concurrent medication or care: 7 participants received not further specified additional treatment Further details: 1. Previous treatment failure: Not applicable (n=15) Intervention 3: Dosage - Low dosage. Cefuroxime axetil: 20 mg/kg/d (maximum dose: 750 mg/d) divided every 12 hours. Duration 20 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Study funded by industry (Glaxo-Wellcome)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus HIGH DOSAGE	

Study	Eppes 2002[66]
Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: EM resolved at 3 weeks; Group 1: 8/12, Group 2: 13/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 3 weeks; Group 1: 12/12, Group 2: 13/15 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 6 months; Group 1: 13/13, Group 2: 15/15 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 12 months; Group 1: 12/12, Group 2: 15/15 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 Protocol outcome 2: Adverse events - Actual outcome: Allergic reaction at 20 days; Group 1: 0/12, Group 2: 0/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Vomiting at 20 days; Group 1: 0/12, Group 2: 0/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Diarrhoea between 2 and 5 days at 20 days; Group 1: 2/12, Group 2: 3/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus LOW DOSAGE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: EM resolved at 3 weeks; Group 1: 8/12, Group 2: 12/13 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 3 weeks; Group 1: 12/12, Group 2: 9/13	

Study	Eppes 2002[66]
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 6 months; Group 1: 12/12, Group 2: 13/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 2 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 12 months; Group 1: 12/12, Group 2: 13/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 2 Protocol outcome 2: Adverse events - Actual outcome: Allergic reaction at 20 days; Group 1: 0/12, Group 2: 0/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Vomiting at 20 days; Group 1: 0/12, Group 2: 1/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 - Actual outcome: Diarrhoea between 2 and 5 days at 20 days; Group 1: 2/12, Group 2: 1/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 1; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSAGE versus LOW DOSAGE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: EM resolved at 3 weeks; Group 1: 13/15, Group 2: 12/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 2 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 3 weeks; Group 1: 13/15, Group 2: 9/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 2 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 6 months; Group 1: 15/15, Group 2: 13/13 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 2 - Actual outcome: Lyme disease symptoms (for example, headache, fever, stiff neck) resolved at 12 months; Group 1: 15/15, Group 2: 13/13

Study	Eppes 2002[66]
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 2 Protocol outcome 2: Adverse events - Actual outcome: Allergic reaction at 20 days; Group 1: 0/15, Group 2: 0/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, 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: Vomiting at 20 days; Group 1: 0/15, Group 2: 1/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, 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: Diarrhoea between 2 and 5 days at 20 days; Group 1: 3/15, Group 2: 1/15 Risk of bias: All domain - High, Selection - High, Blinding - Low, 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; Reduction of symptoms; Symptom relapse

Study	Luft 1996[104]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=246)
Countries and setting	Conducted in USA; Setting: 12 centres from 8 states in the US
Line of therapy	first line
Duration of study	Intervention and follow up: 20 days and 180 days
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: clinical diagnosis
Stratum	Overall: NA
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	Physician-diagnosed EM
Exclusion criteria	Pregnancy or breastfeeding, frank arthritis, objective evidence of CNS or cardiac presentations, meningismus or Bell's palsy with pleocytosis, history of cardiac/rheumatic/nervous system/collagen vascular disease, hypersensitivity to study drugs, antibiotic treatment for Lyme in previous 12 months, any antibiotic treatment within 72 hours before enrolment
Recruitment or selection of participants	not reported
Age, gender and family origin	Age - Mean (SD): Azithromycin group mean age 41.1 years; Amoxicillin group mean age 44.4 years. Gender (M:F): 124/93. Family origin: Not reported
Further population details	1. EM presentation: Single EM 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: No pregnancy
Extra comments	Stratified by presence or absence of flu-like symptoms.
Indirectness of population	No indirectness
Interventions	(n=122) Intervention 1: Antibiotics - Amoxicillin. 500mg 3 times daily. Duration 20 days. Concurrent medication or care: NA Further details: 1. Previous treatment failure: No previous treatment (n=124) Intervention 2: Antibiotics - Azithromycin. 500mg once daily and placebo doses twice daily for 7 days, then placebo doses 3 times daily until day 20. Duration 20 days. Concurrent medication or care: NA Further details: 1. Previous treatment failure: No previous treatment
Funding	Other (Grants from industry, Pfizer Central Research, and government, New York State and National Institutes of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus AZITHROMYCIN	

Study	Luft 1996[104]
	Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: complete response: complete clearance of EM and all objective signs and >75% relief of presenting symptoms at 20 days; Group 1: 93/106, Group 2: 84/111 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Azithromycin group had more participants with multiple EM lesions; Group 1 Number missing: 16, Reason: 5 received <50% of medication due to adverse events, 9 did not return for the follow up examination, 2 were non-compliant; Group 2 Number missing: 13, Reason: 2 received <50% of medication due to adverse events, 8 did not return for follow up examination, 3 did not meet entry criteria Protocol outcome 2: Reduction of symptoms - Actual outcome: partial response: complete clearance of EM with persistent signs and 50-75% relief of symptoms or persistent EM with complete clearance of signs and >75% relief of symptoms at 20 days; Group 1: 13/106, Group 2: 24/111 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Azithromycin group had more participants with multiple EM lesions; Group 1 Number missing: 16, Reason: 5 received <50% of medication due to adverse events, 9 did not return for the follow up examination, 2 were non-compliant; Group 2 Number missing: 13, Reason: 2 received <50% of medication due to adverse events, 8 did not return for follow up examination, 3 did not meet entry criteria Protocol outcome 3: Symptom relapse - Actual outcome: symptom relapse at 180 days; Group 1: 4/103, Group 2: 17/106 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Azithromycin group had more participants with multiple EM lesions; Group 1 Number missing: 16, Reason: 5 received <50% of medication due to adverse events, 9 did not return for the follow up examination, 2 were non-compliant; Group 2 Number missing: 13, Reason: 2 received <50% of medication due to adverse events, 8 did not return for follow up examination, 3 did not meet entry criteria Protocol outcome 4: Adverse events - Actual outcome: adverse events at 20 days; Group 1: 29/122, Group 2: 43/124 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: Azithromycin group had more participants with multiple EM lesions; Group 1 Number missing: 16, Reason: 5 received <50% of medication due to adverse events, 9 did not return for the follow up examination, 2 were non-compliant; Group 2 Number missing: 13, Reason: 2 received <50% of medication due to adverse events, 8 did not return for follow up examination, 3 did not meet entry criteria

Study	Luft 1996[104]
Protocol outcomes not reported by the study	Quality of life at Define

Study	Luger 1995[107]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=232)
Countries and setting	Conducted in USA; Setting: Not reported
Line of therapy	first line
Duration of study	Follow up (post intervention): 1 month
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Physician-documented EM
Exclusion criteria	Breastfeeding or lactating, history of serious adverse reactions to study drugs, gastrointestinal disorders, therapy with systemic antimicrobial agent with known activity against Bb within 10 days before enrolment, unstable concomitant disease
Recruitment or selection of participants	Enrolment between May and November 1990
Age, gender and family origin	Age - Range: 45-47. Gender (M:F): Define. Family origin: 97% white
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=119) Intervention 1: Antibiotics - Cefuroxime axetil. 500 mg twice daily, Ceftin (Glaxo Inc.). Duration 12 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=113) Intervention 2: Antibiotics - Doxycycline. 100 mg 3 times per day, doxycycline hyclate (E R Squibb & Sons). Duration 12 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Study funded by industry (Grant from Glaxo Inc.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFUROXIME AXETIL versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Success (resolution of EM symptoms) at 1 month; Group 1: 67/100, Group 2: 68/94 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 19; Group 2 Number missing: 19 - Actual outcome: Success (resolution of EM symptoms) at 1 year; Group 1: 57/65, Group 2: 48/53 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 54; Group 2 Number missing: 60 Protocol outcome 2: Reduction of symptoms - Actual outcome: Improvement (resolution of EM rash but incomplete resolution of other symptoms) at 1 month; Group 1: 23/100, Group 2: 21/94 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 19; Group 2 Number missing: 19 - Actual outcome: Improvement (resolution of EM rash but incomplete resolution of other symptoms) at 1 year; Group 1: 5/65, Group 2: 5/53 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 54; Group 2 Number missing: 60 Protocol outcome 3: Symptom relapse - Actual outcome: Symptom relapse at 1 month; Group 1: 3/100, Group 2: 1/94 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 19; Group 2 Number missing: 19 - Actual outcome: Symptom relapse at 1 year; Group 1: 3/65, Group 2: 0/53 Risk of bias: All domain - Very high, Selection - Very high, Blinding - High, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 54; Group 2 Number missing: 60 Protocol outcome 4: Adverse events - Actual outcome: One or more adverse events at Unclear; Group 1: 20/119, Group 2: 32/113 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Low, 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

Study	Massarotti 1992[115]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=81)
Countries and setting	Conducted in USA; Setting: Multi-centre study
Line of therapy	first line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Erythema migrans or flu-like symptoms; if only flu-like symptoms then an elevated IgM or IgG antibody response to Bb was required
Exclusion criteria	Evidence of radiculopathy or CSF pleocytosis, facial palsy
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (SD): 45 years (14). Gender (M:F): 30:27. Family origin: Not reported
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not stated or unclear
Indirectness of population	Serious indirectness: Includes participants with disseminated Lyme disease
Interventions	(n=26) Intervention 1: Antibiotics - Azithromycin. 500 mg orally on the first day followed by 250 mg once per day for 4 days. Duration 5 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not stated or unclear (n=29) Intervention 2: Antibiotics - Amoxicillin. 500 mg orally 3 times per day. Duration 10 days. Concurrent medication or care: 500 mg probenecid Further details: 1. Previous treatment failure: Not stated or unclear (n=26) Intervention 3: Antibiotics - Doxycycline. 100 mg orally twice per day. Duration 10 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not stated or unclear
Funding	Other (US Public Health funding and grants from Pfizer)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AZITHROMYCIN versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms)	

Study	Massarotti 1992[115]
- Actual outcome: Symptoms resolved at 10 days; Group 1: 13/16, Group 2: 15/22 Risk of bias: All domain - Very high, Selection - Low, 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: 4 Protocol outcome 2: Symptom relapse - Actual outcome: Development of subsequent symptoms at 30 days; Group 1: 1/16, Group 2: 1/22 Risk of bias: All domain - Very high, Selection - Low, 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: 4 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus AZITHROMYCIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Symptoms resolved at 10 days; Group 1: 16/19, Group 2: 13/16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10; Group 2 Number missing: 10 Protocol outcome 2: Symptom relapse - Actual outcome: Development of subsequent symptoms at 30 days; Group 1: 1/19, Group 2: 1/16 Risk of bias: All domain - Very high, Selection - Low, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 10; Group 2 Number missing: 10 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Symptoms resolved at 10 days; Group 1: 16/19, Group 2: 15/22 Risk of bias: All domain - Very high, Selection - Low, 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: 4 Protocol outcome 2: Symptom relapse - Actual outcome: Development of subsequent symptoms at 30 days; Group 1: 1/16, Group 2: 1/22 Risk of bias: All domain - Very high, Selection - Low, 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: 4	

Study	Massarotti 1992[115]
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Adverse events

Study	Nadelman 1992[125]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=123)
Countries and setting	Conducted in USA; 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 or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	12 years or older, weighing at least 45 kg, diagnosis of early Lyme disease confirmed by the presence of physician-documented EM
Exclusion criteria	Pregnancy or breastfeeding, history of serious adverse reactions to any cephalosporin or tetracycline drug or an immediate hypersensitivity reaction to penicillin, gastrointestinal disorders interfering with absorption of orally-administered antimicrobial agents, therapy with systemic antimicrobial agent with known activity against Bb within 10 days before enrolment, unstable concomitant underlying conditions compromising the ability to respond to infection, advanced Lyme disease
Recruitment or selection of participants	Not reported
Age, gender and family origin	Age - Mean (SD): Cefuroxime group: 44.2 years (16.1); doxycycline group: 45.4 years (15.1). Gender (M:F): 69:54. Family origin: 96% White, 2% Black, 2% Asian
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not applicable 3. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=63) Intervention 1: Antibiotics - Cefuroxime axetil. 500 mg twice daily, Ceftin (Glaxo Inc.). Duration 12 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not stated or unclear (n=60) Intervention 2: Antibiotics - Doxycycline. 100 mg 3 times per day, Doxycycline hyclate (E R Squibb).

Study	Nadelman 1992[125]
	Duration 12 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not stated or unclear
Funding	Study funded by industry (Grant from Glaxo Inc.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFUROXIME AXETIL versus DOXYCYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: Treatment success at 1 month; Group 1: 40/55, Group 2: 33/51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 9 - Actual outcome: Treatment success at 1 year; Group 1: 34/48, Group 2: 29/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 22 Protocol outcome 2: Reduction of symptoms - Actual outcome: Improvement at 1 month; Group 1: 11/55, Group 2: 12/51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 9 - Actual outcome: Improvement at 1 year; Group 1: 9/48, Group 2: 6/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 22 - Actual outcome: Recurrence at 1 month; Group 1: 3/55, Group 2: 2/51 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 8; Group 2 Number missing: 9 - Actual outcome: Recurrence at 1 year; Group 1: 0/48, Group 2: 0/38 Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 15; Group 2 Number missing: 22	
Protocol outcomes not reported by the study	Quality of life; Symptom relapse; Adverse events

Study	Nizič 2012[134]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=135)
Countries and setting	Conducted in Slovenia; Setting: Department of Infectious Disease, University Medical Centre Ljubljana
Line of therapy	first line
Duration of study	Intervention and follow up: 14 days and 12 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: CDC criteria
Stratum	Overall
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	<15 years; untreated solitary EM established by modified CDC criteria; EM <5cm in diameter if they recalled a recent tick bite at the site of EM, had a symptom free interval between the bite and onset of EM, or reported an expanding skin lesion prior to diagnosis
Exclusion criteria	not reported
Recruitment or selection of participants	consecutive participants meeting the inclusion criteria during the recruitment period
Age, gender and family origin	Age - Mean (SD): clarithromycin group 6.46 (3.43); amoxicillin group 6.84 (3.2) years. Gender (M:F): 67/68. Family origin: not reported
Further population details	1. EM presentation: Single EM 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: No pregnancy
Indirectness of population	No indirectness: NA
Interventions	(n=69) Intervention 1: Antibiotics - Amoxicillin. 50mg/kg per day divided into 3 equal doses every 8 hours (max. 500mg/8h) orally . Duration 14 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment (n=66) Intervention 2: Antibiotics - Clarithromycin. 15mg/kg per day divided into 2 equal doses every 12 hours (max. 500mg/12 h) orally . Duration 14 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus CLARITHROMYCIN Protocol outcome 1: Adverse events - Actual outcome: Jarisch-Herxheimer reaction at 12 months; Group 1: 18/64, Group 2: 16/66	

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: 5, Reason: 3 lost to follow up, other 2 unclear; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	**Steere 1983[180]**
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=184)
Countries and setting	Conducted in USA; Setting: Single-centre, outpatients
Line of therapy	first line
Duration of study	Follow up (post intervention): 7 days
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	EM
Exclusion criteria	Not reported
Recruitment or selection of participants	Two study periods (1980-81 and 1982)
Age, gender and family origin	Age - Mean (SD): Adults (1980-1981): penicillin (38, SD 18), erythromycin (37, SD 14), tetracycline (35, SD 13); Adults (1982): 10-day tetracycline (41, SD 13), 20-day tetracycline (35, SD 13); Children (1980-1982): age 2-7 (4, SD 2), age 8-15 (12, SD 2). Gender (M:F): 95:89. Family origin: Not reported
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not stated or unclear
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: Antibiotics - Phenoxymethylpenicillin. 250 mg orally 4 times per day. Duration 10 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not stated or unclear (n=29) Intervention 2: Antibiotics - Erythromycin. 250 mg 4 times per day, orally. Duration 10 days. Concurrent medication or care: Not reported

Study	Steere 1983[180]
	Further details: 1. Previous treatment failure: Not applicable (n=39) Intervention 3: Antibiotics - Tetracycline. 250 mg 4 times per day, orally. Duration 10 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=24) Intervention 4: Antibiotics - Tetracycline. 250 mg 4 times per day, orally. Duration 20 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable (n=25) Intervention 5: Antibiotics - Tetracycline. 250 mg 4 times per day, orally. Duration 10 days. Concurrent medication or care: Not reported Further details: 1. Previous treatment failure: Not applicable
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus ERYTHROMYCIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No late disease at Unclear; Group 1: 16/40, Group 2: 14/29 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 outcome 2: Symptom relapse - Actual outcome: Minor late disease at Unclear; Group 1: 20/40, Group 2: 11/29 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: Major late disease at Unclear; Group 1: 3/40, Group 2: 4/29 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 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PHENOXYMETHYLPENICILLIN versus TETRACYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No late disease at Unclear; Group 1: 16/40, Group 2: 22/39 Risk of bias: All domain - Very high, Selection - Very high, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement -	

Study	Steere 1983[180]
Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: Symptom relapse - Actual outcome: Minor late disease at Unclear; Group 1: 20/40, Group 2: 17/39 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: Major late disease at Unclear; Group 1: 3/40, Group 2: 0/39 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 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROMYCIN versus TETRACYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No late disease at Unclear; Group 1: 14/29, Group 2: 22/39 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 outcome 2: Symptom relapse - Actual outcome: Minor late disease at Unclear; Group 1: 11/29, Group 2: 17/39 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: Major late disease at Unclear; Group 1: 4/29, Group 2: 0/39 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 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TETRACYCLINE versus TETRACYCLINE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: No late disease at Unclear; Group 1: 16/24, Group 2: 17/25 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	

Study	Steere 1983[180]
Protocol outcome 2: Symptom relapse - Actual outcome: Minor late disease at Unclear; Group 1: 8/24, Group 2: 8/25 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: Major late disease at Unclear; Group 1: 0/24, Group 2: 0/25 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; Reduction of symptoms; Adverse events

Study	Strle 1992[190]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Slovenia; Setting: Outpatients' Clinic of the University Department of Infectious Diseases, University of Ljubljana
Line of therapy	first line
Duration of study	Intervention and follow up: 10 or 14 days and 24 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	15 years and over; typical EM
Exclusion criteria	already receiving antibiotics; evidence of late manifestations of LB at time of examination
Recruitment or selection of participants	consecutive participants meeting the inclusion criteria during the recruitment period
Age, gender and family origin	Age - Mean (SD): doxycycline group 39.7 (11.4); phenoxymethylpenicillin group 39.3 (11.9); azithromycin group 38.9 (12.8) years. Gender (M:F): 27/37. Family origin: not reported
Further population details	1. EM presentation: Single EM (mostly single EM participants). 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not stated or unclear
Indirectness of population	No indirectness: NA
Interventions	(n=23) Intervention 1: Antibiotics - Doxycycline. 100mg twice daily orally. Duration 14 days. Concurrent

Study	Strle 1992[190]
	medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear (n=22) Intervention 2: Antibiotics - Azithromycin. 250mg twice daily for 2 days, 250mg once daily for 8 days orally. Duration 10 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear (n=23) Intervention 3: Antibiotics - Phenoxymethylpenicillin. 1 million IU 3 times daily orally. Duration 14 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus AZITHROMYCIN Protocol outcome 1: Adverse events - Actual outcome: exacerbation of local or general symptoms at during treatment; Group 1: 7/23, Group 2: 7/20 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: 2, Reason: 1 excluded due to pregnancy, 1 lost to follow up - Actual outcome: adverse reactions attributed to therapy at during treatment; Group 1: 5/23, Group 2: 2/20 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: 2, Reason: 1 excluded due to pregnancy, 1 lost to follow up RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Adverse events - Actual outcome: exacerbation of local or general symptoms at during treatment; Group 1: 7/23, Group 2: 5/21 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: 2, Reason: 2 excluded due to allergy to penicillin - Actual outcome: adverse reactions attributed to therapy at during treatment; Group 1: 5/23, Group 2: 1/21 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: 2, Reason: 2 excluded due to allergy to penicillin	

Study	Strle 1992[190]
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AZITHROMYCIN versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Adverse events - Actual outcome: exacerbation of local or general symptoms at during treatment; Group 1: 7/20, Group 2: 5/21 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: 1 excluded due to pregnancy, 1 lost to follow up; Group 2 Number missing: 2, Reason: 2 excluded due to allergy to penicillin - Actual outcome: adverse reactions attributed to therapy at during treatment; Group 1: 2/20, Group 2: 1/21 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 2, Reason: 1 excluded due to pregnancy, 1 lost to follow up; Group 2 Number missing: 2, Reason: 2 excluded due to allergy to penicillin	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	Stupica 2012[193]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=225)
Countries and setting	Conducted in Slovenia; Setting: Lyme Borreliosis Outpatient Clinic, University Medical Centre Ljubljana, Slovenia
Line of therapy	first line
Duration of study	Intervention and follow up: 10 or 15 days and 12 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: EM defined by CDC criteria
Stratum	Overall
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	typical solitary erythema migrans as defined by CDC; lesions <5cm in diameter also included if participant recalled a recent tick bite at the site of a later skin lesion, had a symptom-free interval between the bite and onset of the lesion and reported an expanding skin lesion prior to diagnosis
Exclusion criteria	prior antibiotic therapy; history of Lyme borreliosis; multiple erythema migrans; immunocompromised; pregnant or lactating; declined to participate; EM and meningitis; serious adverse reaction to a tetracycline;

Study	Stupica 2012[193]
	intercurrent episode of Lyme borreliosis during follow up
Recruitment or selection of participants	consecutive participants meeting the inclusion criteria during the recruitment period
Age, gender and family origin	Age - Median (IQR): 15 day group 51 (38-60); 10 day group 54 (43.8-62) years. Gender (M:F): 100/125. Family origin: not reported
Further population details	1. EM presentation: Single EM 2. Immunocompromised people: No immunosuppression 3. Pregnant women: No pregnancy
Extra comments	
Indirectness of population	No indirectness: NA
Interventions	(n=117) Intervention 1: Dosage - High dosage. Oral doxycycline 100 mg twice daily. Duration 15 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment (n=108) Intervention 2: Dosage - Low dosage. Oral doxycycline 100 mg twice daily. Duration 10 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment
Funding	Academic or government funding (Slovenian Research Agency)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSAGE versus LOW DOSAGE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: achievement of complete response at 14 days; Group 1: 71/117, Group 2: 60/108 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: achievement of complete response at 2 months; Group 1: 98/113, Group 2: 88/104 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 4; Group 2 Number missing: 4 - Actual outcome: achievement of complete response at 6 months; Group 1: 95/101, Group 2: 81/96 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 16; Group 2 Number missing: 12 - Actual outcome: achievement of complete response at 12 months; Group 1: 85/91, Group 2: 79/86 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 26; Group 2 Number missing: 22	
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Symptom relapse; Adverse events

Study	Weber 1990[209]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=73)
Countries and setting	Conducted in Germany; Setting: various University departments and dermatology offices, Germany
Line of therapy	first line
Duration of study	Intervention and follow up: 5 days or 12 days and 3 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	erythema migrans defined as expanding homogenous or ring-like erythema of the skin, with or without a history of a tick bite in the centre of the lesion
Exclusion criteria	other diagnoses such as non-specific tick bite reaction, Borrelia lymphocytoma and initial acrodermatitis chronica atrophicans
Recruitment or selection of participants	not reported
Age, gender and family origin	Age - Mean (SD): penicillin group 46 (14) years; ceftriaxone group 45 (15) years. Gender (M:F): 33/40. Family origin: not reported
Further population details	1. EM presentation: Not stated or unclear 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not stated or unclear
Indirectness of population	No indirectness: NA
Interventions	(n=40) Intervention 1: Antibiotics - Ceftriaxone. 1g intramuscularly daily . Duration 5 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear (n=33) Intervention 2: Antibiotics - Phenoxymethylpenicillin. 1 million units 3 times daily orally. Duration 12 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Adverse events - Actual outcome: Jarisch-Herxheimer reaction at unclear; Group 1: 9/40, Group 2: 7/33	

Study	Stupica 2012[193]
Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Unclear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: ceftriaxone group had more associated symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Major side effects at unclear; Group 1: 2/40, Group 2: 0/33 Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Unclear; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: ceftriaxone group had more associated symptoms; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	Weber 1993[210]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=65)
Countries and setting	Conducted in Germany; Setting: various University departments and dermatology offices, Germany
Line of therapy	first line
Duration of study	Intervention and follow up: 10 days and 6 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: clinical diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	EM
Exclusion criteria	Not reported
Recruitment or selection of participants	not reported
Age, gender and family origin	Age - Median (range): 46 (19-74) years. Gender (M:F): Define. Family origin: not reported
Further population details	1. EM presentation: Single EM (mostly single EM participants). 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: Not stated or unclear
Indirectness of population	No indirectness: NA
Interventions	(n=32) Intervention 1: Antibiotics - Azithromycin. 500mg once daily orally. Duration 10 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear

Study	Weber 1993[210]
	(n=33) Intervention 2: Antibiotics - Phenoxymethylpenicillin. 1 million U (0.6g) 3 times daily orally . Duration 10 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: Not stated or unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AZITHROMYCIN versus PHENOXYMETHYLPENICILLIN Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: signs and symptoms at 10 days; Group 1: 18/32, Group 2: 29/33; Comments: numbers are participants with signs and symptoms at time of evaluation or any subsequent follow up Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: signs and symptoms at >1 month; Group 1: 12/32, Group 2: 16/33; Comments: numbers are participants with signs and symptoms at time of evaluation or any subsequent follow up Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: signs and symptoms at >3 months; Group 1: 7/32, Group 2: 5/33; Comments: numbers are participants with signs and symptoms at time of evaluation or any subsequent follow up Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: signs and symptoms at >6 months; Group 1: 4/28, Group 2: 4/25; Comments: numbers are participants with signs and symptoms at time of evaluation or any subsequent follow up Risk of bias: All domain - Very high, Selection - High, Blinding - Very high, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 4; Group 2 Number missing: 8 Protocol outcome 2: Adverse events - Actual outcome: adverse events (mild to moderate) at unclear; Group 1: 12/32, Group 2: 5/33 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: 0	
Protocol outcomes not reported by the study	Quality of life; Reduction of symptoms; Symptom relapse

Study	Wormser 2003[213]
Study type	RCT (Participant randomised; Parallel)
Number of studies (number of participants)	1 (n=180)
Countries and setting	Conducted in USA; Setting: walk-in Lyme Disease Diagnostic Center, USA
Line of therapy	first line
Duration of study	Intervention and follow up: 20 days and 30 months
Method of assessment of guideline condition	Adequate method of assessment or diagnosis: clinical diagnosis
Stratum	Overall: NA
Subgroup analysis within study	Stratified then randomised: randomization was stratified by whether participants were symptomatic (any systemic symptoms or multiple EM lesions) or asymptomatic (single EM and no systemic symptoms)
Inclusion criteria	at least 16 years of age; with EM; satisfying the US Center for Disease Control and Prevention's surveillance definition of Lyme disease (annular erythematous skin lesion >5cm in diameter)
Exclusion criteria	pregnancy/lactation; allergy to tetracycline or a B-lactam antibiotic; receipt of antibiotic treatment for Lyme disease for more than 48 hours before enrolment; meningitis or advanced heart block; any underlying condition that might interfere with evaluability or follow-up
Recruitment or selection of participants	not reported
Age, gender and family origin	Age - Range: 16-82 years. Gender (M:F): 116/64. Family origin: 171 White, 4 African American, 4 Hispanic, 1 Asian
Further population details	1. EM presentation: Single EM (mainly single EM). 2. Immunocompromised people: Not stated or unclear 3. Pregnant women: No pregnancy
Indirectness of population	No indirectness: NA
Interventions	(n=60) Intervention 1: Polytherapy. Single 2g dose of intravenous ceftriaxone followed by 10 days of oral doxycycline capsules twice daily, then 10 days of oral placebo. Duration 20 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment (n=61) Intervention 2: Monotherapy. Placebo injection followed by 10 days of oral doxycycline 100mg twice daily, then 10 days of oral placebo twice daily. Duration 20 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment (n=59) Intervention 3: Dosage - High dosage. Placebo injection followed by 20 days of oral doxycycline

Study	Wormser 2003[213]
	100mg twice daily. Duration 20 days. Concurrent medication or care: not reported Further details: 1. Previous treatment failure: No previous treatment
Funding	Academic or government funding (National Institutes of Health)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYTHERAPY versus MONOTHERAPY Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: early treatment response - complete response: resolution of EM and associated symptoms and return to pre-Lyme disease health status at 20 days; Group 1: 34/52, Group 2: 34/48 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 8, Reason: 6 excluded, 2 lost to follow up; Group 2 Number missing: 13, Reason: 11 excluded, 2 lost to follow up - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 3 months; Group 1: 36/48, Group 2: 36/47 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 12, Reason: 7 excluded, 5 lost to follow up; Group 2 Number missing: 14, Reason: 12 excluded, 2 lost to follow up - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 12 months; Group 1: 37/45, Group 2: 36/43 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 15, Reason: 8 excluded, 7 lost to follow up; Group 2 Number missing: 18, Reason: 13 excluded, 5 lost to follow up - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 30 months; Group 1: 32/37, Group 2: 28/31 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 23, Reason: 12 excluded, 11 lost to follow up; Group 2 Number missing: 30, Reason: 14 excluded, 16 lost to follow up Protocol outcome 2: Reduction of symptoms - Actual outcome: early treatment response - partial response: resolution of EM but incomplete resolution or development of subjective symptoms at 20 days; Group 1: 18/52, Group 2: 13/48 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 8, Reason: 6 excluded, 2 lost to follow up; Group 2 Number missing: 13, Reason: 11 excluded, 2 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme	

Study	Wormser 2003[213]
disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 3 months; Group 1: 12/48, Group 2: 10/47 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 12, Reason: 7 excluded, 5 lost to follow up; Group 2 Number missing: 14, Reason: 12 excluded, 2 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 12 months; Group 1: 8/45, Group 2: 6/43 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 15, Reason: 8 excluded, 7 lost to follow up; Group 2 Number missing: 19, Reason: 15 excluded, 4 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 30 months; Group 1: 5/37, Group 2: 2/31 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 23, Reason: 12 excluded, 11 lost to follow up; Group 2 Number missing: 30, Reason: 14 excluded, 16 lost to follow up Protocol outcome 3: Adverse events - Actual outcome: adverse drug events at 20 days; Group 1: 37/60, Group 2: 27/61 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYTHERAPY versus HIGH DOSAGE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: early treatment response - complete response: resolution of EM and associated symptoms and return to pre-Lyme disease health status at 20 days; Group 1: 34/52, Group 2: 29/45 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 8, Reason: 6 excluded, 2 lost to follow up; Group 2 Number missing: 14, Reason: 14 excluded - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 3 months; Group 1: 36/48, Group 2: 30/41 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 12, Reason: 7 excluded, 5 lost to follow up; Group 2 Number missing: 18, Reason: 15 excluded, 3 lost to follow up

Study	Wormser 2003[213]
	- Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 12 months; Group 1: 37/45, Group 2: 30/40 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 15, Reason: 8 excluded, 7 lost to follow up; Group 2 Number missing: 19, Reason: 15 excluded, 4 lost to follow up - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 30 months; Group 1: 32/37, Group 2: 26/31 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 23, Reason: 12 excluded, 11 lost to follow up; Group 2 Number missing: 28, Reason: 19 excluded, 9 lost to follow up Protocol outcome 2: Reduction of symptoms - Actual outcome: early treatment response - partial response: resolution of EM but incomplete resolution or development of subjective symptoms at 20 days; Group 1: 18/52, Group 2: 16/45 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 8, Reason: 6 excluded, 2 lost to follow up; Group 2 Number missing: 14, Reason: 14 excluded, 0 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 3 months; Group 1: 12/48, Group 2: 11/41 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 12, Reason: 7 excluded, 5 lost to follow up; Group 2 Number missing: 18, Reason: 15 excluded, 3 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 12 months; Group 1: 8/45, Group 2: 6/40 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 15, Reason: 8 excluded, 7 lost to follow up; Group 2 Number missing: 19, Reason: 15 excluded, 4 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 30 months; Group 1: 5/37, Group 2: 5/31 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 23, Reason: 12 excluded, 11 lost to follow up; Group 2 Number missing: 28, Reason: 19 excluded, 9 lost to follow up Protocol outcome 3: Adverse events

Study	Wormser 2003[213]
- Actual outcome: adverse drug events at 20 days; Group 1: 37/60, Group 2: 25/59 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 0; Group 2 Number missing: 0 RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: MONOTHERAPY versus HIGH DOSAGE Protocol outcome 1: Cure (resolution of symptoms) - Actual outcome: early treatment response - complete response: resolution of EM and associated symptoms and return to pre-Lyme disease health status at 20 days; Group 1: 34/48, Group 2: 29/45 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 13, Reason: 11 excluded, 2 lost to follow up; Group 2 Number missing: 14, Reason: 14 excluded - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 3 months; Group 1: 36/47, Group 2: 30/41 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 14, Reason: 12 excluded, 2 lost to follow up; Group 2 Number missing: 18, Reason: 15 excluded, 3 lost to follow up - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 12 months; Group 1: 36/43, Group 2: 30/40 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 18, Reason: 13 excluded, 5 lost to follow up; Group 2 Number missing: 19, Reason: 15 excluded, 4 lost to follow up - Actual outcome: late treatment response - complete response: no recurrence of EM or associated symptoms and continued absence of objective rheumatologic, cardiac or neurologic manifestations, with return to pre-Lyme disease health status at 30 months; Group 1: 28/31, Group 2: 26/31 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 30, Reason: 14 excluded, 16 lost to follow up; Group 2 Number missing: 28, Reason: 19 excluded, 9 lost to follow up Protocol outcome 2: Reduction of symptoms - Actual outcome: early treatment response - partial response: resolution of EM but incomplete resolution or development of subjective symptoms at 20 days; Group 1: 13/48, Group 2: 16/45 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, Comments: NA; Baseline details: difference in duration of EM; Group 1	

Study	Wormser 2003[213]
Number missing: 13, Reason: 11 excluded, 2 lost to follow up; Group 2 Number missing: 14, Reason: 14 excluded - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 3 months; Group 1: 10/47, Group 2: 11/41 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 14, Reason: 12 excluded, 2 lost to follow up; Group 2 Number missing: 18, Reason: 15 excluded, 3 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 12 months; Group 1: 6/43, Group 2: 10/40 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 18, Reason: 13 excluded, 5 lost to follow up; Group 2 Number missing: 19, Reason: 15 excluded, 4 lost to follow up - Actual outcome: late treatment response - partial response: no recurrence of EM and the continued absence of objective manifestations of Lyme disease, but incomplete resolution or development of subjective symptoms of uncertain cause at 30 months; Group 1: 2/31, Group 2: 5/31 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, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 30, Reason: 14 excluded, 16 lost to follow up; Group 2 Number missing: 28, Reason: 19 excluded, 9 lost to follow up Protocol outcome 3: Adverse events - Actual outcome: adverse drug events at 20 days; Group 1: 27/61, Group 2: 25/59 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: difference in duration of EM; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Symptom relapse

Appendix E: Forest plots

E.1 Adults

E.1.1 Doxycycline (PO) versus azithromycin (PO)

Figure 2: Cure

Study or Subgroup	Doxycycline Events	Total	Azithromycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsic 2000	29	40	42	48	71.7%	0.83 [0.67, 1.03]
Massarotti 1992	15	22	13	16	28.3%	0.84 [0.58, 1.21]
Total (95% CI)		**62**		**64**	**100.0%**	**0.83 [0.69, 1.00]**
Total events	44		55			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.06)

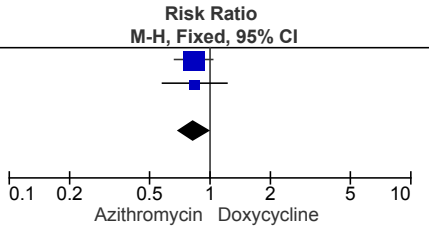


Figure 3: Reduction in symptoms

Study or Subgroup	Doxycycline Events	Total	Azithromycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsic 2000	4	40	4	48	100.0%	1.20 [0.32, 4.50]
Total (95% CI)		**40**		**48**	**100.0%**	**1.20 [0.32, 4.50]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)

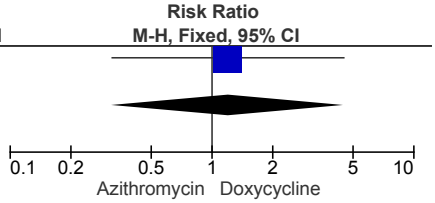


Figure 4: Symptom relapse

Study or Subgroup	Doxycycline Events	Total	Azithromycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsic 2000	7	40	2	48	61.1%	4.20 [0.92, 19.10]
Massarotti 1992	1	22	1	16	38.9%	0.73 [0.05, 10.78]
Total (95% CI)		**62**		**64**	**100.0%**	**2.85 [0.82, 9.87]**
Total events	8		3			

Heterogeneity: Chi² = 1.24, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 1.65 (P = 0.10)

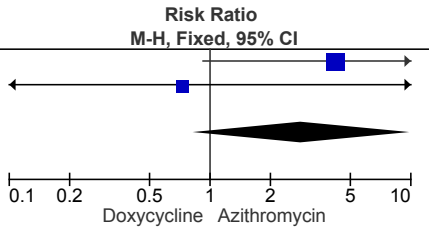
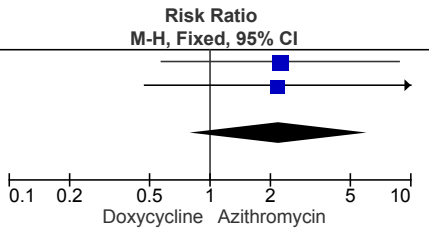


Figure 5: Adverse events

Study or Subgroup	Doxycycline Events	Total	Azithromycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barsic 2000	5	35	3	47	54.5%	2.24 [0.57, 8.74]
Strle 1992	5	23	2	20	45.5%	2.17 [0.47, 10.00]
Total (95% CI)		**58**		**67**	**100.0%**	**2.21 [0.80, 6.11]**
Total events	10		5			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 1.53 (P = 0.13)



E.1.2 Doxycycline (PO) versus cefuroxime axetil (PO)

Figure 6: Cure (at 14 days)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	106	145	105	140	100.0%	0.97 [0.85, 1.12]
Total (95% CI)		**145**		**140**	**100.0%**	**0.97 [0.85, 1.12]**
Total events	106		105			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.37 (P = 0.71)

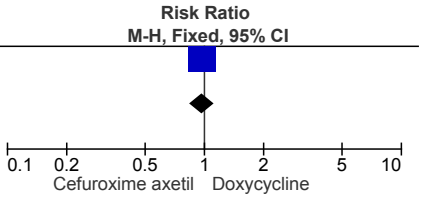


Figure 7: Cure (at 1 month)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luger 1995	68	94	67	100	62.8%	1.08 [0.90, 1.30]
Nadelman 1992	33	51	40	55	37.2%	0.89 [0.69, 1.15]
Total (95% CI)		**145**		**155**	**100.0%**	**1.01 [0.87, 1.17]**
Total events	101		107			

Heterogeneity: Chi² = 1.41, df = 1 (P = 0.23); I² = 29%
Test for overall effect: Z = 0.12 (P = 0.91)

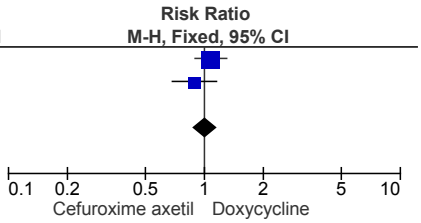


Figure 8: Cure (at 2 months)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	117	136	120	134	100.0%	0.96 [0.88, 1.05]
Total (95% CI)		**136**		**134**	**100.0%**	**0.96 [0.88, 1.05]**
Total events	117		120			

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

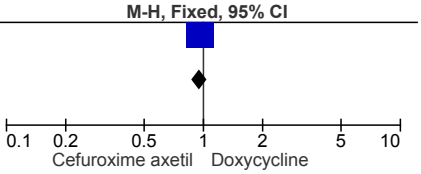


Figure 9: Cure (at 6 months)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	97	102	87	93	100.0%	1.02 [0.95, 1.09]
Total (95% CI)		**102**		**93**	**100.0%**	**1.02 [0.95, 1.09]**
Total events	97		87			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)

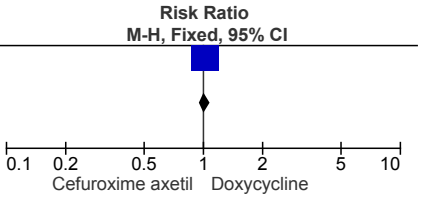


Figure 10: Cure (at 1 year)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	113	116	110	114	57.7%	1.01 [0.96, 1.06]
Luger 1995	48	53	57	65	26.6%	1.03 [0.91, 1.17]
Nadelman 1992	29	38	34	48	15.6%	1.08 [0.84, 1.39]
Total (95% CI)		**207**		**227**	**100.0%**	**1.03 [0.97, 1.09]**
Total events	190		201			

Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.39)

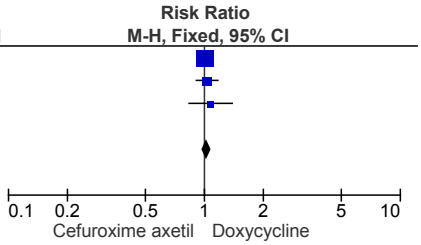


Figure 11: Reduction in symptoms (at 1 month)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luger 1995	21	94	23	100	67.8%	0.97 [0.58, 1.63]
Nadelman 1992	15	51	11	55	32.2%	1.47 [0.75, 2.90]
Total (95% CI)		**145**		**155**	**100.0%**	**1.13 [0.75, 1.71]**
Total events	36		34			

Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)

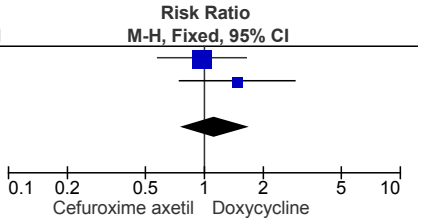


Figure 12: Reduction in symptoms (at 1 year)

Study or Subgroup	Doxycycline Events	Total	Cefuroxime axetil Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luger 1995	5	53	5	65	36.1%	1.23 [0.37, 4.01]
Nadelman 1992	6	38	9	48	63.9%	0.84 [0.33, 2.16]
Total (95% CI)		**91**		**113**	**100.0%**	**0.98 [0.47, 2.04]**
Total events	11		14			

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)

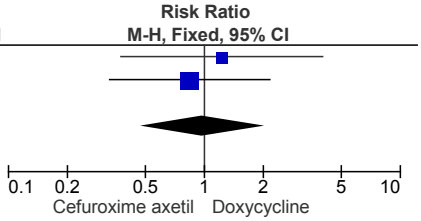


Figure 13: Symptom relapse (at 14 days)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Cefuroxime axetil Events	Cefuroxime axetil Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	38	145	35	140	100.0%	1.05 [0.71, 1.56]
Total (95% CI)		**145**		**140**	**100.0%**	**1.05 [0.71, 1.56]**
Total events	38		35			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

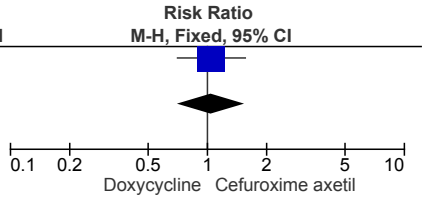


Figure 14: Symptom relapse (at 1 month)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Cefuroxime axetil Events	Cefuroxime axetil Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luger 1995	1	94	3	100	50.2%	0.35 [0.04, 3.35]
Nadelman 1992	2	51	3	55	49.8%	0.72 [0.13, 4.13]
Total (95% CI)		**145**		**155**	**100.0%**	**0.54 [0.14, 2.09]**
Total events	3		6			

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

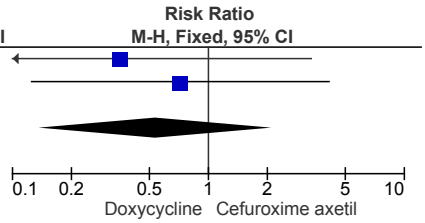


Figure 15: Symptom relapse (at 2 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Cefuroxime axetil Events	Cefuroxime axetil Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	17	136	14	134	100.0%	1.20 [0.61, 2.33]
Total (95% CI)		**136**		**134**	**100.0%**	**1.20 [0.61, 2.33]**
Total events	17		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)

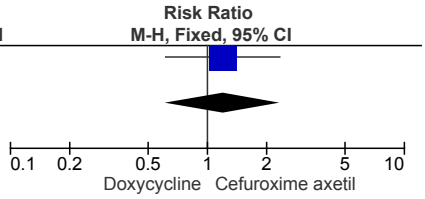


Figure 16: Symptom relapse (at 6 months)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Cefuroxime axetil Events	Cefuroxime axetil Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cerar 2010	3	102	6	93	100.0%	0.46 [0.12, 1.77]
Total (95% CI)		**102**		**93**	**100.0%**	**0.46 [0.12, 1.77]**
Total events	3		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)

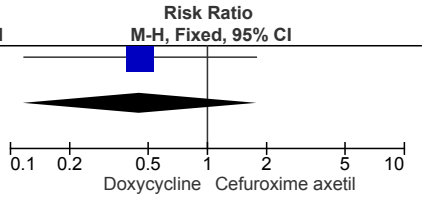


Figure 17: Symptom relapse (at 1 year)

Study or Subgroup	Doxycycline Events	Doxycycline Total	Cefuroxime axetil Events	Cefuroxime axetil Total	Weight	Risk Difference M-H, Fixed, 95% CI
Cerar 2010	1	116	4	114	53.3%	-0.03 [-0.06, 0.01]
Luger 1995	0	53	3	65	27.1%	-0.05 [-0.11, 0.01]
Nadelman 1992	0	38	0	48	19.7%	0.00 [-0.05, 0.05]
Total (95% CI)		**207**		**227**	**100.0%**	**-0.03 [-0.05, 0.00]**
Total events	1		7			

Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)

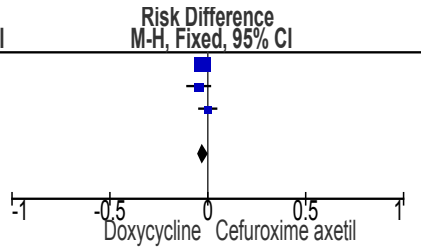
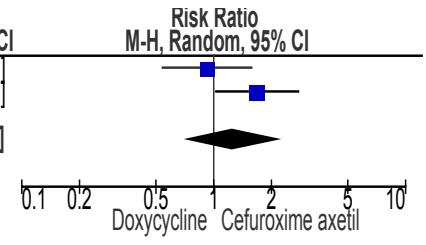


Figure 18: Adverse events

Study or Subgroup	Doxycycline Events	Doxycycline Total	Cefuroxime axetil Events	Cefuroxime axetil Total	Weight	Risk Ratio M-H, Random, 95% CI
Cerar 2010	22	145	23	140	48.5%	0.92 [0.54, 1.58]
Luger 1995	32	113	20	119	51.5%	1.68 [1.03, 2.77]
Total (95% CI)		**258**		**259**	**100.0%**	**1.26 [0.70, 2.27]**
Total events	54		43			

Heterogeneity: Tau² = 0.11; Chi² = 2.60, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.77 (P = 0.44)



E.1.3 Doxycycline (PO) versus amoxicillin (PO) plus probenecid

Figure 19: Cure

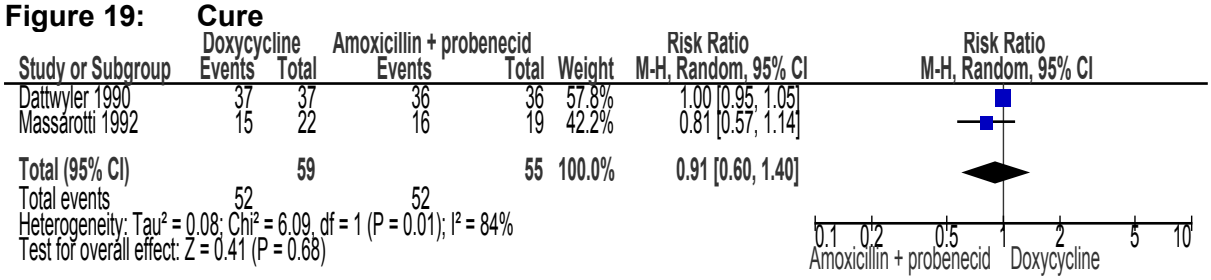


Figure 20: Disease progression to late disease

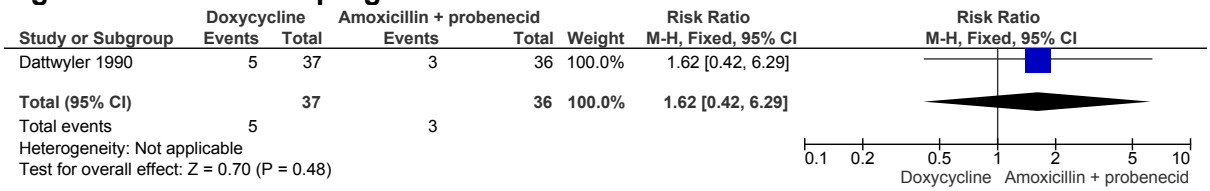
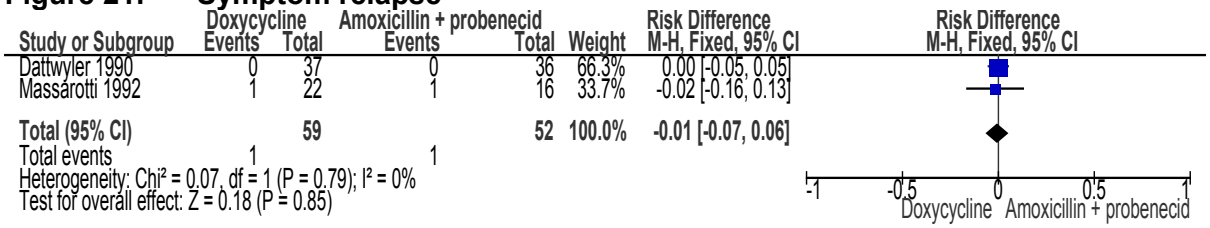


Figure 21: Symptom relapse



E.1.4 Doxycycline (PO) versus ceftriaxone (IV or IM)

Figure 22: Cure (at 3 months)

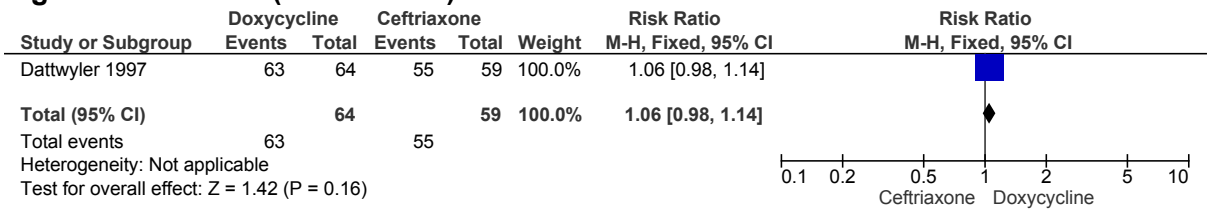


Figure 23: Cure (at 6 months)

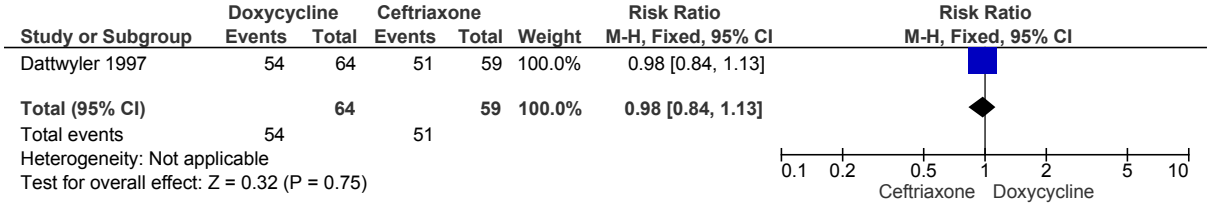


Figure 24: Cure (at 9 months)

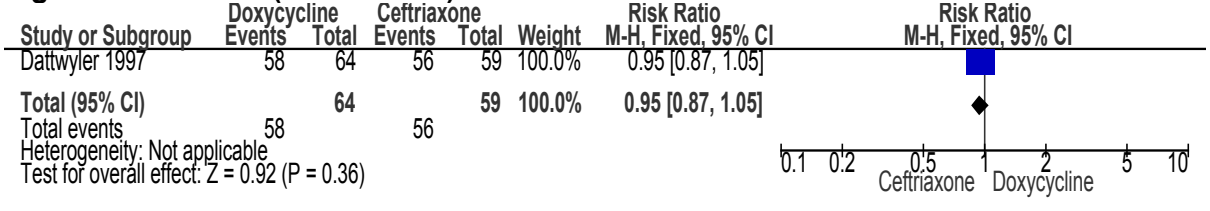
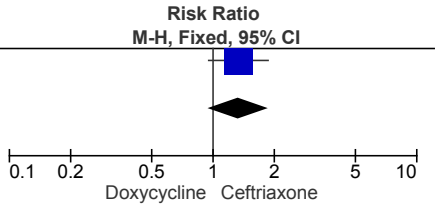


Figure 25: Adverse events

Study or Subgroup	Doxycycline Events	Doxycycline Total	Ceftriaxone Events	Ceftriaxone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dattwyler 1997	39	68	31	72	100.0%	1.33 [0.95, 1.86]
Total (95% CI)		**68**		**72**	**100.0%**	**1.33 [0.95, 1.86]**
Total events	39		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.67 (P = 0.09)

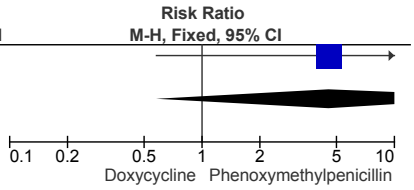


E.1.5 Doxycycline (PO) versus phenoxymethylpenicillin (PO)

Figure 26: Adverse events

Study or Subgroup	Doxycycline Events	Doxycycline Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strle 1992	5	23	1	21	100.0%	4.57 [0.58, 35.96]
Total (95% CI)		**23**		**21**	**100.0%**	**4.57 [0.58, 35.96]**
Total events	5		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)



E.1.6 10-day doxycycline (PO) versus 15-day doxycycline (PO)

Figure 27: Cure (at 14 days)

Study or Subgroup	10-day doxycycline Events	10-day doxycycline Total	15-day doxycycline Events	15-day doxycycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stupica 2012	60	108	71	117	100.0%	0.92 [0.73, 1.14]
Total (95% CI)		**108**		**117**	**100.0%**	**0.92 [0.73, 1.14]**
Total events	60		71			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)

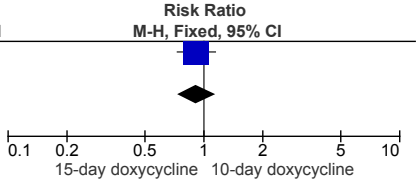


Figure 28: Cure (at 2 months)

Study or Subgroup	10-day doxycycline Events	10-day doxycycline Total	15-day doxycycline Events	15-day doxycycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stupica 2012	88	104	98	113	100.0%	0.98 [0.87, 1.09]
Total (95% CI)		**104**		**113**	**100.0%**	**0.98 [0.87, 1.09]**
Total events	88		98			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.44 (P = 0.66)

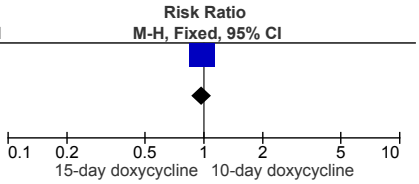


Figure 29: Cure (at 6 months)

Study or Subgroup	10-day doxycycline Events	10-day doxycycline Total	15-day doxycycline Events	15-day doxycycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stupica 2012	81	96	95	101	100.0%	0.90 [0.81, 0.99]
Total (95% CI)		**96**		**101**	**100.0%**	**0.90 [0.81, 0.99]**
Total events	81		95			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.15 (P = 0.03)

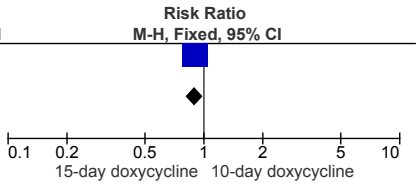
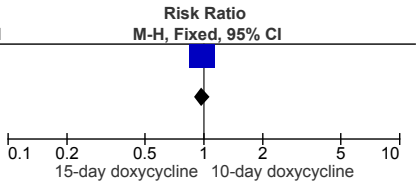


Figure 30: Cure (at 1 year)

Study or Subgroup	10-day doxycycline Events	10-day doxycycline Total	15-day doxycycline Events	15-day doxycycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Stupica 2012	79	86	85	91	100.0%	0.98 [0.90, 1.07]
Total (95% CI)		**86**		**91**	**100.0%**	**0.98 [0.90, 1.07]**
Total events	79		85			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.69)



E.1.7 10-day doxycycline (PO) versus 20-day doxycycline (PO)

Figure 31: Cure (at 20 days)

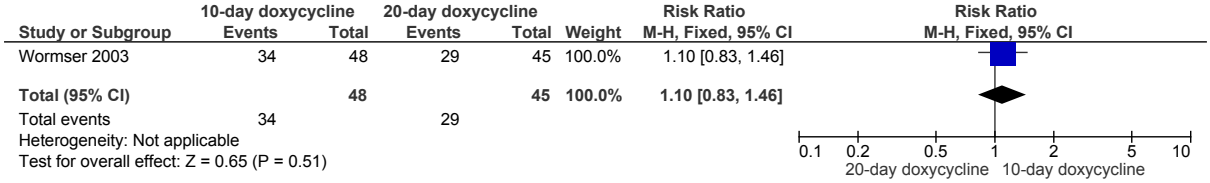


Figure 32: Cure (at 3 months)

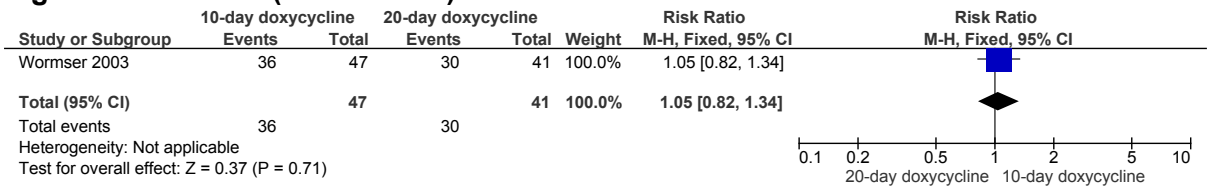


Figure 33: Cure (at 1 year)

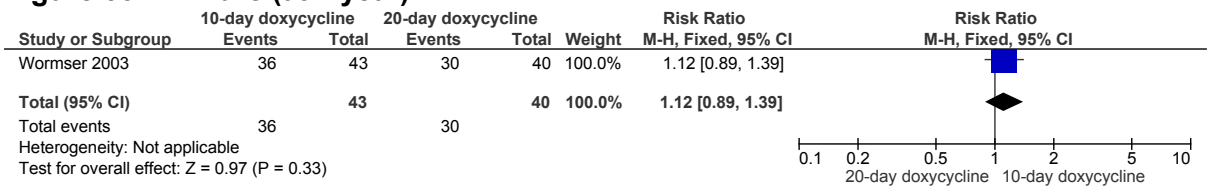


Figure 34: Cure (at 30 months)

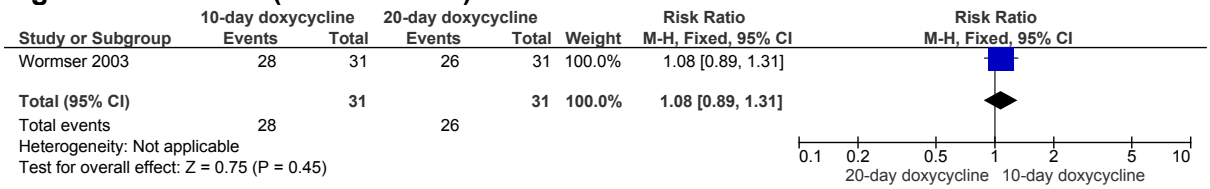


Figure 35: Reduction in symptoms (at 20 days; partial response)

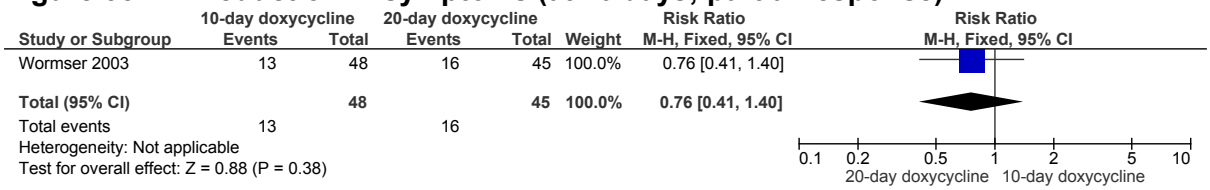


Figure 36: Reduction in symptoms (at 3 months; partial response)

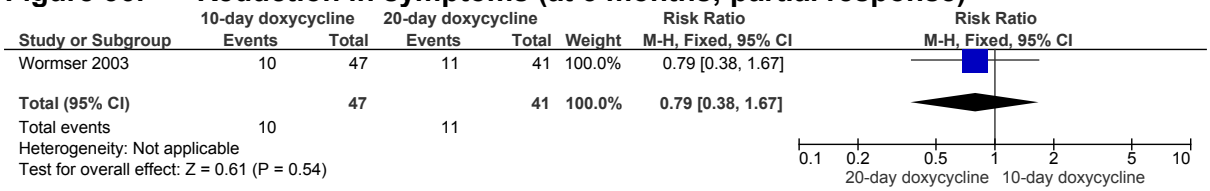


Figure 37: Reduction in symptoms (at 1 year; partial response)

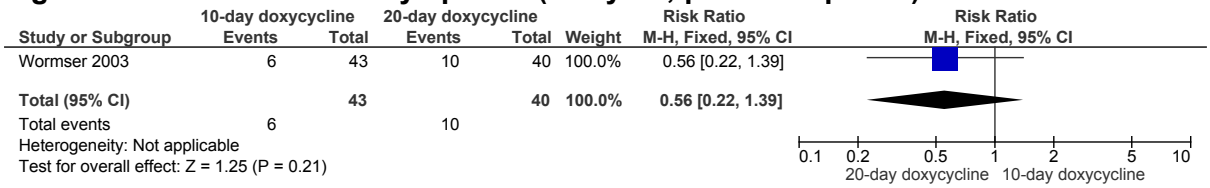


Figure 38: Reduction in symptoms (at 30 months; partial response)

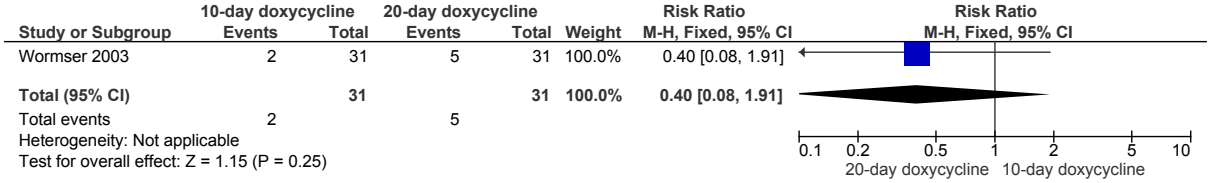
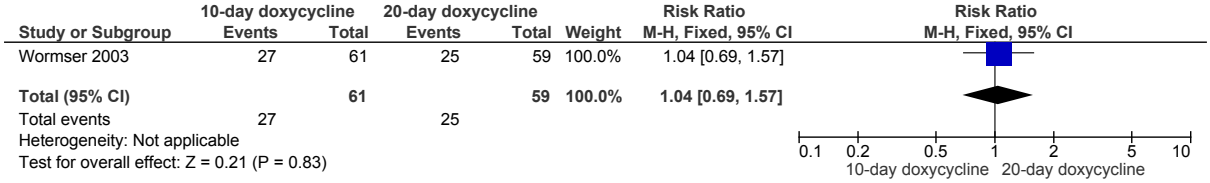


Figure 39: Adverse events



E.1.8 10-day tetracycline (PO) versus 20-day tetracycline (PO)

Figure 40: Cure

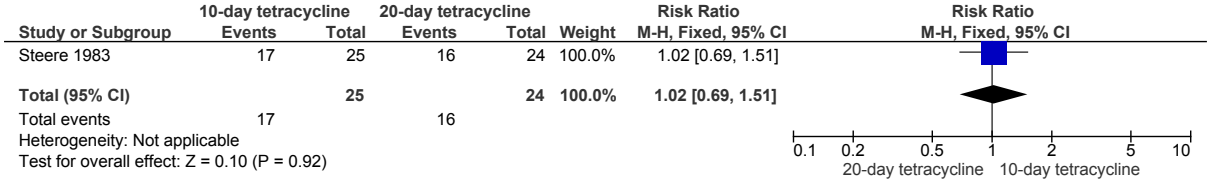


Figure 41: Minor late disease

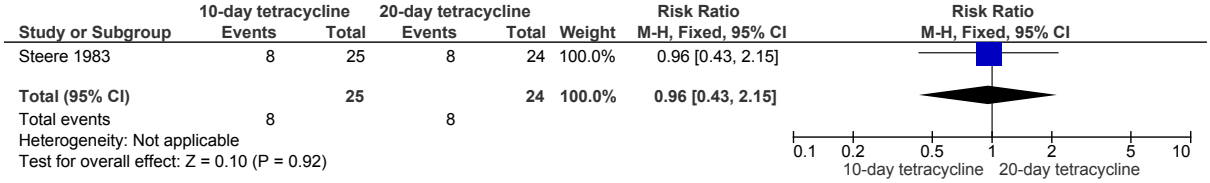
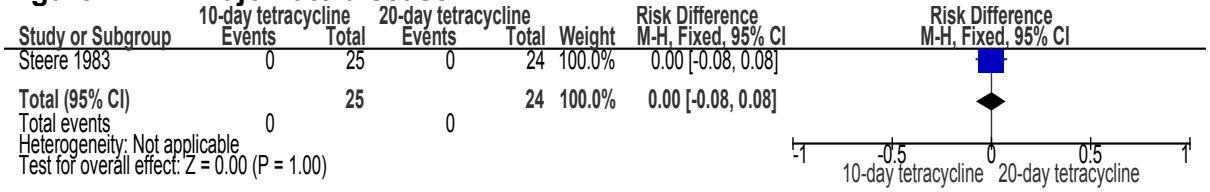


Figure 42: Major late disease



E.1.9 Tetracycline (PO) versus phenoxymethylpenicillin (PO)

Figure 43: Cure

Study or Subgroup	Tetracycline Events	Tetracycline Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	22	39	16	40	100.0%	1.41 [0.88, 2.25]
Total (95% CI)		**39**		**40**	**100.0%**	**1.41 [0.88, 2.25]**
Total events	22		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.44 (P = 0.15)

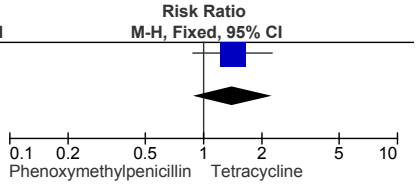


Figure 44: Minor late disease

Study or Subgroup	Tetracycline Events	Tetracycline Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	17	39	20	40	100.0%	0.87 [0.54, 1.40]
Total (95% CI)		**39**		**40**	**100.0%**	**0.87 [0.54, 1.40]**
Total events	17		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

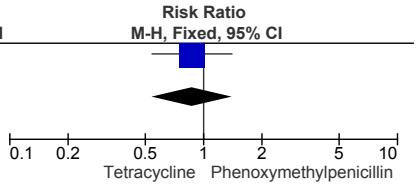
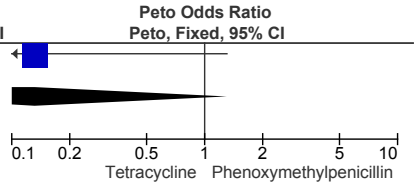


Figure 45: Major late disease

Study or Subgroup	Tetracycline Events	Tetracycline Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Steere 1983	0	39	3	40	100.0%	0.13 [0.01, 1.30]
Total (95% CI)		**39**		**40**	**100.0%**	**0.13 [0.01, 1.30]**
Total events	0		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.73 (P = 0.08)



E.1.10 Amoxicillin (PO) versus azithromycin (PO)

Figure 46: Cure

Study or Subgroup	Amoxicillin Events	Amoxicillin Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luft 1996	93	106	84	111	100.0%	1.16 [1.02, 1.32]
Total (95% CI)		**106**		**111**	**100.0%**	**1.16 [1.02, 1.32]**
Total events	93		84			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.28 (P = 0.02)

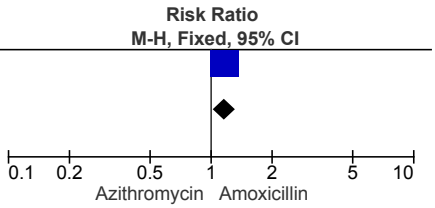


Figure 47: Reduction in symptoms

Study or Subgroup	Amoxicillin Events	Amoxicillin Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luft 1996	13	106	24	111	100.0%	0.57 [0.31, 1.05]
Total (95% CI)		**106**		**111**	**100.0%**	**0.57 [0.31, 1.05]**
Total events	13		24			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)

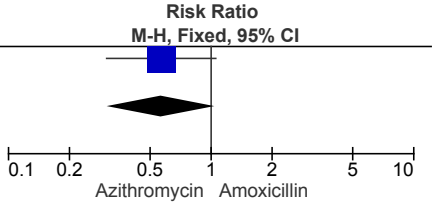


Figure 48: Symptom relapse

Study or Subgroup	Amoxicillin Events	Amoxicillin Total	Azithromycin Events	Azithromycin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Luft 1996	4	103	17	106	100.0%	0.24 [0.08, 0.70]
Total (95% CI)		**103**		**106**	**100.0%**	**0.24 [0.08, 0.70]**
Total events	4		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.63 (P = 0.008)

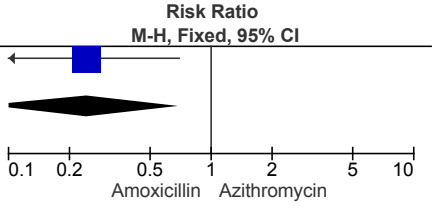
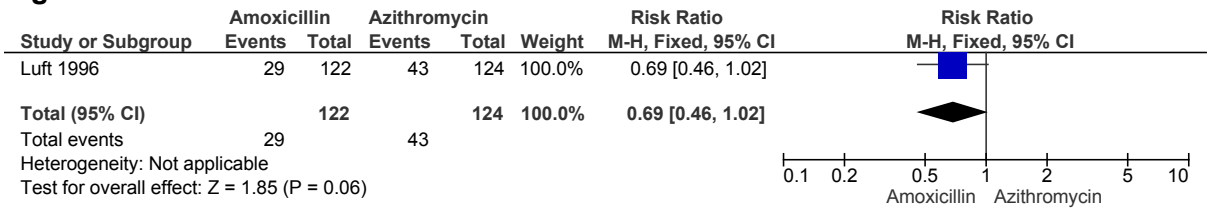


Figure 49: Adverse events



E.1.11 Amoxicillin (PO) plus probenecid versus azithromycin (PO)

Figure 50: Cure

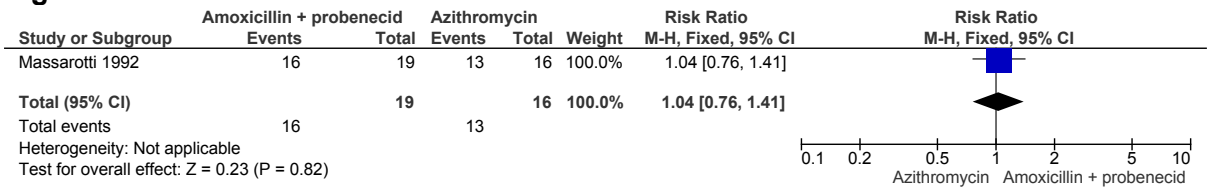
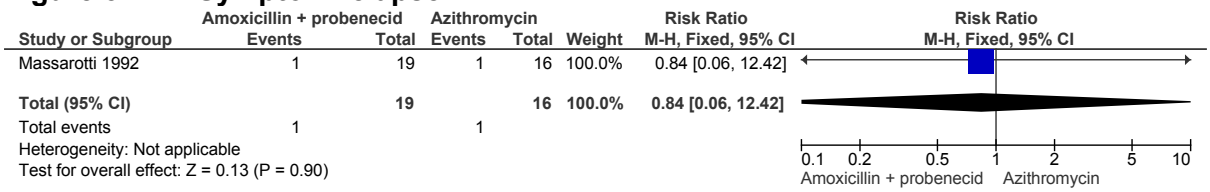


Figure 51: Symptom relapse



E.1.12 Ceftriaxone (IM) versus phenoxymethylpenicillin (PO)

Figure 52: Jarisch-Herxheimer reaction

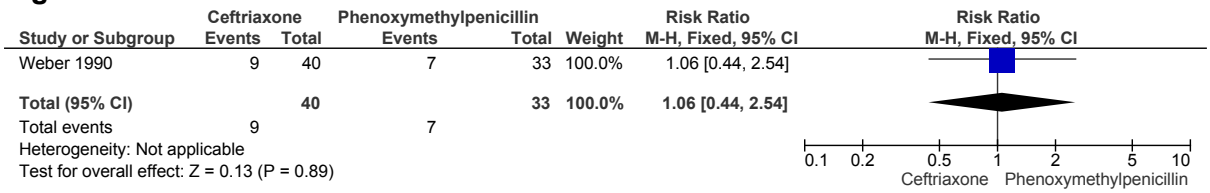
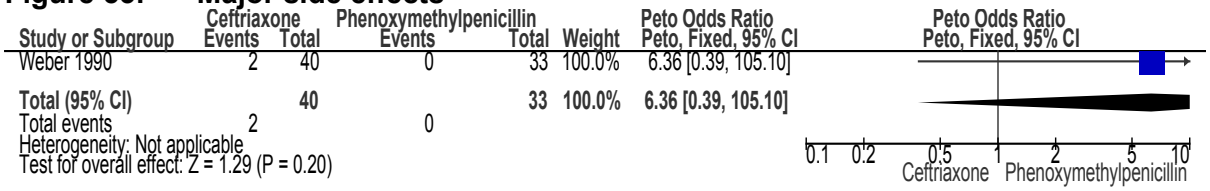


Figure 53: Major side effects



E.1.13 Ceftriaxone (IV) plus doxycycline (PO) versus doxycycline (PO)

Figure 54: Cure (at 20 days)

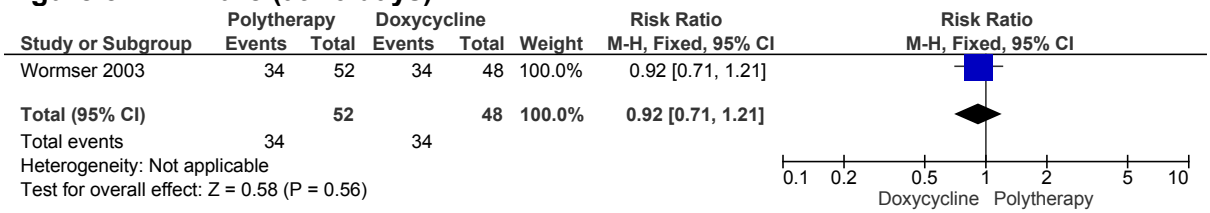


Figure 55: Cure (at 3 months)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	36	48	36	47	100.0%	0.98 [0.78, 1.23]
Total (95% CI)		**48**		**47**	**100.0%**	**0.98 [0.78, 1.23]**
Total events	36		36			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

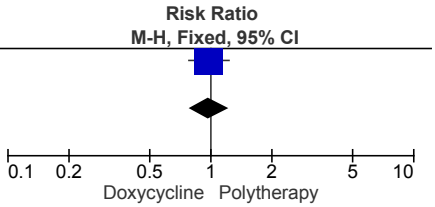


Figure 56: Cure (at 1 year)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	37	45	36	43	100.0%	0.98 [0.81, 1.19]
Total (95% CI)		**45**		**43**	**100.0%**	**0.98 [0.81, 1.19]**
Total events	37		36			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)

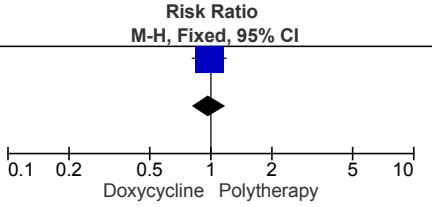


Figure 57: Cure (at 30 months)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	32	37	28	31	100.0%	0.96 [0.81, 1.14]
Total (95% CI)		**37**		**31**	**100.0%**	**0.96 [0.81, 1.14]**
Total events	32		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)

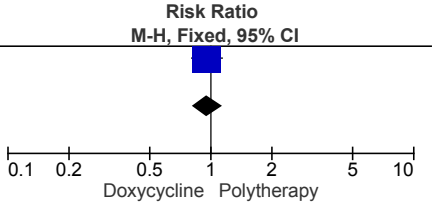


Figure 58: Reduction in symptoms (at 20 days)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	18	52	13	48	100.0%	1.28 [0.70, 2.32]
Total (95% CI)		**52**		**48**	**100.0%**	**1.28 [0.70, 2.32]**
Total events	18		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)

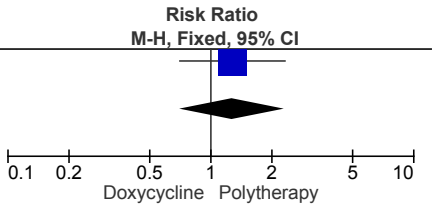


Figure 59: Reduction in symptoms (at 3 months)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	12	48	10	47	100.0%	1.18 [0.56, 2.45]
Total (95% CI)		**48**		**47**	**100.0%**	**1.18 [0.56, 2.45]**
Total events	12		10			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)

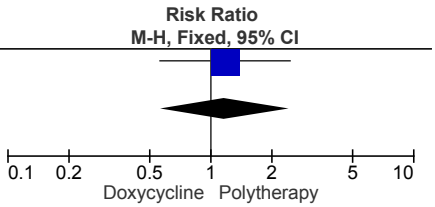


Figure 60: Reduction in symptoms (at 1 year)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	8	45	6	43	100.0%	1.27 [0.48, 3.37]
Total (95% CI)		**45**		**43**	**100.0%**	**1.27 [0.48, 3.37]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.63)

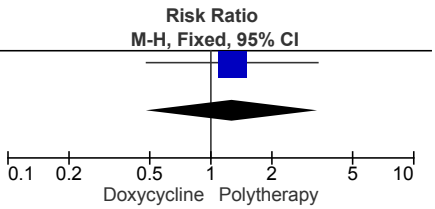


Figure 61: Reduction in symptoms (at 30 months)

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	5	37	2	31	100.0%	2.09 [0.44, 10.06]
Total (95% CI)		**37**		**31**	**100.0%**	**2.09 [0.44, 10.06]**
Total events	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.92 (P = 0.36)

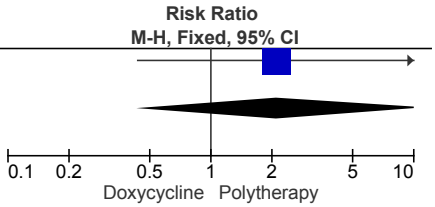
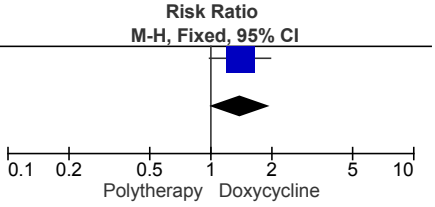


Figure 62: Adverse events

Study or Subgroup	Polytherapy Events	Total	Doxycycline Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Wormser 2003	37	60	27	61	100.0%	1.39 [0.99, 1.97]
Total (95% CI)		**60**		**61**	**100.0%**	**1.39 [0.99, 1.97]**
Total events	37		27			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)



E.1.14 Minocycline (PO) versus phenoxymethylpenicillin (PO)

Figure 63: Cure

Study or Subgroup	Minocycline Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Breier 1996	18	18	21	21	100.0%	1.00 [0.91, 1.10]
Total (95% CI)		**18**		**21**	**100.0%**	**1.00 [0.91, 1.10]**
Total events	18		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

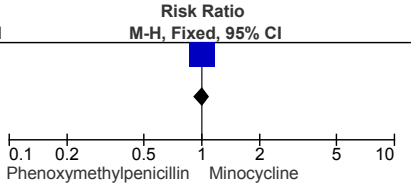
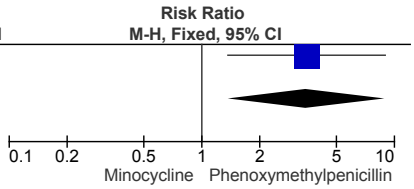


Figure 64: Adverse events

Study or Subgroup	Minocycline Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Breier 1996	12	18	4	21	100.0%	3.50 [1.37, 8.96]
Total (95% CI)		**18**		**21**	**100.0%**	**3.50 [1.37, 8.96]**
Total events	12		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.61 (P = 0.009)



E.1.15 Azithromycin (PO) versus phenoxymethylpenicillin (PO)

Figure 65: Cure (at 10 days – number of participants with signs and symptoms)

Study or Subgroup	Azithromycin Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Weber 1993	18	32	29	33	100.0%	0.64 [0.46, 0.89]
Total (95% CI)		**32**		**33**	**100.0%**	**0.64 [0.46, 0.89]**
Total events	18		29			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.64 (P = 0.008)

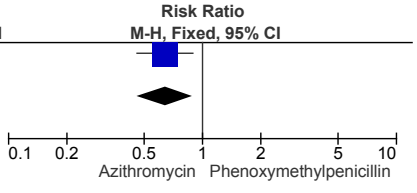


Figure 66: Cure (at 1 month – number of participants with signs and symptoms)

Study or Subgroup	Azithromycin Events	Total	Phenoxymethylpenicillin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Weber 1993	12	32	16	33	100.0%	0.77 [0.44, 1.37]
Total (95% CI)		**32**		**33**	**100.0%**	**0.77 [0.44, 1.37]**
Total events	12		16			

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

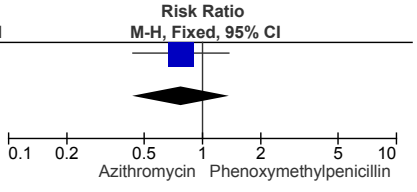


Figure 67: Cure (at 3 months – number of participants with signs and symptoms)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Weber 1993	7	32	5	33	100.0%	1.44 [0.51, 4.08]
Total (95% CI)		**32**		**33**	**100.0%**	**1.44 [0.51, 4.08]**
Total events	7		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

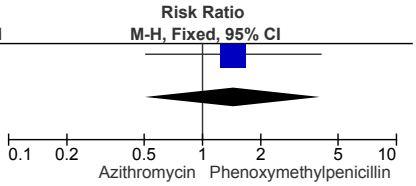


Figure 68: Cure (at 6 months – number of participants with signs and symptoms)

Study or Subgroup	Azithromycin Events	Azithromycin Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Weber 1993	4	28	4	25	100.0%	0.89 [0.25, 3.20]
Total (95% CI)		**28**		**25**	**100.0%**	**0.89 [0.25, 3.20]**
Total events	4		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

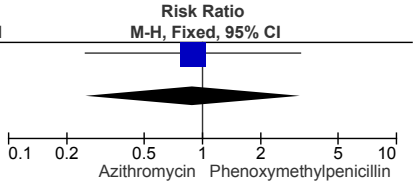
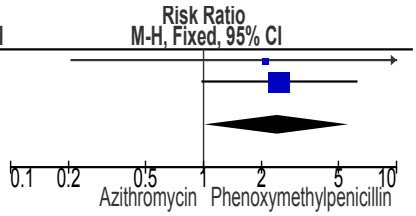


Figure 69: Adverse events

Study or Subgroup	Azithromycin Events	Azithromycin Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Strle 1992	2	20	1	21	16.5%	2.10 [0.21, 21.39]
Weber 1993	12	32	5	33	83.5%	2.48 [0.98, 6.23]
Total (95% CI)		**52**		**54**	**100.0%**	**2.41 [1.02, 5.69]**
Total events	14		6			

Heterogeneity: $Chi^2 = 0.02$, $df = 1$ ($P = 0.90$); $I^2 = 0\%$
Test for overall effect: $Z = 2.01$ ($P = 0.04$)



E.1.16 Erythromycin (PO) versus phenoxymethylpenicillin (PO)

Figure 70: Cure

Study or Subgroup	Erythromycin Events	Erythromycin Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	14	29	16	40	100.0%	1.21 [0.71, 2.06]
Total (95% CI)		**29**		**40**	**100.0%**	**1.21 [0.71, 2.06]**
Total events	14		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

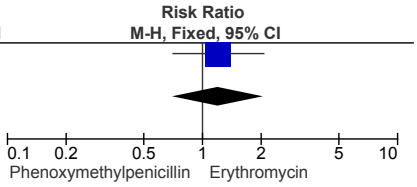


Figure 71: Minor late disease

Study or Subgroup	Erythromycin Events	Erythromycin Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	11	29	20	40	100.0%	0.76 [0.43, 1.33]
Total (95% CI)		**29**		**40**	**100.0%**	**0.76 [0.43, 1.33]**
Total events	11		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

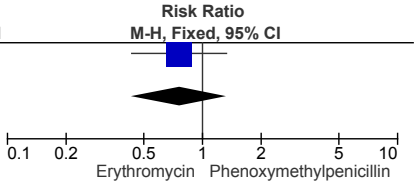
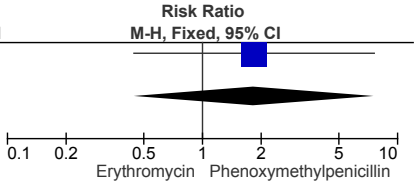


Figure 72: Major late disease

Study or Subgroup	Erythromycin Events	Erythromycin Total	Phenoxymethylpenicillin Events	Phenoxymethylpenicillin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	4	29	3	40	100.0%	1.84 [0.45, 7.60]
Total (95% CI)		**29**		**40**	**100.0%**	**1.84 [0.45, 7.60]**
Total events	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



E.1.17 Erythromycin (PO) versus tetracycline (PO)

Figure 73: Cure

Study or Subgroup	Erythromycin Events	Erythromycin Total	Tetracycline Events	Tetracycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	14	29	22	39	100.0%	0.86 [0.54, 1.37]
Total (95% CI)		**29**		**39**	**100.0%**	**0.86 [0.54, 1.37]**
Total events	14		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

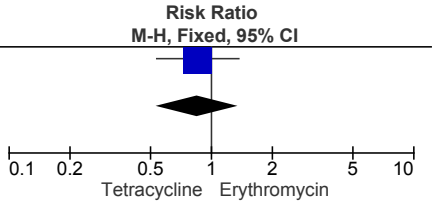


Figure 74: Minor late disease

Study or Subgroup	Erythromycin Events	Erythromycin Total	Tetracycline Events	Tetracycline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Steere 1983	11	29	17	39	100.0%	0.87 [0.48, 1.56]
Total (95% CI)		**29**		**39**	**100.0%**	**0.87 [0.48, 1.56]**
Total events	11		17			

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

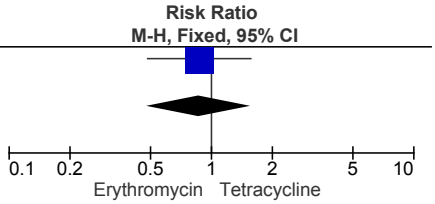
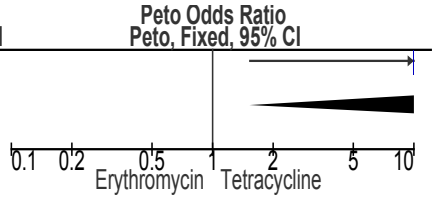


Figure 75: Major late disease

Study or Subgroup	Erythromycin Events	Erythromycin Total	Tetracycline Events	Tetracycline Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Steere 1983	4	29	0	39	100.0%	11.64 [1.53, 88.43]
Total (95% CI)		**29**		**39**	**100.0%**	**11.64 [1.53, 88.43]**
Total events	4		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)



E.2 Children

E.2.1 Amoxicillin (PO) versus high-dose cefuroxime axetil (PO)

Figure 76: EM resolved

Study or Subgroup	Amoxicillin Events	Amoxicillin Total	High-dose cefuroxime Events	High-dose cefuroxime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	8	12	13	15	100.0%	0.77 [0.49, 1.20]
Total (95% CI)		**12**		**15**	**100.0%**	**0.77 [0.49, 1.20]**
Total events	8		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.15 (P = 0.25)

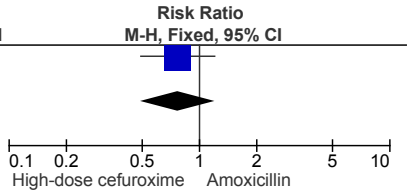


Figure 77: Lyme disease symptoms resolved (at 3 weeks)

Study or Subgroup	Amoxicillin Events	Amoxicillin Total	High-dose cefuroxime Events	High-dose cefuroxime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	12	12	13	15	100.0%	1.14 [0.90, 1.44]
Total (95% CI)		**12**		**15**	**100.0%**	**1.14 [0.90, 1.44]**
Total events	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

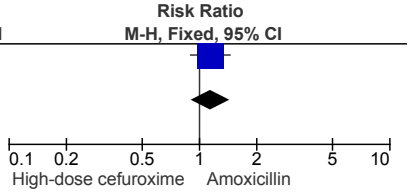


Figure 78: Lyme disease symptoms resolved (at 6 months)

Study or Subgroup	Amoxicillin Events	Amoxicillin Total	High-dose cefuroxime Events	High-dose cefuroxime Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	13	13	15	15	100.0%	1.00 [0.87, 1.14]
Total (95% CI)		**13**		**15**	**100.0%**	**1.00 [0.87, 1.14]**
Total events	13		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

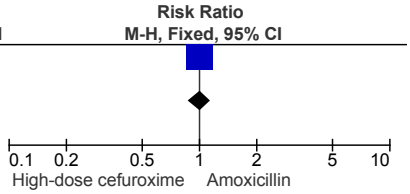


Figure 79: Lyme disease symptoms resolved (at 1 year)

Study or Subgroup	Amoxicillin Events	Total	High-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	12	12	15	15	100.0%	1.00 [0.87, 1.15]
Total (95% CI)		**12**		**15**	**100.0%**	**1.00 [0.87, 1.15]**
Total events	12		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

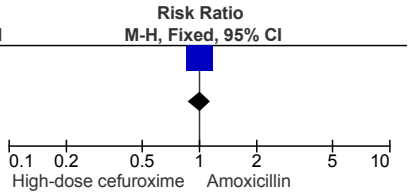


Figure 80: Allergic reaction

Study or Subgroup	Amoxicillin Events	Total	High-dose cefuroxime Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Eppes 2002	0	12	0	15	100.0%	0.00 [-0.13, 0.13]
Total (95% CI)		**12**		**15**	**100.0%**	**0.00 [-0.13, 0.13]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

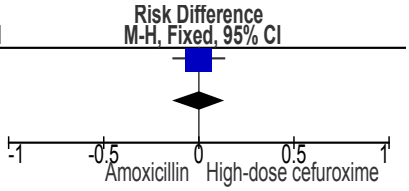


Figure 81: Vomiting

Study or Subgroup	Amoxicillin Events	Total	High-dose cefuroxime Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Eppes 2002	0	12	0	15	100.0%	0.00 [-0.13, 0.13]
Total (95% CI)		**12**		**15**	**100.0%**	**0.00 [-0.13, 0.13]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

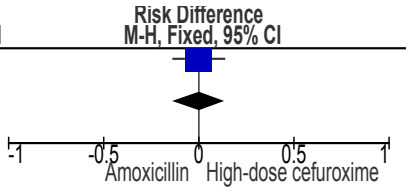
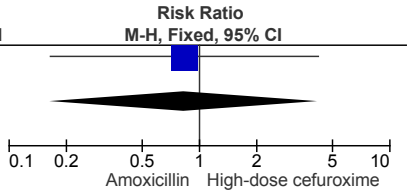


Figure 82: Diarrhoea between 2-5 days

Study or Subgroup	Amoxicillin Events	Total	High-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	2	12	3	15	100.0%	0.83 [0.16, 4.21]
Total (95% CI)		**12**		**15**	**100.0%**	**0.83 [0.16, 4.21]**
Total events	2		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)



E.2.2 Amoxicillin (PO) versus low-dose cefuroxime axetil (PO)

Figure 83: EM resolved

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	8	12	12	13	100.0%	0.72 [0.47, 1.11]
Total (95% CI)		**12**		**13**	**100.0%**	**0.72 [0.47, 1.11]**
Total events	8		12			

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

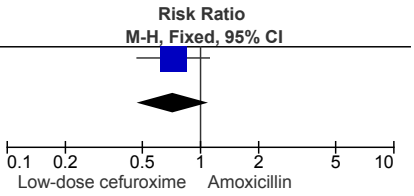


Figure 84: Lyme disease symptoms resolved (at 3 weeks)

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	12	12	9	13	100.0%	1.42 [0.97, 2.06]
Total (95% CI)		**12**		**13**	**100.0%**	**1.42 [0.97, 2.06]**
Total events	12		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)

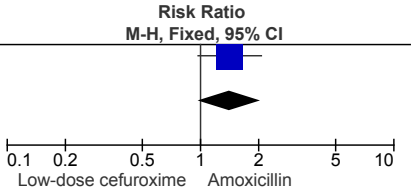


Figure 85: Lyme disease symptoms resolved (at 6 months)

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	12	12	13	13	100.0%	1.00 [0.86, 1.16]
Total (95% CI)		**12**		**13**	**100.0%**	**1.00 [0.86, 1.16]**
Total events	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

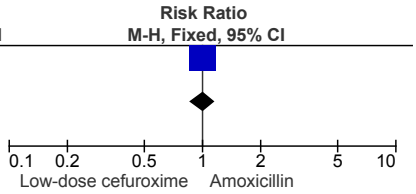


Figure 86: Lyme disease symptoms resolved (at 1 year)

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	12	12	13	13	100.0%	1.00 [0.86, 1.16]
Total (95% CI)		**12**		**13**	**100.0%**	**1.00 [0.86, 1.16]**
Total events	12		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

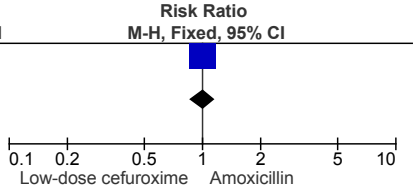


Figure 87: Allergic reaction

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Eppes 2002	0	12	0	15	100.0%	0.00 [-0.13, 0.13]
Total (95% CI)		**12**		**15**	**100.0%**	**0.00 [-0.13, 0.13]**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

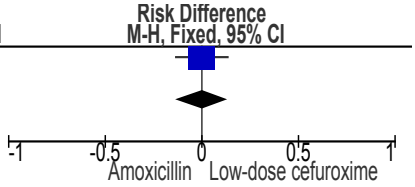


Figure 88: Vomiting

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Eppes 2002	0	12	1	15	100.0%	0.17 [0.00, 8.54]
Total (95% CI)		**12**		**15**	**100.0%**	**0.17 [0.00, 8.54]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)

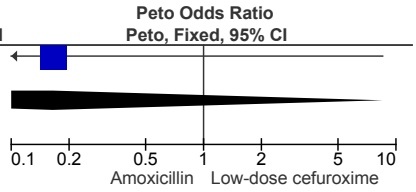
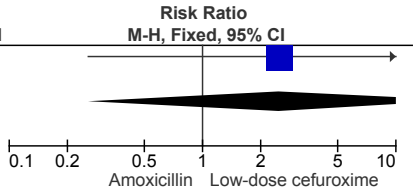


Figure 89: Diarrhoea between 2-5 days

Study or Subgroup	Amoxicillin Events	Total	Low-dose cefuroxime Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Eppes 2002	2	12	1	15	100.0%	2.50 [0.26, 24.38]
Total (95% CI)		**12**		**15**	**100.0%**	**2.50 [0.26, 24.38]**
Total events	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.79 (P = 0.43)

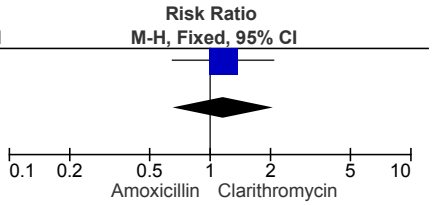


E.2.3 Amoxicillin (PO) versus clarithromycin (PO)

Figure 90: Jarisch-Herxheimer reaction

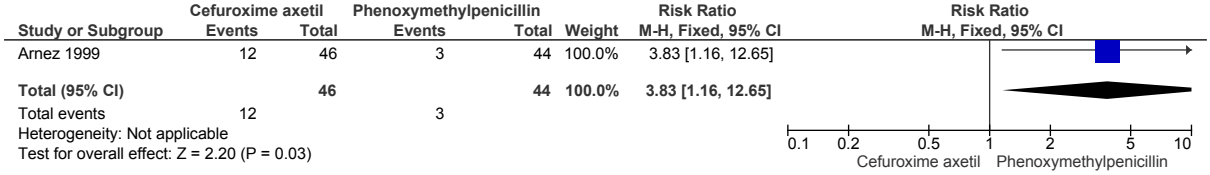
Study or Subgroup	Amoxicillin Events	Total	Clarithromycin Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Nizi 2012	18	64	16	66	100.0%	1.16 [0.65, 2.07]
Total (95% CI)		**64**		**66**	**100.0%**	**1.16 [0.65, 2.07]**
Total events	18		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)



E.2.4 Cefuroxime axetil (PO) versus phenoxymethylpenicillin (PO)

Figure 91: Adverse events



E.2.5 High-dose cefuroxime axetil (PO) versus low-dose cefuroxime axetil (PO)

Figure 92: EM resolved

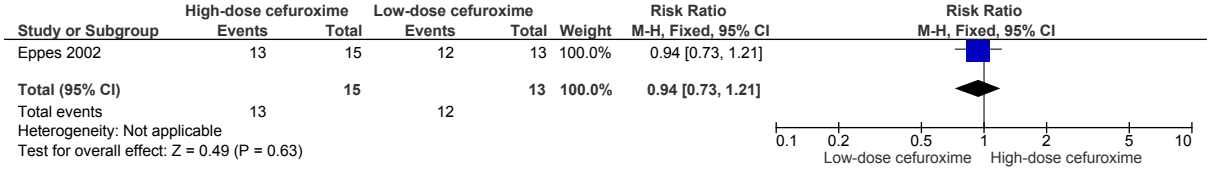


Figure 93: Lyme disease symptoms resolved (at 3 weeks)

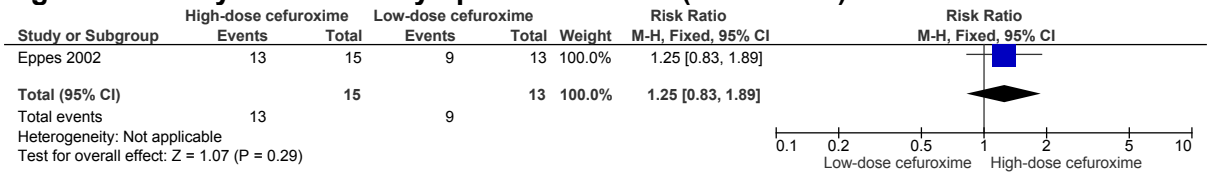


Figure 94: Lyme disease symptoms resolved (at 6 months)

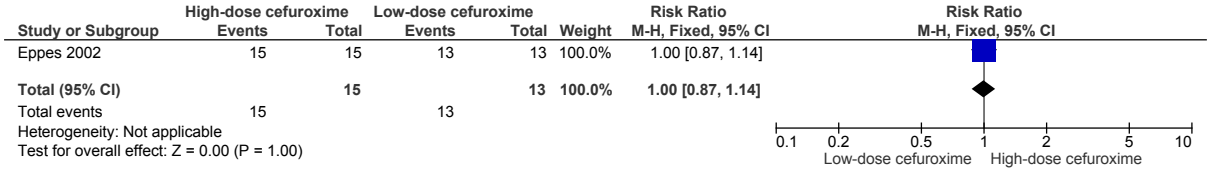


Figure 95: Lyme disease symptoms resolved (at 1 year)

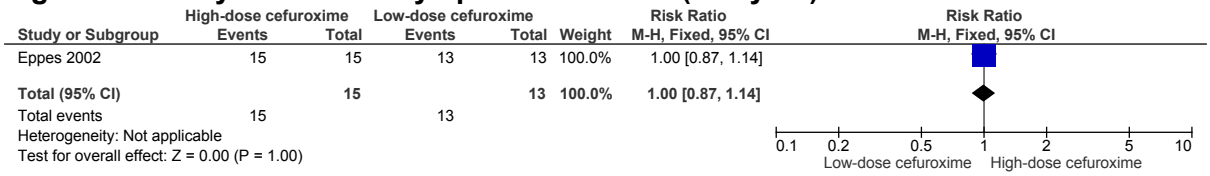


Figure 96: Allergic reaction

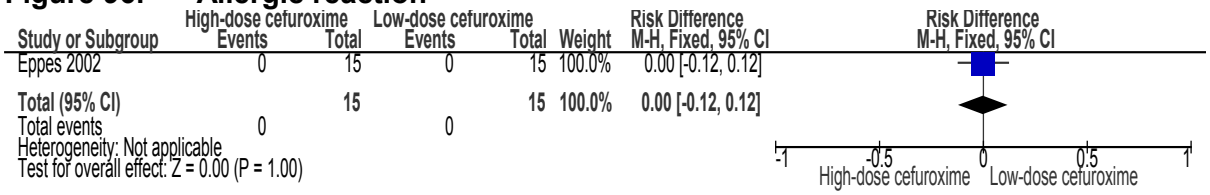


Figure 97: Vomiting

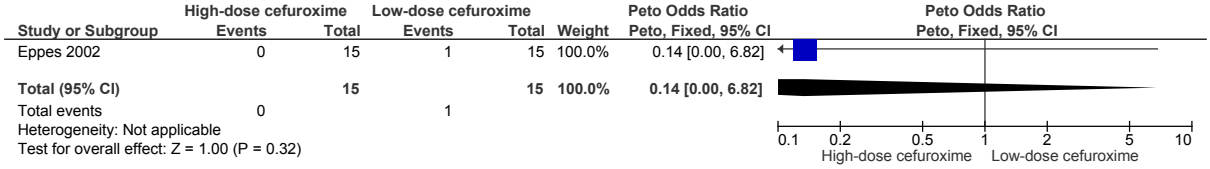
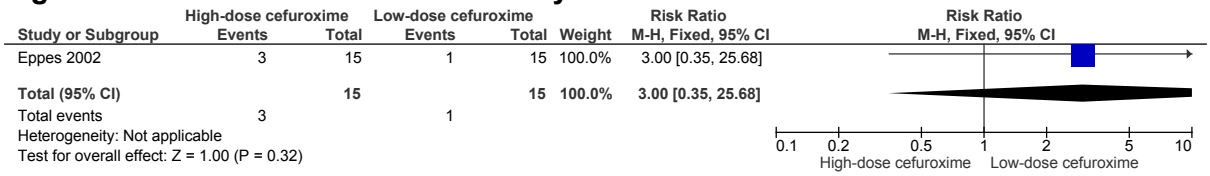


Figure 98: Diarrhoea between 2-5 days



E.2.6 Azithromycin (PO) versus amoxicillin (PO)

Figure 99: Duration of EM symptoms

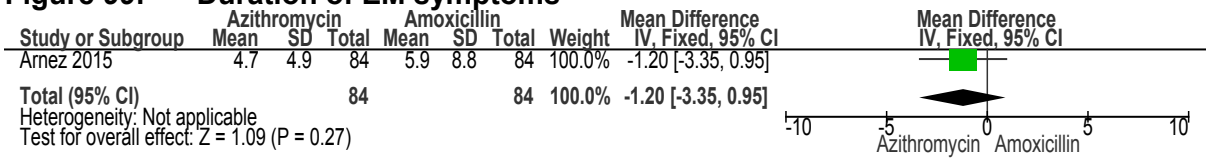


Figure 100: Duration of systemic symptoms

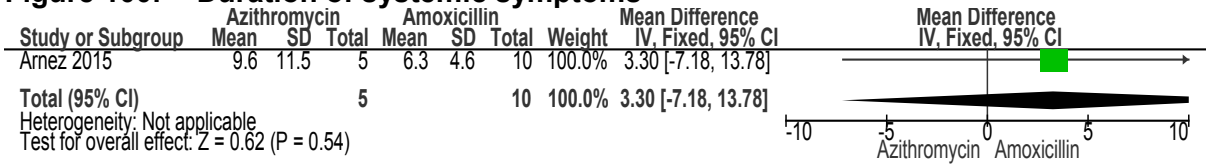


Figure 101: Adverse events

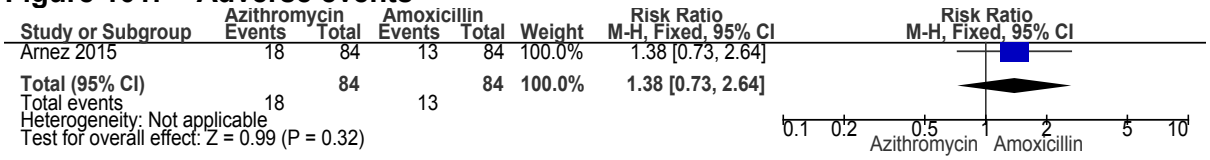
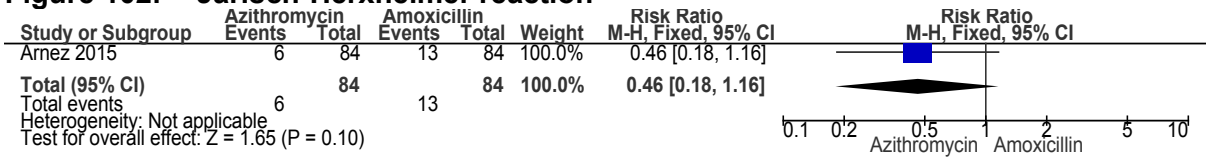
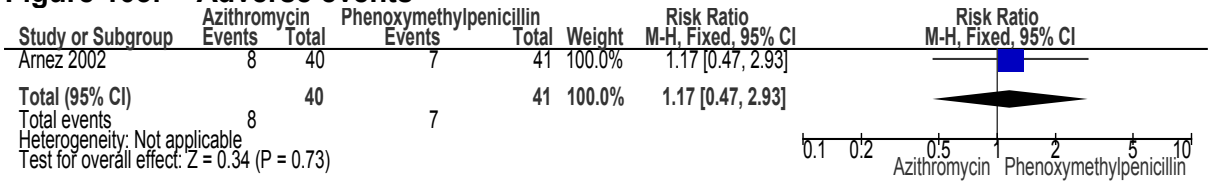


Figure 102: Jarisch-Herxheimer reaction



E.2.7 Azithromycin (PO) versus phenoxymethylpenicillin (PO)

Figure 103: Adverse events



Appendix F: GRADE tables

F.1 Adults

Table 34: Clinical evidence profile: doxycycline (PO) versus azithromycin (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Azithromycin	Relative (95% CI)	Absolute		
Cure												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	44/62 (71%)	55/64 (85.9%)	RR 0.83 (0.69 to 1)	146 fewer per 1,000 (from 266 fewer to 0 more)	⊕OOO VERY LOW	CRITICAL
Reduction in symptoms												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/40 (10%)	4/48 (8.3%)	RR 1.2 (0.32 to 4.5)	17 more per 1,000 (from 57 fewer to 292 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/62 (12.9%)	3/64 (4.7%)	RR 2.85 (0.82 to 9.87)	87 more per 1,000 (from 8 fewer to 416 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/58 (17.2%)	5/67 (7.5%)	RR 2.21 (0.8 to 6.11)	90 more per 1,000 (from 15 fewer to 381 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

Table 35: Clinical evidence profile: doxycycline (PO) versus cefuroxime axetil (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Cefuroxime axetil	Relative (95% CI)	Absolute		
Cure (at 14 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	106/145 (73.1%)	105/140 (75%)	RR 0.97 (0.85 to 1.12)	22 fewer per 1,000 (from 112 fewer to 90 more)	⊕⊕OO LOW	CRITICAL
Cure (at 1 month)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	101/145 (69.7%)	107/155 (69%)	RR 1.01 (0.87 to 1.17)	7 more per 1,000 (from 90 fewer to 117 more)	⊕⊕OO LOW	CRITICAL
Cure (at 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	117/136 (86%)	120/134 (89.6%)	RR 0.96 (0.88 to 1.05)	36 fewer per 1,000 (from 107 fewer to 45 more)	⊕⊕OO LOW	CRITICAL
Cure (at 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	97/102 (95.1%)	87/93 (93.5%)	RR 1.02 (0.95 to 1.09)	19 more per 1,000 (from 47 fewer to 84 more)	⊕⊕OO LOW	CRITICAL
Cure (at 1 year)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	190/207 (91.8%)	201/227 (88.5%)	RR 1.03 (0.97 to 1.09)	27 more per 1,000 (from 27 fewer to 80 more)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (at 1 month)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[1]	none	36/145 (24.8%)	34/155 (21.9%)	RR 1.13 (0.75 to 1.71)	29 more per 1,000 (from 55 fewer to 156 more)	⊕OOO VERY LOW	CRITICAL

Reduction of symptoms (at 1 year)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/91 (12.1%)	14/113 (12.4%)	RR 0.98 (0.47 to 2.04)	2 fewer per 1,000 (from 66 fewer to 129 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse (at 14 days)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	38/145 (26.2%)	35/140 (25%)	RR 1.05 (0.71 to 1.56)	12 more per 1,000 (from 73 fewer to 140 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse (at 1 month)												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/145 (2.1%)	6/155 (3.9%)	RR 0.54 (0.14 to 2.09)	18 fewer per 1,000 (from 33 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse (at 2 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/136 (12.5%)	14/134 (10.4%)	RR 1.2 (0.61 to 2.33)	21 more per 1,000 (from 41 fewer to 139 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse (at 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/102 (2.9%)	6/93 (6.5%)	RR 0.46 (0.12 to 1.77)	35 fewer per 1,000 (from 57 fewer to 50 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse (at 1 year)												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/207 (0.48%)	7/227 (3.1%)	RD -0.03 (-0.05 to 0.00)[3]	27 fewer per 1,000 (from 50 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
2	randomised trials	very serious[1]	Serious[4]	no serious indirectness	serious[2]	none	54/258 (20.9%)	43/259 (16.6%)	RR 1.26 (0.7 to 2.27)	43 more per 1,000 (from 50 fewer to 211 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] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms
[3] Downgraded by 1 increment because of heterogeneity, I^2=50-74%

Table 36: Clinical evidence profile: doxycycline (PO) versus amoxicillin (PO) plus probenecid

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Amoxicillin plus probenecid	Relative (95% CI)	Absolute		
Cure												
2	randomised trials	very serious[1]	very serious[2]	serious[3]	no serious imprecision	none	52/59 (88.1%)	52/55 (94.5%)	RR 0.91 (0.6 to 1.4)	85 fewer per 1,000 (from 378 fewer to 378 more)	⊕OOO VERY LOW	CRITICAL
Disease progression to late disease												
1	randomised trials	very serious[1]	no serious inconsistency	serious[3]	very serious[4]	none	5/37 (13.5%)	3/36 (8.3%)	RR 1.62 (0.42 to 6.29)	52 more per 1,000 (from 48 fewer to 441 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse												
2	randomised trials	very serious[1]	no serious inconsistency	very serious[5]	very serious[4]	none	1/59 (1.7%)	1/52 (1.9%)	RD -0.01 (-0.07 to 0.06)[6]	6 fewer per 1,000 (from 70 fewer to 60 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 2 increments because of heterogeneity, I-squared >75%
[3] Downgraded by 1 increment because of intervention indirectness
[4] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs
[5] Downgraded by 2 increments because of population indirectness and intervention indirectness
[6] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms

Table 37: Clinical evidence profile: doxycycline (PO) versus ceftriaxone (IV or IM)

Quality assessment	Number of participants	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Ceftriaxone	Relative (95% CI)	Absolute		
Cure (at 3 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	63/64 (98.4%)	55/59 (93.2%)	RR 1.06 (0.98 to 1.14)	56 more per 1,000 (from 19 fewer to 131 more)	⊕OOO VERY LOW	CRITICAL
Cure (at 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	54/64 (84.4%)	51/59 (86.4%)	RR 0.98 (0.84 to 1.13)	17 fewer per 1,000 (from 138 fewer to 112 more)	⊕OOO VERY LOW	CRITICAL
Cure (at 9 months)												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	58/64 (90.6%)	56/59 (94.9%)	RR 0.95 (0.87 to 1.05)	47 fewer per 1,000 (from 123 fewer to 47 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	39/68 (57.4%)	31/72 (43.1%)	RR 1.33 (0.95 to 1.86)	142 more per 1,000 (from 22 fewer to 370 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 because of population indirectness
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 38: Clinical evidence profile: doxycycline (PO) versus phenyxymethylpenicillin (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	Phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Adverse events												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/23 (21.7%)	1/21 (4.8%)	RR 4.57 (0.58 to 35.96)	170 more per 1,000 (from 20 fewer to 1,000 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

Table 39: Clinical evidence profile: 10-day doxycycline (PO) versus 15-day doxycycline (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**10-day doxycycline**	**15-day doxycycline**	**Relative (95% CI)**	**Absolute**		
Cure (at 14 days)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	60/108 (55.6%)	71/117 (60.7%)	RR 0.92 (0.73 to 1.14)	49 fewer per 1,000 (from 164 fewer to 85 more)	⊕OOO VERY LOW	CRITICAL
Cure (at 2 months)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	88/104 (84.6%)	98/113 (86.7%)	RR 0.98 (0.87 to 1.09)	17 fewer per 1,000 (from 113 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL
Cure (at 6 months)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	81/96 (84.4%)	95/101 (94.1%)	RR 0.9 (0.81 to 0.99)	94 fewer per 1,000 (from 9 fewer to 179 fewer)	⊕OOO VERY LOW	IMPORTANT
Cure (at 1 year)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	79/86 (91.9%)	85/91 (93.4%)	RR 0.98 (0.9 to 1.07)	19 fewer per 1,000 (from 93 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL

[1] Non-randomised comparative 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 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 40: Clinical evidence profile: 10-day doxycycline (PO) versus 20-day doxycycline (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	10-day doxycycline	20-day doxycycline	Relative (95% CI)	Absolute		
Cure (at 20 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/48 (70.8%)	29/45 (64.4%)	RR 1.1 (0.83 to 1.46)	64 more per 1,000 (from 110 fewer to 296 more)	⊕⊕OO LOW	CRITICAL
Cure (at 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/47 (76.6%)	30/41 (73.2%)	RR 1.05 (0.82 to 1.34)	37 more per 1,000 (from 132 fewer to 249 more)	⊕⊕OO LOW	CRITICAL
Cure (at 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/43 (83.7%)	30/40 (75%)	RR 1.12 (0.89 to 1.39)	90 more per 1,000 (from 83 fewer to 292 more)	⊕⊕OO LOW	CRITICAL
Cure (at 30 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/31 (90.3%)	26/31 (83.9%)	RR 1.08 (0.89 to 1.31)	67 more per 1,000 (from 92 fewer to 260 more)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (at 20 days; partial response)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	13/48 (27.1%)	16/45 (35.6%)	RR 0.76 (0.41 to 1.4)	85 fewer per 1,000 (from 210 fewer to 142 more)	⊕OOO VERY LOW	CRITICAL

Reduction of symptoms (at 3 months; partial response)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	10/47 (21.3%)	11/41 (26.8%)	RR 0.79 (0.38 to 1.67)	56 fewer per 1,000 (from 166 fewer to 180 more)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (at 1 year; partial response)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	6/43 (14%)	10/40 (25%)	RR 0.56 (0.22 to 1.39)	110 fewer per 1,000 (from 195 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (at 30 months; partial response)												
1	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[2]	none	2/31 (6.5%)	5/31 (16.1%)	RR 0.4 (0.08 to 1.91)	97 fewer per 1,000 (from 148 fewer to 147 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	27/61 (44.3%)	25/59 (42.4%)	RR 1.04 (0.69 to 1.57)	17 more per 1,000 (from 131 fewer to 242 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 increment of the majority of the evidence was based on an indirect outcome

Table 41: Clinical evidence profile: 10-day tetracycline (PO) versus 20-day tetracycline (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**10-day tetracycline**	**20-day tetracycline**	**Relative (95% CI)**	**Absolute**		
Cure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/25 (68%)	16/24 (66.7%)	RR 1.02 (0.69 to 1.51)	13 more per 1,000 (from 207 fewer to 340 more)	⊕OOO VERY LOW	CRITICAL

Minor late disease											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/25 (32%)	8/24 (33.3%)	RR 0.96 (0.43 to 2.15)	13 fewer per 1,000 (from 190 fewer to 383 more)	⊕OOO VERY LOW	CRITICAL
Major late disease											
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/25 (0%)	0/24 (0%)	RD 0.00 (-0.08 to 0.08)[3]	0 events in both arms	⊕⊕OO 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] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms

Table 42: Clinical evidence profile: tetracycline (PO) versus phenoxymethylpenicillin (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Tetracycline**	**Phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/39 (56.4%)	16/40 (40%)	RR 1.41 (0.88 to 2.25)	164 more per 1,000 (from 48 fewer to 500 more)	⊕OOO VERY LOW	
Minor late disease												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/39 (43.6%)	20/40 (50%)	RR 0.87 (0.54 to 1.4)	65 fewer per 1,000 (from 230 fewer to 200 more)	⊕OOO VERY LOW	CRITICAL
Major late disease												
1	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[1]	none	0/39 (0%)	3/40 (7.5%)	OR 0.13 (0.01 to 1.3)[3]	65 fewer per 1,000 (from 74 fewer to 20 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] The Peto odds ratio method was used due to a zero event rate in the intervention group

Table 43: Clinical evidence profile: amoxicillin (PO) versus azithromycin (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin	Azithromycin	Relative (95% CI)	Absolute		
Cure												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	93/106 (87.7%)	84/111 (75.7%)	RR 1.16 (1.02 to 1.32)	121 more per 1,000 (from 15 more to 242 more)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/106 (12.3%)	24/111 (21.6%)	RR 0.57 (0.31 to 1.05)	93 fewer per 1,000 (from 149 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Symptom relapse												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/103 (3.9%)	17/106 (16%)	RR 0.24 (0.08 to 0.7)	122 fewer per 1,000 (from 48 fewer to 148 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	29/122 (23.8%)	43/124 (34.7%)	RR 0.69 (0.46 to 1.02)	108 fewer per 1,000 (from 187 fewer to 7 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

Table 44: Clinical evidence profile: amoxicillin (PO) plus probenecid versus azithromycin (PO)

Quality assessment	Number of participants	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin plus probenecid	Azithromycin	Relative (95% CI)	Absolute		
Cure												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	16/19 (84.2%)	13/16 (81.3%)	RR 1.04 (0.76 to 1.41)	32 more per 1,000 (from 195 fewer to 333 more)	⊕OOO VERY LOW	CRITICAL
Symptom relapse												
1	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/19 (5.3%)	1/16 (6.3%)	RR 0.84 (0.06 to 12.42)	10 fewer per 1,000 (from 59 fewer to 714 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 because of intervention indirectness
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 45: Clinical evidence profile: ceftriaxone (IM) versus phenoxymethylpenicillin (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone	Phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Jarisch-Herxheimer reaction												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/40 (22.5%)	7/33 (21.2%)	RR 1.06 (0.44 to 2.54)	13 more per 1,000 (from 119 fewer to 327 more)	⊕OOO VERY LOW	IMPORTANT
Major side effects												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/40 (5%)	0/33 (0%)	OR 6.36 (0.39 to 105.1)[3]	50 more per 1,000 (from 18 more to 118 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 due to a zero event rate in the control group

Table 46: Clinical evidence profile: ceftriaxone (IV) plus doxycycline (PO) versus doxycycline (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus doxycycline	Doxycycline	Relative (95% CI)	Absolute		
Cure (at 20 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	34/52 (65.4%)	34/48 (70.8%)	RR 0.92 (0.71 to 1.21)	57 fewer per 1,000 (from 205 fewer to 149 more)	⊕⊕OO LOW	CRITICAL
Cure (at 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	36/48 (75%)	36/47 (76.6%)	RR 0.98 (0.78 to 1.23)	15 fewer per 1,000 (from 169 fewer to 176 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure (at 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	37/45 (82.2%)	36/43 (83.7%)	RR 0.98 (0.81 to 1.19)	17 fewer per 1,000 (from 159 fewer to 159 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure (at 30 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/37 (86.5%)	28/31 (90.3%)	RR 0.96 (0.81 to 1.14)	36 fewer per 1,000 (from 172 fewer to 126 more)	⊕⊕⊕O MODERATE	CRITICAL
Reduction of symptoms (at 20 days)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/52 (34.6%)	13/48 (27.1%)	RR 1.28 (0.7 to 2.32)	76 more per 1,000 (from 81 fewer to 357 more)	⊕OOO VERY LOW	CRITICAL

Reduction of symptoms (at 3 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/48 (25%)	10/47 (21.3%)	RR 1.17 (0.56 to 2.45)	36 more per 1,000 (from 94 fewer to 309 more)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (at 1 year)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/45 (17.8%)	6/43 (14%)	RR 1.27 (0.48 to 3.37)	38 more per 1,000 (from 73 fewer to 331 more)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (at 30 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/37 (13.5%)	2/31 (6.5%)	RR 2.09 (0.44 to 10.06)	70 more per 1,000 (from 36 fewer to 585 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/60 (61.7%)	27/61 (44.3%)	RR 1.39 (0.99 to 1.97)	173 more per 1,000 (from 4 fewer to 429 more)	⊕⊕OO 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

Table 47: Clinical evidence profile: minocycline (PO) versus phenoxymethylpenicillin (PO)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Minocycline**	**Phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/18 (100%)	21/21 (100%)	RR 1 (0.91 to 1.1)	0 fewer per 1,000 (from 90 fewer to 100 more)	⊕⊕OO LOW	CRITICAL

Adverse events												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/18 (66.7%)	4/21 (19%)	RR 3.5 (1.37 to 8.96)	476 more per 1,000 (from 70 more to 1,000 more)	⊕⊕OO 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

Table 48: Clinical evidence profile: azithromycin (PO) versus phenoxymethylpenicillin (PO)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Azithromycin**	**Phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure (at 10 days; assessed with: number of patients with signs and symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18/32 (56.3%)	29/33 (87.9%)	RR 0.64 (0.46 to 0.89)	316 fewer per 1,000 (from 97 fewer to 475 fewer)	⊕OOO VERY LOW	CRITICAL
Cure (at 1 month; assessed with: number of patients with signs and symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/32 (37.5%)	16/33 (48.5%)	RR 0.77 (0.44 to 1.37)	112 fewer per 1,000 (from 272 fewer to 179 more)	⊕OOO VERY LOW	CRITICAL
Cure (at 3 months; assessed with: number of patients with signs and symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/32 (21.9%)	5/33 (15.2%)	RR 1.44 (0.51 to 4.08)	67 more per 1,000 (from 74 fewer to 467 more)	⊕OOO VERY LOW	CRITICAL
Cure (at 6 months; assessed with: number of patients with signs and symptoms)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/28 (14.3%)	4/25 (16%)	RR 0.89 (0.25 to 3.2)	18 fewer per 1,000 (from 120 fewer to 352 more)	⊕OOO VERY LOW	CRITICAL

Adverse events												
2	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	14/52 (26.9%)	6/54 (11.1%)	RR 2.41 (1.02 to 5.69)	157 more per 1,000 (from 2 more to 521 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

Table 49: Clinical evidence profile: erythromycin (PO) versus phenoxymethylpenicillin (PO)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Erythromycin**	**Phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Cure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/29 (48.3%)	16/40 (40%)	RR 1.21 (0.71 to 2.06)	84 more per 1,000 (from 116 fewer to 424 more)	⊕OOO VERY LOW	CRITICAL
Minor late disease												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/29 (37.9%)	20/40 (50%)	RR 0.76 (0.43 to 1.33)	120 fewer per 1,000 (from 285 fewer to 165 more)	⊕OOO VERY LOW	CRITICAL
Major late disease												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/29 (13.8%)	3/40 (7.5%)	RR 1.84 (0.45 to 7.6)	63 more per 1,000 (from 41 fewer to 495 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 50: Clinical evidence profile: erythromycin (PO) versus tetracycline (PO)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Erythromycin	Tetracycline	Relative (95% CI)	Absolute		
Cure												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/29 (48.3%)	22/39 (56.4%)	RR 0.86 (0.54 to 1.37)	79 fewer per 1,000 (from 259 fewer to 209 more)	⊕OOO VERY LOW	CRITICAL
Minor late disease												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/29 (37.9%)	17/39 (43.6%)	RR 0.87 (0.48 to 1.56)	57 fewer per 1,000 (from 227 fewer to 244 more)	⊕OOO VERY LOW	CRITICAL
Major late disease												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4/29 (13.8%)	0/39 (0%)	OR 11.64 (1.53 to 88.43)[3]	138 more per 1,000 (from 12 more to 263 more)	⊕⊕OO 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 due to a zero event rate in the control group

F.2 Children

Table 51: Clinical evidence profile: amoxicillin (PO) versus high-dose cefuroxime axetil (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin	High-dose cefuroxime	Relative (95% CI)	Absolute		

								axetil				
EM resolved												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/12 (66.7%)	13/15 (86.7%)	RR 0.77 (0.49 to 1.2)	199 fewer per 1,000 (from 442 fewer to 173 more)	⊕OOO VERY LOW	CRITICAL
Lyme disease symptoms resolved (at 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/12 (100%)	13/15 (86.7%)	RR 1.14 (0.9 to 1.44)	121 more per 1,000 (from 87 fewer to 381 more)	⊕OOO VERY LOW	CRITICAL
Lyme disease symptoms resolved (at 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13/13 (100%)	15/15 (100%)	RR 1 (0.87 to 1.14)	0 fewer per 1,000 (from 130 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Lyme disease symptoms resolved (at 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/12 (100%)	15/15 (100%)	RR 1 (0.87 to 1.15)	0 fewer per 1,000 (from 130 fewer to 150 more)	⊕⊕OO LOW	CRITICAL
Allergic reaction												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/12 (0%)	0/15 (0%)	RD 0.00 (-0.13 to 0.13)[3]	0 events in both arms	⊕⊕OO LOW	IMPORTANT
Vomiting												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/12 (0%)	0/15 (0%)	RD 0.00 (-0.13 to 0.13)[3]	0 events in both arms	⊕⊕OO LOW	IMPORTANT
Diarrhoea between 2-5 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/12 (16.7%)	3/15 (20%)	RR 0.83 (0.16 to 4.21)	34 fewer per 1,000 (from 168 fewer to 642 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] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms

Table 52: Clinical evidence profile: amoxicillin (PO) versus low-dose cefuroxime axetil (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin	Low-dose cefuroxime axetil	Relative (95% CI)	Absolute		
EM resolved												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	8/12 (66.7%)	12/13 (92.3%)	RR 0.72 (0.47 to 1.11)	258 fewer per 1,000 (from 489 fewer to 102 more)	⊕OOO VERY LOW	CRITICAL
Lyme disease symptoms resolved (at 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/12 (100%)	9/13 (69.2%)	RR 1.42 (0.97 to 2.06)	291 more per 1,000 (from 21 fewer to 734 more)	⊕OOO VERY LOW	CRITICAL
Lyme disease symptoms resolved (at 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/12 (100%)	13/13 (100%)	RR 1 (0.86 to 1.16)	0 fewer per 1,000 (from 140 fewer to 160 more)	⊕⊕OO LOW	CRITICAL
Lyme disease symptoms resolved (at 1 year)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/12 (100%)	13/13 (100%)	RR 1 (0.86 to 1.16)	0 fewer per 1,000 (from 140 fewer to 160 more)	⊕⊕OO LOW	CRITICAL
Allergic reaction												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/12 (0%)	0/15 (0%)	RD 0.00 (-0.13 to 0.13)[3]	0 events in both arms	⊕⊕OO LOW	IMPORTANT

Vomiting												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/12 (0%)	1/15 (6.7%)	OR 0.17 (0 to 8.54)[4]	55 fewer per 1,000 (from 67 fewer to 312 more)	⊕OOO VERY LOW	IMPORTANT
Diarrhoea between 2-5 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/12 (16.7%)	1/15 (6.7%)	RR 2.5 (0.26 to 24.38)	100 more per 1,000 (from 49 fewer to 1,000 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] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms
[4] The Peto odds ratio method was used due to a zero event rate in the intervention group

Table 53: Clinical evidence profile: amoxicillin (PO) versus clarithromycin (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amoxicillin**	**Clarithromycin**	**Relative (95% CI)**	**Absolute**		
Jarisch-Herxheimer reaction												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	18/64 (28.1%)	16/66 (24.2%)	RR 1.16 (0.65 to 2.07)	39 more per 1,000 (from 85 fewer to 259 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

Table 54: Clinical evidence profile: cefuroxime axetil (PO) versus phenoxymethylpenicillin (PO)

Quality assessment	Number of participants	Effect	Quality	Importance

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefuroxime axetil	Phenoxymethylpenicillin	Relative (95% CI)	Absolute		
Adverse events												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/46 (26.1%)	3/44 (6.8%)	RR 3.83 (1.16 to 12.65)	193 more per 1,000 (from 11 more to 794 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

Table 55: Clinical evidence profile: high-dose cefuroxime axetil (PO) versus low-dose cefuroxime axetil (PO)

Quality assessment							Number of participants		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-dose cefuroxime axetil	Low-dose cefuroxime axetil	Relative (95% CI)	Absolute		
EM resolved												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/15 (86.7%)	12/13 (92.3%)	RR 0.94 (0.73 to 1.21)	55 fewer per 1,000 (from 249 fewer to 194 more)	⊕OOO VERY LOW	CRITICAL
Lyme disease symptoms resolved (at 3 weeks)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13/15 (86.7%)	9/13 (69.2%)	RR 1.25 (0.83 to 1.89)	173 more per 1,000 (from 118 fewer to 616 more)	⊕OOO VERY LOW	CRITICAL
Lyme disease symptoms resolved (at 6 months)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/15 (100%)	13/13 (100%)	RR 1 (0.87 to 1.14)	0 fewer per 1,000 (from 130 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Lyme disease symptoms resolved (at 12 months)												

1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	15/15 (100%)	13/13 (100%)	RR 1 (0.87 to 1.14)	0 fewer per 1,000 (from 130 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Allergic reaction												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/15 (0%)	0/15 (0%)	RD 0.00 (-0.12 to 0.12)[3]	0 events in both arms	⊕⊕OO LOW	IMPORTANT
Vomiting												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/15 (0%)	1/15 (6.7%)	OR 0.14 (0 to 6.82)[4]	57 fewer per 1,000 (from 67 fewer to 261 more)	⊕OOO VERY LOW	IMPORTANT
Diarrhoea between 2-5 days												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/15 (20%)	1/15 (6.7%)	RR 3 (0.35 to 25.68)	133 more per 1,000 (from 43 fewer to 1,000 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] Risk difference is given because one of the studies included in the meta-analysis had a zero event rate in both arms
[4] The Peto odds ratio method was used due to a zero event rate in the intervention group

Table 56: Clinical evidence profile: azithromycin (PO) versus phenoxymethylpenicicllin (PO)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Azithromycin**	**Phenoxymethylpenicillin**	**Relative (95% CI)**	**Absolute**		
Adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/40 (20%)	7/41 (17.1%)	RR 1.17 (0.47 to 2.93)	29 more per 1,000 (from 90 fewer to 330 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

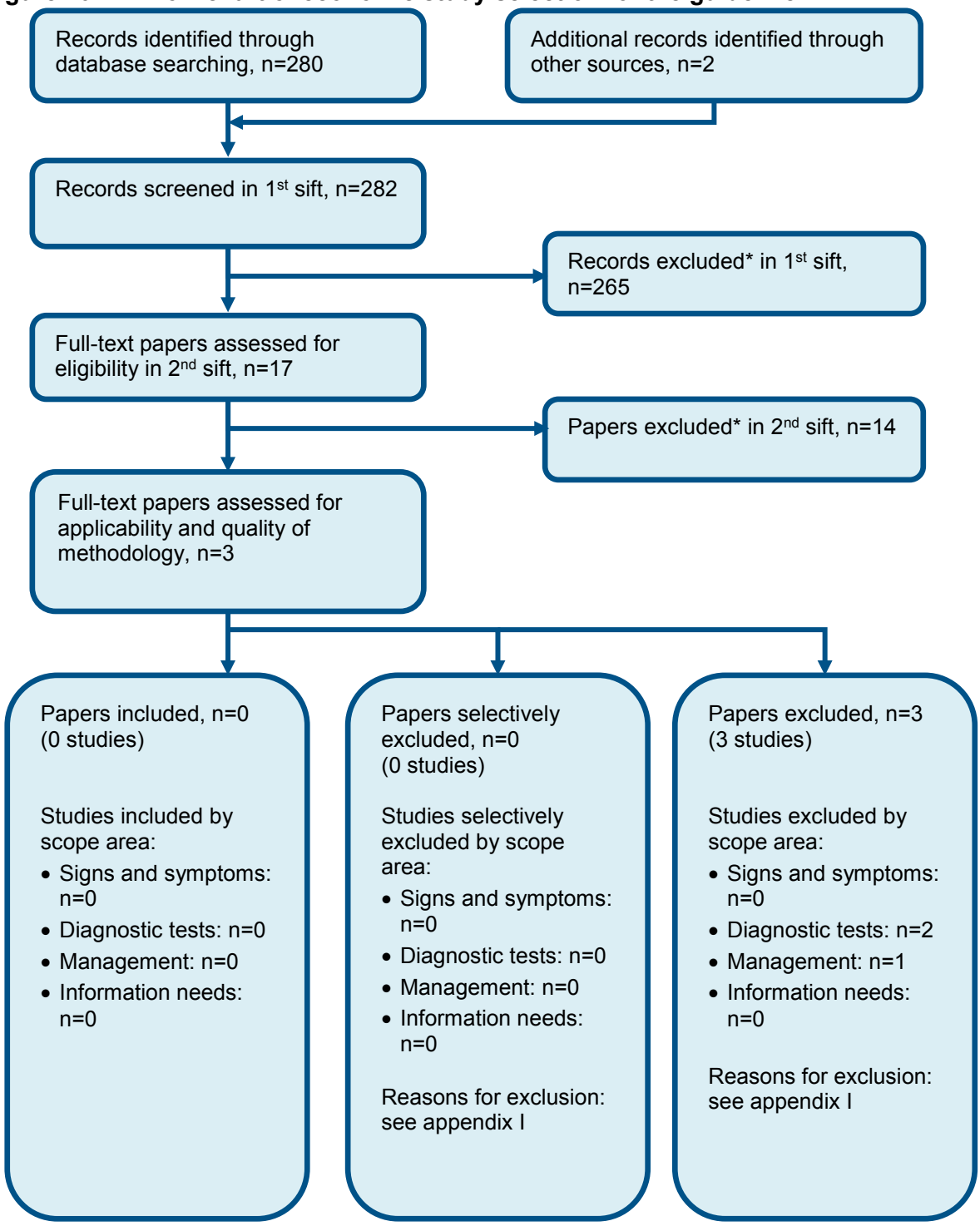
Table 57: Clinical evidence profile: azithromycin (PO) versus amoxicillin (PO)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Amoxicillin	Relative (95% CI)	Absolute		
Duration of EM symptoms (Better indicated by lower values)												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	84	84	-	MD 1.2 lower (3.35 lower to 0.95 higher)	⊕OOO VERY LOW	CRITICAL
Duration of systemic symptoms (Better indicated by lower values)												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5	10	-	MD 3.3 higher (7.18 lower to 13.78 higher)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1	observational studies[1]	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	18/84 (21.4%)	13/84 (15.5%)	RR 1.38 (0.73 to 2.64)	59 more per 1,000 (from 42 fewer to 254 more)	⊕OOO VERY LOW	IMPORTANT
Jarisch-Herxheimer reaction												
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	6/84 (7.1%)	13/84 (15.5%)	RR 0.46 (0.18 to 1.16)	84 fewer per 1,000 (from 127 fewer to 25 more)	⊕OOO VERY LOW	IMPORTANT

[1] Non-randomised comparative 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 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 104: 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 58: 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[14]	Excluded due to an incorrect study design
Auwaerter 2004[15]	Excluded due to an incorrect study design
Bennet 2003[18]	Excluded due to an incorrect study design
Berende 2014[19]	Excluded due to an incorrect study design
Berger 1988[21]	Excluded due to an incorrect study design
Berger 1986[20]	Excluded due to an incorrect study design
Bernardino 2009[22]	Excluded due to an incorrect study design
Bhate 2011[23]	Excluded due to an incorrect study design
Bjark 2016[24]	Not available
Borg 2005[27]	Excluded due to an incorrect study design
Bratton 2008[28]	Excluded due to an incorrect study design
Bremell 2014[30]	Excluded due to an incorrect study design
British Infection Association 2011[31]	Excluded due to an incorrect study design
Butler 1978[32]	Excluded due to an incorrect population
Cadavid 2016[33]	Excluded due to an incorrect study design
Canadian Paediatric Society 1992[34]	Excluded due to an incorrect study design
Chen 1999[37]	Excluded due to an incorrect outcome
Choo-Kang 2010[38]	Excluded due to an incorrect study design
Christian 1992[39]	Excluded due to an incorrect study design
Cimmino 1992[41]	Excluded due to an incorrect study design
Cimmino 1997[40]	Excluded due to an incorrect study design
Cimperman 1999[42]	Excluded due to an incorrect study design
Coblyn 1981[43]	Excluded due to an incorrect study design
Committee on Infectious Diseases 1991[45]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Cuisset 2008[47]	Excluded due to an incorrect study design
Dattwyler 1996[49]	Excluded due to an incorrect comparison
Dattwyler 1987[50]	Excluded due to an incorrect study design
Dattwyler 1988[51]	Excluded due to an incorrect population
Dattwyler 2005[54]	Excluded due to an incorrect population
Dersch 2015[56]	Excluded due to an incorrect study design
Dersch 2016[59]	Excluded due to an incorrect study design
Dersch 2014[57]	Excluded due to an incorrect study design
Dersch 2017[58]	Not available
Dhoot 2011[60]	Excluded due to an incorrect study design
Dinser 2005[61]	Excluded due to an incorrect study design
Dotevall 1988[62]	Excluded due to an incorrect study design
Eliassen 2017[63]	Excluded due to an incorrect study design
Eliassen 2017[64]	Excluded due to an incorrect intervention
Eppes 2003[65]	Excluded due to an incorrect study design
Esposito 2013[67]	Excluded due to an incorrect study design
Fallon 1999[69]	Excluded due to an incorrect intervention
Fallon 2008[68]	Excluded due to an incorrect outcome
Galev 2005[70]	Excluded due to an incorrect study design
Garkowski 2017[71]	Systematic review
Gasser 1996[73]	Not available
Gasser 1995[74]	Excluded due to an incorrect study design
Gasser 1995[72]	Excluded due to an incorrect study design
Gerber 1996[75]	Excluded due to an incorrect intervention
Gillies 2015[76]	Excluded due to an incorrect study design
Goodwin 1990[77]	Excluded due to an incorrect study design
Hansen 1992[78]	Excluded due to an incorrect intervention
Hassler 1990[79]	Excluded due to an incorrect population
Horton 2017[80]	Conference abstract
Hu 2001[81]	Excluded due to an incorrect study design
Inboriboon 2010[82]	Excluded due to an incorrect study design
Kaplan 2003[83]	Excluded due to an incorrect population
Karkkonen 2001[84]	Excluded due to an incorrect study design
Karlsson 1996[85]	Excluded due to an incorrect outcome
Kersten 1995[86]	Excluded due to an incorrect study design
Kilic Muftuoglu 2016[87]	Excluded due to an incorrect study design
Klempner 2013[89]	Excluded due to an incorrect study design
Korenberg 1996[90]	Excluded due to an incorrect intervention
Kowalski 2010[92]	Excluded due to an incorrect outcome
Kowalski 2011[91]	Excluded due to an incorrect study design
Krbkova 1996[93]	Excluded due to an incorrect comparison
Kuhn 2012[94]	Excluded due to an incorrect study design
Laasila 2003[95]	Excluded due to an incorrect population
Lantos 2013[96]	Excluded due to an incorrect study design
Lauhio 1994[97]	Excluded due to an incorrect population

Reference	Reason for exclusion
Lauhio 1991[98]	Excluded due to an incorrect population
Lempner 2002[88]	Excluded due to an incorrect study design
Liegner 1992[99]	Excluded due to an incorrect study design
Lipsker 2002[100]	Excluded due to an incorrect study design
Ljostad 2008[101]	Study abstract
Loewen 1999[102]	Excluded due to an incorrect study design
Loewen 2000[103]	Excluded due to an incorrect study design
Luft 1988[106]	Excluded due to an incorrect outcome
Luft 1989[105]	Excluded due to an incorrect population
Maraspin 1995[113]	Excluded due to an incorrect study design
Maraspin 1996[108]	Excluded due to an incorrect study design
Maraspin 1999[109]	Excluded due to an incorrect study design
Maraspin 2002[110]	Excluded due to an incorrect study design
Maraspin 1999[111]	Excluded due to an incorrect study design
Maraspin 2002[112]	Excluded due to an incorrect population
Marks 2016[114]	Excluded due to an incorrect study design
McGill 1965[116]	Excluded due to an incorrect population
Meyerhoff 2002[117]	Excluded due to an incorrect study design
Meyerhoff 2016[118]	Excluded due to an incorrect study design
Millner 1996[119]	Excluded due to an incorrect outcome
Millner 1996[120]	Excluded due to an incorrect outcome
Morales 2000[121]	Excluded due to an incorrect study design
Muellegger 1995[123]	Excluded due to an incorrect study design
Muellegger 1996[122]	Excluded due to an incorrect comparison
Mullegger 1991[124]	Excluded due to an incorrect outcome
Nadelman 1993[127]	Excluded due to an incorrect study design
Nadelman 2001[126]	Excluded due to an incorrect population
Naglo 1989[128]	Excluded due to an incorrect study design
Neumann 1987[131]	Excluded due to an incorrect study design
Nimmrich 2014[133]	Excluded due to an incorrect study design
Nowakowski 2000[135]	Excluded due to an incorrect study design
Nowakowski 1995[136]	Excluded due to an incorrect study design
Ogrinc 2006[137]	Excluded due to an incorrect population
Oksi 1999[138]	Excluded due to an incorrect study design
Oksi 2007[139]	Excluded due to an incorrect population
Oksi 1998[140]	Excluded due to an incorrect population
Peltomaa 1998[141]	Excluded due to an incorrect comparison
Pena 1999[142]	Excluded due to an incorrect study design
Perronne 2015[143]	Not available
Pfister 1988[144]	Excluded due to an incorrect outcome
Pirila 1951[147]	Excluded due to an incorrect study design
Plorer 1993[148]	Excluded due to an incorrect study design
Plotkin 1991[149]	Excluded due to an incorrect study design
Puchalska 1996[150]	Excluded due to an incorrect study design
Puri 2015[151]	Excluded due to an incorrect comparison

Reference	Reason for exclusion
Puri 2015[152]	Excluded due to an incorrect study design
Rebman 2015[153]	Excluded due to an incorrect study design
Renaud 2004[154]	Excluded due to an incorrect study design
Rohacova 1996[155]	Excluded due to an incorrect comparison
Rose 1994[156]	Excluded due to an incorrect study design
Rose 1996[157]	Excluded due to an incorrect intervention
Rubin 1992[158]	Excluded due to an incorrect study design
Salazar 2005[159]	Excluded due to an incorrect intervention
Salazar 1993[160]	Excluded due to an incorrect study design
Sanchez 2016[161]	Excluded due to an incorrect study design
Sandstrom 1989[162]	Excluded due to an incorrect study design
Schmidt 1995[163]	Excluded due to an incorrect study design
Selby 2008[164]	Excluded due to an incorrect study design
Shadick 1994[165]	Excluded due to an incorrect study design
Shadick 1999[166]	Excluded due to an incorrect study design
Shemenski 2016[167]	Excluded due to an incorrect study design
Shoemaker 2006[168]	Excluded due to an incorrect intervention
Sjowall 2012[170]	Excluded due to an incorrect intervention
Sjowall 2011[169]	Excluded due to an incorrect study design
Skogman 2003[172]	Excluded due to an incorrect intervention
Skogman 2008[171]	Excluded due to an incorrect study design
Skoldenberg 1988[173]	Excluded due to an incorrect study design
Smith 2002[174]	Excluded due to an incorrect study design
Solomon 1998[175]	Excluded due to an incorrect intervention
Spathling 1992[176]	Article not in English
Stanek 1999[177]	Excluded due to an incorrect study design
Steere 1980[181]	Excluded due to an incorrect study design
Steere 1983[182]	Excluded due to an incorrect study design
Steere 1987[178]	Excluded due to an incorrect study design
Steurer 2016[183]	Article not in English
Stricker 2011[184]	Excluded due to an incorrect study design
Stricker 2010[185]	Excluded due to an incorrect study design
Strle 1996[186]	Excluded due to an incorrect outcome
Strle 1996[187]	Excluded due to an incorrect outcome
Strle 1992[188]	Excluded due to an incorrect study design
Strle 1993[189]	Excluded due to an incorrect outcome
Stupica 2015[192]	Excluded due to an incorrect comparison
Stupica 2011[191]	Excluded due to an incorrect comparison
Suarez-Magdalena 2017[194]	Not available
Thompson 2012[195]	Excluded due to an incorrect study design
Thorstrand 2002[196]	Excluded due to an incorrect study design
Thyresson 1949[197]	Excluded due to an incorrect study design
Torbahn 2016[199]	Excluded due to an incorrect study design
Tory 2010[200]	Excluded due to an incorrect comparison
Tseng 2017[201]	Excluded due to an incorrect outcome

Reference	Reason for exclusion
Valesova 1996[202]	Excluded due to an incorrect comparison
Vazquez 2003[204]	Excluded due to an incorrect study design
Vazquez-Lopez 2016[203]	Excluded due to an incorrect study design
Wahlberg 1994[206]	Excluded due to an incorrect intervention
Weber 1988[208]	Excluded due to an incorrect study design
Weber 1987[207]	Excluded due to an incorrect population
Weissenbacher 2005[211]	Excluded due to an incorrect intervention
White 2013[212]	Excluded due to an incorrect study design
Zochling 1996[214]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Table 59: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None

Appendix J: Research recommendations

J.1 Development of a core outcome set for studies of management of Lyme disease

Research question: Can a core outcome set be developed for clinical trials of management of Lyme disease?

Why this is important: Antibiotic treatment is the mainstay of management for Lyme disease. The studies published on the management of Lyme disease use differing outcomes, which are often poorly defined. The development of a core outcome set has been identified as a high priority because it would allow comparison across trials and allow appropriate meta-analysis to strengthen results. The methods used should be patient-focused and include patient input on priority outcomes and how they should be measured.

Criteria for selecting high-priority research recommendations:

PICO question	To establish an accepted core outcome set relevant to clinical trials for the management of various clinical presentations of Lyme disease
Importance to patients or the population	The lack of well-defined outcomes makes it difficult to assess treatment options for their clinical effectiveness. There is also a discrepancy between clinical outcomes in trials and outcomes considered important by patients, such as long-term recovery and subjective symptoms.
Relevance to NICE guidance	A core outcome set is essential to allow for comparison across trials. Using well-defined outcomes will allow appropriate meta-analyses to strengthen results and provide a better understanding of the effectiveness of treatment options for Lyme disease.
Relevance to the NHS	An agreed core outcome set will help identify clinically effective treatment for Lyme disease, which in return will improve patient outcomes and reduce unnecessary costs related to ineffective treatment.
National priorities	No
Current evidence base	Many of the studies identified for the reviews on the management of Lyme disease used poorly defined outcomes, which made a valid interpretation of the effectiveness of interventions difficult.
Equality	None relevant
Study design	The development of a core outcome set requires a multi-step approach: 1. Systematic review of the literature 2. Broad healthcare professional and patient/public (including young people and their parents) stakeholder involvement including Delphi survey, stakeholder meeting(s) etc.
Feasibility	This research is feasible as it involves a comprehensive and systematic literature review, Delphi and other well-established methods.
Other comments	Many studies, including some recommended in this guideline, are dependent on a core outcome set being developed.
Importance	High: the research is essential to inform future trials of diagnosis and management of Lyme Disease globally.

J.2 Antimicrobial management of Lyme disease

Research question: What are the most clinically and cost effective treatment options for different clinical presentations of Lyme disease in the UK?

Why this is important:

The evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme diseases is of poor quality, out-dated and often based on small studies. No relevant cost effectiveness evidence was identified. A series of prospective multicentre studies is needed to compare the clinical and cost effectiveness of different dosages and length of treatments required and the clinical and cost effectiveness of oral compared to intravenous treatments for different presentations of Lyme disease. This is felt to be of high priority as it has enormous implications for people with Lyme disease and for NHS costs. There is currently insufficient quality evidence on the most effective drug and dose and the effectiveness of extended treatment or retreatment regimens in those with continuing symptoms remains uncertain, leading to multiple referrals in search of alternative diagnoses. Clarification could improve outcomes, reduce costs and may minimise unnecessary treatment.

Criteria for selecting high-priority research recommendations:

PICO question	Population: all people with Lyme disease Intervention(s): antimicrobial treatment (in particular doxycycline, amoxicillin, azithromycin, ceftriaxone, cefuroxime axetil and phenoxymethylpenicillin) and corticosteroids in specific clinical situations. Comparison: ideally, all treatment options should be compared to current best practice. In practice, consideration of an adaptive clinical trial design is essential to test comparators sequentially and/or if new evidence emerges from elsewhere. Placebo or no treatment is not indicated as a valid comparator for an infectious disease. Outcome(s): core outcome set with short and long term follow up
Importance to patients or the population	Adequate treatment is of the utmost importance to patients. More severe forms of Lyme disease have the potential to be catastrophic and long-term illness has a profound impact on people's lives. It is therefore important that patients receive appropriate and effective treatment to avoid any complications or poor long-term outcomes, including the inability to work or a reduced health-related quality of life.
Relevance to NICE guidance	Many of the studies identified in the reviews on the management of Lyme disease used potentially sub-therapeutic doses of antibiotics and/or courses of treatment that may have been too short to clear infection. Some studies used long courses of antibiotics that can cause harm. Recommendations in this guideline for the management of various clinical presentations of Lyme disease were based on current clinical practice and expert opinion. Well-conducted clinical trials will provide data on the effectiveness of different treatment options in relation to current standard of care.
Relevance to the NHS	Inappropriate or ineffective treatment has the potential to lead to poor long-term outcomes for patients. These patients may incur high costs for the NHS due to their ongoing morbidity and repeated multiple referrals attempting to deal with continuing illness. Conversely, repeated long-term use of antibiotic treatment or repeat testing for Lyme disease in the absence of robust evidence is also costly, may delay alternative diagnosis and treatment and may cause antimicrobial resistance problems for the individuals concerned.
National priorities	No
Current evidence base	Many of the identified studies in the reviews on the management of Lyme disease used potentially sub-therapeutic doses of antibiotics, which do not reflect current clinical practice and standard of care.
Equality	None relevant
Study design	Randomised controlled trials are required and these need to encompass the different clinical presentations of Lyme disease including people with ongoing or recurring symptoms. Given the relatively small number of some clinical presentations of Lyme disease, such as acrodermatitis chronica atrophicans, multi-centre trials should be conducted

	internationally to reach the necessary size of the study population.
Feasibility	As there is equipoise on what is correct treatment regimen, randomising to different treatment arms is feasible and ethical. The study will be able to be conducted via existing NIHR networks including primary, secondary and tertiary care.
Other comments	Studies should be of a size required to achieve statistical power. The treatment arms should reflect current standard of practice regarding dosage of antibiotics, recommended in this guideline. Adaptive designs should be considered given the complexity of the current management recommendations.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.