National Institute for Health and Care Excellence

Final

Lyme disease: diagnosis and management

[B] Evidence review for diagnostic accuracy of signs and symptoms

NICE guideline 95

Intervention evidence review

April 2018

Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: In people with suspected (or under investigation for) Lyme disease, how accurate are signs and symptoms to identify whether Lyme disease is present?

1.2 Introduction

Lyme disease is the occurrence of symptoms associated with infection with *Borrelia burgdorferi sensu lato* (*Borrelia burgdorferi s.l.*). The incubation period is variable generally from a few days to 1 month but this can be longer. A circular, target-like rash usually centred on the bite, known as erythema migrans, is considered pathognomonic for Lyme disease but other symptoms are less specific to Lyme disease.

Knowing the diagnostic accuracy of individual signs and symptoms may aid the clinician in making a decision on whether to consider Lyme disease and assist the clinician in carrying out appropriate testing to determine if Lyme disease can safely be ruled out. This section includes the report of an evidence review on diagnostic accuracy and other factors that contributed to the recommendations.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with suspected (or under investigation for) Lyme disease.
Target condition	Lyme disease Specifically, conditions caused by *Borrelia burgdorferi sensu lato*
Index tests (comparators)	Signs and symptoms: • acrodermatitis chronica atrophicans (ACA) • erythema migrans (EM) • facial palsy • heart block or arrhythmias • lymphocytoma. The review will assess the accuracy of individual signs and symptoms or any combinations to identify whether Lyme disease is present.
Reference standards	• *Borrelia burgdorferi s.l.* culture (Spirochaete is difficult to culture, grows slowly, and is therefore not compatible with providing a rapid diagnostic result). • Polymerase chain reaction (PCR) • Clinical diagnosis
Statistical measures	Detecting Lyme disease • Sensitivity • Specificity • Positive Predictive Value (PPV)

	• Negative Predictive Value (NPV) • Receiver Operating Characteristic (ROC) curve or area under curve
Study design	Include: • Cross-sectional studies, in which the index test(s) and the reference standard test are applied to the same people Exclude (unless there is insufficient evidence and agreed to include with committee): • Two-gate/case-control study designs that compare the results of the index test in people with an established diagnosis with its results in healthy controls. Exclude: • Case series • Case reports

Some of the more non-specific signs and symptoms such as fever, fatigue, and headache were not included in the evidence review because the guideline committee agreed to prioritise more clearly defined signs and symptoms as evidence was more likely to be found for these.

1.4 Clinical evidence

1.4.1 Included studies

Sixteen studies were included in the review.[5,6,17,34,37,41,43,45,60,67,69,70,76,79,80,86] These are summarised in Table 2 below. Seven studies were in adults[5,17,34,37,41,60,79] and 9 studies were in children.[6,43,45,67,69,70,76,80,86] Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, sensitivity and specificity forest plots and receiver operating characteristics (ROC) curves in appendix E, and study evidence tables in appendix D.

No cross-sectional diagnostic accuracy studies were identified. The majority of the included studies were not designed with the aim of determining the diagnostic accuracy of signs and symptoms. Most included studies were cohort and case-control studies aiming to characterise Lyme disease patients, study patient outcomes, or report the incidence of Lyme disease among those investigated. For the purposes of this review, where studies reported the proportions of positive and negative Lyme disease cases with the pre-specified signs or symptoms, this data was used to determine the diagnostic accuracy. As cohort studies are considered to be of higher quality than case-control studies, separate analyses were conducted.

1.4.2 Excluded studies

See the excluded studies list in appendix H.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
Aucott	n=165	Lyme	Erythema	Centers for disease	Retrospective

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
2009[5]	People presenting for possible early Lyme disease Age: not reported	disease	migrans	control and prevention (CDC) case definition confirmed/probable	cohort study
Avery 2005[6]	n=108 Children presenting to hospital with Lyme serology and Lyme CSF-PCR performed during the same hospital encounter Age, mean (range): Lyme meningitis 9 years (2.7-13), aseptic meningitis 9.6 years (3.1-17.8)	Lyme disease	Erythema migrans	CDC criteria (EM or positive serology including Western blot confirmation)	Retrospective cohort study EM (index test) formed part of the criteria for the reference standard
Engervall 1995[17]	n=446 People with acute peripheral facial palsy Age, median (range): borreliosis people 38 years (4-82), no *Borrelia burgdorferi s.l.* infection 49 years (3-88)	Lyme disease	Facial palsy (complete facial palsy)	One or more of the following: serum antibody titres >1,000 in IgG ELISA or >1,500 in IgM ELISA, serum antibody titres of 500-1,000 in IgG ELISA and/ 800-1,500 in IgM ELISA if at least 2-fold increase in titres between 2 examinations, CSF *Borrelia burgdorferi s.l.* antibody titres >8 in IgG ELISA or >10 in IgM ELISA, recent history of presence of typical *Borrelia burgdorferi s.l.* skin manifestations	Prospective cohort study Index test was complete facial palsy rather than presence/absence of facial palsy. 423 adults, 23 children
Lipsker 2001[34]	n=132 Adults examined for suspected Lyme borreliosis	Lyme disease	Erythema migrans	Culture or PCR	Prospective cohort study All 132 people had a clinical diagnosis of Lyme disease

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
	Age, mean (range): 54 years (15-92)				according to US epidemiological case definitions for Lyme borreliosis, 41 of these had the culture/PCR testing
Nadelman 1990[37]	n=104 People who had an illness compatible with Lyme disease Age, range: culture positive people 16-63 years, culture negative people not reported	Lyme disease	Erythema migrans Facial palsy	Culture from blood samples	Prospective cohort study
Ogrinc 2008[41]	n=339 People with suspected Lyme disease Age, median (range): 53 years (15-81)	Lyme disease	Facial palsy (cranial nerve involvement)	Serological evidence of Lyme disease: serum dilutions of 1:256 or higher interpreted as positive	Prospective cohort study Exclusion of people with current erythema migrans 30.1% of people had already been treated when they received the evaluation Indirectness: cranial nerve involvement used as index test rather than facial palsy
Peltomaa 1998[43]	n=49 Paediatric cases of acute peripheral facial palsy Age, mean: 9.1	Lyme disease	Erythema migrans	At least 1 of the following: positive levels of serum/CSF antibodies against *B. burgdorferi*, EM in the history of the people or concomitantly with facial palsy, positive	Prospective cohort study EM (index test) formed part of the criteria for the reference

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
	years			PCR test	standard
Pikelj-Pecnik 2002[45]	n=147 cases, 148 controls Children with typical EM (cases) and healthy children of comparable ages and gender distribution (controls) Age, mean (SE): people 5.74 years (3.13), controls 5.68 (3.18)	Lyme disease	Arrhythmia	EM (diagnosis established clinically according to modified CDC criteria)	Case-control study
Sangha 1998[60]	n=176 cases, 160 controls Adults who reported a previous diagnosis of Lyme disease/history of a positive result on a serologic test for *B. burgdorferi* (cases) and adults who reported no history of Lyme disease, with or without symptoms suggestive of previous Lyme disease (controls) Age, mean: cases 47.8 years, controls 49.7 years	Lyme disease	Heart block/arrhythmia (bradycardia, tachycardia, non-sinus rhythm, first-degree atrioventricular block, any bundle-branch block)	CDC case definition: EM (>5cm) or laboratory confirmation of infection and at least 1 late manifestation	Case control study
Shah 2005[67]	n=175 Children with Lyme or enteroviral meningitis	Lyme disease	Erythema migrans Facial palsy	Serological evidence of Lyme disease, CSF pleocytosis, negative CSF bacterial culture, and absence of virus detectable by CSF	Prospective cohort study

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
	Age, median (range): Lyme disease: 10.5 years (4.1-16.9); enteroviral: 5.5 years (0-17.2)			culture or PCR	
Skogman 2008[69]	n=354 Children referred for evaluation of clinically suspected neuroborreliosis including a lumbar puncture (cases), random sample of Swedish population from the Swedish national register of statistics (controls) Age, median (range): confirmed neuroborreliosis 6 years (1-14), possible neuroborreliosis 7 years (1-18), not determined 12 years (2-18), controls were matched for age	Lyme disease	EM or lymphocytoma Facial palsy	Confirmed: pleocytosis in CSF, *Borrelia burgdorferi s.l.* antibodies in CSF. Possible: pleocytosis in CSF, no *Borrelia burgdorferi s.l.* antibodies in CSF, may have *Borrelia burgdorferi s.l.* antibodies in serum. Not determined: no pleocytosis in CSF, no *Borrelia burgdorferi s.l.* antibodies in CSF, may have antibodies in serum	Prospective cohort/case-control study 82 additional children evaluated for neuroborreliosis during the same period but not asked to participate – no explanation given. People categorised as 'possible neuroborreliosis' not included in the analysis; 'not determined' used as disease controls.
Skogman 2015[70]	n=239 Children being evaluated for neuroborreliosis and children being evaluated and diagnosed with other infectious immunological and neurological diseases (controls) Age, median	Lyme disease	NeBoP score (3 or more of the following: facial palsy, fever, fatigue, EM/lymphocytoma, pleocytosis in CSF)	European guidelines: definite and possible neuroborreliosis based on neurological symptoms and laboratory findings in CSF	Mixed methods: retrospective cohort/case-control study Calculations based on 'definite' and 'possible' Lyme neuroborreliosis as positive cases and 'non-Lyme neuroborreliosis' and

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
	(range): children evaluated for Lyme disease 10 years (1-19), controls 10 years (0-19)				'controls' as controls Indirectness: index test included fever, fatigue and pleocytosis in CSF
Sundin 2012[76]	n=124 Children with neurological complaints Age, median (range): neuroborreliosis 6.7 years (2-15), TBE 8.7 years (3-17), no tick-borne central nervous system (CNS) infection 9 years (1-17)	Lyme disease	Facial palsy	Positive anti-*Borrelia burgdorferi s.l.* IgM or an increased titre (≥4-fold) of anti-*Borrelia burgdorferi s.l.* IgG between acute and convalescent samples	Prospective cohort study 'Other diagnoses' group included 3 cutaneous borreliosis
Tjernberg 2011[79]	n=261 People investigated for suspected Lyme neuroborreliosis Age, range: 2-87 years	Lyme disease	Facial palsy (cranial nerve palsy)	European Federation of Neurological Societies guidelines (CSF anti-*Borrelia burgdorferi s.l.* anti-bodies and presence of pleocytosis)	Retrospective cohort study Definite Lyme neuroborreliosis and non-Lyme neuroborreliosis groups used in analysis, possible Lyme neuroborreliosis group excluded
Tveitnes 2012[80]	n=211 Children with CSF pleocytosis Age, median (interquartile range): Lyme meningitis 6 years (5-8), bacterial meningitis 3 years (0-6), non-Lyme	Lyme disease	Erythema migrans Facial palsy	Confirmed Lyme meningitis: neurological symptoms suggestive of neuroborreliosis without other obvious reasons, intrathecal *Borrelia burgdorferi s.l.* antibody production/ Probable Lyme meningitis: neurological symptoms suggestive of neuroborreliosis	Retrospective cohort study People group included 91 with confirmed and 51 with probable Lyme disease. Six from the disease control group were not included in the analysis

Study	Population	Target condition	Index test (sign or symptom)	Reference standard	Comments
	aseptic meningitis 7 years (3.5-9)			without other obvious reasons, *B. burgdorferi* antibody in serum and/or EM	
Waespe 2010[86]	n=181 Children hospitalised with clinical signs of aseptic meningitis and/or peripheral facial nerve palsy Age, range: 20 months to 16 years	Lyme disease	Facial palsy	Evidence of intrathecal synthesis of *B. burgdorferi* antibodies in CSF (confirmed) or in serum or CSF, both confirmed by immunoblot (probable)	Retrospective cohort study Index test positive people were those with facial palsy and those with facial palsy plus aseptic meningitis. 159/181 people were tested for Lyme disease.

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: diagnostic accuracy of signs and symptoms in adults (cohort studies)

Index Test	Number of studies	n	Quality	Sensitivity (95% CI)	Specificity (95% CI)
Erythema migrans					
	3	310	VERY LOW[1,2] due to very serious risk of bias, very serious imprecision	Pooled[4]: 0.67 [0.21-0.94]	Pooled[4]: 0.88 [0.52-0.99]
Facial palsy					
	1	104	VERY LOW[1,2] due to very serious risk of bias, very serious imprecision	0.29 [0.04-0.71]	0.96 [0.90-0.99]
	1	216	VERY LOW[1,3] due to very serious risk of bias, serious indirectness	0.52 [0.42-0.61]	0.86 [0.77-0.92]
Complete facial palsy					
	1	399	VERY LOW[1,2] due to very serious risk of bias, serious imprecision	0.20 [0.07-0.41]	0.69 [0.64-0.74]
Cranial nerve involvement					
	1	278	VERY LOW[1,3] due to very serious risk of bias, serious indirectness	0.00 [0.00-0.05]	0.98 [0.95-0.99]

The assessment of the evidence quality was conducted with emphasis on test sensitivity as the committee identified this as the primary measure in guiding decision-making.

1 *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias*

2 *Imprecision was assessed based on inspection of the confidence region of sensitivity in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate was 40%, and downgraded by 2 increments when there was a range of >40%*

3 *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect*

4 *Pooled sensitivity/specificity from diagnostic meta-analysis. One was added to 0 values in order to calculate a pooled estimate*

Table 4: Clinical evidence summary: diagnostic accuracy of signs and symptoms in adults (case-control studies)

Index Test	Number of studies	n	Quality	Sensitivity (95% CI)	Specificity (95% CI)
Heart block/arrhythmias					
Bradycardia	1	336	VERY LOW[1] due to very serious risk of bias	0.05 [0.02-0.09]	0.98 [0.95-1.00]
Tachycardia	1	336	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.02]	1.00 [0.98-1.00]
Nonsinus rhythm	1	336	VERY LOW[1] due to very serious risk of bias	0.01 [0.00-0.04]	0.97 [0.93-0.99]
First-degree atrioventricular block	1	336	VERY LOW[1] due to very serious risk of bias	0.10 [0.06-0.15]	0.95 [0.90-0.98]
Any bundle-branch block	1	336	VERY LOW[1] due to very serious risk of bias	0.16 [0.11-0.23]	0.84 [0.78-0.90]

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was identified by the committee as the primary measure in guiding decision-making.

1 Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias

Table 5: Clinical evidence summary: diagnostic accuracy of signs and symptoms in children (cohort studies)

Index Test	Number of studies	n	Quality	Sensitivity (95% CI)	Specificity (95% CI)
Erythema migrans					
	4	537	VERY LOW[1,2] due to very serious risk of bias, very serious imprecision	Pooled[4] 0.40 [0.15-0.71]	Pooled[4] 0.99 [0.96-1.00]
Facial palsy					
	4	653	VERY LOW[1,2] due to very serious risk of bias, very serious imprecision	Pooled[4] 0.56 [0.24-0.84]	Pooled[4] 0.92 [0.69-0.99]
Facial palsy (TBE controls)	1	105	VERY LOW[1,2] due to very serious risk of bias,	0.43 [0.22-0.66]	1.00 [0.96-1.00]

Index Test	Number of studies	n	Quality	Sensitivity (95% CI)	Specificity (95% CI)
			very serious imprecision		
Neuroborreliosis prediction test (NeBoP) score					
3 or more of the following: facial palsy, fever, fatigue, EM, lymphocytoma, pleocytosis in CSF indicates high probability of Lyme neuroborreliosis	1	239	VERY LOW[1,3] due to very serious risk of bias, serious indirectness	0.90 [0.82-0.96]	0.90 [0.85-0.95]

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was identified by the committee as the primary measure in guiding decision-making.

1 *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias*

2 *Imprecision was assessed based on inspection of the confidence region of sensitivity in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate was 20-40%, and downgraded by 2 increments when there was a range of >40%*

3 *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies were seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect.*

4 *Pooled sensitivity/specificity from diagnostic meta-analysis. One was added to 0 values in order to calculate a pooled estimate*

Table 6: Clinical evidence summary: diagnostic accuracy of signs and symptoms in children (case-control studies)

Index Test	Number of studies	n	Quality	Sensitivity (95% CI)	Specificity (95% CI)
EM or lymphocytoma					
	1	131	VERY LOW[1] due to very serious risk of bias	0.18 [0.10-0.29]	0.88 [0.77-0.95]
Facial palsy					
Facial palsy (disease controls)	1	131	VERY LOW[1,2] due to very serious risk of bias, serious imprecision	0.60 [0.47-0.71]	0.66 [0.53-0.78]
Facial palsy (healthy controls)	1	246	VERY LOW[1,2] due to very serious risk of bias,	0.60 [0.47-0.71]	1.00 [0.98-1.00]

Index Test	Number of studies	n	Quality	Sensitivity (95% CI)	Specificity (95% CI)
			serious imprecision		
Arrhythmia					
	1	295	VERY LOW[1] due to serious risk of bias	0.05 [0.02-0.10]	0.79 [0.72-0.85]

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was identified by the committee as the primary measure in guiding decision-making.

1 Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment if the majority of studies were rated at high risk of bias and downgraded by 2 increments if the majority of studies were rated at very high risk of bias

2 Imprecision was assessed based on inspection of the confidence region of sensitivity in the diagnostic meta-analysis or, where diagnostic meta-analysis has not been conducted, assessed according to the range of confidence intervals in the individual studies. The evidence was downgraded by 1 increment when the range of the confidence interval around the point estimate was 20-40% and downgraded by 2 increments when there was a range of >40%

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies were identified and excluded.

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

1.6 Resource impact

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

1.7 Evidence statements

1.7.1 Clinical evidence statements

Adults and young people:

- Very Low quality evidence from 3 cohort studies showed a low sensitivity of 67% and a high specificity of 88% for erythema migrans.
- Very Low quality evidence from 2 cohort studies showed a low sensitivity of 29% and 52% and a high specificity of 86% and 96% for facial palsy in general. Very Low quality evidence from 1 cohort study showed a very low sensitivity of 20% and a low specificity of 69% for complete facial palsy. Very Low quality evidence from 1 cohort study found a high specificity of 98% for cranial involvement. Cranial nerve involvement was not suitable as a marker for detecting Lyme disease with a sensitivity of 0%.
- Very Low quality evidence from 1 case-control study showed a very low sensitivity but high specificity for various cardiac signs and symptoms. Sensitivity for various cardiac signs and symptoms ranged from 0% to 16% and specificity ranged from 84% to 100%.

Children:

- Very Low quality evidence from 4 cohort studies showed a low sensitivity of 40% and a high specificity of 99% for erythema migrans.
- Very Low quality from 1 case-control study showed a very low sensitivity of 18% and a specificity of 88% for erythema migrans or lymphocytoma.
- Very Low quality evidence from 4 cohort studies showed a low sensitivity of 56% but a high specificity of 92% for facial palsy. Very Low quality evidence from 1 other cohort study, however, found a lower sensitivity of 43% and a higher specificity of 100% for facial palsy. Very Low quality evidence from 2 case-control studies showed a low sensitivity of 60% for facial palsy. The specificity was 66% when people with other diseases functioned as controls and 100% when healthy controls were included in the analysis.
- Very Low quality evidence from 1 study found the NeBoP score, a neuroborreliosis prediction test, to have a high sensitivity of 90% and high specificity of 90%.
- Very Low quality evidence from 1 case-control study showed a very low sensitivity of 5% and a low specificity of 79% for arrhythmias.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The diagnostic measures that matter most

Diagnostic accuracy studies where the accuracy of a sign or symptom for Lyme disease was measured against a reference standard (*Borrelia burgdorferi s.l.* culture or polymerase chain reaction) were used in this review.

The guideline committee identified 5 key clinical signs and symptoms: erythema migrans (EM), lymphocytoma, facial palsy, acrodermatitis chronica atrophicans (ACA), and heart block or arrhythmia. The aim of this review was to assess whether these signs and symptoms, alone or in combination, could be used to identify if a person had Lyme disease. Erythema migrans is only associated with Lyme disease, although not every person with Lyme disease develops an erythema migrans rash. Acrodermatitis chronica atrophicans is associated with Lyme disease, but other types of acrodermatitis can occur as part of other conditions. Lymphocytoma, facial palsy and heart block or arrhythmia are not specific to Lyme disease.

Sensitivity was considered the most important measure. The sensitivity of a sign or symptom describes the proportion of positive Lyme disease results that are correctly identified as such. It is the extent to which people with Lyme disease (true positives) are not missed or overlooked. False negatives, those people with Lyme disease who do not have the sign or symptom, are few.

The listed signs and symptoms cannot, however, be used to rule out Lyme disease as not all people with Lyme disease develop every sign or symptom. Specificity, the proportion of negative Lyme disease results that are correctly identified as such, is of less use than sensitivity.

1.8.1.2 The quality of the evidence

Thirteen cohort studies comprising 2,534 children and adults and 3 case-control studies comprising 677 children and adults were included in this review. The evidence was of very low quality because of risk of bias, imprecision and indirectness. There were particular concerns about how the signs and symptoms were described and assessed as well as the inadequate reference standard (culture, PCR or clinical diagnosis in the absence of a gold standard), that is, how Lyme disease was determined.

Evidence derived from case-control studies could potentially be an overestimate of the true sensitivity and specificity values. Populations in case-control studies tend to differ from 'true populations' found in clinical practice as cases tend to be more severely ill than the average patient population in clinical practice. Controls are usually drawn from a healthy population or include known specific cross-reactivity controls. Therefore, evidence from case-control studies started at low quality and could be further downgraded according to issues of risk of bias, imprecision and indirectness.

1.8.1.3 Benefits and harms

1.8.1.3.1 Acrodermatitis chronica atrophicans (ACA)

No evidence for acrodermatitis chronica atrophicans was identified. The guideline committee were aware of ACA as a possible symptom of Lyme disease and considered the potential harm of missing a Lyme disease diagnosis if ACA is not recognised as such. It was therefore decided to recommend that the possibility of Lyme disease be considered in those presenting with ACA.

1.8.1.3.2 Erythema migrans (EM)

Pooled evidence from 3 cohort studies showed a low sensitivity for erythema migrans in children and adults. Sensitivity of the rash was lower in children than in adults, with 40% and 67%, respectively. Specificity was high, with 99% and 88% in children and adults respectively. The evidence showing high specificity supported current practice to diagnose and treat EM as Lyme disease. The guideline committee considered that the potential harm of Lyme disease dissemination if this was to change and therefore decided to recommend diagnosis of Lyme disease in people with EM, despite the low quality of the evidence.

1.8.1.3.3 Facial palsy

The evidence showed a low sensitivity but high specificity for facial palsy in children and adults. In adults, evidence from 2 cohort studies showed that facial palsy had a sensitivity of 29% and 52%, and a specificity of 96% and 86%. Pooled evidence from cohort studies in children showed a sensitivity of 56% and a specificity of 92%. Evidence from 1 case-control study in children showed a sensitivity of 60%, with a specificity of 66% and 100% for disease controls and healthy controls, respectively.

There was a high degree of variability in the degree and type of facial palsy. A cohort study in adults who all had an acute peripheral facial palsy showed that a complete facial palsy had a sensitivity of 20% and a specificity of 69%. Another cohort study assessing the accuracy of any kind of cranial nerve involvement in diagnosing Lyme disease in adults resulted in a sensitivity of 0%, indicating that none of the people with Lyme disease in this study had cranial nerve involvement and a specificity of 98%.

The guideline committee did not consider the evidence to be strong enough to recommend diagnosis of Lyme disease based on facial palsy alone. It did, however, acknowledge the evidence of high specificity and the potential harm of missing a Lyme disease diagnosis if facial palsy is not considered as a possible symptom. It was therefore decided to recommend that the possibility of Lyme disease be considered in those presenting with facial palsy.

1.8.1.3.4 Heart block or arrhythmia

The limited evidence showed a very low sensitivity of 0%-16% and a high specificity for heart block or arrhythmia in adults and a sensitivity of 5% for arrhythmia only in children.

The guideline committee did not consider the evidence to be strong enough to recommend diagnosis of Lyme disease based on heart block or arrhythmia alone. It did, however, acknowledge the evidence of high specificity and the potential harm of missing a Lyme disease diagnosis if heart block and arrhythmia are not considered as possible symptoms. It was therefore decided to recommend that the possibility of Lyme disease be considered in those presenting with heart block or arrhythmia.

1.8.1.3.5 Lymphocytoma

No evidence for lymphocytoma alone was identified. Evidence from 1 case-control study in children showed a very low sensitivity of 18% and a specificity of 88% for either an erythema migrans rash or a lymphocytoma.

The guideline committee did not consider the evidence to be strong enough to recommend diagnosis of Lyme disease based on a lymphocytoma alone. It did, however, acknowledge the evidence of high specificity and the potential harm of missing a Lyme disease diagnosis if lymphocytoma is not considered as a possible symptom. It was therefore decided to recommend that the possibility of Lyme disease be considered in those presenting with a lymphocytoma.

1.8.1.3.6 Other measures

One study in children assessed the diagnostic accuracy of the NeBoP score, a weighted score derived from facial palsy, fever, fatigue, erythema migrans or lymphocytoma, and pleocytosis in CSF. Designed to differentiate between a high and low probability of having neuroborreliosis, the NeBoP has a maximum score of 5 points. A score of 3 or more of these variables had a sensitivity of 90% and a specificity of 90%. The guideline committee agreed that the score seemed promising in terms of its high sensitivity and specificity relative to the other individual signs and symptoms. However, the committee considered that the quality and quantity of the evidence available was too low to make a recommendation for its use.

1.8.2 Cost effectiveness and resource use

No health economic evidence was identified. Assessment of the signs and symptoms is unlikely to be an additional cost to the NHS, as these people will be assessed anyway. These signs and symptoms, however, will help to identify the population that should be considered for testing or empiric treatment.

The diagnostic evidence showed that where accuracy data was available all symptoms had high specificity and low sensitivity, which means that false positives are few but false negatives are high. As a result, few people who do not have Lyme disease are identified as having Lyme disease, but many people with Lyme disease will be missed.

The committee agreed to recommend diagnosis of Lyme disease based on EM alone (no diagnostic testing), as it is considered pathognomonic for Lyme disease. This is already done in current practice and so should have no impact on NHS resources.

The committee, however, noted that the evidence was not strong enough to recommend further diagnostic testing or diagnosis and treatment based on the presentation of any of the other symptoms alone. The committee noted the importance of considering the possibility of Lyme disease if a number of these symptoms are accompanied by supportive history of tick exposure. These recommendations are not expected to have a resource impact.

1.8.3 Other factors the committee took into account

While erythema migrans is considered pathognomonic for Lyme disease, the committee considered that it might be unfamiliar to some healthcare professionals, so a recommendation describing the rash and its characteristics was developed. The committee also developed a recommendation to describe an inflammatory reaction to a tick bite in case this was mistaken for erythema migrans.

The committee used the evidence review and their knowledge of presentations of Lyme disease to develop recommendations for possible presentations associated with Lyme

disease. The committee acknowledged that some non-specific symptoms associated with Lyme disease are difficult to describe; for example, a cognitive impairment such as the difficulty of remembering what a person has just read is often described as 'brain fog'. Clinicians should also be aware that persons with cognitive impairment might find it difficult to describe their symptoms. The committee felt that it was important to include an awareness of these non-specific signs and symptoms in the recommendations because although Lyme disease would not be diagnosed based on them alone, they can be valuable in the context of other symptoms and history of exposure.

The committee acknowledged that most people presenting with symptoms or signs associated with Lyme disease will not have Lyme disease. Lyme disease is a possible but uncommon cause of these symptoms. The majority of people presenting with arrhythmia, for example, would not require testing for Lyme disease, as there would be more likely causes to investigate. An exploration of the history of symptoms and possible exposure to ticks is required, but a lack of clear history of tick bite should not rule out the further investigation. Symptoms take time to develop following a tick bite so care is required when taking the history and examining the time course of the person's illness. Clinical judgement of the presentation with awareness of Lyme disease as a possible cause is required.

The committee expressed the need for evidence on the proportion of individual signs and symptoms in which Lyme disease is the possible underlying cause. For example, knowing the proportion of facial palsies that are caused by Lyme disease could provide a better understanding of different clinical presentations of Lyme disease and therefore help guide clinical decision-making. This information could be collected through the recommendation for research on the clinical epidemiology of Lyme disease.

While there is concern that Lyme disease may be missed, the committee also recognised the harm that might be done by missing an alternative diagnosis or providing inappropriate treatment. The committee considered that an acknowledgement that symptoms and signs associated with Lyme disease are similar to symptoms or signs of many other disorders and that no specific medical cause might be found for some symptoms might be helpful for people undergoing investigation.

Signs and symptoms of Lyme disease in children were considered. The committee recognised that children might not be able to articulate their symptoms in the same way as adults. Clinical assessment is therefore particularly important and often requires assessment of behaviour rather than clear verbal account. The committee did not, however, think separate recommendations were warranted. Fever in children during the summer months when respiratory infections are less common was identified as a circumstance when Lyme disease in children might be more likely when associated with a relevant clinical history. While the committee wished all clinicians to be aware of possible presentations of Lyme disease they considered that children and young people (younger than 18 years) who are presenting with possible Lyme disease and non-EM, for example facial palsy, should have their diagnosis and management discussed with a specialist, as these presentations are unusual and the importance of accurate diagnosis and treatment is essential. This is discussed further in evidence report D.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol for signs and symptoms

Question number: 2

Relevant section of Scope: assessment and diagnosis

Field	Content
Review question	In people with suspected (or under investigation for) Lyme disease, how accurate are signs and symptoms to identify whether Lyme disease is present?
Type of review question	Diagnostic 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	To evaluate the accuracy of signs and symptoms in diagnosing Lyme disease and determine if testing is required or if treatment can or should be started without any further testing.
Eligibility criteria – population / disease / condition / issue / domain	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with suspected (or under investigation for) Lyme disease. Target condition: Lyme disease (specifically, conditions caused by *Borrelia burgdorferi sensu lato*)
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Signs and symptoms: • acrodermatitis chronica atrophicans • erythema migrans • facial palsy • heart block or arrhythmias • lymphocytoma. The review will assess the accuracy of individual signs and symptoms or any combinations to identify whether Lyme disease is present.
Eligibility criteria – comparator(s) / control or reference (gold) standard	*Borrelia burgdorferi s.l.* culture (Spirochaete is difficult to culture, grows slowly and is therefore not compatible with providing a rapid diagnostic result). PCR
Outcomes and prioritisation	• Detecting Lyme disease • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Receiver Operating Characteristic (ROC) curve or area under curve
Eligibility criteria – study design	Include: Cross-sectional studies, in which the index test(s) and the reference standard test are applied to the same people.

Field	Content
	Exclude (unless there is insufficient evidence and agreed to include with committee): Two-gate/case-control study designs that compare the results of the index test in people with an established diagnosis with its results in healthy controls. Exclude: • Case series • Case reports
Other inclusion exclusion criteria	Date limits for search: none Language: English only Setting: all settings where NHS care is provided or commissioned
Proposed sensitivity / subgroup analysis, or meta-regression	Stratum: • Children (under 12 years); adults and young people (12 years and over) • Timing of symptom presentation less than 6 weeks; 6 weeks to 6 months; over 6 months from tick bite or infection Subgroups (to be investigated if heterogeneity is identified): • People who are immunocompromised • People who have been partially treated (are or have been on antibiotics or steroids)
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)	• Sensitivity and specificity will be calculated using Cochrane Review Manager (RevMan5). • Diagnostic meta-analyses will be conducted using WinBUGS14 and graphically presented using RevMan5. • Bibliographies, citations, study sifting and reference management will be managed using EndNote.
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library all years Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias will be evaluated for each outcome on a study level using the QUADAS-2 checklist.

Field	Content
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual.
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. The quality of the evidence per outcome across studies will be assessed using an adapted GRADE approach.
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 National Guideline Centre (NGC) and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 8: 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).[38]

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 9: 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 10: 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"/

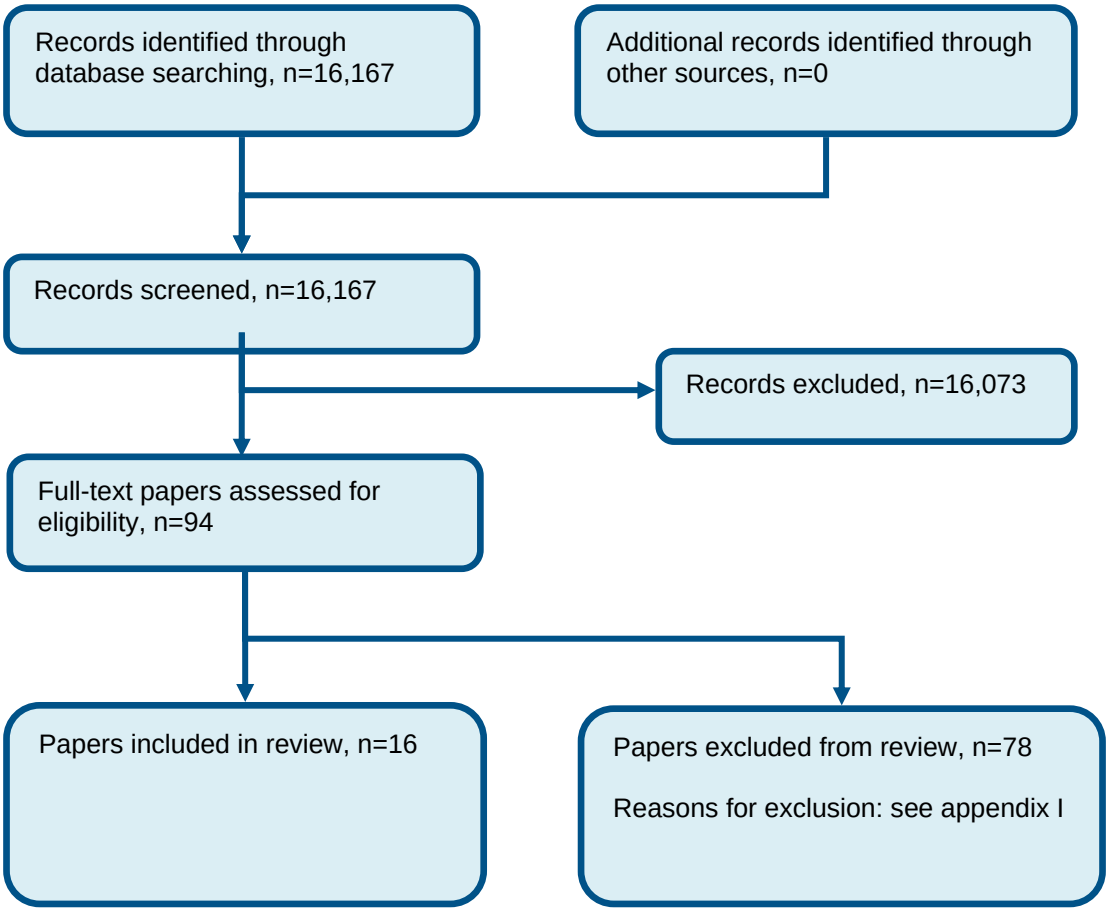
59.	short form 12/ or short form 20/ or short form 36/ or short form 8/
60.	sickness impact profile/
61.	(quality adj2 (wellbeing or well being)).ti,ab.
62.	sickness impact profile.ti,ab.
63.	disability adjusted life.ti,ab.
64.	(qal* or qtime* or qwb* or daly*).ti,ab.
65.	(euroqol* or eq5d* or eq 5*).ti,ab.
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 review of diagnostic accuracy of signs and symptoms



Appendix D: Clinical evidence tables

Reference	Aucott 2009[5]
Study type	Cohort study
Study methodology	Data source: people presenting for possible early Lyme disease to a community-based Lyme disease referral practice Recruitment: consecutive
Number of patients	n=165
Patient characteristics	Age: not reported Gender (male to female ratio): not reported Family origin: not reported Setting: community-based Lyme disease referral practice Country: USA Inclusion criteria: all people referred with acute symptoms ≤12 weeks of duration Exclusion criteria: not reported Time from onset of symptoms to evaluation: ≤12 weeks
Target condition(s)	Lyme disease
Index test(s) and reference standard	Index tests EM Reference standard

Reference	**Aucott 2009[5]**				
	CDC case definition confirmed/probable Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	88	0	88	
	Index test −	13	64	77	
	Total	101	64	165	
Statistical measures	Index test: EM Sensitivity 0.87 Specificity 1.00 PPV 1.00 NPV 0.83				
Source of funding	Not reported				
Limitations	Risk of bias: index test, reference standard Indirectness: none				
Comments					

Reference	Avery 2005[6]
Study type	Cohort study
Study methodology	Data source: children presenting to hospital with Lyme serology and Lyme CSF-PCR performed during the same hospital encounter Recruitment: consecutive
Number of patients	n=108
Patient characteristics	Age, mean (range): Lyme meningitis 9 years (2.7-13), aseptic meningitis 9.6 years (3.1-17.8) Gender (male to female ratio): Lyme meningitis 30% female, aseptic meningitis 31% female Family origin: Lyme meningitis 95% White, aseptic meningitis 68% White Setting: tertiary care children's hospital Country: USA Inclusion criteria: Lyme serology and Lyme CSF-PCR performed during the same hospital encounter, documented meningitis (CSF white blood cell count >8mm3) Exclusion criteria: past history of Lyme meningitis, people being evaluated for an ongoing chronic neurological condition, traumatic lumbar puncture, positive CSF Gram stain for bacteria Time from onset of symptoms to evaluation: not reported
Target condition(s)	Lyme disease
Index test(s) and reference standard	Index tests EM Reference standard CDC criteria (EM or positive serology including Western blot confirmation) Time between measurement of index test and reference standard: not reported

Reference	**Avery 2005[6]**				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	12	0	12	
	Index test −	8	88	96	
	Total	20	88	108	
Statistical measures	Index test: EM Sensitivity 0.60 Specificity 1.00 PPV 1.00 NPV 0.92				
Source of funding	Not reported				
Limitations	Risk of bias: index test, reference standard Indirectness: none				
Comments	EM formed part of the reference standard				

Reference	Engervall 1995[17]
Study type	Cohort study
Study methodology	Data source: people with acute peripheral facial palsy presenting to 10 Swedish ear, nose and throat clinics Recruitment: consecutive
Number of patients	n=446
Patient characteristics	Age, median (range): people with borreliosis 38 years (4-82), no *Borrelia burgdorferi s.l.* infection 49 years (3-88) Gender (male to female ratio): not reported Family origin: not reported Setting: 10 ear, nose and throat clinics Country: Sweden Inclusion criteria: acute peripheral facial palsy Exclusion criteria: palsy of known aetiology such as trauma, tumour, herpes zoster infection or otitis media, hospitalised people with meningitis in whom facial palsy occurred as a secondary sign Time from onset of symptoms to evaluation: not reported
Target condition(s)	Lyme disease
Index test(s) and reference standard	Index tests Complete facial palsy Reference standard One or more of the following: serum antibody titres >1,000 in IgG ELISA or >1,500 in IgM ELISA, serum antibody titres of 500-1,000 in IgG ELISA and 800-1,500 in IgM ELISA if at least 2-fold increase in titres between 2 examinations, CSF *Borrelia* antibody titres >8 in IgG ELISA or >10 in IgM ELISA, recent history of presence of typical *Borrelia* skin manifestations

Reference	**Engervall 1995[17]**			
	Time between measurement of index test and reference standard: not reported			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	5	115	120
	Index test −	20	259	279
	Total	25	374	399
Statistical measures	Index test: Complete facial palsy Sensitivity 0.20 Specificity 0.69 PPV 0.04 NPV 0.93			
Source of funding	Not reported			
Limitations	Risk of bias: index test, reference standard, flow and timing Indirectness: none			
Comments	Index test was complete facial palsy rather than presence/absence of facial palsy. 423 adults, 23 children			

Reference	**Lipsker 2001[34]**				
Study type	Cohort study				
Study methodology	Data source: adults examined for suspected Lyme borreliosis at 1 hospital in France Recruitment: consecutive				
Number of patients	n=132				
Patient characteristics	Age, mean (range): 54 years (15-92) Gender (male to female ratio): 62/70 Family origin: White Setting: 1 hospital (people monitored in the dermatology, infectious diseases, rheumatology, neurology, internal medicine rehabilitation, cardiology, chest diseases and surgery departments) Country: France Inclusion criteria: US epidemiological case definitions for Lyme borreliosis Exclusion criteria: not reported Time from onset of symptoms to evaluation: not clearly reported				
Target condition(s)	Lyme disease				
Index test(s) and reference standard	Index tests EM Reference standard Culture or PCR Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard	Reference standard −	Total	

Reference	Lipsker 2001[34]				
		+			
	Index test +	5	4	9	
	Index test −	5	27	32	
	Total	10	31	41	
Statistical measures	Index test: EM Sensitivity 0.50 Specificity 0.87 PPV 0.56 NPV 0.84				
Source of funding	Not reported				
Limitations	Risk of bias: index test, reference standard, flow and timing Indirectness: none				
Comments	All 132 people had a clinical diagnosis of Lyme disease according to US epidemiological case definitions for Lyme borreliosis, 41 of these had the culture/PCR testing				

Reference	Nadelman 1990[37]
Study type	Cohort study
Study methodology	Data source: people who had an illness compatible with Lyme disease Recruitment: not clearly reported
Number of patients	n=104
Patient characteristics	Age, range: culture positive people 16-63 years, culture negative people not reported Gender (male to female ratio): culture positive people 1/6, culture negative people not reported Family origin: not reported Setting: not reported

Reference	Nadelman 1990[37]				
	Country: USA Inclusion criteria: not reported Exclusion criteria: not reported Time from onset of symptoms to evaluation, range: culture positive people 3-14 days, culture negative people not reported				
Target condition(s)	Lyme disease				
Index test(s) and reference standard	Index tests EM Facial palsy Reference standard Culture from blood samples Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	4	19	23	
	Index test −	3	78	81	
	Total	7	97	104	
2x2 table		Reference standard +	Reference standard -	Total	
	Index test +	2	4	6	
	Index test -	5	93	98	
	Total	7	97	104	
Statistical measures	Index test: EM Sensitivity 0.57 Specificity 0.80				

Reference	Nadelman 1990[37]
	PPV 0.17 NPV 0.96 Index test: Facial palsy Sensitivity 0.29 Specificity 0.96 PPV 0.33 NPV 0.95
Source of funding	National Institutes of Allergy and Infectious Diseases and Westchester Health Fund
Limitations	Risk of bias: people selection, index test, reference standard Indirectness: none
Comments	

Reference	Ogrinc 2008[41]
Study type	Cohort study
Study methodology	Data source: people with suspected Lyme disease at outpatient's clinic Recruitment: consecutive
Number of patients	n=339
Patient characteristics	Age, median (range): 53 years (15-81) Gender (male to female ratio): 154/185 Family origin: not reported Setting: outpatient's clinic Country: Slovenia

Reference	Ogrinc 2008[41]			
	Inclusion criteria: suspected Lyme disease, aged >15 years Exclusion criteria: current erythema migrans Time from onset of symptoms to evaluation (median, range): 9.5 months (1-480)			
Target condition(s)	Lyme disease			
Index test(s) and reference standard	Index tests Cranial nerve involvement Reference standard serological evidence of Lyme disease: serum dilutions of 1:256 or higher interpreted as positive Time between measurement of index test and reference standard: not reported			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	0	4	4
	Index test −	72	202	274
	Total	72	206	278
Statistical measures	Index test: cranial nerve involvement Sensitivity 0.00 Specificity 0.98 PPV 0.00 NPV 0.74			
Source of funding	Not reported			
Limitations	Risk of bias: index test, reference standard Indirectness: cranial nerve involvement used as index test rather than facial palsy			
Comments	Disease controls; exclusion of people with current erythema migrans; 30.1% of people had already been treated when they received the evaluation			

Reference	Peltomaa 1998[43]
Study type	Cohort study
Study methodology	Data source: paediatric cases of acute peripheral facial palsy referred to the otorhinolaryngological outpatient department of 1 hospital Recruitment: consecutive
Number of patients	n=49
Patient characteristics	Age, mean: 9.1 years Gender (male to female ratio): 21/28 Family origin: not reported Setting: otorhinolaryngological outpatient department of 1 hospital Country: Finland Inclusion criteria: not reported Exclusion criteria: not reported Time from onset of symptoms to evaluation: not clearly reported
Target condition(s)	Lyme disease
Index test(s) and reference standard	Index tests EM Reference standard At least 1 of the following: positive levels of serum/CSF antibodies against *B. burgdorferi*, EM in the history of the person or concomitantly with facial palsy, positive PCR test Time between measurement of index test and reference standard: not reported

Reference	**Peltomaa 1998[43]**			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	10	0	10
	Index test −	7	32	39
	Total	17	32	49
Statistical measures	Index test: EM Sensitivity 0.59 Specificity 1.00 PPV 1.00 NPV 0.82			
Source of funding	Paulo Foundation, University Hospital of Helsinki and Clinical Research Institute of the University Central Hospital of Helsinki			
Limitations	Risk of bias: index test, reference standard, Indirectness: none			
Comments	All people had facial palsy. EM (index test) formed part of the criteria for the reference standard			

Reference	**Pikelj-Pecnik 2002[45]**
Study type	Case-control study
Study methodology	Data source: children with typical EM at the Department of Infectious Diseases at a medical centre in Slovenia and healthy children of comparable ages and gender distribution Recruitment: consecutive
Number of patients	n=147 patients, 148 controls
Patient characteristics	Age, mean (SE): patients 5.74 years (3.13), controls 5.68 (3.18) Gender (male to female ratio): 163/132 Family origin: not reported

Reference	Pikelj-Pecnik 2002[45]			
	Setting: Department of Infectious Diseases at a medical centre Country: Slovenia Inclusion criteria: <15 years of age, typical EM (diagnosis established clinically according to modified CDC criteria) Exclusion criteria: not reported Time from onset of symptoms to evaluation, median (range): duration of single EM 4 days (0-40), duration of multiple EM 5 days (0-60)			
Target condition(s)	Lyme disease			
Index test(s) and reference standard	Index tests Arrhythmia Reference standard EM (diagnosis established clinically according to modified CDC criteria) Time between measurement of index test and reference standard: not reported			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	8	31	39
	Index test −	139	117	256
	Total	147	148	295
Statistical measures	Index test: Arrhythmia Sensitivity 0.05 Specificity 0.79 PPV 0.21 NPV 0.46			
Source of funding	Not reported			
Limitations	Risk of bias: reference standard			

Reference	Pikelj-Pecnik 2002[45]
	Indirectness: none
Comments	

Reference	Sangha 1998[60]
Study type	Case-control study
Study methodology	Data source: Adults who reported a previous diagnosis of Lyme disease or a history of a positive result on a serologic test for *B. burgdorferi* (cases) and adults who reported no history of Lyme disease, with or without symptoms suggestive of previous Lyme disease (controls) Recruitment: random sampling from participants surveyed (5 cases: 2 controls)
Number of patients	n=336
Patient characteristics	Age, mean: cases 47.8 years, controls 49.7 years Gender (male to female ratio): 173/163 Family origin: not reported Setting: Nantucket Island Country: USA Inclusion criteria: previous diagnosis of Lyme disease or a history of a positive result on a serologic test for *B. burgdorferi*, meeting CDC criteria (cases), no history of Lyme disease, with or without symptoms suggestive of previous Lyme disease (controls), complete data on medical history and a 12-lead electrocardiogram Exclusion criteria: no electrocardiogram or uninterpretable due to technical difficulties Time from onset of symptoms to evaluation (mean): 5.2 years
Target condition(s)	Lyme disease
Index test(s)	Index tests

Reference	**Sangha 1998[60]**				
and reference standard	Bradycardia Tachycardia Nonsinus rhythm First-degree atrioventricular block Any bundle-branch block Reference standard CDC case definition: EM (>5cm) or laboratory confirmation of infection and at least 1 late manifestation Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	9	3	12	
	Index test −	167	157	324	
	Total	176	160	336	
2x2 table		Reference standard +	Reference standard −	Total	
	Index test +	0	0	0	
	Index test −	176	160	336	
	Total	176	160	336	
2x2 table		Reference standard +	Reference standard −	Total	
	Index test +	2	5	7	
	Index test −	174	155	329	
	Total	176	160	336	
2x2 table		Reference standard +	Reference standard −	Total	
	Index test +	17	8	25	
	Index test −	159	152	311	
	Total	176	160	336	

Reference	**Sangha 1998[60]**				
2x2 table		Reference standard +	Reference standard −	Total	
	Index test +	29	25	54	
	Index test −	147	135	282	
	Total	176	160	336	
Statistical measures	Index test: Bradycardia Sensitivity 0.05 Specificity 0.98 PPV 0.75 NPV 0.49 Index test: Tachycardia Sensitivity 0.00 Specificity 1.00 PPV 0.00 NPV 0.48 Index test: Nonsinus rhythm Sensitivity 0.01 Specificity 0.97 PPV 0.29 NPV 0.47 Index test: First-degree atrioventricular block Sensitivity 0.10 Specificity 0.95 PPV 0.68 NPV 0.49 Index test: Any bundle-branch block Sensitivity 0.16				

Reference	Sangha 1998[60]
	Specificity 0.84 PPV 0.54 NPV 0.48
Source of funding	National Institutes of Health Grants, German Academic Exchange Service
Limitations	Risk of bias: patient selection, reference standard Indirectness: none
Comments	

Reference	Shah 2005[67]
Study type	Cohort study
Study methodology	Data source: medical records of people who underwent testing for Lyme meningitis or enteroviral meningitis Recruitment: consecutive
Number of patients	n=175 Lyme disease (n=24), enteroviral disease (n=151)
Patient characteristics	Age, median (range): Lyme disease: 10.5 years (4.1-16.9); enteroviral: 5.5 years (0-17.2) Gender (male to female ratio): Lyme disease: 63% boys; enteroviral: 62% boys Family origin: not reported Setting: urban tertiary children's hospital Country: USA Inclusion criteria: serological evidence of Lyme disease, CSF pleocytosis, negative CSF bacterial culture, and absence of virus

Reference	Shah 2005[67]			
	detectable by CSF culture or PCR Exclusion criteria: underlying immunodeficiency, ventricular shunt, isolation of fungi or pathogenic bacteria from cultures, lumbar puncture not performed during initial evaluation Time from onset of symptoms to evaluation: not reported			
Target condition(s)	Lyme disease			
Index test(s) and reference standard	Index tests Erythema migrans rash (by history or on examination) Facial palsy Reference standard serological evidence of Lyme disease, CSF pleocytosis, negative CSF bacterial culture, and absence of virus detectable by CSF culture or PCR Time between measurement of index test and reference standard: not reported			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	6	0	6
	Index test −	18	151	169
	Total	24	151	175
		Reference standard +	Reference standard −	Total
	Index test +	7	0	7
	Index test −	17	151	168
	Total	24	151	175
Statistical measures	Index test: EM Sensitivity 0.25 Specificity 1.00 PPV 1.00			

Reference	Shah 2005[67]
	NPV 0.89 Index text: facial palsy Sensitivity 0.29 Specificity 1.00 PPV 1.00 NPV 0.90
Source of funding	Not reported
Limitations	Risk of bias: index test, reference standard Indirectness: none
Comments	Disease controls

Reference	Skogman 2008[69]
Study type	Cohort/case-control study
Study methodology	Data source: children referred to 5 paediatric clinics in Sweden for evaluation of clinically suspected neuroborreliosis including a lumbar puncture (cases), random sample of Swedish population from the Swedish national register of statistics (controls) Recruitment: consecutive
Number of patients	n=354
Patient characteristics	Age, median (range): confirmed neuroborreliosis 6 years (1-14), possible neuroborreliosis 7 years (1-18), not determined 12 years (2-18), controls were matched for age Gender (male to female ratio): cases 88/89, controls matched for gender Family origin: not reported Setting: 5 paediatric clinics

Reference	Skogman 2008[69]				
	Country: Sweden Inclusion criteria: children referred for evaluation of clinically suspected neuroborreliosis including a lumbar puncture Exclusion criteria: enteroviral meningitis, Epstein Barr virus infection, rheumatoid arthritis, sarcoidosis, missing data, controls with former *Borrelia* infection Time from onset of symptoms to evaluation: <1 week n=66, 1-4 weeks n=81, 1-2 months n=17, >2 months n=13				
Target condition(s)	Lyme disease				
Index test(s) and reference standard	Index tests Facial palsy EM or lymphocytoma Reference standard Confirmed: pleocytosis in CSF, *Borrelia* antibodies in CSF. Possible: pleocytosis in CSF, no *Borrelia* antibodies in CSF, may have *Borrelia* antibodies in serum. Not determined: no pleocytosis in CSF, no *Borrelia* antibodies in CSF, may have antibodies in serum Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard +	Reference standard −	Total	Disease controls (neuroborreliosis not determined)
	Index test +	43	20	63	
	Index test −	29	39	68	
	Total	72	59	131	
2x2 table		Reference standard +	Reference standard −	Total	Healthy controls (6 month follow up)
	Index test +	43	0	43	
	Index test −	29	174	203	
	Total	72	174	246	
2x2 table		Reference standard +	Reference standard −	Total	Disease controls (neuroborreliosis not determined)
	Index test +	13	7	20	

Reference	Skogman 2008[69]				
	Index test −	59	52	111	
	Total	72	59	131	
Statistical measures	Index test: Facial palsy (disease controls) Sensitivity 0.60 Specificity 0.66 PPV 0.68 NPV 0.57 Index test: Facial palsy (healthy controls) Sensitivity 0.60 Specificity 1.00 PPV 1.00 NPV 0.86 Index test: EM or lymphocytoma (disease controls) Sensitivity 0.18 Specificity 0.88 PPV 0.65 NPV 0.47				
Source of funding	The Health Research Council in the South East of Sweden, The County Council on Ostergotland, The Centre for Clinical Research in Dalarna, The Lions Foundation and The Samariten Foundation				
Limitations	Risk of bias: people selection, index test, reference standard Indirectness: none				
Comments	82 additional children evaluated for neuroborreliosis during the same period but not asked to participate – no explanation given. People categorised as ‘possible neuroborreliosis’ not included in the analysis; ‘not determined’ used as disease controls.				

Reference	**Skogman 2015[70]**				
Study type	Cohort/case control study				
Study methodology	Data source: children being evaluated for neuroborreliosis and children being evaluated and diagnosed with other infectious immunological and neurological diseases at 7 paediatric clinics in Sweden Recruitment: consecutive				
Number of patients	n=239				
Patient characteristics	Age, median (range): children evaluated for Lyme disease 10 years (1-19), controls 10 years (0-19) Gender (male to female ratio): 108/131 Family origin: not reported Setting: 7 paediatric clinics Country: Sweden Inclusion criteria: not reported Exclusion criteria: missing data Time from onset of symptoms to evaluation: not reported				
Target condition(s)	Lyme disease				
Index test(s) and reference standard	Index tests NeBoP score (3 or more of the following: facial palsy, fever, fatigue, EM/lymphocytoma, pleocytosis in CSF) Reference standard European guidelines: definite and possible neuroborreliosis based on neurological symptoms and laboratory findings in CSF Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard	Reference standard −	Total	

Reference	Skogman 2015[70]			
		+		
	Index test +	75	15	90
	Index test −	8	141	149
	Total	83	156	239
Statistical measures	Index test: NeBoP score Sensitivity 0.90 Specificity 0.90 PPV 0.83 NPV 0.95			
Source of funding	Not reported			
Limitations	Risk of bias: index test, reference standard Indirectness: index test			
Comments	Calculations based on 'definite' and 'possible' Lyme neuroborreliosis as people and 'non-Lyme neuroborreliosis' and 'controls' as controls 7			

Reference	Sundin 2012[76]
Study type	Cohort study
Study methodology	Data source: children with neurological complaints at the paediatric emergency department of a children's hospital in Sweden Recruitment: consecutive
Number of patients	n=124
Patient characteristics	Age, median (range): Neuroborreliosis 6.7 years (2-15), TBE8.7 years (3-17), no tick-borne CNS infection 9 years (1-17) Gender (male to female ratio): not reported Family origin: not reported Setting: paediatric emergency department in a children's hospital (primary care unit and referrals from GPs)

Reference	Sundin 2012[76]				
	Country: Sweden Inclusion criteria: altered sensorium, back pain, behavioural changes, confusion, focal neurological signs, headache, motor dysfunction, neck stiffness, seizures and vertigo/balance problems Exclusion criteria: recent head injury, known convulsive disorder with suboptimal treatment and infancy (<12 months of age) Time from onset of symptoms to evaluation: not reported				
Target condition(s)	Lyme disease				
Index test(s) and reference standard	Index tests Cranial nerve facial palsy Reference standard Positive anti-*Borrelia* IgM or an increased titre (≥4-fold) of anti-*Borrelia* IgG between acute and convalescent samples Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard +	Reference standard −	Total	Disease controls (tick-borne encephalitis)
	Index test +	9	0	9	
	Index test −	12	10	22	
	Total	21	10	31	
2x2 table		Reference standard +	Reference standard −	Total	Disease controls (other diagnoses)
	Index test +	9	9	18	
	Index test −	12	84	96	
	Total	21	93	114	
Statistical measures	Index test: Cranial nerve palsy (TBE controls) Sensitivity 0.43 Specificity 1.00 PPV 1.00				

Reference	**Sundin 2012[76]**
	NPV 0.45 Index test: Cranial nerve palsy (other diagnoses controls) Sensitivity 0.43 Specificity 0.90 PPV 0.50 NPV 0.88
Source of funding	Karolinska Institutet, Stockholm County Council and the Swedish Association of Persons with Neurological Disabilities
Limitations	Risk of bias: index test, reference standard Indirectness: none
Comments	'Other diagnoses' group included 3 cutaneous borreliosis

Reference	**Tjernberg 2011[79]**
Study type	Cohort study
Study methodology	Data source: people investigated for suspected Lyme neuroborreliosis Recruitment: not clearly reported
Number of patients	n=261
Patient characteristics	Age, range: 2-87 years Gender (male to female ratio): 157/104 Family origin: not reported Setting: Department of Clinical Microbiology Country: Sweden

Reference	Tjernberg 2011[79]			
	Inclusion criteria: lumbar puncture performed because of suspected Lyme neuroborreliosis Exclusion criteria: incomplete CSF/serum sample material Time from onset of symptoms to evaluation, median (range): definite Lyme neuroborreliosis 3 weeks (0-32), non-Lyme neuroborreliosis 4 weeks (0-730)			
Target condition(s)	Lyme disease			
Index test(s) and reference standard	Index tests Cranial nerve palsy Reference standard European Federation of Neurological Societies guidelines (CSF anti-*Borrelia* anti-bodies and presence of pleocytosis) Time between measurement of index test and reference standard: not reported			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	64	13	77
	Index test −	60	79	139
	Total	124	92	216
Statistical measures	Index test: Cranial nerve palsy Sensitivity 0.52 Specificity 0.86 PPV 0.83 NPV 0.57			
Source of funding	Not reported			
Limitations	Risk of bias: people selection, index test, reference standard Indirectness: population (adults and children)			
Comments	Definite Lyme neuroborreliosis and non-Lyme neuroborreliosis groups used in analysis, possible Lyme neuroborreliosis group excluded.			

Reference	Tveitnes 2012[80]
Study type	Cohort study
Study methodology	Data source: children with CSF pleocytosis at the paediatric department of a hospital in Norway Recruitment: consecutive
Number of patients	n=211
Patient characteristics	Age, median (interquartile range): Lyme meningitis 6 years (5-8), bacterial meningitis 3 years (0-6), non-Lyme aseptic meningitis 7 years (3.5-9) Gender (male to female ratio): 107/98 Family origin: not reported Setting: paediatric department in a coastal Lyme disease endemic region Country: Norway Inclusion criteria: children with pleocytosis from 3 months of age up to their 14th birthday Exclusion criteria: non-infectious causes of CSF pleocytosis Time from onset of symptoms to evaluation (median, interquartile range): Lyme meningitis 5 days (2-14), bacterial meningitis 1 day (1-3), non-Lyme aseptic meningitis 3 days (1-7)
Target condition(s)	Lyme disease
Index test(s) and reference standard	Index tests EM Acute facial palsy Reference standard Confirmed Lyme meningitis: neurological symptoms suggestive of neuroborreliosis without other obvious reasons, intrathecal *B. burgdorferi* antibody production/ Probable Lyme meningitis: neurological symptoms suggestive of neuroborreliosis without other obvious reasons, *B. burgdorferi* antibody in serum or EM

Reference	Tveitnes 2012[80]				
	Time between measurement of index test and reference standard: not reported				
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	33	0	33	
	Index test −	109	63	172	
	Total	142	63	205	
2×2 table		Reference standard +	Reference standard −	Total	
	Index test +	104	3	107	
	Index test -	38	60	98	
	Total	142	63	205	
Statistical measures	Index test: EM Sensitivity 0.23 Specificity 1.00 PPV 1.00 NPV 0.37 Index test: Acute facial palsy Sensitivity 0.73 Specificity 0.95 PPV 0.97 NPV 0.61				
Source of funding	The Western Norway Regional Health Authority				
Limitations	Risk of bias: index test, reference standard Indirectness: none				
Comments	People group included 91 with confirmed and 51 with probable Lyme disease. Six from the disease control group were not included in the analysis due to intracranial infection complicating upper airway infection (3), infection in a ventriculo-peritoneal shunt (1), antibiotics before lumbar puncture (1) and tuberculous meningitis (1).				

Reference	Waespe 2010[86]
Study type	Cohort study
Study methodology	Data source: children hospitalised with clinical signs of aseptic meningitis or peripheral facial nerve palsy at a children's hospital in Switzerland Recruitment: consecutive
Number of patients	n=181
Patient characteristics	Age, range: 20 months to 16 years Gender (male to female ratio): 118/63 Family origin: not reported Setting: 1 children's hospital Country: Switzerland Inclusion criteria: ≥12 months of age, hospitalised with clinical signs of aseptic meningitis or peripheral facial nerve palsy Exclusion criteria: people with missing CSF sample results Time from onset of symptoms to evaluation, mean (interquartile range): people with neuroborreliosis 7.6 days (3-9)
Target condition(s)	Lyme disease
Index test(s) and reference standard	Index tests Peripheral facial nerve palsy Reference standard Evidence of intrathecal synthesis of *B. burgdorferi* antibodies in CSF (confirmed) or in serum or CSF, both confirmed by immunoblot (probable)

Reference	Waespe 2010[86]			
	Time between measurement of index test and reference standard: not reported			
2×2 table		Reference standard +	Reference standard −	Total
	Index test +	25	32	57
	Index test −	9	93	102
	Total	34	125	159
Statistical measures	Index test: Peripheral facial nerve palsy Sensitivity 0.74 Specificity 0.74 PPV 0.44 NPV 0.91			
Source of funding	Not reported			
Limitations	Risk of bias: index test, reference standard, flow and timing Indirectness: none			
Comments	Index test positive people were those with facial palsy and those with facial palsy plus aseptic meningitis. 159/181 people were tested for Lyme disease.			

Appendix E: Coupled sensitivity and specificity forest plots and sROC curves

E.1 Coupled sensitivity and specificity forest plots (adults)

E.1.1 Evidence from cohort studies

Figure 2: Sensitivity and specificity of Erythema migrans for diagnosing Lyme disease in adults

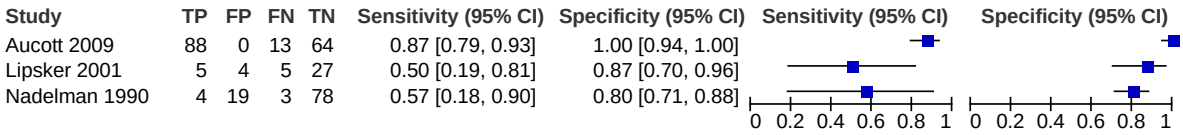


Figure 3: Sensitivity and specificity of facial palsy for diagnosing Lyme disease in adults

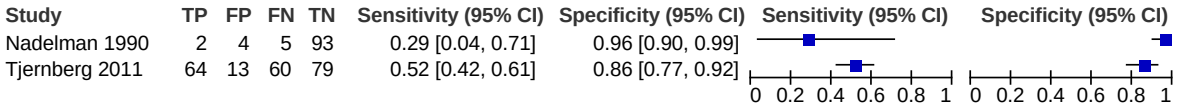


Figure 4: Sensitivity and specificity of complete facial palsy for diagnosing Lyme disease in adults

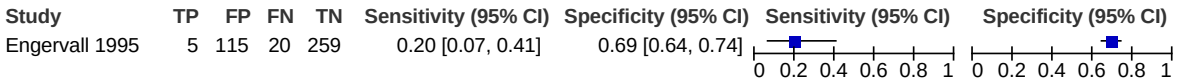
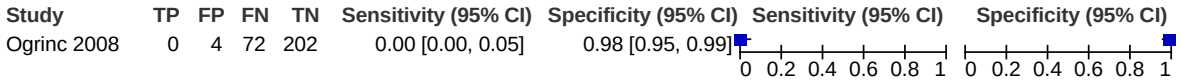


Figure 5: Sensitivity and specificity of cranial nerve involvement for diagnosing Lyme disease in adults



E.1.2 Evidence from case-control studies

Figure 6: Sensitivity and specificity of arrhythmia (bradycardia) for diagnosing Lyme disease in adults

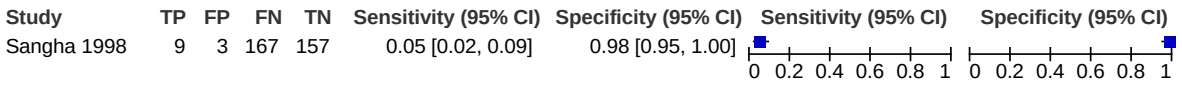


Figure 7: Sensitivity and specificity of arrhythmia (tachycardia) for diagnosing Lyme disease in adults

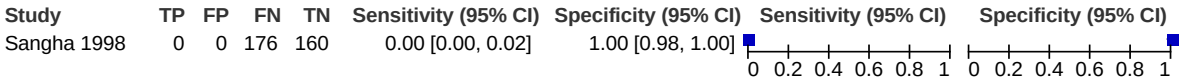


Figure 8: Sensitivity and specificity of arrhythmia (non-sinus rhythm) for diagnosing Lyme disease in adults

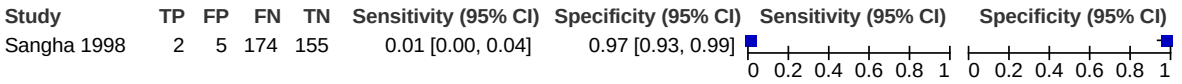


Figure 9: Sensitivity and specificity of heart block (atrioventricular block) for diagnosing Lyme disease in adults

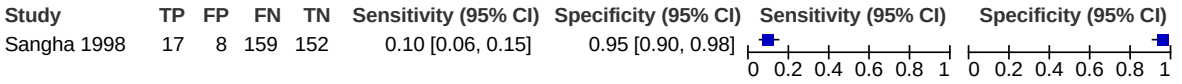
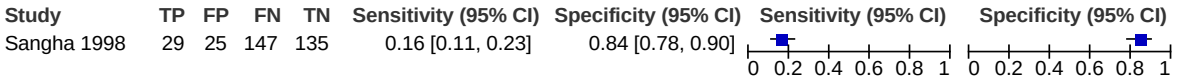


Figure 10: Sensitivity and specificity of heart block (any bundle-branch block) for diagnosing Lyme disease in adults



E.2 Coupled sensitivity and specificity forest plots (children)

E.2.1 Evidence from cohort studies

Figure 11: Sensitivity and specificity of Erythema migrans for diagnosing Lyme disease in children

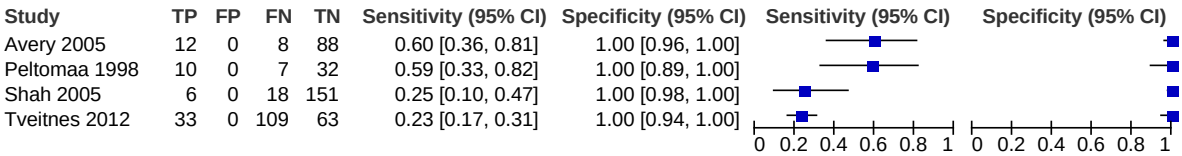


Figure 12: Sensitivity and specificity of facial palsy for diagnosing Lyme disease in children

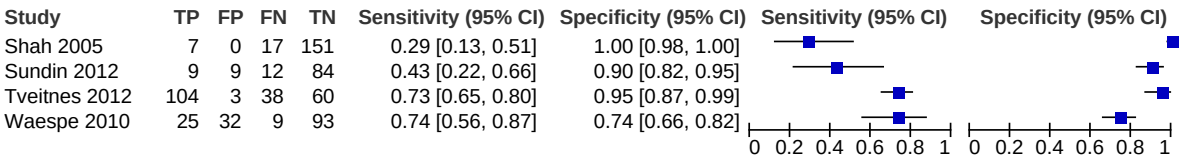


Figure 13: Sensitivity and specificity of facial palsy (TBE controls) for diagnosing Lyme disease in children

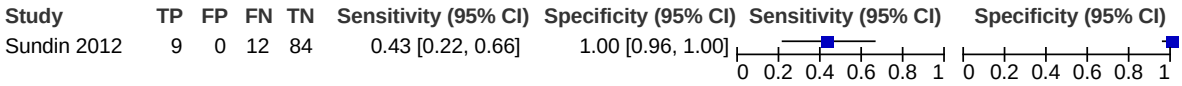
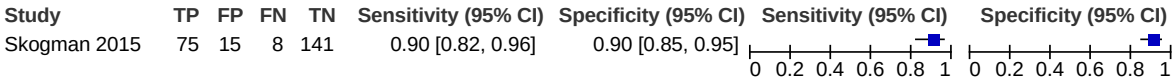


Figure 14: Sensitivity and specificity of NeBoP score for diagnosing Lyme disease in children



E.2.2 Evidence from case-control studies

Figure 15: Sensitivity and specificity of Erythema migrans and lymphocytoma for diagnosing Lyme disease in children

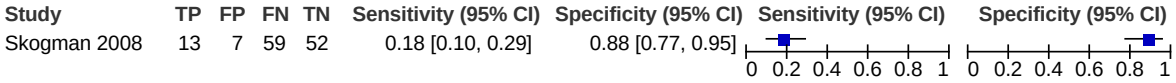


Figure 16: Sensitivity and specificity of facial palsy (disease controls) for diagnosing Lyme disease in children

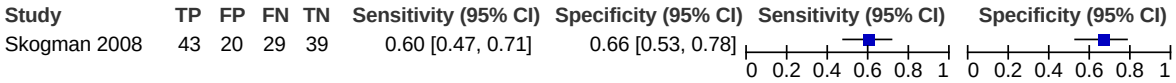


Figure 17: Sensitivity and specificity of facial palsy (healthy controls) for diagnosing Lyme disease in children

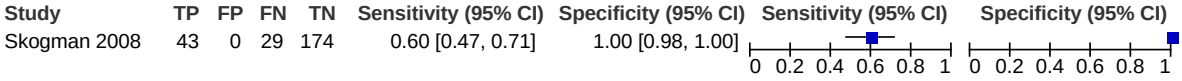
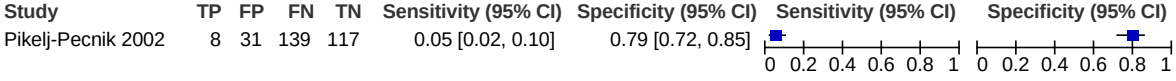


Figure 18: Sensitivity and specificity of arrhythmia for diagnosing Lyme disease in children



E.3 ROC curves

Figure 19: sROC curve with pooled sensitivity and specificity of erythema migrans for diagnosing Lyme disease in adults (cohort studies)

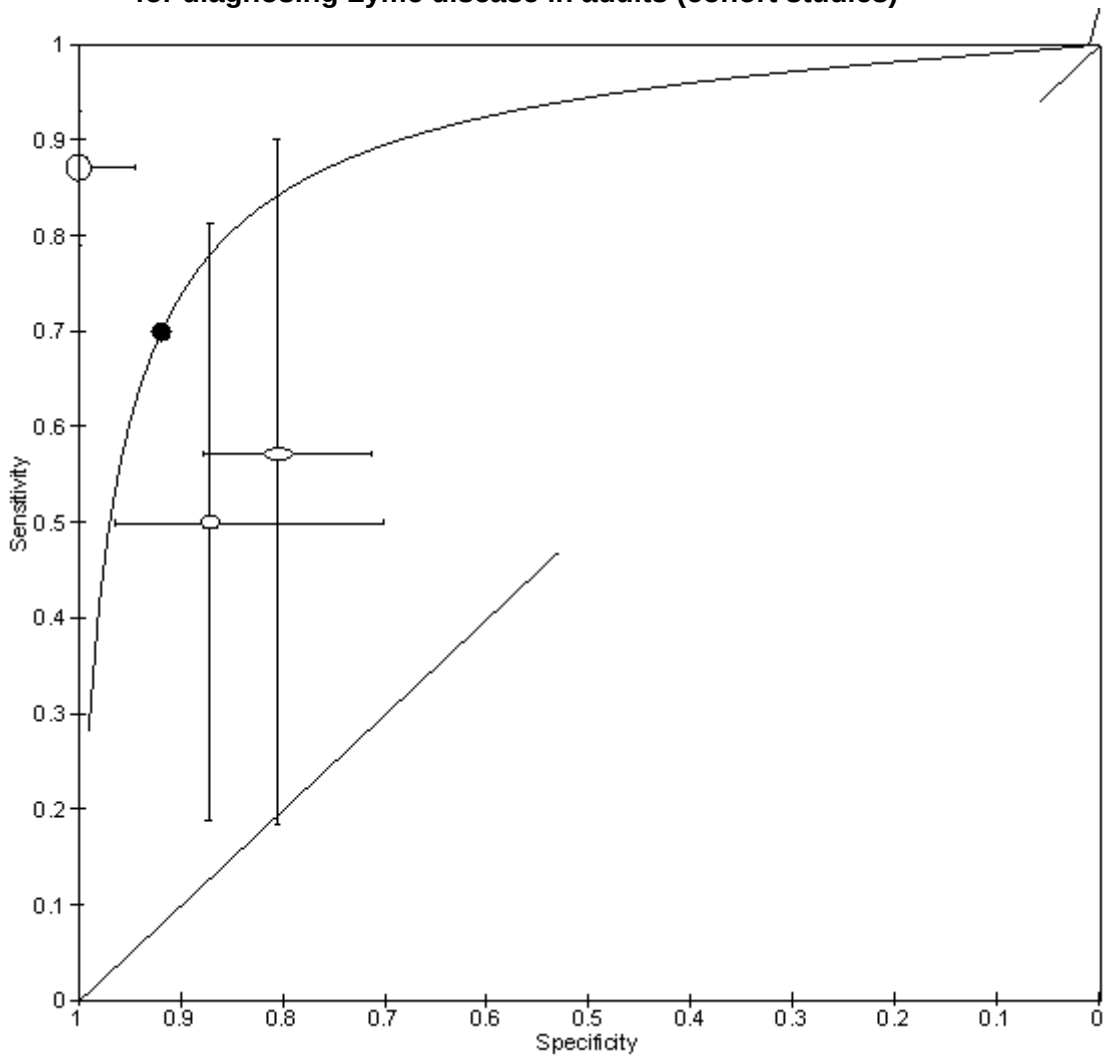


Figure 20: sROC curve with pooled sensitivity and specificity of erythema migrans for diagnosing Lyme disease in children (cohort studies)

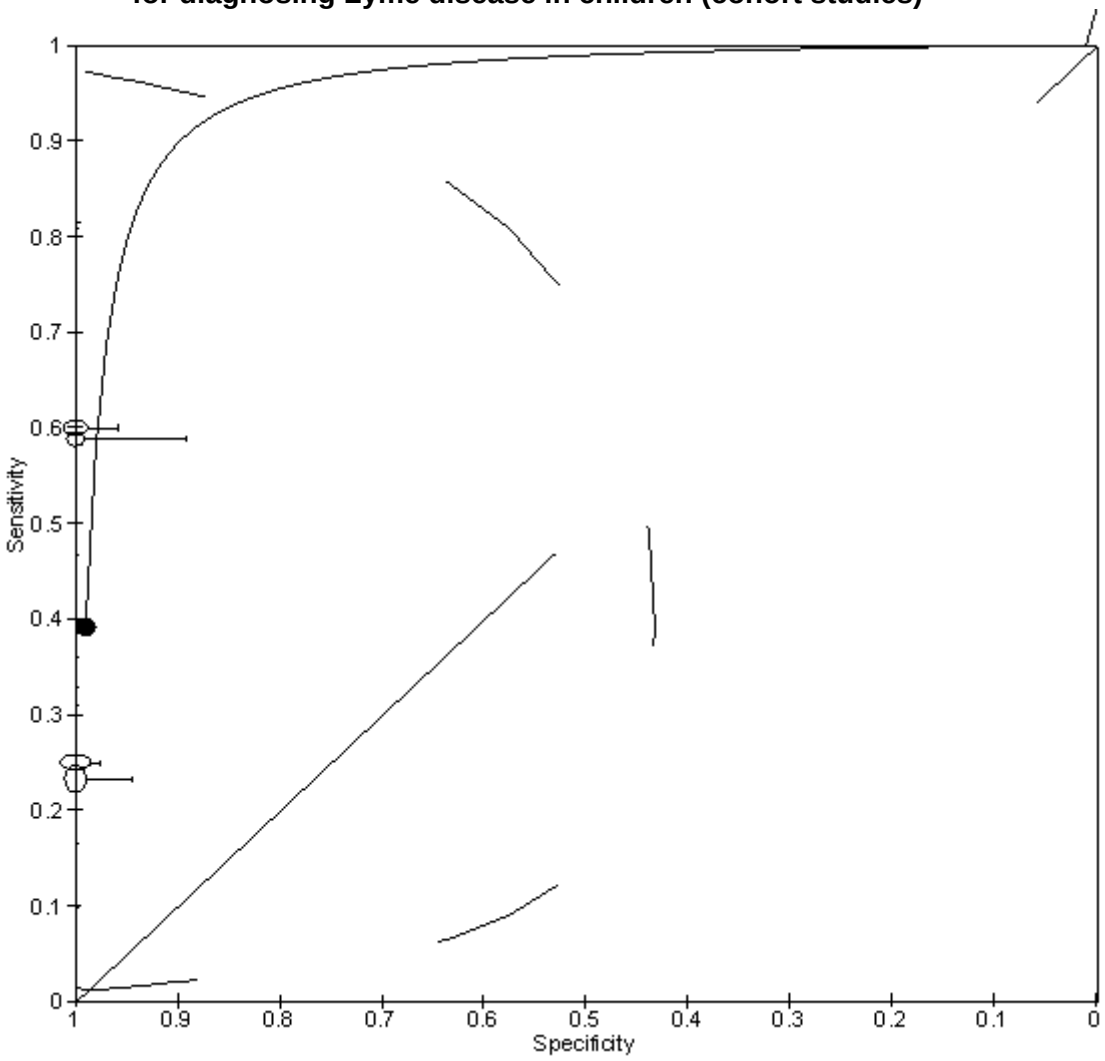
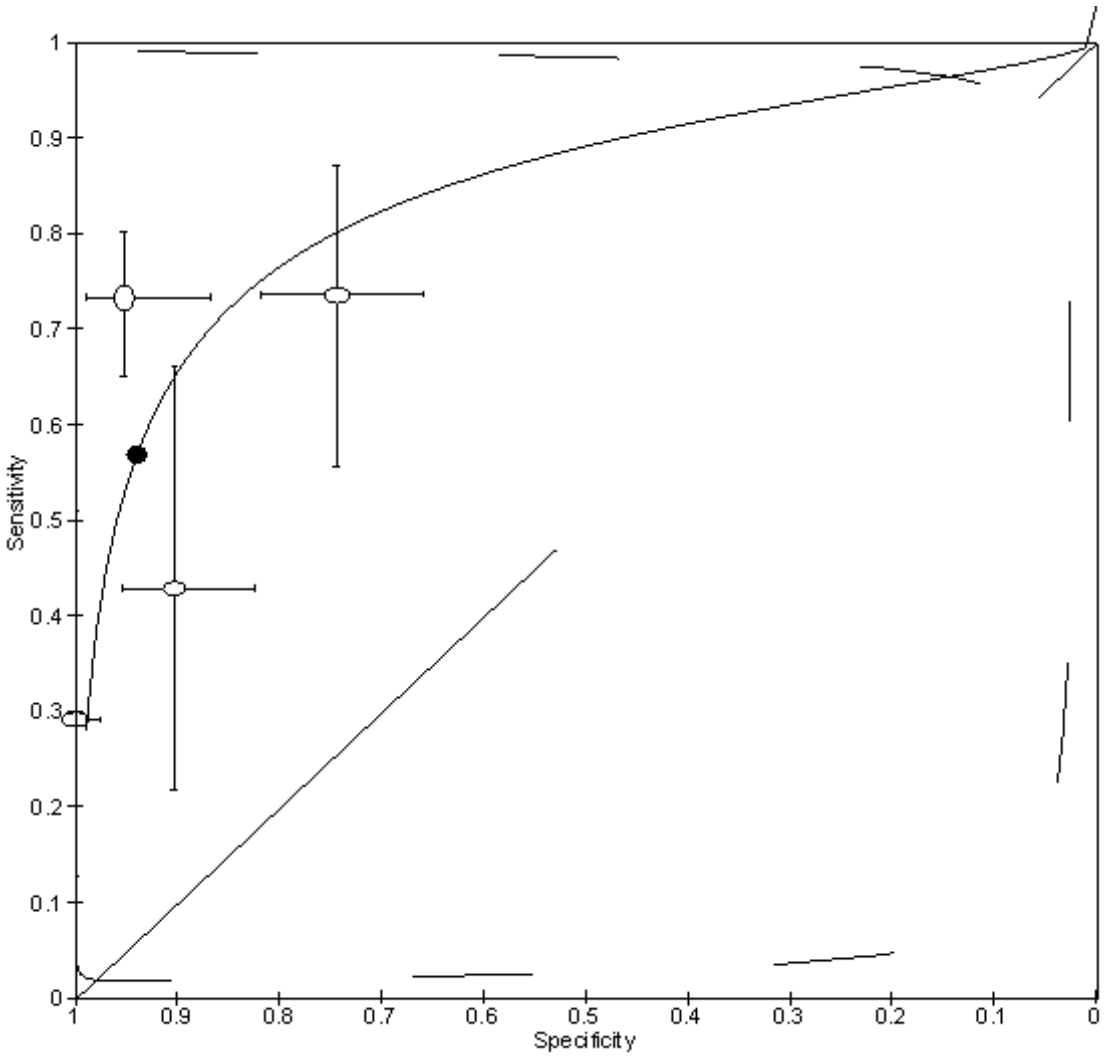


Figure 21: sROC curve with pooled sensitivity and specificity of facial palsy for diagnosing Lyme disease in children (cohort studies)

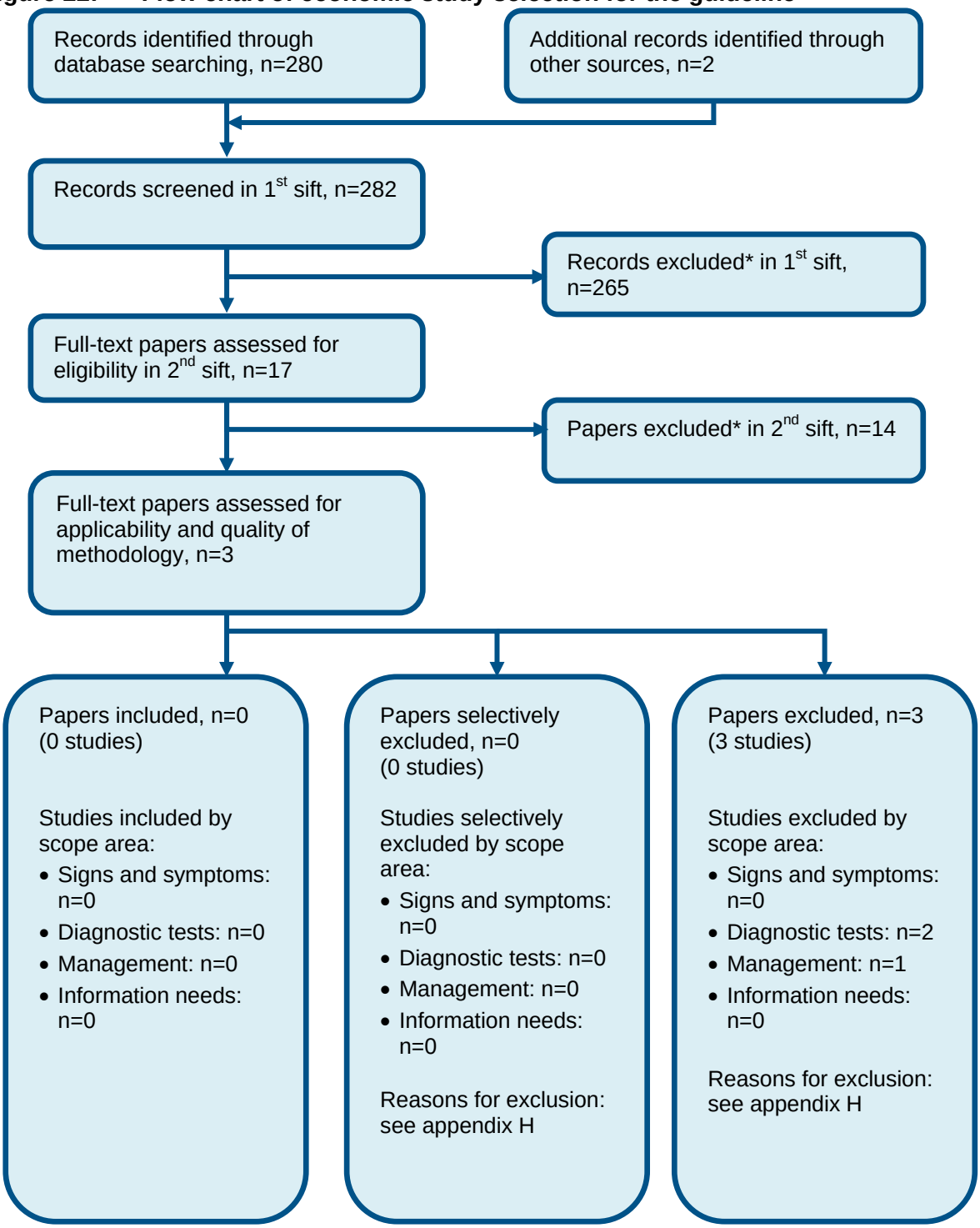


E.4 Area under the curve

No graphs.

Appendix F:Health economic evidence selection

Figure 22: Flow chart of economic study selection for the guideline



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

Appendix G: Health economic evidence tables

None.

Appendix H: Excluded studies

H.1 Excluded clinical studies

Table 11: Studies excluded from the clinical review

Reference	Reason for exclusion
Afari 2016[1]	Excluded due to an incorrect study design
Ahmed 2005[2]	Excluded due to an incorrect study design
Arnez 2003[3]	Excluded due to an incorrect population
Asbrink 1986[4]	Excluded due to an incorrect study design
Bartunek 1995[7]	Unable to obtain paper
Biese 2006[8]	Excluded due to an incorrect study design
Broekhuijsen-van Henten 2010[9]	Excluded due to an incorrect study design
Caruso 1985[10]	Excluded due to an incorrect study design
Coumou 2015[11]	Excluded due to an incorrect analysis
Dillon 2010[12]	Excluded due to an incorrect study design
Dolbec 2010[13]	Excluded due to an incorrect study design
Doorey 1991[14]	Excluded due to an incorrect study design
Dunand 1998[15]	Excluded due to an incorrect study design
Earl 2010[16]	Excluded due to an incorrect study design
Esposito 2013[18]	Excluded due to an incorrect study design
Fahrer 1991[19]	Excluded due to an incorrect analysis
Feder 1995[20]	Excluded due to an incorrect outcome
Felz 1999[21]	Excluded due to an incorrect study design
Gissler 2002[22]	Excluded due to an incorrect abstract only
Goos 1971[23]	Excluded due to an incorrect study design
Grandsaerd 2000[24]	Excluded due to an incorrect study design
Halperin 1990[25]	Excluded due to an incorrect study design
Hanner 1993[26]	Excluded due to an incorrect study design
Holland 2004[27]	Excluded due to an incorrect population
Hufschmidt 2009[28]	Excluded due to an incorrect analysis
Jenke 2011[29]	Excluded due to an incorrect study design
Keh 2012[30]	Excluded due to an incorrect study design
Kimball 1989[31]	Excluded due to an incorrect study design
Kindler 2015[32]	Excluded due to an incorrect population
Kindstrand 1997[33]	Excluded due to an incorrect analysis
Lotric-Furlan 1999[35]	Excluded due to an incorrect analysis
Malane 1991[36]	Excluded due to an incorrect study design
Neubert 1986[39]	Excluded due to an incorrect analysis
Nigrovic 2008[40]	Excluded due to an incorrect analysis
Oymar 2009[42]	Excluded due to an incorrect analysis
Petersen 1989[44]	Excluded due to an incorrect analysis
Pohl-Koppe 1998[46]	Excluded due to an incorrect study design
Puri 2014[47]	Excluded due to an incorrect analysis
Qureshi 2002[48]	Excluded due to an incorrect analysis

Reference	Reason for exclusion
Randazzo 1993[49]	Excluded due to an incorrect study design
Ranki 1994[50]	Excluded due to an incorrect analysis
Rattner 1948[51]	Excluded due to an incorrect study design
Rees 1994[52]	Excluded due to an incorrect population
Reid 1998[53]	Excluded due to an incorrect analysis
Richier 2013[54]	Not in English
Rijpkema 1997[55]	Excluded due to an incorrect analysis
Rose 1991[58]	Excluded due to an incorrect analysis
Rose 1994[57]	Excluded due to an incorrect analysis
Rose 1994[56]	Excluded due to an incorrect analysis
Ross 1989[59]	Excluded due to an incorrect study design
Santino 2008[61]	Excluded due to an incorrect analysis
Schmidt 1995[62]	Excluded due to an incorrect analysis
Schwartz 1993[63]	Excluded due to an incorrect analysis
Scrimenti 1970[64]	Excluded due to an incorrect study design
Seltzer 2000[65]	Excluded due to an incorrect analysis
Seltzer 1996[66]	Excluded due to an incorrect study design
Sigal 1990[68]	Excluded due to an incorrect symptom
Smith 2002[71]	Excluded due to an incorrect analysis
Smouha 1997[72]	Excluded due to an incorrect study design
Sood 1998[73]	Excluded due to an incorrect study design
Steere 1993[74]	Excluded due to an incorrect analysis
Steinberg 1996[75]	Excluded due to an incorrect study design
Thompson 2009[77]	Excluded due to an incorrect analysis
Tibbles 2007[78]	Excluded due to an incorrect study design
Tveitnes 2015[81]	Excluded due to an incorrect analysis
Tveitnes 2007[82]	Excluded due to an incorrect analysis
Vegsundvag 1993[83]	Excluded due to an incorrect study design
Von Stedingk 1995[84]	Excluded due to an incorrect analysis
Vrethem 2011[85]	Excluded due to an incorrect analysis
Wakkers Garritsen 1974[87]	Excluded due to an incorrect study design
Weber 1986[88]	Excluded due to an incorrect study design
Wetter 2011[89]	Excluded due to an incorrect study design
Wienecke 1995[90]	Excluded due to an incorrect analysis
Wise 1946[91]	Excluded due to an incorrect study design
Woolf 1991[92]	Excluded due to an incorrect analysis
Wormser 2013[93]	Excluded due to an incorrect analysis
Younger 2010[94]	Excluded due to an incorrect study design
Zajkowska 2011[95]	Excluded due to an incorrect study design

H.2 Excluded health economic studies

Table 12: Studies excluded from the health economic review

Reference	Reason for exclusion
None	