National Institute for Health and Care Excellence

Draft for Consultation

Lyme disease: diagnosis and management

[C] Evidence reviews for diagnostic tests

NICE guideline

Diagnostic evidence review

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Draft for Consultation

This evidence review was developed by the National Guideline Centre

1

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ISBN:

Contents

1

Introduction

The symptoms of Lyme disease, other than erythema migrans (EM), such as facial palsy, joint pains or nerve pains can be seen in many other conditions. Diagnostic tests are used to identify those cases in which Lyme disease is the cause, so that appropriate treatment can be given and ensure that other important diseases are not misdiagnosed as Lyme disease. It is important that the tests used have both the ability to identify infection with the Lyme disease bacteria and to discriminate this from other causes of infection or disease.

Blood tests looking for antibodies to the Lyme bacteria *Borrelia burgdorferi* (serological tests) are the most common tests performed when Lyme disease is suspected. Other tests such a polymerase chain reaction (PCR) can identify fragments of bacteria; however, they are not useful for the majority of people with Lyme disease. There are numerous Lyme disease diagnostic tests available using different antigens from the range of genospecies of *B. burgdorferi*.

This chapter covers 3 review questions that aim to determine the most accurate initial test, confirmatory test and test combination:

- In people with suspected (or under investigation for) Lyme disease, what is the most accurate initial test to identify whether Lyme disease is present?
- In people with a positive test for Lyme disease, what is the most accurate test to confirm or rule out Lyme disease?
- In people with suspected (or under investigation for) Lyme disease, what is the most accurate combination of tests to identify whether Lyme disease is present?

1 Initial tests for Lyme disease

1.1 Review question: In people with suspected (or under investigation for) Lyme disease, what is the most accurate initial test to identify whether Lyme disease is present?

1.2 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	Serology assays: • *Borrelia* recomLine IgG (Mikrogen) • *Borrelia* Virastripe IgM/IgG (Viramed) • C6 ELISA (Immunetics) • Diasorin LIAISON *Borrelia* IgM Quant • Enzygnost Lyme link IgG/VlsE (Siemens) • VIDAS Lyme IgM and IgG (Biomerieux) • Other assays used elsewhere in the world: ○ Anti-*Borrelia* EUROLINE-RN-AT IgG (Euroimmun) ○ Anti-*Borrelia* EUROLINE-WB IgG, IgM (Euroimmun) ○ Anti-*Borrelia* EUROLONE-RN-AT IgM (Euroimmun) ○ Anti-*Borrelia* plus VlsE ELISA (IgG) & anti-*Borrelia* ELISA (IgM; Euroimmun) ○ *B Burgdorferi* IgG EIA (Diagnostic Automation) ○ *Borrelia* ViraChip IgG/IgM assay (ViraMed) ○ Capita™ *B. burgdorferi* IgG.IgM EIA (Trinity Biotech) ○ Genzyme Virotech *Borrelia* Europe Line (Virotech) ○ Immunoblot IgG (IGeneX) ○ MardX EU Lyme and VLSE Immunoblots (Trinity Biotech) ○ NovaLisa IgG EIA (Nova Tec) ○ Premier Lyme EIA IgG/IgM (Meridian Bioscience Inc.) ○ recomBead *Borrelia* IgG/IgM v2.0 (Mikrogen) ○ RecomLine *Borrelia* IgG/IgM Immunoblot (Mikrogen) ○ RecomWell *Borrelia* IgG/IgM (Mikrogen) ○ SeraSpot Anti-*Borrelia* IgG/IgM (Seramun Diagnostica GmbH) ○ VIR-ELISA anti-*Borrelia* IgG/IgM (VIRO-IMMUN Labor-Diagnostika GmbH) Direct microscopic visualisation • Biopsy/histology Lymphocyte transformation tests: • EliSpot • LTT-MELISA® • SpiroFind™ assay (Boulder Diagnostics) CD57 test

	Inflammatory markers: • C-reactive protein (CRP) • Erythrocyte sedimentation rate (ESR) Full blood count: • Eosinophil • Haemoglobin • Lymphocyte • Monocyte • Neutrophil/Band/ANC • Platelet • White blood cell (WBC) CXCL13 (from a cerebrospinal fluid [CSF] or serum sample) PCR • CSF analysis Synovial fluid analysis
Reference standards	• *Borrelia* culture (Spirochaete is difficult to culture and grows slowly; therefore, it is not compatible with providing a rapid diagnostic result). • Clinical diagnosis • PCR All index tests compared with all reference tests and reference tests compared with each other (in this case clinical diagnosis will be the reference standard).

Statistical measures	Detecting Lyme disease
	• Critical:
	  ○ Sensitivity
	• Important:
	  ○ Specificity
	  ○ Positive Predictive Value
	  ○ Negative Predictive Value
	  ○ 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 in a cross-sectional design Exclude (unless there is insufficient evidence and agreed to include with the committee): • Two-gate or 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

We searched for studies assessing the diagnostic test accuracy of any of the above-mentioned tests to identify whether Lyme disease is present. The search found a very large number of studies because we could not define any limits for our clinical evidence search

without risking the omission of relevant papers. It was not possible to identify whether a study provided evidence for the review question on initial tests, confirmatory tests or combination of tests based on the title and abstract alone. Therefore, one search was undertaken and sifted to identify the clinical evidence for all 3 review questions. The PRISMA flow-chart (appendix C) and the excluded studies list (appendix I) reflect this approach in all 3 subchapters of this evidence report: initial tests, confirmatory tests and combination of tests for Lyme disease.

1.3 Clinical evidence

1.3.1 Included studies

One hundred-twenty studies (123 papers) were included in the review.[8 ,14 ,16-18 ,21 ,24 ,27 ,32-34 ,39 ,45 ,48 ,49 ,53 ,54 ,62 ,74 ,85 ,90 ,108 ,123 ,124 ,126 ,129 ,132 ,135 ,139 ,140 ,145 ,154 ,161 ,162 ,164 ,165 ,167 ,172 ,175-177 ,182 ,186 ,190 ,194 ,199 ,200 ,202 ,204 ,207 ,211 ,215 ,221 ,225 ,226 ,228 ,229 ,231 ,236 ,238 ,241 ,243 ,247 ,253 ,267 ,272 ,279 ,281 ,288 ,297 ,302 ,304 ,305 ,307 ,308 ,313 ,332-335 ,344 ,349 ,355 ,356 ,364 ,371 ,382-384 ,392 ,393 ,406 ,409 ,411 ,416 ,422-424 ,431 ,433 ,439 ,443 ,446 ,448 ,455 ,458 ,462 ,463 ,466 ,474 ,475 ,477 ,481 ,485 ,492-494 ,497 ,498 ,510 ,517 ,519 ,532] These are summarised in Table 2, Table 3, Table 4, Table 5 and Table 6 below.

One hundred-eleven studies (114 papers) were in adults; 102 case-control studies (105 papers)[8 ,14 ,17 ,32-34 ,45 ,48 ,49 ,53 ,54 ,62 ,74 ,85 ,90 ,108 ,123 ,124 ,126 ,132 ,135 ,139 ,140 ,145 ,161 ,162 ,164 ,165 ,167 ,177 ,182 ,186 ,190 ,194 ,199 ,200 ,202 ,204 ,207 ,215 ,221 ,225 ,226 ,228 ,229 ,231 ,236 ,238 ,241 ,247 ,267 ,272 ,279 ,281 ,288 ,297 ,302 ,304 ,305 ,307 ,308 ,313 ,332-334 ,344 ,349 ,355 ,356 ,364 ,371 ,382-384 ,392 ,393 ,406 ,409 ,411 ,416 ,422-424 ,431 ,433 ,439 ,443 ,448 ,455 ,458 ,462 ,463 ,466 ,475 ,477 ,481 ,485 ,492-494 ,497 ,498 ,510 ,517 ,519] and 9 cross-sectional studies.[24 ,27 ,39 ,154 ,175 ,176 ,253 ,335 ,474]

Nine studies were in children; these included 5 case-control studies[129 ,172 ,211 ,446 ,532] and 4 cross-sectional studies.[16 ,18 ,21 ,243]

Evidence from the included studies is summarised in the clinical evidence profile below. See also the study selection flow chart in appendix C, sensitivity and specificity forest plots in appendix E, study evidence tables in appendix D and exclusion list in appendix I.

Some studies included a very wide age range. We included these in the evidence for adults as the mean or median age of the study population was well above 18, indicating that the majority of included people were adults. There were no studies specifically conducted in young people aged 12 to 17.

The included studies varied significantly by test, study population and clinical presentation, which made it impossible to meta-analyse the large number of results. Given the general lack of evidence from cross-sectional studies, which are the most robust study design for diagnostic accuracy studies, case-control studies were also included in this review. The committee considered the entirety of the evidence when making recommendations.

Three different reference standards were identified for this review: *Borrelia* culture, polymerase chain reaction (PCR) and clinical diagnosis. *B burgdorferi* is difficult to culture and grows slowly; therefore, it is not compatible with providing a rapid diagnostic result. As a result, culture is rarely used as a reference standard in clinical studies. In cases where *Borrelia* culture or PCR were used as an index test in any of the included studies, clinical diagnosis would function as the reference standard.

Overall, the committee found the evidence difficult to interpret due to the differences within and between the studies, which meant that meta-analyses were not possible. Studies varied widely in populations, both cases and controls, the types of tests used, test implementation and interpretation of test results. To improve comparability between results only healthy controls were included in the analyses if possible.

1.3.2 Excluded studies

See the excluded studies list in appendix I.

1.3.3 Summary of clinical studies included in the evidence review

Table 2: Summary of included case-control studies (adults)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Ang 2015[8]	n=369 EM (n=214) Acrodermatitis chronica atrophicans (ACA; n=28) Neuroborreliosis (n=102) Arthritis (n=25) Age: not reported	n=228 Healthy controls	Enzyme immunoassay (EIA) Western blot (WB)	*IgM and IgG* Enzyme-linked immunosorbent assay (ELISA): Diacheck Moran, Switzerland Enzygnost Siemans, Germany *Borrelia* microplate plus VlsE Euroimmun *Borrelia* ELISA test kit Sekisui/Virotech Serion ELISA classic Virion, Germany RecomWell Mikrogen, Germany *Borrelia* EISA Medac	Serum	ESCMID Study Group for Lyme Borrelioisis(ESGBOR) guidelines Clinical diagnosis PCR confirmation Histopathology CSF pleocytosis	IgM and IgG equals positive result for IgMor IgG Borderline results excluded from the analysis as the study authors did not necessarily interpret them as positive evidence of infection

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				Laison DiaSorin, Italy Western blot: RecomLine Mikrogen, Germany			
Åsbrink 1985[14]	n=123 EM (n=88) ACA (n=26) EM-related extracutaneous manifestations (n=9) Age: not reported	n=185 Aged: 17-80 years	ELISA	*IgM and IgG* ELISA	Serum	Clinical diagnosis	
Bacon 2003[17]	n=280 Acute Lyme (n=80) Early convalescent (n=106) Early neurological (n=15) Early neurological convalescent (n=11) Arthritis (n=33) Arthritis convalescent (n=24) Late neurologic (n=11)	n=257 Healthy controls	ELISA	*IgM and IgG* rVlsE1 IgG kELISA rVlsE1 IgM kELISA C6-IgG kELISA pep10 IgM kELISA	Serum	Clinical diagnosis CDC criteria	
Branda 2010[32]	n=162 Massachusetts: Culture-confirmed EM (n=79) Acute neuritis or carditis	n=195 Healthy controls (n=166) Other	EIA WB	*IgM and IgG* VIDAS Lyme IgG and IgM BioMerieux SA Wampole *B burgdorferi*	Serum	Clinical diagnosis CDC surveillance criteria for	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	(n=12) Arthritis or late neuritis (n=23) Westchester: Culture-confirmed EM (n=27) Acute neuritis or carditis (n=15) Arthritis or late neuritis (n=6) Age: not reported	illness (n=29)		IgG/M ELISA II assay *Borrelia* B31 IgM Virablot Viramed *Borrelia* B31 IgG Birablot plus VlsE Viramed		Lyme disease	
Branda 2011[33]	n=169 EM (n=114) Acute neuritis or carditis (n=26) Arthritis or late neuritis (n=29) Age: not reported	n=1,300 Healthy controls	EIA	*IgM and IgG* C6 *B burgdorferi* ELISA Immunetics	Serum	Clinical diagnosis CDC surveillance criteria for Lyme disease	
Branda 2013[34]	n=64 Early or late Lyme disease Age: not reported	n=100 Healthy controls	ELISA Immunoblot (IB)	*IgM and IgG* <u>ELISA:</u> Enzygnost Borreliosis Siemens, Germany Ezygnost Lyme Link VlsE/IgG Siemens, Germany	Serum	Clinical diagnosis European Lyme disease criteria	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				Wampole *B burgdorferi* IgG/IgM ELISA II Alere Inc., USA C6 B burgdorferi Immunetics Inc., USA <u>Immunoblot:</u> *Borrelia* MiQ and VlsE IgM test kit Viramed, Germany *Borrelia* MiQ and VlsE IgG test kit Viramed, Germany *Borrelia* B31 ViraBlot IgM test kit Viramed, Germany *Borrelia* B31 plus VlsE ViraBlot IgG test kit Viramed, Germany			
Callister 2002[45]	n=34 EM Age: not reported	n=34 Other symptoms unrelated to Lyme	Western blot	*IgM and IgG* Western blot MRL Diagnostics, USA	Serum	Clinical diagnosis	
Cerar 2006[49]	n=383	n=49	IFA	*IgM and IgG*	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Lyme suspected (n=198) EM (n=76) Neuroborreliosis (n=28) Early Lyme <6 months (n=60) Chronic Lyme >6 months (n=21) Age: not reported	Healthy blood donors		IFA			
Cerar 2010[48]	n=61 Clinically evident neuroborreliosis (n=34), clinically suspected neuroborreliosis (n=27) Age (median) Evident: 56 years Suspected: 52 years	n=32 TBE	ELISA	*IgM and IgG* IDEIA kit DakoCytomation Denmark, Denmark	CSF Serum	Clinical diagnosis	Only confirmed neuroborreliosis included in analysis; Borderline results were excluded
Christova 2003[53]	n=105 EM Age: not reported	n=90 Healthy blood donors	ELISA	*IgM and IgG* ELISA BoehringWerke, Germany	Serum	Clinical diagnosis	
Cinco 2006[54]	n=76 EM (n=54) Lyme arthritis (n=15) Neuroborreliosis (n=6) Age: not reported	n=59 Blood donors	ELISA	*IgM and IgG* C6-ELISA kit Immunetics, USA	Serum	Clinical diagnosis Culture for EM	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Coyle 1993[62]	n=77 Clinical evidence of *B burgdorferi* infection and neurological problems Age (mean): 34 years (3-84)	n=34 Other neurological diseases	ELISA	*IgG* ELISA	CSF	Clinical diagnosis	
D'Arco 2017[74]	n=171 Early Lyme disease (n=152), Lyme arthritis (n=19) Age: not reported	n=139 Healthy individuals	ELISA	ELISA C6	Serum	Clinical diagnosis	
Dessau 2010[85]	n=117 Neuroborreliosis Assumed active infection with *B. burgdorferi* Age (median): 50 years (3-87) 33 children, 26 adults up to 50 years, 57 adults above 50 years	n=815 Healthy blood donor sera	ELISA	*IgM and IgG* IDEIA *Borrelia burgdorferi* IgM and IgG UK	Serum	Clinical diagnosis, positive test for intrathecal antibody production, leucocyte count in CSF of 5x10^6/L	
Dressler 1993[90]	Retrospective study: n=100 EM (n=25) Meningitis (n=25)	Retrospective study: n=125 MS (n=15) Influenza	ELISA IB	*IgM and IgG* ELISA Miniblot	Serum	Clinical diagnosis	Time point: mean 8 days after onset of symptoms for people with EM

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Arthritis (n=25) Late neuroborreliosis (n=25) Age: not reported Prospective study: n=54 Lyme arthritis (n=25) Lyme neuroborreliosis (n=29) Age: not reported	vaccination (n=25) ALS (n=10) RA (n=15) SLE (n=10) CFS (n=25) Syphilis (n=25) Prospective study: n=139 Fibromyalgia (n=32), other rheumatic (n=62), other neurologic (n=45)		Bio-Rad Lab, CA, USA			
Fallon 2014[108]	n=37 Post treatment Lyme syndrome Age (mean): 46.5 years (SD 10.5)	n=40 Healthy controls	ELISA WB	*IgM and IgG* C6 ELISA Western blot	Serum	Clinical diagnosis (n=37) Positive IgG Western blot (n=26)	
Flisiak 1996[123]	n=42 EM (n=18) Arthritis (n=7)	n=27 Healthy volunteers	EIA	*IgM and IgG* <u>ELISA:</u> Lyme borreliosis	Serum	Clinical diagnosis CDC	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Neuroborreliosis (n=17) Age: not reported			Dako, Denmark Borrelio Recombinant Biomedica, Austria VIDAS Lyme Screen II bioMerieux, France		definitions	
Flisiak 1998[124]	n=48 EM (n=19) Arthritis (n=21) Neuroborreliosis (n=8) Age: not reported	n=26 Healthy controls	EIA WB	*IgM and IgG* ELISA: Lyme borreliosis Dako, Denmark VIDAS Lyme Screen II bioMerieux, France Western blot: Germany	Serum	Clinical diagnosis CDC definitions	
Fung 1994[126]	n=75 EM Age: not reported	n=106 Influenza vaccine (n=15) MS (n=12) ALS (n=9) RA (n=12) SLE (n=9) CFS (n=19) Syphilis (n=30)	ELISA WB	*IgM and IgG* ELISA Mini-Protean II western blot BioRad	Serum	Clinical diagnosis	
Goettner	n=85	n=110	WB	*IgG*	Serum	Clinical	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
2005[132]	EM (n=15) Neuroborreliosis (n=50) ACA (n=10) Lyme arthritis (n=10)	Healthy blood donors (n=60) Syphilis (n=10) Rheumatoid factor positive (n=10) Fever of unknown origin (n=30)	Lineblot			diagnosis	
Gomes-Solecki 2001[135]	n=120 EM or abnormalities related to late Lyme disease such as arthritis, AV-block or neurological symptoms Age: not reported	n=100 Healthy controls from endemic area	ELISA RRA	*IgM and IgG* ELISA Wampole Laboratories Recombinant Rapid Assay	Serum	Clinical diagnosis	
Goossens 2000[140] [Goossens 1999[139]]	n=39 Early Lyme (n=26) Late Lyme (n=13) Age: not reported	n=190 Healthy controls (n=62)	EIA WB	*IgM and IgG* <u>ELISA:</u> Behring EIA Boehringer EIA Dako EIA	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				Genzyme Virotech EIA IBL, EIA Milenia EIA <u>Western blot:</u> Genzyme Virotech WB MRL WB			
Grodzicki 1988[145]	n=30 Early Lyme disease Age: not reported	n=20 Healthy controls	Immunoblot	*IgM and IgG* Immunoblot	Serum	Clinical diagnosis	Time point: acute phase samples taken within 31 days of onset of EM, convalescence samples taken 2-4 weeks later
Hanrahan 1984[161]	n=207 Lyme disease Age (mean): 28 years (1-79)	n=329 Healthy controls	IFA	*IgG* IFA	Serum	Clinical diagnosis Based on: EM, aseptic meningitis, facial nerve palsy, or large joint arthritis	
Hansen 1988[164]	n=54 Lymphocytic	Serum (n=315): Healthy controls	ELISA	IgM and IgG Sonic extract ELISA	Serum CSF	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	meningoradiculitis following Lyme disease Age (median): 51 years (6-74)	(n=200) Aseptic meningitis (n=11) Guillain-Barré (n=14) Encephalitis (n=13) Syphilis (n=55) Leptospirosis (n=22) CSF (n=106) Aseptic meningitis (n=11) Guillain-Barré (n=14) Encephalitis (n=13) Neurosyphilis (n=14) People undergoing myelography (n=54)		Flagellum ELISA			
Hansen 1989[162]	n=157 EM (n=107)	n=200 Healthy	ELISA	*IgM and IgG* Sonic extract ELISA	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	ACA (n=50) Age (median): EM: 54 years (6-83) ACA: 61 years (28-89)	controls		Flagellum ELISA		Plus histopathology for ACA	
Hansen 1991[167]	n=198 EM (n=50) Neuroborreliosis (n=100) ACA (n=48) Age (median): EM: 45 years (6-71) Neuroborreliosis: 47 years (5-74) ACA: 54 years (17-80)	n=200 Healthy controls	ELISA	*IgM and IgG* Indirect ELISA	Serum	Clinical diagnosis	
Hansen 1991a[165]	n=100 Neuroborreliosis: second-stage lymphocytic meningoradiculitis (n=91), third-stage chronic progressive encephalomyelitis (n=9) Age: not reported	n=29 Multiple sclerosis (n=17), Guillain-Barré syndrome (n=8), neurosyphilis (n=4)	ELISA	*IgM and IgG* ELISA	CSF Serum	Clinical diagnosis, lymphocytic pleocytosis, elevated protein concentration	Time point: pre-treatment samples 4 days to 6 years (median 26 days) after onset of neurological symptoms
Hernandez-Novoa 2003[177]	n=42 Localised (EM, n=24) Disseminated (disseminated EM or	n=129 Healthy controls (n=53)	Immunoblot	*IgM and IgG* BAG-*Borrelia* Blot Germany	Serum	Clinical diagnosis CDC definition	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	neuroborreliosis, n=18) Age: not reported	Other infectious diseases (n=76)					
Hunfeld 2002[182]	n=226 EM (n=148) Neuroborreliosis (n=35) ACA and Lyme arthritis (n=43) Age: not reported	n=1107 Healthy blood donors	ELISA	*IgM and IgG* ELISA Biotest, Germany	Serum	Clinical diagnosis	
Jaulhac 1996[186]	n=12 Lyme arthritis All persons had been bitten by ticks and had an EM Previous positive serological result (n=10), seronegative result with recent acute monoarthritis within 1 month of a typical EM (n=2) Age (mean): 44 years (7-71)	n=29	PCR	N/A	Synovia	Clinical diagnosis CDC definition of Lyme arthritis or objective joint swelling in 1 or a few large joints following a recent well-documented EM	
Johnson 1996[190]	n=111 EM (n=58) Early neurologic (n=3) Lyme arthritis (n=36)	n=113 Healthy blood donors	ELISA	*IgM and IgG* FLA-ELISA	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Late neurologic (n=14) Age: not reported						
Jovicic 2003[194]	n=94 EM (n=40) Tick bite (n=40) Lyme carditis (n=4) Neuroborreliosis or Lyme arthritis (n=50) Age: not reported	n=120 Healthy blood donors (n=80), syphilis or rheumatoid arthritis or SLE (n=40)	ELISA IF IB	*IgM and IgG* ELISA IF Immunoblot	Serum	Clinical diagnosis	Time point: 31 samples collected 2-6 weeks and 9 samples collected 2-6 months after tick bite
Kaiser 1998[199]	n=67 Neuroborreliosis Age: not reported	n=14 Syphilis	ELISA	*IgM and IgG* ELISA	CSF Serum	Clinical diagnosis CSF pleocytosis IgM/IgG serum diagnostic	Leukos pro microliter in CSF (median): Acute neuroborreliosis: 246 (7-600) Chronic neuroborreliosis: 60 (10-135)
Kaiser 1999[200]	n=96 Neuroborreliosis Age: not reported	n=80 Healthy controls	EIA	*IgM and IgG* EIA	Serum	Clinical diagnosis	Leukos pro microliter in CSF (median): Acute neuroborreliosis: 172 (7-600) Chronic neuroborreliosis: 60 (10-135) Total protein in

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
							CSF mg/L (median): Acute neuroborreliosis: 1,300 (460-3600) Chronic neuroborreliosis: 2,700 (500-7,500)
Karlsson 1989[204]	n=68 Neuroborreliosis Age (median): 46 years (6-73)	n=44 Non-*Borrelia* meningitis or encephalitis	ELISA WB	*IgM and IgG* ELISA Western blot	CSF Serum	Clinical diagnosis Pleocytosis or neurological signs and symptoms with an EM	
Karlsson 1989a[202]	n=77 EM (n=30) Neuroborreliosis (n=37) ACA (n=10) Age: not reported	n=73 Non-*Borrelia* meningitis (n=35) MS (n=8) Syphilis (n=10) EBV (n=10) RA-positive (n=10)	ELISA Capture assay	*IgM* ELISA (indirect and capture)	Serum	Clinical diagnosis neuroborreliosis: plus pleocytosis in CSF	Time point: EM: up until 2 months after onset of EM neuroborreliosis: up until 11 months after onset of neurological symptoms ACA: up until 20 years after onset of symptoms
Klempner	n=21	n=10	Western	IgG	Serum	Clinical	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
2001[207]	Acute Lyme disease Age: not reported	Healthy persons	blot or Immunoblot	MarDX Diagnostics, USA		diagnosis based on CDC criteria	
Lahey 2015[215]	n=84 Early Lyme disease (n=79) Late Lyme disease (n=5) Age: not reported	n=26 Healthy controls	EIA	VlsE/prpC10 EIA	Serum	Clinical diagnosis	
Lange 1992[221]	n=36 EM Age: not reported	n=100 Blood donors	ELISA IB	*IgM* Flagellum ELISA (Dako) IgM Sonicate ELISA (Virimmun) IgM Immunoblot	Serum	Clinical diagnosis	
Lawrenz 1999[225]	n=81 EM (n=41) Acute neuroborreliosis (n=17) LA (23) Age: not reported	n=50 None Lyme disease	ELISA	*IgM and IgG* VlsE ELISA Whole-cell ELISA	Serum	Clinical diagnosis (People with EM were culture confirmed)	
Lebech 1992[228]	n=10 Neuroborreliosis	n=50 Healthy controls	PCR	PCR	CSF Urine	Clinical diagnosis	Previous neuroborreliosis group not included in

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Age: 41.5 years (SD 24)	(n=25) Urinary tract infections (n=10) Multiple sclerosis (n=5) Central nervous system infections (n=10)					diagnostic accuracy calculation
Lebech 1998[226]	n=150 Early neuroborreliosis (n=148) Chronic neuroborreliosis (n=2)	n=70 Other neurologic diseases without clinical suspicion of Lyme disease	PCR	PCR	CSF	Clinical diagnosis	
Lebech 2000[229]	n=61 EM (n=31) Neuroborreliosis (n=30)	n=33 Healthy controls (n=7) Other neurological diseases (n=20) High-dose antibiotic treatment	PCR	PCR	Skin biopsy CSF	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
		for other infectious diseases (n=6)					
Ledue 2008[231]	n=60 Early localised (EM, n=19) Early disseminated (Multiple EM, arthritis, arthralgia, abdominal pain, generalised lymphadenopathy, CNS involvement, n=41)	n=807 Healthy donors (n=600) Other infectious diseases (n=196) LYMErix vaccine (n=11)	ELISA	*IgM and IgG* C6 *B burgdorferi* ELISA kit Bio-Tek Instruments, USA LIAISON VlsE DiaSorin, USA	Serum	Culture	
Lencakova 2008[236]	n=74 Skin manifestations (n=54) Lyme neuroborreliosis (n=7) LA (n=13) Age: not reported	n=60 Healthy persons (n=40) Rheumatoid factor (n=10) Fever (n=10)	ELISA IF IB	*IgM and IgG* Whole cell lysate ELISA (IgM and IgG) IF (IgM and IgG) Recombinant line Immunoblot (IgM and IgG)	Serum	Clinical diagnosis	
Leung 1989[238]	n=10 Lyme disease Age: not reported	n=29 Syphilis (n=14) Infectious mononucleosis (n=4)	ELISA	*IgM and IgG* Colorimetric ELISA (Lyme STAT Test Kit Whittaker Bioproducts) FASTLYME	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
		Rheumatoid factor (n=11)					
Liebling 1993[241]	n=44 Lyme disease Age: not reported	n=47 Other inflammatory, autoimmune or infectious diseases	PCR	PCR	Serum CSF Synovial fluid Urine	Clinical diagnosis	
Liu 2013[247]	n=159 EM (n=52) Neuroborreliosis (n=65) ACA (n=28) Lyme arthritis (n=14) Age: not reported	n=292 Healthy blood donors (n=105) Syphilis (n=58) Leptospirosis (n=75) RA (n=54)	ELISA WB	*IgM and IgG* ELISA Western blot	Serum	Clinical diagnosis	
Magnarelli 1988[267]	n=102 EM plus later manifestations Age: not reported	n=77 Syphilis (n=15) Yaws (n=8) Louse-borne relapsing	ELISA	*IgM and IgG* ELISA	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
		fever (n=11) Tick-borne relapsing fever (n=8) Leptospirosis (n=12) Rocky Mountain spotted fever (n=16) RA (=7)					
Magnarelli 1992[272]	n=53 EM with antibodies (n=17) EM without antibodies (n=36) Age: not reported	n=40 Healthy persons	ELISA	*IgG* Unabsorbed standard ELISA with whole cells Unabsorbed standard ELISA with p41-G Biotin streptavidin amplified ELISA whole cells Biotin streptavidin amplified ELISA p41-G	Serum	Clinical diagnosis	
Marangoni 2005[281]	n=45 EM Age: 42.8 years (29-65)	n=234 Healthy blood donors	ELISA	*IgM and IgG* RecomWell *Borrelia* test (Mikrogen; IgG and IgM) Enzygnost Borreliosis (DADE Behring; IgG and	Serum	Culture	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				IgM) Quick ELISA C6 *Borrelia* assay (Immunetics)			
Marangoni 2008[279]	n=66 EM Age: 45.3 years (mean)	n=300 Blood bank Bologna	CLIA	*IgM and IgG* *ELISA:* Enzygnost Lyme link VlsE/IgG Enzygnost Borreliosis IgM Enzygnost system *CLIA:* LIAISON *Borrelia* system LIAISON *Borrelia* IgG LIAISON *Borrelia* IgM	Serum	Culture-confirmed EM	
Mathiesen 1996[288]	n=117 EM (n=47) Lyme neuroborreliosis (n=60) ACA (n=20) Age: not reported	n=100 Blood donors	ELISA WB	*IgM and IgG* ELISA (IgG and IgM) Western blot	Serum	Clinical diagnosis (EM was culture confirmed)	Disease duration (median): EM: 3 weeks (<1 week to 1 year) Lyme neuroborreliosis: 3 weeks (1 week to 1.5 years after onset of

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
							neurological symptoms) ACA: 4 years (8 months to 10 years)
Merljak Skocir 2008[297]	n=50 EM Age: not reported	n=50 Blood donors	Western blot	*IgG and IgM* Euroline-western blot (Euroimmun)	Serum	Clinical diagnosis	
Mitchell 1994[302]	n=51 EM Age (range): 2-76 years	n=16 Healthy subjects	IF EIA	*IgM and IgG* IgM indirect fluorescent antibody test IgG-IgM fluorescence EIA (3M Diagnostics) P39 EIA (General Biometrics)	Serum	Culture	
Molins 2014[308]	n=124 Early Lyme disease with EM acute phase (n=40) Early Lyme disease with EM convalescent phase (n=38) Early disseminated Lyme carditis (n=7) Early disseminated neuroborreliosis (n=10) Late Lyme disease, LA	n=203 Healthy persons	EIA WB Culture PCR	*IgM and IgG* Whole cell sonicate EIA (VIDAS Lyme IgM and IgG Polyvalent assay, bioMerieux) IgM and IgG western blots (MarDx Diagnostics) Culture	Serum Blood Skin Heart tissue	Clinical diagnosis	Standard CDC algorithm used for ELISA (IgM and IgG) and Immunoblot (IgM and IgG) – IgG used only after 1 month

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	(29)			PCR			
Molins 2015[304]	n=202 Early Lyme disease Age: 9-83 years	n=158 Healthy endemic (n=64) Healthy nonendemic (94)	EIA CLIA Immunoblot	*IgM and IgG* CLIA: VIDAS Lyme IgM and IgG assay (bioMerieux) ELISA: C6 EIA (Immunetics) Western blot: IgM and IgG immunoblots (MarDx Diagnostics)	Serum	At least 1 EM present in initial clinic visit or clinical diagnosis (majority had positive culture/PCR test)	
Molins 2016[307]	n=124 Acute and convalescent stage (n=78) Lyme neuroborreliosis (n=10) Lyme carditis (n=7) LA (n=29) Age: not reported	n=203 Healthy donors	EIA IB	*IgM and IgG* ELISA: C6 *B. burgdorferi* Lyme ELISA (Immunetics) Western blot: Marblot IgM and IgG immunoblot assays (MarDx Diagnostics) *Borrelia* ViraStripe IgM and IgG assay (plus VlsE on the IgG immunoblot; ViraMed, Biotech AG)	Serum	Clinical diagnosis	Densitometer reading taken over visual reading for VIDAS/ViraStripe combination
Molins 2017[305]	n=124 Acute EM (n=40), convalescent EM (n=38),	n=203 Healthy controls	ELISA	*IgM/IgG* VIDAS Lyme (IgM/IgG),bioMerieux,	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Neuroborreliosis (n=10), Lyme carditis (n=7), Lyme arthritis (n29) Age: not reported			USA			
Moter 1994[313]	n=22 EM (n=10) ACA (n=12) Age: not reported	n=4 Normal skin	PCR	PCR	Skin biopsy	Clinical diagnosis	1 person sampled twice 2 people did not have reference standard (tick bites) – data not included in analysis
Nocton 1994[333]	n=127 LA Age (mean): Test positive: 29 (8-67) Test negative: 38 (3-62)	n=69 Other forms of arthritis	PCR	PCR	Synovial fluid	Clinical diagnosis (criteria: brief intermittent attacks of oligoarticular arthritis, exposure in an area of endemic disease, elevated antibody response to *B. burgdorferi* on ELISA and exclusion of other known	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
						forms of arthritis)	
Nocton 1996[332]	n=60 Lyme neuroborreliosis Age: Test positive: 41 (10-76) Test negative: 40 (8-81)	n=42 Seronegative with no history of Lyme disease (n=22) Evaluated for possible herpes simplex virus encephalitis (n=20)	PCR	PCR	CSF	Clinical diagnosis	
Nohlmans 1994[334]	n=44 Early Lyme disease (EM, n=13) Late Lyme disease (arthralgia, arthritis, ACA, n=21) Age: not reported	n=84 Healthy controls	EIA IFA	*IgM and IgG* Dako EIA Diamedix EIA Whittaker EIA Diagast EIA	Serum	Clinical diagnosis	
Oksi 1995[344]	n=41 Late Lyme disease Age: 37.6 years (4-76)	n=37 Healthy controls	ELISA	*IgM and IgG* In house sonicate antigen ELISA (IgM, IgG, or both) 41-kDa flagellin ELISA	Serum	Diagnosis based on clinical symptoms and positive culture or PCR	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				(IgM, IgG, or both; DAKO) Recombinant P39 protein ELISA (ImmunoWeLL)			
Padula 1994[349]	n=74 EM	n=76 Healthy individuals (n=70) Severe periodontitis (n=6)	ELISA IB	*IgM and IgG* Whole cell ELISA (IgM and IgG) rOspC ELISA (IgM) IgM and IgG immunoblot assays	Serum	Culture	
Panelius 2001[355]	n=28 Lyme neuroborreliosis (n=14) LA (n=14) Age: not reported	n=23 Syphilis (n=10) Healthy donors (n=13)	ELISA WB	*IgM and IgG* IgG and IgM Western blot with rFlaA antigen IgG and IgM rFlaA ELISA	Serum	Clinical diagnosis (based on CDC guidelines)	
Panelius 2008[356]	n=102 EM (n=25) Lyme neuroborreliosis (n=67) ACA (n=10) Age: not reported	n=40 Blood donors (n=20) CSF samples from healthy individuals (n=20)	ELISA IB	Recombinant IgG OspE ELISA	Serum CSF	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Peltomaa 2004[364]	n=47 Lyme facial paralysis	n=86 Healthy subjects	Western blot	IgM and IgG Western blot (MarDx)	Serum	Clinical diagnosis (based on CDC criteria)	
Phillips 1998[371]	n=47 Lyme disease and had failed or relapsed after extended oral and intravenous antibiotic therapy Age: median 35 years (4-74)	n=23 Chronic illnesses other than Lyme disease	Culture	Culture	Blood	Clinical diagnosis	
Pomelova 2015[382]	n=146 EM	n=197 Blood donors	ELISA	C6 Lyme ELISA Kit (Immunetics; IgM/IgG)	Serum	Clinical diagnosis	
Porwancher 2011[383]	n=242 Culture-proven early acute Lyme (n=79) Early convalescent-phase (n=78) Culture-proven EM (n=4) Stage-II and III Lyme (n=47) Sera from people receiving treatment (PTLDS, n=34) Age: not reported	n=794 Healthy blood donors from New Mexico (n=300) Healthy blood donors from New England (n=300) People undergoing	WB ELISA	*IgM and IgG* MarDX IgM and IgG WB MarDx Diagnostics Inc., USA	Serum	Culture (only n=83) Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
		routine screening (n=99) EBV (n=20) Toxoplasmosis (n=10) RA (n=10) ANA-positive (n=10) Leptospirosis (n=10) Syphilis (n=10) Rubella (n=10) Other conditions (n=15)					
Priem 1997[384]	n=22 Lyme neuroborreliosis Age (mean, neuroborreliosis only): 44 (7-82)	n=58 Rheumatic diseases (n=37) Central nervous system diseases (n=21)	PCR	PCR	CSF	Clinical diagnosis	
Rauer 1995[392]	n=210 EM (n=118) Lyme neuroborreliosis	n=82 No current symptoms/h	ELISA	P83-ELISA (IgM and IgG)	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	(n=33) LA (n=17) ACA (n=42) Age: not reported	istory of Lyme disease					
Rauer 1998[393]	n=104 EM Age: not reported	n=154 Healthy controls	ELISA	IgM ELISA OspC-14-kDa antigen ELISA	Serum	Clinical diagnosis	
Roux 2007[406]	n=11 Lyme meningoradiculitis Age (mean): 62 years (SD 15)	n=16 Consecutive people referred for suspected Lyme meningoradiculitis	ELISA EIA WB	*IgM and IgG* VIDAS ELISA (IgM and IgG together) Dade-Behring enzyme immunoassay (EIA Enzygnost Borreliosis) IgM and IgG separately In-house IgG immunoblot (western blot)	Serum CSF	Clinical diagnosis	Median CRP: 4 mg/L (3-228) Pleocytosis of an average of 120 elements (range 9-380) Protein levels in CSF (mean): 0.84 g/L (0.4-1.53)
Russell 1984[409]	n=45 Lyme disease	n=100 Well persons	ELISA IF	*IgM and IgG* ELISA IFA	Serum	Clinical diagnosis	
Ruzic-Sabljic 2002[411]	n=117 EM	n=96 Healthy persons	IF WB	*IgM and IgG* In-house indirect IF test (IgG and IgM)	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Age: not reported			Western blot (Mikrogen; IgG and IgM)			
Sapi 2013[416]	n=72 Lyme disease Age (mean, range): 42 years (3-80)	n=48 Healthy persons	Culture	Culture	Blood	Clinical diagnosis	
Schnarr 2001[422]	n=16 Lyme arthritis Age: not reported	n=31 Rheumatoid arthritis	PCR	PCR	Synovial fluid	Clinical diagnosis	
Schulte-Spechtel 2004[423] [Schulte-Spechtel 2003[424]]	n=36 Neuroborreliosis Age: not reported	n=67 Blood donors (n=49) Syphilis (n=10) Rheumatoid factor (n=8)	Immunoblot	*IgG* New recombinant immunoblot Old recombinant immunoblot Whole cell lysate immunoblot	Serum	Clinical diagnosis	
Schwartz 1992[431]	n=35 Untreated EM Age: not reported	n=10 Undergoing plastic surgery	PCR	PCR	Skin biopsy	Clinical diagnosis	Treated EM and rashes of uncertain aetiology not included in the analysis
Senel 2010[433]	n=37	n=89	CXCL13	ELISA (Quantikine, R&D Systems) for detection of	CSF	Clinical diagnosis	CSF/serum albumin

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Definite neuroborreliosis (n=28) Systemic borreliosis (n=9) Age: 58 years (32-70)	CNS bacterial infections (n=16) Viral CNS diseases (n=18) Guillain-Barré syndrome (n=11) Bell's palsy (n=19) Other cranial nerve palsies (n=5) Cephalgia (n=20)		CXCL13			concentration ratio for neuroborreliosis: (x10^-3): 13.8 (9.7-23.3)
Sillanpaa 2007[439]	n=70 European people: EM (n=42) neuroborreliosis (n=14) LA (n=14)	n=83 Syphilis (n=10) Rheumatoid factor (n=8) Anti-streptolysin antibodies (n=13) EBV (n=11) Anti-nuclear	ELISA	*IgG* Quick ELISA C6 (Immunetics)	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
		antibodies (n=12) Salmonella (n=5) Yersinia enterocolitica (n=4) Healthy blood donors (n=20)					
Sivak 1996[443]	n=44 EM Age: not reported	n=272 Asymptomatic healthy controls	Immunoblot	*IgM* Immunoblot assay MarDx Diagnostics, USA	Serum	Culture	
Smismans 2006[448]	n=45 Early localised cutaneous (n=23) Early disseminated (n=22): arthritis (n=2), cranial neuritis (n=9), radiculoneuropathy (n=3), EM with dissemination (n=7), polyneuropathy (n1) Age: not reported	n=40 Epstein-Barr virus (n=10) Acute cytomegalovirus (n=10) Syphilis (n=10) Rheumatoid factor positivity (n=10)	Immunoassays	*IgM and IgG* QuickEL-ISA C6 *Borrelia* kit (Immunetics) IDEIA *B. burgdorferi* IgM IDEIA *B. burgdorferi* IgG (Dako) *B. burgdorferi* second-generation IgM *B. burgdorferi* second-generation IgG (Serion)	Serum	Clinical diagnosis	
Stanek 1999[455]	n=99	n=100	EIA	In-house EIA (IgG and	Serum	Clinical	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	EM Age: Female: (n=55): median 49 years (10-80) Male (n=44): median 51 (18-77)	Blood donors		IgM)		diagnosis	
Steere 2008[458]	n=134 EM (n=76) Acute neurologic or cardiac involvement (n=13) Arthritis or chronic neurologic involvement (n=31) Post-Lyme disease symptoms (n=14)	n=136 Healthy subjects	ELISA	*IgG and IgM* Sonicate ELISA VlsE C6 peptide ELISA	Serum	EM: CDC criteria and culture-positive	Only people with EM received reference standard Positive 2-tier serology required for case inclusion of neurologic, cardiac or joint involvement
Stiernstedt 1986[463] [Stiernstedt 1985[462]]	n=26 EM Age (median): 38 years (18-66)	n=63 (for IFA) n=120 (for ELISA)	ELISA IF	*IgM and IgG* ELISA IF	Serum	Clinical diagnosis	Median time from onset: 5 weeks (3 days to 18 weeks) WBC count >10x10^9/L: n=1 (4%) ESR >20 mm/h: n=6 (24%)
Stricker 2001[466]	n=83	n=22	CD57	CD57	Not	Clinical	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Acute Lyme disease (n=10) Chronic Lyme disease (n=73) Age (mean): Acute Lyme disease: Male: 36 (13-52) Female: 43 (37-50) Chronic Lyme disease: Male: 45 (14-71) Female: 43 (15-76)	People with AIDS			reported	diagnosis (based on CDC criteria)	
Tjernberg 2007[475]	n=273 EM (n=158) neuroborreliosis (n=26) Acrodermatitis (n=9) Lyme arthritis (n=3) Possible Lyme disease (n=31) Age (median): 54.5 years (4-85)	n=200 Blood donors	ELISA CLIA	*IgM and IgG* Quick ELISA C6 *Borrelia* assay kit (Immunetics) Virotech *Borrelia* burgdorferi ELISA (IgG/IgM test kit (Genzyme Virotech) LIAISON *Borrelia* IgM IgG CLIA	Serum	Clinical diagnosis	
Tjernberg 2009[477]	n=148 EM Age: median 58 years (7-84)	n=200 Blood donors	ELISA	C6 ELISA (Immunetics)	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Trevejo 2001[481]	n=74 EM Acute phase (n=66) Convalescent phase (n=55) Age: median 41 years (3-83)	n=38 Healthy controls	EIA WB	*IgM and IgG* Vidas bioMerieux, France Marblot MarDx Diagnostics, USA	Serum	Clinical diagnosis	Simplified approach – only equivocal results on ELISA were tested by Immunoblot Acute phase sera taken a median of 4 days after illness onset (range 0-19); convalescent sera taken a median of 36 days after illness onset (range 21-161)
van Burgel 2011[492]	n=95 Lyme neuroborreliosis (n=59) Lyme borreliosis (n=36) Age (mean, SD): Lyme neuroborreliosis: 39 years (SD 24) LB: 51 years (SD 17)	n=143 Infectious meningitis/encephalitis (n=69) Neurological controls (n=74)	ELISA	*IgM and IgG* C6 Lyme ELISA kit (Immunetics)	Serum CSF	Lyme neuroborreliosis: 4 of the following 5 criteria: detection of *B. burgdorferi* antibodies in serum, CSF pleocytosis, absence of other evident cause of meningitis,	Reference standard for people with Lyme disease not reported CSF Leukos (per microliter; mean): Neuroborreliosis: 135 (SD 159) LB: 1 (SD 1)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
						evidence of intrathecal production of specific *B. burgdorferi* antibodies, objective neurological complaints with favourable outcome after treatment	
van der Heijden 1999[493]	n=4 Lyme arthritis Age (median): 28 years (17-38)	n=9 Other arthritis forms	PCR	PCR	Synovial fluid and tissue	Clinical diagnosis	Time point: median disease duration 9 months (4-60)
Vasiliu 1998[494]	n=20 LA Age (mean): 39.2 years (SD 13.2)	n=10 Rheumatic diseases	PCR	PCR	Synovial fluid	Clinical diagnosis	
von Baehr 2012[497]	n=94 EM (n=28) Acute mono-arthritis (n=14) Bannwarth's syndrome (n=6) Migrating arthromyalgias	n=208 Blood donors (n=120) Autoimmune diseases	Lymphocyte transformation test	Lymphocyte transformation test	Venous blood	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	(n=34) Facial palsy (n=5) Acute neuroborreliosis (n=7)	(n=40) Seropositive clinically healthy outdoor workers (n=48)					
von Stedingk 1995[498]	n=62 EM (n=26) ACA (n=36) Age: not reported	n=76 Skin removed during plastic surgery (n=67) Volunteers among medical staff (n=5) Non-*Borrelial* disorders (n=4)	PCR	PCR assay	Skin biopsy	Clinical diagnosis	76 skin samples from 10 control subjects Duration of EM at time of biopsy: median 2 weeks (2 days – 10 months) Duration of ACA lesions at time of biopsy: median 1.5 years (3 months – over 10 years)
Widhe 2004[510]	n=56 Lyme neuroborreliosis (n=39) EM (n=12) ACA (n=5) Age: not reported	n=23 Healthy blood donors	ELISA	*IgM and IgG* ELISA	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Wilske 1993[517]	n=134 EM (n=31) Lyme neuroborreliosis (n=60) Late Lyme disease: LA (n=24) ACA (n=19) Age: not reported	n=142 Blood donors (n=100) Antibodies against T. pallidum (n=20) Antibodies against Epstein-Barr virus (n=12) Rheumatoid factor (n=10)	IF ELISA IB	*IgM and IgG* Indirect immunofluorescence absorption test (IgG and IgM) OGP-ELISA (IgG and IgM) FLA-ELISA (IgG and IgM) Recombinant immunoblot (IgG) Recombinant immunoblot (IgM)	Serum	Clinical diagnosis	
Wilske 1999[519]	n=147 EM (n=66) Lyme neuroborreliosis (n=42) Acrodermatitis (n=29) LA (n=10) Age: not reported	n=139 Blood donors (n=118) Syphilis (n=11) Rheumatoid factor (n=10)	Immunoblot	*IgG* Whole cell lysate immunoblot Old Recombinant immunoblot (p83/100, p39, OspC, p41i) New Recombinant immunoblot (Osp17, p58; IgG)	Serum	Clinical diagnosis	

Table 3: Summary of included cross-sectional studies (adults)

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
Bil-Lula 2015[24]	n=577 Age (median): 45 years (20-65)	*Borrelia burgdorferi sensu lato* infection	PCR ELISA WB	*IgM and IgG* Real Time 7000 PCR System v 1.1 Life Technologies, USA Anti-*Borrelia* plus VIse ELISA (IgG) Anti-*Borrelia* ELISA (IgM) Euroimmun, Poland Western blot (confirmatory test: only ELISA-positive results tested) Euroline *Borrelia*-RN-AT test Euroimmun, Poland	Serum	CDC recommendation: clinical diagnosis (erythema migrans, palsy of facial nerve or arthritis), medical history, assessment of risk exposure, diagnostic tests including the assessment of antibodies to *Borrelia* spp class IgM and IgG	PCR used as reference standard Borderline results included as positive
Blaauw 1999[27]	n=105 Diagnosed or suspected chronic Lyme with musculoskeletal complaints Age (mean): 48.7 years (6-82)	Lyme disease	ELISA	*IgG* ELISA Dako, Denmark	Serum	Clinical diagnosis	Included in unspecified Lyme disease forest plot as people exhibited a variety of different signs and symptoms Previous Lyme disease not

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
							included in the analysis as there was no reference standard
Brunner 2001[39]	n=169 People evaluated for Lyme disease at the Robert Wood Johnson Medical Center; CDC prevention collection Age: not reported	Lyme disease	ELISA Western blot/Immunoblot	*IgM and IgG* MarDX ELISA (IgM/IgG) CDC flagellin-enriched ELISA MarDX Diagnostics, USA	Serum	Clinical diagnosis: active Lyme disease (present or previous EM plus early or late dissemination), previous Lyme disease (successfully treated with antibiotics)	
Gyllemark 2017[154]	n=165 Definite Lyme neuroborreliosis (n=49), possible neuroborreliosis (n=28), non-neuroborreliosis (n=88) Age, median (range): Definite neuroborreliosis: 32 years (4-72 Possible	Neuroborreliosis	CXCL13	CXCL13	CSF	Definite neuroborreliosis: CSF pleocytosis and *Borrelia*-specific antibodies in CSF Possible neuroborreliosis: symptoms strongly	Duration of symptoms (median, range): Definite neuroborreliosis: 2 weeks (0.1-104) Possible neuroborreliosis with pleocytosis: 0.5 weeks (0.1-3.0) Possible neuroborreliosis

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
	neuroborreliosis with pleocytosis: 8.5 years (3-39) Possible neuroborreliosis without pleocytosis: 62 years (32-82) Non- neuroborreliosis: 23 years (1-83)					suggestive of neuroborreliosis, short duration of symptoms and CSF pleocytosis but not *Borrelia*-specific antibodies in CSF Possible neuroborreliosis: *Borrelia*-specific antibodies in CSF, but no pleocytosis and symptoms were less suggestive of neuroborreliosis	with AI: 2.0 weeks (0.1-156) Non-neuroborreliosis: 4.0 weeks (0.1-520) Possible neuroborreliosis without pleocytosis not included in analysis
Henningsson 2014[175]	n=175 Definite neuroborreliosis (n=52) Possible neuroborreliosis (n=4)	Neuroborreliosis	EIA	*IgM and IgG* IDEIA Lyme neuroborreliosis VIDAS IgG	CSF Serum	Clinical diagnosis	Non-Lyme neuroborreliosis people with pleocytosis for other reasons were used as the control group

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
	Healthy blood donors (n=90) Pleocytosis for other reasons (n=29) Age (median): Definite neuroborreliosis: 39 years (3-85) Possible neuroborreliosis: 30 years (4-49)			bioMerieux, France recomBead *Borrelia* IgM and IgG assay Mikrogen, Germany			in the analysis Equivocal results regarded as positive by the authors
Henningsson 2016[176]	n=135 Definite Lyme neuroborreliosis (n=35), possible neuroborreliosis (n=43), non-neuroborreliosis (n=83) Age (median, range): Definite neuroborreliosis: 38 years (3-72) Possible neuroborreliosis with pleocytosis: 21 years (3-55) Possible neuroborreliosis with AI: 64 years (50-81)	Neuroborreliosis	CXCL13	CXCL13 Quantikine ELISA, R&D Systems, USA CXCL13 RecomBead, Mikrogen, Germany	CSF	Definite Lyme neuroborreliosis: according to European guidelines Possible Lyme neuroborreliosis: Clinical diagnosis based on CSF pleocytosis and neurological symptoms strongly suggestive	Duration of symptoms (median, range): Definite neuroborreliosis: 14 days (2-730) Possible neuroborreliosis with pleocytosis: 5 days (1-28) Possible neuroborreliosis with AI: 294 days (21-730) Non-neuroborreliosis: 28 days (1-3650) Possible neuroborreliosis with AI not

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
	Non-neuroborreliosis: 39 years (1-83)					of neuroborreliosis but normal AI Possible Lyme neuroborreliosis: based on elevated *Borrelia*-specific AI but no CSF pleocytosis	included in analysis
Ljostad 2008[253]	n=59 Definite neuroborreliosis (n=37) Probable neuroborreliosis (n=7) Not neuroborreliosis (n=8) >18 years	Neuroborreliosis	CXCL13	ELISA (Quantikine, R&D Systems) for detection of CXCL13	CSF	Clinical diagnosis based on criteria: New neurological symptoms & objective findings suggestive of neuroborreliosis Lymphocytic pleocytosis (>5 leucocytes/ mm3) Intrarthecal *Borrelia* antibody	

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
						production	
Nordberg 2012[335]	n=117 Suspected neuroborreliosis Age (median): 58 years (6-87)	Neuroborreliosis	ELISPOT	IFN-gamma ELISPOT	CSF	Clinical diagnosis plus CSF lymphocytic pleocytosis ≥5 mononuclear leucocytes per µL and intrathecal production of specific anti-*Borrelia* IgG antibodies	
Tjernberg 2011[474]	n=261 People examined for suspected Lyme neuroborreliosis Age (range) 2-87 years	Lyme neuroborreliosis	ELISA CXCL13	CXCL13 measured by ELISA (Quantikine, R&D Systems) IgG and IgM C6 Lyme ELISA kit (Immunestics)	CSF Serum	European Federation of Neurological Societies guidelines	Samples had been stored for 3-6 years

Table 4: Summary of included case-control studies (children)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Gerber 1995[129]	n=82 EM Age (median): 6 years (1-18)	n=50	ELISA IB	IgM WC ELISA rOspC ELISA	Serum	Clinical diagnosis	Time point: samples collected 0-30 days after EM was first detected

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Children			Immunoblot			
Heikkilä 2002[172]	n=52 Lyme arthritis Children	n=40	ELISA	IgG ELISA Boehringer Mannheim, Germany	Serum	Clinical diagnosis Plus: Neuroborreliosis and LA: ELISA positive EM: PCR confirmed	
Krbkova 2016[211]	n=116 Proven neuroborreliosis (n=86) Suspicion of neuroborreliosis (n=30) Children	n=66 Other neuroinfections	ELISA WB	IgM and IgG EIA *Borrelia* garinii Testline, Czech Republic Updated ELISA Testline, Czech Republic Western blot EUROIMMUN Germany	CSF Serum	Clinical diagnosis	Suspicion of neuroborreliosis not included in analysis because there is no clear reference standard
Skogman 2008[446]	n=24 Children with confirmed neuroborreliosis (n=24)	n=36 Children with other neurological diseases (n=20) Adults with no proven infection (n=16)	ELISA	IgG ELISA Antigen panel (DbpA, BBK32, OspC, IR6) Positive if ≥2, negative if ≤1	Serum CSF	Clinical diagnosis (based on clinical features and lab findings)	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Wutte 2011[532]	n=22 Definite neuroborreliosis Children (n=15), adults (n=7)	n=300 Healthy blood donors	CXCL13	CXCL13 ELISA Quantikine, Germany	Serum	Clinical diagnosis German Neurological Society guidelines	15 children, 7 adults Time point: mean duration of illness was 3 days (1-7) CSF leukos (median, range): Definite neuroborreliosis: 116 (4-501) Blood donors: not done Probable neuroborreliosis: 70 (20-267) Seropos controls: 3 (0-174) Seroneg controls: 51 (1-624) Other diagnoses: 4 (0-213)

Table 5: Summary of included cross-sectional studies (children)

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
Avery 2006[16]	n=108	Lyme meningitis	PCR	PCR	CSF	Clinical diagnosis	

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
	Meningitis and suspected Lyme disease (defined as both Lyme serology and Lyme CSF-PCR ordered by physician) Children					(EM) plus positive serology	
Barstad 2017[18]	n=210 Neuroborreliosis or other possible causes of aseptic meningitis were suspected based on symptoms identified by attending physician and if a lumbar puncture and a Bb Ab in the CSF were ordered for clinical reasons Children	Neuroborreliosis	CXCL13	CXCL13	CSF	Clinical diagnosis	Children who had antibiotics prior to admission were excluded Trained physician assessing samples was blinded to all other variables Youden index performed to determine best cut-off values for CXCL13
Bennet 2008[21]	n=267 Children	Neuroborreliosis	ELISA	IgM and IgG IDEIA *B burgdorferi* IgG and IgM Oxoid td, UK IDEIA Lyme neuroborreliosis Oxoid Ltd, UK	CSF Serum	Clinical assessment Based on history, presenting symptoms, clinical examinations, CSF and	Unclear if samples taken before beginning of antibiotic treatment

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
						serum analyses, response to antibiotic treatment	
Lipsett 2016 [243]	n=944 Children and adolescents undergoing serologic evaluation for Lyme disease Age (median and IQR): 10.9 (6.4-15.2) years	Lyme disease	EIA Immunoblot	Whole cell sonicate Lyme EIA (MarDx; Trinity Biotech) C6 Lyme EIA test (Immunetics)	Serum	Clinician-diagnosed EM or a positive 2-tiered serologic result in the presence of a Lyme disease-associated clinical syndrome	Unclear what proportion of the Lyme disease people were clinically diagnosed versus seropositive and Lyme disease associated syndrome

Table 6: Additional data that could not be included in the forest plots (Tumani 1995[485])

Study	Population and target condition	Control group	Tests	Results	Comments
Tumani 1995[485]	n=24 Acute neuroborreliosis (25% recalled a tick bite) No reference standard Age: not reported	n=73 Disease controls (n=45) Healthy controls (n=28)	Bb-IgM-AI Bb-IgG-AI All CSF values 3 out of 4 CSF values	Sensitivity: 0.79 Specificity: 0.96 Sensitivity: 0.63 Specificity: 0.89 Sensitivity: 0.70 Specificity: 0.98 Sensitivity: 0.80 Specificity: 0.98	CSF values (lymphocytic pleocytosis, activated B-cells with IgM predominance in CSF, intrathecal humoral immune response with IgM predominance, blood-CSF barrier dysfunction)

See appendix D for full evidence tables.

1.3.4 Quality assessment of clinical studies included in the evidence review

Table 7: Clinical evidence summary: initial tests for Lyme disease (adults, cross-sectional studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Neuroborreliosis: ELISA (IgM/IgG)				
Henningsson 2014 (recomBead; serum)	81	LOW[1] due to very serious risk of bias	0.87 [0.74-0.94]	0.76 [0.56-0.90]
Henningsson 2014 (VIDAS; serum)	81	LOW[1] due to very serious risk of bias	0.92 [0.81-0.98]	0.72 [0.53-0.87]
Neuroborreliosis: ELISA (IgG) – antibody index				
Henningsson 2014 (VIDAS; CSF/serum)	81	LOW[1] due to very serious risk of bias	0.87 [0.74-0.94]	0.93 [0.77-0.99]
Neuroborreliosis: ELISA (IgM/IgG) – antibody index				
Henningsson 2014 (IDEIA; CSF/serum)	81	LOW[1] due to very serious risk of bias	0.92 [0.81-0.98]	0.97 [0.82-1.00]
Henningsson 2014 (recomBead; CSF/serum)	81	LOW[1] due to very serious risk of bias	1.00 [0.93-1.00]	0.90 [0.73-0.98]
Neuroborreliosis: ELISA C6				
Tjernberg 2011 (CSF)	216	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.94 [0.89-0.98]	0.98 [0.92-1.00]
Neuroborreliosis: ELISPOT				
Nordberg 2012 (cut-off 10 spots or more; CSF)	117	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.21 [0.05-0.51]	0.92 [0.85-0.97]
Nordberg 2012 (cut-off 5 spots or more; CSF)	117	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.36 [0.13-0.65]	0.82 [0.73-0.89]
Neuroborreliosis: CXCL13				
Gyllemark 2017 (cut-off >142 pg/ml; CSF)	151	LOW[1]	0.84 [0.73-0.92]	0.99 [0.94-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Gyllemark 2017 (cut-off >250 pg/ml; CSF)	151	LOW[1] due to very serious risk of bias	0.81 [0.69-0.90]	1.00 [0.96-1.00]
Henningsson 2016 (Quantikine; CSF)	126	LOW[1] due to very serious risk of bias	0.91 [0.78-0.97]	1.00 [0.96-1.00]
Henningsson 2016 (RecomBead; CSF)	126	LOW[1] due to very serious risk of bias	0.93 [0.81-0.99]	1.00 [0.96-1.00]
Ljostad 2008 (CSF)	45	LOW[1] due to very serious risk of bias	1.00 [0.91-1.00]	0.63 [0.24-0.91]
Tjernberg 2011 (CSF)	216	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.98 [0.94-1.00]	0.98 [0.92-1.00]
Unspecified Lyme disease: ELISA (IgM)				
Bil-Lula 2015 (serum)	577	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.33 [0.13-0.59]	0.71 [0.67-0.75]
Brunner 2001 (CDC; serum)	37	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.78 [0.40-0.97]	0.43 [0.24-0.63]
Brunner 2001 (RWJM; serum)	131	LOW[1] due to very serious risk of bias	0.66 [0.53-0.77]	0.76 [0.64-0.86]
Unspecified Lyme disease: ELISA (IgG)				
Bil-Lula 2015 (serum)	577	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.39 [0.17-0.64]	0.61 [0.56-0.65]
Blaauw 1999 (serum)	54	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.73 [0.57-0.85]
Brunner 2001 (CDC; serum)	37	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.78 [0.40-0.97]	0.57 [0.37-0.76]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Brunner (RWJM; serum)	131	LOW[1] due to very serious risk of bias	0.58 [0.45-0.70]	0.87 [0.76-0.94]
Unspecified Lyme disease: ELISA (IgM/IgG)				
Brunner 2001 (CDC; serum)	38	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.66-1.00]	0.17 [0.06-0.36]
Unspecified Lyme disease: Immunoblot (IgM)				
Bil-Lula 2015 (serum)	577	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.22 [0.06-0.48]	0.84 [0.81-0.87]
Brunner 2001 (CDC; serum)	38	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.56 [0.21-0.86]	0.62 [0.42-0.79]
Brunner 2001 (RWJM; serum)	131	LOW[1] due to very serious risk of bias	0.58 [0.45-0.70]	0.84 [0.73-0.92]
Unspecified Lyme disease: Immunoblot (IgG)				
Bil-Lula 2015 (serum)	577	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.61 [0.36-0.83]	0.45 [0.41-0.49]
Brunner 2001 (CDC; serum)	38	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.89 [0.52-1.00]	0.59 [0.39-0.76]
Brunner 2001 (RWJM; serum)	131	LOW[1] due to very serious risk of bias	0.44 [0.31-0.57]	0.93 [0.83-0.98]

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) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect.*
3) *Imprecision was assessed based on inspection of the confidence interval of sensitivity in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%.*
4) *Inconsistency could not be assessed, as the committee was unable to set a sensitivity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

Table 8: Clinical evidence summary: initial tests for Lyme disease (adults, case-control studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Erythema migrans: ELISA (IgM):				
Ang 2015 (Diacheck; serum)	28	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.25]	1.00 [0.78-1.00]
Ang 2015 (Enzygnost; serum)	188	VERY LOW[1] due to very serious risk of bias	0.14 [0.07-0.23]	0.91 [0.83-0.95]
Ang 2015 (Euroimmun; serum)	15	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.52]	1.00 [0.69-1.00]
Ang 2015 (Liaison; serum)	284	VERY LOW[1] due to very serious risk of bias	0.09 [0.03-0.19]	0.97 [0.94-0.99]
Ang 2015 (Medac; serum)	123	VERY LOW[1] due to very serious risk of bias	0.13 [0.04-0.30]	0.99 [0.94-1.00]
Ang 2015 (Mikrogen; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.52]	1.00 [0.78-1.00]
Ang 2015 (Serion; serum)	142	VERY LOW[1] due to very serious risk of bias	0.50 [0.33-0.67]	0.73 [0.63-0.81]
Ang 2015 (Virotech; serum)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.08 [0.00-0.36]	1.00 [0.77-1.00]
Asbrink 1985 (before treatment; serum)	273	VERY LOW[1] due to very serious risk of bias	0.11 [0.06-0.20]	0.95 [0.91-0.98]
Bacon 2003 (acute EM; rVlsE; serum)	292	VERY LOW[1] due to very serious risk of bias	0.09 [0.02-0.23]	0.98 [0.96-0.99]
Bacon 2003 (acute EM; serum)	292	VERY LOW[1] due to very serious risk of bias	0.20 [0.08-0.37]	1.00 [0.99-1.00]
Bacon 2003 (convalescent EM; rVlsE; serum)	314	VERY LOW[1] due to very serious risk of bias	0.42 [0.29-0.56]	0.98 [0.96-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Bacon 2003 (convalescent EM; serum)	314	VERY LOW[1] due to very serious risk of bias	0.40 [0.28-0.54]	1.00 [0.99-1.00]
Branda 2013 (EU; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.19-0.64]	0.98 [0.93-1.00]
Christova 2003 (serum)	195	VERY LOW[1] due to very serious risk of bias	0.49 [0.39-0.59]	0.93 [0.86-0.98]
Flisiak 1996 (flagella; serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.61 [0.36-0.83]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.39 [0.17-0.64]	0.70 [0.50-0.86]
Fung 1994 (acute disseminated; serum)	165	VERY LOW[1] due to very serious risk of bias	0.61 [0.47-0.73]	0.98 [0.93-1.00]
Fung 1994 (acute localised; serum)	122	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.25 [0.07-0.52]	0.98 [0.93-1.00]
Fung 1994 (convalescent disseminated; serum)	165	VERY LOW[1] due to very serious risk of bias	0.80 [0.67-0.89]	0.98 [0.93-1.00]
Fung 1994 (convalescent localised; serum)	122	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.50 [0.25-0.75]	0.98 [0.93-1.00]
Goossens 2000 (Behring; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.77 [0.56-0.91]	0.98 [0.91-1.00]
Goossens 2000 (Boehringer; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.17-0.56]	1.00 [0.94-1.00]
Goossens 2000 (Dako; serum)	88	VERY LOW[1,3] due to very serious risk of bias and	0.65 [0.44-0.83]	0.95 [0.87-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Goossens 2000 (Genzyme Virotech; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.81 [0.61-0.93]	0.98 [0.91-1.00]
Goossens 2000 (IBL; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.65 [0.44-0.83]	0.90 [0.80-0.96]
Hansen 1989 (flagellum; multiple; serum)	216	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.41-0.89]	0.95 [0.91-0.98]
Hansen 1989 (flagellum; serum)	307	VERY LOW[1] due to very serious risk of bias	0.45 [0.35-0.55]	0.95 [0.91-0.98]
Hansen 1989 (flagellum; single; serum)	291	VERY LOW[1] due to very serious risk of bias	0.40 [0.29-0.50]	0.95 [0.91-0.98]
Hansen 1989 (sonic; serum)	307	VERY LOW[1] due to very serious risk of bias	0.17 [0.10-0.25]	0.94 [0.90-0.97]
Hansen 1991 (serum)	250	VERY LOW[1] due to very serious risk of bias	0.64 [0.49-0.77]	1.00 [0.98-1.00]
Hernandez-Novoa 2003 (localised; serum)	153	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.19-0.59]	0.95 [0.89-0.98]
Hunfeld 2002 (serum)	1255	VERY LOW[1] due to very serious risk of bias	0.61 [0.53-0.69]	0.92 [0.90-0.94]
Karlsson 1989a (capture ELISA; serum)	103	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.33 [0.17-0.53]	0.97 [0.90-1.00]
Karlsson 1989a (indirect ELISA; serum)	103	VERY LOW[1] due to very serious risk of bias	0.27 [0.12-0.46]	0.90 [0.81-0.96]
Lange 1992 (flagellum; serum)	136	VERY LOW[1] due to very serious risk of bias	0.33 [0.19-0.51]	0.94 [0.87-0.98]
Lange 1992 (sonicated; serum)	136	VERY LOW[1]	0.28 [0.14-0.45]	0.96 [0.90-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.63 [0.49-0.76]	0.98 [0.91-1.00]
Liu 2013 (serum)	344	VERY LOW[1] due to very serious risk of bias	0.58 [0.43-0.71]	0.80 [0.75-0.85]
Magnarelli 1988 (serum)	179	VERY LOW[1] due to very serious risk of bias	0.84 [0.76-0.91]	0.58 [0.47-0.70]
Marangoni 2005 (Enzygnost; serum)	329	VERY LOW[1] due to very serious risk of bias	0.71 [0.60-0.79]	0.96 [0.93-0.98]
Marangoni 2005 (RecomWell; serum)	329	VERY LOW[1] due to very serious risk of bias	0.56 [0.45-0.66]	1.00 [0.98-1.00]
Marangoni 2008 (serum)	366	VERY LOW[1] due to very serious risk of bias	0.55 [0.42-0.67]	0.97 [0.94-0.98]
Mathiesen 1996 (serum)	147	VERY LOW[1] due to very serious risk of bias	0.40 [0.26-0.56]	0.99 [0.95-1.00]
Molins 2017 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.60 [0.43-0.75]	0.89 [0.83-0.93]
Molins 2017 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.79 [0.63-0.90]	0.89 [0.83-0.93]
Rauer 1995 (recombinant; serum)	200	VERY LOW[1] due to very serious risk of bias	0.06 [0.02-0.12]	0.96 [0.90-0.99]
Rauer 1998 (recombinant; serum)	258	VERY LOW[1] due to very serious risk of bias	0.46 [0.36-0.56]	0.95 [0.90-0.98]
Rauer 1998 (whole-cell; serum)	258	VERY LOW[1] due to very serious risk of bias	0.45 [0.35-0.55]	0.95 [0.90-0.98]
Smismans 2006 (purified; serum)	63	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.61 [0.39-0.80]	0.78 [0.62-0.89]
Smismans 2006 (synthetic C6; serum)	63	VERY LOW[1] due to very serious risk of bias	0.91 [0.72-0.99]	0.93 [0.80-0.98]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Smismans 2006 (whole-cell; serum)	63	VERY LOW[1] due to very serious risk of bias	0.91 [0.72-0.99]	0.53 [0.36-0.68]
Stanek 1999 (serum)	199	VERY LOW[1] due to very serious risk of bias	0.05 [0.02-0.11]	0.99 [0.95-1.00]
Stiernstedt 1986 (serum)	25	VERY LOW[1] due to very serious risk of bias	0.08 [0.01-0.26]	Cannot be estimated[5]
Widhe 2004 (serum)	28	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.80 [0.28-0.99]	1.00 [0.85-1.00]
Wilske 1993 (flagellin; serum)	173	VERY LOW[1] due to very serious risk of bias	0.39 [0.22-0.58]	0.96 [0.91-0.98]
Wilske 1993 (OGP-ELISA; serum)	173	VERY LOW[1] due to very serious risk of bias	0.45 [0.27-0.64]	0.97 [0.93-0.99]
Erythema migrans: ELISA (IgG)				
Asbrink 1985 (before treatment; serum)	273	VERY LOW[1] due to very serious risk of bias	0.18 [0.11-0.28]	0.95 [0.91-0.98]
Bacon 2003 (acute EM; rVlsE; serum)	292	VERY LOW[1] due to very serious risk of bias	0.20 [0.08-0.37]	0.99 [0.97-1.00]
Bacon 2003 (acute EM; serum)	292	VERY LOW[1] due to very serious risk of bias	0.43 [0.26-0.61]	1.00 [0.99-1.00]
Bacon 2003 (convalescent EM; rVlsE; serum)	314	VERY LOW[1] due to very serious risk of bias	0.44 [0.31-0.58]	0.99 [0.97-1.00]
Bacon 2003 (convalescent EM; serum)	314	VERY LOW[1] due to very serious risk of bias	0.58 [0.44-0.71]	1.00 [0.99-1.00]
Branda 2013 (EU; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.65 [0.41-0.85]	0.98 [0.93-1.00]
Christova 2003 (serum)	195	VERY LOW[1] due to very serious risk of bias	0.17 [0.10-0.26]	0.97 [0.91-0.99]
Flisiak 1996 (flagella; serum)	45	VERY LOW[1,3]	0.11 [0.01-0.35]	1.00 [0.87-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious imprecision		
Flisiak 1996 (recombinant; serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.33 [0.13-0.59]	1.00 [0.87-1.00]
Fung 1994 (acute disseminated; serum)	165	VERY LOW[1] due to very serious risk of bias	0.34 [0.22-0.47]	0.86 [0.78-0.92]
Fung 1994 (acute localised; serum)	122	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.11-0.59]	0.86 [0.78-0.92]
Fung 1994 (convalescent disseminated; serum)	165	VERY LOW[1] due to very serious risk of bias	0.51 [0.37-0.64]	0.86 [0.78-0.92]
Fung 1994 (convalescent localised; serum)	122	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.44 [0.20-0.70]	0.86 [0.78-0.92]
Goossens 2000 (Behring; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.48-0.86]	0.85 [0.74-0.93]
Goossens 2000 (Boehringer; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.20-0.59]	0.89 [0.78-0.95]
Goossens 2000 (Dako; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.50 [0.30-0.70]	0.97 [0.89-1.00]
Goossens 2000 (Genzyme Virotech; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.54 [0.33-0.73]	0.94 [0.84-0.98]
Goossens 2000 (IBL; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.27-0.67]	0.87 [0.76-0.94]
Hansen 1989 (flagellum; multiple; serum)	216	VERY LOW[1,3]	0.38 [0.15-0.65]	0.96 [0.92-0.98]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious imprecision		
Hansen 1989 (flagellum; serum)	307	VERY LOW[1] due to very serious risk of bias	0.36 [0.27-0.45]	0.96 [0.92-0.98]
Hansen 1989 (flagellum; single; serum)	291	VERY LOW[1] due to very serious risk of bias	0.36 [0.26-0.47]	0.96 [0.92-0.98]
Hansen 1989 (sonic; serum)	307	VERY LOW[1] due to very serious risk of bias	0.11 [0.06-0.19]	0.94 [0.90-0.97]
Hansen 1991 (serum)	250	VERY LOW[1] due to very serious risk of bias	0.56 [0.41-0.70]	1.00 [0.98-1.00]
Hernandez-Novoa 2003 (localised; serum)	153	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.21 [0.07-0.42]	0.57 [0.48-0.66]
Hunfeld 2002 (serum)	1255	VERY LOW[1] due to very serious risk of bias	0.22 [0.16-0.30]	0.95 [0.93-0.96]
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.43 [0.29-0.57]	0.98 [0.91-1.00]
Liu 2013 (serum)	344	VERY LOW[1] due to very serious risk of bias	0.79 [0.65-0.89]	0.77 [0.72-0.82]
Magnarelli 1988 (serum)	172	VERY LOW[1] due to very serious risk of bias	0.77 [0.67-0.85]	0.78 [0.67-0.87]
Magnarelli 1992 (biotin; recombinant; serum)	93	VERY LOW[1] due to very serious risk of bias	0.36 [0.23-0.50]	1.00 [0.91-1.00]
Magnarelli 1992 (biotin; whole-cell; serum)	93	VERY LOW[1] due to very serious risk of bias	0.38 [0.25-0.52]	1.00 [0.91-1.00]
Magnarelli 1992 (unabsorbed; recombinant; serum)	93	VERY LOW[1] due to very serious risk of bias	0.34 [0.22-0.48]	1.00 [0.91-1.00]
Magnarelli 1992 (unabsorbed; whole-cell; serum)	93	VERY LOW[1] due to very serious risk of bias	0.32 [0.20-0.46]	1.00 [0.91-1.00]
Marangoni 2005 (Enzygnost; serum)	329	VERY LOW[1]	0.37 [0.27-0.47]	0.88 [0.84-0.92]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Marangoni 2005 (RecomWell; serum)	329	VERY LOW[1] due to very serious risk of bias	0.58 [0.47-0.68]	0.97 [0.94-0.99]
Marangoni 2008 (serum)	366	VERY LOW[1] due to very serious risk of bias	0.56 [0.43-0.68]	0.98 [0.96-0.99]
Mathiesen 1996 (serum)	147	VERY LOW[1] due to very serious risk of bias	0.30 [0.17-0.45]	1.00 [0.96-1.00]
Molins 2017 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.50 [0.34-0.66]	0.98 [0.95-0.99]
Molins 2017 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.74 [0.57-0.87]	0.98 [0.95-0.99]
Nohlmans 1994 (Dako; serum)	97	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.62 [0.32-0.86]	0.99 [0.94-1.00]
Nohlmans 1994 (Diagast; serum)	97	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.96-1.00]
Panelius 2008 (acute; serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.60 [0.39-0.79]	1.00 [0.83-1.00]
Panelius 2008 (convalescent; serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.64 [0.43-0.82]	1.00 [0.83-1.00]
Rauer 1995 (recombinant; serum)	200	VERY LOW[1] due to very serious risk of bias	0.14 [0.08-0.21]	1.00 [0.96-1.00]
Sillanpaa 2007 (acute; serum)	125	VERY LOW[1] due to very serious risk of bias	0.60 [0.43-0.74]	1.00 [0.96-1.00]
Sillanpaa 2007 (convalescent; serum)	105	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.41 [0.21-0.64]	1.00 [0.96-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Smismans 2006 (purified; serum)	52	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.42 [0.15-0.72]	1.00 [0.91-1.00]
Smismans 2006 (synthetic C6; serum)	52	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.62-1.00]	0.93 [0.80-0.98]
Smismans 2006 (whole-cell; serum)	52	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.83 [0.52-0.98]	0.93 [0.80-0.98]
Stanek 1999 (serum)	199	VERY LOW[1] due to very serious risk of bias	0.24 [0.16-0.34]	0.95 [0.89-0.98]
Stiernstedt 1986 (serum)	25	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.07-0.41]	Cannot be estimated[5]
Widhe 2004 (serum)	28	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.20 [0.01-0.72]	1.00 [0.85-1.00]
Wilske 1993 (flagellin; serum)	173	VERY LOW[1] due to very serious risk of bias	0.39 [0.22-0.58]	0.94 [0.88-0.97]
Wilske 1993 (OGP-ELISA; serum)	173	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.19-0.55]	0.97 [0.93-0.99]
Erythema migrans: ELISA (IgM/IgG)				
Ang 2015 (Diacheck; serum)	28	VERY LOW[1] due to very serious risk of bias	0.92 [0.94-1.00]	0.93 [0.68-1.00]
Ang 2015 (Enzygnost; serum)	188	VERY LOW[1] due to very serious risk of bias	0.95 [0.88-0.99]	0.88 [0.80-0.93]
Ang 2015 (Euroimmun; serum)	19	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.80 [0.28-0.99]	0.86 [0.57-0.98]
Ang 2015 (Liaison; serum)	284	VERY LOW[1]	0.91 [0.81-0.97]	0.92 [0.87-0.95]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Ang 2015 (Medac; serum)	123	VERY LOW[1] due to very serious risk of bias	0.81 [0.63-0.93]	0.97 [0.91-0.99]
Ang 2015 (Mikrogen; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.48-1.00]	1.00 [0.78-1.00]
Ang 2015 (Serion; serum)	142	VERY LOW[1] due to very serious risk of bias	0.83 [0.67-0.94]	0.72 [0.62-0.80]
Ang 2015 (Virotech; serum)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	1.00 [0.77-1.00]
Branda 2010 (acute; serum)	301	VERY LOW[1] due to very serious risk of bias	0.43 [0.34-0.53]	0.96 [0.92-0.98]
Branda 2010 (convalescent; serum)	301	VERY LOW[1] due to very serious risk of bias	0.92 [0.84-0.96]	0.96 [0.92-0.98]
Branda 2011 (serum)	1414	VERY LOW[1] due to very serious risk of bias	0.56 [0.47-0.65]	0.98 [0.98-0.99]
Branda 2013 (EU; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.75 [0.51-0.91]	0.96 [0.90-0.99]
Branda 2013 (USA; C6; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.70 [0.46-0.88]	1.00 [0.96-1.00]
Branda 2013 (USA; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.70 [0.46-0.88]	0.97 [0.91-0.99]
Flisiak 1996 (flagella; serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.41-0.87]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	45	VERY LOW[1,3] due to very serious risk of bias and	0.72 [0.47-0.90]	0.70 [0.50-0.86]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Fung 1994 (acute disseminated; serum)	165	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.61 [0.40-0.73]	0.85 [0.77-0.91]
Fung 1994 (acute localised; serum)	122	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.15-0.65]	0.85 [0.77-0.91]
Fung 1994 (convalescent disseminated; serum)	165	VERY LOW[1] due to very serious risk of bias	0.81 [0.69-0.90]	0.85 [0.77-0.91]
Fung 1994 (convalescent localised; serum)	122	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.63 [0.35-0.85]	0.85 [0.77-0.91]
Goossens 2000 (Milenia; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.14-0.52]	0.95 [0.87-0.99]
Grodzicki 1988 (acute; serum)	50	VERY LOW[1] due to very serious risk of bias	0.30 [0.15-0.49]	1.00 [0.83-1.00]
Grodzicki 1988 (convalescent; serum)	50	VERY LOW[1] due to very serious risk of bias	0.60 [0.41-0.77]	1.00 [0.83-1.00]
Hernandez-Novoa 2003 (localised; serum)	24	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.50 [0.29-0.71]	Cannot be estimated[5]
Hunfeld 2002 (serum)	148	VERY LOW[1] due to very serious risk of bias	0.68 [0.59-0.75]	Cannot be estimated[5]
Johnson 1996 (serum)	171	VERY LOW[1] due to very serious risk of bias	0.47 [0.33-0.60]	0.96 [0.90-0.99]
Lahey 2015 (serum)	105	VERY LOW[1] due to very serious risk of bias	0.52 [0.40-0.63]	0.96 [0.80-1.00]
Lawrenz 1999 (recombinant; serum)	91	VERY LOW[1] due to very serious risk of bias	0.63 [0.47-0.78]	0.98 [0.89-1.00]
Lawrenz 1999 (whole-cell; serum)	91	VERY LOW[1]	0.61 [0.45-0.76]	0.94 [0.83-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Ledue 2008 (serum)	826	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.58 [0.33-0.80]	0.98 [0.97-0.99]
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.89 [0.77-0.96]	0.97 [0.88-1.00]
Leung 1989 (colorimetric; serum)	39	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.70 [0.35-0.93]	0.45 [0.26-0.64]
Leung 1989 (sonicated; serum)	39	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.76 [0.56-0.90]
Marangoni 2005 (Enzygnost; serum)	329	VERY LOW[1] due to very serious risk of bias	0.78 [0.68-0.86]	0.85 [0.79-0.89]
Marangoni 2005 (Quick C6; serum)	329	VERY LOW[1] due to very serious risk of bias	0.62 [0.52-0.72]	0.97 [0.93-0.99]
Marangoni 2005 (RecomWell; serum)	329	VERY LOW[1] due to very serious risk of bias	0.74 [0.64-0.82]	0.97 [0.94-0.99]
Mitchell 1994 (multiple EM; serum)	48	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.11]	1.00 [0.79-1.00]
Mitchell 1994 (single EM; serum)	35	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.05 [0.00-0.26]	1.00 [0.79-1.00]
Molins 2014 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.68 [0.51-0.81]	0.93 [0.89-0.96]
Molins 2014 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.89 [0.75-0.97]	0.93 [0.89-0.96]
Molins 2016 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.57 [0.41-0.73]	0.98 [0.94-0.99]
Molins 2016 (convalescent; serum)	241	VERY LOW[1]	0.84 [0.69-0.94]	0.98 [0.94-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Nohlmans 1994 (Diamedix; serum)	97	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.54 [0.25-0.81]	1.00 [0.96-1.00]
Nohlmans 1994 (Whittaker; serum)	97	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.09-0.61]	1.00 [0.96-1.00]
Pomelova 2015 (serum)	324	VERY LOW[1] due to very serious risk of bias	0.31 [0.24-0.40]	0.51 [0.44-0.58]
Rauer 1995 (recombinant; serum)	200	VERY LOW[1] due to very serious risk of bias	0.20 [0.13-0.29]	0.96 [0.90-0.99]
Russell 1984 (serum)	134	VERY LOW[1] due to very serious risk of bias	0.50 [0.32-0.68]	0.96 [0.90-0.99]
Smismans 2006 (purified; serum)	63	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.78 [0.56-0.93]	0.78 [0.62-0.89]
Smismans 2006 (synthetic C6; serum)	63	VERY LOW[1] due to very serious risk of bias	0.91 [0.72-0.99]	0.93 [0.80-0.98]
Smismans 2006 (whole-cell; serum)	63	VERY LOW[1] due to very serious risk of bias	1.00 [0.85-1.00]	0.50 [0.34-0.66]
Steere 2008 (acute; multiple EM; serum)	176	VERY LOW[1] due to very serious risk of bias	0.38 [0.23-0.54]	0.96 [0.92-0.99]
Steere 2008 (acute; single EM; serum)	172	VERY LOW[1] due to very serious risk of bias	0.19 [0.08-0.36]	0.96 [0.92-0.99]
Steere 2008 (convalescent; multiple EM; serum)	176	VERY LOW[1] due to very serious risk of bias	0.63 [0.46-0.77]	0.96 [0.92-0.99]
Steere 2008 (convalescent; single EM; serum)	172	VERY LOW[1] due to very serious risk of bias	0.47 [0.30-0.65]	0.96 [0.92-0.99]
Stiernstedt 1986 (serum)	145	VERY LOW[1,3] due to very serious risk of bias and	0.28 [0.12-0.49]	0.91 [0.84-0.95]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Tjernberg 2007 (Quick C6; serum)	358	VERY LOW[1] due to very serious risk of bias	0.37 [0.29-0.45]	0.08 [0.05-0.13]
Tjernberg 2007 (Virotech; serum)	358	VERY LOW[1] due to very serious risk of bias	0.46 [0.38-0.54]	0.24 [0.18-0.31]
Tjernberg 2009 (cut-off 0.0689; serum)	319	VERY LOW[1] due to very serious risk of bias	0.66 [0.57-0.73]	0.97 [0.93-0.99]
Tjernberg 2009 (cut-off 0.15; serum)	319	VERY LOW[1] due to very serious risk of bias	0.51 [0.43-0.60]	1.00 [0.98-1.00]
Trevejo 2001 (acute; serum)	103	VERY LOW[1] due to very serious risk of bias	0.42 [0.30-0.55]	0.97 [0.86-1.00]
Trevejo 2001 (convalescent; serum)	92	VERY LOW[1] due to very serious risk of bias	0.78 [0.65-0.88]	0.97 [0.86-1.00]
Erythema migrans: ELISA C6				
Cinco 2006 (serum)	78	VERY LOW[1] due to very serious risk of bias	0.63 [0.49-0.76]	1.00 [0.86-1.00]
Erythema migrans: ELISA C6 (IgA)				
D'Arco 2017 (IgA; serum)	276	VERY LOW[1] due to very serious risk of bias	0.30 [0.23-0.39]	0.99 [0.95-1.00]
Erythema migrans: ELFA				
Flisiak 1996 (serum)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.61 [0.36-0.83]	0.93 [0.76-0.99]
Mitchell 1994 (multiple EM; serum)	48	VERY LOW[1] due to very serious risk of bias	0.56 [0.38-0.74]	1.00 [0.79-1.00]
Mitchell 1994 (single EM; serum)	35	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.26 [0.09-0.51]	1.00 [0.79-1.00]
Erythema migrans: CLIA (IgM)				
Marangoni 2008 (serum)	366	VERY LOW[1]	0.24 [0.15-0.36]	0.94 [0.90-0.96]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Erythema migrans: CLIA (IgG)				
Marangoni 2008 (serum)	366	VERY LOW[1] due to very serious risk of bias	0.39 [0.28-0.52]	0.97 [0.94-0.99]
Erythema migrans: CLIA (IgM/IgG)				
Ledue 2008 (serum)	826	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.68 [0.43-0.87]	0.98 [0.97-0.99]
Tjernberg 2007 (serum)	358	VERY LOW[1] due to very serious risk of bias	0.42 [0.34-0.50]	0.19 [0.14-0.25]
Erythema migrans: Western blot/Immunoblot (IgM)				
Ang 2015 (Mikrogen; serum)	187	VERY LOW[1] due to very serious risk of bias	0.22 [0.13-0.32]	0.97 [0.92-0.99]
Branda 2010 (acute; serum)	301	VERY LOW[1] due to very serious risk of bias	0.30 [0.22-0.40]	1.00 [0.98-1.00]
Branda 2010 (convalescent; serum)	301	VERY LOW[1] due to very serious risk of bias	0.60 [0.50-0.70]	1.00 [0.98-1.00]
Branda 2013 (EU; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.15-0.59]	0.91 [0.84-0.96]
Branda 2013 (USA; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.10 [0.01-0.32]	1.00 [0.96-1.00]
Dressler 1993 (retrospective; acute; serum)	150	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.21-0.61]	0.99 [0.96-1.00]
Dressler 1993 (retrospective; conval.; serum)	150	VERY LOW[1] due to very serious risk of bias	0.60 [0.39-0.79]	0.99 [0.96-1.00]
Fung 1994 (acute; serum)	181	VERY LOW[1] due to very serious risk of bias	0.59 [0.47-0.70]	0.98 [0.93-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Fung 1994 (convalescent; serum)	181	VERY LOW[1] due to very serious risk of bias	0.73 [0.62-0.83]	0.98 [0.93-1.00]
Goettner 2005 (line blot; serum)	125	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.73 [0.45-0.92]	0.99 [0.95-1.00]
Goettner 2005 (line blot plus; serum)	125	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	0.98 [0.94-1.00]
Goettner 2005 (WB; serum)	125	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.16-0.68]	0.98 [0.94-1.00]
Goossens 2000 (Genzyme Virotech; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.50 [0.30-0.70]	0.89 [0.78-0.95]
Goossens 2000 (MRL; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.27-0.67]	0.98 [0.91-1.00]
Lange 1992 (serum)	136	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.81 [0.64-0.92]	1.00 [0.96-1.00]
Lencakova 2008 (serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.61 [0.47-0.74]	0.98 [0.91-1.00]
Liu 2013 (serum)	344	VERY LOW[1] due to very serious risk of bias	0.46 [0.32-0.61]	0.94 [0.91-1.00]
Mathiesen 1996 (serum)	147	VERY LOW[1] due to very serious risk of bias	0.36 [0.23-0.51]	0.99 [0.95-1.00]
Merljak Skocir 2008 (serum)	51	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.16 [0.05-0.36]	1.00 [0.87-1.00]
Molins 2014 (acute; serum)	243	VERY LOW[1]	0.35 [0.21-0.52]	0.98 [0.95-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Molins 2014 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.53 [0.36-0.69]	0.98 [0.95-0.99]
Molins 2016 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.53 [0.36-0.68]	0.94 [0.90-0.97]
Molins 2016 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.76 [0.60-0.89]	0.94 [0.90-0.97]
Porwancher 2011 (early acute; serum)	79	VERY LOW[1] due to very serious risk of bias	0.37 [0.26-0.48]	Cannot be estimated[5]
Porwancher 2011 (early convalescent; serum)	82	VERY LOW[1] due to very serious risk of bias	0.73 [0.62-0.82]	Cannot be estimated[5]
Ruzic-Sabljic 2002 (culture: positive versus negative; serum)	117	VERY LOW[1] due to very serious risk of bias	0.50 [0.37-0.63]	0.55 [0.40-0.69]
Ruzic-Sabljic 2002 (serum)	213	VERY LOW[1] due to very serious risk of bias	0.48 [0.39-0.57]	0.78 [0.69-0.86]
Sivak 1996 (acute EM; serum)	316	VERY LOW[1] due to very serious risk of bias	0.25 [0.13-0.40]	0.97 [0.94-0.99]
Sivak 1996 (convalescent EM; serum)	316	VERY LOW[1] due to very serious risk of bias	0.70 [0.55-0.83]	0.97 [0.94-0.99]
Sivak 1996 (EM over 7 days; serum)	316	VERY LOW[1] due to very serious risk of bias	0.82 [0.67-0.92]	0.97 [0.94-0.99]
Wilske 1993 (OspC-blot; serum)	173	VERY LOW[1] due to very serious risk of bias	0.45 [0.27-0.64]	0.97 [0.93-0.99]
Wilske 1993 (p100-blot; serum)	173	VERY LOW[1] due to very serious risk of bias	0.10 [0.02-0.26]	0.99 [0.96-1.00]
Wilske 1993 (p41/i-blot; serum)	173	VERY LOW[1] due to very serious risk of bias	0.10 [0.02-0.26]	0.99 [0.96-1.00]
Erythema migrans: Western blot/Immunoblot (IgG)				
Branda 2010 (acute; serum)	301	VERY LOW[1]	0.06 [0.02-0.12]	0.99 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Branda 2010 (convalescent; serum)	301	VERY LOW[1] due to very serious risk of bias	0.11 [0.06-0.19]	0.99 [0.97-1.00]
Branda 2013 (EU; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.15-0.59]	1.00 [0.96-1.00]
Branda 2013 (USA; serum)	115	VERY LOW[1] due to very serious risk of bias	0.10 [0.01-0.32]	1.00 [0.96-1.00]
Dressler 1993 (retrospective (acute; serum)	150	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.14]	1.00 [0.97-1.00]
Dressler 1993 (retrospective; conval.; serum)	150	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.16 [0.05-0.36]	1.00 [0.97-1.00]
Fung 1994 (acute; serum)	181	VERY LOW[1] due to very serious risk of bias	0.47 [0.35-0.59]	0.94 [0.88-0.98]
Fung 1994 (convalescent; serum)	181	VERY LOW[1] due to very serious risk of bias	0.57 [0.45-0.69]	0.94 [0.88-0.98]
Goettner 2005 (line blot; serum)	125	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.47 [0.21-0.73]	1.00 [0.97-1.00]
Goettner 2005 (line blot plus; serum)	125	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.53 [0.27-0.79]	0.99 [0.95-1.00]
Goettner 2005 (WB; serum)	125	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.33 [0.12-0.62]	0.99 [0.95-1.00]
Goossens 2000 (Genzyme Virotech; serum)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.27 [0.12-0.48]	0.82 [0.70-0.91]
Goossens 2000 (MRL; serum)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.54 [0.40-0.67]	1.00 [0.94-1.00]
Liu 2013 (serum)	344	VERY LOW[1] due to very serious risk of bias	0.67 [0.53-0.80]	0.98 [0.96-0.99]
Mathiesen 1996 (serum)	147	VERY LOW[1] due to very serious risk of bias	0.26 [0.14-0.40]	0.96 [0.90-0.99]
Merljak Skocir 2008 (serum)	51	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.32 [0.15-0.54]	0.73 [0.52-0.88]
Molins 2014 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.20 [0.09-0.36]	0.99 [0.96-1.00]
Molins 2014 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.37 [0.22-0.54]	0.99 [0.96-1.00]
Molins 2016 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.13 [0.04-0.27]	0.99 [0.96-1.00]
Molins 2016 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.29 [0.15-0.46]	0.99 [0.96-1.00]
Porwancher 2011 (early acute; serum)	79	VERY LOW[1] due to very serious risk of bias	0.08 [0.03-0.16]	Cannot be estimates[5]
Porwancher 2011 (early convalescent; serum)	82	VERY LOW[1] due to very serious risk of bias	0.21 [0.13-0.31]	Cannot be estimated[5]
Ruzic-Sabljic 2002 (culture: positive versus negative; serum)	117	VERY LOW[1] due to very serious risk of bias	0.30 [0.20-0.43]	0.69 [0.54-0.81]
Ruzic-Sabljic 2002 (serum)	213	VERY LOW[1] due to very serious risk of bias	0.31 [0.23-0.40]	0.73 [0.63-0.81]
Wilske 1993 (OspC-blot; serum)	173	VERY LOW[1] due to very serious risk of bias	0.10 [0.02-0.26]	0.99 [0.96-1.00]
Wilske 1993 (p100-blot; serum)	173	VERY LOW[1] due to very serious risk of bias	0.23 [0.10-0.41]	0.94 [0.88-0.97]
Wilske 1993 (p41/i-blot; serum)	173	VERY LOW[1]	0.06 [0.01-0.21]	0.96 [0.91-0.98]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Wilske 1999 (recombinant - new; serum)	205	VERY LOW[1] due to very serious risk of bias	0.11 [0.04-0.21]	0.98 [0.94-1.00]
Wilske 1999 (recombinant - old; serum)	205	VERY LOW[1] due to very serious risk of bias	0.05 [0.01-0.13]	0.98 [0.94-1.00]
Wilske 1999 (whole-cell; serum)	205	VERY LOW[1] due to very serious risk of bias	0.33 [0.22-0.46]	0.98 [0.94-1.00]
Erythema migrans: Western blot/Immunoblot (IgM/IgG)				
Ang 2015 (Mikrogen; serum)	187	VERY LOW[1] due to very serious risk of bias	0.80 [0.69-0.88]	0.92 [0.85-0.97]
Branda 2010 (acute; serum)	301	VERY LOW[1] due to very serious risk of bias	0.34 [0.25-0.44]	0.99 [0.97-1.00]
Branda 2010 (convalescent; serum)	301	VERY LOW[1] due to very serious risk of bias	0.66 [0.56-0.75]	0.99 [0.97-1.00]
Branda 2013 (EU; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.55 [0.32-0.77]	0.91 [0.84-0.96]
Branda 2013 (US; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.06-0.44]	1.00 [0.96-1.00]
Callister 2002 (multiple EM; serum)	46	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.83 [0.52-0.98]	0.91 [0.76-0.98]
Callister 2002 (single EM; serum)	56	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.55 [0.32-0.76]	0.91 [0.76-0.98]
Fung 1994 (acute; serum)	181	VERY LOW[1] due to very serious risk of bias	0.65 [0.53-0.76]	0.92 [0.86-0.97]
Fung 1994 (convalescent; serum)	181	VERY LOW[1] due to very serious risk of bias	0.80 [0.69-0.88]	0.92 [0.86-0.97]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.93 [0.82-0.98]	0.98 [0.91-1.00]
Molins 2014 (acute; serum)	221	VERY LOW[1] due to very serious risk of bias	1.00 [0.81-1.00]	0.97 [0.94-0.99]
Molins 2014 (convalescent; serum)	252	VERY LOW[1] due to very serious risk of bias	0.55 [0.40-0.69]	0.97 [0.94-0.99]
Molins 2016 (acute; serum)	243	VERY LOW[1] due to very serious risk of bias	0.55 [0.38-0.71]	0.93 [0.88-0.96]
Molins 2016 (convalescent; serum)	241	VERY LOW[1] due to very serious risk of bias	0.79 [0.63-0.90]	0.93 [0.88-0.96]
Porwancher 2011 (early acute; serum)	529	VERY LOW[1] due to very serious risk of bias	0.39 [0.28-0.51]	0.95 [0.93-0.97]
Porwancher 2011 (early convalescent; serum)	532	VERY LOW[1] due to very serious risk of bias	0.77 [0.66-0.85]	0.95 [0.93-0.97]
Trevejo 2001 (acute; serum)	104	VERY LOW[1] due to very serious risk of bias	0.38 [0.26-0.51]	0.97 [0.86-1.00]
Trevejo 2001 (convalescent; serum)	94	VERY LOW[1] due to very serious risk of bias	0.30 [0.19-0.44]	0.97 [0.86-1.00]
Erythema migrans: IFA (IgM)				
Cerar 2006 (serum)	125	VERY LOW[1] due to very serious risk of bias	0.04 [0.01-0.11]	1.00 [0.93-1.00]
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.37 [0.24-0.51]	0.98 [0.91-1.00]
Mitchell 1994 (multiple EM; serum)	48	VERY LOW[1] due to very serious risk of bias	1.00 [0.89-1.00]	1.00 [0.79-1.00]
Mitchell 1994 (single EM; serum)	35	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.42 [0.20-0.67]	1.00 [0.79-1.00]
Ruzic-Sabljic 2002 (culture: positive versus negative; serum)	117	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.05]	0.96 [0.87-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Ruzic-Sabljic 2002 (serum)	213	VERY LOW[1] due to very serious risk of bias	0.02 [0.00-0.06]	1.00 [0.96-1.00]
Wilske 1993 (IFA-ABS; serum)	173	VERY LOW[1] due to very serious risk of bias	0.32 [0.17-0.51]	0.97 [0.93-0.99]
Erythema migrans: IFA (IgG)				
Cerar 2006 (serum)	125	VERY LOW[1] due to very serious risk of bias	0.33 [0.23-0.45]	0.82 0.68-0.91]
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.44 [0.31-0.59]	0.98 [0.91-1.00]
Ruzic-Sabljic 2002 (culture: positive versus negative; serum)	117	VERY LOW[1] due to very serious risk of bias	0.02 [0.00-0.08]	0.96 [0.87-1.00]
Ruzic-Sabljic 2002 (serum)	213	VERY LOW[1] due to very serious risk of bias	0.03 [0.01-0.07]	0.98 [0.93-1.00]
Wilske 1993 (IFA-ABS; serum)	173	VERY LOW[1] due to very serious risk of bias	0.45 [0.27-0.64]	0.97 [0.93-0.99]
Erythema migrans: IFA (IgM/IgG)				
Lencakova 2008 (serum)	114	VERY LOW[1] due to very serious risk of bias	0.67 [0.53-0.79]	0.98 [0.91-1.00]
Russell 1984 (serum)	134	VERY LOW[1] due to very serious risk of bias	0.50 [0.32-0.68]	1.00 [0.96-1.00]
Erythema migrans: IFA				
Stiernstedt 1986 (serum)	88	VERY LOW[1] due to very serious risk of bias	0.12 [0.03-0.31]	0.95 [0.87-0.99]
Erythema migrans: PCR				
Lebech 2000 (skin)	69	VERY LOW[1] due to very serious risk of bias	0.71 [0.52-0.86]	1.00 [0.91-1.00]
Molins 2014 (blood and skin)	39	VERY LOW[1] due to very serious risk of bias	0.62 [0.45-0.77]	Cannot be estimated[5]
Moter 1994 (skin)	14	VERY LOW[1,3]	0.80 [0.44-0.97]	1.00 [0.40-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious imprecision		
Schwartz 1992 (skin)	45	VERY LOW[1] due to very serious risk of bias	0.57 [0.39-0.74]	0.90 [0.55-1.00]
von Stedingk 1995 (skin)	102	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.48-0.86]	1.00 [0.95-1.00]
Erythema migrans: Culture				
Molins 2014 (blood and skin)	39	VERY LOW[1] due to very serious risk of bias	0.44 [0.28-0.60]	Cannot be estimated[5]
Neuroborreliosis: ELISA (IgM)				
Ang 2015 (Diacheck; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.52]	1.00 [0.78-1.00]
Ang 2015 (Enzygnost; serum)	157	VERY LOW[1] due to very serious risk of bias	0.10 [0.03-0.22]	0.91 [0.83-0.95]
Ang 2015 (Euroimmun; serum)	15	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.97]	1.00 [0.77-1.00]
Ang 2015 (Liaison; serum)	281	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.07]	0.97 [0.94-0.99]
Ang 2015 (Medac; serum)	117	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.99 [0.94-1.00]
Ang 2015 (Mikrogen; serum)	16	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.97]	1.00 [0.78-1.00]
Ang 2015 (Serion; serum)	132	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.20-0.59]	0.73 [0.63-0.81]
Ang 2015 (Virotech; serum)	19	VERY LOW[1,3] due to very serious risk of bias and	0.00 [0.00-0.52]	1.00 [0.77-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		very serious imprecision		
Bacon 2003 (conval. neurologic; rVlsE; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.55 [0.23-0.83]	0.98 [0.96-0.99]
Bacon 2003 (conval. neurologic; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.36 [0.11-0.69]	1.00 [0.99-1.00]
Bacon 2003 (early neurologic; rVlsE; serum)	272	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.73 [0.45-0.92]	0.98 [0.96-0.99]
Bacon 2003 (early neurologic; serum)	272	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.53 [0.27-0.79]	1.00 [0.99-1.00]
Bacon 2003 (late neurologic; rVlsE; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.09 [0.00-0.41]	0.98 [0.96-0.99]
Bacon 2003 (late neurologic; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.18 [0.02-0.52]	1.00 [0.99-1.00]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.80 [0.52-0.96]	0.98 [0.93-1.00]
Cerar 2010 (CSF)	66	VERY LOW[1] due to very serious risk of bias	0.21 [0.09-0.38]	1.00 [0.89-1.00]
Cerar 2010 (serum)	66	VERY LOW[1] due to very serious risk of bias	0.47 [0.30-0.65]	0.97 [0.84-1.00]
Dessau 2010 (serum)	932	VERY LOW[1] due to very serious risk of bias	0.55 [0.45-0.64]	0.97 [0.95-0.98]
Flisiak 1996 (flagella; serum)	44	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.71 [0.44-0.90]	0.85 [0.66-0.96]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (recombinant; serum)	44	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.71 [0.44-0.90]	0.70 [0.50-0.86]
Fung 1994 (chronic neuroborreliosis; serum)	131	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.07-0.41]	0.98 [0.93-1.00]
Fung 1994 (meningitis/facial palsy; serum)	146	VERY LOW[1] due to very serious risk of bias	0.72 [0.56-0.85]	0.98 [0.93-1.00]
Hansen 1991 (serum)	300	VERY LOW[1] due to very serious risk of bias	0.37 [0.28-0.47]	1.00 [0.98-1.00]
Hunfeld 2002 (serum)	1142	VERY LOW[1] due to very serious risk of bias	0.74 [0.57-0.88]	0.92 [0.90-0.94]
Kaiser 1998 (recombinant; CSF)	81	VERY LOW[1] due to very serious risk of bias	0.42 [0.30-0.54]	1.00 [0.77-1.00]
Kaiser 1998 (recombinant; serum)	81	VERY LOW[1] due to very serious risk of bias	0.79 [0.67-0.88]	1.00 [0.77-1.00]
Kaiser 1998 (sonicated; CSF)	81	VERY LOW[1] due to very serious risk of bias	0.07 [0.02-0.17]	1.00 [0.77-1.00]
Kaiser 1998 (sonicated; serum)	81	VERY LOW[1] due to very serious risk of bias	0.43 [0.31-0.56]	1.00 [0.77-1.00]
Kaiser 1999 (recombinant; serum)	176	VERY LOW[1] due to very serious risk of bias	0.84 [0.76-0.91]	0.93 [0.84-0.97]
Kaiser 1999 (whole-cell; serum)	176	VERY LOW[1] due to very serious risk of bias	0.53 [0.43-0.63]	0.90 [0.81-0.96]
Karlsson 1989 (CSF)	112	VERY LOW[1] due to very serious risk of bias	0.57 [0.45-0.69]	0.98 [0.88-1.00]
Karlsson 1989 (serum)	112	VERY LOW[1] due to very serious risk of bias	0.34 [0.23-0.46]	0.98 [0.88-1.00]
Karlsson 1989a (capture ELISA; serum)	110	VERY LOW[1] due to very serious risk of bias	0.54 [0.37-0.71]	0.97 [0.90-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989a (indirect ELISA; serum)	110	VERY LOW[1] due to very serious risk of bias	0.38 [0.22-0.55]	0.90 [0.81-0.96]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.43 [0.10-0.82]	0.98 [0.91-1.00]
Liu 2013 (serum)	357	VERY LOW[1] due to very serious risk of bias	0.62 [0.49-0.73]	0.80 [0.75-0.85]
Mathiesen 1996 (serum)	150	VERY LOW[1] due to very serious risk of bias	0.66 [0.51-0.79]	0.99 [0.95-1.00]
Molins 2017 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.89 [0.83-0.093]
Panelius 2001 (serum)	19	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.58 [0.33-0.80]	Cannot be estimated[5]
Rauer 1995 (recombinant; serum)	115	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.11]	0.96 [0.90-0.99]
Roux 2007 (serum)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.64 [0.31-0.89]	0.94 [0.70-1.00]
Widhe 2004 (serum)	51	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.39 [0.22-0.59]	1.00 [0.85-1.00]
Wilske 1993 (flagellin; serum)	202	VERY LOW[1] due to very serious risk of bias	0.50 [0.37-0.63]	0.96 [0.91-0.98]
Wilske 1993 (OGP-ELISA; serum)	202	VERY LOW[1] due to very serious risk of bias	0.62 [0.48-0.74]	0.97 [0.93-0.99]
Neuroborreliosis: ELISA (IgG)				
Bacon 2003 (conval. neurologic; rVlsE; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.64 [0.31-0.89]	0.99 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Bacon 2003 (conval. neurologic; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.64 [0.31-0.89]	1.00 [0.99-1.00]
Bacon 2003 (early neurologic; rVlsE; serum)	272	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.78-1.00]	0.99 [0.97-1.00]
Bacon 2003 (early neurologic; serum)	272	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.60 [0.32-0.84]	1.00 [0.99-1.00]
Bacon 2003 (late neurologic; rVlsE; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.72-1.00]	0.99 [0.97-1.00]
Bacon 2003 (late neurologic; serum)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.73 [0.39-0.94]	1.00 [0.99-1.00]
Branda 2013 (EU; serum)	115	VERY LOW[1] due to very serious risk of bias	0.87 [0.60-0.98]	0.98 [0.93-1.00]
Cerar 2010 (CSF)	66	VERY LOW[1] due to very serious risk of bias	0.41 [0.25-0.59]	0.97 [0.84-1.00]
Cerar 2010 (serum)	66	VERY LOW[1] due to very serious risk of bias	0.71 [0.53-0.85]	0.50 [0.32-0.68]
Dessau 2010 (serum)	932	VERY LOW[1] due to very serious risk of bias	0.44 [0.34-0.53]	0.98 [0.97-0.99]
Dressler 1993 (prospective; serum)	168	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.59 [0.39-0.76]	0.96 [0.92-0.99]
Flisiak 1996 (flagella; serum)	44	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.14-0.62]	1.00 [0.87-1.00]
Flisiak 1996 (recombinant; serum)	44	VERY LOW[1,3] due to very serious risk of bias and	0.29 [0.10-0.56]	1.00 [0.87-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Fung 1994 (chronic neuroborreliosis; serum)	131	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.36 [0.18-0.57]	0.86 [0.78-0.92]
Fung 1994 (meningitis/facial palsy; serum)	146	VERY LOW[1] due to very serious risk of bias	0.65 [0.48-0.79]	0.86 [0.78-0.92]
Hansen 1991 (serum)	300	VERY LOW[1] due to very serious risk of bias	0.84 [0.75-0.91]	1.00 [0.98-1.00]
Hunfeld 2002 (serum)	1,142	VERY LOW[1] due to very serious risk of bias	0.51 [0.34-0.69]	0.95 [0.93-0.96]
Kaiser 1998 (recombinant; CSF)	81	VERY LOW[1] due to very serious risk of bias	0.58 [0.46-0.70]	1.00 [0.77-1.00]
Kaiser 1998 (recombinant; serum)	81	VERY LOW[1] due to very serious risk of bias	0.64 [0.52-0.76]	1.00 [0.77-1.00]
Kaiser 1998 (sonicated; CSF)	81	VERY LOW[1] due to very serious risk of bias	0.31 [0.21-0.44]	0.29 [0.08-0.58]
Kaiser 1998 (sonicated; serum)	81	VERY LOW[1] due to very serious risk of bias	0.93 [0.83-0.98]	0.29 [0.08-0.58]
Kaiser 1999 (recombinant; serum)	176	VERY LOW[1] due to very serious risk of bias	0.80 [0.71-0.88]	0.82 [0.72-0.90]
Kaiser 1999 (whole-cell; serum)	176	VERY LOW[1] due to very serious risk of bias	0.78 [0.69-0.86]	0.00 [0.00-0.05]
Karlsson 1989 (CSF)	112	VERY LOW[1] due to very serious risk of bias	0.57 [0.45-0.69]	0.95 [0.85-0.99]
Karlsson 1989 (serum)	112	VERY LOW[1] due to very serious risk of bias	0.38 [0.27-0.51]	0.93 [0.81-0.99]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.57 [0.18-0.90]	0.98 [0.91-1.00]
Liu 2013 (serum)	357	VERY LOW[1]	0.85 [0.74-0.92]	0.77 [0.72-0.82]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Mathiesen 1996 (serum)	150	VERY LOW[1] due to very serious risk of bias	0.42 [0.28-0.57]	1.00 [0.96-1.00]
Molins 2017 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.98 [0.95-0.99]
Panelius 2001 (serum)	19	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.74 [0.49-0.91]	Cannot be estimated[5]
Panelius 2008 (CSF)	72	VERY LOW[1] due to very serious risk of bias	0.37 [0.24-0.51]	1.00 [0.83-1.00]
Panelius 2008 (serum)	87	VERY LOW[1] due to very serious risk of bias	0.84 [0.73-0.92]	1.00 [0.83-1.00]
Rauer 1995 (recombinant; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.33 [0.18-0.52]	1.00 [0.96-1.00]
Roux 2007 (CSF)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.59-1.00]	0.75 [0.48-0.93]
Roux 2007 (serum)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.64 [0.31-0.99]	0.63 [0.35-0.85]
Sillanpaa 2007 (serum)	97	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Widhe 2004 (serum)	52	VERY LOW[1] due to very serious risk of bias	0.79 [0.60-0.92]	1.00 [0.85-1.00]
Wilske 1993 (flagellin; serum)	202	VERY LOW[1] due to very serious risk of bias	0.75 [0.62-0.85]	0.94 [0.88-1.00]
Wilske 1993 (OGP-ELISA; serum)	202	VERY LOW[1] due to very serious risk of bias	0.45 [0.32-0.58]	0.97 [0.93-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Neuroborreliosis: ELISA (IgM/IgG)				
Ang 2015 (Diacheck; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.80 [0.28-0.99]	0.93 [0.68-1.00]
Ang 2015 (Enzygnost; serum)	157	VERY LOW[1] due to very serious risk of bias	0.98 [0.89-1.00]	0.88 [0.80-0.93]
Ang 2015 (Euroimmun; serum)	15	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.03-1.00]	0.86 [0.57-0.98]
Ang 2015 (Liaison; serum)	281	VERY LOW[1] due to very serious risk of bias	1.00 [0.93-1.00]	0.92 [0.87-0.95]
Ang 2015 (Medac; serum)	117	VERY LOW[1] due to very serious risk of bias	1.00 [0.86-1.00]	0.97 [0.91-0.99]
Ang 2015 (Mikrogen; serum)	16	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.03-1.00]	1.00 [0.78-1.00]
Ang 2015 (Serion; serum)	132	VERY LOW[1] due to very serious risk of bias	0.92 [0.75-0.99]	0.72 [0.62-0.80]
Ang 2015 (Virotech; serum)	19	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.48-1.00]	1.00 [0.77-1.00]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.78-1.00]	0.96 [0.90-0.99]
Branda 2013 (USA; C6; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	1.00 [0.96-1.00]
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	0.97 [0.91-0.99]
Coyle 1993 (CSF)	111	VERY LOW[1,2]	0.49 [0.38-0.61]	0.97 [0.85-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias, serious indirectness		
Flisiak 1996 (flagella; serum)	44	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.88 [0.64-0.99]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	44	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.82 [0.57-0.96]	0.70 [0.50-0.86]
Fung 1994 (chronic neuroborreliosis; serum)	131	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.48 [0.28-0.69]	0.85 [0.77-0.91]
Fung 1994 (meningitis/facial palsy; serum)	146	VERY LOW[1] due to very serious risk of bias	0.88 [0.73-0.96]	0.85 [0.77-0.91]
Hunfeld 2002 (serum)	35	VERY LOW[1] due to very serious risk of bias	0.86 [0.70-0.95]	Cannot be estimated[5]
Johnson 1996 (serum)	130	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.94 [0.71-1.00]	0.96 [0.90-0.99]
Karlsson 1989 (CSF)	68	VERY LOW[1] due to very serious risk of bias	0.65 [0.52-0.76]	Cannot be estimated[5]
Karlsson 1989 (serum)	112	VERY LOW[1] due to very serious risk of bias	0.59 [0.46-0.71]	0.91 [0.78-0.97]
Lawrenz 1999 (recombinant; serum)	67	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.80-1.00]	0.98 [0.89-1.00]
Lawrenz 1999 (whole-cell; serum)	67	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.80-1.00]	0.94 [0.83-0.99]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.97 [0.88-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.93 [0.89-0.96]
Molins 2016 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.98 [0.94-0.99]
Rauer 1995 (recombinant; serum)	115	VERY LOW[1] due to very serious risk of bias	0.42 [0.25-0.61]	0.96 [0.90-0.99]
Roux 2007 (CSF)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.59-1.00]	0.75 [0.48-0.93]
Roux 2007 (serum)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.59-1.00]	0.63 [0.35-0.85]
Russell 1984 (serum)	126	VERY LOW[1] due to very serious risk of bias	1.00 [0.87-1.00]	0.96 [0.90-0.99]
Tjernberg 2007 (Quick C6; serum)	226	VERY LOW[1] due to very serious risk of bias	0.88 [0.70-0.98]	0.08 [0.05-0.13]
Tjernberg 2007 (Virotech; serum)	226	VERY LOW[1] due to very serious risk of bias	0.96 [0.80-1.00]	0.24 [0.18-0.31]
van Burgel 2011 (antibody index)	202	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.95 [0.86-0.99]	0.97 [0.92-0.99]
Neuroborreliosis: ELISA C6				
Cinco 2006 (serum)	30	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.54-1.00]	1.00 [0.86-1.00]
Neuroborreliosis: ELFA				
Flisiak 1996 (serum)	44	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.94 [0.71-1.00]	0.93 [0.76-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Neuroborreliosis: CLIA (IgM/IgG)				
Tjernberg 2007 (serum)	226	VERY LOW[1,2] due to very serious risk of bias and serious imprecision	0.85 [0.65-0.96]	0.19 [0.14-0.25]
Neuroborreliosis: Western blot/Immunoblot (IgM)				
Ang 2015 (Mikrogen; serum)	171	VERY LOW[1] due to very serious risk of bias	0.07 [0.02-0.17]	0.97 [0.92-0.99]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.80 [0.52-0.96]	0.91 [0.84-0.96]
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.16-0.68]	1.00 [0.96-1.00]
Goettner 2005 (line blot; serum)	160	VERY LOW[1] due to very serious risk of bias	0.46 [0.32-0.61]	0.99 [0.95-1.00]
Goettner 2005 (line blot plus; serum)	160	VERY LOW[1] due to very serious risk of bias	0.70 [0.55-0.82]	0.98 [0.94-1.00]
Goettner 2005 (WB; serum)	160	VERY LOW[1] due to very serious risk of bias	0.40 [0.26-0.55]	0.98 [0.94-1.00]
Karlsson 1989 (serum)	112	VERY LOW[1] due to very serious risk of bias	0.68 [0.55-0.78]	0.89 [0.75-0.96]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.29 [0.04-0.71]	0.98 [0.91-1.00]
Liu 2013 (serum)	357	VERY LOW[1] due to very serious risk of bias	0.49 [0.37-0.62]	0.94 [0.91-0.97]
Mathiesen 1996 (serum)	150	VERY LOW[1] due to very serious risk of bias	0.60 [0.45-0.74]	0.99 [0.95-1.00]
Molins 2014 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and	1.00 [0.69-1.00]	0.98 [0.95-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Molins 2016 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.94 [0.90-0.97]
Wilske 1993 (OspC-blot; serum)	202	VERY LOW[1] due to very serious risk of bias	0.43 [0.31-0.57]	0.97 [0.93-0.99]
Wilske 1993 (p100-blot; serum)	202	VERY LOW[1] due to very serious risk of bias	0.12 [0.05-0.23]	0.99 [0.96-1.00]
Wilske 1993 (p41/i-blot; serum)	202	VERY LOW[1] due to very serious risk of bias	0.20 [0.11-0.32]	0.99 [0.96-1.00]
Neuroborreliosis: Western blot/Immunoblot (IgG)				
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.60 [0.32-0.84]	1.00 [0.96-1.00]
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.16-0.68]	1.00 [0.96-1.00]
Dressler 1993 (prospective; serum)	168	VERY LOW[1] due to very serious risk of bias	0.72 [0.53-0.87]	0.95 [0.90-0.98]
Goettner 2005 (line blot; serum)	160	VERY LOW[1] due to very serious risk of bias	0.86 [0.73-0.94]	1.00 [0.97-1.00]
Goettner 2005 (line blot plus; serum)	160	VERY LOW[1] due to very serious risk of bias	0.88 [0.76-0.95]	0.99 [0.95-1.00]
Goettner 2005 (WB; serum)	160	VERY LOW[1] due to very serious risk of bias	0.72 [0.58-0.84]	0.99 [0.95-1.00]
Karlsson 1989 (serum)	112	VERY LOW[1] due to very serious risk of bias	0.65 [0.52-0.76]	0.89 [0.75-0.96]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.57 [0.18-0.90]	1.00 [0.94-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Liu 2013 (serum)	357	VERY LOW[1] due to very serious risk of bias	0.69 [0.57-0.80]	0.98 [0.96-0.99]
Mathiesen 1996 (serum)	150	VERY LOW[1] due to very serious risk of bias	0.46 [0.32-0.61]	0.96 [0.90-0.99]
Molins 2014 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.07-0.65]	0.99 [0.96-1.00]
Molins 2016 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.12-0.74]	0.99 [0.96-1.00]
Panelius 2001 (serum)	14	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.71 [0.42-0.92]	Cannot be estimated[5]
Peltomaa 2004 (serum)	133	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	1.00 [0.92-1.00]	0.95 [0.89-0.99]
Roux 2007 (CSF)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.82 [0.48-0.98]	0.94 [0.70-1.00]
Roux 2007 (serum)	27	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.64 [0.31-0.89]	0.63 [0.35-0.85]
Schulte-Spechtel 2004 (recombinant; serum)	103	VERY LOW[1] due to very serious risk of bias	0.86 [0.71-0.95]	1.00 [0.95-1.00]
Schulte-Spechtel 2004 (whole-cell; serum)	103	VERY LOW[1] due to very serious risk of bias	0.64 [0.46-0.79]	0.97 [0.90-1.00]
Wilske 1993 (OspC-blot; serum)	202	VERY LOW[1] due to very serious risk of bias	0.15 [0.07-0.27]	0.99 [0.96-1.00]
Wilske 1993 (p100-blot; serum)	202	VERY LOW[1] due to very serious risk of bias	0.43 [0.31-0.57]	0.94 [0.88-0.97]
Wilske 1993 (p41/i-blot; serum)	202	VERY LOW[1]	0.25 [0.15-0.38]	0.96 [0.91-0.98]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Wilske 1999 (recombinant - new; serum)	181	VERY LOW[1] due to very serious risk of bias	0.45 [0.30-0.61]	0.98 [0.94-1.00]
Wilske 1999 (recombinant - old; serum)	181	VERY LOW[1] due to very serious risk of bias	0.29 [0.16-0.45]	0.98 [0.94-1.00
Wilske 1999 (whole-cell; serum)	181	VERY LOW[1] due to very serious risk of bias	0.57 [0.41-0.72]	0.98 [0.94-1.00]
Neuroborreliosis: Western blot/Immunoblot (IgM/IgG)				
Ang 2015 (Mikrogen; serum)	171	VERY LOW[1] due to very serious risk of bias	0.97 [0.97-1.00]	0.92 [0.85-0.97]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	0.91 [0.84-0.96]
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.53 [0.27-0.79]	1.00 [0.96-1.00]
Karlsson 1989 (serum)	112	VERY LOW[1] due to very serious risk of bias	0.78 [0.66-0.87]	0.82 [0.67-0.92]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.98 [0.91-1.00]
Molins 2014 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.97 [0.94-0.99]
Molins 2016 (serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.93 [0.88-0.96]
Neuroborreliosis: IFA (IgM)				
Cerar 2006 (serum)	77	VERY LOW[1] due to very serious risk of bias	0.07 [0.01-0.24]	1.00 [0.93-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.14 [0.00-0.58]	0.98 [0.91-1.00]
Wilske 1993 (IFA-ABS; serum)	202	VERY LOW[1] due to very serious risk of bias	0.30 [0.19-0.43]	0.97 [0.93-0.99]
Neuroborreliosis: IFA (IgG)				
Cerar 2006 (serum)	77	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.75 [0.55-0.89]	0.82 [0.68-0.91]
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.14 [0.00-0.58]	0.98 [0.91-1.00]
Wilske 1993 (IFA-ABS; serum)	202	VERY LOW[1] due to very serious risk of bias	0.75 [0.62-0.85]	0.97 [0.93-0.99]
Neuroborreliosis: IFA (IgM/IgG)				
Lencakova 2008 (serum)	67	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.29 [0.04-0.71]	0.98 [0.91-1.00]
Russell 1984 (serum)	126	VERY LOW[1] due to very serious risk of bias	0.92 [0.75-0.99]	1.00 [0.96-1.00]
Neuroborreliosis: PCR				
Lebech 1992 (CSF)	25	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.03-0.56]	1.00 [0.78-1.00]
Lebech 1992 (urine)	45	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.90-1.00]
Lebech 1998 (CSF)	220	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.21 [0.14-0.28]	0.99 [0.92-1.00]
Lebech 2000 (CSF)	50	VERY LOW[1,2]	0.17 [0.06-0.35]	1.00 [0.83-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious indirectness		
Molins 2014 (blood and skin)	8	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.25 [0.03-0.65]	Cannot be estimated[5]
Nocton 1996 (CSF)	102	VERY LOW[1] due to very serious risk of bias	0.28 [0.17-0.41]	1.00 [0.92-1.00]
Priem 1997 (CSF)	52	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.79 [0.54-0.94]	1.00 [0.89-1.00]
Neuroborreliosis: Culture				
Molins 2014 (blood and skin)	6	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.33 [0.04-0.78]	Cannot be estimated[5]
Neuroborreliosis: CXCL13				
Senel 2010 (cut-off 337 ng/g; CSF)	97	VERY LOW[1] due to very serious risk of bias	0.96 [0.82-1.00]	0.97 [0.90-1.00]
Lyme arthritis: ELISA (IgM)				
Ang 2015 (Diacheck; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.52]	1.00 [0.78-1.00]
Ang 2015 (Enzygnost; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.08 [0.00-0.36]	0.91 [0.83-0.95]
Ang 2015 (Liaison; serum)	234	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.41]	0.97 [0.94-0.99]
Ang 2015 (Serion; serum)	108	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.84]	0.73 [0.63-0.81]
Ang 2015 (Virotech; serum)	19	VERY LOW[1,3]	0.20 [0.01-0.72]	1.00 [0.77-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and very serious imprecision		
Bacon 2003 (arthritis; rVlsE; serum)	290	VERY LOW[1] due to very serious risk of bias	0.39 [0.23-0.58]	0.98 [0.96-0.99]
Bacon 2003 (arthritis; serum)	290	VERY LOW[1] due to very serious risk of bias	0.09 [0.02-0.24]	1.00 [0.99-1.00]
Bacon 2003 (conval. arthritis; rVlsE; serum)	281	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.42 [0.22-0.63]	0.98 [0.96-0.99]
Bacon 2003 (conval. arthritis; serum)	281	VERY LOW[1] due to very serious risk of bias	0.08 [0.01-0.27]	1.00 [0.99-1.00]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.60 [0.32-0.84]	0.98 [0.93-1.00]
Flisiak 1996 (flagella; serum)	34	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.71 [0.29-0.96]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	34	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.70 [0.50-0.86]
Fung 1994 (serum)	155	VERY LOW[1] due to very serious risk of bias	0.45 [0.31-0.60]	0.98 [0.93-1.00]
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.25]	0.98 [0.91-1.00]
Molins 2017 (serum)	232	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.66 [0.46-0.82]	0.89 [0.83-0.93]
Panelius 2001 (serum)	19	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.37 [0.16-0.62]	Cannot be estimated[5]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Rauer 1995 (recombinant; serum)	99	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.20]	0.96 [0.90-0.99]
Lyme arthritis: ELISA (IgG)				
Bacon 2003 (arthritis; rVlsE; serum)	290	VERY LOW[1] due to very serious risk of bias	0.97 [0.84-1.00]	0.99 [0.97-1.00]
Bacon 2003 (arthritis; serum)	290	VERY LOW[a] due to very serious risk of bias	0.94 [0.80-0.99]	1.00 [0.99-1.00]
Bacon 2003 (conval. arthritis; rVlsE; serum)	281	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.88 [0.68-0.97]	0.99 [0.97-1.00]
Bacon 2003 (conval. arthritis; serum)	281	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.88 [0.68-0.97]	1.00 [0.99-1.00]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.78-1.00]	0.98 [0.93-1.00]
Dressler 1993 (prospective; serum)	164	VERY LOW[1] due to very serious risk of bias	0.88 [0.69-0.97]	0.96 [0.92-0.99]
Flisiak 1996 (flagella; serum)	34	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.14 [0.00-0.41]	1.00 [0.87-1.00]
Flisiak 1996 (recombinant; serum)	34	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.41]	1.00 [0.87-1.00]
Fung 1994 (serum)	155	VERY LOW[1] due to very serious risk of bias	0.84 [0.70-0.93]	0.86 [0.78-0.92]
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	0.98 [0.91-1.00]
Molins 2017 (serum)	232	VERY LOW[1]	1.00 [0.88-1.00]	0.98 [0.95-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Panelius 2001 (serum)	19	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.79 [0.54-0.94]	Cannot be estimated[5]
Rauer 1995 (recombinant; serum)	99	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.82 [0.57-0.96]	1.00 [0.96-1.00]
Sillanpaa 2007 (serum)	97	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.93 [0.66-1.00]	1.00 [0.96-1.00]
Lyme arthritis: ELISA (IgM/IgG)				
Ang 2015 (Diacheck; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.80 [0.28-0.99]	0.93 [0.68-1.00]
Ang 2015 (Enzygnost; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	0.88 [0.80-0.93]
Ang 2015 (Liaison; serum)	234	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.92 [0.87-0.95]
Ang 2015 (Serion; serum)	108	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.16-1.00]	0.72 [0.62-0.80]
Ang 2015 (Virotech; serum)	19	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.48-1.00]	1.00 [0.77-1.00]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.78-1.00]	0.96 [0.90-0.99]
Branda 2013 (USA; C6; serum)	115	VERY LOW[1,3] due to very serious risk of bias and	1.00 [0.78-1.00]	1.00 [0.96-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.93 [0.68-1.00]	0.97 [0.91-0.99]
Flisiak 1996 (flagella; serum)	34	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.71 [0.29-0.96]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	34	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.70 [0.50-0.86]
Fung 1994 (serum)	155	VERY LOW[1] due to very serious risk of bias	0.88 [0.75-0.95]	0.85 [0.77-0.91]
Johnson 1996 (serum)	149	VERY LOW[1] due to very serious risk of bias	0.89 [0.74-0.97]	0.96 [0.90-0.99]
Lahey 2015 (serum)	31	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.48-1.00]	0.96 [0.80-1.00]
Lawrenz 1999 (recombinant; serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.66-0.97]	0.98 [0.89-1.00]
Lawrenz 1999 (whole-cell; serum)	73	VERY LOW[1] due to very serious risk of bias	0.96 [0.78-1.00]	0.94 [0.83-0.99]
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	0.97 [0.88-1.00]
Molins 2014 (serum)	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.96 [0.92-0.98]
Molins 2016 (serum)	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.98 [0.94-0.99]
Rauer 1995 (recombinant; serum)	99	VERY LOW[1,3] due to very serious risk of bias and	0.94 [0.71-1.00]	0.96 [0.90-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Russell 1984 (serum)	138	VERY LOW[1] due to very serious risk of bias	1.00 [0.91-1.00]	0.96 [0.90-0.99]
Tjernberg 2007 (Quick C6; serum)	203	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.67 [0.09-0.99]	0.08 [0.05-0.13]
Tjernberg 2007 (Virotech; serum)	203	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.67 [0.09-0.99]	0.24 [0.18-0.31]
Lyme arthritis: ELISA C6				
Cinco 2006 (serum)	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.79-1.00]	1.00 [0.86-1.00]
Lyme arthritis: ELISA C6 (IgA)				
D'Arco 2017 (IgA; serum)	152	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.18 [0.04-0.43]	0.99 [0.95-1.00]
Lyme arthritis: ELFA				
Flisiak 1996 (serum)	34	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.93 [0.76-0.99]
Lyme arthritis: CLIA (IgM/IgG)				
Tjernberg 2007 (serum)	203	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.67 [0.09-0.99]	0.19 [0.14-0.25]
Lyme arthritis: Western blot/Immunoblot (IgM)				
Ang 2015 (Mikrogen; serum)	112	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.37]	0.97 [0.92-0.99]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and	0.67 [0.38-0.88]	0.91 [0.84-0.96]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.27 [0.08-0.55]	1.00 [0.96-1.00]
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.25]	0.98 [0.91-1.00]
Molins 2014 (serum)	232	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.15-0.51]	0.98 [0.95-0.99]
Molins 2016 (serum)	232	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.59 [0.39-0.76]	0.94 [0.90-0.97]
Porwancher 2011 (serum)	29	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.66 [0.46-0.82]	Cannot be estimated[5]
Lyme arthritis: Western blot/Immunoblot (IgG)				
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	1.00 [0.96-1.00]
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.38-0.88]	1.00 [0.96-1.00]
Dressler 1993 (prospective; serum)	164	VERY LOW[1] due to very serious risk of bias	0.96 [0.80-1.00]	0.95 [0.90-0.98]
Goettner 2005 (line blot; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.97-1.00]
Goettner 2005 (line blot plus; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.99 [0.95-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Goettner 2005 (WB; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.99 [0.95-1.00]
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	1.00 [0.94-1.00]
Molins 2014 (serum)	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.99 [0.96-1.00]
Molins 2016 (serum)	232	VERY LOW[1] due to very serious risk of bias	0.97 [0.82-1.00]	0.99 [0.96-1.00]
Panelius 2001 (serum)	14	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.86 [0.57-0.98]	Cannot be estimated[5]
Porwancher 2011 (serum)	82	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.34 [0.24-0.45]	Cannot be estimated[5]
Lyme arthritis: Western blot/Immunoblot (IgM/IgG)				
Ang 2015 (Mikrogen; serum)	112	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.63-1.00]	0.92 [0.85-0.97]
Branda 2013 (EU; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.93 [0.68-1.00]	0.91 [0.84-0.96]
Branda 2013 (USA; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.73 [0.45-0.92]	1.00 [0.96-1.00]
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	0.98 [0.91-1.00]
Molins 2014 (serum)	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.97 [0.94-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016 (serum)	232	VERY LOW[1] due to very serious risk of bias	0.97 [0.82-1.00]	0.93 [0.88-0.96]
Porwancher 2011 (serum)	479	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.95 [0.93-0.97]
Lyme arthritis: IFA (IgM)				
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.25]	0.98 [0.91-1.00]
Lyme arthritis: IFA (IgG)				
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.77 [0.46-0.95]	0.98 [0.91-1.00]
Lyme arthritis: IFA (IgM/IgG)				
Lencakova 2008 (serum)	73	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.77 [0.46-0.95]	0.98 [0.91-1.00]
Russell 1984 (serum)	138	VERY LOW[1] due to very serious risk of bias	1.00 [0.91-1.00]	1.00 [0.96-1.00]
Lyme arthritis: PCR				
Jaulhac 1996 (SF)	41	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.42 [0.15-0.72]	1.00 [0.88-1.00]
Molins 2014 (SF)	18	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.39 [0.17-0.64]	Cannot be estimated[5]
Nocton 1994 (SF)	152	VERY LOW[1] due to very serious risk of bias	0.85 [0.76-0.92]	1.00 [0.94-1.00]
Schnarr 2001 (SF)	47	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.41-0.89]	1.00 [0.89-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
van der Heijden 1999 (SF)	13	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.75 [0.19-0.99]	1.00 [0.66-1.00]
Vasiliu 1998 (SF)	30	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.65 [0.41-0.85]	1.00 [0.69-1.00]
Lyme carditis: ELISA (IgM)				
Molins 2017 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.71 [0.29-0.96]	0.89 [0.83-0.93]
Lyme carditis: ELISA (IgG)				
Molins 2017 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.98 [0.95-0.99]
Lyme carditis: ELISA (IgM/IgG)				
Molins 2014 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.96 [0.92-0.98]
Molins 2016 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.98 [0.94-0.99]
Russell 1984 (serum)	106	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.54-1.00]	0.96 [0.90-0.99]
Lyme carditis: IFA (IgM/IgG)				
Russell 1984 (serum)	106	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.54-1.00]	1.00 [0.96-1.00]
Lyme carditis: Western blot/Immunoblot (IgM)				
Molins 2014 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and	0.57 [0.18-0.90]	0.98 [0.95-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		very serious imprecision		
Molins 2016 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.71 [0.29-0.96]	0.94 [0.90-0.97]
Lyme carditis: Western blot/Immunoblot (IgG)				
Molins 2014 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.57 [0.18-0.90]	0.99 [0.96-1.00]
Molins 2016 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.71 [0.29-0.96]	0.99 [0.96-1.00]
Lyme carditis: Western blot/Immunoblot (IgM/IgG)				
Molins 2014 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.97 [0.94-0.99]
Molins 2016 (serum)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.93 [0.88-0.96]
Lyme carditis: PCR				
Molins 2014 (blood skin and heart)	7	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.29 [0.04-0.71]	Cannot be estimated[5]
Lyme carditis: Culture				
Molins 2014 (blood skin and heart)	4	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.60]	Cannot be estimated[5]
Acrodermatitis chronica atrophicans: ELISA (IgM)				
Ang 2015 (Diacheck; serum)	21	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.46]	1.00 [0.78-1.00]
Ang 2015 (Enzygnost; serum)	121	VERY LOW[1,3]	0.00 [0.00-0.23]	0.91 [0.83-0.95]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious imprecision		
Ang 2015 (Liaison; serum)	236	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.34]	0.97 [0.94-0.99]
Ang 2015 (Medac; serum)	94	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.84]	0.99 [0.94-1.00]
Ang 2015 (Serion; serum)	108	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.84]	0.73 [0.63-0.81]
Ang 2015 (Virotech; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.46]	1.00 [0.77-1.00]
Asbrink 1985 (after treatment; serum)	211	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.15 [0.04-0.35]	0.95 [0.91-0.98]
Asbrink 1985 (before treatment; serum)	211	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.27 [0.12-0.48]	0.95 [0.91-0.98]
Branda 2013 (EU; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.83 [0.52-0.98]	0.96 [0.90-0.99]
Hansen 1989 (flagellum; serum)	250	VERY LOW[1] due to very serious risk of bias	0.12 [0.05-0.24]	0.95 [0.91-0.98]
Hansen 1989 (sonic; serum)	250	VERY LOW[1] due to very serious risk of bias	0.22 [0.12-0.36]	0.94 [0.90-0.97]
Hansen 1991 (serum)	248	VERY LOW[1] due to very serious risk of bias	0.10 [0.03-0.23]	1.00 [0.98-1.00]
Karlsson 1989a (capture ELISA; serum)	83	VERY LOW[1,3] due to very serious risk of bias and	0.00 [0.00-0.31]	0.97 [0.90-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		very serious imprecision		
Karlsson 1989a (indirect ELISA; serum)	83	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.07-0.65]	0.90 [0.81-0.96]
Mathiesen 1996 (serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.15 [0.03-0.38]	0.99 [0.95-1.00]
Rauer 1995 (recombinant; serum)	124	VERY LOW[1] due to very serious risk of bias	0.00 [0.00-0.08]	0.96 [0.90-0.99]
Widhe 2004 (serum)	28	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.60 [0.15-0.95]	1.00 [0.85-1.00]
Acrodermatitis chronica atrophicans: ELISA (IgG)				
Asbrink 1985 (after treatment; serum)	211	VERY LOW[1] due to very serious risk of bias	0.92 [0.75-0.99]	0.95 [0.91-0.98]
Asbrink 1985 (before treatment; serum)	211	VERY LOW[1] due to very serious risk of bias	1.00 [0.87-1.00]	0.95 [0.91-0.98]
Branda 2013 (EU; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	0.98 [0.93-1.00]
Hansen 1989 (flagellum; serum)	250	VERY LOW[1] due to very serious risk of bias	1.00 [0.93-1.00]	0.96 [0.92-0.98]
Hansen 1989 (sonic; serum)	250	VERY LOW[1] due to very serious risk of bias	0.98 [0.89-1.00]	0.94 [0.90-0.97]
Hansen 1991 (serum)	248	VERY LOW[1] due to very serious risk of bias	1.00 [0.93-1.00]	1.00 [0.98-1.00]
Mathiesen 1996 (serum)	120	VERY LOW[1] due to very serious risk of bias	1.00 [0.83-1.00]	1.00 [0.96-1.00]
Panelius 2008 (serum)	30	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.80 [0.44-0.97]	1.00 [0.83-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Rauer 1995 (recombinant; serum)	124	VERY LOW[1] due to very serious risk of bias	0.33 [0.20-0.50]	1.00 [0.96-1.00]
Widhe 2004 (serum)	28	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.48-1.00]	1.00 [0.85-1.00]
Acrodermatitis chronica atrophicans: ELISA (IgM/IgG)				
Ang 2015 (Diacheck; serum)	21	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.54-1.00]	0.93 [0.68-1.00]
Ang 2015 (Enzygnost; serum)	121	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	0.88 [0.80-0.93]
Ang 2015 (Liaison; serum)	235	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.63-1.00]	0.92 [0.87-0.95]
Ang 2015 (Medac; serum)	94	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.16-1.00]	0.97 [0.91-0.99]
Ang 2015 (Serion; serum)	108	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.16-1.00]	0.72 [0.62-0.80]
Ang 2015 (Virotech; serum)	20	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.54-1.00]	1.00 [0.77-1.00]
Branda 2013 (EU; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	0.96 [0.90-0.99]
Branda 2013 (USA; C6; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Branda 2013 (USA; serum)	114	VERY LOW[1,3]	1.00 [0.77-1.00]	0.97 [0.91-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious imprecision		
Rauer 1995 (recombinant; serum)	124	VERY LOW[1] due to very serious risk of bias	0.86 [0.71-0.95]	0.96 [0.90-0.99]
Tjernberg 2007 (Quick C6; serum)	209	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.89 [0.52-1.00]	0.08 [0.05-0.13]
Tjernberg 2007 (Virotech; serum)	209	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.66-1.00]	0.24 [0.18-0.31]
Acrodermatitis chronica atrophicans: CLIA (IgM/IgG)				
Tjernberg 2007 (serum)	209	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.30-0.93]	0.19 [0.14-0.25]
Acrodermatitis chronica atrophicans: Western blot/Immunoblot (IgM)				
Ang 2015 (Mikrogen; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.28]	0.97 [0.92-0.99]
Branda 2013 (EU; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.36 [0.13-0.65]	0.91 [0.84-0.96]
Branda 2013 (USA; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.29 [0.08-0.58]	1.00 [0.96-1.00]
Mathiesen 1996 (serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.10 [0.01-0.32]	0.99 [0.95-1.00]
Acrodermatitis chronica atrophicans: Western blot/Immunoblot (IgG)				
Branda 2013 (EU; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (USA; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Goettner 2005 (line blot; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	1.00 [0.97-1.00]
Goettner 2005 (line blot plus; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.99 [0.95-1.00]
Goettner 2005 (WB; serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.99 [0.95-1.00]
Mathiesen 1996 (serum)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.05 [0.00-0.25]	0.96 [0.90-0.99]
Acrodermatitis chronica atrophicans: Western blot/Immunoblot (IgM/IgG)				
Ang 2015 (Mikrogen; serum)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.72-1.00]	0.92 [0.85-0.97]
Branda 2013 (EU; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	0.91 [0.84-0.96]
Branda 2013 (USA; serum)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Acrodermatitis chronica atrophicans: PCR				
Moter 1994 (skin)	16	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.62-1.00]	1.00 [0.40-1.00]
von Stedingk 1995 (skin)	112	VERY LOW[1] due to very serious risk of bias	0.61 [0.43-0.77]	1.00 [0.95-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Unspecified Lyme disease: ELISA (IgM)				
Flisiak 1996 (flagella; serum)	69	VERY LOW[1] due to very serious risk of bias	0.64 [0.48-0.78]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	69	VERY LOW[1] due to very serious risk of bias	0.60 [0.43-0.74]	0.70 [0.50-0.86]
Flisiak 1998 (serum)	74	VERY LOW[1] due to very serious risk of bias	0.58 [0.43-0.72]	0.88 [0.70-0.98]
Goossens 2000 (late; Behring; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.62 [0.32-0.86]	0.98 [0.91-1.00]
Goossens 2000 (late; Boehring; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.94-1.00]
Goossens 2000 (late; Dako; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.39-0.91]	0.95 [0.87-0.99]
Goossens 2000 (late; Genzyme Virotech; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.62 [0.32-0.86]	0.98 [0.91-1.00]
Goossens 2000 (late; IBL; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.62 [0.32-0.86]	0.90 [0.80-0.96]
Hernandez-Novoa 2003 (disseminated; serum)	147	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.41-0.87]	0.95 [0.89-0.98]
Hunfeld 2002 (serum)	1150	VERY LOW[1] due to very serious risk of bias	0.09 [0.03-0.22]	0.92 [0.90-0.94]
Karlsson 1989a (capture ELISA; serum)	150	VERY LOW[1] due to very serious risk of bias	0.39 [0.28-0.51]	0.97 [0.90-1.00]
Karlsson 1989a (indirect ELISA; serum)	150	VERY LOW[1] due to very serious risk of bias	0.31 [0.21-0.43]	0.90 [0.81-0.96]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Smismans 2006 (purified; serum)	53	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.39-0.91]	0.78 [0.62-0.89]
Smismans 2006 (synthetic C6; serum)	53	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	0.93 [0.80-0.98]
Smismans 2006 (whole-cell; serum)	53	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	0.53 [0.36-0.68]
Wilske 1993 (all Lyme disease; flagellin; serum)	276	VERY LOW[1] due to very serious risk of bias	0.36 [0.28-0.45]	0.96 [0.91-0.98]
Wilske 1993 (all Lyme disease; OGP-ELISA; serum)	276	VERY LOW[1] due to very serious risk of bias	0.46 [0.38-0.55]	0.97 [0.93-0.99]
Wilske 1993 (late; flagellin; serum)	185	VERY LOW[1] due to very serious risk of bias	0.14 [0.05-0.28]	0.96 [0.91-0.98]
Wilske 1993 (late; OGP-ELISA; serum)	185	VERY LOW[1] due to very serious risk of bias	0.23 [0.12-0.39]	0.97 [0.93-0.99]
Unspecified Lyme disease: ELISA (IgG)				
Flisiak 1996 (flagella; serum)	69	VERY LOW[1] due to very serious risk of bias	0.24 [0.12-0.39]	1.00 [0.87-1.00]
Flisiak 1996 (recombinant; serum)	69	VERY LOW[1] due to very serious risk of bias	0.29 [0.16-0.45]	1.00 [0.87-1.00]
Flisiak 1998 (serum)	74	VERY LOW[1] due to very serious risk of bias	0.46 [0.31-0.61]	1.00 [0.87-1.00]
Goossens 2000 (late; Behring; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	0.85 [0.74-0.93]
Goossens 2000 (late; Boehring; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.54 [0.25-0.81]	0.89 [0.78-0.95]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 2000 (late; Dako; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.77 [0.46-0.95]	0.97 [0.89-1.00]
Goossens 2000 (late; Genzyme Virotech; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	0.94 [0.84-0.98]
Goossens 2000 (late; IBL; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.39-0.91]	0.87 [0.76-0.94]
Hernandez-Novoa 2003 (disseminated; serum)	147	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.22 [0.06-0.48]	0.57 [0.48-0.66]
Hunfeld 2002 (serum)	1150	VERY LOW[1] due to very serious risk of bias	0.93 [0.81-0.99]	0.95 [0.93-0.96]
Nohlmans 1994 (late; Dako; serum)	105	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.86 [0.64-0.97]	0.99 [0.94-1.00]
Nohlmans 1994 (late; Diagast; serum)	105	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.86 [0.64-0.97]	1.00 [0.96-1.00]
Smismans 2006 (purified; serum)	62	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.59 [0.36-0.79]	1.00 [0.91-1.00]
Smismans 2006 (synthetic C6; serum)	62	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.71-0.99]	0.93 [0.80-0.98]
Smismans 2006 (whole-cell; serum)	62	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.71-0.99]	0.93 [0.80-0.98]
Wilske 1993 (all Lyme disease; flagellin; serum)	276	VERY LOW[1] due to very serious risk of bias	0.71 [0.62-0.78]	0.94 [0.88-0.97]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Wilske 1993 (all Lyme disease; OGP-ELISA; serum)	276	VERY LOW[1] due to very serious risk of bias	0.60 [0.51-0.68]	0.97 [0.93-0.99]
Wilske 1993 (flagellin; serum)	185	VERY LOW[1] due to very serious risk of bias	0.88 [0.75-0.96]	0.94 [0.88-0.97]
Wilske 1993 (OGP-ELISA; serum)	185	VERY LOW[1] due to very serious risk of bias	1.00 [0.92-1.00]	0.97 [0.93-0.99]
Unspecified Lyme disease: ELISA (IgM/IgG)				
Branda 2010 (serum)	251	VERY LOW[1] due to very serious risk of bias	1.00 [0.94-1.00]	0.96 [0.92-0.98]
Branda 2011 (early disseminated; serum)	1326	VERY LOW[1] due to very serious risk of bias	1.00 [0.87-1.00]	0.98 [0.98-0.99]
Branda 2011 (late; serum)	1329	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.98 [0.98-0.99]
Flisiak 1996 (flagella; serum)	69	VERY LOW[1] due to very serious risk of bias	0.76 [0.61-0.88]	0.85 [0.66-0.96]
Flisiak 1996 (recombinant; serum)	69	VERY LOW[1] due to very serious risk of bias	0.81 [0.66-0.91]	0.70 [0.50-0.86]
Flisiak 1998 (serum)	74	VERY LOW[1] due to very serious risk of bias	0.77 [0.63-0.88]	0.88 [0.70-0.98]
Gomes-Solecki 2001 (whole-cell; serum)	220	VERY LOW[1] due to very serious risk of bias	0.71 [0.62-0.79]	0.95 [0.89-0.98]
Goossens 2000 (late; Milenia; serum)	75	VERY LOW[1] due to very serious risk of bias	0.69 [0.39-0.91]	0.95 [0.87-0.99]
Hernandez-Novoa 2003 (disseminated; serum)	18	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.78 [0.52-0.94]	Cannot be estimated[5]
Hunfeld 2002 (serum)	43	VERY LOW[1] due to very serious risk of bias	0.95 [0.84-0.99]	Cannot be estimated[5]
Johnson 1996 (serum)	224	VERY LOW[1] due to very serious risk of bias	0.68 [0.58-0.76]	0.96 [0.90-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Jovicic 2003 (serum)	214	VERY LOW[1] due to very serious risk of bias	0.67 [0.57-0.76]	0.93 [0.87-0.97]
Ledue 2008 (early disseminated; serum)	848	VERY LOW[1] due to very serious risk of bias	0.80 [0.65-0.91]	0.98 [0.97-0.99]
Molins 2014 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.85 [0.78-0.91]	0.93 [0.89-0.96]
Molins 2015 (early Lyme disease; serum)	338	VERY LOW[1] due to very serious risk of bias	0.56 [0.49-0.63]	0.99 [0.96-1.00]
Molins 2016 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.81 [0.73-0.87]	0.98 [0.94-0.99]
Nohlmans 1994 (late; Diamedix; serum)	105	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.86 [0.64-0.97]	1.00 [0.96-1.00]
Nohlmans 1994 (late; Whittaker; serum)	105	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.71 [0.48-0.89]	1.00 [0.96-1.00]
Oksi 1995 (flagella; serum)	78	VERY LOW[1] due to very serious risk of bias	0.41 [0.26-0.58]	0.86 [0.71-0.95]
Oksi 1995 (recombinant; serum)	78	VERY LOW[1] due to very serious risk of bias	0.15 [0.06-0.29]	0.95 [0.82-0.99]
Oksi 1995 (sonicated; serum)	78	VERY LOW[1] due to very serious risk of bias	0.78 [0.62-0.89]	0.89 [0.75-0.97]
Smismans 2006 (purified; serum)	62	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.71-0.99]	0.78 [0.62-0.89]
Smismans 2006 (synthetic C6; serum)	62	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.91 [0.71-0.99]	0.93 [0.80-0.98]
Smismans 2006 (whole-cell; serum)	62	VERY LOW[1] due to very serious risk of bias	1.00 [0.85-1.00]	0.50 [0.34-0.66]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Steere 2008 (acute disseminated; serum)	149	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	0.96 [0.92-0.99]
Steere 2008 (chronic disseminated; serum)	167	VERY LOW[1] due to very serious risk of bias	1.00 [0.89-1.00]	0.96 [0.92-0.99]
Unspecified Lyme disease: ELFA				
Flisiak 1996 (serum)	69	VERY LOW[1] due to very serious risk of bias	0.79 [0.63-0.90]	0.93 [0.76-0.99]
Flisiak 1998 (serum)	74	VERY LOW[1] due to very serious risk of bias	0.81 [0.67-0.91]	0.92 [0.75-0.99]
Unspecified Lyme disease: Western blot/Immunoblot (IgM)				
Branda 2010 (serum)	251	VERY LOW[1] due to very serious risk of bias	0.50 [0.36-0.64]	1.00 [0.98-1.00]
Goossens 2000 (late; Genzyme Virotech; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.62 [0.32-0.86]	0.89 [0.78-0.95]
Goossens 2000 (late; MRL; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.54 [0.25-0.81]	0.98 [0.91-1.00]
Molins 2014 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.46 [0.37-0.55]	0.98 [0.95-0.99]
Molins 2015 (early Lyme disease; serum)	338	VERY LOW[1] due to very serious risk of bias	0.33 [0.26-0.41]	0.97 [0.93-0.99]
Molins 2016 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.65 [0.56-0.74]	0.94 [0.90-0.97]
Wilske 1993 (all Lyme disease; OspC-blot; serum)	276	VERY LOW[1] due to very serious risk of bias	0.43 [0.35-0.52]	0.97 [0.93-0.99]
Wilske 1993 (all Lyme disease; p100-blot; serum)	276	VERY LOW[1] due to very serious risk of bias	0.13 [0.08-0.20]	0.99 [0.96-1.00]
Wilske 1993 (all Lyme disease; p41/i-blot; serum)	276	VERY LOW[1]	0.15 [0.09-0.22]	0.99 [0.96-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Wilske 1993 (late; OspC-blot; serum)	185	VERY LOW[1] due to very serious risk of bias	0.40 [0.25-0.56]	0.97 [0.93-0.99]
Wilske 1993 (late; p100-blot; serum)	185	VERY LOW[1] due to very serious risk of bias	0.19 [0.08-0.33]	0.99 [0.96-1.00]
Wilske 1993 (late; p41/i-blot; serum)	185	VERY LOW[1] due to very serious risk of bias	0.12 [0.04-0.25]	0.99 [0.96-1.00]
Unspecified Lyme disease: Western blot/Immunoblot (IgG)				
Branda 2010 (serum)	251	VERY LOW[1] due to very serious risk of bias	0.86 [0.74-0.94]	0.99 [0.97-1.00]
Flisiak 1998 (serum)	74	VERY LOW[1] due to very serious risk of bias	0.50 [0.35-0.65]	1.00 [0.87-1.00]
Goettner 2005 (line blot; serum)	195	VERY LOW[1] due to very serious risk of bias	0.81 [0.71-0.89]	1.00 [0.97-1.00]
Goettner 2005 (line blot plus; serum)	195	VERY LOW[1] due to very serious risk of bias	0.85 [0.75-0.92]	0.99 [0.95-1.00]
Goettner 2005 (WB; serum)	195	VERY LOW[1] due to very serious risk of bias	0.71 [0.60-0.80]	0.99 [0.95-1.00]
Goossens 2000 (late; Genzyme Virotech; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.82 [0.70-0.91]
Goossens 2000 (late; MRL; serum)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.97 [0.89-1.00]
Klempner 2001 (serum)	31	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.43-0.85]	1.00 [0.69-1.00]
Molins 2014 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.47 [0.38-0.56]	0.99 [0.96-1.00]
Molins 2015 (early Lyme disease; serum)	338	VERY LOW[1]	0.04 [0.02-0.08]	1.00 [0.98-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Molins 2016 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.43 [0.34-0.52]	0.99 [0.96-1.00]
Wilske 1993 (all Lyme disease; OspC-blot; serum)	276	VERY LOW[1] due to very serious risk of bias	0.14 [0.09-0.21]	0.99 [0.96-1.00]
Wilske 1993 (all Lyme disease; p100-blot; serum)	276	VERY LOW[1] due to very serious risk of bias	0.51 [0.42-0.59]	0.94 [0.88-0.97]
Wilske 1993 (all Lyme disease; p41/i-blot; serum)	276	VERY LOW[1] due to very serious risk of bias	0.32 [0.24-0.41]	0.96 [0.91-0.98]
Wilske 1993 (late; OspC-blot; serum)	185	VERY LOW[1] due to very serious risk of bias	0.16 [0.07-0.31]	0.99 [0.96-1.00]
Wilske 1993 (late; p100-blot; serum)	185	VERY LOW[1] due to very serious risk of bias	1.00 [0.92-1.00]	0.94 [0.88-0.97]
Wilske 1993 (late; p41/i-blot; serum)	185	VERY LOW[1] due to very serious risk of bias	0.60 [0.44-0.75]	0.96 [0.91-0.98]
Wilske 1999 (late; recomb - new; serum)	178	VERY LOW[1] due to very serious risk of bias	0.97 [0.87-1.00]	0.98 [0.94-1.00]
Wilske 1999 (late; recomb - old; serum)	178	VERY LOW[1] due to very serious risk of bias	0.74 [0.58-0.87]	0.98 [0.94-1.00]
Wilske 1999 (late; whole-cell; serum)	178	VERY LOW[1] due to very serious risk of bias	1.00 [0.91-1.00]	0.98 [0.94-1.00]
Unspecified Lyme disease: Western blot/Immunoblot (IgM/IgG)				
Branda 2010 (serum)	251	VERY LOW[1] due to very serious risk of bias	0.98 [0.90-1.00]	0.99 [0.97-1.00]
Grodzicki 1988 (acute; serum)	50	VERY LOW[1] due to very serious risk of bias	0.53 [0.34-0.72]	1.00 [0.83-1.00]
Grodzicki 1988 (convalescent; serum)	50	VERY LOW[1] due to very serious risk of bias	0.83 [0.65-0.94]	1.00 [0.83-1.00]
Jovicic 2003 (serum)	214	VERY LOW[1]	0.93 [0.85-0.97]	0.96 [0.91-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Molins 2014 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.73 [0.64-0.80]	0.97 [0.94-0.99]
Molins 2015 (early Lyme disease; serum)	338	VERY LOW[1] due to very serious risk of bias	0.08 [0.05-0.13]	1.00 [0.98-1.00]
Molins 2016 (serum)	327	VERY LOW[1] due to very serious risk of bias	0.77 [0.69-0.84]	0.93 [0.88-0.96]
Unspecified Lyme disease: CLIA (IgM/IgG)				
Ledue 2008 (early disseminated; serum)	848	VERY LOW[1] due to very serious risk of bias	0.76 [0.60-0.88]	0.98 [0.98-0.99]
Molins 2015 (early Lyme disease; serum)	338	VERY LOW[1] due to very serious risk of bias	0.61 [0.54-0.68]	0.91 [0.86-0.95]
Unspecified Lyme disease: IFA (IgM)				
Cerar 2006 (chronic Lyme disease over 6mo; serum)	70	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.14 [0.03-0.36]	1.00 [0.93-1.00]
Cerar 2006 (early Lyme disease under 6mo; serum)	109	VERY LOW[1] due to very serious risk of bias	0.10 [0.04-0.21]	1.00 [0.93-1.00]
Wilske 1993 (all Lyme disease; IFA-ABS; serum)	276	VERY LOW[1] due to very serious risk of bias	0.23 [0.16-0.31]	0.97 [0.93-0.99]
Wilske 1993 (late; IFA-ABS; serum)	185	VERY LOW[1] due to very serious risk of bias	0.05 [0.01-0.16]	0.97 [0.93-0.99]
Unspecified Lyme disease: IFA (IgG)				
Cerar 2006 (chronic Lyme disease over 6 months; serum)	70	VERY LOW[1] due to very serious risk of bias	1.00 [0.84-1.00]	0.82 [0.68-0.91]
Cerar 2006 (early Lyme disease under 6 months; serum)	109	VERY LOW[1] due to very serious risk of bias	0.58 [0.45-0.71]	0.82 [0.68-0.91]
Hanrahan 1984 (titre 1:128; serum)	489	VERY LOW[1] due to very serious risk of bias	0.55 [0.47-0.63]	1.00 [0.98-1.00]
Hanrahan 1984 (titre 1:256; serum)	489	VERY LOW[1,2]	0.36 [0.28-0.44]	1.00 [0.99-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious indirectness		
Hanrahan 1984 (titre 1:64; serum)	489	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.70 [0.62-0.77]	0.97 [0.94-0.99]
Wilske 1993 (all Lyme disease; IFA-ABS; serum)	276	VERY LOW[1] due to very serious risk of bias	0.76 [0.68-0.83]	0.97 [0.93-0.99]
Wilske 1993 (late; IFA-ABS; serum)	185	VERY LOW[1] due to very serious risk of bias	1.00 [0.92-1.00]	0.97 [0.93-0.99]
Unspecified Lyme disease: IFA (IgM/IgG)				
Jovicic 2003 (serum)	214	VERY LOW[1] due to very serious risk of bias	0.36 [0.27-0.47]	0.89 [0.82-0.94]
Unspecified Lyme disease: Recombinant Rapid Assay				
Gomes-Solecki 2001 (recombinant; serum)	220	VERY LOW[1] due to very serious risk of bias	0.72 [0.64-0.80]	0.97 [0.91-0.99]
Unspecified Lyme disease: PCR				
Liebling 1993 (CSF)	28	VERY LOW[1] due to very serious risk of bias	1.00 [0.75-1.00]	0.93 [0.68-1.00]
Liebling 1993 (serum)	28	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.59 [0.36-0.79]	1.00 [0.54-1.00]
Liebling 1993 (SF)	27	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.80 [0.28-0.99]	1.00 [0.85-1.00]
Liebling 1993 (urine)	16	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.29-1.00]	0.92 [0.64-1.00]
Unspecified Lyme disease: CD57				
Stricker 2001 (acute Lyme disease)	32	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.31]	0.82 [0.60-0.95]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Stricker 2001 (chronic Lyme disease)	53	VERY LOW[1] due to very serious risk of bias	1.00 [0.89-1.00]	0.82 [0.60-0.95]
Unspecified Lyme disease: Culture				
Phillips 1998 (blood)	70	VERY LOW[1] due to very serious risk of bias	0.91 [0.80-0.98]	1.00 [0.85-1.00]
Unspecified Lyme disease: Lymphocyte transformation test				
von Baehr 2012 (stimulation index 3+; venous)	254	VERY LOW[1] due to very serious risk of bias	0.89 [0.81-0.95]	0.99 [0.96-1.00]
Post-treatment Lyme Disease Syndrome: ELISA (IgM/IgG)				
Fallon 2014 (commercial lab; serum)	77	VERY LOW[1] due to very serious risk of bias	0.68 [0.50-0.82]	0.93 [0.80-0.98]
Fallon 2014 (speciality lab A; serum)	77	VERY LOW[1] due to very serious risk of bias	0.68 [0.50-0.82]	0.97 [0.87-1.00]
Fallon 2014 (speciality lab B; serum)	77	VERY LOW[1] due to very serious risk of bias	0.68 [0.50-0.82]	0.93 [0.80-0.98]
Fallon 2014 (university reference; serum)	77	VERY LOW[1] due to very serious risk of bias	0.62 [0.45-0.76]	0.88 [0.73-0.96]
Post-treatment Lyme Disease Syndrome: Western blot/Immunoblot (IgM)				
Fallon 2014 (commercial lab; serum)	77	VERY LOW[1] due to very serious risk of bias	0.16 [0.06-0.32]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab A; serum)	77	VERY LOW[1] due to very serious risk of bias	0.03 [0.00-0.14]	0.97 [0.87-1.00]
Fallon 2014 (speciality lab B; serum)	77	VERY LOW[1] due to very serious risk of bias	0.43 [0.27-0.61]	0.80 [0.64-0.91]
Fallon 2014 (university reference; serum)	77	VERY LOW[1] due to very serious risk of bias	0.22 [0.10-0.38]	0.88 [0.73-0.96]
Porwancher 2011 (serum)	34	VERY LOW[1] due to very serious risk of bias	0.38 [0.22-0.56]	Cannot be estimated[5]
Post-treatment Lyme Disease Syndrome: Western blot/Immunoblot (IgG)				

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab; serum)	77	VERY LOW[1] due to very serious risk of bias	0.43 [0.27-0.61]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab A; serum)	77	VERY LOW[1] due to very serious risk of bias	0.43 [0.27-0.61]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab B; serum)	77	VERY LOW[1] due to very serious risk of bias	0.49 [0.32-0.66]	0.93 [0.80-0.98]
Fallon 2014 (university reference; serum)	77	VERY LOW[1] due to very serious risk of bias	0.57 [0.39-0.73]	0.97 [0.87-1.00]
Porwancher 2011 (serum)	34	VERY LOW[1] due to very serious risk of bias	0.50 [0.32-0.68]	Cannot be estimated[5]
Post-treatment Lyme Disease Syndrome: Western blot/Immunoblot (IgM/IgG)				
Porwancher 2011 (serum)	484	VERY LOW[1] due to very serious risk of bias	0.68 [0.49-0.83]	0.95 [0.93-0.97]
Time point – less than 6 weeks: ELISA (IgM)				
Hansen 1988 (NB; flagellum; CSF)	149	VERY LOW[1] due to very serious risk of bias	0.88 [0.75-0.96]	1.00 [0.97-1.00]
Hansen 1988 (NB; flagellum; serum)	358	VERY LOW[1] due to very serious risk of bias	0.51 [0.35-0.67]	0.97 [0.94-0.98]
Hansen 1988 (NB; sonic extract; CSF)	149	VERY LOW[1] due to very serious risk of bias	0.81 [0.67-0.92]	1.00 [0.97-1.00]
Hansen 1988 (NB; sonic extract; serum)	358	VERY LOW[1] due to very serious risk of bias	0.40 [0.25-0.56]	0.97 [0.94-0.98]
Hansen 1991 (EM; serum)	237	VERY LOW[1] due to very serious risk of bias	0.35 [0.20-0.53]	1.00 [0.98-1.00]
Hansen 1991 (NB; serum)	270	VERY LOW[1] due to very serious risk of bias	0.46 [0.34-0.58]	1.00 [0.98-1.00]
Hansen 1991a (NB; CSF)	99	VERY LOW[1] due to very serious risk of bias	0.71 [0.59-0.82]	1.00 [0.88-1.00]
Hansen 1991a (NB; serum)	99	VERY LOW[1]	0.61 [0.49-0.73]	1.00 [0.88-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Karlsson 1989 (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.36 [0.24-0.50]	0.98 [0.88-1.00]
Karlsson 1989a (EM; capture; serum)	101	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.29 [0.13-0.49]	0.97 [0.90-1.00]
Karlsson 1989a (EM; indirect; serum)	101	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.25 [0.11-0.45]	0.90 [0.81-0.96]
Karlsson 1989a (NB; capture; serum)	100	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.63 [0.42-0.81]	0.97 [0.90-1.00]
Karlsson 1989a (NB; indirect; serum)	100	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.44 [0.25-0.65]	0.90 [0.81-0.96]
Marangoni 2005 (EM; Enzygnost; serum)	309	VERY LOW[1] due to very serious risk of bias	0.69 [0.58-0.79]	0.96 [0.93-0.98]
Marangoni 2005 (EM; RecomWell; serum)	309	VERY LOW[1] due to very serious risk of bias	0.56 [0.44-0.67]	1.00 [0.98-1.00]
Padula 1994 (EM; recombinant; serum)	115	VERY LOW[1] due to very serious risk of bias	0.74 [0.58-0.87]	1.00 [0.95-1.00]
Padula 1994 (EM; whole-cell; serum)	115	VERY LOW[1] due to very serious risk of bias	0.64 [0.47-0.79]	1.00 [0.95-1.00]
Time point – less than 6 weeks: ELISA (IgG)				
Hansen 1988 (NB; flagellum; CSF)	149	VERY LOW[1] due to very serious risk of bias	0.58 [0.42-0.73]	1.00 [0.97-1.00]
Hansen 1988 (NB; flagellum; serum)	358	VERY LOW[1] due to very serious risk of bias	0.70 [0.54-0.83]	0.97 [0.95-0.99]
Hansen 1988 (NB; sonic extract; CSF)	149	VERY LOW[1] due to very serious risk of bias	0.51 [0.35-0.67]	1.00 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1988 (NB; sonic extract; serum)	358	VERY LOW[1] due to very serious risk of bias	0.28 [0.15-0.44]	0.96 [0.93-0.98]
Hansen 1991 (EM; serum)	237	VERY LOW[1] due to very serious risk of bias	0.22 [0.10-0.38]	1.00 [0.98-1.00]
Hansen 1991 (NB; serum)	270	VERY LOW[1] due to very serious risk of bias	0.77 [0.66-0.86]	1.00 [0.98-1.00]
Hansen 1991a (NB; CSF)	99	VERY LOW[1] due to very serious risk of bias	0.84 [0.74-0.92]	0.93 [0.77-0.99]
Hansen 1991a (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.77 [0.66-0.86]	0.97 [0.82-1.00]
Karlsson 1989 (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.27 [0.16-0.41]	0.93 [0.81-0.99]
Marangoni 2005 (EM; Enzygnost; serum)	309	VERY LOW[1] due to very serious risk of bias	0.69 [0.58-0.79]	0.88 [0.84-0.92]
Marangoni 2005 (EM; RecomWell; serum)	309	VERY LOW[1] due to very serious risk of bias	0.51 [0.39-0.62]	0.97 [0.94-0.99]
Time point – less than 6 weeks: ELISA (IgM/IgG)				
Karlsson 1989 (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.51 [0.37-0.65]	0.91 [0.78-0.97]
Marangoni 2005 (EM; Enzygnost; serum)	309	VERY LOW[1] due to very serious risk of bias	0.76 [0.65-0.85]	0.85 [0.79-0.89]
Marangoni 2005 (EM; Quick C6)	309	VERY LOW[1] due to very serious risk of bias	0.57 [0.45-0.69]	0.97 [0.93-0.99]
Marangoni 2005 (EM; RecomWell; serum)	309	VERY LOW[1] due to very serious risk of bias	0.68 [0.56-0.78]	0.97 [0.94-0.99]
Time point – less than 6 weeks: Western blot/Immunoblot (IgM)				
Karlsson 1989 (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.67 [0.53-0.79]	0.89 [0.75-0.96]
Padula 1994 (EM; serum)	115	VERY LOW[1]	0.72 [0.55-0.85]	0.97 [0.91-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Time point – less than 6 weeks: Western blot/Immunoblot (IgG)				
Karlsson 1989 (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.58 [0.44-0.71]	0.89 [0.75-0.96]
Time point – less than 6 weeks: Western blot/Immunoblot (IgM/IgG)				
Karlsson 1989 (NB; serum)	99	VERY LOW[1] due to very serious risk of bias	0.75 [0.61-0.85]	0.82 [0.67-0.92]
Time point – less than 6 weeks: Culture				
Sapi 2013 (blood)	120	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.47 [0.35-0.59]	1.00 [0.93-1.00]
Time point – 6 weeks to 6 months: ELISA (IgM)				
Hansen 1988 (NB; flagellum; CSF)	119	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	1.00 [0.97-1.00]
Hansen 1988 (NB; flagellum; serum)	328	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.97 [0.94-0.98]
Hansen 1988 (NB; sonic extract; CSF)	119	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	1.00 [0.97-1.00]
Hansen 1988 (NB; sonic extract; serum)	328	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.23 [0.05-0.54]	0.97 [0.94-0.98]
Hansen 1991 (EM; serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.23 [0.05-0.54]	1.00 [0.98-1.00]
Hansen 1991 (NB; serum)	230	VERY LOW[1] due to very serious risk of bias	0.17 [0.06-0.35]	1.00 [0.98-1.00]
Hansen 1991a (NB; CSF)	48	VERY LOW[1,3] due to very serious risk of bias and	0.84 [0.60-0.97]	1.00 [0.88-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		serious imprecision		
Hansen 1991a (NB; serum)	48	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.58 [0.33-0.80]	1.00 [0.88-1.00]
Kaiser 1999 (NB; less than 6 months; serum)	161	VERY LOW[1] due to very serious risk of bias	0.60 [0.49-0.71]	0.90 [0.81-0.96]
Karlsson 1989 (NB; over 6 weeks; serum)	57	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.23 [0.05-0.54]	0.98 [0.88-1.00]
Karlsson 1989a (EM; capture; serum)	75	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.16-1.00]	0.97 [0.90-1.00]
Karlsson 1989a (EM; indirect; serum)	75	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.50 [0.01-0.99]	0.90 [0.81-0.96]
Karlsson 1989a (NB; capture; serum)	83	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.07-0.65]	0.97 [0.90-1.00]
Karlsson 1989a (NB; indirect; serum)	83	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.03-0.56]	0.90 [0.81-0.96]
Marangoni 2005 (EM; Enzygnost; serum)	254	VERY LOW[1] due to very serious risk of bias	0.75 [0.51-0.91]	0.96 [0.93-0.98]
Marangoni 2005 (EM; RecomWell; serum)	254	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.55 [0.32-0.77]	1.00 [0.98-1.00]
Padula 1994 (EM; recombinant; serum)	91	VERY LOW[1] due to very serious risk of bias	0.67 [0.38-0.88]	1.00 [0.95-1.00]
Padula 1994 (EM; whole-cell; serum)	91	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.80 [0.52-0.96]	1.00 [0.95-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Time point – 6 weeks to 6 months: ELISA (IgG)				
Hansen 1988 (NB; flagellum; CSF)	119	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	1.00 [0.97-1.00]
Hansen 1988 (NB; flagellum; serum)	328	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	0.97 [0.95-0.99]
Hansen 1988 (NB; sonic extract; CSF)	119	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	1.00 [0.97-1.00]
Hansen 1988 (NB; sonic extract; serum)	328	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	0.96 [0.93-0.98]
Hansen 1991 (EM; serum)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.98-1.00]
Hansen 1991 (NB; serum)	230	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	1.00 [0.98-1.00]
Hansen 1991a (NB; CSF)	48	VERY LOW[1] due to very serious risk of bias	1.00 [0.82-1.00]	0.93 [0.77-0.99]
Hansen 1991a (NB; serum)	48	VERY LOW[1] due to very serious risk of bias	1.00 [0.82-1.00]	0.97 [0.82-1.00]
Kaiser 1999 (NB; less than 6 months; serum)	161	VERY LOW[1] due to very serious risk of bias	0.43 [0.32-0.55]	0.68 [0.56-0.78]
Karlsson 1989 (NB; over 6 weeks; serum)	57	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	0.93 [0.81-0.99]
Marangoni 2005 (EM; Enzygnost; serum)	254	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.45 [0.23-0.68]	0.88 [0.84-0.92]
Marangoni 2005 (EM; RecomWell; serum)	254	VERY LOW[1,3]	0.85 [0.62-0.97]	0.97 [0.94-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias and serious imprecision		
Time point – 6 weeks to 6 months: ELISA (IgM/IgG)				
Karlsson 1989 (NB; over 6 weeks; serum)	57	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.64-1.00]	0.91 [0.78-0.97]
Marangoni 2005 (EM; Enzygnost; serum)	254	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.62-0.97]	0.85 [0.79-0.89]
Marangoni 2005 (EM; Quick C6)	254	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.80 [0.56-0.94]	0.97 [0.93-0.99]
Marangoni 2005 (EM; RecomWell; serum)	254	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.95 [0.75-1.00]	0.97 [0.94-0.99]
Time point – 6 weeks to 6 months: Western blot/Immunoblot (IgM)				
Karlsson 1989 (NB; over 6 weeks; serum)	57	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.69 [0.39-0.91]	0.89 [0.75-0.96]
Padula 1994 (EM; serum)	91	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	0.97 [0.91-1.00]
Time point – 6 weeks to 6 months: Western blot/Immunoblot (IgG)				
Karlsson 1989 (NB; over 6 weeks; serum)	57	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.61-1.00]	0.89 [0.75-0.96]
Time point – 6 weeks to 6 months: Western blot/Immunoblot (IgM/IgG)				
Karlsson 1989 (NB; over 6 weeks; serum)	57	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.92 [0.61-1.00]	0.82 [0.67-0.92]
Time point – 6 weeks to 6 months: Culture				

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Sapi 2013 (16 weeks; blood)	120	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.94 [0.86-0.98]	1.00 [0.93-1.00]
Sapi 2013 (8 weeks; blood)	120	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	0.83 [0.73-0.91]	1.00 [0.93-1.00]
Time point – more than 6 months: ELISA (IgM)				
Hansen 1991a (NB; CSF)	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.09 [0.00-0.41]	1.00 [0.88-1.00]
Hansen 1991a (NB; serum)	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.18 [0.02-0.52]	1.00 [0.88-1.00]
Kaiser 1999 (NB; over 6 months; serum)	95	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.13 [0.02-0.40]	0.90 [0.81-0.96]
Time point – more than 6 months: ELISA (IgG)				
Hansen 1991a (NB; CSF)	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.72-1.00]	0.93 [0.77-0.99]
Hansen 1991a (NB; serum)	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.72-1.00]	0.97 [0.82-1.00]
Kaiser 1999 (NB; over 6 months; serum)	95	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.78-1.00]	0.68 [0.56-0.78]

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) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect.*
3) *Imprecision was assessed based on inspection of the confidence interval of sensitivity in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%.*

4) Inconsistency could not be assessed, as the committee was unable to set a sensitivity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.
5) Specificity could not be calculated because data on false positive and true negative results were not reported.

Table 9: Clinical evidence summary: initial tests for Lyme disease (children, cross-sectional studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Erythema migrans: ELISA (IgM)				
Bennet 2008 (serum)	182	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.83 [0.36-1.00]	0.81 [0.74-0.86]
Erythema migrans: ELISA (IgG)				
Bennet 2008 (serum)	182	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.00 [0.00-0.46]	0.98 [0.95-1.00]
Neuroborreliosis: ELISA (IgM)				
Bennet 2008 (serum)	246	LOW[1] due to very serious risk of bias	0.74 [0.62-0.84]	0.81 [0.74-0.86]
Neuroborreliosis: ELISA (IgG)				
Bennet 2008 (serum)	246	LOW[1] due to very serious risk of bias	0.47 [0.35-0.59]	0.98 [0.95-1.00]
Neuroborreliosis: CXCL13				
Barstad 2017 (CSF; cut-off 18 pg/ml)	178	MODERATE[1] Due to serious risk of bias	0.97 [0.88-1.00]	0.97 [0.93-0.99]
Barstad 2017 (CSF; cut-off 81 pg/ml)	178	MODERATE[1] Due to serious risk of bias	0.93 [0.84-0.98]	0.98 [0.94-1.00]
Barstad 2017 (CSF; cut-off 213 pg/ml)	178	MODERATE[1] Due to serious risk of bias	0.92 [0.81-0.97]	1.00 [0.97-1.00]
Facial palsy: ELISA (IgM)				
Bennet 2008 (serum)	191	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.47 [0.21-0.73]	0.81 [0.74-0.86]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Facial palsy: ELISA (IgG)				
Bennet 2008 (serum)	191	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.00 [0.00-0.22]	0.98 [0.95-1.00]
Lyme arthritis: PCR				
Avery 2006 (CSF)	108	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.05 [0.00-0.25]	0.99 [0.94-1.00]
Unspecified Lyme disease: ELISA C6				
Lipsett 2016 (serum)	944	LOW[1] due to very serious risk of bias	0.80 [0.71-0.87]	0.94 [0.92-0.96]
Unspecified Lyme disease: ELISA WCS				
Lipsett 2016 (serum)	944	LOW[1] due to very serious risk of bias	0.88 [0.80-0.93]	0.81 [0.78-0.83]

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) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect.*
3) *Imprecision was assessed based on inspection of the confidence interval of sensitivity in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*
4) *Inconsistency could not be assessed, as the committee was unable to set a sensitivity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

Table 10: Clinical evidence summary: initial tests for Lyme disease (children, case-control studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Erythema migrans: ELISA (IgM)				
Gerber 1995 (rOspC; serum)	132	VERY LOW[1] due to very serious risk of bias	0.46 [0.35-0.58]	0.98 [0.89-1.00]
Gerber 1995 (whole-cell; serum)	132	VERY LOW[1] due to very serious risk of bias	0.28 [0.19-0.39]	1.00 [0.93-1.00]
Erythema migrans: Western blot/Immunoblot (IgM)				
Gerber 1995 (serum)	132	VERY LOW[1]	0.29 [0.20-0.40]	1.00 [0.93-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
		due to very serious risk of bias		
Neuroborreliosis: ELISA (IgM)				
Krbkova 2016 (recombinant; CSF)	152	VERY LOW[1] due to very serious risk of bias	0.26 [0.17-0.36]	1.00 [0.95-1.00]
Krbkova 2016 (recombinant; serum)	152	VERY LOW[1] due to very serious risk of bias	0.50 [0.39-0.61]	0.94 [0.85-0.98]
Krbkova 2016 (whole-cell; CSF)	152	VERY LOW[1] due to very serious risk of bias	0.43 [0.32-0.54]	1.00 [0.95-1.00]
Krbkova 2016 (whole-cell; serum)	152	VERY LOW[1] due to very serious risk of bias	0.55 [0.44-0.65]	0.83 [0.72-0.91]
Neuroborreliosis: ELISA (IgG)				
Krbkova 2016 (recombinant; CSF)	152	VERY LOW[1] due to very serious risk of bias	0.80 [0.70-0.88]	0.97 [0.89-1.00]
Krbkova 2016 (recombinant; serum)	152	VERY LOW[1] due to very serious risk of bias	0.87 [0.78-0.93]	0.82 [0.70-0.90]
Krbkova 2016 (whole-cell; CSF)	152	VERY LOW[1] due to very serious risk of bias	0.64 [0.53-0.74]	1.00 [0.95-1.00]
Krbkova 2016 (whole-cell; serum)	152	VERY LOW[1] due to very serious risk of bias	0.73 [0.63-0.82]	0.80 [0.69-0.89]
Skogman 2008 (recombinant; CSF)	76	VERY LOW[1] due to very serious risk of bias	0.80 [0.64-0.91]	1.00 [0.90-1.00]
Neuroborreliosis: Western blot/Immunoblot (IgM)				
Krbkova 2016 (CSF)	152	VERY LOW[1] due to very serious risk of bias	0.13 [0.07-0.22]	1.00 [0.95-1.00]
Krbkova 2016 (serum)	152	VERY LOW[1] due to very serious risk of bias	0.36 [0.26-0.47]	0.97 [0.89-1.00]
Neuroborreliosis: Western blot/Immunoblot (IgG)				
Krbkova 2016 (CSF)	152	VERY LOW[1] due to very serious risk of bias	0.36 [0.26-0.47]	0.97 [0.89-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity (95% CI)	Specificity (95% CI)
Krbkova 2016 (serum)	152	VERY LOW[1] due to very serious risk of bias	0.55 [0.44-0.65]	0.91 [0.81-0.97]
Neuroborreliosis: CXCL13				
Wutte 2011 (serum) 100 pg/ml	322	VERY LOW[1,2,3] due to very serious risk of bias, serious indirectness and serious imprecision	0.73 [0.50-0.89]	0.87 [0.83-0.91]
Lyme arthritis: ELISA (IgG)				
Heikkila 2002 (serum)	92	VERY LOW[1] due to very serious risk of bias	0.77 [0.63-0.87]	0.95 [0.83-0.99]

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) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect.*
3) *Imprecision was assessed based on inspection of the confidence interval of sensitivity in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*
4) *Inconsistency could not be assessed, as the committee was unable to set a sensitivity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

1.4 Economic evidence

1.4.1 Included studies

No relevant health economic studies were identified.

1.4.2 Excluded studies

Two economic studies relating to this review question were identified but were excluded due to a combination of limited applicability and very serious methodological limitations.[184 ,292] These are listed in appendix I, with reasons for exclusion given.

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

1.4.3 Health economic exploratory analysis

An exploratory analysis was conducted to estimate the additional cost of 2-tier testing (ELISA including C6 IgM and IgG followed by confirmatory immunoblot if ELISA is positive) over initial testing only (ELISA including C6 IgM and IgG) in people with suspected Lyme disease and evaluate what the cost of a misdiagnosis (either false positive or false negative) would need to be for 2-tier testing to be cost-neutral. A detailed write up of this analysis is available in appendix H.

The results of this exploratory analysis indicate that the cost of a misdiagnosis would need to be between £69 and £381 (depending on data inputs used) for the 2-tier testing to be cost neutral compared to initial testing only.

Overall, the committee considered that a misdiagnosis was very likely to cost at least £381, as these people would have a number of healthcare interactions whether the misdiagnosis was a false positive or a false negative. Therefore, the committee agreed that 2-tier testing is very likely to be at least cost neutral compared to initial testing only and that it may even be cost saving.

1.4.4 Unit costs

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

Table 11: NHS costs of Lyme disease tests

Test	Unit cost (a)
C6 antigen-based ELISA (combined IgG and IgM)	£25.45
Lyme immunoblot (IgG and IgM) and ELISA (as above)	£95.56
Lyme PCR (b)	£42.23

Source: Public Health England Rare and Imported Pathogens Laboratory, April 2016-March 2017.[385]
(a) A handling fee may be added onto these published costs by local pathology laboratories.
(b) For testing joint fluid, biopsy tissue and cerebrospinal fluid.

1.5 Resource impact

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

1.6 Evidence statements

1.6.1 Clinical evidence statements

Overall, the evidence was of Very Low quality due to the case-control study design, risk of bias and imprecision. The included studies varied significantly by test, study population and clinical presentation. It was not possible to meta-analyse the large number of results because studies with comparable tests differed in how clinical presentations were reported, how tests were conducted and analysed and how the test results were interpreted.

Generally, combined IgM/IgG tests showed better sensitivity and specificity results for different clinical presentations of Lyme disease than IgM-only and IgG-only tests. There was no clear advantage of ELISAs over immunoblots or western blots or vice versa for any clinical presentation. *Borrelia* culture and polymerase chain reaction (PCR), which also functioned as reference standards in this review, showed poor results when compared to clinical diagnosis. There was only limited evidence for other tests, which required caution when interpreting the results.

The analyses by time point did not show any clear advantage of 1 test over the other. IgM tests tended to have a higher sensitivity in the early stages of Lyme disease, such as the erythema migrans, and a lower sensitivity in later stages of Lyme disease. By contrast, the sensitivity of IgG test increased with disease progression.

There was only limited evidence in children. The sensitivity of tests was generally lower in children than in adults. There was no noticeable difference in specificity between adults and children for different clinical presentations of Lyme disease.

1.6.2 Health economic evidence statements

One original exploratory analysis found that the cost of a misdiagnosis (false positive or false negative) would need to be between £69 and £381 (depending on data inputs used) for 2-tier testing (ELISA and immunoblot) to be cost neutral compared to initial testing only (ELISA) in people with suspected Lyme disease. This analysis was assessed as partially applicable with potentially serious limitations.

2 Confirmatory tests for Lyme disease

2.1 Review question: In people with a positive test for Lyme disease, what is the most accurate test to confirm or rule out Lyme disease?

2.2 PICO table

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

Table 12: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with a positive test for Lyme disease
Target condition	Lyme disease, specifically conditions caused by *Borrelia burgdorferi sensu lato*
Index tests	Serology assays: • *Borrelia* recomLine IgG (Mikrogen) • *Borrelia* Virastripe IgM/IgG (Viramed) • C6 ELISA (Immunetics) • Diasorin LIAISON *Borrelia* IgM Quant • Enzygnost Lyme link IgG/VlsE (Siemens) • VIDAS Lyme IgM and IgG (Biomerieux) • Other assays used elsewhere in the world: ○ Anti-*Borrelia* EUROLINE-RN-AT IgG (Euroimmun) ○ Anti-*Borrelia* EUROLINE-WB IgG, IgM (Euroimmun) ○ Anti-*Borrelia* EUROLONE-RN-AT IgM (Euroimmun) ○ Anti-*Borrelia* plus VlsE ELISA (IgG) & anti-*Borrelia* ELISA (IgM; Euroimmun) ○ *B Burgdorferi* IgG EIA (Diagnostic Automation) ○ *Borrelia* ViraChip IgG/IgM assay (ViraMed) ○ Capita™ B. burgdorferi IgG.IgM EIA (Trinity Biotech) ○ Genzyme Virotech *Borrelia* Europe Line (Virotech) ○ Immunoblot IgG (IGeneX) ○ MardX EU Lyme and VLSE Immunoblots (Trinity Biotech) ○ NovaLisa IgG EIA (Nova Tec) ○ Premier Lyme EIA IgG/IgM (Meridian Bioscience Inc.) ○ recomBead *Borrelia* IgG/IgM v2.0 (Mikrogen) ○ RecomLine *Borrelia* IgG/IgM Immunoblot (Mikrogen) ○ RecomWell *Borrelia* IgG/IgM (Mikrogen) ○ SeraSpot Anti-*Borrelia* IgG/IgM (Seramun Diagnostica GmbH) ○ VIR-ELISA anti-*Borrelia* IgG/IgM (VIRO-IMMUN Labor-Diagnostika GmbH) Direct microscopic visualisation • Biopsy/histology Lymphocyte transformation tests: • EliSpot • LTT-MELISA® • SpiroFind™ assay (Boulder Diagnostics) CD57 test

	Inflammatory markers: • C-reactive protein (CRP) • Erythrocyte sedimentation rate (ESR) Full blood count: • Eosinophil • Haemoglobin • Lymphocyte • Monocyte • Neutrophil/Band/ANC • Platelet • White blood cell (WBC) CXCL13 (from a CSF or serum sample) PCR • Cerebrospinal fluid (CSF) analysis • Synovial fluid analysis
Reference standards	• *Borrelia* culture (Spirochaete is difficult to culture, grows slowly, and is therefore not compatible with providing a rapid diagnostic result). • PCR • Clinical diagnosis All index tests compared with all reference tests and reference tests compared with each other (in this case, clinical diagnosis will be the reference standard).

Statistical measures	Confirming Lyme disease:
	• Critical
	  ○ Specificity
	• Important
	  ○ Sensitivity
	  - Positive Predictive Value
	  ○ Negative Predictive Value
	  ○ 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 in a cross-sectional design Exclude (unless there is insufficient evidence and agreed to include with committee): • Two-gate or 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 reports • Case series

We searched for studies assessing the diagnostic test accuracy of any of the above-mentioned tests to identify whether Lyme disease is present. The search found a very large number of studies because we could not define any limits for our clinical evidence search without risking the omission of relevant papers. It was not possible to identify whether a study

provided evidence for the review question on initial tests, confirmatory tests or combination of tests based on the title and abstract alone. Therefore, one search was undertaken and sifted to identify the clinical evidence for all 3 review questions. The PRISMA flow-chart (appendix C) and the excluded studies list (appendix I) reflect this approach in all 3 subchapters of this evidence report: initial tests, confirmatory tests and combination of tests for Lyme disease.

2.3 Clinical evidence

2.3.1 Included studies

Five studies were included in the review; 4 case-control studies[53,62,272,481] and 1 cross-sectional study.[27] These are summarised in Table 13, Table 14 and Table 15 below. No studies in children were identified for this review. Evidence from the included studies is summarised in the clinical evidence profile below. See also the study selection flow chart in appendix C, sensitivity and specificity forest plots in appendix E, study evidence tables in appendix D and exclusion list in appendix I.

One study[481] also provided evidence on the number of positive results of confirmatory tests following a negative initial test result. A summary is provided in Table 15 below.

Some studies in adults with a very wide age range also included children and young people. These studies were, however, included in the evidence in adults as the mean or median age of the study population was well above 18, indicating that the majority of included people were adults. There were no studies specifically conducted in young people aged 12 to 17.

The included studies varied significantly by test, study population and clinical presentation, which made it impossible to meta-analyse the large number of results. Given the general lack of evidence from cross-sectional studies, which are the most robust study design for diagnostic accuracy studies, case-control studies were also included in this review. The committee considered the entirety of the evidence when making recommendations.

Three different reference standards were identified for this review: *Borrelia* culture, polymerase chain reaction (PCR) and clinical diagnosis. Spirochaete is difficult to culture, grows slowly, and is therefore not compatible with providing a rapid diagnostic result. As a result, it is rarely used as a reference standard in clinical studies. In case *Borrelia* culture or PCR were used as an index test in any of the included studies, clinical diagnosis would function as the reference standard.

Overall, the committee found the evidence difficult to interpret due to the differences within and between the studies, which meant that meta-analyses were not possible. Studies varied widely in populations, both cases and controls, the types of tests used, test implementation and interpretation of test results. To improve comparability between results only healthy controls were included in the analyses if possible.

2.3.2 Excluded studies

See the excluded studies list in appendix I.

2.3.3 Summary of clinical studies included in the evidence review

Table 13: Summary of included case-control studies (adults)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Coyle 1993[62]	n=77 Clinical evidence of *B burgdorferi* infection and neurological problems Age (mean): 34 years (3-84)	n=34 Other neurological diseases	Western blot	*IgG* Western blot	CSF	Clinical diagnosis	
Christova 2003[53]	n=105 EM Age: not reported	n=90 Healthy blood donors	IFA Recombinant immunoblot	*IgM and IgG* IFA Recombinant immunoblot	Serum	Clinical diagnosis	
Magnarelli 1992[272]	n=53 EM with antibodies (n=17) EM without antibodies (n=36) Age: not reported	n=40 Healthy persons	ELISA	*IgG* Biotin streptavidin amplified ELISA whole cells Biotin streptavidin amplified ELISA p41-G	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Trevejo 2001[481]	n=74 EM With a positive initial test: Acute phase (n=28) Convalescent phase (n=43) Age: median 41 years (3-83)	n=38 Healthy controls	Western blot	*IgM and IgG* Marblot MarDx Diagnostics, USA	Serum	Clinical diagnosis	Acute phase sera taken a median of 4 days after illness onset (range 0-19); convalescent sera taken a median of 36 days after illness onset (range 21-161)

Table 14: Summary of included cross-sectional studies (adults)

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
Blaauw 1999[27]	n=105 Diagnosed or suspected chronic Lyme with musculoskeletal complaints Age (mean): 48.7 years (6-82)	Lyme disease	Western blot	*IgG* Immunoblot	Serum	Clinical diagnosis	Previous Lyme disease not included in the analysis as there was no reference standard

See appendix D for full evidence tables.

Table 15: Additional data

Study	Population and target condition	Control group	Tests	Results	Comments
Trevejo 2001[481]	n=74 EM Acute phase (n=66) Convalescent phase (n=55) Age: median 41 years (3-83)	n=38 Healthy controls	*IgM and IgG* Vidas bioMerieux, France Marblot MarDx Diagnostics, USA	Negative initial test followed by a positive confirmatory test: <u>Acute EM:</u> Initial EIA positive: 25 (37.9%) Confirmatory western blot positive: 19 (76%) Confirmatory western blot negative: 6 (24%) Initial EIA equivocal: 3 (4.5%) Confirmatory western blot positive: 2 (66.7%) Confirmatory western blot negative: 1 (33.3%) Initial EIA negative: 38 (57.6%) Confirmatory western blot positive: 4 (10.5%) Confirmatory western blot negative: 34 (89.5%)	Acute phase sera taken a median of 4 days after illness onset (range 0-19); convalescent sera taken a median of 36 days after illness onset (range 21-161) No data on convalescent phase EM reported

2.3.4 Quality assessment of clinical studies included in the evidence review

Table 16: Clinical evidence summary: confirmatory tests for Lyme disease (adults, cross-sectional studies)

Index Test (Threshold)	n	Quality[3]	Sensitivity % (95% CI)	Specificity % (95% CI)
<u>Unspecified Lyme disease: Immunoblot (IgG)</u>				

Index Test (Threshold)	n	Quality[3]	Sensitivity % (95% CI)	Specificity % (95% CI)
Blaauw 1999 (serum)	22	VERY LOW[1,2] due to very serious risk of bias and serious imprecision	1.00 [0.69-1.00]	0.42 [0.15-0.72]

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 interval of specificity in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%.*
3) *Inconsistency could not be assessed, as the committee was unable to set a specificity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

Table 17: Clinical evidence summary: confirmatory tests for Lyme disease (adults, case-control studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Erythema migrans: ELISA (IgG)				
Magnarelli 1992 (recombinant; serum)	57	VERY LOW[1] due to very serious risk of bias	0.94 [0.71-1.00]	1.00 [0.91-1.00]
Magnarelli 1992 (whole-cell; serum)	57	VERY LOW[1] due to very serious risk of bias	1.00 [0.80-1.00]	1.00 [0.91-1.00]
Erythema migrans: Immunoblot (IgM)				
Christova 2003 (serum)	141	VERY LOW[1] due to very serious risk of bias	0.71 [0.56-0.83]	1.00 [0.96-1.00]
Erythema migrans: Immunoblot (IgG)				
Christova 2003 (serum)	108	VERY LOW[1] due to very serious risk of bias	0.67 [0.41-0.87]	1.00 [0.96-1.00]
Erythema migrans: Immunoblot (IgM/IgG)				
Trevejo 2001 (acute; serum)	104	VERY LOW[1] due to very serious risk of bias	0.75 [0.55-0.89]	0.97 [0.86-1.00]
Trevejo 2001 (convalescent; serum)	91	VERY LOW[1] due to very serious risk of bias	0.37 [0.23-0.53]	0.97 [0.86-1.00]
Erythema migrans: IFA (IgM)				
Christova 2003 (serum)	141	VERY LOW[1] due to very serious risk of bias	0.47 [0.33-0.62]	1.00 [0.96-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Erythema migrans: IFA (IgG)				
Christova 2003 (serum)	108	VERY LOW[1] due to very serious risk of bias	0.83 [0.59-0.96]	1.00 [0.96-1.00]
Neuroborreliosis: Immunoblot (IgG)				
Coyle 1993 (CSF)	33	VERY LOW[1,2,3] due to very serious risk of bias, serious imprecision and serious indirectness	0.55 [0.32-0.76]	1.00 [0.72-1.00]

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 intervals in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, 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 are seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect.*
4) *Inconsistency could not be assessed, as the committee was unable to set a specificity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

2.4 Economic evidence

2.4.1 Included studies

No relevant health economic studies were identified.

2.4.2 Excluded studies

Two economic studies relating to this review question were identified but were excluded due to a combination of limited applicability and very serious methodological limitations.[184 ,292] These are listed in appendix I, with reasons for exclusion given.

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

2.4.3 Health economic exploratory analysis

An exploratory analysis was conducted to estimate the additional cost of 2-tier testing (ELISA including C6 IgM and IgG followed by confirmatory immunoblot if ELISA is positive) over initial testing only (ELISA including C6 IgM and IgG) in people with suspected Lyme disease and evaluate what the cost of a misdiagnosis (either false positive or false negative) would need to be for 2-tier testing to be cost-neutral. A detailed write up of this analysis is available in appendix H.

The results of this exploratory analysis indicate that the cost of a misdiagnosis would need to be between £69 and £381 (depending on data inputs used) for the 2-tier testing to be cost neutral compared to initial testing only.

Overall, the committee considered that a misdiagnosis was very likely to cost at least £381, as these people would have a number of healthcare interactions whether the misdiagnosis was a false positive or a false negative. Therefore, the committee agreed that 2-tier testing is very likely to be at least cost neutral compared to initial testing only and that it may even be cost saving.

2.4.4 Unit costs

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

Table 18: NHS costs of Lyme disease tests

Test	Unit cost (a)
C6 antigen-based ELISA (combined IgG and IgM)	£25.45
Lyme immunoblot (IgG and IgM) and ELISA (as above)	£95.56
Lyme PCR (b)	£42.23

Source: Public Health England Rare and Imported Pathogens Laboratory, April 2016-March 2017[385]
(a) A handling fee may be added onto these published costs by local pathology laboratories.
(b) For testing joint fluid, biopsy tissue and cerebrospinal fluid.

2.5 Resource impact

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

2.6 Evidence statements

2.6.1 Clinical evidence statements

Evidence on the accuracy of confirmatory tests in confirming Lyme disease was very limited. Very Low quality evidence from 3 case-control studies in adults showed a higher sensitivity of IgG-specific tests compared to a test detecting IgM antibodies for confirming Lyme disease in people with an erythema migrans. Specificity across the included studies was generally very high although there is a risk of overestimation due to the case-control study design. Very Low quality evidence from 1 cross-sectional study showed a very high sensitivity, but low specificity of an IgG-specific immunoblot for confirming Lyme disease in adults. The very limited evidence on combined IgM/IgG immunoblots was inconclusive.

No evidence in children could be identified.

2.6.2 Health economic evidence statements

One original exploratory analysis found that the cost of a misdiagnosis (false positive or false negative) would need to be between £69 and £381 (depending on data inputs used) for 2-tier testing (ELISA and immunoblot) to be cost neutral compared to initial testing only (ELISA) in people with suspected Lyme disease. This analysis was assessed as partially applicable with potentially serious limitations.

3 Combination of diagnostic tests for Lyme disease

3.1 Review question: In people with suspected (or under investigation for) Lyme disease, what is the most accurate combination of tests to identify whether Lyme disease is present?

3.2 PICO table

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

Table 19: 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	Any combination of the test listed below:
	
	Serology assays:
	• *Borrelia* recomLine IgG (Mikrogen)
	• *Borrelia* Virastripe IgM/IgG (Viramed)
	• C6 ELISA (Immunetics)
	• Diasorin LIAISON *Borrelia* IgM Quant
	• Enzygnost Lyme link IgG/VlsE (Siemens)
	• VIDAS Lyme IgM and IgG (Biomerieux)
	• Other assays used elsewhere in the world:
	  ○ Anti-*Borrelia* EUROLINE-RN-AT IgG (Euroimmun)
	  ○ Anti-*Borrelia* EUROLINE-WB IgG, IgM (Euroimmun)
	  ○ Anti-*Borrelia* EUROLONE-RN-AT IgM (Euroimmun)
	  ○ Anti-*Borrelia* plus VlsE ELISA (IgG) & Anti-*Borrelia* ELISA (IgM; Euroimmun)
	  ○ *B Burgdorferi* IgG EIA (Diagnostic Automation)
	  ○ *Borrelia* ViraChip IgG/IgM assay (ViraMed)
	  ○ Capita™ *B. burgdorferi* IgG.IgM EIA (Trinity Biotech)
	  ○ Genzyme Virotech *Borrelia* Europe Line (Virotech)
	  ○ Immunoblot IgG (IGeneX)
	  ○ MardX EU Lyme and VLSE Immunoblots (Trinity Biotech)
	  ○ NovaLisa IgG EIA (Nova Tec)
	  ○ Premier Lyme EIA IgG/IgM (Meridian Bioscience Inc.)
	  ○ recomBead *Borrelia* IgG/IgM v2.0 (Mikrogen)
	  ○ RecomLine *Borrelia* IgG/IgM Immunoblot (Mikrogen)
	  ○ RecomWell *Borrelia* IgG/IgM (Mikrogen)
	  ○ SeraSpot Anti-*Borrelia* IgG/IgM (Seramun Diagnostica GmbH)
	  ○ VIR-ELISA anti-*Borrelia* IgG/IgM (VIRO-IMMUN Labor-Diagnostika GmbH)
	
	Direct microscopic visualisation
	• Biopsy/histology

	Lymphocyte transformation tests: • EliSpot • LTT-MELISA® • SpiroFind™ assay (Boulder Diagnostics) CD57 test Inflammatory markers: • C-reactive protein (CRP) • Erythrocyte sedimentation rate (ESR) Full blood count: • Eosinophil • Haemoglobin • Lymphocyte • Monocyte • Neutrophil/Band/ANC • Platelet • White blood cell (WBC) CXCL13 (from a CSF or serum sample) PCR • Cerebrospinal fluid (CSF) analysis • Synovial fluid analysis
Reference standards	• *Borrelia* culture (Spirochaete is difficult to culture and grows slowly; therefore, it is not compatible with providing a rapid diagnostic result). • Clinical diagnosis • PCR All index test combinations compared with all reference tests. *Borrelia* culture or PCR can also be part of the test combinations, in which case clinical diagnosis functions as the reference standard.

Statistical measures	Detecting Lyme disease
	• Critical:
	  ○ Sensitivity
	• Important:
	  ○ Specificity
	  ○ Positive Predictive Value
	  ○ Negative Predictive Value
	  ○ 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 in a cross-sectional design Exclude (unless there is insufficient evidence and agreed to include with the committee): • Two-gate or 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 reports

- Case series

We searched for studies assessing the diagnostic test accuracy of any of the above-mentioned tests to identify whether Lyme disease is present. The search found a very large number of studies because we could not define any limits for our clinical evidence search without risking the omission of relevant papers. It was not possible to identify whether a study provided evidence for the review question on initial tests, confirmatory tests or combination of tests based on the title and abstract alone. Therefore, one search was undertaken and sifted to identify the clinical evidence for all 3 review questions. The PRISMA flow-chart (appendix C) and the excluded studies list (appendix I) reflect this approach in all 3 subchapters of this evidence report: initial tests, confirmatory tests and combination of tests for Lyme disease.

3.3 Clinical evidence

3.3.1 Included studies

Fifteen studies (16 papers) were included in the review;[8 ,17 ,32-34 ,108 ,139 ,140 ,190 ,243 ,307 ,308 ,364 ,458 ,481 ,506] these are summarised in Table 20 and Table 21: Summary of included cross-sectional studies (children)

Study	Population	Target condition	Type of index test	Index test	Sample
Lipsett 2016[243]	n=944 Children and adolescents undergoing serologic evaluation for Lyme disease Age (median and IQR): 10.9 (6.4-15.2) years	Lyme disease	EIA Immunoblot	Whole cell sonicate Lyme EIA (MarDx; Trinity Biotech) C6 Lyme EIA test (Immunetics) IgG and IgM Western Immunoblots (MarDx; Trinity Biotech)	Serum

below. Fourteen studies were in adults[8 ,17 ,32-34 ,108 ,139 ,140 ,190 ,307 ,308 ,364 ,458 ,481 ,506] and 1 study was in children.[243] All studies in adults and young people were of a case-control study design. The single study in children was of a cross-sectional study design. Evidence from the included studies is summarised in the clinical evidence profile below. See also the study selection flow chart in appendix C, sensitivity and specificity forest plots in appendix E, study evidence tables in appendix D and exclusion list in appendix I.

Some studies in adults with a very wide age range also included children and young people. These studies were, however, included in the evidence in adults as the mean or median age of the study population was well above 18, indicating that the majority of included people were adults. There were no studies specifically conducted in young people aged 12 to 17.

The included studies varied significantly by test, study population and clinical presentation, which made it impossible to meta-analyse the large number of results. Given the general lack of evidence from cross-sectional studies, which are the most robust study design for

diagnostic accuracy studies, case-control studies were also included in this review. The committee considered the entirety of the evidence when making recommendations.

Three different reference standards were identified for this review: *Borrelia* culture, polymerase chain reaction (PCR) and clinical diagnosis. Spirochaete is difficult to culture and grows slowly; therefore, it is not compatible with providing a rapid diagnostic result. As a result, it is rarely used as a reference standard in clinical studies. In case *Borrelia* culture or PCR were used as an index test in any of the included studies, clinical diagnosis would function as the reference standard.

Overall, the committee found the evidence difficult to interpret due to the differences within and between the studies, which meant that meta-analyses were not possible. Studies varied widely in populations, both cases and controls, the types of tests used, test implementation and interpretation of test results. To improve comparability between results only healthy controls were included in the analyses if possible.

3.3.2 Excluded studies

See the excluded studies list in appendix I.

3.3.3 Summary of clinical studies included in the evidence review

Table 20: Summary of included case-control studies (adults)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Ang 2015[8]	n=316 EM (n=214) Neuroborreliosis (n=102) Age: not reported	n=228 Healthy controls	EIA WB	IgM and IgG ELISA: C6-ELISA Immunetics, USA Enzygnost Siemans, Germany Western blot: RecomLine Mikrogen, Germany	Serum	ESGBOR guidelines Clinical diagnosis PCR confirmation Histopathology CSF pleocytosis	IgM and IgG equals positive result for IgMor IgG Borderline results excluded from the analysis as the study authors did not necessarily interpret them as positive evidence of infection
Bacon 2003[17]	n=280 Acute Lyme (n=80) Early convalescent (n=106) Early neurological (n=15) Early neurological convalescent (n=11) Arthritis (n=33) Arthritis convalescent (n=24)	n=257 Healthy persons	ELISA	IgM and IgG ELISA Vidas BioMerieux Vitek Marblot MarDx Diagnostics	Serum	Clinical diagnosis CDC criteria	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Late neurologic (n=11) Age: not reported						
Branda 2010[32]	n=56 Massachusetts: Acute neuritis or carditis (n=12) Arthritis or late neuritis (n=23) Westchester: Acute neuritis or carditis (n=15) Arthritis or late neuritis (n=6) Age: not reported	n=166 Healthy controls	EIA WB	IgM and IgG VIDAS Lyme IgG and IgM BioMerieux SA Wampole *B burgdorferi* IgG/M ELISA II assay *Borrelia* B31 IgM Virablot Viramed *Borrelia* B31 IgG Birablot plus VlsE Viramed	Serum	Clinical diagnosis CDC surveillance criteria for Lyme disease	
Branda 2011[33]	n=169 EM (n=114) Acute neuritis or carditis (n=26) Arthritis or late neuritis (n=29) Age: not reported	n=1,300 Healthy controls	EIA WB	IgM and IgG VIDAS Lyme IgG and IgM BioMerieux SA Wampole *B burgdorferi* IgG/M ELISA II assay C6 *B burgdorferi*	Serum	Clinical diagnosis CDC surveillance criteria for Lyme disease	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				ELISA Immunetics *Borrelia* B31 IgM Virablot Viramed *Borrelia* B31 IgG Birablot plus VlsE Viramed			
Branda 2013[34]	n=64 Early or late Lyme disease Age: not reported	n=100 Healthy controls	ELISA IB	IgM and IgG Enzygnost Borreliosis Siemens, Germany Ezygnost Lyme Link VlsE/IgG Siemens, Germany Wampole *B burgdorferi* IgG/IgM ELISA II Alere Inc., USA C6 *B burgdorferi* Immunetics Inc., USA	Serum	Clinical diagnosis European Lyme disease criteria	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				Borrelia MiQ and VlsE IgM test kit Viramed, Germany *Borrelia* MiQ and VlsE IgG test kit Viramed, Germany *Borrelia* B31 ViraBlot IgM test kit Viramed, Germany *Borrelia* B31 and VlsE ViraBlot IgG test kit Viramed, Germany			
Fallon 2014[108]	n=37 Post treatment Lyme syndrome Age (mean): 46.5 years (SD 10.5)	n=40 Healthy controls	ELISA WB	IgM and IgG C6 ELISA ELISA Western blot	Serum	Clinical diagnosis (n=37) Positive IgG western blot (n=26)	
Goossens 1999[139] Goossens 2000[140]	n=39 Early Lyme (n=26) Late Lyme (n=13)	n=62 Healthy controls	EIA WB	IgM and IgG EIA: Behring EIA	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Age: not reported			Boehringer EIA Dako EIA Genzyme Virotech EIA IBL, EIA Milenia EIA Western blot: Genzyme Virotech WB MRL WB			
Johnson 1996[190]	n=111 EM (n=58) Early neurologic (n=3) Lyme arthritis (n=36) Late neurologic (n=14) Age: not reported	n=113 Healthy blood donors	ELISA IB	IgM and IgG FLA-ELISA MarDx Diagnostics IB USA	Serum	Clinical diagnosis	
Molins 2014[308]	n=124 Early Lyme disease with EM acute phase (n=40) Early Lyme disease	n=203 Healthy persons	EIA WB	Whole cell sonicate EIA (VIDAS Lyme IgM and IgG Polyvalent assay, bioMerieux)	Serum	Clinical diagnosis	Standard CDC algorithm used for ELISA (IgM and IgG) and Immunoblot (IgM and IgG) – IgG used only after 1 month

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	with EM convalescent phase (n=38) Early disseminated Lyme carditis (n=7) Early disseminated Lyme neuroborreliosis (n=10) Late Lyme disease, LA (29)			IgM and IgG western blots (MarDx Diagnostics)			
Molins 2016[307]	n=124 Acute and convalescent stage (n=78) Lyme neuroborreliosis (n=10) Lyme carditis (n=7) LA (n=29) Age: not reported	n=203 Healthy donors	EIA IB	IgM and IgG VIDAS Lyme IgM and IgG polyvalent whole cell sonicate EIA (bioMerieux) C6 *B. burgdorferi* Lyme ELISA (Immunetics) Marblot IgM and IgG immunoblot assays (MarDx Diagnostics) *Borrelia* ViraStripe IgM and IgG assay (plus VlsE on the IgG immunoblot; ViraMed, Biotech AG)	Serum	Clinical diagnosis	Densitometer reading taken over visual reading for VIDAS/ViraStripe combination
Peltomaa	n=47	n=86	ELISA	IgM and IgG	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
2004[364]	Lyme facial paralysis Age: 35 years (4-74)	Healthy subjects	WB	VlsE (IR6) peptide ELISA Western blot (MarDx)		(based on CDC criteria)	
Steere 2008[458]	n=134 EM (n=76) Acute neurologic or cardiac involvement (n=13) Arthritis or chronic neurologic involvement (n=31) Post-Lyme disease symptoms (n=14) Age: not reported	n=137 Healthy subjects	ELISA WB	IgM and IgG Sonicate ELISA VlsE C6 peptide ELISA Western blot	Serum	EM: CDC criteria and culture-positive	Reference standard: culture for people with EM, clinical diagnosis for all other presentations Positive 2-tier serology required for case inclusion of neurologic, cardiac or joint involvement Combination review: people post Lyme disease not extracted as there was no reference standard
Trevejo 2001[481]	n=74 EM Acute phase (n=66) Convalescent phase (n=55) Age: median 41 years	n=38 Healthy controls	EIA WB	IgM and IgG Vidas bioMerieux, France Marblot MarDx Diagnostics, USA	Serum	Clinical diagnosis	Simplified approach – only equivocal results on ELISA were tested by Immunoblot

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	(3-83)						
Weiner 2015[506]	n=70 Lyme with EM Acute and convalescent Lyme (n=46) Neuroborreliosis (n=10) Lyme carditis (n=6) Lyme arthritis (n=8) Age: not reported	n=32 Healthy people	ELISA IB	IgM and IgG ELISA Miniblotter45 Immunetics, USA	Serum	Clinical diagnosis	Standard CDC algorithm used for Immunoblot (IgG only after 30 days)

Table 21: Summary of included cross-sectional studies (children)

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments

Study	Population	Target condition	Type of index test	Index test	Sample	Reference standard	Comments
Lipsett 2016[243]	n=944 Children and adolescents undergoing serologic evaluation for Lyme disease Age (median and IQR): 10.9 (6.4-15.2) years	Lyme disease	EIA Immunoblot	Whole cell sonicate Lyme EIA (MarDx; Trinity Biotech) C6 Lyme EIA test (Immunetics) IgG and IgM Western Immunoblots (MarDx; Trinity Biotech)	Serum	Clinician-diagnosed EM or a positive 2-tiered serologic result in the presence of a Lyme disease-associated clinical syndrome	Unclear what proportion of people with Lyme disease were clinically diagnosed versus seropositive and Lyme disease associated syndrome

See appendix D for full evidence tables.

3.3.4 Quality assessment of clinical studies included in the evidence review

Table 22: Clinical evidence summary: combination of tests for Lyme disease (adults, case-control studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Erythema migrans: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Ang 2015	148	VERY LOW[1] due to very serious risk of bias	0.69 [0.55-0.80]	1.00 [0.96-1.00]
Bacon 2003 (acute disseminated EM)	295	VERY LOW[1] due to very serious risk of bias	0.50 [0.33-0.67]	1.00 [0.99-1.00]
Bacon 2003 (acute single EM)	299	VERY LOW[1] due to very serious risk of bias	0.26 [0.14-0.42]	1.00 [0.99-1.00]
Bacon 2003 (early convalescent disseminated	303	VERY LOW[1]	0.72 [0.57-0.84]	1.00 [0.99-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
EM)		due to very serious risk of bias		
Bacon 2003 (early convalescent single EM)	317	VERY LOW[1] due to very serious risk of bias	0.63 [0.50-0.75]	1.00 [0.99-1.00]
Branda 2011	1414	VERY LOW[1] due to very serious risk of bias	0.42 [0.33-0.52]	0.99 [0.99-1.00]
Branda 2013 (European tests)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.55 [0.32-0.77]	0.99 [0.95-1.00]
Branda 2013 (US tests)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.06-0.44]	1.00 [0.96-1.00]
Johnson 1996 (disseminated EM; FLA-ELISA and Immunoblot)	121	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.63-1.00]	1.00 [0.97-1.00]
Johnson 1996 (localised EM; FLA-ELISA and Immunoblot)	163	VERY LOW[1] due to very serious risk of bias	0.58 [0.43-0.72]	1.00 [0.97-1.00]
Molins 2014 (EM acute phase)	243	VERY LOW[1] due to very serious risk of bias	0.40 [0.25-0.57]	0.99 [0.96-1.00]
Molins 2014 (EM convalescent phase)	241	VERY LOW[1] due to very serious risk of bias	0.61 [0.43-0.64]	0.99 [0.96-1.00]
Molins 2016 (EM acute)	243	VERY LOW[1] due to very serious risk of bias	0.47 [0.32-0.64]	0.98 [0.95-0.99]
Molins 2016 (EM convalescent)	241	VERY LOW[1] due to very serious risk of bias	0.63 [0.46-0.78]	0.98 [0.95-0.99]
Steere 2008 (EM acute with dissemination)	178	VERY LOW[1] due to very serious risk of bias	0.43 [0.27-0.59]	0.99 [0.95-1.00]
Steere 2008 (EM acute without dissemination)	174	VERY LOW[1] due to very serious risk of bias	0.17 [0.06-0.33]	0.99 [0.95-1.00]
Steere 2008 (EM convalescent no dissemination)	174	VERY LOW[1] due to very serious risk of bias	0.53 [0.35-0.70]	0.99 [0.95-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Steere 2008 (EM convalescent with dissemination)	178	VERY LOW[1] due to very serious risk of bias	0.75 [0.59-0.87]	0.99 [0.95-1.00]
Tevejo 2001 (acute phase simplified approach)	103	VERY LOW[1] due to very serious risk of bias	0.41 [0.29-0.54]	1.00 [0.91-1.00]
Trevejo 2001 (acute phase; CDC approach)	103	VERY LOW[1] due to very serious risk of bias	0.32 [0.21-0.44]	1.00 [0.91-1.00]
Trevejo 2001 (convalescent phase CDC approach)	92	VERY LOW[1] due to very serious risk of bias	0.29 [0.18-0.43]	1.00 [0.91-1.00]
Trevejo 2001 (convalescent; simplified approach)	92	VERY LOW[1] due to very serious risk of bias	0.71 [0.57-0.82]	1.00 [0.91-1.00]
Weiner 2015 (EM acute phase)	55	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.13-0.53]	1.00 [0.89-1.00]
Weiner 2015 (EM convalescent phase)	55	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.78 [0.56-0.93]	1.00 [0.89-1.00]
Erythema migrans: ELISA C6 and Immunoblot (IgM/IgG)				
Ang 2015	170	VERY LOW[1] due to very serious risk of bias	0.64 [0.51-0.75]	1.00 [0.97-1.00]
Branda 2013 (US tests)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.20 [0.06-0.44]	1.00 [0.96-1.00]
Molins 2016 (EM acute C6 and Marblot Immunoblot)	243	VERY LOW[1] due to very serious risk of bias	0.40 [0.25-0.57]	0.99 [0.96-1.00]
Molins 2016 (EM acute C6 and ViraStripe Immunoblot)	243	VERY LOW[1] due to very serious risk of bias	0.43 [0.27-0.59]	1.00 [0.97-1.00]
Molins 2016 (EM convalescent C6 and Marblot Immunoblot)	241	VERY LOW[1] due to very serious risk of bias	0.63 [0.46-0.78]	0.99 [0.96-1.00]
Molins 2016 (EM convalescent C6 and ViraStripe Immunoblot)	241	VERY LOW[1] due to very serious risk of bias	0.63 [0.46-0.78]	1.00 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Erythema migrans: ELISA WCS and ELISA C6				
Branda 2011	1414	VERY LOW[1] due to very serious risk of bias	0.53 [0.43-0.62]	0.99 [0.99-1.00]
Branda 2013 (US tests)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.65 [0.41-0.85]	1.00 [0.96-1.00]
Molins 2016 (EM acute)	243	VERY LOW[1] due to very serious risk of bias	0.50 [0.34-0.66]	1.00 [0.97-1.00]
Molins 2016 (EM convalescent)	241	VERY LOW[1] due to very serious risk of bias	0.79 [0.63-0.90]	1.00 [0.97-1.00]
Erythema migrans: ELISA WCS and Immunoblot (VlsE)				
Molins 2016 (EM acute)	243	VERY LOW[1] due to very serious risk of bias	0.48 [0.32-0.64]	1.00 [0.97-1.00]
Molins 2016 (EM convalescent)	241	VERY LOW[1] due to very serious risk of bias	0.74 [0.57-0.87]	1.00 [0.97-1.00]
Erythema migrans: ELISA (IgM/IgG) and Immunoblot (IgM)				
Molins 2014 (EM acute phase)	243	VERY LOW[1] due to very serious risk of bias	0.30 [0.17-0.47]	1.00 [0.97-1.00]
Molins 2014 (EM convalescent phase)	241	VERY LOW[1] due to very serious risk of bias	0.53 [0.36-0.69]	1.00 [0.97-1.00]
Steere 2008 (EM acute with dissemination)	177	VERY LOW[1] due to very serious risk of bias	0.38 [0.23-0.54]	0.99 [0.96-1.00]
Steere 2008 (EM acute without dissemination)	173	VERY LOW[1] due to very serious risk of bias	0.11 [0.03-0.26]	0.99 [0.96-1.00]
Steere 2008 (EM convalescent no dissemination)	173	VERY LOW[1] due to very serious risk of bias	0.39 [0.23-0.57]	0.99 [0.96-1.00]
Steere 2008 (EM convalescent with dissemination)	177	VERY LOW[1] due to very serious risk of bias	0.70 [0.53-0.83]	0.99 [0.96-1.00]
Weiner 2015 (EM acute phase)	23	VERY LOW[1,3] due to very serious risk of bias and	0.30 [0.13-0.53]	Not estimable

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		serious imprecision		
Weiner 2015 (EM convalescent phase)	55	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.70 [0.47-0.87]	1.00 [0.89-1.00]
Erythema migrans: ELISA (IgM/IgG) and Immunoblot (IgG)				
Molins 2014 (EM acute phase)	243	VERY LOW[1] due to very serious risk of bias	0.20 [0.09-0.36]	0.99 [0.96-1.00]
Molins 2014 (EM convalescent phase)	237	VERY LOW[1] due to very serious risk of bias	0.34 [0.20-0.51]	0.99 [0.96-1.00]
Steere 2008 (EM acute with dissemination)	177	VERY LOW[1] due to very serious risk of bias	0.15 [0.06-0.30]	0.99 [0.96-1.00]
Steere 2008 (EM acute without dissemination)	173	VERY LOW[1] due to very serious risk of bias	0.06 [0.01-0.19]	0.99 [0.96-1.00]
Steere 2008 (EM convalescent no dissemination)	173	VERY LOW[1] due to very serious risk of bias	0.17 [0.06-0.33]	0.99 [0.96-1.00]
Steere 2008 (EM convalescent with dissemination)	177	VERY LOW[1] due to very serious risk of bias	0.20 [0.09-0.36]	0.99 [0.96-1.00]
Weiner 2015 (EM acute phase)	55	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.22]	1.00 [0.89-1.00]
Weiner 2015 (EM convalescent phase)	55	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.13-0.53]	1.00 [0.89-1.00]
Neuroborreliosis: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Ang 2015	120	VERY LOW[1] due to very serious risk of bias	0.97 [0.83-1.00]	1.00 [0.96-1.00]
Bacon 2003 (early neurologic convalescent)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.82 [0.48-0.98]	1.00 [0.99-1.00]
Bacon 2003 (early neurologic)	272	VERY LOW[1,3] due to very serious risk of bias and	0.87 [0.60-0.98]	1.00 [0.99-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		serious imprecision		
Bacon 2003 (late neurologic)	268	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.72-1.00]	1.00 [0.99-1.00]
Branda 2013 (European tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	0.99 [0.95-1.00]
Branda 2013 (US tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.16-0.68]	1.00 [0.96-1.00]
Johnson 1996 (early neurologic; FLA-ELISA and Immunoblot)	116	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.29-1.00]	1.00 [0.97-1.00]
Johnson 1996 (Late neurologic; FLA-ELISA and Immunoblot)	127	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.97-1.00]
Molins 2014	215	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.99 [0.97-1.00]
Molins 2016	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.80 [0.44-0.97]	0.98 [0.95-0.99]
Peltomaa 2004 (facial paralysis)	135	VERY LOW[1,2] due to very serious risk of bias and serious indirectness	1.00 [0.92-1.00]	0.98 [0.92-1.00]
Weiner 2015	42	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.89-1.00]
Neuroborreliosis: ELISA C6 and Immunoblot (IgM/IgG)				
Ang 2015	155	VERY LOW[1] due to very serious risk of bias	0.92 [0.81-0.98]	1.00 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Branda 2013 (US tests)	120	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.12-0.54]	1.00 [0.96-1.00]
Molins 2016 (C6 and Marblot Immunoblot)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	0.99 [0.96-1.00]
Molins 2016 (C6 and ViraStripe Immunoblot)	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.97-1.00]
Neuroborreliosis: ELISA WCS and ELISA C6				
Branda 2013 (US tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.87 [0.60-0.98]	1.00 [0.96-1.00]
Molins 2016	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.97-1.00]
Neuroborreliosis: ELISA (IgM/IgG) and Immunoblot (IgM)				
Molins 2014	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.97-1.00]
Weiner 2015	42	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.89-1.00]
Neuroborreliosis: ELISA (IgM/IgG) and Immunoblot (IgG)				
Molins 2014	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.30 [0.07-0.65]	0.99 [0.96-1.00]
Weiner 2015	42	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.40 [0.12-0.74]	1.00 [0.89-1.00]
Neuroborreliosis: ELISA (WCS and Immunoblot (VlsE)				

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Molins 2016	213	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.90 [0.55-1.00]	1.00 [0.97-1.00]
Lyme arthritis: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Bacon 2003 (arthritis convalescent)	281	VERY LOW[1] due to very serious risk of bias	0.96 [0.79-1.00]	1.00 [0.99-1.00]
Bacon 2003 (arthritis)	290	VERY LOW[1] due to very serious risk of bias	0.97 [0.84-1.00]	1.00 [0.99-1.00]
Branda 2013 (European tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.93 [0.68-1.00]	0.99 [0.95-1.00]
Branda 2013 (US tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.60 [0.32-0.84]	1.00 [0.96-1.00]
Johnson 1996 (LA; FLA-ELISA and Immunoblot)	149	VERY LOW[1] due to very serious risk of bias	1.00 [0.90-1.00]	1.00 [0.97-1.00]
Molins 2014	234	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.99 [0.97-1.00]
Molins 2016	232	VERY LOW[1] due to very serious risk of bias	0.97 [0.82-1.00]	0.98 [0.95-0.99]
Weiner 2015	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.63-1.00]	1.00 [0.89-1.00]
Lyme arthritis: ELISA C6 and Immunoblot (IgM/IgG)				
Branda 2013 (US tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.38-0.88]	1.00 [0.96-1.00]
Molins 2016 (C6 and Marblot Immunoblot)	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.99 [0.96-1.00]
Molins 2016 (C6 and ViraStripe Immunoblot)	232	VERY LOW[1]	0.97 [0.82-1.00]	1.00 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		due to very serious risk of bias		
Lyme arthritis: ELISA WCS and ELISA C6				
Branda 2013 (US tests)	115	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.93 [0.68-1.00]	1.00 [0.96-1.00]
Molins 2016	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	1.00 [0.97-1.00]
Lyme arthritis: ELISA (IgM/IgG) and Immunoblot (IgM)				
Molins 2014	232	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.15-0.51]	1.00 [0.97-1.00]
Weiner 2015	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.13 [0.00-0.53]	1.00 [0.89-1.00]
Lyme arthritis: ELISA (IgM/IgG) and Immunoblot (IgG)				
Molins 2014	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.99 [0.96-1.00]
Weiner 2015	40	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.63-1.00]	1.00 [0.89-1.00]
Lyme arthritis: ELISA WCS and Immunoblot (VlsE)				
Molins 2016	232	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	1.00 [0.97-1.00]
Lyme carditis: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Molins 2014	212	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.99 [0.97-1.00]
Molins 2016	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	1.00 [0.59-1.00]	0.98 [0.95-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Weiner 2015	38	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.83 [0.36-1.00]	1.00 [0.89-1.00]
Lyme carditis: ELISA (IgM/IgG) and Immunoblot (IgM)				
Molins 2014	210	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.57 [0.18-0.90]	1.00 [0.97-1.00]
Weiner 2015	38	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.67 [0.22-0.96]	1.00 [0.89-1.00]
Lyme carditis: ELISA (IgM/IgG) and Immunoblot (IgG)				
Molins 2014	210	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.57 [0.18-0.90]	0.99 [0.96-1.00]
Weiner 2015	38	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.50 [0.12-0.88]	1.00 [0.89-1.00]
Lyme carditis: ELISA WCS and ELISA C6				
Molins 2016	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	1.00 [0.97-1.00]
Lyme carditis: ELISA WCS and Immunoblot (VlsE)				
Molins 2016	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	1.00 [0.97-1.00]
Lyme carditis: ELISA C6 and Immunoblot (IgM/IgG)				
Molins 2016 (C6 and Marblot Immunoblot)	210	VERY LOW[1,3] due to very serious risk of bias and very serious imprecision	0.86 [0.42-1.00]	0.99 [0.96-1.00]
Molins 2016 (C6 and ViraStripe Immunoblot)	210	VERY LOW[1,3] due to very serious risk of bias and	0.86 [0.42-1.00]	1.00 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		very serious imprecision		
Acrodermatitis chronica atrophicans: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Branda 2013 (European tests)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	0.99 [0.95-1.00]
Branda 2013 (US tests)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Acrodermatitis chronica atrophicans: ELISA WCS and ELISA C6				
Branda 2013 (US tests)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Acrodermatitis chronica atrophicans: ELISA C6 and Immunoblot (IgM/IgG)				
Branda 2013 (US tests)	114	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.77-1.00]	1.00 [0.96-1.00]
Acute neuritis/carditis: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Branda 2010	193	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.63 [0.42-0.81]	1.00 [0.98-1.00]
Branda 2011	1326	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.73 [0.52-0.88]	0.99 [0.99-1.00]
Steere 2008	151	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	1.00 [0.75-1.00]	0.99 [0.95-1.00]
Acute neuritis/carditis: ELISA (IgM/IgG) and VlsE band				
Branda 2010	193	VERY LOW[1] due to very serious risk of bias	0.96 [0.81-1.00]	1.00 [0.98-1.00]
Acute neuritis/carditis: ELISA (IgM/IgG) and Immunoblot (IgG with VlsE band)				
Branda 2010	193	VERY LOW[1]	0.96 [0.81-1.00]	1.00 [0.98-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		due to very serious risk of bias		
Acute neuritis/carditis: ELISA WCS and ELISA C6				
Branda 2011	1326	VERY LOW[1] due to very serious risk of bias	1.00 [0.87-1.00]	0.99 [0.99-1.00]
Acute neurologic/cardiac: ELISA (IgM/IgG) and Immunoblot (IgM)				
Steere 2008	150	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	0.99 [0.96-1.00]
Acute neurologic/cardiac: ELISA (IgM/IgG) and Immunoblot (IgG)				
Steere 2008	150	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.85 [0.55-0.98]	0.99 [0.96-1.00]
Arthritis/late neuritis: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Branda 2010	195	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	1.00 [0.98-1.00]
Branda 2011	1329	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.99 [0.99-1.00]
Steere 2008	169	VERY LOW[1] due to very serious risk of bias	1.00 [0.89-1.00]	0.99 [0.95-1.00]
Arthritis/late neuritis: ELISA (IgM/IgG) and VlsE band				
Branda 2010	195	VERY LOW[1] due to very serious risk of bias	0.97 [0.82-1.00]	1.00 [0.98-1.00]
Arthritis/late neuritis: ELISA (IgM/IgG) and Immunoblot (IgG with VlsE band)				
Branda 2010	195	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	1.00 [0.99-1.00]
Arthritis/late neuritis: ELISA WCS and ELISA C6				
Branda 2011	1329	VERY LOW[1] due to very serious risk of bias	1.00 [0.88-1.00]	0.99 [0.99-1.00]
Lyme arthritis/chronic neurologic: ELISA (IgM/IgG) and Immunoblot (IgM)				

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Steere 2008	168	VERY LOW[1] due to very serious risk of bias	0.23 [0.10-0.41]	0.99 [0.96-1.00]
Lyme arthritis/chronic neurologic: ELISA (IgM/IgG) and Immunoblot (IgG)				
Steere 2008	168	VERY LOW[1] due to very serious risk of bias	1.00 [0.89-1.00]	0.99 [0.96-1.00]
Early Lyme disease: ELISA (IgM) and Immunoblot (IgM)				
Goossens 1999 (Behring EIA and Genzyme Virotech IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.27-0.67]	1.00 [0.94-1.00]
Goossens 1999 (Behring EIA and MRL IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.27-0.67]	1.00 [0.94-1.00]
Goossens 1999 (Boehringer and Genzyme Virotech)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.14-0.52]	1.00 [0.94-1.00]
Goossens 1999 (Boehringer EIA and MRL IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.17-0.56]	1.00 [0.94-1.00]
Goossens 1999 (Dako EIA and Genzyme Virotech IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.17-0.56]	1.00 [0.94-1.00]
Goossens 1999 (Dako EIA and MRL IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.42 [0.23-0.63]	1.00 [0.94-1.00]
Goossens 1999 (Genzyme Virotech EIA and GV IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.50 [0.30-0.70]	1.00 [0.94-1.00]
Goossens 1999 (Genzyme Virotech EIA and MRL IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.27-0.67]	1.00 [0.94-1.00]
Goossens 1999 (IBL EIA and Genzyme Virotech	88	VERY LOW[1,3]	0.35 [0.17-0.56]	0.97]0.89-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
IB)		due to very serious risk of bias and serious imprecision		
Goossens 1999 (IBL EIA and MRL IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.27-0.67]	1.00 [0.94-1.00]
Early Lyme disease: ELISA (IgG) and Immunoblot (IgG)				
Goossens 1999 (Behring EIA and Genzyme Virotech IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.23 [0.09-0.44]	0.94 [0.84-0.98]
Goossens 1999 (Behring EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]
Goossens 1999 (Boehringer and Genzyme Virotech)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.15 [0.04-0.35]	0.94 [0.84-0.98]
Goossens 1999 (Boehringer EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]
Goossens 1999 (Dako EIA and Genzyme Virotech IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.19 [0.07-0.39]	0.97 [0.89-1.00]
Goossens 1999 (Dako EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]
Goossens 1999 (Genzyme Virotech EIA and GV IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.19 [0.07-0.39]	0.95 [0.87-0.99]
Goossens 1999 (Genzyme Virotech EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]
Goossens 1999 (IBL EIA and Genzyme Virotech IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.15 [0.04-0.35]	0.94 [0.84-0.98]
Goossens 1999 (IBL EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Early Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgM)				
Goossens 1999 (Milenia EIA and Genzyme Virotech IB)	88	VERY LOW[1] due to very serious risk of bias	0.12 [0.02-0.30]	0.95 [0.87-0.99]
Goossens 1999 (Milenia EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]
Early Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgG)				
Goossens 1999 (Milenia EIA and Genzyme Virotech IB)	88	VERY LOW[1] due to very serious risk of bias	0.12 [0.02-0.30]	0.95 [0.87-0.99]
Goossens 1999 (Milenia EIA and MRL IB)	88	VERY LOW[1] due to very serious risk of bias	0.04 [0.00-0.20]	0.97 [0.89-1.00]
Late Lyme disease: ELISA (IgM) and Immunoblot (IgM)				
Goossens 1999 (Behring EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	1.00 [0.94-1.00]
Goossens 1999 (Behring EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.94-1.00]
Goossens 1999 (Boehringer and Genzyme Virotech)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.09-0.61]	1.00 [0.94-1.00]
Goossens 1999 (Boehringer EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.94-1.00]
Goossens 1999 (Dako EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	1.00 [0.94-1.00]
Goossens 1999 (Dako EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.94-1.00]
Goossens 1999 (Genzyme Virotech EIA and GV IB)	75	VERY LOW[1,3] due to very serious risk of bias and	0.38 [0.14-0.68]	1.00 [0.94-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		serious imprecision		
Goossens 1999 (Genzyme Virotech EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	1.00 [0.94-1.00]
Goossens 1999 (IBL EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.09-0.61]	0.97]0.89-1.00]
Goossens 1999 (IBL EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	1.00 [0.94-1.00]
Late Lyme disease: ELISA (IgG) and Immunoblot (IgG)				
Goossens 1999 (Behring EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.94 [0.84-0.98]
Goossens 1999 (Behring EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	0.97 [0.89-1.00]
Goossens 1999 (Boehringer and Genzyme Virotech)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.94 [0.84-0.98]
Goossens 1999 (Boehringer EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	0.97 [0.89-1.00]
Goossens 1999 (Dako EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	0.97 [0.89-1.00]
Goossens 1999 (Dako EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	0.97 [0.89-1.00]
Goossens 1999 (Genzyme Virotech EIA and GV IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	0.95 [0.87-0.98]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Goossens 1999 (Genzyme Virotech EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.38 [0.14-0.68]	0.97 [0.89-1.00]
Goossens 1999 (IBL EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.09-0.61]	0.94 [0.84-0.98]
Goossens 1999 (IBL EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.31 [0.09-0.61]	0.97 [0.89-1.00]
Late Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgM)				
Goossens 1999 (Milenia EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.15 [0.02-0.45]	0.95 [0.87-0.99]
Goossens 1999 (Milenia EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.08 [0.00-0.36]	0.97 [0.89-1.00]
Late Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgG)				
Goossens 1999 (Milenia EIA and Genzyme Virotech IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.95 [0.87-0.99]
Goossens 1999 (Milenia EIA and MRL IB)	75	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.46 [0.19-0.75]	0.97 [0.89-1.00]
Unspecified Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)				
Bacon 2003	537	VERY LOW[1] due to very serious risk of bias	0.68 [0.62-0.73]	1.00 [0.99-1.00]
Branda 2011	1469	VERY LOW[1] due to very serious risk of bias	0.57 [0.49-0.64]	0.99 [0.99-1.00]
Branda 2013 (European tests)	164	VERY LOW[1] due to very serious risk of bias	0.81 [0.70-0.90]	0.99 [0.95-1.00]
Branda 2013 (US tests)	164	VERY LOW[1]	0.52 [0.39-0.64]	1.00 [0.96-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		due to very serious risk of bias		
Johnson 1996 (unspecified Lyme disease; FLA-ELISA and IB)	224	VERY LOW[1] due to very serious risk of bias	0.81 [0.73-0.88]	1.00 [0.97-1.00]
Molins 2014	327	VERY LOW[1] due to very serious risk of bias	0.67 [0.58-0.75]	0.99 [0.96-1.00]
Molins 2016	327	VERY LOW[1] due to very serious risk of bias	0.69 [0.60-0.77]	0.98 [0.95-0.99]
Weiner 2015	102	VERY LOW[1] due to very serious risk of bias	0.67 [0.55-0.78]	1.00 [0.89-1.00]
Unspecified Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgM)				
Weiner 2015	102	VERY LOW[1] due to very serious risk of bias	0.53 [0.41-0.65]	1.00 [0.89-1.00]
Unspecified Lyme disease: ELISA (IgM/IgG) and Immunoblot (IgM)				
Weiner 2015	102	VERY LOW[1] due to very serious risk of bias	0.33 [0.22-0.45]	1.00 [0.89-1.00]
Unspecified Lyme disease: ELISA C6 and Immunoblot (IgM/IgG)				
Branda 2013 (US tests)	164	VERY LOW[1] due to very serious risk of bias	0.53 [0.40-0.66]	1.00 [0.96-1.00]
Molins 2016 (C6 and Marblot IB)	327	VERY LOW[1] due to very serious risk of bias	0.68 [0.59-0.76]	0.99 [0.96-1.00]
Molins 2016 (C6 and ViraStripe IB)	327	VERY LOW[1] due to very serious risk of bias	0.68 [0.59-0.76]	1.00 [0.97-1.00]
Unspecified Lyme disease: ELISA WCS and ELISA C6				
Branda 2011	1469	VERY LOW[1] due to very serious risk of bias	0.68 [0.60-0.75]	0.99 [0.99-1.00]
Branda 2013 (US tests)	164	VERY LOW[1] due to very serious risk of bias	0.84 [0.73-0.92]	1.00 [0.96-1.00]
Molins 2016	327	VERY LOW[1] due to very serious risk of bias	0.76 [0.67-0.83]	1.00 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Unspecified Lyme disease: ELISA WCS and Immunoblot (VlsE)				
Molins 2016	327	VERY LOW[1] due to very serious risk of bias	0.73 [0.65-0.81]	1.00 [0.97-1.00]
Post-treatment Lyme Disease Syndrome: ELISA and Immunoblot (IgG)				
Fallon 2014 (commercial lab)	77	VERY LOW[1] due to very serious risk of bias	0.41 [0.25-0.58]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab A)	77	VERY LOW[1] due to very serious risk of bias	0.38 [0.22-0.55]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab B)	77	VERY LOW[1] due to very serious risk of bias	0.43 [0.27-0.61]	0.98 [0.87-1.00]
Fallon 2014 (University reference lab)	69	VERY LOW[1] due to very serious risk of bias	0.49 [0.32-0.66]	1.00 [0.91-1.00]
Post-treatment Lyme Disease Syndrome: ELISA C6 and Immunoblot (IgG)				
Fallon 2014 (speciality lab A)	77	VERY LOW[1] due to very serious risk of bias	0.41 [0.25-0.58]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab B)	77	VERY LOW[1] due to very serious risk of bias	0.46 [0.29-0.63]	1.00 [0.91-1.00]
Post-treatment Lyme Disease Syndrome: ELISA and ELISA C6				
Fallon 2014 (speciality lab A)	77	VERY LOW[1] due to very serious risk of bias	0.59 [0.42-0.75]	1.00 [0.91-1.00]
Fallon 2014 (speciality lab B)	77	VERY LOW[1] due to very serious risk of bias	0.49 [0.32-0.66]	1.00 [0.91-1.00]

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) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect and downgraded by 2 increments if the majority of studies are very seriously indirect.*
3) *Imprecision was assessed based on inspection of the confidence region of sensitivity in the in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate, and downgraded by 2 increments when there was a range of >40%.*
4) *Inconsistency could not be assessed, as the committee was unable to set a sensitivity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

Table 23: Clinical evidence summary: combination of tests for Lyme disease (children, cross-sectional studies)

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Unspecified Lyme disease: ELISA C6 and Immunoblot (IgM/IgG)				
Lipsett 2016 (serum)	944	LOW[1] due to very serious risk of bias	0.78 [0.69-0.85]	0.99 [0.97-0.99]
Unspecified Lyme disease: ELISA WCS and ELISA C6				
Lipsett 2016 (serum)	944	LOW[1] due to very serious risk of bias	0.80 [0.71-0.87]	0.97 [0.95-0.98]
Unspecified Lyme disease: ELISA WCS and Immunoblot (IgM/IgG)				
Lipsett 2016 (serum)	944	LOW[1,3] due to very serious risk of bias	0.82 [0.73-0.88]	0.99 [0.98-0.99]

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) *Indirectness was assessed using the QUADAS-2 checklist items referring to applicability. The evidence was downgraded by 1 increment if the majority of studies are seriously indirect, and downgraded by 2 increments if the majority of studies are very seriously indirect.*
3) *Imprecision was assessed based on inspection of the confidence region of sensitivity in the in the individual study. The evidence was downgraded by 1 increment when there was a 20-40% range of the confidence interval around the point estimate and downgraded by 2 increments when there was a range of >40%.*
4) *4 Inconsistency could not be assessed, as the committee was unable to set a sensitivity threshold as an acceptable level to recommend a test. This was due to the lack of a good reference standard and the fact that studies, populations, tests and conditions were very heterogeneous.*

3.4 Economic evidence

3.4.1 Included studies

No relevant health economic studies were identified.

3.4.2 Excluded studies

Two economic studies relating to this review question were identified but were excluded due combination of applicability and very serious methodological limitations.[184,292] These are listed in appendix I, with reasons for exclusion given.

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

3.4.3 Health economic exploratory analysis

An exploratory analysis was conducted to estimate the additional cost of 2-tier testing (ELISA including C6 IgM and IgG followed by confirmatory immunoblot if ELISA was positive) over initial testing only (ELISA including C6 IgM and IgG) in people with suspected Lyme disease and evaluate what the cost of a misdiagnosis (either false positive or false negative) would need to be for 2-tier testing to be cost-neutral. A detailed write up of this analysis is available in appendix H.

The results of this exploratory analysis indicate that the cost of a misdiagnosis would need to be between £69 and £381 (depending on data inputs used) for the 2-tier testing to be cost neutral compared to initial testing only.

Overall, the committee considered that a misdiagnosis was very likely to cost at least £381, as these people would have a number of healthcare interactions whether the misdiagnosis was a false positive or a false negative. Therefore, the committee agreed that 2-tier testing is very likely to be at least cost neutral compared to initial testing only, and it may even be cost saving.

3.4.4 Unit costs

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

Table 24: NHS costs of Lyme disease tests

Test	Unit cost (a)
C6 antigen-based ELISA (combined IgG and IgM)	£25.45
Lyme immunoblot (IgG and IgM) and ELISA (as above)	£95.56
Lyme PCR(b)	£42.23

Source: Public Health England Rare and Imported Pathogens Laboratory, April 2016-March 2017.[385]
(a) A handling fee may be added onto these published costs by local pathology laboratories.
(b) For testing joint fluid, biopsy tissue and cerebrospinal fluid.

3.5 Resource impact

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

3.6 Evidence statements

3.6.1 Clinical evidence statements

Overall, the evidence was of Very Low quality due to the case-control study design, risk of bias and imprecision. The included studies varied significantly by test and test combinations, study population and clinical presentation. It was not possible to meta-analyse the large number of results because studies with comparable test combinations differed in how clinical presentations were reported, how tests were conducted and analysed and how the test results were interpreted.

Very Low quality evidence from 14 case-control studies in adults showed that a combination of ELISAs and immunoblots where both tests detect both IgM and IgG antibodies had the highest coupled sensitivity and specificity for detecting and confirming Lyme disease. Overall sensitivity of test combinations increased with disease progression.

Although tests that are less frequently used in clinical practice, such as C6 or WCS ELISAs, also showed a relatively high sensitivity, there was considerably higher variance around the point estimates and the point estimates of these less frequently used tests were mostly lower than for combined IgM/IgG ELISAs.

Low quality evidence from 1 cross-sectional study in children showed similarly high sensitivity and specificity point estimates for C6 and WCS ELISAs in combination with IgM/IgG immunoblots for detecting and confirming Lyme disease. No evidence in widely used combined IgM/IgG ELISAs in children was, however, identified.

Nearly all of the identified evidence showed a specificity of 99% to 100%.

3.6.2 Health economic evidence statements

One original exploratory analysis found that the cost of a misdiagnosis (false positive or false negative) would need to be between £69 and £381 (depending on data inputs used) for 2-tier testing (ELISA and immunoblot) to be cost neutral compared to initial testing only (ELISA) in people with suspected Lyme disease. This analysis was assessed as partially applicable with potentially serious limitations.

4 Recommendations

C1. Diagnose and treat Lyme disease without laboratory testing in people with erythema migrans.

C2. Offer testing if there is a clinical suspicion of Lyme disease, using an enzyme-linked immunosorbent assay (ELISA) for Lyme disease that tests for both IgM and IgG antibodies and is based on C6 peptide or an equivalent purified or synthetic VIsE antigen.

C3. If the ELISA is positive or equivocal, offer an immunoblot test to confirm diagnosis of Lyme disease.

C4. If the ELISA for Lyme disease is negative and the person still has symptoms, review their history and symptoms again, and consider whether an alternative diagnosis is likely.

C5. For people with a negative ELISA who were tested within 4 weeks from symptom onset, consider repeating the ELISA 4 to 6 weeks after the first ELISA test if Lyme disease is still suspected.

C6. For people with a negative ELISA who have had symptoms for 12 weeks or more and Lyme disease is still suspected:

- repeat the ELISA **and**
- perform an immunoblot test.

C7. Consider treatment with antibiotics (see evidence reports D–L) before test results become available if there is a high probability that the person has Lyme disease.

C8. If Lyme disease is confirmed with ELISA and immunoblot tests, and the person has focal symptoms, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or paediatric rheumatologist), without delaying treatment.

C9. If ELISA and immunoblot tests are negative but unexplained symptoms persist, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or paediatric rheumatologist) to:

- review whether further tests may be needed for suspected Lyme disease, for example synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis **or**
- consider alternative diagnoses.

C10. Be aware that people, particularly those living in high-prevalence areas, may have positive serology but do not have Lyme disease because antibodies can remain in the body for some years.

C11. Carry out tests for Lyme disease only at NHS-accredited laboratories that:

- use validated tests (validation should include published evidence on the test methodology, its relation to Lyme disease and independent reports of performance)
- participate in a formal external quality assurance programme.

C12. When tests have been done in laboratories that do not fulfil the criteria in recommendation C11, do not diagnose Lyme disease, but carry out testing again using an NHS-accredited laboratory.

4.1.1 Information about tests for Lyme disease

C13. Discuss with the person the accuracy and limitations of the different tests for diagnosing Lyme disease.

C14. Explain to people being tested that most tests for Lyme disease assess for the presence of an immune response (antibodies) to borreliosis infection, and that the accuracy of blood tests may be reduced if:

- testing is carried out too early (before antibodies have developed)
- the person has reduced immunity, which might affect the development of antibodies, for example people on immunosuppressant treatments.

C15. Advise people that tests available privately (including from overseas) may not have been fully evaluated or meet the standards needed to diagnose Lyme disease.

C16. Discuss with people who may have Lyme disease that:

- the symptoms and signs associated with Lyme disease are similar to those for other conditions
- symptoms such as tiredness, headache and muscle pain are common and a specific medical cause is often not found.

4.2 Research recommendations

RR1. What is the most clinically and cost effective serological antibody-based test, biomarker (such as CXCL13), lymphocyte transformation and ELISPOT for diagnosing Lyme in the UK at all stages, including reinfection?

RR2. What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections (such as babesiosis, ehrlichiosis, anaplasmosis, bartonellosis or Q fever) in people in the UK when performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?

See also the rationales in appendix J.

4.3 Rationale and impact

4.3.1 Why the committee made the recommendations

Many symptoms associated with Lyme disease have more common causes, so testing is helpful to ensure accurate diagnosis and appropriate treatment.

The majority of Lyme disease tests rely on examination of blood for presence of antibodies and need careful interpretation alongside clinical assessment.

There is uncertainty over which test or combination of tests are most helpful in diagnosing Lyme disease. The committee agreed that initial testing with a combination IgM and IgG ELISA for Lyme disease should be offered because the evidence generally showed better accuracy (both sensitivity and specificity) for combined tests compared to IgM-only and IgG-only tests. There was evidence that tests based on the C6 synthetic peptide or validated sets of purified antigens have a relatively high degree of sensitivity for detecting people with Lyme disease so this was also specified in the recommendation to provide greater accuracy and consistency across results.

If the initial ELISA test is positive or equivocal, the committee agreed that an immunoblot test should be offered to confirm diagnosis. The evidence suggested that the combination of initial IgM and IgG ELISA and confirmatory IgM and IgG immunoblot testing had a high sensitivity and specificity, particularly for Lyme arthritis, Lyme carditis and acrodermatitis chronica atrophicans.

For people with a negative ELISA result who continue to have symptoms clinical review is recommended to ensure that alternative diagnoses are not missed. Since antibodies take

some time to develop repeat testing is recommended for people who may have had the initial test too early, before an immune response has developed. If symptoms have been present for 12 weeks, the committee agreed that the ELISA may be repeated and an immunoblot should be carried out, which will help rule out or confirm diagnosis where uncertainty still remains.

Because of the limitations of tests for Lyme disease the committee also agreed that people with negative test results who continue to have symptoms might be discussed with or referred to an infectious disease specialist or a specialist appropriate for the person's symptoms to review whether further tests are needed or to consider alternative diagnoses.

Diagnostic tests should be validated before they are used to diagnose Lyme disease as otherwise tests may yield unreliable and misleading results, which may lead to misdiagnosis. The committee agreed that testing should be done in NHS-accredited laboratories.

The committee agreed that *Borrelia* infection does not behave differently in children than adults, but acknowledged that a young child's immune responses might not be as rapid and effective. The limited evidence in children did not show a noticeable difference in test accuracy compared to adults.

4.3.2 Impact of the recommendations on practice

A 2-tiered testing system is used in current practice, in which a positive result on an initial ELISA leads to a confirmatory immunoblot test. A negative result on an initial ELISA would not usually lead to a confirmatory immunoblot test. Therefore, the recommendation to repeat the ELISA and carry out an immunoblot test, despite an initial negative ELISA when there is clinical suspicion of Lyme disease would be a change to practice and increase the number of people receiving these tests. However, this would only apply to a small population, so this recommendation is not likely to have a significant resource impact.

4.4 The committee's discussion of the evidence

4.4.1 Interpreting the evidence

4.4.1.1 The diagnostic measures that matter most

Diagnostic accuracy studies where the accuracy of a given test for Lyme disease was measured against a reference standard (*Borrelia* culture, polymerase chain reaction, clinical diagnosis) were used in this review. Tests commonly performed are designed to assess immunological response to the presence of *Borrelia*.

Current practice includes 2-tier testing, where a sensitive initial test is performed first and followed by a specific confirmatory test in case of a positive initial test result. In first-line testing, a test with a high sensitivity is preferred in order to reduce the number of false negative test results, that is, the number of people with Lyme disease who incorrectly received a negative test result. A confirmatory test is required to show a high specificity, indicating that false positive test results in people without Lyme disease are few. Therefore, the committee considered sensitivity the most important measure for the assessment of diagnostic test accuracy of initial tests and test combinations. For the accuracy of confirmatory tests, they considered specificity the most important measure.

Sensitivity and specificity were prioritised over positive predictive value and negative predictive value because they are intrinsic to the test and do not depend on the prevalence of Lyme disease.

The overwhelming majority of evidence presented in this report was for initial tests for Lyme disease, particularly on ELISA tests and immunoblots. There was a general lack of evidence

on confirmatory tests with the 4 included studies providing data only on the clinical presentations of erythema chronicum migrans, neuroborreliosis and unspecified Lyme disease. Although the review on test combinations identified evidence for all clinical presentations of Lyme disease, the majority of the evidence identified was on the combination of an initial ELISA test followed by a confirmatory immunoblot. There was little evidence on any of the other tests listed in the protocol.

4.4.1.2 The quality of the evidence

Cross-sectional studies and case-control studies for children and adults were included in this review. The majority of the evidence was from case-control studies and was of very low quality because of risk of bias, study design and imprecision. There were particular concerns about the selection of people, the lack of blinding, the limited information on the index tests, and the inadequate reference standard. Many studies were of US populations or were old studies using discontinued tests. No studies were on UK populations. There is a strong potential of the results being an overestimate of the true sensitivity and specificity values due to the way case-control studies are conducted. 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 in order to fit inclusion criteria of studies. Controls, on the other hand, are usually drawn from a healthy population or include known specific cross-reactivity controls.

The evidence from cross-sectional studies was of low to very low quality. This was mainly due to issues around the index tests and reference standards. Similarly to the case-control studies, the majority of cross-sectional studies did not provide sufficient information on the tests used. There were also concerns about the lack of blinding. Many of the included studies were small and included samples from less than 100 participants. The evidence on tests other than ELISA or immunoblot was often based on single studies. The committee acknowledged these study limitations when discussing the evidence.

4.4.1.3 Benefits and harms

The committee found the evidence difficult to interpret due to the differences within and between the studies, which meant that meta-analyses were not possible. Studies varied widely in populations, both cases and controls, the types of tests used, test implementation and interpretation of test results.

Evidence from 2 cross-sectional studies suggested that 'modern' ELISAs—tests based on the C6 or validated sets of purified antigens—have a relatively high degree of sensitivity for detecting Lyme disease in people with neuroborreliosis. Other types of ELISAs do not include highly immunogenic antigens, such as C6, which cause an early antibody response useful for diagnostic testing. The committee therefore noted that evidence for modern types of ELISAs could not necessarily be extrapolated to other types of ELISAs.

The committee considered evidence from studies on people with unspecified Lyme disease symptoms, or those reporting diagnostic accuracy data for people with different combinations of presentations to be the most difficult to interpret. This was because the time between the point of infection and the test, which can affect the test result, was likely to be very heterogeneous.

The evidence suggested that the combination of initial combined IgM and IgG/ELISA and confirmatory IgM and IgG immunoblot testing had a high sensitivity and specificity, particularly for Lyme arthritis, Lyme carditis and acrodermatitis chronica atrophicans. Only 1 of the studies in Lyme arthritis was conducted in a European setting. All studies in Lyme carditis and acrodermatitis chronica atrophicans were conducted in the US.

For initial tests, the evidence generally showed better sensitivity and specificity results for combined IgM and IgG tests for different clinical presentations of Lyme disease compared to IgM-only and IgG-only tests. There was no clear advantage of ELISA tests over immunoblots or vice versa for any clinical presentation.

The analyses by time point did not show any clear advantage of 1 test over the other. IgM tests tended to have a higher sensitivity in the early stages of Lyme disease, such as the EM rash, and a lower sensitivity in later stages of Lyme disease. By contrast, the sensitivity of IgG test increased with disease progression. This is in keeping with the general understanding of how an immunological response to infection develops.

There was a general lack of evidence on confirmatory tests. Evidence from 3 case-control studies showed a higher sensitivity of IgG-specific tests compared to IgM-specific tests for confirming Lyme disease in people with an EM rash. Specificity across the studies was generally high although there is a risk of overestimation due to the case-control study design.

The committee discussed the value of diagnostic tests for neuroborreliosis using CSF samples. It was suggested that the decision to perform a lumbar puncture might depend on whether the person lives in an area where Lyme disease is more common, where a positive serology may not necessarily indicate an active infection. However, the evidence was not strong enough to inform a recommendation.

Evidence from a relatively small number of studies suggested a high sensitivity and high specificity of CXCL13 levels for diagnosing neuroborreliosis. The committee did not consider the quality or quantity of the evidence to be strong enough to inform a recommendation. The value of CXCL13, a biological marker that is not specific to Lyme disease, in helping to build a diagnosis was discussed. The committee also considered the apparent trend towards a good diagnostic accuracy of CXCL13 for neuroborreliosis and recommended that further research on this test should be undertaken.

Borrelia culture and polymerase chain reaction are considered the best diagnostic tests for Lyme disease and were used as reference standards in the evidence review. The tests, however, showed relatively low sensitivity and specificity when compared with clinical diagnosis. The committee noted that the relatively low-test accuracy could be due to a sampling error, as the bacteria may not exist in the entirety of the sample taken; for example, an aspirate of joint fluid may not grow *Borrelia* as the organisms may be localised to the synovium.

4.4.2 Cost effectiveness and resource use

No relevant health economic studies were identified for diagnostic tests. The unit costs from Public Health England's national laboratory (Rare and Imported Pathogens Laboratory, RIPL) for the C6 IgG and IgM combination ELISA and IgG and IgM immunoblot were presented to the committee. The C6 ELISA costs £25.45 and the combined C6 ELISA and immunoblot costs £95.56. It was noted that the local pathology laboratories might add a handling fee to these costs. Furthermore, the initial C6 ELISA may be done locally where the equipment is already available for other purposes.

The committee recommended that the diagnosis for those presenting with erythema migrans should be made without laboratory testing, as the rash is very specific to Lyme disease and the benefits of prompt treatment outweigh the potential harms in waiting for a positive test. Furthermore, this is current practice in the NHS and is not considered to have any resource impact.

An exploratory analysis was conducted to estimate the additional cost of 2-tier testing (ELISA including C6 IgM and IgG followed by confirmatory immunoblot if ELISA is positive) over initial testing only (ELISA including C6 IgM and IgG) in people with suspected Lyme disease and to evaluate what the cost of a misdiagnosis (either false positive or false negative) would

need to be for 2-tier testing to be cost neutral. The results of this exploratory analysis indicate that the cost of a misdiagnosis would need to be between £69 and £381 (depending on data used) for the 2-tier testing to be cost neutral compared to initial testing only. Overall, the committee considered that a misdiagnosis was very likely to cost at least £381, as these people would have a number of healthcare interactions whether the misdiagnosis was a false positive or a false negative. Therefore, the committee agreed that 2-tier testing is very likely to be at least cost neutral compared to initial testing only and that it may even be cost saving. A limitation of this analysis is that it did not account for health benefits. If these had been incorporated, the committee considered that 2-tier testing would likely be cost-effective compared to initial testing only.

Based on the analysis above and the clinical evidence the committee agreed to recommend 2-tier testing as is done in current practice.

The committee also considered circumstances where people have a negative test result to the initial C6 ELISA but continue to be symptomatic. The committee agreed that their history and symptoms should be reviewed and consider whether an alternative diagnosis is likely. If Lyme disease is still suspected and the initial test may have been done too early, the committee agreed that the initial C6 ELISA should be repeated 4-6 weeks after the initial test.

The committee considered that this additional test is highly likely to be cost effective as it will reduce the number of people with Lyme disease being missed (false negatives) and ensure they receive appropriate treatment in a timely manner. This should reduce any spending on the management of long-term complications of undiagnosed Lyme disease and any unnecessary referrals and investigations of people whose symptoms are unexplained and who are looking for a cause for their symptoms. Furthermore, it will ensure that those who have a second negative result from an initial test are appropriately managed and alternative diagnoses are explored.

The committee noted that it is considered standard practice in many other infectious diseases to repeat serological testing at a later time point to allow time for an antibody response. In addition, it was noted that RIPL already informs the requesting laboratories that a negative result does not rule out Lyme disease and that a repeat test may be required.

The committee made a further recommendation for those who test negative to the C6 ELISA and continue to be symptomatic for greater than 12 weeks. They considered that in this subset of people the C6 ELISA should be repeated along with an immunoblot. The committee noted that although this would be more costly, as these people would be receiving additional tests, they agreed that it would likely be offset by the reduction in additional healthcare visits. The committee noted that the proportion of people to whom this new recommendation would apply would be small relative to the number of people being tested currently, as it would only be those who have tested negative and who continue to be symptomatic after 12 weeks. Public Health England (PHE) reports that there are approximately 1,000 serologically confirmed cases of Lyme disease each year in England and Wales. The committee has indicated that about 14-15 times this number is tested at the RIPL. In addition, some initial testing is carried out locally; these are not accounted for in this estimate but are expected to be fewer than the number tested at RIPL. For this recommendation of an additional C6 ELISA test and an immunoblot to be considered to have a significant resource impact, it would need to be applicable to over 10,000 people based on the current cost of these tests. It was concluded therefore that this additional recommendation would not have a significant resource impact.

Finally, the committee recommended that when both the ELISA and immunoblot are negative, but unexplained symptoms persist, to consider discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or paediatric rheumatologist) to review whether further tests may be needed for suspected Lyme disease, for example, synovial fluid aspirate or biopsy. Referral

to a specialist and additional testing would currently be done as part of a differential diagnosis in these types of cases. The RIPL unit cost for a Lyme PCR is £42.23.

4.4.3 Other factors the committee took into account

It is current practice to treat people presenting with an EM rash for Lyme disease without the need for diagnostic testing. The committee felt that an erythema migrans rash was very specific to Lyme disease and that the benefits of prompt antibiotic treatment would significantly outweigh any potential harms.

The committee noted that people might present with an atypical rash or multiple EM-like rashes without any recollection of a tick bite. It was decided that these presentations are unusual enough to justify diagnostic testing but treatment would be appropriate without waiting for test results.

When making the decision to test a person for Lyme disease rather than diagnosing and treating them on presentation, the committee considered a pragmatic approach to be the most appropriate. The benefits of testing include improved confidence in the diagnosis in positive cases and avoidance of inappropriate treatment, delay in investigation of other causes and potential attribution of future symptoms to Lyme disease in negative cases. For each person, these should be weighed against the potential risks of causing additional worry to the person and a localised infection developing to a disseminated one. In some cases, it may be appropriate to give a 'possible' or 'probable' diagnosis of Lyme disease and treat accordingly. In cases where Lyme disease is highly likely, it may also be appropriate to begin treatment before test results become available.

The committee noted that evidence on sensitivity and specificity did not take into account pre-test probability, which must be considered in the clinical setting. The committee emphasised the importance of clinical history in the context of diagnostic tests; interpretation of test results must be related to the individual person who is presenting with symptoms or concerns. The committee also discussed the potential effect of early treatment with antibiotics or immunosuppressants on a person's immune response. Case studies have been used to suggest that antibiotics can abrogate antibody response and some manufacturers of tests also state this to explain results. While accepting that this lack of response is not impossible it is not widely accepted among the medical community who consider that this does not occur with other organisms and that if the patient was inadequately treated the organism would go on replicating after a recovery period and an antibody response would develop. This area was not systematically examined in the guideline and the committee recognised that further investigation on immunological response to exposure to *Borrelia* is ongoing.

The committee also discussed that different tests use different antigens from the main pathogenic genospecies of *Borrelia burgdorferi sensu* lato. It is possible for 1 blood sample to test positive with 1 test and negative with another. Newer tests use synthetic antigens to overcome some of these problems. European infections show a different response to tests than North American infections, and this complicates the interpretation of diagnostic studies.

Based on the identified evidence, current clinical practice and their clinical experience, the committee decided to recommend a combination of an initial C6 IgM and IgG ELISA if there is suspicion of Lyme disease. A confirmatory immunoblot should be done in cases of a positive or equivocal ELISA test result. If the ELISA test result is negative, an alternative diagnosis should be considered given that the relatively low prevalence of Lyme disease combined with the accuracy of the ELISA test makes other diagnoses possible. The committee recognised the quality of the evidence for different tests but considered it important to develop a strong recommendation for testing. Laboratory testing is a standard method of assessing exposure to infectious diseases and given the potential significance of

complications associated with Lyme disease information from testing that may help support or refute a diagnosis is worthwhile.

The timing of the initial ELISA test is, however, crucial. If the test is carried out too early for the person to develop an immune response, it could result in a false negative result. The committee also acknowledged that the immune response could fluctuate in the first 3 months of an infection. In the current 2-tiered testing system, a negative result on an initial ELISA would not usually lead to a confirmatory immunoblot test, unless a second ELISA test performed at a later time point is positive. It was therefore agreed that if their symptoms persist, people with a negative initial ELISA test should be offered a repeat test 4 to 6 weeks after their first test. For people with a negative test result and unexplained symptoms for more than 12 weeks, the committee decided to recommend that both the initial ELISA and the confirmatory immunoblot be repeated. The rationale behind this approach was that the overwhelming majority of these people would not have Lyme disease and the combination of tests could help provide clarity for them. Alternative diagnoses would have to be considered in this case. Ensuring that a determined attempt is made to detect any antigenic response is in the interests of patient safety and to help in providing a diagnosis. In contrast, people living in high-prevalence areas may be seropositive for Lyme disease and therefore receive a positive test result, but may not have active Lyme disease. This is because antibodies can last for some time even after an infection has been treated and the pathogen successfully eradicated.

If Lyme disease is confirmed through a positive initial ELISA and a positive confirmatory immunoblot, treatment should be started immediately to avoid dissemination of the disease. The committee noted that for persons with focal symptoms, that is, symptoms that can be attributed to a specific organ system, discussion with a specialist appropriate for the symptoms should be considered. Treatment should be started immediately, however, and not be delayed.

This is to ensure that people with more complex conditions, such as neuroborreliosis, can be referred for a full assessment and appropriate treatment.

The committee recommended that tests for Lyme disease should be carried out at a laboratory that uses validated tests and participates in an external quality assurance programme. The clinical relevance of the test should also be clear and reported performance of tests published independently. The committee discussed the approach to tests not carried out according to these criteria and considered that Lyme disease should not be diagnosed and tests repeated in these situations. Some tests performed at small private laboratories across the world have not been validated; therefore, it is not clear whether these tests actually assess an immunoresponse to the presence of Borrelia.

The committee also agreed that for persons with unexplained symptoms and negative test results, a referral to a specialist appropriate for the symptoms or an infectious diseases specialist should be considered. This is because in certain cases the bacteria may not exist in the sample taken. For example, in persons with Lyme arthritis, an aspirate of joint fluid may not contain *Borrelia* detectable by PCR as the organisms may be localised to the synovium.

The committee identified the need for effective communication with people about the issues surrounding diagnostic testing for Lyme disease. People with suspected Lyme disease should be informed that the tests are not definitive proof of the presence or absence of a *Borrelia* infection. Cases where there are 2 negative initial tests or a negative confirmatory test also require careful communication. It is important that people still feel that they will receive investigation and treatment if not for Lyme disease then to establish an alternative diagnosis. Establishing an alternative diagnosis might be easier for some clinical presentations, such as arthritis, than for more non-specific symptoms, such as myalgia. The committee recognised the frustrations caused by the lack of a diagnosis and treatment plan

when people have non-specific symptoms and that acknowledgement and communication about medical uncertainty is important.

The committee was aware of a European registry, comprising unpublished data from more than 70 laboratories. The registry certifies laboratories if their tests 'correctly' identify Lyme disease. Using the same samples, tests at different laboratories might provide different numerical results. The interpretation of these results should, however, always lead to the same conclusions. It was highlighted that datasets such as these would be useful in evaluating the diagnostic accuracy of different tests.

The committee agreed to develop a research recommendation for diagnostic tests to ensure a full evaluation of the available tests and to evaluate newer tests that may also be of value. There is a need for well-conducted cross-sectional studies that use well-defined criteria as a reference standard for Lyme disease and ensure that the index test and reference standard are interpreted without the knowledge of previous test results. There is also a general lack of evidence on newer tests, such as CSXL13, which warrants further research.

The committee also developed a research recommendation to determine the seroprevalence of Lyme disease to improve understanding of the natural history of Lyme disease serology and improve interpretation of serological results.

References

1. Aberer E, Bergmann AR, Derler AM, Schmidt B. Course of Borrelia burgdorferi DNA shedding in urine after treatment. Acta Dermato-Venereologica. 2007; 87(1):39-42

2. Aberer E, Schwantzer G. Course of antibody response in Lyme borreliosis patients before and after therapy. ISRN Immunology. 2012; 2012:719821

3. Aguero-Rosenfeld ME. Laboratory aspects of tick-borne diseases: Lyme, human granulocytic ehrlichiosis and babesiosis. Mount Sinai Journal of Medicine. 2003; 70(3):197-206

4. Ai CX, Zhang WF, Zhao JH. Sero-epidemiology of Lyme disease in an endemic area in China. Microbiology and Immunology. 1994; 38(7):505-509

5. Al-Sharif B, Hall MC. Lyme disease testing in children in an endemic area. Wisconsin Medical Journal. 2011; 110(5):228-233

6. Albisetti M, Schaer G, Good M, Boltshauser E, Nadal D. Diagnostic value of cerebrospinal fluid examination in children with peripheral facial palsy and suspected Lyme borreliosis. Neurology. 1997; 49(3):817-824

7. Ananjeva LP, Skripnikova IA, Barskova VG, Steere AC. Clinical and serologic features of Lyme borreliosis in Russia. Journal of Rheumatology. 1995; 22(4):689-694

8. Ang CW, Brandenburg AH, van Burgel ND, Bijlmer HA, Herremans T, Stelma F et al. A Dutch nationwide evaluation of serological assays for detection of Borrelia antibodies in clinically well-defined patients. Diagnostic Microbiology and Infectious Disease. 2015; 83(3):222-228

9. Ang CW, Notermans DW, Hommes M, Simoons-Smit AM, Herremans T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. European Journal of Clinical Microbiology and Infectious Diseases. 2011; 30(8):1027-1032

10. Arnez M, Pleterski-Rigler D, Luznik-Bufon T, Ruzic-Sabljic E, Strle F. Children with multiple erythema migrans: are there any pre-treatment symptoms and/or signs suggestive for central nervous system involvement? Wiener Klinische Wochenschrift. 2002; 114(13-14):524-529

11. Arteaga F, Golightly MG, Garcia Perez A, Barral M, Anda P, Garcia-Monco JC. Disparity between serological reactivity to Borrelia burgdorferi and evidence of past disease in a high-risk group. Clinical Infectious Diseases. 1998; 27(5):1210-1213

12. Artsob H. Western Blot as a confirmatory test for Lyme disease. Canadian Journal of Infectious Diseases. 1993; 4(2):115-116

13. Artsob H, Garvie M. Quality control assessment of Canadian laboratories testing for Lyme disease. Canadian Journal of Infectious Diseases. 1991; 2(1):41-45

14. Asbrink E, Hovmark A, Hederstedt B. Serologic studies of erythema chronicum migrans Afzelius and acrodermatitis chronica atrophicans with indirect immunofluorescence and enzyme-linked immunosorbent assays. Acta Dermato-Venereologica. 1985; 65(6):509-514

15. Aucott JN, Soloski MJ, Rebman AW, Crowder LA, Lahey LJ, Wagner CA et al. CCL19 as a chemokine risk factor for post-treatment Lyme disease syndrome: a

prospective clinical cohort study. Clinical & Vaccine Immunology: CVI. 2016; 23(9):757-766

16. Avery RA, Frank G, Eppes SC. Diagnostic utility of Borrelia burgdorferi cerebrospinal fluid polymerase chain reaction in children with lyme meningitis. Pediatric Infectious Disease Journal. 2005; 24(8):705-708

17. Bacon RM, Biggerstaff BJ, Schriefer ME, Gilmore RD, Jr., Philipp MT, Steere AC et al. Serodiagnosis of Lyme disease by kinetic enzyme-linked immunosorbent assay using recombinant VlsE1 or peptide antigens of Borrelia burgdorferi compared with 2-tiered testing using whole-cell lysates. Journal of Infectious Diseases. 2003; 187(8):1187-1199

18. Barstad B, Tveitnes D, Noraas S, Ask IS, Saeed M, Bosse F et al. Cerebrospinal fluid B-lymphocyte chemoattractant CXCL 13 in the diagnosis of acute lyme neuroborreliosis in children. Pediatric Infectious Disease Journal. 2017; Epublication

19. Bazovska S, Kondas M, Simkovicova M, Kmety E, Traubner P. Significance of specific antibody determination in Lyme borreliosis diagnosis. Bratislavske Lekarske Listy. 2001; 102(10):454-457

20. Bednarova J. Cerebrospinal-fluid profile in neuroborreliosis and its diagnostic significance. Folia Microbiologica. 2006; 51(6):599-603

21. Bennet R, Lindgren V, Zweygberg Wirgart B. Borrelia antibodies in children evaluated for Lyme neuroborreliosis. Infection. 2008; 36(5):463-466

22. Bergstrom S, Sjostedt A, Dotevall L, Kaijser B, Ekstrand-Hammarstrom B, Wallberg C et al. Diagnosis of Lyme borreliosis by an enzyme immunoassay detecting immunoglobulin G reactive to purified Borrelia burgdorferi cell components. European Journal of Clinical Microbiology and Infectious Diseases. 1991; 10(5):422-427

23. Berti A, Felicetti M, Volpe A, Bortolotti R, Cavatorta F, Barausse G et al. Higher levels of anti-borrelia IgG associate with arthritis in lyme disease at presentation: a Northern Italy referral center cohort. Annals of the Rheumatic Diseases. 2016; 75:848

24. Bil-Lula I, Matuszek P, Pfeiffer T, Wozniak M. Lyme Borreliosis - the utility of improved real-time PCR assay in the detection of Borrelia burgdorferi infections. Advances in Clinical & Experimental Medicine. 2015; 24(4):663-670

25. Binnicker MJ, Jespersen DJ, Harring JA, Rollins LO, Bryant SC, Beito EM. Evaluation of two commercial systems for automated processing, reading, and interpretation of Lyme borreliosis Western blots. Journal of Clinical Microbiology. 2008; 46(7):2216-2221

26. Bizzaro N, Bonelli F, Tonutti E, Tozzoli R, Villalta D. New coupled-particle light-scattering assay for detection of Ro/SSA (52 and 60 kilodaltons) and La/SSB autoantibodies in connective tissue diseases. Clinical and Diagnostic Laboratory Immunology. 2001; 8(5):922-925

27. Blaauw AA, van Loon AM, Schellekens JF, Bijlsma JW. Clinical evaluation of guidelines and two-test approach for lyme disease. Rheumatology. 1999; 38(11):1121-1126

28. Blaauw I, Dijkmans B, Bouma P, Van Der Linden S. Rational diagnosis and treatment in unclassified arthritis: how clinical data may guide requests for Lyme serology and antibiotic treatment. Annals of the Rheumatic Diseases. 1993; 52(3):206-210

29. Blanc F, Jaulhac B, Fleury M, De Seze J, De Martino SJ, Remy V et al. Relevance of the antibody index to diagnose Lyme neuroborreliosis among seropositive patients. Neurology. 2007; 69(10):953-958

30. Borde JP, Meier S, Fingerle V, Klier C, Hubner J, Kern WV. CXCL13 may improve diagnosis in early neuroborreliosis with atypical laboratory findings. BMC Infectious Diseases. 2012; 12:344

31. Bounas-Pyrros N, Todorova A, Biedermann T, Hofmann H, Traidl-Hoffmann C. Establishing and validating a new flow cytometric method for diagnosis of Lyme borreliosis. Journal of Investigative Dermatology. 2016; 136 ((9 Supplement 2)):S232

32. Branda JA, Aguero-Rosenfeld ME, Ferraro MJ, Johnson BJ, Wormser GP, Steere AC. 2-tiered antibody testing for early and late Lyme disease using only an immunoglobulin G blot with the addition of a VlsE band as the second-tier test. Clinical Infectious Diseases. 2010; 50(1):20-26

33. Branda JA, Linskey K, Kim YA, Steere AC, Ferraro MJ. Two-tiered antibody testing for Lyme disease with use of 2 enzyme immunoassays, a whole-cell sonicate enzyme immunoassay followed by a VlsE C6 peptide enzyme immunoassay. Clinical Infectious Diseases. 2011; 53(6):541-547

34. Branda JA, Strle F, Strle K, Sikand N, Ferraro MJ, Steere AC. Performance of United States serologic assays in the diagnosis of Lyme borreliosis acquired in Europe. Clinical Infectious Diseases. 2013; 57(3):333-340

35. Bremell D, Mattsson N, Edsbagge M, Blennow K, Andreasson U, Wikkelso C et al. Cerebrospinal fluid CXCL13 in Lyme neuroborreliosis and asymptomatic HIV infection. BMC Neurology. 2013; 13:2

36. Brettschneider S, Bruckbauer H, Klugbauer N, Hofmann H. Diagnostic value of PCR for detection of Borrelia burgdorferi in skin biopsy and urine samples from patients with skin borreliosis. Journal of Clinical Microbiology. 1998; 36(9):2658-2665

37. Bretz AG, Ryffel K, Hutter P, Dayer E, Peter O. Specificities and sensitivities of four monoclonal antibodies for typing of Borrelia burgdorferi sensu lato isolates. Clinical and Diagnostic Laboratory Immunology. 2001; 8(2):376-384

38. Brissette CA, Rossmann E, Bowman A, Cooley AE, Riley SP, Hunfeld KP et al. The borrelial fibronectin-binding protein RevA is an early antigen of human Lyme disease. Clinical and Vaccine Immunology. 2010; 17(2):274-280

39. Brunner M, Sigal LH. Use of serum immune complexes in a new test that accurately confirms early Lyme disease and active infection with Borrelia burgdorferi. Journal of Clinical Microbiology. 2001; 39(9):3213-3221

40. Brunner M, Stein S, Mitchell PD, Sigal LH. Immunoglobulin M capture assay for serologic confirmation of early lyme disease: analysis of immune complexes with biotinylated Borrelia burgdorferi sonicate enhanced with flagellin peptide epitope. Journal of Clinical Microbiology. 1998; 36(4):1074-1080

41. Bucak O, Kocoglu ME, Tas T, Mengeloglu FZ. Evaluation of Borrelia burgdorferi sensu lato seroprevalence in the province of Bolu, Turkey. Turkish Journal of Medical Sciences. 2016; 46(3):727-732

42. Buffrini L, Grignolo MC, Rovetta G, Monteforte P. Polymerase chain reaction in Lyme borreliosis. Drugs Under Experimental and Clinical Research. 2000; 26(2):67-70

43. Burbelo PD, Issa AT, Ching KH, Cohen JI, Iadarola MJ, Marques A. Rapid, simple, quantitative, and highly sensitive antibody detection for Lyme disease. Clinical and Vaccine Immunology. 2010; 17(6):904-909

44. Busson L, Reynders M, Van den Wijngaert S, Dahma H, Decolvenaer M, Vasseur L et al. Evaluation of commercial screening tests and blot assays for the diagnosis of Lyme borreliosis. Diagnostic Microbiology and Infectious Disease. 2012; 73(3):246-251

45. Callister SM, Jobe DA, Agger WA, Schell RF, Kowalski TJ, Lovrich SD et al. Ability of the borreliacidal antibody test to confirm lyme disease in clinical practice. Clinical and Diagnostic Laboratory Immunology. 2002; 9(4):908-912

46. Callister SM, Jobe DA, Schell RF, Pavia CS, Lovrich SD. Sensitivity and specificity of the borreliacidal-antibody test during early Lyme disease: a 'gold standard'? Clinical and Diagnostic Laboratory Immunology. 1996; 3(4):399-402

47. Cerar T, Ogrinc K, Cimperman J, Lotric-Furlan S, Strle F, Ruzic-Sabljic E. Validation of cultivation and PCR methods for diagnosis of Lyme neuroborreliosis. Journal of Clinical Microbiology. 2008; 46(10):3375-3379

48. Cerar T, Ogrinc K, Strle F, Ruzic-Sabljic E. Humoral immune responses in patients with lyme neuroborreliosis. Clinical & Vaccine Immunology: CVI. 2010; 17(4):645-650

49. Cerar T, Ruzic-Sabljic E, Cimperman J, Strle F. Comparison of immunofluorescence assay (IFA) and LIAISON in patients with different clinical manifestations of Lyme borreliosis. Wiener Klinische Wochenschrift. 2006; 118(21-22):686-690

50. Cerar T, Ruzic-Sabljic E, Glinsek U, Zore A, Strle F. Comparison of PCR methods and culture for the detection of Borrelia spp. in patients with erythema migrans. Clinical Microbiology and Infection. 2008; 14(7):653-658

51. Cermakova Z, Ryskova O, Honegr K, Cermakova E, Hanovcova I. Diagnosis of Lyme borreliosis using enzyme immunoanalysis. Medical Science Monitor. 2005; 11(4):BR121-BR125

52. Chan SS, Wong YC, Hodgkiss IJ. A preliminary study of C-reactive protein in the diagnosis and monitoring of Lyme disease. Biomedical and Environmental Sciences. 1996; 9(4):424-429

53. Christova I. Enzyme-linked immunosorbent assay, immunofluorescent assay, and recombinant immunoblotting in the serodiagnosis of early Lyme borreliosis. International Journal of Immunopathology and Pharmacology. 2003; 16(3):261-268

54. Cinco M, Murgia R. Evaluation of the C6 enzyme-linked immunoadsorbent assay for the serodiagnosis of Lyme borreliosis in north-eastern Italy. New Microbiologica. 2006; 29(2):139-141

55. Coleman AS, Rossmann E, Yang X, Song H, Lamichhane CM, Iyer R et al. BBK07 immunodominant peptides as serodiagnostic markers of Lyme disease. Clinical & Vaccine Immunology: CVI. 2011; 18(3):406-413

56. Commins SP, James HR, Kelly LA, Pochan SL, Workman LJ, Perzanowski MS et al. The relevance of tick bites to the production of IgE antibodies to the mammalian oligosaccharide galactose-alpha-1,3-galactose. Journal of Allergy and Clinical Immunology. 2011; 127(5):1286-1293

57. Cook MJ, Puri BK. Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. International Journal of General Medicine. 2016; 9:427-440

58. Cook MJ, Puri BK. Application of Bayesian decision-making to laboratory testing for Lyme disease and comparison with testing for HIV. International Journal of General Medicine. 2017; 10:113-123

59. Cooke WD, Bartenhagen NH. Seroreactivity to Borrelia burgdorferi antigens in the absence of Lyme disease. Journal of Rheumatology. 1994; 21(1):126-131

60. Cottle LE, Mekonnen E, Beadsworth MBJ, Miller ARO, Beeching NJ. Lyme disease in a British referral clinic. QJM. 2012; 105(6):537-543

61. Coulter P, Lema C, Flayhart D, Linhardt AS, Aucott JN, Auwaerter PG et al. Two-year evaluation of Borrelia burgdorferi culture and supplemental tests for definitive diagnosis of Lyme disease. Journal of Clinical Microbiology. 2005; 43(10):5080-5084

62. Coyle PK, Deng Z, Schutzer SE, Belman AL, Benach J, Krupp LB et al. Detection of Borrelia burgdorferi antigens in cerebrospinal fluid. Neurology. 1993; 43(6):1093-1097

63. Coyle PK, Krupp LB, Doscher C, Amin K. Borrelia burgdorferi reactivity in patients with severe persistent fatigue who are from a region in which Lyme disease is endemic. Clinical Infectious Diseases. 1994; 18(Suppl 1):S24-S27

64. Coyle PK, Schutzer SE, Belman AL, Krupp LB, Golightly MG. Cerebrospinal fluid immune complexes in patients exposed to Borrelia burgdorferi: detection of Borrelia-specific and -nonspecific complexes. Annals of Neurology. 1990; 28(6):739-744

65. Coyle PK, Schutzer SE, Deng Z, Krupp LB, Belman AL, Benach JL et al. Detection of Borrelia burgdorferi-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease. Neurology. 1995; 45(11):2010-2015

66. Craft JE, Grodzicki RL, Steere AC. Antibody response in Lyme disease: evaluation of diagnostic tests. Journal of Infectious Diseases. 1984; 149(5):789-795

67. Cretella S, Gordon S, Flavell RA, Fikrig E. Evaluation of a Lyme disease enzyme immunoassay using the 41-G fragment of flagellin. European Journal of Clinical Microbiology and Infectious Diseases. 1995; 14(7):609-613

68. Cruz M, Hansen K, Ernerudh J, Steere AC, Link H. Lyme arthritis: oligoclonal anti-Borrelia burgdorferi IgG antibodies occur in joint fluid and serum. Scandinavian Journal of Immunology. 1991; 33(1):61-71

69. Curtis L, Burns A. Unit costs of health and social care 2016. Canterbury. Personal Social Services Research Unit University of Kent, 2016. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2016/

70. Cutler SJ, Wright DJ. Evaluation of three commercial tests for Lyme disease. Diagnostic Microbiology and Infectious Disease. 1990; 13(3):271-272

71. Cutler SJ, Wright DJ. Predictive value of serology in diagnosing Lyme borreliosis. Journal of Clinical Pathology. 1994; 47(4):344-349

72. Cutler SJ, Wright DJM. Comparison of immunofluorescence and enzyme linked immunosorbent assays for diagnosing Lyme disease. Journal of Clinical Pathology. 1989; 42(8):869-871

73. Cyr TL, Jenkins MC, Hall RD, Masters EJ, McDonald GA. Improving the specificity of 16S rDNA-based polymerase chain reaction for detecting Borrelia burgdorferi sensu lato-causative agents of human Lyme disease. Journal of Applied Microbiology. 2005; 98(4):962-970

74. D'Arco C, Dattwyler RJ, Arnaboldi PM. Borrelia burgdorferi-specific IgA in Lyme disease. EBioMedicine. 2017; 19:91-97

75. Dattwyler RJ, Gomes-Solecki M. A rapid test for detection of Lyme disease antibodies. American Clinical Laboratory. 1999; 18(6):6

76. Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to Borrelia burgdorferi. New England Journal of Medicine. 1988; 319(22):1441-1446

77. Davidson MM, Chisholm SM, Wiseman AD, Joss AW, Ho-Yen DO. Improved serodiagnosis of Lyme disease. Clinical Molecular Pathology. 1996; 49(2):M80-M84

78. Davidson MM, Ling CL, Chisholm SM, Wiseman AD, Joss AW, Ho-Yen DO. Evidence-based diagnosis of Lyme disease. European Journal of Clinical Microbiology and Infectious Diseases. 1999; 18(7):484-489

79. Deanehan JK, Nigrovic PA, Milewski MD, Tan Tanny SP, Kimia AA, Smith BG et al. Synovial fluid findings in children with knee monoarthritis in lyme disease endemic areas. Pediatric Emergency Care. 2014; 30(1):16-19

80. Dehnert M, Fingerle V, Klier C, Talaska T, Schlaud M, Krause G et al. Seropositivity of Lyme borreliosis and associated risk factors: a population-based study in children and adolescents in Germany (KiGGS). PloS One. 2012; 7 (8):e41321

81. Demaerschalck I, Ben Messaoud A, De Kesel M, Hoyois B, Lobet Y, Hoet P et al. Simultaneous presence of different Borrelia burgdorferi genospecies in biological fluids of Lyme disease patients. Journal of Clinical Microbiology. 1995; 33(3):602-608

82. Department of Health. NHS reference costs 2015-16. 2016. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016 Last accessed: 4 April 2017.

83. Dessau RB. Diagnostic accuracy and comparison of two assays for Borrelia-specific IgG and IgM antibodies: proposals for statistical evaluation methods, cut-off values and standardization. Journal of Medical Microbiology. 2013; 62(12):1835-1844

84. Dessau RB, Bangsborg JM, Ejlertsen T, Skarphedinsson S, Schonheyder HC. Utilization of serology for the diagnosis of suspected Lyme borreliosis in Denmark: survey of patients seen in general practice. BMC Infectious Diseases. 2010; 10:317

85. Dessau RB, Ejlertsen T, Hilden J. Simultaneous use of serum IgG and IgM for risk scoring of suspected early Lyme borreliosis: graphical and bivariate analyses. APMIS. 2010; 118(4):313-323

86. Dessau RB, Fryland L, Wilhelmsson P, Ekerfelt C, Nyman D, Forsberg P et al. Study of a cohort of 1,886 persons to determine changes in antibody reactivity to borrelia burgdorferi 3 months after a tick bite. Clinical and Vaccine Immunology. 2015; 22(7):823-827

87. Dessau RB, Moller JK, Kolmos B, Henningsson AJ. Multiplex assay (Mikrogen recomBead) for detection of serum IgG and IgM antibodies to 13 recombinant antigens of borrelia burgdorferi sensu lato in patients with neuroborreliosis: The more the better? Journal of Medical Microbiology. 2015; 64(3):224-231

88. Dhôte R, Basse-Guerineau AL, Beaumesnil V, Christoforov B, Assous MV. Full spectrum of clinical, serological, and epidemiological features of complicated forms of Lyme borreliosis in the Paris, France, area. European Journal of Clinical Microbiology and Infectious Diseases. 2000; 19(11):809-815

89. Dickeson DJ, Chen SC, Sintchenko VG. Concordance of four commercial enzyme immunoassay and three immunoblot formats for the detection of Lyme borreliosis

antibodies in human serum: the two-tier approach remains. Pathology. 2016; 48(3):251-256

90. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. Journal of Infectious Diseases. 1993; 167(2):392-400

91. Dressler F, Yoshinari NH, Steere AC. The T-cell proliferative assay in the diagnosis of Lyme disease. Annals of Internal Medicine. 1991; 115(7):533-539

92. Du W, Ma X, Nyman D, Povlsen K, Akguen N, Schneider EM. Antigen biochips verify and extend the scope of antibody detection in Lyme borreliosis. Diagnostic Microbiology and Infectious Disease. 2007; 59(4):355-363

93. Dumler JS. Molecular diagnosis of lyme disease: review and meta-analysis. Molecular Diagnosis. 2001; 6(1):1-11

94. Dunaj J, Moniuszko A, Zajkowska J, Pancewicz S. The role of PCR in diagnostics of Lyme borreliosis. Przeglad Epidemiologiczny. 2013; 67(1):35-39, 119-123

95. Durovska J, Bazovska S, Ondrisova M, Pancak J. Our experience with examination of antibodies against antigens of Borrelia burgdorferi in patients with suspected lyme disease. Bratislavske Lekarske Listy. 2010; 111(3):153-155

96. Eichenfield AH. Diagnosis and management of Lyme disease. Pediatric Annals. 1986; 15(9):583-584, 587, 591-594

97. Eisendle K, Grabner T, Zelger B. Focus floating microscopy: "gold standard" for cutaneous borreliosis? American Journal of Clinical Pathology. 2007; 127(2):213-222

98. Ekerfelt C, Ernerudh J, Forsberg P, Jonsson AL, Vrethem M, Arlehag L et al. Lyme borreliosis in Sweden-diagnostic performance of five commercial Borrelia serology kits using sera from well-defined patient groups. APMIS. 2004; 112(1):74-78

99. Embers ME, Hasenkampf NR, Barnes MB, Didier ES, Philipp MT, Tardo AC. Five-antigen fluorescent bead-based assay for diagnosis of Lyme disease. Clinical & Vaccine Immunology: CVI. 2016; 23(4):294-303

100. Embers ME, Wormser GP, Schwartz I, Martin DS, Philipp MT. Borrelia burgdorferi spirochetes that harbor only a portion of the lp28-1 plasmid elicit antibody responses detectable with the C6 test for Lyme disease. Clinical and Vaccine Immunology. 2007; 14(1):90-93

101. Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. Journal of Clinical Microbiology. 1995; 33(2):419-427

102. Eshoo MW, Crowder CC, Rebman AW, Rounds MA, Matthews HE, Picuri JM et al. Direct molecular detection and genotyping of Borrelia burgdorferi from whole blood of patients with early Lyme disease. PloS One. 2012; 7(5):e36825

103. Evans R, Mavin S, Ho-Yen DO. Audit of the laboratory diagnosis of Lyme disease in Scotland. Journal of Medical Microbiology. 2005; 54(Pt 12):1139-1141

104. Evans R, Mavin S, McDonagh S, Chatterton JM, Milner R, Ho-Yen DO. More specific bands in the IgG western blot in sera from Scottish patients with suspected Lyme borreliosis. Journal of Clinical Pathology. 2010; 63(8):719-721

105. Exner MM, Lewinski MA. Isolation and detection of Borrelia burgdorferi DNA from cerebral spinal fluid, synovial fluid, blood, urine, and ticks using the Roche MagNA Pure system and real-time PCR. Diagnostic Microbiology and Infectious Disease. 2003; 46(4):235-240

106. Fahrer H, Sauvain MJ, Zhioua E, Van Hoecke C, Gern LE. Longterm survey (7 years) in a population at risk for Lyme borreliosis: What happens to the seropositive individuals? European Journal of Epidemiology. 1998; 14(2):117-123

107. Fahrer H, Van der Linden SM, Sauvain MJ, Gern L, Zhioua E, Aeschlimann A. The prevalence and incidence of clinical and asymptomatic Lyme borreliosis in a population at risk. Journal of Infectious Diseases. 1991; 163(2):305-310

108. Fallon BA, Pavlicova M, Coffino SW, Brenner C. A comparison of Lyme disease serologic test results from 4 laboratories in patients with persistent symptoms after antibiotic treatment. Clinical Infectious Diseases. 2014; 59(12):1705-1710

109. Fawcett PT, Gibney KM, Rose CD, Dubbs SB, Doughty RA. Frequency and specificity of antibodies that crossreact with Borrelia burgdorferi antigens. Journal of Rheumatology. 1992; 19(4):582-587

110. Fawcett PT, Rose C, Gibney KM, Chase CA, Kiehl B, Doughty RA. Detection of antibodies to the recombinant P39 protein of Borrelia burgdorferi using enzyme immunoassay and immunoblotting. Journal of Rheumatology. 1993; 20(4):734-738

111. Fawcett PT, Rose CD, Gibney KM, Doughty RA. Comparison of immunodot and Western blot assays for diagnosing Lyme borreliosis. Clinical and Diagnostic Laboratory Immunology. 1998; 5(4):503-506

112. Feder HM, Jr., Gerber MA, Luger SW, Ryan RW. Persistence of serum antibodies to Borrelia burgdorferi in patients treated for Lyme disease. Clinical Infectious Diseases. 1992; 15(5):788-793

113. Feder HM, Jr., Hunt MS. Pitfalls in the diagnosis and treatment of Lyme disease in children. JAMA. 1995; 274(1):66-68

114. Felz MW, Chandler FW, Jr., Oliver JH, Jr., Rahn DW, Schriefer ME. Solitary erythema migrans in Georgia and South Carolina. Archives of Dermatology. 1999; 135(11):1317-1326

115. Fidelus-Gort R, Gilmour RW, Kashatus WC. Serological responses in Lyme disease: the influence of sex, age, and environment. Annals of Clinical and Laboratory Science. 1993; 23(3):221-229

116. Figueroa R, Bracero LA, Aguero-Rosenfeld M, Beneck D, Coleman J, Schwartz I. Confirmation of Borrelia burgdorferi spirochetes by polymerase chain reaction in placentas of women with reactive serology for Lyme antibodies. Gynecologic and Obstetric Investigation. 1996; 41(4):240-243

117. Fikrig E, Coyle PK, Schutzer SE, Chen M, Deng Z, Flavell RA. Preferential presence of decorin-binding protein B (BBA25) and BBA50 antibodies in cerebrospinal fluid of patients with neurologic Lyme disease. Journal of Clinical Microbiology. 2004; 42(3):1243-1246

118. Fikrig E, Huguenel ED, Berland R, Rahn DW, Hardin JA, Flavell RA. Serologic diagnosis of Lyme disease using recombinant outer surface proteins A and B and flagellin. Journal of Infectious Diseases. 1992; 165(6):1127-1132

119. Fister RD, Weymouth LA, McLaughlin JC, Ryan RW, Tilton RC. Comparative evaluation of three products for the detection of Borrelia burgdorferi antibody in human serum. Journal of Clinical Microbiology. 1989; 27(12):2834-2837

120. Fix AD, Strickland GT, Grant J. Tick bites and Lyme disease in an endemic setting: problematic use of serologic testing and prophylactic antibiotic therapy. JAMA. 1998; 279(3):206-210

121. Fleming RV, Marques AR, Klempner MS, Schmid CH, Dally LG, Martin DS et al. Pre-treatment and post-treatment assessment of the C(6) test in patients with persistent symptoms and a history of Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 2004; 23(8):615-618

122. Flisiak I, Sckwartz RA, Chodynicka B. Clinical features and specific immunological response to Borrelia afzelii in patients with acrodermatitis chronica atrophicans. Journal of Medicine. 1999; 30(3-4):267-278

123. Flisiak R, Kalinowska A, Bobrowska E, Prokopowicz D. Enzyme immunoassay in the diagnosis of Lyme borreliosis. Roczniki Akademii Medycznej w Białymstoku (1995). 1996; 41(1):83-89

124. Flisiak R, Wierzbicka I, Prokopowicz D. Western blot banding pattern in early Lyme borreliosis among patients from an endemic region of north-eastern Poland. Roczniki Akademii Medycznej w Białymstoku (1995). 1998; 43:210-220

125. Fujita H, Sato T, Ohara Y, Homma M. An indirect microhemagglutination test for Lyme disease. Microbiology and Immunology. 1991; 35(7):589-592

126. Fung BP, McHugh GL, Leong JM, Steere AC. Humoral immune response to outer surface protein C of Borrelia burgdorferi in Lyme disease: role of the immunoglobulin M response in the serodiagnosis of early infection. Infection and Immunity. 1994; 62(8):3213-3221

127. Furuta Y, Kawabata H, Ohtani F, Watanabe H. Western blot analysis for diagnosis of Lyme disease in acute facial palsy. Laryngoscope. 2001; 111(4 Pt 1):719-723

128. Garro AC, Rutman M, Simonsen K, Jaeger JL, Chapin K, Lockhart G. Prospective validation of a clinical prediction model for Lyme meningitis in children. Pediatrics. 2009; 123(5):e829-e834

129. Gerber MA, Shapiro ED, Bell GL, Sampieri A, Padula SJ. Recombinant outer surface protein C ELISA for the diagnosis of early Lyme disease. Journal of Infectious Diseases. 1995; 171(3):724-727

130. Ghayad Z, Hou C. Erythema migrans in early disseminated lyme disease. The Journal of the American Osteopathic Association. 2012; 112(11):748

131. Glatz M, Golestani M, Kerl H, Mullegger RR. Clinical relevance of different IgG and IgM serum antibody responses to Borrelia burgdorferi after antibiotic therapy for erythema migrans: long-term follow-up study of 113 patients. Archives of Dermatology. 2006; 142(7):862-868

132. Goettner G, Schulte-Spechtel U, Hillermann R, Liegl G, Wilske B, Fingerle V. Improvement of Lyme borreliosis serodiagnosis by a newly developed recombinant immunoglobulin G (IgG) and IgM line immunoblot assay and addition of VlsE and DbpA homologues. Journal of Clinical Microbiology. 2005; 43(8):3602-3609

133. Gomes-Solecki MJ, Dunn JJ, Luft BJ, Castillo J, Dykhuizen DE, Yang X et al. Recombinant chimeric Borrelia proteins for diagnosis of Lyme disease. Journal of Clinical Microbiology. 2000; 38(7):2530-2535

134. Gomes-Solecki MJ, Meirelles L, Glass J, Dattwyler RJ. Epitope length, genospecies dependency, and serum panel effect in the IR6 enzyme-linked immunosorbent assay for detection of antibodies to Borrelia burgdorferi. Clinical & Vaccine Immunology: CVI. 2007; 14(7):875-879

135. Gomes-Solecki MJ, Wormser GP, Persing DH, Berger BW, Glass JD, Yang X et al. A first-tier rapid assay for the serodiagnosis of Borrelia burgdorferi infection. Archives of Internal Medicine. 2001; 161(16):2015-2020

136. Gomes-Solecki MJ, Wormser GP, Schriefer M, Neuman G, Hannafey L, Glass JD et al. Recombinant assay for serodiagnosis of Lyme disease regardless of OspA vaccination status. Journal of Clinical Microbiology. 2002; 40(1):193-197

137. Goodlad JR, Davidson MM, Gordon P, Billington R, Ho-Yen DO. Morphoea and Borrelia burgdorferi: results from the Scottish Highlands in the context of the world literature. Molecular Pathology. 2002; 55(6):374-378

138. Gooskens J, Templeton KE, Claas EC, van Dam AP. Evaluation of an internally controlled real-time PCR targeting the ospA gene for detection of Borrelia burgdorferi sensu lato DNA in cerebrospinal fluid. Clinical Microbiology and Infection. 2006; 12(9):894-900

139. Goossens HA, van den Bogaard AE, Nohlmans MK. Evaluation of fifteen commercially available serological tests for diagnosis of Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 1999; 18(8):551-560

140. Goossens HA, van den Bogaard AE, Nohlmans MK. Reduced specificity of combined IgM and IgG enzyme immunoassay testing for lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 2000; 19(5):400-402

141. Goossens HA, van den Bogaard AE, Nohlmans MK. Serodiagnosis of Lyme borreliosis using detection of different immunoglobulin (sub)classes by enzyme-linked immunosorbent assay and Western blotting. Clinical Laboratory. 2001; 47(1-2):41-49

142. Gordillo G, Torres J, Solorzano F, Cedillo-Rivera R, Tapia-Conyer R, Munoz O. Serologic evidences suggesting the presence of Borrelia burgdorferi infection in Mexico. Archives of Medical Research. 1999; 30(1):64-68

143. Gospodinova M, Christova I. Lyme borreliosis in patients over 60-years-old. Problems of Infectious and Parasitic Diseases. 2010; 38(2):20-24

144. Grabe HJ, Spitzer C, Ludemann J, Guertler L, Kramer A, John U et al. No association of seropositivity for anti-Borrelia IgG antibody with mental and physical complaints. Nordic Journal of Psychiatry. 2008; 62(5):386-391

145. Grodzicki RL, Steere AC. Comparison of immunoblotting and indirect enzyme-linked immunosorbent assay using different antigen preparations for diagnosing early Lyme disease. Journal of Infectious Diseases. 1988; 157(4):790-797

146. Gross DM, Steere AC, Huber BT. T helper 1 response is dominant and localized to the synovial fluid in patients with Lyme arthritis. Journal of Immunology. 1998; 160(2):1022-1028

147. Grusell M, Widhe M, Ekerfelt C. Increased expression of the Th1-inducing cytokines interleukin-12 and interleukin-18 in cerebrospinal fluid but not in sera from patients with Lyme neuroborreliosis. Journal of Neuroimmunology. 2002; 131(1-2):173-178

148. Grygorczuk S, Chmielewski T, Zajkowska J, Swierzbinska R, Pancewicz S, Kondrusik M et al. Concentration of TGF-beta1 in the supernatant of peripheral blood mononuclear cells cultures from patients with early disseminated and chronic Lyme borreliosis. Advances in Medical Sciences. 2007; 52:174-178

149. Guellec D, Narbonne V, Cornec D, Marhadour T, Varache S, Dougados M et al. Diagnostic impact of routine Lyme serology in recent-onset arthritis: results from the ESPOIR cohort. RMD Open. 2016; 2(1):e000120

150. Gutierrez J, Guerrero M, Nunez F, Soto MJ, Piedrola G, Maroto MC. Antibodies to Borrelia burgdorferi in European populations. Journal of Clinical Laboratory Analysis. 2000; 14(1):20-26

151. Gutierrez J, Maroto MC, De La Higuera A, Guerrero M, Padilla E, Piedrola G. Three-year study of antibody to Borrelia burgdorferi in Southern Spain. European Journal of Clinical Microbiology and Infectious Diseases. 1995; 14(6):542-546

152. Guy EC, Bateman DE, Martyn CN, Heckels JE, Lawton NF. Lyme disease: prevalence and clinical importance of Borrelia burgdorferi specific IgG in forestry workers. Lancet. 1989; 1(8636):484-486

153. Guy EC, Stanek G. Detection of Borrelia burgdorferi in patients with Lyme disease by the polymerase chain reaction. Journal of Clinical Pathology. 1991; 44(7):610-611

154. Gyllemark P, Forsberg P, Ernerudh J, Henningsson AJ. Intrathecal Th17- and B cell-associated cytokine and chemokine responses in relation to clinical outcome in Lyme neuroborreliosis: a large retrospective study. Journal of Neuroinflammation. 2017; 14(1):27

155. Halpern MD, Molins CR, Schriefer M, Jewett MW. Simple objective detection of human Lyme disease infection using immuno-PCR and a single recombinant hybrid antigen. Clinical & Vaccine Immunology: CVI. 2014; 21(8):1094-1105

156. Hamann-Brand A, Flondor M, Brade V. Evaluation of a passive haemagglutination assay as screening test and of a recombinant immunoblot as confirmatory test for serological diagnosis of Lyme disease. European Journal of Clinical Microbiology and Infectious Diseases. 1994; 13(7):572-575

157. Hammers-Berggren S, Lebech AM, Karlsson M, Andersson U, Hansen K, Stiernstedt G. Serological follow-up after treatment of Borrelia arthritis and acrodermatitis chronica atrophicans. Scandinavian Journal of Infectious Diseases. 1994; 26(3):339-347

158. Hammers-Berggren S, Lebech AM, Karlsson M, Svenungsson B, Hansen K, Stiernstedt G. Serological follow-up after treatment of patients with erythema migrans and neuroborreliosis. Journal of Clinical Microbiology. 1994; 32(6):1519-1525

159. Hammouda NA, Hegazy IH, el-Sawy EH. ELISA screening for Lyme disease in children with chronic arthritis. Journal of the Egyptian Society of Parasitology. 1995; 25(2):525-533

160. Hanner P, Edstrom S, Slagsvold P, Kaijser B. Peripheral facial palsy: antibody levels to Borrelia in serum and CSF. Clinical Otolaryngology and Allied Sciences. 1993; 18(5):419-422

161. Hanrahan JP, Benach JL, Coleman JL, Bosler EM, Grabau JC, Morse DL. Epidemiologic features of Lyme disease in New York. Yale Journal of Biology and Medicine. 1984; 57(4):643-650

162. Hansen K, Asbrink E. Serodiagnosis of erythema migrans and acrodermatitis chronica atrophicans by the Borrelia burgdorferi flagellum enzyme-linked immunosorbent assay. Journal of Clinical Microbiology. 1989; 27(3):545-551

163. Hansen K, Cruz M, Link H. Oligoclonal Borrelia burgdorferi-specific IgG antibodies in cerebrospinal fluid in Lyme neuroborreliosis. Journal of Infectious Diseases. 1990; 161(6):1194-1202

164. Hansen K, Hindersson P, Pedersen NS. Measurement of antibodies to the Borrelia burgdorferi flagellum improves serodiagnosis in Lyme disease. Journal of Clinical Microbiology. 1988; 26(2):338-346

165. Hansen K, Lebech AM. Lyme neuroborreliosis: a new sensitive diagnostic assay for intrathecal synthesis of Borrelia burgdorferi-specific immunoglobulin G, A, and M. Annals of Neurology. 1991; 30(2):197-205

166. Hansen K, Lebech AM. The clinical and epidemiological profile of Lyme neuroborreliosis in Denmark 1985-1990: a prospective study of 187 patients with Borrelia burgdorferi specific intrathecal antibody production. Brain. 1992; 115(2):399-424

167. Hansen K, Pii K, Lebech AM. Improved immunoglobulin M serodiagnosis in Lyme borreliosis by using a mu-capture enzyme-linked immunosorbent assay with biotinylated Borrelia burgdorferi flagella. Journal of Clinical Microbiology. 1991; 29(1):166-173

168. Hauser U, Krahl H, Peters H, Fingerle V, Wilske B. Impact of strain heterogeneity on Lyme disease serology in Europe: comparison of enzyme-linked immunosorbent assays using different species of Borrelia burgdorferi sensu lato. Journal of Clinical Microbiology. 1998; 36(2):427-436

169. Hauser U, Lehnert G, Wilske B. Diagnostic value of proteins of three borrelia species (Borrelia burgdorferi sensu lato) and implications for development and use of recombinant antigens for serodiagnosis of Lyme borreliosis in Europe. Clinical and Diagnostic Laboratory Immunology. 1998; 5(4):456-462

170. Hauser U, Lehnert G, Wilske B. Validity of interpretation criteria for standardized western blots (immunoblots) for serodiagnosis of Lyme borreliosis based on sera collected throughout Europe. Journal of Clinical Microbiology. 1999; 37(7):2241-2247

171. Hauser U, Wilske B. Enzyme-linked immunosorbent assays with recombinant internal flagellin fragments derived from different species of Borrelia burgdorferi sensu lato for the serodiagnosis of Lyme neuroborreliosis. Medical Microbiology and Immunology. 1997; 186(2-3):145-151

172. Heikkila T, Seppala I, Saxen H, Panelius J, Peltomaa M, Huppertz HI et al. Cloning of the gene encoding the decorin-binding protein B (DbpB) in Borrelia burgdorferi sensu lato and characterisation of the antibody responses to DbpB in Lyme borreliosis. Journal of Medical Microbiology. 2002; 51(8):641-648

173. Heikkila T, Seppala I, Saxen H, Panelius J, Peltomaa M, Julin T et al. Recombinant BBK32 protein in serodiagnosis of early and late Lyme borreliosis. Journal of Clinical Microbiology. 2002; 40(4):1174-1180

174. Heikkila T, Seppala I, Saxen H, Panelius J, Yrjanainen H, Lahdenne P. Species-specific serodiagnosis of Lyme arthritis and neuroborreliosis due to Borrelia burgdorferi sensu stricto, B. afzelii, and B. garinii by using decorin binding protein A. Journal of Clinical Microbiology. 2002; 40(2):453-460

175. Henningsson AJ, Christiansson M, Tjernberg I, Lofgren S, Matussek A. Laboratory diagnosis of Lyme neuroborreliosis: a comparison of three CSF anti-Borrelia antibody assays. European Journal of Clinical Microbiology and Infectious Diseases. 2014; 33(5):797-803

176. Henningsson AJ, Gyllemark P, Lager M, Skogman BH, Tjernberg I. Evaluation of two assays for CXCL13 analysis in cerebrospinal fluid for laboratory diagnosis of Lyme neuroborreliosis. APMIS. 2016; 124(11):985-990

177. Hernandez-Novoa B, Orduna A, Bratos MA, Eiros JM, Fernandez JM, Gutierrez MP et al. Utility of a commercial immunoblot kit (BAG-Borrelia blot) in the diagnosis of the preliminary stages of Lyme disease. Diagnostic Microbiology and Infectious Disease. 2003; 47(1):321-329

178. Hilton E, Devoti J, Sood S. Recommendation to include OspA and OspB in the new immunoblotting criteria for serodiagnosis of Lyme disease. Journal of Clinical Microbiology. 1996; 34(6):1353-1354

179. Hjetland R, Nilsen RM, Grude N, Ulvestad E. Seroprevalence of antibodies to Borrelia burgdorferi sensu lato in healthy adults from western Norway: risk factors and methodological aspects. APMIS. 2014; 122(11):1114-1124

180. Hofmann H. Lyme borreliosis - problems of serological diagnosis. Infection. 1996; 24(6):470-472

181. Hofstad H, Matre R, Nyland H, Ulvestad E. Bannwarth's syndrome: serum and CSF IgG antibodies against Borrelia burgdorferi examined by ELISA. Acta Neurologica Scandinavica. 1987; 75(1):37-45

182. Hunfeld KP, Ernst M, Zachary P, Jaulhac B, Sonneborn HH, Brade V. Development and laboratory evaluation of a new recombinant ELISA for the serodiagnosis of Lyme disease. Wiener Klinische Wochenschrift. 2002; 114(13-14):580-585

183. Huppertz HI, Schmidt H, Karch H. Detection of Borrelia burgdorferi by nested polymerase chain reaction in cerebrospinal fluid and urine of children with neuroborreliosis. European Journal of Pediatrics. 1993; 152(5):414-417

184. Jansson C, Carlsson SA, Granlund H, Wahlberg P, Nyman D. Analysis of Borrelia burgdorferi IgG antibodies with a combination of IgG ELISA and VlsE C6 peptide ELISA. Clinical Microbiology and Infection. 2005; 11(2):147-150

185. Jarefors S, Bennet L, You E, Forsberg P, Ekerfelt C, Berglund J et al. Lyme borreliosis reinfection: Might it be explained by a gender difference in immune response? Immunology. 2006; 118(2):224-232

186. Jaulhac B, Chary-Valckenaere I, Sibilia J, Javier RM, Piemont Y, Kuntz JL et al. Detection of Borrelia burgdorferi by DNA amplification in synovial tissue samples from patients with Lyme arthritis. Arthritis and Rheumatism. 1996; 39(5):736-745

187. Jiang Y, Wan KL, Geng Z, Hou XX. Standard criteria of Western blot for the diagnosis of Lyme disease caused by Borrelia garinii in China. Chinese Journal of Microbiology and Immunology. 2005; 25(7):594-598

188. Jin C, Roen DR, Lehmann PV, Kellermann GH. An enhanced ELISPOT assay for sensitive detection of antigen-specific T cell responses to Borrelia burgdorferi. Cells. 2013; 2(3):607-620

189. Jobe DA, Lovrich SD, Asp KE, Mathiason MA, Albrecht SE, Schell RF et al. Significantly improved accuracy of diagnosis of early Lyme disease by peptide enzyme-linked immunosorbent assay based on the borreliacidal antibody epitope of Borrelia burgdorferi OspC. Clinical & Vaccine Immunology: CVI. 2008; 15(6):981-985

190. Johnson BJ, Robbins KE, Bailey RE, Cao BL, Sviat SL, Craven RB et al. Serodiagnosis of Lyme disease: accuracy of a two-step approach using a flagella-based ELISA and immunoblotting. Journal of Infectious Diseases. 1996; 174(2):346-353

191. Johnston AM, Kober M, Callaway TH. Enzyme immunoassay with western blot confirmation for Lyme disease testing. Laboratory Medicine. 1992; 23(10):663-666

192. Jones KL, Seward RJ, Ben-Menachem G, Glickstein LJ, Costello CE, Steere AC. Strong IgG antibody responses to Borrelia burgdorferi glycolipids in patients with Lyme arthritis, a late manifestation of the infection. Clinical Immunology. 2009; 132(1):93-102

193. Jonsson L, Stiernstedt G, Carlson J, Stromberg A, Sjoberg O, Larsson A. Serum and cerebrospinal fluid examinations in the diagnosis of Borrelia infection in Bell's palsy. Acta Oto-Laryngologica. 1990; 110(5-6):421-426

194. Jovicic V, Grego EM, Lako BL, Ristovic BM, Lepsanovic ZA, Stajkovic NT. Improved serodiagnosis of early Lyme borreliosis: immunoblot with local Borrelia afzelii strain. APMIS. 2003; 111(11):1053-1059

195. Kaiser R. Variable CSF findings in early and late Lyme neuroborreliosis: a follow-up study in 47 patients. Journal of Neurology. 1994; 242(1):26-36

196. Kaiser R. Intrathecal immune response in patients with neuroborreliosis: specificity of antibodies for neuronal proteins. Journal of Neurology. 1995; 242(5):319-325

197. Kaiser R. False-negative serology in patients with neuroborreliosis and the value of employing of different borrelial strains in serological assays. Journal of Medical Microbiology. 2000; 49(10):911-915

198. Kaiser R, Lucking CH. Intrathecal synthesis of specific antibodies in neuroborreliosis: comparison of different ELISA techniques and calculation methods. Journal of the Neurological Sciences. 1993; 118(1):64-72

199. Kaiser R, Rauer S. Analysis of the intrathecal immune response in neuroborreliosis to a sonicate antigen and three recombinant antigens of Borrelia burgdorferi sensu stricto. European Journal of Clinical Microbiology and Infectious Diseases. 1998; 17(3):159-166

200. Kaiser R, Rauer S. Serodiagnosis of neuroborreliosis: comparison of reliability of three confirmatory assays. Infection. 1999; 27(3):177-182

201. Kalish RA, McHugh G, Granquist J, Shea B, Ruthazer R, Steere AC. Persistence of immunoglobulin M or immunoglobulin G antibody responses to Borrelia burgdorferi 10-20 years after active Lyme disease. Clinical Infectious Diseases. 2001; 33(6):780-785

202. Karlsson M, Granstrom M. An IgM-antibody capture enzyme immunoassay for serodiagnosis of Lyme borreliosis. Serodiagnosis and Immunotherapy in Infectious Disease. 1989; 3(6):413-421

203. Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. Neurology. 1994; 44(7):1203-1207

204. Karlsson M, Mollegard I, Stiernstedt G, Wretlind B. Comparison of Western blot and enzyme-linked immunosorbent assay for diagnosis of Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 1989; 8(10):871-877

205. Keller TL, Halperin JJ, Whitman M. PCR detection of Borrelia burgdorferi DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. Neurology. 1992; 42(1):32-42

206. Kepa L, Oczko-Grzesik B, Sobala-Szczygiel B, Boron-Kaczmarska A. Chemokine CXCL13 concentration in cerebrospinal fluid in patients with neuroborreliosis-own observations. Przeglad Epidemiologiczny. 2015; 69(4):705-710, 851-705

207. Klempner MS, Schmid CH, Hu L, Steere AC, Johnson G, McCloud B et al. Intralaboratory reliability of serologic and urine testing for Lyme disease. American Journal of Medicine. 2001; 110(3):217-219

208. Kolmel HW, Neumann P, Schneider T, Barnick L, Lange R. Prevalence of antibodies to Borrelia burgdorferi in serum and cerebrospinal fluid samples from patients with neurological disorders in Berlin. Zentralblatt fur Bakteriologie. 1992; 277(4):504-511

209. Kondrusik M, Grygorczuk S, Skotarczak B, Wodecka B, Rymaszewska A, Pancewicz S et al. Molecular and serological diagnosis of Borrelia burgdorferi infection among patients with diagnosed erythema migrans. Annals of Agricultural and Environmental Medicine. 2007; 14(2):209-213

210. Kowarik MC, Cepok S, Sellner J, Grummel V, Weber MS, Korn T et al. CXCL13 is the major determinant for B cell recruitment to the CSF during neuroinflammation. Journal of Neuroinflammation. 2012; 16(9):93

211. Krbkova L, Bednarova J, Cermakova Z. Improvement of diagnostic approach to Lyme neuroborreliosis in children by using recombinant antigens in detection of intrathecally produced IgM/IgG. Epidemiologie, Mikrobiologie, Imunologie. 2016; 65(2):112-117

212. Kuiper H, Cairo I, Van Dam A, De Jongh B, Ramselaar T, Spanjaard L et al. Solitary erythema migrans: A clinical, laboratory and epidemiological study of 77 Dutch patients. British Journal of Dermatology. 1994; 130(4):466-472

213. Lahdenne P, Panelius J, Saxen H, Heikkila T, Sillanpaa H, Peltomaa M et al. Improved serodiagnosis of erythema migrans using novel recombinant borrelial BBK32 antigens. Journal of Medical Microbiology. 2003; 52(7):563-567

214. Lahdenne P, Sarvas H, Kajanus R, Eholuoto M, Sillanpaa H, Seppala I. Antigenicity of borrelial protein BBK32 fragments in early Lyme borreliosis. Journal of Medical Microbiology. 2006; 55(Pt 11):1499-1504

215. Lahey LJ, Panas MW, Mao R, Delanoy M, Flanagan JJ, Binder SR et al. Development of a multiantigen panel for improved detection of Borrelia burgdorferi infection in early Lyme disease. Journal of Clinical Microbiology. 2015; 53(12):3834-3841

216. Lakos A. Comparison of four serological tests for Borrelia burgdorferi in Bell's palsy. Serodiagnosis and Immunotherapy in Infectious Disease. 1990; 4(4):271-275

217. Lakos A, Ferenczi E, Komoly S, Granstrom M. Different B-cell populations are responsible for the peripheral and intrathecal antibody production in neuroborreliosis. International Immunology. 2005; 17(12):1631-1637

218. Lakos A, Igari Z, Solymosi N. Recent lesson from a clinical and seroepidemiological survey: low positive predictive value of Borrelia burgdorferi antibody testing in a high risk population. Advances in Medical Sciences. 2012; 57(2):356-363

219. Lakos A, Reiczigel J, Solymosi N. The positive predictive value of Borrelia burgdorferi serology in the light of symptoms of patients sent to an outpatient service for tick-borne diseases. Inflammation Research. 2010; 59(11):959-964

220. Lane RS, Lennette ET, Madigan JE. Interlaboratory and intralaboratory comparisons of indirect immunofluorescence assays for serodiagnosis of Lyme disease. Journal of Clinical Microbiology. 1990; 28(8):1774-1779

221. Lange R, Bocklage H, Schneider T, Kolmel HW, Heesemann J, Karch H. Ovalbumin blocking improves sensitivity and specificity of immunoglobulin M immunoblotting for

serodiagnosis of patients with erythema migrans. Journal of Clinical Microbiology. 1992; 30(1):229-232

222. Lange R, Schneider T, Topel U. Borrelia burgdorferi antibody-tests: comparison of IFT. ELISA Western-blot. Laboratory Medicine. 1991; 15:128-129

223. Lantos PM, Branda JA, Boggan JC, Chudgar SM, Wilson EA, Ruffin F et al. Poor positive predictive value of lyme disease serologic testing in an area of low disease incidence. Clinical Infectious Diseases. 2015; 61(9):1374-1380

224. Lantos PM, Lipsett SC, Nigrovic LE. False positive Lyme disease IgM immunoblots in children. Journal of Pediatrics. 2016; 174:267-269

225. Lawrenz MB, Hardham JM, Owens RT, Nowakowski J, Steere AC, Wormser GP et al. Human antibody responses to VlsE antigenic variation protein of Borrelia burgdorferi. Journal of Clinical Microbiology. 1999; 37(12):3997-4004

226. Lebech AM. Diagnostic detection and direct genotyping of Borrelia burgdorferi by polymerase chain reaction in cerebrospinal fluid in Lyme neuroborreliosis. Molecular Diagnosis. 1998; 3(3):131-141

227. Lebech AM. Polymerase chain reaction in diagnosis of Borrelia burgdorferi infections and studies on taxonomic classification. APMIS Supplementum. 2002; (105):1-40

228. Lebech AM, Hansen K. Detection of Borrelia burgdorferi DNA in urine samples and cerebrospinal fluid samples from patients with early and late Lyme neuroborreliosis by polymerase chain reaction. Journal of Clinical Microbiology. 1992; 30(7):1646-1653

229. Lebech AM, Hansen K, Brandrup F, Clemmensen O, Halkier-Sorensen L. Diagnostic value of PCR for detection of Borrelia burgdorferi DNA in clinical specimens from patients with erythema migrans and Lyme neuroborreliosis. Molecular Diagnosis. 2000; 5(2):139-150

230. Ledue TB, Collins MF, Craig WY. New laboratory guidelines for serologic diagnosis of Lyme disease: evaluation of the two-test protocol. Journal of Clinical Microbiology. 1996; 34(10):2343-2350

231. Ledue TB, Collins MF, Young J, Schriefer ME. Evaluation of the recombinant VlsE-based liaison chemiluminescence immunoassay for detection of Borrelia burgdorferi and diagnosis of Lyme disease. Clinical & Vaccine Immunology: CVI. 2008; 15(12):1796-1804

232. Lee SH, Vigliotti JS, Vigliotti VS, Jones W, Shearer DM. Detection of Borreliae in archived sera from patients with clinically suspect Lyme disease. International Journal of Molecular Sciences. 2014; 15(3):4284-4298

233. Lee SH, Vigliotti VS, Vigliotti JS, Jones W, Williams J, Walshon J. Early Lyme disease with spirochetemia - diagnosed by DNA sequencing. BMC Research Notes. 2010; 3:273

234. Leeflang MM, Ang CW, Berkhout J, Bijlmer HA, Van Bortel W, Brandenburg AH et al. The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. BMC Infectious Diseases. 2016; 16:140

235. Leinweber B, Colli C, Chott A, Kerl H, Cerroni L. Differential diagnosis of cutaneous infiltrates of B lymphocytes with follicular growth pattern. American Journal of Dermatopathology. 2004; 26(1):4-13

236. Lencakova D, Fingerle V, Stefancikova A, Schulte-Spechtel U, Petko B, Schreter I et al. Evaluation of recombinant line immunoblot for detection of Lyme disease in Slovakia: Comparison with two other immunoassays. Vector-Borne and Zoonotic Diseases. 2008; 8(3):381-390

237. Lencakova D, Stefancikova A, Ivanova R, Petko B. Immune complexes in early Lyme disease. Canadian Journal of Microbiology. 2007; 53(12):1375-1377

238. Leung SS, Scott JR. A fluorescence ELISA for Lyme disease: a comparison with other diagnostic techniques. Journal of Clinical Immunoassay. 1989; 12(3):154-157

239. Li X, McHugh GA, Damle N, Sikand VK, Glickstein L, Steere AC. Burden and viability of Borrelia burgdorferi in skin and joints of patients with erythema migrans or lyme arthritis. Arthritis and Rheumatism. 2011; 63(8):2238-2247

240. Liang FT, Steere AC, Marques AR, Johnson BJ, Miller JN, Philipp MT. Sensitive and specific serodiagnosis of Lyme disease by enzyme-linked immunosorbent assay with a peptide based on an immunodominant conserved region of Borrelia burgdorferi vlsE. Journal of Clinical Microbiology. 1999; 37(12):3990-3996

241. Liebling MR, Nishio MJ, Rodriguez A, Sigal LH, Jin T, Louie JS. The polymerase chain reaction for the detection of Borrelia burgdorferi in human body fluids. Arthritis and Rheumatism. 1993; 36(5):665-675

242. Lin TM, Schubert CM, Shih FF, Ahmad P, Lopez M, Horst H. Use of flagellin-enriched antigens in a rapid, simple and specific quantitative enzyme immunoassay for Lyme disease antibodies in human serum samples. Journal of Immunoassay. 1991; 12(3):325-346

243. Lipsett SC, Branda JA, McAdam AJ, Vernacchio L, Gordon CD, Gordon CR et al. Evaluation of the C6 Lyme enzyme immunoassay for the diagnosis of Lyme disease in children and adolescents. Clinical Infectious Diseases. 2016; 63(7):922-928

244. Lipsett SC, Pollock NR, Branda JA, Gordon CD, Gordon CR, Lantos PM et al. The positive predictive value of lyme ELISA for the diagnosis of Lyme disease in children. Pediatric Infectious Disease Journal. 2015; 34(11):1260-1262

245. Liu W, Liu HX, Zhang L, Hou XX, Wan KL, Hao Q. Evaluation of six recombinant proteins for serological diagnosis of Lyme borreliosis in China. Biomedical and Environmental Sciences. 2016; 29(5):323-330

246. Liu W, Liu HX, Zhang L, Hou XX, Wan KL, Hao Q. A novel isothermal assay of Borrelia burgdorferi by recombinase polymerase amplification with lateral flow detection. International Journal of Molecular Sciences. 2016; 17(8):1250

247. Liu ZY, Hao Q, Hou XX, Jiang Y, Geng Z, Wu YM et al. A study of the technique of western blot for diagnosis of lyme disease caused by Borrelia afzelii in China. Biomedical and Environmental Sciences. 2013; 26(3):190-200

248. Liveris D, Schwartz I, Bittker S, Cooper D, Iyer R, Cox ME et al. Improving the yield of blood cultures from patients with early Lyme disease. Journal of Clinical Microbiology. 2011; 49(6):2166-2168

249. Liveris D, Schwartz I, McKenna D, Nowakowski J, Nadelman R, DeMarco J et al. Comparison of five diagnostic modalities for direct detection of Borrelia burgdorferi in patients with early Lyme disease. Diagnostic Microbiology and Infectious Disease. 2012; 73(3):243-245

250. Liveris D, Schwartz I, McKenna D, Nowakowski J, Nadelman RB, DeMarco J et al. Quantitation of cell-associated borrelial DNA in the blood of Lyme disease patients

with erythema migrans. European Journal of Clinical Microbiology and Infectious Diseases. 2012; 31(5):791-795

251. Liveris D, Wang G, Girao G, Byrne DW, Nowakowski J, McKenna D et al. Quantitative detection of Borrelia burgdorferi in 2-millimeter skin samples of erythema migrans lesions: correlation of results with clinical and laboratory findings. Journal of Clinical Microbiology. 2002; 40(4):1249-1253

252. Livermore AL, Brunelle LA. Comparison of serologic lyme testing with the immunetics C6 ELISA, EUROIMMUN EUROLINE-WB and Viramed Biotech Virastripe assays. Clinical Chemistry. 2016; 62 ((10 Supplement 1)):S136

253. Ljostad U, Mygland A. CSF B-lymphocyte chemoattractant (CXCL13) in the early diagnosis of acute Lyme neuroborreliosis. Journal of Neurology. 2008; 255(5):732-737

254. Ljostad U, Okstad S, Topstad T, Mygland A, Monstad P. Acute peripheral facial palsy in adults. Journal of Neurology. 2005; 252(6):672-676

255. Ljostad U, Skarpaas T, Mygland A. Clinical usefulness of intrathecal antibody testing in acute Lyme neuroborreliosis. European Journal of Neurology. 2007; 14(8):873-876

256. Londono D, Cadavid D, Drouin EE, Strle K, McHugh G, Aversa JM et al. Antibodies to endothelial cell growth factor and obliterative microvascular lesions in the synovium of patients with antibiotic-refractory Lyme arthritis. Arthritis and Rheumatology. 2014; 66(8):2124-2133

257. Lotric-Furlan S, Cimperman J, Maraspin V, Ruzic-Sabljic E, Logar M, Jurca T et al. Lyme borreliosis and peripheral facial palsy. Wiener Klinische Wochenschrift. 1999; 111(22-23):970-975

258. Luft BJ, Dunn JJ, Dattwyler RJ, Gorgone G, Gorevic PD, Schubach WH. Cross-reactive antigenic domains of the flagellin protein of Borrelia burgdorferi. Research in Microbiology. 1993; 144(4):251-257

259. Luft BJ, Steinman CR, Neimark HC, Muralidhar B, Rush T, Finkel MF et al. Invasion of the central nervous system by Borrelia burgdorferi in acute disseminated infection. JAMA. 1992; 267(10):1364-1367

260. Luger SW, Krauss E. Serologic tests for Lyme disease. Interlaboratory variability. Archives of Internal Medicine. 1990; 150(4):761-763

261. Lukac J, Cucnik S, Kveder T, Strle F, Rozman B. Anti-beta2-glycoprotein I antibodies in Lyme borreliosis: differences in disease stage and immunoglobulin class distribution. Current Rheumatology Reviews. 2006; 2(4):349-351

262. Ma B, Christen B, Leung D, Vigo-Pelfrey C. Serodiagnosis of Lyme borreliosis by western immunoblot: Reactivity of various significant antibodies against Borrelia burgdorferi. Journal of Clinical Microbiology. 1992; 30(2):370-376

263. Mackensen F, Zimmermann S, Alle W, Max R, Jakob E, Becker MD et al. Difficulties of interpreting Borrelia serology in patients with uveitis. Ocular Immunology and Inflammation. 2011; 19(4):227-231

264. Mackworth-Young CG. Cross-reactive idiotypes in sera from patients with leprosy, lupus and Lyme disease and from healthy individuals. Clinical and Experimental Immunology. 1990; 79(1):78-82

265. Maes L, Carolus T, De Preter V, Ignoul S, Cartuyvels R, Braeken L et al. Technical and clinical validation of three commercial real-time PCR kits for the diagnosis of

neuroborreliosis in cerebrospinal fluid on three different real-time PCR platforms. European Journal of Clinical Microbiology and Infectious Diseases. 2017; 36(2):273-279

266. Magnarelli LA, Anderson JF. Early detection and persistence of antibodies to Borrelia burgdorferi in persons with Lyme disease. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1987; 263(3):392-399

267. Magnarelli LA, Anderson JF. Enzyme-linked immunosorbent assays for the detection of class-specific immunoglobulins to Borrelia burgdorferi. American Journal of Epidemiology. 1988; 127(4):818-825

268. Magnarelli LA, Anderson JF. Adsorption and biotin-streptavidin amplification in serologic tests for diagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 1991; 29(9):1761-1764

269. Magnarelli LA, Anderson JF, Barbour AG. Enzyme-linked immunosorbent assays for Lyme disease: reactivity of subunits of Borrelia burgdorferi. Journal of Infectious Diseases. 1989; 159(1):43-49

270. Magnarelli LA, Anderson JF, Johnson RC. Cross-reactivity in serological tests for Lyme disease and other spirochetal infections. Journal of Infectious Diseases. 1987; 156(1):183-188

271. Magnarelli LA, Dumler JS, Anderson JF, Johnson RC, Fikrig E. Coexistence of antibodies to tick-borne pathogens of babesiosis, ehrlichiosis, and Lyme borreliosis in human sera. Journal of Clinical Microbiology. 1995; 33(11):3054-3057

272. Magnarelli LA, Fikrig E, Berland R, Anderson JF, Flavell RA. Comparison of whole-cell antibodies and an antigenic flagellar epitope of Borrelia burgdorferi in serologic tests for diagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 1992; 30(12):3158-3162

273. Magnarelli LA, Fikrig E, Padula SJ, Anderson JF, Flavell RA. Use of recombinant antigens of Borrelia burgdorferi in serologic tests for diagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 1996; 34(2):237-240

274. Magnarelli LA, Ijdo JW, Padula SJ, Flavell RA, Fikrig E. Serologic diagnosis of Lyme borreliosis by using enzyme-linked immunosorbent assays with recombinant antigens. Journal of Clinical Microbiology. 2000; 38(5):1735-1739

275. Magnarelli LA, Lawrenz M, Norris SJ, Fikrig E. Comparative reactivity of human sera to recombinant VlsE and other Borrelia burgdorferi antigens in class-specific enzyme-linked immunosorbent assays for Lyme borreliosis. Journal of Medical Microbiology. 2002; 51(8):649-655

276. Magnarelli LA, Meegan JM, Anderson JF, Chappell WA. Comparison of an indirect fluorescent-antibody test with an enzyme-linked immunosorbent assay for serological studies of Lyme disease. Journal of Clinical Microbiology. 1984; 20(2):181-184

277. Magnarelli LA, Miller JN, Anderson JF, Riviere GR. Cross-reactivity of nonspecific treponemal antibody in serologic tests for Lyme disease. Journal of Clinical Microbiology. 1990; 28(6):1276-1279

278. Mansy F, Hoyois B, De Vos MJ, Van Elsen A, Bollen A, Godfroid E. Colorimetric solid-phase capture hybridization assay for detection of amplified Borrelia burgdorferi DNA. Biotechniques. 1996; 21(1):122-125

279. Marangoni A, Moroni A, Accardo S, Cevenini R. Borrelia burgdorferi VlsE antigen for the serological diagnosis of Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 2008; 27(5):349-354

280. Marangoni A, Sambri V, Accardo S, Cavrini F, Mondardini V, Moroni A et al. A decrease in the immunoglobulin G antibody response against the VlsE protein of Borrelia burgdorferi sensu lato correlates with the resolution of clinical signs in antibiotic-treated patients with early Lyme disease. Clinical & Vaccine Immunology: CVI. 2006; 13(4):525-529

281. Marangoni A, Sparacino M, Cavrini F, Storni E, Mondardini V, Sambri V et al. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed Lyme disease in Italy. Journal of Medical Microbiology. 2005; 54(4):361-367

282. Marangoni A, Sparacino M, Mondardini V, Cavrini F, Storni E, Donati M et al. Comparative evaluation of two enzyme linked immunosorbent assay methods and three Western Blot methods for the diagnosis of culture-confirmed early Lyme borreliosis in Italy. New Microbiologica. 2005; 28(1):37-43

283. Markowicz M, Kivaranovic D, Stanek G. Testing patients with non-specific symptoms for antibodies against Borrelia burgdorferi sensu lato does not provide useful clinical information about their aetiology. Clinical Microbiology and Infection. 2015; 21(12):1098-1103

284. Marques A, Brown MR, Fleisher TA. Natural killer cell counts are not different between patients with post-Lyme disease syndrome and controls. Clinical & Vaccine Immunology: CVI. 2009; 16(8):1249-1250

285. Marques AR, Hornung RL, Dally L, Philipp MT. Detection of immune complexes is not independent of detection of antibodies in Lyme disease patients and does not confirm active infection with Borrelia burgdorferi. Clinical and Diagnostic Laboratory Immunology. 2005; 12(9):1036-1040

286. Marques AR, Stock F, Gill V. Evaluation of a new culture medium for Borrelia burgdorferi. Journal of Clinical Microbiology. 2000; 38(11):4239-4241

287. Mathiesen MJ, Christiansen M, Hansen K, Holm A, Asbrink E, Theisen M. Peptide-based OspC enzyme-linked immunosorbent assay for serodiagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 1998; 36(12):3474-3479

288. Mathiesen MJ, Hansen K, Axelsen N, Halkier-Sorensen L, Theisen M. Analysis of the human antibody response to outer surface protein C (OspC) of Borrelia burgdorferi sensu stricto, B. garinii, and B. afzelii. Medical Microbiology and Immunology. 1996; 185(3):121-129

289. Mavin S, Evans R, Milner RM, Chatterton JM, Ho-Yen DO. Local Borrelia burgdorferi sensu stricto and Borrelia afzelii strains in a single mixed antigen improves western blot sensitivity. Journal of Clinical Pathology. 2009; 62(6):552-554

290. Mavin S, McDonagh S, Evans R, Milner RM, Chatterton JMW, Ho-Yen DO. Interpretation criteria in Western blot diagnosis of Lyme borreliosis. British Journal of Biomedical Science. 2011; 68(1):5-10

291. Mavin S, Milner RM, Evans R, Chatterton JM, Joss AW, Ho-Yen DO. The use of local isolates in Western blots improves serological diagnosis of Lyme disease in Scotland. Journal of Medical Microbiology. 2007; 56(1):47-51

292. Mavin S, Watson EJ, Evans R. Laboratory diagnosis of Lyme borreliosis in Scottish patients: a novel approach. British Journal of Biomedical Science. 2014; 71(2):51-54

293. Mayne PJ. Clinical determinants of Lyme borreliosis, babesiosis, bartonellosis, anaplasmosis, and ehrlichiosis in an Australian cohort. International Journal of General Medicine. 2014; 8:15-26

294. Melby K, Steinbakk M, Jensenius M, Figenschau KJ. Detection of serum antibodies against Borrelia burgdorferi with some commercially available serological tests. NIPH Annals. 1990; 13(2):37-44

295. Melchers W, Meis J, Rosa P, Claas E, Nohlmans L, Koopman R et al. Amplification of Borrelia burgdorferi DNA in skin biopsies from patients with Lyme disease. Journal of Clinical Microbiology. 1991; 29(11):2401-2406

296. Melski JW, Reed KD, Mitchell PD, Barth GD. Primary and secondary erythema migrans in central Wisconsin. Archives of Dermatology. 1993; 129(6):709-716

297. Merljak Skocir L, Ruzic-Sabljic E, Maraspin-Carman V, Lotric-Furlan S, Logar M, Strle F. Comparison of different Borrelia burgdorferi sensu lato strains for detection of immune response in patients with erythema migrans. International Journal of Medical Microbiology. 2008; 298(5-6):493-504

298. Mikkila H, Seppala I, Leirisalo-Repo M, Karma A. The significance of serum anti-Borrelia antibodies in the diagnostic work-up of uveitis. European Journal of Ophthalmology. 1997; 7(3):251-255

299. Milewski MD, Cruz AI, Jr., Miller CP, Peterson AT, Smith BG. Lyme arthritis in children presenting with joint effusions. Journal of Bone & Joint Surgery - American Volume. 2011; 93(3):252-260

300. Millner M, Schimek MG, Spork D, Schnizer M, Stanek G. Lyme borreliosis in children. A controlled clinical study based on ELISA values. European Journal of Pediatrics. 1989; 148(6):527-530

301. Millner MM, Mullegger RR, Spork KD, Stanek G. Lyme borreliosis of central nervous system (CNS) in children: a diagnostic challenge. Infection. 1991; 19(4):273-278

302. Mitchell PD, Reed KD, Aspeslet TL, Vandermause MF, Melski JW. Comparison of four immunoserologic assays for detection of antibodies to Borrelia burgdorferi in patients with culture-positive erythema migrans. Journal of Clinical Microbiology. 1994; 32(8):1958-1962

303. Mogilyansky E, Loa CC, Adelson ME, Mordechai E, Tilton RC. Comparison of Western immunoblotting and the C6 Lyme antibody test for laboratory detection of Lyme disease. Clinical and Diagnostic Laboratory Immunology. 2004; 11(5):924-929

304. Molins CR, Ashton LV, Wormser GP, Hess AM, Delorey MJ, Mahapatra S et al. Development of a metabolic biosignature for detection of early lyme disease. Clinical Infectious Diseases. 2015; 60(12):1767-1775

305. Molins CR, Delorey MJ, Replogle A, Sexton C, Schriefer ME. Evaluation of bioMérieux's dissociated VIDAS Lyme IgM II (LYM) and IgG II (LYG) as a first-tier diagnostic assay for Lyme disease. Journal of Clinical Microbiology. 2017; 55(6):1698-1706

306. Molins CR, Delorey MJ, Sexton C, Schriefer ME. Lyme borreliosis serology: performance of several commonly used laboratory diagnostic tests and a large resource panel of well-characterized patient samples. Journal of Clinical Microbiology. 2016; 54(11):2726-2734

307. Molins CR, Delorey MJ, Sexton C, Schriefer ME. Lyme borreliosis serology: performance with several commonly used laboratory diagnostic tests and a large

resource panel of well-characterized patient samples. Journal of Clinical Microbiology. 2016; 54(11):2726-2734

308. Molins CR, Sexton C, Young JW, Ashton LV, Pappert R, Beard CB et al. Collection and characterization of samples for establishment of a serum repository for Lyme disease diagnostic test development and evaluation. Journal of Clinical Microbiology. 2014; 52(10):3755-3762

309. Moniuszko A, Czupryna P, Pancewicz S, Rutkowski K, Zajkowska O, Swierzbinska R et al. Evaluation of CXCL8, CXCL10, CXCL11, CXCL12 and CXCL13 in serum and cerebrospinal fluid of patients with neuroborreliosis. Immunology Letters. 2014; 157(1-2):45-50

310. Moniuszko A, Dunaj J, Zajkowska J, Czupryna P, Swierzbinska R, Guziejko K et al. Comparison of detection of Borrelia burgdorferi DNA and anti-Borrelia burgdorferi antibodies in patients with erythema migrans in north-eastern Poland. Postepy Dermatologii I Alergologii. 2015; 32(1):11-14

311. Moniuszko A, Pancewicz S, Czupryna P, Grygorczuk S, Swierzbinska R, Kondrusik M et al. SsICAM-1, IL-21 and IL-23 in patients with tick borne encephalitis and neuroborreliosis. Cytokine. 2012; 60(2):468-472

312. Moravcova L, Picha D, Lasikova S, Maresova V. Assessment of specific anti-Borrelia antibodies in cerebrospinal fluid by means of two tests with different antigens - Borrelia garinii and Borrelia afzelii. Klinicka Mikrobiologie a Infekcni Lekarstvi. 2001; 7(3):77-79

313. Moter SE, Hofmann H, Wallich R, Simon MM, Kramer MD. Detection of Borrelia burgdorferi sensu lato in lesional skin of patients with erythema migrans and acrodermatitis chronica atrophicans by ospA-specific PCR. Journal of Clinical Microbiology. 1994; 32(12):2980-2988

314. Mouritsen CL, Wittwer CT, Litwin CM, Yang L, Weis JJ, Martins TB et al. Polymerase chain reaction detection of Lyme disease: Correlation with clinical manifestations and serologic responses. American Journal of Clinical Pathology. 1996; 105(5):647-654

315. Mueller M, Bunk S, Diterich I, Weichel M, Rauter C, Hassler D et al. Identification of Borrelia burgdorferi ribosomal protein L25 by the phage surface display method and evaluation of the protein's value for serodiagnosis. Journal of Clinical Microbiology. 2006; 44(10):3778-3780

316. Mullegger RR, Means TK, Shin JJ, Lee M, Jones KL, Glickstein LJ et al. Chemokine signatures in the skin disorders of Lyme borreliosis in Europe: predominance of CXCL9 and CXCL10 in erythema migrans and acrodermatitis and CXCL13 in lymphocytoma. Infection and Immunity. 2007; 75(9):4621-4628

317. Murray N, Kristoferitsch W, Stanek G, Steck AJ. Specificity of CSF antibodies against components of Borrelia burgdorferi in patients with meningopolyneuritis Garin-Bujadoux-Bannwarth. Journal of Neurology. 1986; 233(4):224-227

318. Nachamkin I, Riddle DL, Feldman M, Edelstein PH. Utilization of tests for Lyme disease antibody at a University hospital. Clinical and Diagnostic Laboratory Immunology. 1996; 3(3):287-289

319. Nadal D, Wunderli W, Briner H, Hansen K. Prevalence of antibodies to Borrelia burgdorferi in forestry workers and blood donors from the same region in Switzerland. European Journal of Clinical Microbiology and Infectious Diseases. 1989; 8(11):992-995

320. Nadelman RB, Nowakowski J, Forseter G, Goldberg NS, Bittker S, Cooper D et al. The clinical spectrum of early Lyme borreliosis in patients with culture-confirmed erythema migrans. American Journal of Medicine. 1996; 100(5):502-508

321. Nadelman RB, Pavia CS, Magnarelli LA, Wormser GP. Isolation of Borrelia burgdorferi from the blood of seven patients with Lyme disease. American Journal of Medicine. 1990; 88(1):21-26

322. Nagel T, Gajovic-Eichelmann N, Tobisch S, Schulte-Spechtel U, Bier FF. Serodiagnosis of Lyme borreliosis infection using surface plasmon resonance. Clinica Chimica Acta. 2008; 394(1-2):110-113

323. Naktin JP. Quantitative Versus Qualitative Use of Lyme Enzyme-Linked Immunosorbent Assay. Clinical Infectious Diseases. 2017; 64(8):1144

324. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

325. Nayak S, Sridhara A, Melo R, Richer L, Chee NH, Kim J et al. Microfluidics-based point-of-care test for serodiagnosis of Lyme disease. Scientific Reports. 2016; 6:35069

326. Neubert U, Krampitz HE, Engl H. Microbiological findings in erythema (chronicum) migrans and related disorders. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1986; 263(1-2):237-252

327. Neumann A, Schlesier M, Schneider H, Vogt A, Peter HH. Frequencies of Borrelia burgdorferi-reactive T lymphocytes in Lyme arthritis. Rheumatology International. 1989; 9(3-5):237-241

328. NHS Business Services Authority. NHS electronic drug tariff March 2017. Available from: http://www.drugtariff.nhsbsa.nhs.uk/#/00446515-DC_2/DC00446511/Home Last accessed: 4 April 2017.

329. Nichol G, Dennis DT, Steere AC, Lightfoot R, Wells G, Shea B et al. Test-treatment strategies for patients suspected of having Lyme disease: a cost-effectiveness analysis. Annals of Internal Medicine. 1998; 128(1):37-48

330. Nigrovic LE, Cohn KA, Lyons TW, Thompson AD, Hines EM, Welsh EJ et al. Enteroviral testing and length of hospital stay for children evaluated for Lyme meningitis. Journal of Emergency Medicine. 2013; 44(6):1196-1200

331. Nilsson I, von Rosen IA. Serum antibodies against Borrelia afzelii, Borrelia burgdorferi sensu stricto and the 41-kiloDalton flagellin in patients from a Lyme borreliosis endemic area: analysis by EIA and immunoblot. APMIS. 1996; 104(12):907-914

332. Nocton JJ, Bloom BJ, Rutledge BJ, Persing DH, Logigian EL, Schmid CH et al. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in cerebrospinal fluid in Lyme neuroborreliosis. Journal of Infectious Diseases. 1996; 174(3):623-627

333. Nocton JJ, Dressler F, Rutledge BJ, Rys PN, Persing DH, Steere AC. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in synovial fluid from patients with Lyme arthritis. New England Journal of Medicine. 1994; 330(4):229-234

334. Nohlmans MK, Blaauw AA, van den Bogaard AE, van Boven CP. Evaluation of nine serological tests for diagnosis of Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 1994; 13(5):394-400

335. Nordberg M, Forsberg P, Nyman D, Skogman BH, Nyberg C, Ernerudh J et al. Can ELISPOT be applied to a clinical setting as a diagnostic utility for neuroborreliosis? Cells. 2012; 1(2):153-167

336. Norman GL, Antig JM, Bigaignon G, Hogrefe WR. Serodiagnosis of Lyme borreliosis by Borrelia burgdorferi sensu stricto, B. garinii, and B. afzelii Western blots (immunoblots). Journal of Clinical Microbiology. 1996; 34(7):1732-1738

337. Nowakowski J, McKenna D, Nadelman RB, Bittker S, Cooper D, Pavia C et al. Blood cultures for patients with extracutaneous manifestations of Lyme disease in the United States. Clinical Infectious Diseases. 2009; 49(11):1733-1735

338. Nowakowski J, Schwartz I, Liveris D, Wang G, Aguero-Rosenfeld ME, Girao G et al. Laboratory diagnostic techniques for patients with early Lyme disease associated with erythema migrans: a comparison of different techniques. Clinical Infectious Diseases. 2001; 33(12):2023-2027

339. Ogden NH, Arsenault J, Hatchette TF, Mechai S, Lindsay LR. Antibody responses to Borrelia burgdorferi detected by Western blot vary geographically in Canada. PloS One. 2017; 12(2):e0171731

340. Ogrinc K, Lotric-Furlan S, Maraspin V, Cimperman J, Ruzic-Sabljic E, Strle F. Cerebrospinal fluid findings in patients with symptoms suggesting chronic Lyme borreliosis. Wiener Klinische Wochenschrift. 2002; 114(13-14):535-538

341. Ogrinc K, Lotric-Furlan S, Maraspin V, Lusa L, Cerar T, Ruzic-Sabljic E et al. Suspected early Lyme neuroborreliosis in patients with erythema migrans. Clinical Infectious Diseases. 2013; 57(4):501-509

342. Oksi J, Marjamaki M, Nikoskelainen J, Viljanen MK. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Annals of Medicine. 1999; 31(3):225-232

343. Oksi J, Marttila H, Soini H, Aho H, Uksila J, Viljanen MK. Early dissemination of Borrelia burgdorferi without generalized symptoms in patients with erythema migrans. APMIS. 2001; 109(9):581-588

344. Oksi J, Uksila J, Marjamaki M, Nikoskelainen J, Viljanen MK. Antibodies against whole sonicated Borrelia burgdorferi spirochetes, 41- kilodalton flagellin, and P39 protein in patients with PCR- or culture- proven late Lyme borreliosis. Journal of Clinical Microbiology. 1995; 33(9):2260-2264

345. Olsson I, Stedingk LV, Hanson HS, Stedingk M, Asbrink E, Hovmark A. Comparison of four different serological methods for detection of antibodies to Borrelia burgdorferi in erythema migrans. Acta Dermato-Venereologica. 1991; 71(2):127-133

346. Oschmann P, Wellensiek HJ, Dorndorf W, Pflughaupt KW. Intrathecal synthesis of specific antibodies in neuroborreliosis: comparison of immunoblotting, indirect immunofluorescence assay and enzyme-linked immunosorbent assay. Laboratoriums Medizin. 1997; 21(10):528-534

347. Pachner AR, Delaney E. The polymerase chain reaction in the diagnosis of Lyme neuroborreliosis. Annals of Neurology. 1993; 34(4):544-550

348. Pachner AR, Ricalton NS. Western blotting in evaluating Lyme seropositivity and the utility of a gel densitometric approach. Neurology. 1992; 42(11):2185-2192

349. Padula SJ, Dias F, Sampieri A, Craven RB, Ryan RW. Use of recombinant OspC from Borrelia burgdorferi for serodiagnosis of early Lyme disease. Journal of Clinical Microbiology. 1994; 32(7):1733-1738

350. Palacios R, Osorio LE, Giraldo LE, Torres AJ, Philipp MT, Ochoa MT. Positive IgG Western blot for Borrelia burgdorferi in Colombia. Memorias do Instituto Oswaldo Cruz. 1999; 94(4):499-503

351. Palecek T, Kuchynka P, Hulinska D, Schramlova J, Hrbackova H, Vitkova I et al. Presence of Borrelia burgdorferi in endomyocardial biopsies in patients with new-onset unexplained dilated cardiomyopathy. Medical Microbiology and Immunology. 2010; 199(2):139-143

352. Paluchowska E, Samochocki Z, Tarka S, Raczka A, Zabielski S. Borrelia burgdorferi antigen in patients with skin changes after insect bite. International Review of Allergology and Clinical Immunology. 1996; 2(2):62-65

353. Panelius J, Lahdenne P, Heikkila T, Peltomaa M, Oksi J, Seppala I. Recombinant OspC from Borrelia burgdorferi sensu stricto, B. afzelii and B. garinii in the serodiagnosis of Lyme borreliosis. Journal of Medical Microbiology. 2002; 51(9):731-739

354. Panelius J, Lahdenne P, Saxen H, Carlsson SA, Heikkila T, Peltomaa M et al. Diagnosis of Lyme neuroborreliosis with antibodies to recombinant proteins DbpA, BBK32, and OspC, and VlsE IR6 peptide. Journal of Neurology. 2003; 250(11):1318-1327

355. Panelius J, Lahdenne P, Saxen H, Heikkila T, Seppala I. Recombinant flagellin A proteins from Borrelia burgdorferi sensu stricto, B. afzelii, and B. garinii in serodiagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 2001; 39(11):4013-4019

356. Panelius J, Meri T, Seppala I, Eholuoto M, Alitalo A, Meri S. Outer surface protein E antibody response and its effect on complement factor H binding to OspE in Lyme borreliosis. Microbes and Infection. 2008; 10(2):135-142

357. Panelius J, Sillanpaa H, Seppala I, Sarvas H, Lahdenne P. Antibodies to recombinant decorin-binding proteins A and B in the cerebrospinal fluid of patients with Lyme neuroborreliosis. Scandinavian Journal of Infectious Diseases. 2007; 39(9):775-780

358. Pappas MG, Ballou WR, Gray MR, Takafuji ET, Miller RN, Hockmeyer WT. Rapid serodiagnosis of leptospirosis using the IgM-specific Dot-ELISA: comparison with the microscopic agglutination test. American Journal of Tropical Medicine and Hygiene. 1985; 34(2):346-354

359. Park SH, Hwang KJ, Chu H, Park MY. Serological detection of Lyme borreliosis agents in patients from Korea, 2005-2009. Osong Public Health & Research Perspectives. 2011; 2(1):29-33

360. Patriquin G, LeBlanc J, Heinstein C, Roberts C, Lindsay R, Hatchette TF. Cross-reactivity between Lyme and syphilis screening assays: Lyme disease does not cause false-positive syphilis screens. Diagnostic Microbiology and Infectious Disease. 2016; 84(3):184-186

361. Paul H, Gerth HJ, Ackermann R. Infectiousness for humans of Ixodes ricinus containing Borrelia burgdorferi. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1987; 263(3):473-476

362. Pavia CS, Wormser GP, Bittker S, Cooper D. An indirect hemagglutination antibody test to detect antibodies to Borrelia burgdorferi in patients with Lyme disease. Journal of Microbiological Methods. 2000; 40(2):163-173

363. Pavlickova P, Hug H. A streptavidin-biotin-based microarray platform for immunoassays. Methods in Molecular Biology. 2004; 264:73-83

364. Peltomaa M, McHugh G, Steere AC. The VlsE (IR6) peptide ELISA in the serodiagnosis of lyme facial paralysis. Otology & Neurotology. 2004; 25(5):838-841

365. Peltomaa M, Pyykko I, Seppala I, Viljanen M. Lyme borreliosis - an unusual cause of vertigo. Auris, Nasus, Larynx. 1998; 25(3):233-242

366. Pennell DR, Wand PJ, Schell RF. Evaluation of a quantitative fluorescence immunoassay (FIAX) for detection of serum antibody to Borrelia burgdorferi. Journal of Clinical Microbiology. 1987; 25(11):2218-2220

367. Peter O, Bretz AG, Postic D, Dayer E. Association of distinct species of Borrelia burgdorferi sensu lato with neuroborreliosis in Switzerland. Clinical Microbiology and Infection. 1997; 3(4):423-431

368. Petersen E, Tolstrup M, Capuano F, Ellermann-Eriksen S. Population-based study of diagnostic assays for Borrelia infection: comparison of purified flagella antigen assay (Ideia, Dako Cytomation) and recombinant antigen assay (Liaison, DiaSorin). BMC Clinical Pathology. 2008; 8:4

369. Pfluger KH, Reimers CD, Neubert U, Meisel C, Trapp B, Leititis J et al. Lyme-borreliosis and possible association with HLA-antigens. Tissue Antigens. 1989; 33(3):375-381

370. Philipp MT, Masters E, Wormser GP, Hogrefe W, Martin D. Serologic evaluation of patients from Missouri with erythema migrans-like skin lesions with the C6 Lyme test. Clinical & Vaccine Immunology: CVI. 2006; 13(10):1170-1171

371. Phillips SE, Mattman LH, Hulinska D, Moayad H. A proposal for the reliable culture of Borrelia burgdorferi from patients with chronic Lyme disease, even from those previously aggressively treated. Infection. 1998; 26(6):364-367

372. Picha D, Moravcova L, Holeckova D, Zd'arsky E, Valesova M, Maresova V et al. Examination of specific DNA by PCR in patients with different forms of Lyme borreliosis. International Journal of Dermatology. 2008; 47(10):1004-1010

373. Picha D, Moravcova L, Smiskova D. Prospective study on the chemokine CXCL13 in neuroborreliosis and other aseptic neuroinfections. Journal of the Neurological Sciences. 2016; 368:214-220

374. Picha D, Moravcova L, Vanousova D, Hercogova J, Blechova Z. DNA persistence after treatment of Lyme borreliosis. Folia Microbiologica. 2014; 59(2):115-125

375. Picha D, Moravcova L, Zdarsky E, Maresova V, Hulinsky V. PCR in lyme neuroborreliosis: a prospective study. Acta Neurologica Scandinavica. 2005; 112(5):287-292

376. Picken MM, Picken RN, Han D, Cheng Y, Ruzic-Sabljic E, Cimperman J et al. A two year prospective study to compare culture and polymerase chain reaction amplification for the detection and diagnosis of Lyme borreliosis. Molecular Pathology. 1997; 50(4):186-193

377. Pierer K, Stunzner D, Feichtinger M, Homann CN, Kleinert G, Kessler HH et al. Is IgM of diagnostic value in case of delayed intrathecal production of IgG antibodies? Wiener Klinische Wochenschrift. 1999; 111(22-23):957-960

378. Pietikainen A, Maksimow M, Kauko T, Hurme S, Salmi M, Hytonen J. Cerebrospinal fluid cytokines in Lyme neuroborreliosis. Journal of Neuroinflammation. 2016; 13(1):273

379. Pietruczuk A, Swierzbinska R, Pancewicz S, Pietruczuk M, Hermanowska-Szpakowicz T. Serum levels of interleukin-18 (IL-18), interleukin-1beta (IL-1beta), its soluble receptor sIL-1RII and C-reactive protein (CRP) in patients with Lyme arthritis. Infection. 2006; 34(3):158-162

380. Pleyer U, Priem S, Bergmann L, Burmester G, Hartmann C, Krause A. Detection of Borrelia burgdorferi DNA in urine of patients with ocular Lyme borreliosis. British Journal of Ophthalmology. 2001; 85(5):552-555

381. Plorer A, Sepp N, Schmutzhard E, Krabichler S, Trobos S, Schauer G et al. Effects of adequate versus inadequate treatment of cutaneous manifestations of Lyme borreliosis on the incidence of late complications and late serologic status. Journal of Investigative Dermatology. 1993; 100(2):103-109

382. Pomelova VG, Korenberg EI, Kuznetsova TI, Bychenkova TA, Bekman NI, Osin NS. C6 Peptide-Based Multiplex Phosphorescence Analysis (PHOSPHAN) for Serologic Confirmation of Lyme Borreliosis. PloS One. 2015; 10(7):e0130048

383. Porwancher RB, Hagerty CG, Fan J, Landsberg L, Johnson BJ, Kopnitsky M et al. Multiplex immunoassay for Lyme disease using VlsE1-IgG and pepC10-IgM antibodies: improving test performance through bioinformatics. Clinical & Vaccine Immunology: CVI. 2011; 18(5):851-859

384. Priem S, Rittig MG, Kamradt T, Burmester GR, Krause A. An optimized PCR leads to rapid and highly sensitive detection of Borrelia burgdorferi in patients with Lyme borreliosis. Journal of Clinical Microbiology. 1997; 35(3):685-690

385. Public Health England. Rare and Imported Pathogens Laboratory (RIPL): Specimen referral guidelines and service user manual. Public Health England, 2017.

386. Public Health England. Zoonoses report: UK 2015. London. Public Health England, 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/621094/UK_Zoonoses_report_2015.pdf

387. Puri BK, Segal DR, Monro JA. Diagnostic use of the lymphocyte transformation test-memory lymphocyte immunostimulation assay in confirming active Lyme borreliosis in clinically and serologically ambiguous cases. International Journal of Clinical and Experimental Medicine. 2014; 7(12):5890-5892

388. Qiu B, Brunner M, Zhang G, Sigal L, Stein S. Selection of continuous epitope sequences and their incorporation into poly(ethylene glycol)-peptide conjugates for use in serodiagnostic immunoassays: application to lyme disease. Biopolymers - Peptide Science Section. 2000; 55(4):319-333

389. Ranki A, Aavik E, Peterson P, Schauman K, Nurmilaakso P. Successful amplification of DNA specific for Finnish Borrelia burgdorferi isolates in erythema chronicum migrans but not in circumscribed scleroderma lesions. Journal of Investigative Dermatology. 1994; 102(3):339-345

390. Rasiah C, Rauer S, Gassmann GS, Vogt A. Use of a hybrid protein consisting of the variable region of the Borrelia burgdorferi flagellin and part of the 83-kDa protein as antigen for serodiagnosis of Lyme disease. Journal of Clinical Microbiology. 1994; 32(4):1011-1017

391. Rauer S, Beitlich P, Neubert U, Rasiah C, Kaiser R. Avidity determination of Borrelia burgdorferi-specific IgG antibodies in Lyme disease. Scandinavian Journal of Infectious Diseases. 2001; 33(11):809-811

392. Rauer S, Kayser M, Neubert U, Rasiah C, Vogt A. Establishment of enzyme-linked immunosorbent assay using purified recombinant 83-kilodalton antigen of Borrelia burgdorferi sensu stricto and Borrelia afzelii for serodiagnosis of lyme disease. Journal of Clinical Microbiology. 1995; 33(10):2596-2600

393. Rauer S, Spohn N, Rasiah C, Neubert U, Vogt A. Enzyme-linked immunosorbent assay using recombinant OspC and the internal 14-kDa flagellin fragment for serodiagnosis of early lyme disease. Journal of Clinical Microbiology. 1998; 36(4):857-861

394. Rebman AW, Crowder LA, Kirkpatrick A, Aucott JN. Characteristics of seroconversion and implications for diagnosis of post-treatment Lyme disease syndrome: acute and convalescent serology among a prospective cohort of early Lyme disease patients. Clinical Rheumatology. 2015; 34(3):585-589

395. Rehse-Kupper B, Ackermann R. Demonstration of locally synthesized borrelia antibodies in cerebrospinal fluid. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1987; 263(3):407-411

396. Reiber H, Ressel CB, Spreer A. Diagnosis of neuroborreliosis - improved knowledge base for qualified antibody analysis and cerebrospinal fluid data pattern related interpretations. Neurology Psychiatry and Brain Research. 2013; 19(4):159-169

397. Riesbeck K, Hammas B. Comparison of an automated Borrelia indirect chemiluminescent immunoassay (CLIA) with a VlsE/C6 ELISA and Immunoblot. European Journal of Clinical Microbiology and Infectious Diseases. 2007; 26(7):517-519

398. Rijpkema S, Groen J, Molkenboer M, Herbrink P, Osterhaus A, Schellekens J. Serum antibodies to the flagellum of Borrelia burgdorferi measured with an inhibition enzyme-linked immunosorbent assay are diagnostic for Lyme borreliosis. Serodiagnosis and Immunotherapy in Infectious Disease. 1994; 6(2):61-67

399. Rijpkema SG, Tazelaar DJ, Molkenboer MJ, Noordhoek GT, Plantinga G, Schouls LM et al. Detection of Borrelia afzelii, Borrelia burgdorferi sensu stricto, Borrelia garinii and group VS116 by PCR in skin biopsies of patients with erythema migrans and acrodermatitis chronica atrophicans. Clinical Microbiology and Infection. 1997; 3(1):109-116

400. Robertson J, Guy E, Andrews N, Wilske B, Anda P, Granstrom M et al. A European multicenter study of immunoblotting in serodiagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 2000; 38(6):2097-2102

401. Rodiger S, Hanschmann H, Steidle M, Schroder C, Schierack P, Lehmann W. Detection of borrelia, bordetella and HPV with the looptag realtime PCR probe system. International Journal of Medical Microbiology. 2013; 303(Suppl 1):12-13

402. Rose CD, Fawcett PT, Eppes SC, Klein JD, Gibney K, Doughty RA. Pediatric Lyme arthritis: clinical spectrum and outcome. Journal of Pediatric Orthopaedics. 1994; 14(2):238-241

403. Rose CD, Fawcett PT, Singsen BH, Dubbs SB, Doughty RA. Use of Western blot and enzyme-linked immunosorbent assays to assist in the diagnosis of Lyme disease. Pediatrics. 1991; 88(3):465-470

404. Rosslhuber F, Schausberger C, Emberger M, Mustafa L. Detection of Borrelia burgdorferi in formalin fixed paraffin embedded skin biopsies. Clinical Chemistry and Laboratory Medicine. 2012; 50(10):A288

405. Rossmann E, Richards G, Fingerle V, Sing A, Bechtel M. Evaluation of a new Lyme borreliosis immunoblot including EBV and syphilis antigens as differential diagnosis tools. International Journal of Medical Microbiology. 2009; 299(Suppl 1):32-33

406. Roux F, Boyer E, Jaulhac B, Dernis E, Closs-Prophette F, Puechal X. Lyme meningoradiculitis: prospective evaluation of biological diagnosis methods. European Journal of Clinical Microbiology and Infectious Diseases. 2007; 26(10):685-693

407. Rudenko N, Golovchenko M, Nemec J, Volkaert J, Mallatova N, Grubhoffer L. Improved method of detection and molecular typing of Borrelia burgdorferi sensu lato in clinical samples by polymerase chain reaction without DNA purification. Folia Microbiologica. 2005; 50(1):31-39

408. Rupprecht TA, Pfister HW, Angele B, Kastenbauer S, Wilske B, Koedel U. The chemokine CXCL13 (BLC): a putative diagnostic marker for neuroborreliosis. Neurology. 2005; 65(3):448-450

409. Russell H, Sampson JS, Schmid GP, Wilkinson HW, Plikaytis B. Enzyme-linked immunosorbent assay and indirect immunofluorescence assay for Lyme disease. Journal of Infectious Diseases. 1984; 149(3):465-470

410. Rutkowski S, Busch DH, Huppertz HI. Lymphocyte proliferation assay in response to Borrelia burgdorferi in patients with Lyme arthritis: analysis of lymphocyte subsets. Rheumatology International. 1997; 17(4):151-158

411. Ruzic-Sabljic E, Maraspin V, Cimperman J, Lotric-Furlan S, Strle F. Evaluation of immunofluorescence test (IFT) and immuno (western) blot (WB) test in patients with erythema migrans. Wiener Klinische Wochenschrift. 2002; 114(13-14):586-590

412. Ruzic-Sabljic E, Maraspin V, Stupica D, Rojko T, Bogovic P, Strle F et al. Comparison of MKP and BSK-H media for the cultivation and isolation of Borrelia burgdorferi sensu lato. PloS One. 2017; 12(2):e0171622

413. Ryffel K, Peter O, Binet L, Dayer E. Interpretation of immunoblots for Lyme borreliosis using a semiquantitative approach. Clinical Microbiology and Infection. 1998; 4(4):205-212

414. Salazar CA, Rothemich M, Drouin EE, Glickstein L, Steere AC. Human Lyme arthritis and the immunoglobulin G antibody response to the 37-kilodalton arthritis-related protein of Borrelia burgdorferi. Infection and Immunity. 2005; 73(5):2951-2957

415. Santino I, Berlutti F, Pantanella F, Sessa R, del Piano M. Detection of Borrelia burgdorferi sensu lato DNA by PCR in serum of patients with clinical symptoms of Lyme borreliosis. FEMS Microbiology Letters. 2008; 283(1):30-35

416. Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Improved culture conditions for the growth and detection of Borrelia from human serum. International Journal of Medical Sciences. 2013; 10(4):362-376

417. Schempp C, Bocklage H, Lange R, Kolmel HW, Orfanos CE, Gollnick H. Further evidence for Borrelia burgdorferi infection in morphea and lichen sclerosus et atrophicus confirmed by DNA amplification. Journal of Investigative Dermatology. 1993; 100(5):717-720

418. Schenk J, Doebis C, Kusters U, Von Baehr V. Evaluation of a new multiparametric microspot array for serodiagnosis of Lyme borreliosis. Clinical Laboratory. 2015; 61(11):1715-1725

419. Schmidt BL, Aberer E, Stockenhuber C, Klade H, Breier F, Luger A. Detection of Borrelia burgdorferi DNA by polymerase chain reaction in the urine and breast milk of patients with Lyme borreliosis. Diagnostic Microbiology and Infectious Disease. 1995; 21(3):121-128

420. Schmidt C, Plate A, Angele B, Pfister HW, Wick M, Koedel U et al. A prospective study on the role of CXCL13 in Lyme neuroborreliosis. Neurology. 2011; 76(12):1051-1058

421. Schmitz JL, Powell CS, Folds JD. Comparison of seven commercial kits for detection of antibodies to Borrelia burgdorferi. European Journal of Clinical Microbiology and Infectious Diseases. 1993; 12(6):419-424

422. Schnarr S, Putschky N, Jendro MC, Zeidler H, Hammer M, Kuipers JG et al. Chlamydia and Borrelia DNA in synovial fluid of patients with early undifferentiated oligoarthritis: Results of a prospective study. Arthritis and Rheumatism. 2001; 44(11):2679-2685

423. Schulte-Spechtel U, Lehnert G, Liegl G, Fingerle V, Heimerl C, Johnson B et al. Significant improvement of the recombinant Borrelia IgG immunoblot for serodiagnosis of early neuroborreliosis. International Journal of Medical Microbiology. 2004; 293 (Suppl.37):158-160

424. Schulte-Spechtel U, Lehnert G, Liegl G, Fingerle V, Heimerl C, Johnson BJB et al. Significant improvement of the recombinant Borrelia-specific immunoglobulin G immunoblot test by addition of VlsE and a DbpA homologue derived from Borrelia garinii for diagnosis of early neuroborreliosis. Journal of Clinical Microbiology. 2003; 41(3):1299-1303

425. Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to Borrelia burgdorferi in immune complexes in seronegative Lyme disease. Lancet. 1990; 335(8685):312-315

426. Schutzer SE, Coyle PK, Krupp LB, Deng Z, Belman AL, Dattwyler R et al. Simultaneous expression of Borrelia OspA and OspC and IgM response in cerebrospinal fluid in early neurologic Lyme disease. Journal of Clinical Investigation. 1997; 100(4):763-767

427. Schutzer SE, Coyle PK, Reid P, Holland B. Borrelia burgdorferi-specific immune complexes in acute lyme disease. JAMA. 1999; 282(20):1942-1946

428. Schwaiger M, Peter O, Cassinotti P. Routine diagnosis of Borrelia burgdorferi (sensu lato) infections using a real-time PCR assay. Clinical Microbiology and Infection. 2001; 7(9):461-469

429. Schwartz BS, Nadelman RB, Fish D, Childs JE, Forseter G, Wormser GP. Entomologic and demographic correlates of anti-tick saliva antibody in a prospective study of tick bite subjects in Westchester County, New York. American Journal of Tropical Medicine and Hygiene. 1993; 48(1):50-57

430. Schwartz I, Bittker S, Bowen SL, Cooper D, Pavia C, Wormser GP. Polymerase chain reaction amplification of culture supernatants for rapid detection of Borrelia burgdorferi. European Journal of Clinical Microbiology and Infectious Diseases. 1993; 12(11):879-882

431. Schwartz I, Wormser GP, Schwartz JJ, Cooper D, Weissensee P, Gazumyan A et al. Diagnosis of early Lyme disease by polymerase chain reaction amplification and culture of skin biopsies from erythema migrans lesions. Journal of Clinical Microbiology. 1992; 30(12):3082-3088

432. Schwarzova K, Kost'Anova Z, Holeckova K, Spitalska E, Boldis V. Direct detection of borrelia burgdorferi spirochetes in patients with early disseminated Lyme borreliosis. Central European Journal of Public Health. 2009; 17(4):179-182

433. Senel M, Rupprecht TA, Tumani H, Pfister HW, Ludolph AC, Brettschneider J. The chemokine CXCL13 in acute neuroborreliosis. Journal of Neurology, Neurosurgery and Psychiatry. 2010; 81(8):929-933

434. Seppala IJT, Kroneld R, Schauman K, Forsen KO, Lassenius R. Diagnosis of Lyme borreliosis: non-specific serological reactions with Borrelia burgdorferi sonicate antigen caused by IgG2 antibodies. Journal of Medical Microbiology. 1994; 40(4):293-302

435. Seriburi V, Ndukwe N, Chang Z, Cox ME, Wormser GP. High frequency of false positive IgM immunoblots for Borrelia burgdorferi in clinical practice. Clinical Microbiology and Infection. 2012; 18(12):1236-1240

436. Shrestha M, Grodzicki RL, Steere AC. Diagnosing early Lyme disease. American Journal of Medicine. 1985; 78(2):235-240

437. Sieper J, Braun J, Reichardt M, Eggens U. The value of specific antibody detection and culture in the diagnosis of reactive arthritis. Clinical Rheumatology. 1993; 12(2):245-252

438. Sikand VK, Rothel JS, Martin RM. Diagnosis of Lyme borreliosis by a whole-blood gamma interferon assay for cell-mediated immune responses. Clinical and Diagnostic Laboratory Immunology. 1999; 6(3):445

439. Sillanpaa H, Lahdenne P, Sarvas H, Arnez M, Steere A, Peltomaa M et al. Immune responses to borrelial VlsE IR6 peptide variants. International Journal of Medical Microbiology. 2007; 297(1):45-52

440. Sillanpaa H, Skogman BH, Sarvas H, Seppala IJ, Lahdenne P. Antibodies to decorin-binding protein B (DbpB) in the diagnosis of Lyme neuroborreliosis in children. International Journal of Infectious Diseases. 2014; 28:160-163

441. Sillanpaa H, Skogman BH, Sarvas H, Seppala IJT, Lahdenne P. Cerebrospinal fluid chemokine CXCL13 in the diagnosis of neuroborreliosis in children. Scandinavian Journal of Infectious Diseases. 2013; 45(7):526-530

442. Simpson WJ, Schrumpf ME, Schwan TG. Reactivity of human Lyme borreliosis sera with a 39-kilodalton antigen specific to Borrelia burgdorferi. Journal of Clinical Microbiology. 1990; 28(6):1329-1337

443. Sivak SL, Aguero-Rosenfeld ME, Nowakowski J, Nadelman RB, Wormser GP. Accuracy of IgM immunoblotting to confirm the clinical diagnosis of early lyme disease. Archives of Internal Medicine. 1996; 156(18):2105-2109

444. Sjostedt A, Dotevall L, Elmros T, Bergstrom S. Lymphocyte reactivity against purified Lyme disease Borrelia cell components in individuals with neuroborreliosis. Serodiagnosis and Immunotherapy in Infectious Disease. 1994; 6(2):54-60

445. Skarpaas T, Ljostad U, Sobye M, Mygland A. Sensitivity and specificity of a commercial C6 peptide enzyme immuno assay in diagnosis of acute Lyme

neuroborreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 2007; 26(9):675-677

446. Skogman BH, Croner S, Forsberg P, Ernerudh J, Lahdenne P, Sillanpaa H et al. Improved laboratory diagnostics of Lyme neuroborreliosis in children by detection of antibodies to new antigens in cerebrospinal fluid. Pediatric Infectious Disease Journal. 2008; 27(7):605-612

447. Skogman BH, Ekerfelt C, Ludvigsson J, Forsberg P. Seroprevalence of Borrelia IgG antibodies among young Swedish children in relation to reported tick bites, symptoms and previous treatment for Lyme borreliosis: a population-based survey. Archives of Disease in Childhood. 2010; 95(12):1013-1016

448. Smismans A, Goossens VJ, Nulens E, Bruggeman CA. Comparison of five different immunoassays for the detection of Borrelia burgdorferi IgM and IgG antibodies. Clinical Microbiology and Infection. 2006; 12(7):648-655

449. Smit PW, Kurkela S, Kuusi M, Vapalahti O. Evaluation of two commercially available rapid diagnostic tests for Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 2015; 34(1):109-113

450. Smouha EE, Coyle PK, Shukri S. Facial nerve palsy in Lyme disease: evaluation of clinical diagnostic criteria. American Journal of Otology. 1997; 18(2):257-261

451. Soloski MJ, Crowder LA, Lahey LJ, Wagner CA, Robinson WH, Aucott JN. Serum inflammatory mediators as markers of human Lyme disease activity. PloS One. 2014; 9(4):e93243

452. Sood SK, Rubin LG, Blader ME, Ilowite NT. Positive serology for Lyme borreliosis in patients with juvenile rheumatoid arthritis in a Lyme borreliosis endemic area: analysis by immunoblot. Journal of Rheumatology. 1993; 20(4):739-741

453. Sood SK, Zemel LS, Ilowite NT. Interpretation of immunoblot in pediatric Lyme arthritis. Journal of Rheumatology. 1995; 22(4):758-761

454. Sroka-Oleksiak A, Ufir K, Salamon D, Bulanda M, Gosiewski T. Nested-PCR real time as alternative molecular tool for detection of Borrelia burgdorferi compared to the classical serological diagnosis of the blood. Medycyna Doswiadczalna i Mikrobiologia. 2016; 68(1):47-56

455. Stanek G, Breier F, Menzinger G, Schaar B, Hafner M, Partsch H. Erythema migrans and serodiagnosis by enzyme immunoassay and immunoblot with three borrelia species. Wiener Klinische Wochenschrift. 1999; 111(22-23):951-956

456. Steere AC, Grodzicki RL, Kornblatt AN, Craft JE, Barbour AG, Burgdorfer W et al. The spirochetal etiology of Lyme disease. New England Journal of Medicine. 1983; 308(13):733-740

457. Steere AC, Hardin JA, Malawista SE. Erythema chronicum migrans and Lyme arthritis: cryoimmunoglobulins and clinical activity of skin and joints. Science. 1977; 196(4294):1121-1122

458. Steere AC, McHugh G, Damle N, Sikand VK. Prospective study of serologic tests for lyme disease. Clinical Infectious Diseases. 2008; 47(2):188-195

459. Steere AC, Taylor E, McHugh GL, Logigian EL. The overdiagnosis of Lyme disease. JAMA. 1993; 269(14):1812-1816

460. Stefancikova A, Pet'ko B, Rozicka I, Salyova N, Ohlasova D. Epidemiological survey of human borreliosis diagnosed in Eastern Slovakia. Annals of Agricultural and Environmental Medicine. 2001; 8(2):171-175

461. Steinberg SH, Strickland GT, Pena C, Israel E. Lyme disease surveillance in Maryland, 1992. Annals of Epidemiology. 1996; 6(1):24-29

462. Stiernstedt G. Tick-borne Borrelia infection in Sweden. Scandinavian Journal of Infectious Diseases. 1985; Supplementum. 45:1-70

463. Stiernstedt G, Eriksson G, Enfors W, Jorbeck H, Svenungsson B, Skoldenberg B et al. Erythema chronicum migrans in Sweden: clinical manifestations and antibodies to Ixodes ricinus spirochete measured by indirect immunofluorescence and enzyme-linked immunosorbent assay. Scandinavian Journal of Infectious Diseases. 1986; 18(3):217-224

464. Stiernstedt G, Granstrom M. Borrelia arthritis in Sweden. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1986; 263(1-2):285-287

465. Stiernstedt GT, Granstrom M, Hederstedt B, Skoldenberg B. Diagnosis of spirochetal meningitis by enzyme-linked immunosorbent assay and indirect immunofluorescence assay in serum and cerebrospinal fluid. Journal of Clinical Microbiology. 1985; 21(5):819-825

466. Stricker RB, Winger EE. Decreased CD57 lymphocyte subset in patients with chronic Lyme disease. Immunology Letters. 2001; 76(1):43-48

467. Strle K, Stupica D, Drouin EE, Steere AC, Strle F. Elevated levels of IL-23 in a subset of patients with post-Lyme disease symptoms following erythema migrans. Clinical Infectious Diseases. 2014; 58(3):372-380

468. Strle K, Sulka KB, Pianta A, Crowley JT, Arvikar SL, Anselmo A et al. TH17 cell Cytokine responses in Lyme disease correlate with Borrelia burgdorferi antibodies during early infection and with autoantibodies late in the illness in patients with antibiotic-refractory Lyme arthritis. Clinical Infectious Diseases. 2017; 64(7):930-938

469. Stubs G, Fingerle V, Wilske B, Gobel UB, Zahringer U, Schumann RR et al. Acylated cholesteryl galactosides are specific antigens of borrelia causing Lyme disease and frequently induce antibodies in late stages of disease. Journal of Biological Chemistry. 2009; 284(20):13326-13334

470. Sundin M, Hansson ME, Engman ML, Orvell C, Lindquist L, Wide K et al. Pediatric tick-borne infections of the central nervous system in an endemic region of Sweden: a prospective evaluation of clinical manifestations. European Journal of Pediatrics. 2012; 171(2):347-352

471. Tammemagi MC, Frank JW, LeBlanc M, Artsob H. Intra- and interlaboratory reproducibility of an ELISA serological test for Lyme disease. Canadian Journal of Infectious Diseases. 1995; 6(2):90-95

472. Thompson A, Mannix R, Bachur R. Acute pediatric monoarticular arthritis: distinguishing Lyme arthritis from other etiologies. Pediatrics. 2009; 123(3):959-965

473. Tilton RC, Sand MN, Manak M. The Western immunoblot for Lyme disease: determination of sensitivity, specificity, and interpretive criteria with use of commercially available performance panels. Clinical Infectious Diseases. 1997; 25(Suppl 1):S31-S34

474. Tjernberg I, Henningsson AJ, Eliasson I, Forsberg P, Ernerudh J. Diagnostic performance of cerebrospinal fluid chemokine CXCL13 and antibodies to the C6-peptide in Lyme neuroborreliosis. Journal of Infection. 2011; 62(2):149-158

475. Tjernberg I, Kruger G, Eliasson I. C6 peptide ELISA test in the serodiagnosis of Lyme borreliosis in Sweden. European Journal of Clinical Microbiology and Infectious Diseases. 2007; 26(1):37-42

476. Tjernberg I, Schon T, Ernerudh J, Wistedt AC, Forsberg P, Eliasson I. C6-peptide serology as diagnostic tool in neuroborreliosis. APMIS. 2008; 116(5):393-399

477. Tjernberg I, Sillanpaa H, Seppala I, Eliasson I, Forsberg P, Lahdenne P. Antibody responses to borrelia IR(6) peptide variants and the C6 peptide in Swedish patients with erythema migrans. International Journal of Medical Microbiology. 2009; 299(6):439-446

478. Tokarska-Rodak M, Fota-Markowska H, Smiechowicz F, Gajownik B, Prokop M, Modrzewska R et al. Antibodies against in vivo B. burgdorferi antigens evaluated in patients with Lyme arthritis with reference to treatment. Advances in Clinical & Experimental Medicine. 2010; 19(4):489-496

479. Tokarska-Rodak M, Koziol-Montewka M, Fota-Markowska H, Bielec D, Modrzewka R, Panczuk A. Frequency and specificity of the antibodies against Borrelia burgdorferi tested by Western blot method in patients with symptoms of arthritis. Central-European Journal of Immunology. 2008; 33(4):220-223

480. Treib J, Woessner R, Grauer MT, Mueller-Reiland D, Haass A, Schimrigk K. Prevalence of antibodies to tick-borne encephalitis virus and borrelia burgdorferi sensu lato in samples from patients with abnormalities in the cerebrospinal fluid. Zentralblatt fur Bakteriologie. 1998; 288(2):253-266

481. Trevejo RT, Krause PJ, Schriefer ME, Dennis DT. Evaluation of a two-test serodiagnostic method for community assessment of Lyme disease in an endemic area. American Journal of Tropical Medicine and Hygiene. 2001; 65(5):563-566

482. Trevejo RT, Krause PJ, Sikand VK, Schriefer ME, Ryan R, Lepore T et al. Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. Journal of Infectious Diseases. 1999; 179(4):931-938

483. Trevisan G, Stinco G, Nobile C, Bonin S, Stanta G. Detection of Borrelia burgdorferi in skin biopsies from patients with morphea by polymerase chain reaction. Journal of the European Academy of Dermatology and Venereology. 1996; 6(1):15-19

484. Trnovcova M, Bazovska S, Svecova D. Antibodies to Borrelia burgdorferi in erythema migrans patients. Bratislavske Lekarske Listy. 2007; 108(9):399-402

485. Tumani H, Nolker G, Reiber H. Relevance of cerebrospinal fluid variables for early diagnosis of neuroborreliosis. Neurology. 1995; 45(9):1663-1670

486. Tuuminen T, Hedman K, Soderlund-Venermo M, Seppala I. Acute parvovirus B19 infection causes nonspecificity frequently in Borrelia and less often in Salmonella and Campylobacter serology, posing a problem in diagnosis of infectious arthropathy. Clinical & Vaccine Immunology: CVI. 2011; 18(1):167-172

487. Tveitnes D, Natas OB, Skadberg O, Oymar K. Lyme meningitis, the major cause of childhood meningitis in an endemic area: a population based study. Archives of Disease in Childhood. 2012; 97(3):215-220

488. Tylewska-Wierzbanowska S, Chmielewski T. Limitation of serological testing for Lyme borreliosis: evaluation of ELISA and Western blot in comparison with PCR and culture methods. Wiener Klinische Wochenschrift. 2002; 114(13-14):601-605

489. Ulvestad E, Kanestrom A, Sonsteby LJ, Jureen R, Omland T, Edvardsen B et al. Diagnostic and biological significance of anti-p41 IgM antibodies against Borrelia burgdorferi. Scandinavian Journal of Immunology. 2001; 53(4):416-421

490. Valentine-Thon E, Ilsemann K, Sandkamp M. A novel lymphocyte transformation test (LTT-MELISA) for Lyme borreliosis. Diagnostic Microbiology and Infectious Disease. 2007; 57(1):27-34

491. van Burgel ND, Bakels F, Kroes AC, van Dam AP. Discriminating Lyme neuroborreliosis from other neuroinflammatory diseases by levels of CXCL13 in cerebrospinal fluid. Journal of Clinical Microbiology. 2011; 49(5):2027-2030

492. van Burgel ND, Brandenburg A, Gerritsen HJ, Kroes AC, van Dam AP. High sensitivity and specificity of the C6-peptide ELISA on cerebrospinal fluid in Lyme neuroborreliosis patients. Clinical Microbiology and Infection. 2011; 17(10):1495-1500

493. van der Heijden IM, Wilbrink B, Rijpkema SG, Schouls LM, Heymans PH, van Embden JD et al. Detection of Borrelia burgdorferi sensu stricto by reverse line blot in the joints of Dutch patients with Lyme arthritis. Arthritis and Rheumatism. 1999; 42(7):1473-1480

494. Vasiliu V, Herzer P, Rossler D, Lehnert G, Wilske B. Heterogeneity of Borrelia burgdorferi sensu lato demonstrated by an ospA-type-specific PCR in synovial fluid from patients with Lyme arthritis. Medical Microbiology and Immunology. 1998; 187(2):97-102

495. Vermeersch P, Resseler S, Nackers E, Lagrou K. The C6 Lyme antibody test has low sensitivity for antibody detection in cerebrospinal fluid. Diagnostic Microbiology and Infectious Disease. 2009; 64(3):347-349

496. Vienecke R, Schlupen EM, Zochling N, Neubert U, Meurer M, Volkenandt M. No evidence for Borrelia burgdorferi - specific DNA in lesions of localized scleroderma. Journal of Investigative Dermatology. 1995; 104(1):23-26

497. von Baehr V, Doebis C, Volk HD, von Baehr R. The lymphocyte transformation test for Borrelia detects active lyme borreliosis and verifies effective antibiotic treatment. Open Neurology Journal. 2012; 6(SPEC.ISS.1):104-112

498. Von Stedingk LV, Olsson I, Hanson HS, Asbrink E, Hovmark A. Polymerase chain reaction for detection of Borrelia burgdorferi DNA in skin lesions of early and late Lyme borreliosis. European Journal of Clinical Microbiology and Infectious Diseases. 1995; 14(1):1-5

499. von Wissmann B, Hautmann W, Sing A, Hizo-Teufel C, Fingerle V. Assessing the risk of human granulocytic anaplasmosis and Lyme borreliosis after a tick bite in Bavaria, Germany. International Journal of Medical Microbiology. 2015; 305(7):736-741

500. Vrethem M, Widhe M, Ernerudh J, Garpmo U, Forsberg P. Clinical, diagnostic and immunological characteristics of patients with possible neuroborreliosis without intrathecal ig-synthesis against borrelia antigen in the cerebrospinal fluid. Neurology International. 2011; 3(1):4-8

501. Waddell LA, Greig J, Mascarenhas M, Harding S, Lindsay R, Ogden N. The accuracy of diagnostic tests for Lyme disease in humans, a systematic review and meta-analysis of North American research. PloS One. 2016; 11(12):e0168613

502. Wang P, Kapasi A, Fan S, Hilton E. Enhanced macrophage apoptosis in patients with Lyme disease. Journal of Spirochetal and Tick-borne Diseases. 2000; 7(FALL):73-78

503. Wang WZ, Fredrikson S, Xiao BG, Sun JB, Kostulas V, Link H. Lyme neuroborreliosis: cerebrospinal fluid contains myelin protein-reactive cells secreting interferon-gamma. European Journal of Neurology. 1996; 3(2):122-129

504. Wang ZY, Hansen K, Siden A, Cruz M. Intrathecal synthesis of anti-Borrelia burgdorferi antibodies in neuroborreliosis: a study with special emphasis on oligoclonal IgM antibody bands. Scandinavian Journal of Immunology. 1993; 37(3):369-376

505. Weber K, Neubert U. Clinical features of early erythema migrans disease and related disorders. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1986; 263(1-2):209-228

506. Weiner ZP, Crew RM, Brandt KS, Ullmann AJ, Schriefer ME, Molins CR et al. Evaluation of selected Borrelia burgdorferi lp54 plasmid-encoded gene products expressed during mammalian infection as antigens to improve serodiagnostic testing for early Lyme disease. Clinical & Vaccine Immunology: CVI. 2015; 22(11):1176-1186

507. Weiss NL, Sadock VA, Sigal LH, Phillips M, Merryman PF, Abramson SB. False positive seroreactivity to Borrelia burgdorferi in systemic lupus erythematosus: the value of immunoblot analysis. Lupus. 1995; 4(2):131-137

508. Weller M, Stevens A, Sommer N, Wietholter H, Dichgans J. Cerebrospinal fluid interleukins, immunoglobulins, and fibronectin in neuroborreliosis. Archives of Neurology. 1991; 48(8):837-841

509. Werner M, Nordin P, Arnholm B, Elgefors B, Krantz I. Borrelia burgdorferi antibodies in outdoor and indoor workers in south-west Sweden. Scandinavian Journal of Infectious Diseases. 2001; 33(2):128-131

510. Widhe M, Jarefors S, Ekerfelt C, Vrethem M, Bergstrom S, Forsberg P et al. Borrelia-specific interferon-gamma and interleukin-4 secretion in cerebrospinal fluid and blood during lyme borreliosis in humans: association with clinical outcome. Journal of Infectious Diseases. 2004; 189(10):1881-1891

511. Widhe M, Skogman BH, Jarefors S, Eknefelt M, Enestrom G, Nordwall M et al. Up-regulation of Borrelia-specific IL-4- and IFN-gamma-secreting cells in cerebrospinal fluid from children with Lyme neuroborreliosis. International Immunology. 2005; 17(10):1283-1291

512. Wienecke R, Neubert U, Volkenandt M. Molecular detection of Borrelia burgdorferi in formalin-fixed, paraffin-embedded lesions of Lyme disease. Journal of Cutaneous Pathology. 1993; 20(5):385-388

513. Wienecke R, Schlupen EM, Zochling N, Neubert U, Meurer M, Volkenandt M. No evidence for Borrelia burgdorferi-specific DNA in lesions of localized scleroderma. Journal of Investigative Dermatology. 1995; 104(1):23-26

514. Wieneke CA, Lovrich SD, Callister SM, Jobe DA, Marks JA, Schell RF. Evaluation of whole-cell and OspC enzyme-linked immunosorbent assays for discrimination of early Lyme borreliosis from OspA vaccination. Journal of Clinical Microbiology. 2000; 38(1):313-317

515. Wilhelmsson P, Fryland L, Lindblom P, Sjowall J, Ahlm C, Berglund J et al. A prospective study on the incidence of Borrelia burgdorferi sensu lato infection after a

tick bite in Sweden and on the Aland Islands, Finland (2008-2009). Ticks and Tick-Borne Diseases. 2016; 7(1):71-79

516. Wilkinson HW. Immunodiagnostic tests for Lyme disease. Yale Journal of Biology and Medicine. 1984; 57(4):567-572

517. Wilske B, Fingerle V, Herzer P, Hofmann A, Lehnert G, Peters H et al. Recombinant immunoblot in the serodiagnosis of Lyme borreliosis. Comparison with indirect immunofluorescence and enzyme-linked immunosorbent assay. Medical Microbiology and Immunology. 1993; 182(5):255-270

518. Wilske B, Fingerle V, Preac-Mursic V, Jauris-Heipke S, Hofmann A, Loy H et al. Immunoblot using recombinant antigens derived from different genospecies of Borrelia burgdorferi sensu lato. Medical Microbiology and Immunology. 1994; 183(1):43-59

519. Wilske B, Habermann C, Fingerle V, Hillenbrand B, Jauris-Heipke S, Lehnert G et al. An improved recombinant IgG immunoblot for serodiagnosis of Lyme borreliosis. Medical Microbiology and Immunology. 1999; 188(3):139-144

520. Wilske B, Schierz G, Preac-Mursic V, Weber K, Pfister HW, Einhaupl K. Serological diagnosis of erythema migrans disease and related disorders. Infection. 1984; 12(5):331-337

521. Wise DJ, Weaver TL. Detection of the Lyme disease bacterium, Borrelia burgdorferi, by using the polymerase chain reaction and a nonradioisotopic gene probe. Journal of Clinical Microbiology. 1991; 29(7):1523-1526

522. Wojciechowska-Koszko I, Maczynska I, Szych Z, Giedrys-Kalemba S. Serodiagnosis of borreliosis: indirect immunofluorescence assay, enzyme-linked immunosorbent assay and immunoblotting. Archivum Immunologiae et Therapiae Experimentalis. 2011; 59(1):69-77

523. Wokke JH, van Doorn PA, Brand A, Schreuder GM, Vermeulen M. Association of HLA-DR2 antigen with serum IgG antibodies against Borrelia burgdorferi in Bannwarth's syndrome. Journal of Neurology. 1988; 235(7):415-417

524. Wormser GP, Bittker S, Cooper D, Nowakowski J, Nadelman RB, Pavia C. Comparison of the yields of blood cultures using serum or plasma from patients with early Lyme disease. Journal of Clinical Microbiology. 2000; 38(4):1648-1650

525. Wormser GP, Carbonaro C, Miller S, Nowakowski J, Nadelman RB, Sivak S et al. A limitation of 2-stage serological testing for Lyme disease: enzyme immunoassay and immunoblot assay are not independent tests. Clinical Infectious Diseases. 2000; 30(3):545-548

526. Wormser GP, Levin A, Soman S, Adenikinju O, Longo MV, Branda JA. Comparative cost-effectiveness of two-tiered testing strategies for serodiagnosis of Lyme disease with noncutaneous manifestations. Journal of Clinical Microbiology. 2013; 51(12):4045-4049

527. Wormser GP, Liveris D, Hanincova K, Brisson D, Ludin S, Stracuzzi VJ et al. Effect of Borrelia burgdorferi genotype on the sensitivity of C6 and 2-tier testing in North American patients with culture-confirmed Lyme disease. Clinical Infectious Diseases. 2008; 47(7):910-914

528. Wormser GP, Nowakowski J, Nadelman RB, Bittker S, Cooper D, Pavia C. Improving the yield of blood cultures for patients with early Lyme disease. Journal of Clinical Microbiology. 1998; 36(1):296-298

529. Wormser GP, Schriefer M, Aguero-Rosenfeld ME, Levin A, Steere AC, Nadelman RB et al. Single-tier testing with the C6 peptide ELISA kit compared with two-tier testing for Lyme disease. Diagnostic Microbiology and Infectious Disease. 2013; 75(1):9-15

530. Wormser GP, Tang AT, Schimmoeller NR, Bittker S, Cooper D, Visintainer P et al. Utility of serodiagnostics designed for use in the United States for detection of Lyme borreliosis acquired in Europe and vice versa. Medical Microbiology and Immunology. 2014; 203(1):65-71

531. Wutte N, Archelos J, Crowe BA, Zenz W, Daghofer E, Fazekas F et al. Laboratory diagnosis of Lyme neuroborreliosis is influenced by the test used: comparison of two ELISAs, immunoblot and CXCL13 testing. Journal of the Neurological Sciences. 2014; 347(1-2):96-103

532. Wutte N, Berghold A, Loffler S, Zenz W, Daghofer E, Krainberger I et al. CXCL13 chemokine in pediatric and adult neuroborreliosis. Acta Neurologica Scandinavica. 2011; 124(5):321-328

533. Ye L, Huang NL, Du YX, Schneider M, Du WD. Succinyl-beta-cyclodextrin modified gold biochip improved seroimmunological detection sensitivity for Lyme disease. Analytica Chimica Acta. 2017; 953:48-56

534. Ye L, Huang NL, Ma XL, Schneider M, Huang XJ, Du WD. Establishment of N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC) modified biochip enabling concurrent detection of serum infectious antibodies in neuroborreliosis. Biosensors and Bioelectronics. 2016; 78:404-410

535. Yu Z, Carter JM, Huang SY, Lackland H, Sigal LH, Stein S. Presentation of peptide antigens as albumin conjugates for use in detection of serum antibodies by enzyme-linked immunosorbent assay. Bioconjugate Chemistry. 1996; 7(3):338-342

536. Yu Z, Carter JM, Sigal LH, Stein S. Multi-well ELISA based on independent peptide antigens for antibody capture. Application to Lyme disease serodiagnosis. Journal of Immunological Methods. 1996; 198(1):25-33

537. Zajkowska J, Hermanowska-Szpakowicz T, Swierzbinska R. Concentration of soluble CD4, CD8 and CD25 receptors in early localized and early disseminated Lyme borreliosis. Infection. 2001; 29(2):71-74

538. Zajkowska J, Lelental N, Kulakowska A, Mroczko B, Pancewicz S, Bucki R et al. Application of multiplexing technology to the analysis of the intrathecally released immunoglobulins against B. burgdorferi antigens in neuroborreliosis. Immunology Letters. 2015; 168(1):58-63

539. Zajkowska JM, Hermanowska-Szpakowicz T, Wysocka J, Kondrusik M, Pancewicz SA, Grygorczuk S. Analysis of some peripheral blood lymphocyte subsets in relation to Borrelia burgdorferi antibodies in patients with Lyme disease. Roczniki Akademii Medycznej w Białymstoku (1995). 2000; 45:184-198

540. Zbinden R, Goldenberger D, Lucchini GM, Altwegg M. Comparison of two methods for detecting intrathecal synthesis of Borrelia burgdorferi-specific antibodies and PCR for diagnosis of Lyme neuroborreliosis. Journal of Clinical Microbiology. 1994; 32(7):1795-1798

541. Zhang L, Zhu X, Hou X, Geng Z, Chen H, Hao Q. Test of 259 serums from patients with arthritis or neurological symptoms confirmed existence of lyme disease in Hainan Province, China. International Journal of Clinical and Experimental Medicine. 2015; 8(6):9531-9536

542. Zhang YQ, Mathiesen D, Kolbert CP, Anderson J, Schoen RT, Fikrig E et al. Borrelia burgdorferi enzyme-linked immunosorbent assay for discrimination of OspA vaccination from spirochete infection. Journal of Clinical Microbiology. 1997; 35(1):233-238

543. Zhioua E, Gern L, Aeschlimann A, Sauvain MJ, Van der Linden S, Fahrer H. Longitudinal study of Lyme borreliosis in a high risk population in Switzerland. Parasite. 1998; 5(4):383-386

544. Ziemer M, Grabner T, Eisendle K, Baltaci M, Zelger B. Granuloma annulare - a manifestation of infection with Borrelia? Journal of Cutaneous Pathology. 2008; 35(11):1050-1057

545. Zoller L, Burkard S, Schafer H. Validity of western immunoblot band patterns in the serodiagnosis of Lyme borreliosis. Journal of Clinical Microbiology. 1991; 29(1):174-182

546. Zoller L, Haude M, Sonntag HG. Validity of the standard assays in the serodiagnosis of Lyme borreliosis and effects of methodical modifications. Laboratory Medicine. 1990; 14:404-411

547. Zweitzig DR, Tibbe AG, Nguyen AT, van Rijn CJ, Kopnitsky MJ, Cichonski K et al. Feasibility of a simple microsieve-based immunoassay platform. Journal of Immunological Methods. 2016; 437:21-27

Appendices

Appendix A: Review protocols

Table 25: Review protocol for initial diagnostic tests

Question number: 3.1

Relevant section of Scope: diagnosis

Field	Content
Review question	In people with suspected (or under investigation for) Lyme disease, what is the most accurate initial test 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 initial tests in diagnosing Lyme disease. The intended use of an initial test is to identify who has Lyme disease, who has had Lyme disease, who requires further tests, or in whom a diagnosis can be ruled out.
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)	Serology assays: • *Borrelia* recomLine IgG (Mikrogen) • *Borrelia* Virastripe IgM/IgG (Viramed) • C6 ELISA (Immunetics) • Diasorin LIAISON *Borrelia* IgM Quant • Enzygnost Lyme link IgG/VlsE (Siemens) • VIDAS Lyme IgM and IgG (Biomerieux) • Other assays used elsewhere in the world: ○ Anti-*Borrelia* EUROLINE-RN-AT IgG (Euroimmun) ○ Anti-*Borrelia* EUROLINE-WB IgG, IgM (Euroimmun) ○ Anti-*Borrelia* EUROLONE-RN-AT IgM (Euroimmun) ○ Anti-*Borrelia* plus VlsE ELISA (IgG) & anti-*Borrelia* ELISA (IgM; Euroimmun) ○ *B Burgdorferi* IgG EIA (Diagnostic Automation) ○ *Borrelia* ViraChip IgG/IgM assay (ViraMed) ○ Capita™ *B. burgdorferi* IgG.IgM EIA (Trinity Biotech) ○ Genzyme Virotech *Borrelia* Europe Line (Virotech) ○ Immunoblot IgG (IGeneX) ○ MardX EU Lyme and VLSE Immunoblots (Trinity Biotech) ○ NovaLisa IgG EIA (Nova Tec) ○ Premier Lyme EIA IgG/IgM (Meridian Bioscience Inc.) ○ recomBead *Borrelia* IgG/IgM v2.0 (Mikrogen)

Field	Content
	○ RecomLine *Borrelia* IgG/IgM Immunoblot (Mikrogen) ○ RecomWell *Borrelia* IgG/IgM (Mikrogen) ○ SeraSpot Anti-*Borrelia* IgG/IgM (Seramun Diagnostica GmbH) ○ VIR-ELISA anti-*Borrelia* IgG/IgM (VIRO-IMMUN Labor-Diagnostika GmbH) Direct microscopic visualisation • Biopsy/histology Lymphocyte transformation tests: • EliSpot • LTT-MELISA® • SpiroFind™ assay (Boulder Diagnostics) CD57 test Inflammatory markers: • C-reactive protein (CRP) • Erythrocyte sedimentation rate (ESR) Full blood count: • Eosinophil • Haemoglobin • Lymphocyte • Monocyte • Neutrophil/Band/ANC • Platelet • White blood cell (WBC) CXCL13 (from a CSF or serum sample) PCR • Cerebrospinal fluid (CSF) analysis • Synovial fluid analysis Biopsy/histology
Eligibility criteria – comparator(s) / control or reference (gold) standard	• *Borrelia* culture (Spirochaete is difficult to culture and grows slowly and is therefore not compatible with providing a rapid diagnostic result). • Clinical diagnosis • PCR All index tests compared with all reference tests and reference tests compared with each other (in this case, clinical diagnosis will be the reference standard).
Outcomes and prioritisation	Detecting Lyme disease • Sensitivity • Specificity • Positive Predictive Value • Negative Predictive Value • Receiver Operating Characteristic (ROC) curve or area under curve

Field	Content
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 Exclude (unless there is insufficient evidence and agreed to include with the 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 reports • Case series
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); young people and adults (12 years and over; this stratification only applies to immunologic tests) • Focal organ disease; non-specified symptoms; no symptoms • People who have not had a test previously; people who already have had a test with a negative result • Timing of test 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): • Pregnant women • People who are immunocompromised • People with ehrlichiosis (and synonyms) • 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

Field	Content
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.
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 the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 26: Review protocol for confirmatory diagnostic tests

Question number: 3.2

Relevant section of Scope: diagnosis

Field	Content
Review question	In people with a positive test for Lyme disease, what is the most accurate test to confirm or rule out Lyme disease?
Type of review question	Diagnostic

Field	Content
	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 confirmatory tests in diagnosing Lyme disease. In people with a positive test result for Lyme disease, the intended use of a confirmatory test is to confirm who has Lyme disease, who has had Lyme disease, or in whom a diagnosis can be ruled out. A confirmatory test may be needed if the initial test has a relatively low specificity.
Eligibility criteria – population / disease / condition / issue / domain	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with a positive test for Lyme disease. Target condition: Lyme disease (specifically, conditions caused by *Borrelia burgdorferi sensu lato*)

Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Serology assays:
	• *Borrelia* recomLine IgG (Mikrogen)
	• *Borrelia* Virastripe IgM/IgG (Viramed)
	• C6 ELISA (Immunetics)
	• Diasorin LIAISON *Borrelia* IgM Quant
	• Enzygnost Lyme link IgG/VlsE (Siemens)
	• VIDAS Lyme IgM and IgG (Biomerieux)
	• Other assays used elsewhere in the world:
	  ○ Anti-*Borrelia* EUROLINE-RN-AT IgG (Euroimmun)
	  ○ Anti-*Borrelia* EUROLINE-WB IgG, IgM (Euroimmun)
	  ○ Anti-*Borrelia* EUROLONE-RN-AT IgM (Euroimmun)
	  ○ Anti-*Borrelia* plus VlsE ELISA (IgG) & anti-*Borrelia* ELISA (IgM; Euroimmun)
	  ○ *B Burgdorferi* IgG EIA (Diagnostic Automation)
	  ○ *Borrelia* ViraChip IgG/IgM assay (ViraMed)
	  ○ Capita™ *B. burgdorferi* IgG.IgM EIA (Trinity Biotech)
	  ○ Genzyme Virotech *Borrelia* Europe Line (Virotech)
	  ○ Immunoblot IgG (IGeneX)
	  ○ MardX EU Lyme and VLSE Immunoblots (Trinity Biotech)
	  ○ NovaLisa IgG EIA (Nova Tec)
	  ○ Premier Lyme EIA IgG/IgM (Meridian Bioscience Inc.)
	  ○ recomBead *Borrelia* IgG/IgM v2.0 (Mikrogen)
	  ○ RecomLine *Borrelia* IgG/IgM Immunoblot (Mikrogen)
	  ○ RecomWell *Borrelia* IgG/IgM (Mikrogen)
	  ○ SeraSpot Anti-*Borrelia* IgG/IgM (Seramun Diagnostica GmbH)
	  ○ VIR-ELISA anti-*Borrelia* IgG/IgM (VIRO-IMMUN Labor-Diagnostika GmbH)
	
	Direct microscopic visualisation
	• Biopsy/histology
	
	Lymphocyte transformation tests:
	• EliSpot
	• LTT-MELISA®
	• SpiroFind™ assay (Boulder Diagnostics)
	
	CD57 test

Field	Content
	Inflammatory markers: • C-reactive protein (CRP) • Erythrocyte sedimentation rate (ESR) Full blood count: • Eosinophil • Haemoglobin • Lymphocyte • Monocyte • Neutrophil/Band/ANC • Platelet • White blood cell (WBC) CXCL13 (from a CSF or serum sample) PCR • Synovial fluid analysis • Cerebrospinal fluid (CSF) analysis Biopsy/histology
Eligibility criteria – comparator(s) / control or reference (gold) standard	• *Borrelia* culture (Spirochaete is difficult to culture and grows slowly and is therefore not compatible with providing a rapid diagnostic result). • Clinical diagnosis • PCR All index tests compared with all reference tests and reference tests compared with each other (in this case clinical diagnosis will be the reference standard).
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 Exclude (unless there is insufficient evidence and agreed to include with the 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 reports Case series
Other inclusion exclusion criteria	Date limits for search: none Language: English only

Field	Content
	Setting: all settings where NHS care is provided or commissioned
Proposed sensitivity / subgroup analysis, or meta-regression	Stratum: Focal organ disease; non-specified symptoms; no symptoms Children (under 12 years); young people and adults (12 years and over; this stratification only applies to immunologic tests) Timing of test 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): • Pregnant women • People who are immunocompromised • People with ehrlichiosis (and synonyms) • 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 and study sifting will be managed using EndNote
Information sources – databases and dates	Medline, Embase, The Cochrane Library
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 using the QUADAS-2 checklist.
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

Field	Content
	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 the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 27: Review protocol for combination of diagnostic tests

Question number: 3.3

Relevant section of Scope: diagnosis

Field	Content
Review question	In people with suspected (or under investigation for) Lyme disease, what is the most accurate combination of tests to diagnose or rule out Lyme disease?
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 2-tiered testing for Lyme disease. It is current standard practice to use an initial test for Lyme disease and – if a positive test result is obtained – confirm the diagnosis through a confirmatory test. This review aims to determine which combination of initial tests (either an initial test followed by a confirmatory test, or 2 or more initial tests combined) is the most accurate for diagnosing or ruling out Lyme disease.
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)	Serology assays: • *Borrelia* recomLine IgG (Mikrogen) • *Borrelia* Virastripe IgM/IgG (Viramed) • C6 ELISA (Immunetics)

Field	Content

	• Diasorin LIAISON *Borrelia* IgM Quant
	• Enzygnost Lyme link IgG/VlsE (Siemens)
	• VIDAS Lyme IgM and IgG (Biomerieux)
	• Other assays used elsewhere in the world:
	  ○ Anti-*Borrelia* EUROLINE-RN-AT IgG (Euroimmun)
	  ○ Anti-*Borrelia* EUROLINE-WB IgG, IgM (Euroimmun)
	  ○ Anti-*Borrelia* EUROLONE-RN-AT IgM (Euroimmun)
	  ○ Anti-*Borrelia* plus VlsE ELISA (IgG) & anti-*Borrelia* ELISA (IgM; Euroimmun)
	  ○ *B Burgdorferi* IgG EIA (Diagnostic Automation)
	  ○ *Borrelia* ViraChip IgG/IgM assay (ViraMed)
	  ○ Capita™ *B. burgdorferi* IgG.IgM EIA (Trinity Biotech)
	  ○ Genzyme Virotech *Borrelia* Europe Line (Virotech)
	  ○ Immunoblot IgG (IGeneX)
	  ○ MardX EU Lyme and VLSE Immunoblots (Trinity Biotech)
	  ○ NovaLisa IgG EIA (Nova Tec)
	  ○ Premier Lyme EIA IgG/IgM (Meridian Bioscience Inc.)
	  ○ recomBead *Borrelia* IgG/IgM v2.0 (Mikrogen)
	  ○ RecomLine *Borrelia* IgG/IgM Immunoblot (Mikrogen)
	  ○ RecomWell *Borrelia* IgG/IgM (Mikrogen)
	  ○ SeraSpot Anti-*Borrelia* IgG/IgM (Seramun Diagnostica GmbH)
	  ○ VIR-ELISA anti-*Borrelia* IgG/IgM (VIRO-IMMUN Labor-Diagnostika GmbH)
	
	Direct microscopic visualisation
	• Biopsy/histology
	
	Lymphocyte transformation tests:
	• EliSpot
	• LTT-MELISA®
	• SpiroFind™ assay (Boulder Diagnostics)
	
	CD57 test
	
	Inflammatory markers:
	• C-reactive protein (CRP)
	• Erythrocyte sedimentation rate (ESR)
	
	Full blood count:
	• Eosinophil
	• Haemoglobin
	• Lymphocyte
	• Monocyte
	• Neutrophil/Band/ANC
	• Platelet
	• White blood cell (WBC)
	
	CXCL13 (from a CSF or serum sample)
	
	PCR
	• Synovial fluid analysis

Field	Content
	• Cerebrospinal fluid (CSF) analysis Biopsy/histology
Eligibility criteria – comparator(s) / control or reference (gold) standard	*Borrelia* culture (Spirochaete is difficult to culture and grows slowly and is therefore not compatible with providing a rapid diagnostic result). PCR Clinical diagnosis All index tests compared with all reference tests and reference tests compared with each other (in this case, clinical diagnosis will be the reference standard).
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 Exclude (unless there is insufficient evidence and agreed to include with the 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 reports • Case series
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); young people and adults (12 years and over; this stratification only applies to immunologic tests) • Focal organ disease; non-specified symptoms; no symptoms • People who have not had a test previously; people who already have had a test with a negative result • Timing of test 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): • Pregnant women • People who are immunocompromised • People with ehrlichiosis (and synonyms) • 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.

Field	Content
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 and study sifting will be managed using EndNote
Information sources – databases and dates	Medline, Embase, The Cochrane Library
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.
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 the NGC to develop guidelines for those working in the

Field	Content
	NHS, public health and social care in England.
PROSPERO registration number	Not registered

1 **Table 28: 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).[324] **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.

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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 29: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

1 **Embase (Ovid) search terms**

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

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

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

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

B.2 Health Economics literature search strategy

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

Table 30: Database date parameters and filters used

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

Medline (Ovid) search terms

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

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

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

1 **Embase (Ovid) search terms**

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

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

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

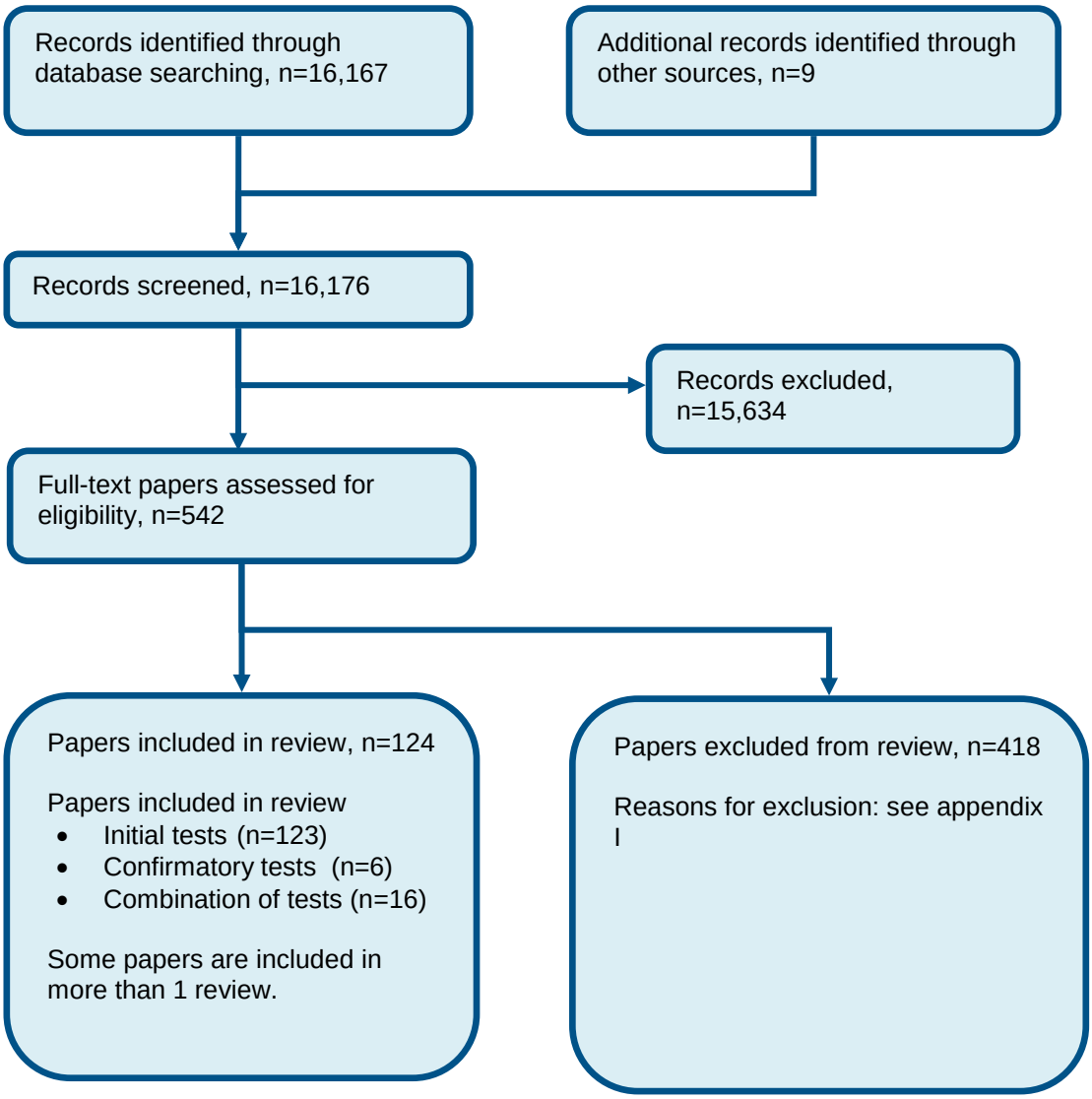
1 **NHS EED and HTA (CRD) search terms**

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

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the reviews of initial tests, confirmatory tests and combination of tests for Lyme disease



Appendix D: Clinical evidence tables

Please see appendix D in a separate document.

Appendix E: Coupled sensitivity and specificity forest plots

E.1 Initial tests: Coupled sensitivity and specificity forest plots for adults

E.1.1 Evidence from cross-sectional studies

E.1.1.1 Neuroborreliosis

Figure 2: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Henningsson 2014 (recomBead) (serum)	45	7	7	22	0.87 [0.74, 0.94]	0.76 [0.56, 0.90]
Henningsson 2014 (VIDAS) (serum)	48	8	4	21	0.92 [0.81, 0.98]	0.72 [0.53, 0.87]

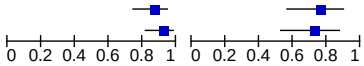


Figure 3: ELISA (IgG) – antibody index

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Henningsson 2014 (VIDAS) (CSF/serum)	45	2	7	27	0.87 [0.74, 0.94]	0.93 [0.77, 0.99]

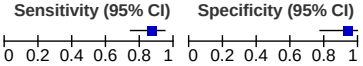


Figure 4: ELISA (IgM/IgG) – antibody index

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Henningsson 2014 (IDEIA) (CSF/serum)	48	1	4	28	0.92 [0.81, 0.98]	0.97 [0.82, 1.00]
Henningsson 2014 (recomBead) (CSF/serum)	52	3	0	26	1.00 [0.93, 1.00]	0.90 [0.73, 0.98]

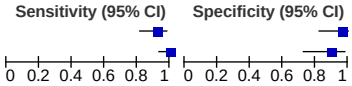


Figure 5: ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Tjernberg 2011 (CSF)	117	2	7	90	0.94 [0.89, 0.98]	0.98 [0.92, 1.00]

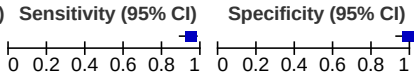


Figure 6: ELISPOT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nordberg 2012 (cut-off 10 spots or more) (CSF)	3	8	11	95	0.21 [0.05, 0.51]	0.92 [0.85, 0.97]
Nordberg 2012 (cut-off 5 spots or more) (CSF)	5	19	9	84	0.36 [0.13, 0.65]	0.82 [0.73, 0.89]

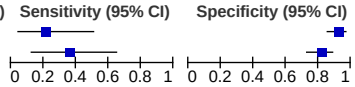
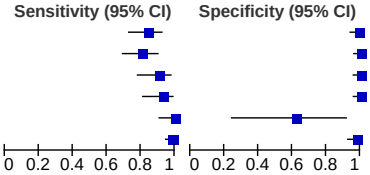


Figure 7: CXCL13

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gyllemark 2017 (142 pg/ml) (CSF)	53	1	10	87	0.84 [0.73, 0.92]	0.99 [0.94, 1.00]
Gyllemark 2017 (250 pg/ml) (CSF)	51	0	12	88	0.81 [0.69, 0.90]	1.00 [0.96, 1.00]
Henningsson 2016 (Quantikine) (CSF)	39	0	4	83	0.91 [0.78, 0.97]	1.00 [0.96, 1.00]
Henningsson 2016 (recomBead) (CSF)	40	0	3	83	0.93 [0.81, 0.99]	1.00 [0.96, 1.00]
Ljostad 2008 (CSF)	37	3	0	5	1.00 [0.91, 1.00]	0.63 [0.24, 0.91]
Tjernberg 2011 (CSF)	122	2	2	90	0.98 [0.94, 1.00]	0.98 [0.92, 1.00]



1 E.1.1.2 Unspecified Lyme disease

Figure 8: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bil-Lula 2015 (serum)	6	160	12	399	0.33 [0.13, 0.59]	0.71 [0.67, 0.75]
Brunner 2001 (CDC) (serum)	7	16	2	12	0.78 [0.40, 0.97]	0.43 [0.24, 0.63]
Brunner 2001 (RWJM) (serum)	42	16	22	51	0.66 [0.53, 0.77]	0.76 [0.64, 0.86]

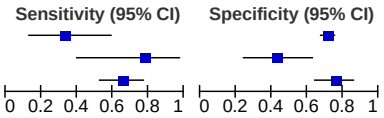


Figure 9: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bil-Lula 2015 (serum)	7	220	11	339	0.39 [0.17, 0.64]	0.61 [0.56, 0.65]
Blaauw 1999 (serum)	10	12	0	32	1.00 [0.69, 1.00]	0.73 [0.57, 0.85]
Brunner 2001 (CDC) (serum)	7	12	2	16	0.78 [0.40, 0.97]	0.57 [0.37, 0.76]
Brunner 2001 (RWJM) (serum)	37	9	27	58	0.58 [0.45, 0.70]	0.87 [0.76, 0.94]

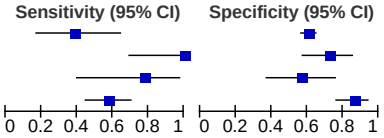


Figure 10: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brunner 2001 (CDC) (serum)	9	24	0	5	1.00 [0.66, 1.00]	0.17 [0.06, 0.36]

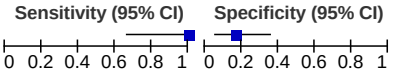
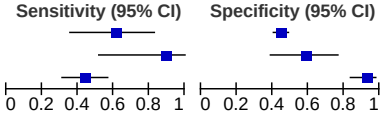


Figure 11: Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bil-Lula 2015 (serum)	4	87	14	472	0.22 [0.06, 0.48]	0.84 [0.81, 0.87]
Brunner 2001 (CDC) (serum)	5	11	4	18	0.56 [0.21, 0.86]	0.62 [0.42, 0.79]
Brunner 2001 (RWJM) (serum)	37	11	27	56	0.58 [0.45, 0.70]	0.84 [0.73, 0.92]

Figure 12: Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bil-Lula 2015 (serum)	11	309	7	250	0.61 [0.36, 0.83]	0.45 [0.41, 0.49]
Brunner 2001 (CDC) (serum)	8	12	1	17	0.89 [0.52, 1.00]	0.59 [0.39, 0.76]
Brunner 2001 (RWJM) (serum)	28	5	36	62	0.44 [0.31, 0.57]	0.93 [0.83, 0.98]



E.1.2 Evidence from case-control studies

E.1.2.1 Erythema migrans (EM)

Figure 13: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	0	0	13	15	0.00 [0.00, 0.25]	1.00 [0.78, 1.00]
Ang 2015 (Enzygnost) (serum)	11	10	70	97	0.14 [0.07, 0.23]	0.91 [0.83, 0.95]
Ang 2015 (Euroimmun) (serum)	0	0	5	10	0.00 [0.00, 0.52]	1.00 [0.69, 1.00]
Ang 2015 (Liaison) (serum)	5	6	52	221	0.09 [0.03, 0.19]	0.97 [0.94, 0.99]
Ang 2015 (Medac) (serum)	4	1	27	91	0.13 [0.04, 0.30]	0.99 [0.94, 1.00]
Ang 2015 (Mikrogen) (serum)	0	0	5	15	0.00 [0.00, 0.52]	1.00 [0.78, 1.00]
Ang 2015 (Serion) (serum)	18	29	18	77	0.50 [0.33, 0.67]	0.73 [0.63, 0.81]
Ang 2015 (Virotech) (serum)	1	0	12	14	0.08 [0.00, 0.36]	1.00 [0.77, 1.00]
Asbrink 1985 (before treatment) (serum)	10	9	78	176	0.11 [0.06, 0.20]	0.95 [0.91, 0.98]
Bacon 2003 (acute, ECM) (rVlsE) (serum)	3	5	32	252	0.09 [0.02, 0.23]	0.98 [0.96, 0.99]
Bacon 2003 (acute, ECM) (serum)	7	0	28	257	0.20 [0.08, 0.37]	1.00 [0.99, 1.00]
Bacon 2003 (convalescent, ECM) (rVlsE) (serum)	24	5	33	252	0.42 [0.29, 0.56]	0.98 [0.96, 0.99]
Bacon 2003 (convalescent, ECM) (serum)	23	0	34	257	0.40 [0.28, 0.54]	1.00 [0.99, 1.00]
Branda 2013 (EU) (serum)	8	2	12	98	0.40 [0.19, 0.64]	0.98 [0.93, 1.00]
Christova 2003 (serum)	51	6	54	84	0.49 [0.39, 0.59]	0.93 [0.86, 0.98]
Flisiak 1996 (flagella) (serum)	11	4	7	23	0.61 [0.36, 0.83]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	7	8	11	19	0.39 [0.17, 0.64]	0.70 [0.50, 0.86]
Fung 1994 (acute disseminated) (serum)	36	2	23	104	0.61 [0.47, 0.73]	0.98 [0.93, 1.00]
Fung 1994 (acute localised) (serum)	4	2	12	104	0.25 [0.07, 0.52]	0.98 [0.93, 1.00]
Fung 1994 (convalescent disseminated) (serum)	47	2	12	104	0.80 [0.67, 0.89]	0.98 [0.93, 1.00]
Fung 1994 (convalescent localised) (serum)	8	2	8	104	0.50 [0.25, 0.75]	0.98 [0.93, 1.00]
Goossens 2000 (Behring) (serum)	20	1	6	61	0.77 [0.56, 0.91]	0.98 [0.91, 1.00]
Goossens 2000 (Boehringer) (serum)	9	0	17	62	0.35 [0.17, 0.56]	1.00 [0.94, 1.00]
Goossens 2000 (Dako) (serum)	17	3	9	59	0.65 [0.44, 0.83]	0.95 [0.87, 0.99]
Goossens 2000 (Genzyme Virotech) (serum)	21	1	5	61	0.81 [0.61, 0.93]	0.98 [0.91, 1.00]
Goossens 2000 (IBL) (serum)	17	6	9	56	0.65 [0.44, 0.83]	0.90 [0.80, 0.96]
Hansen 1989 (flagellum) (multiple) (serum)	11	10	5	190	0.69 [0.41, 0.89]	0.95 [0.91, 0.98]
Hansen 1989 (flagellum) (serum)	48	10	59	190	0.45 [0.35, 0.55]	0.95 [0.91, 0.98]
Hansen 1989 (flagellum) (single) (serum)	36	10	55	190	0.40 [0.29, 0.50]	0.95 [0.91, 0.98]
Hansen 1989 (sonic) (serum)	18	11	89	189	0.17 [0.10, 0.25]	0.94 [0.90, 0.97]
Hansen 1991 (serum)	32	0	18	200	0.64 [0.49, 0.77]	1.00 [0.98, 1.00]
Hernandez-Novoa 2003 (localised) (serum)	9	7	15	122	0.38 [0.19, 0.59]	0.95 [0.89, 0.98]
Hunfeld 2002 (serum)	91	87	57	1020	0.61 [0.53, 0.69]	0.92 [0.90, 0.94]
Karlsson 1989a (capture ELISA) (serum)	10	2	20	71	0.33 [0.17, 0.53]	0.97 [0.90, 1.00]
Karlsson 1989a (indirect ELISA) (serum)	8	7	22	66	0.27 [0.12, 0.46]	0.90 [0.81, 0.96]
Lange 1992 (flagellum) (serum)	12	6	24	94	0.33 [0.19, 0.51]	0.94 [0.87, 0.98]
Lange 1992 (sonicated) (serum)	10	4	26	96	0.28 [0.14, 0.45]	0.96 [0.90, 0.99]
Lencakova 2008 (serum)	34	1	20	59	0.63 [0.49, 0.76]	0.98 [0.91, 1.00]
Liu 2013 (serum)	30	58	22	234	0.58 [0.43, 0.71]	0.80 [0.75, 0.85]
Magnarelli 1988 (serum)	86	32	16	45	0.84 [0.76, 0.91]	0.58 [0.47, 0.70]
Marangoni 2005 (Enzygnost) (serum)	67	9	28	225	0.71 [0.60, 0.79]	0.96 [0.93, 0.98]
Marangoni 2005 (RecomWell) (serum)	53	0	42	234	0.56 [0.45, 0.66]	1.00 [0.98, 1.00]
Marangoni 2008 (serum)	36	10	30	290	0.55 [0.42, 0.67]	0.97 [0.94, 0.98]
Mathiesen 1996 (serum)	19	1	28	99	0.40 [0.26, 0.56]	0.99 [0.95, 1.00]
Molins 2017 (acute) (serum)	24	23	16	180	0.60 [0.43, 0.75]	0.89 [0.83, 0.93]
Molins 2017 (convalescent) (serum)	30	23	8	180	0.79 [0.63, 0.90]	0.89 [0.83, 0.93]
Rauer 1995 (recombinant) (serum)	7	3	111	79	0.06 [0.02, 0.12]	0.96 [0.90, 0.99]
Rauer 1998 (recombinant) (serum)	48	8	56	146	0.46 [0.36, 0.56]	0.95 [0.90, 0.98]
Rauer 1998 (whole-cell) (serum)	47	8	57	146	0.45 [0.35, 0.55]	0.95 [0.90, 0.98]
Smismans 2006 (purified) (serum)	14	9	9	31	0.61 [0.39, 0.80]	0.78 [0.62, 0.89]
Smismans 2006 (synthetic C6) (serum)	21	3	2	37	0.91 [0.72, 0.99]	0.93 [0.80, 0.98]
Smismans 2006 (whole-cell) (serum)	21	19	2	21	0.91 [0.72, 0.99]	0.53 [0.36, 0.68]
Stanek 1999 (serum)	5	1	94	99	0.05 [0.02, 0.11]	0.99 [0.95, 1.00]
Stiernstedt 1986 (serum)	2	0	23	0	0.08 [0.01, 0.26]	Not estimable
Widhe 2004 (serum)	4	0	1	23	0.80 [0.28, 0.99]	1.00 [0.85, 1.00]
Wilske 1993 (flagellin) (serum)	12	6	19	136	0.39 [0.22, 0.58]	0.96 [0.91, 0.98]
Wilske 1993 (OGP-ELISA) (serum)	14	4	17	138	0.45 [0.27, 0.64]	0.97 [0.93, 0.99]

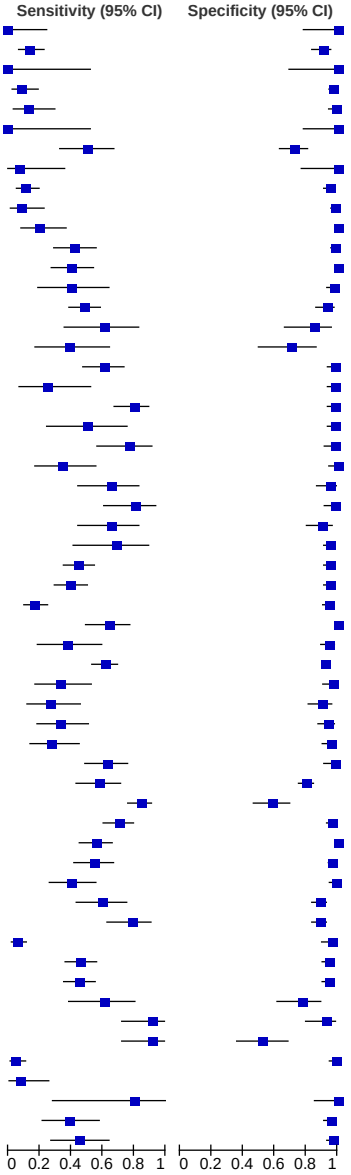


Figure 14: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Asbrink 1985 (before treatment) (serum)	16	9	72	176	0.18 [0.11, 0.28]	0.95 [0.91, 0.98]
Bacon 2003 (acute, ECM) (rVlsE) (serum)	7	2	28	255	0.20 [0.08, 0.37]	0.99 [0.97, 1.00]
Bacon 2003 (acute, ECM) (serum)	15	0	20	257	0.43 [0.26, 0.61]	1.00 [0.99, 1.00]
Bacon 2003 (convalescent, ECM) (rVlsE) (serum)	25	2	32	255	0.44 [0.31, 0.58]	0.99 [0.97, 1.00]
Bacon 2003 (convalescent, ECM) (serum)	33	0	24	257	0.58 [0.44, 0.71]	1.00 [0.99, 1.00]
Branda 2013 (EU) (serum)	13	2	7	98	0.65 [0.41, 0.85]	0.98 [0.93, 1.00]
Christova 2003 (serum)	18	3	87	87	0.17 [0.10, 0.26]	0.97 [0.91, 0.99]
Flisiak 1996 (flagella) (serum)	2	0	16	27	0.11 [0.01, 0.35]	1.00 [0.87, 1.00]
Flisiak 1996 (recombinant) (serum)	6	0	12	27	0.33 [0.13, 0.59]	1.00 [0.87, 1.00]
Fung 1994 (acute disseminated) (serum)	20	15	39	91	0.34 [0.22, 0.47]	0.86 [0.78, 0.92]
Fung 1994 (acute localised) (serum)	5	15	11	91	0.31 [0.11, 0.59]	0.86 [0.78, 0.92]
Fung 1994 (convalescent disseminated) (serum)	30	15	29	91	0.51 [0.37, 0.64]	0.86 [0.78, 0.92]
Fung 1994 (convalescent localised) (serum)	7	15	9	91	0.44 [0.20, 0.70]	0.86 [0.78, 0.92]
Goossens 2000 (Behring) (serum)	18	9	8	53	0.69 [0.48, 0.86]	0.85 [0.74, 0.93]
Goossens 2000 (Boehringer) (serum)	10	7	16	55	0.38 [0.20, 0.59]	0.89 [0.78, 0.95]
Goossens 2000 (Dako) (serum)	13	2	13	60	0.50 [0.30, 0.70]	0.97 [0.89, 1.00]
Goossens 2000 (Genzyme Virotech) (serum)	14	4	12	58	0.54 [0.33, 0.73]	0.94 [0.84, 0.98]
Goossens 2000 (IBL) (serum)	12	8	14	54	0.46 [0.27, 0.67]	0.87 [0.76, 0.94]
Hansen 1989 (flagellum) (multiple) (serum)	6	8	10	192	0.38 [0.15, 0.65]	0.96 [0.92, 0.98]
Hansen 1989 (flagellum) (serum)	38	8	69	192	0.36 [0.27, 0.45]	0.96 [0.92, 0.98]
Hansen 1989 (flagellum) (single) (serum)	33	8	58	192	0.36 [0.26, 0.47]	0.96 [0.92, 0.98]
Hansen 1989 (sonic) (serum)	12	12	95	188	0.11 [0.06, 0.19]	0.94 [0.90, 0.97]
Hansen 1991 (serum)	28	0	22	200	0.56 [0.41, 0.70]	1.00 [0.98, 1.00]
Hernandez-Novoa 2003 (localised) (serum)	5	55	19	74	0.21 [0.07, 0.42]	0.57 [0.48, 0.66]
Hunfeld 2002 (serum)	33	60	115	1047	0.22 [0.16, 0.30]	0.95 [0.93, 0.96]
Lencakova 2008 (serum)	23	1	31	59	0.43 [0.29, 0.57]	0.98 [0.91, 1.00]
Liu 2013 (serum)	41	67	11	225	0.79 [0.65, 0.89]	0.77 [0.72, 0.82]
Magnarelli 1988 (serum)	73	17	22	60	0.77 [0.67, 0.85]	0.78 [0.67, 0.87]
Magnarelli 1992 (biotin) (recombinant) (serum)	19	0	34	40	0.36 [0.23, 0.50]	1.00 [0.91, 1.00]
Magnarelli 1992 (biotin) (whole-cell) (serum)	20	0	33	40	0.38 [0.25, 0.52]	1.00 [0.91, 1.00]
Magnarelli 1992 (unadsorbed) (recombinant) (serum)	18	0	35	40	0.34 [0.22, 0.48]	1.00 [0.91, 1.00]
Magnarelli 1992 (unadsorbed) (whole-cell) (serum)	17	0	36	40	0.32 [0.20, 0.46]	1.00 [0.91, 1.00]
Marangoni 2005 (Enzygnost) (serum)	35	27	60	207	0.37 [0.27, 0.47]	0.88 [0.84, 0.92]
Marangoni 2005 (RecomWell) (serum)	55	7	40	227	0.58 [0.47, 0.68]	0.97 [0.94, 0.99]
Marangoni 2008 (serum)	37	5	29	295	0.56 [0.43, 0.68]	0.98 [0.96, 0.99]
Mathiesen 1996 (serum)	14	0	33	100	0.30 [0.17, 0.45]	1.00 [0.96, 1.00]
Molins 2017 (acute) (serum)	20	4	20	199	0.50 [0.34, 0.66]	0.98 [0.95, 0.99]
Molins 2017 (convalescent) (serum)	28	4	10	199	0.74 [0.57, 0.87]	0.98 [0.95, 0.99]
Nohlmans 1994 (Dako) (serum)	8	1	5	83	0.62 [0.32, 0.86]	0.99 [0.94, 1.00]
Nohlmans 1994 (Diagast) (serum)	6	0	7	84	0.46 [0.19, 0.75]	1.00 [0.96, 1.00]
Panelius 2008 (acute) (serum)	15	0	10	20	0.60 [0.39, 0.79]	1.00 [0.83, 1.00]
Panelius 2008 (convalescent) (serum)	16	0	9	20	0.64 [0.43, 0.82]	1.00 [0.83, 1.00]
Rauer 1995 (recombinant) (serum)	16	0	102	82	0.14 [0.08, 0.21]	1.00 [0.96, 1.00]
Sillanpaa 2007 (acute) (serum)	25	0	17	83	0.60 [0.43, 0.74]	1.00 [0.96, 1.00]
Sillanpaa 2007 (convalescent) (serum)	9	0	13	83	0.41 [0.21, 0.64]	1.00 [0.96, 1.00]
Smismans 2006 (purified) (serum)	5	0	7	40	0.42 [0.15, 0.72]	1.00 [0.91, 1.00]
Smismans 2006 (synthetic C6) (serum)	11	3	1	37	0.92 [0.62, 1.00]	0.93 [0.80, 0.98]
Smismans 2006 (whole-cell) (serum)	10	3	2	37	0.83 [0.52, 0.98]	0.93 [0.80, 0.98]
Stanek 1999 (serum)	24	5	75	95	0.24 [0.16, 0.34]	0.95 [0.89, 0.98]
Stiernstedt 1986 (serum)	5	0	20	0	0.20 [0.07, 0.41]	Not estimable
Widhe 2004 (serum)	1	0	4	23	0.20 [0.01, 0.72]	1.00 [0.85, 1.00]
Wilske 1993 (flagellin) (serum)	12	9	19	133	0.39 [0.22, 0.58]	0.94 [0.88, 0.97]
Wilske 1993 (OGP-ELISA) (serum)	11	4	20	138	0.35 [0.19, 0.55]	0.97 [0.93, 0.99]

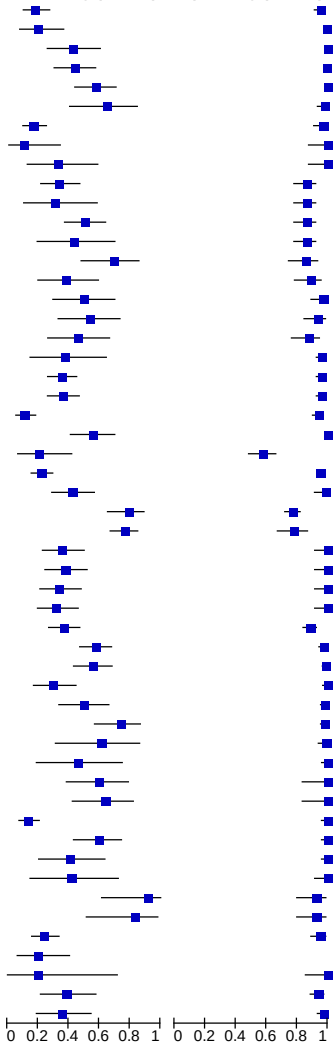


Figure 15: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	12	1	1	14	0.92 [0.64, 1.00]	0.93 [0.68, 1.00]
Ang 2015 (Enzygnost) (serum)	77	13	4	94	0.95 [0.88, 0.99]	0.88 [0.80, 0.93]
Ang 2015 (Euroimmun) (serum)	4	2	1	12	0.80 [0.28, 0.99]	0.86 [0.57, 0.98]
Ang 2015 (Liaison) (serum)	52	19	5	208	0.91 [0.81, 0.97]	0.92 [0.87, 0.95]
Ang 2015 (Medac) (serum)	25	3	6	89	0.81 [0.63, 0.93]	0.97 [0.91, 0.99]
Ang 2015 (Mikrogen) (serum)	5	0	0	15	1.00 [0.48, 1.00]	1.00 [0.78, 1.00]
Ang 2015 (Serion) (serum)	30	30	6	76	0.83 [0.67, 0.94]	0.72 [0.62, 0.80]
Ang 2015 (Virotech) (serum)	13	0	0	14	1.00 [0.75, 1.00]	1.00 [0.77, 1.00]
Branda 2010 (acute) (serum)	46	8	60	187	0.43 [0.34, 0.53]	0.96 [0.92, 0.98]
Branda 2010 (convalescent) (serum)	97	8	9	187	0.92 [0.84, 0.96]	0.96 [0.92, 0.98]
Branda 2011 (serum)	64	21	50	1279	0.56 [0.47, 0.65]	0.98 [0.98, 0.99]
Branda 2013 (EU) (serum)	15	4	5	96	0.75 [0.51, 0.91]	0.96 [0.90, 0.99]
Branda 2013 (USA) (C6) (serum)	14	0	6	100	0.70 [0.46, 0.88]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	14	3	6	97	0.70 [0.46, 0.88]	0.97 [0.91, 0.99]
Flisiak 1996 (flagella) (serum)	12	4	6	23	0.67 [0.41, 0.87]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	13	8	5	19	0.72 [0.47, 0.90]	0.70 [0.50, 0.86]
Fung 1994 (acute disseminated) (serum)	36	16	23	90	0.61 [0.47, 0.73]	0.85 [0.77, 0.91]
Fung 1994 (acute localised) (serum)	6	16	10	90	0.38 [0.15, 0.65]	0.85 [0.77, 0.91]
Fung 1994 (convalescent disseminated) (serum)	48	16	11	90	0.81 [0.69, 0.90]	0.85 [0.77, 0.91]
Fung 1994 (convalescent localised) (serum)	10	16	6	90	0.63 [0.35, 0.85]	0.85 [0.77, 0.91]
Goossens 2000 (Milenia) (serum)	8	3	18	59	0.31 [0.14, 0.52]	0.95 [0.87, 0.99]
Grodzicki 1988 (acute) (serum)	9	0	21	20	0.30 [0.15, 0.49]	1.00 [0.83, 1.00]
Grodzicki 1988 (convalescent) (serum)	18	0	12	20	0.60 [0.41, 0.77]	1.00 [0.83, 1.00]
Hernandez-Novoa 2003 (localised) (serum)	12	0	12	0	0.50 [0.29, 0.71]	Not estimable
Hunfeld 2002 (serum)	100	0	48	0	0.68 [0.59, 0.75]	Not estimable
Johnson 1996 (serum)	27	5	31	108	0.47 [0.33, 0.60]	0.96 [0.90, 0.99]
Lahey 2015 (serum)	41	1	38	25	0.52 [0.40, 0.63]	0.96 [0.80, 1.00]
Lawrenz 1999 (recombinant) (serum)	26	1	15	49	0.63 [0.47, 0.78]	0.98 [0.89, 1.00]
Lawrenz 1999 (whole-cell) (serum)	25	3	16	47	0.61 [0.45, 0.76]	0.94 [0.83, 0.99]
Ledue 2008 (serum)	11	17	8	790	0.58 [0.33, 0.80]	0.98 [0.97, 0.99]
Lencakova 2008 (serum)	48	2	6	58	0.89 [0.77, 0.96]	0.97 [0.88, 1.00]
Leung 1989 (colorimetric) (serum)	7	16	3	13	0.70 [0.35, 0.93]	0.45 [0.26, 0.64]
Leung 1989 (sonicated) (serum)	9	7	1	22	0.90 [0.55, 1.00]	0.76 [0.56, 0.90]
Marangoni 2005 (Enzygnost) (serum)	74	36	21	198	0.78 [0.68, 0.86]	0.85 [0.79, 0.89]
Marangoni 2005 (Quick C6) (serum)	59	8	36	226	0.62 [0.52, 0.72]	0.97 [0.93, 0.99]
Marangoni 2005 (RecomWell) (serum)	70	7	25	227	0.74 [0.64, 0.82]	0.97 [0.94, 0.99]
Mitchell 1994 (multiple ECM) (serum)	0	0	32	16	0.00 [0.00, 0.11]	1.00 [0.79, 1.00]
Mitchell 1994 (single ECM) (serum)	1	0	18	16	0.05 [0.00, 0.26]	1.00 [0.79, 1.00]
Molins 2014 (acute) (serum)	27	14	13	189	0.68 [0.51, 0.81]	0.93 [0.89, 0.96]
Molins 2014 (convalescent) (serum)	34	14	4	189	0.89 [0.75, 0.97]	0.93 [0.89, 0.96]
Molins 2016 (acute) (serum)	23	5	17	198	0.57 [0.41, 0.73]	0.98 [0.94, 0.99]
Molins 2016 (convalescent) (serum)	32	5	6	198	0.84 [0.69, 0.94]	0.98 [0.94, 0.99]
Nohlmans 1994 (Diamedix) (serum)	7	0	6	84	0.54 [0.25, 0.81]	1.00 [0.96, 1.00]
Nohlmans 1994 (Whittaker) (serum)	4	0	9	84	0.31 [0.09, 0.61]	1.00 [0.96, 1.00]
Pomelova 2015 (serum)	40	96	87	101	0.31 [0.24, 0.40]	0.51 [0.44, 0.58]
Rauer 1995 (recombinant) (serum)	24	3	94	79	0.20 [0.13, 0.29]	0.96 [0.90, 0.99]
Russell 1984 (serum)	17	4	17	96	0.50 [0.32, 0.68]	0.96 [0.90, 0.99]
Smismans 2006 (purified) (serum)	18	9	5	31	0.78 [0.56, 0.93]	0.78 [0.62, 0.89]
Smismans 2006 (synthetic C6) (serum)	21	3	2	37	0.91 [0.72, 0.99]	0.93 [0.80, 0.98]
Smismans 2006 (whole-cell) (serum)	23	20	0	20	1.00 [0.85, 1.00]	0.50 [0.34, 0.66]
Steere 2008 (acute) (multiple ECM) (serum)	15	5	25	131	0.38 [0.23, 0.54]	0.96 [0.92, 0.99]
Steere 2008 (acute) (single ECM) (serum)	7	5	29	131	0.19 [0.08, 0.36]	0.96 [0.92, 0.99]
Steere 2008 (convalescent) (multiple ECM) (serum)	25	5	15	131	0.63 [0.46, 0.77]	0.96 [0.92, 0.99]
Steere 2008 (convalescent) (single ECM) (serum)	17	5	19	131	0.47 [0.30, 0.65]	0.96 [0.92, 0.99]
Stiernstedt 1986 (serum)	7	11	18	109	0.28 [0.12, 0.49]	0.91 [0.84, 0.95]
Tjernberg 2007 (Quick C6) (serum)	58	184	100	16	0.37 [0.29, 0.45]	0.08 [0.05, 0.13]
Tjernberg 2007 (Virotech) (serum)	73	152	85	48	0.46 [0.38, 0.54]	0.24 [0.18, 0.31]
Tjernberg 2009 (cut-off 0.0689) (serum)	97	5	51	166	0.66 [0.57, 0.73]	0.97 [0.93, 0.99]
Tjernberg 2009 (cut-off 0.15) (serum)	76	0	72	171	0.51 [0.43, 0.60]	1.00 [0.98, 1.00]
Trevejo 2001 (acute) (serum)	28	1	38	36	0.42 [0.30, 0.55]	0.97 [0.86, 1.00]
Trevejo 2001 (convalescent) (serum)	43	1	12	36	0.78 [0.65, 0.88]	0.97 [0.86, 1.00]

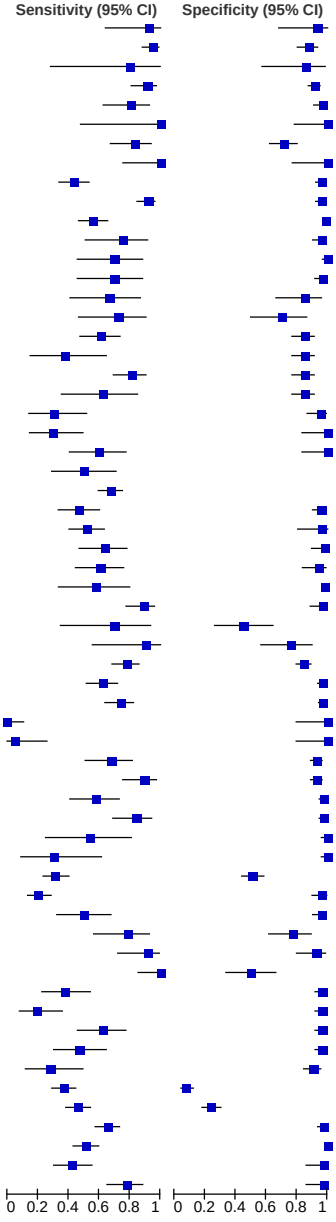


Figure 16: ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cinco 2006 (serum)	34	0	20	24	0.63 [0.49, 0.76]	1.00 [0.86, 1.00]

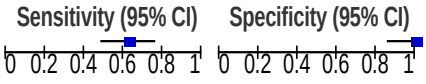


Figure 17: ELISA C6 (IgA)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
D'Arco 2017 (IgA) (serum)	43	2	98	133	0.30 [0.23, 0.39]	0.99 [0.95, 1.00]

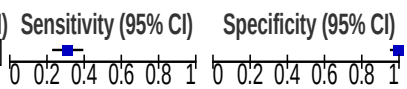


Figure 18: ELFA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (serum)	11	2	7	25	0.61 [0.36, 0.83]	0.93 [0.76, 0.99]
Mitchell 1994 (multiple ECM) (serum)	18	0	14	16	0.56 [0.38, 0.74]	1.00 [0.79, 1.00]
Mitchell 1994 (single ECM) (serum)	5	0	14	16	0.26 [0.09, 0.51]	1.00 [0.79, 1.00]

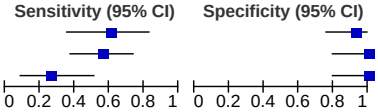


Figure 19: CLIA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Marangoni 2008 (serum)	16	19	50	281	0.24 [0.15, 0.36]	0.94 [0.90, 0.96]

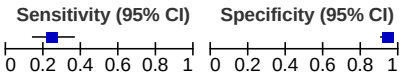


Figure 20: CLIA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Marangoni 2008 (serum)	26	9	40	291	0.39 [0.28, 0.52]	0.97 [0.94, 0.99]

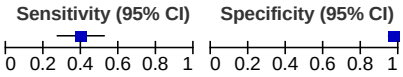


Figure 21: CLIA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ledue 2008 (serum)	13	16	6	791	0.68 [0.43, 0.87]	0.98 [0.97, 0.99]
Tjernberg 2007 (serum)	66	162	92	38	0.42 [0.34, 0.50]	0.19 [0.14, 0.25]

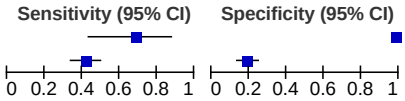


Figure 22: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	18	3	65	101	0.22 [0.13, 0.32]	0.97 [0.92, 0.99]
Branda 2010 (acute) (serum)	32	0	74	195	0.30 [0.22, 0.40]	1.00 [0.98, 1.00]
Branda 2010 (convalescent) (serum)	64	0	42	195	0.60 [0.50, 0.70]	1.00 [0.98, 1.00]
Branda 2013 (EU) (serum)	7	9	13	91	0.35 [0.15, 0.59]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	2	0	18	100	0.10 [0.01, 0.32]	1.00 [0.96, 1.00]
Dressler 1993 (retrospective (acute) (serum)	10	1	15	124	0.40 [0.21, 0.61]	0.99 [0.96, 1.00]
Dressler 1993 (retrospective) (conval.) (serum)	15	1	10	124	0.60 [0.39, 0.79]	0.99 [0.96, 1.00]
Fung 1994 (acute) (serum)	44	2	31	104	0.59 [0.47, 0.70]	0.98 [0.93, 1.00]
Fung 1994 (convalescent) (serum)	55	2	20	104	0.73 [0.62, 0.83]	0.98 [0.93, 1.00]
Goettner 2005 (line blot) (serum)	11	1	4	109	0.73 [0.45, 0.92]	0.99 [0.95, 1.00]
Goettner 2005 (line plut plus) (serum)	13	2	2	108	0.87 [0.60, 0.98]	0.98 [0.94, 1.00]
Goettner 2005 (WB) (serum)	6	2	9	108	0.40 [0.16, 0.68]	0.98 [0.94, 1.00]
Goossens 2000 (Genzyme Virotech) (serum)	13	7	13	55	0.50 [0.30, 0.70]	0.89 [0.78, 0.95]
Goossens 2000 (MRL) (serum)	12	1	14	61	0.46 [0.27, 0.67]	0.98 [0.91, 1.00]
Lange 1992 (serum)	29	0	7	100	0.81 [0.64, 0.92]	1.00 [0.96, 1.00]
Lencakova 2008 (serum)	33	1	21	59	0.61 [0.47, 0.74]	0.98 [0.91, 1.00]
Liu 2013 (serum)	24	17	28	275	0.46 [0.32, 0.61]	0.94 [0.91, 0.97]
Mathiesen 1996 (serum)	17	1	30	99	0.36 [0.23, 0.51]	0.99 [0.95, 1.00]
Merljak Skocir 2008 (serum)	4	0	21	26	0.16 [0.05, 0.36]	1.00 [0.87, 1.00]
Molins 2014 (acute) (serum)	14	4	26	199	0.35 [0.21, 0.52]	0.98 [0.95, 0.99]
Molins 2014 (convalescent) (serum)	20	4	18	199	0.53 [0.36, 0.69]	0.98 [0.95, 0.99]
Molins 2016 (acute) (serum)	21	12	19	191	0.53 [0.36, 0.68]	0.94 [0.90, 0.97]
Molins 2016 (convalescent) (serum)	29	12	9	191	0.76 [0.60, 0.89]	0.94 [0.90, 0.97]
Porwancher 2011 (early acute) (serum)	29	0	50	0	0.37 [0.26, 0.48]	Not estimable
Porwancher 2011 (early convalescent) (serum)	60	0	22	0	0.73 [0.62, 0.82]	Not estimable
Ruzic-Sabljic 2002 (culture: pos vs neg) (serum)	33	23	33	28	0.50 [0.37, 0.63]	0.55 [0.40, 0.69]
Ruzic-Sabljic 2002 (serum)	56	21	61	75	0.48 [0.39, 0.57]	0.78 [0.69, 0.86]
Sivak 1996 (acute ECM) (serum)	11	8	33	264	0.25 [0.13, 0.40]	0.97 [0.94, 0.99]
Sivak 1996 (convalescent ECM) (serum)	31	8	13	264	0.70 [0.55, 0.83]	0.97 [0.94, 0.99]
Sivak 1996 (ECM over 7 days) (serum)	36	8	8	264	0.82 [0.67, 0.92]	0.97 [0.94, 0.99]
Wilske 1993 (OspC-blot) (serum)	14	4	17	138	0.45 [0.27, 0.64]	0.97 [0.93, 0.99]
Wilske 1993 (p100-blot) (serum)	3	1	28	141	0.10 [0.02, 0.26]	0.99 [0.96, 1.00]
Wilske 1993 (p41/i-blot) (serum)	3	1	28	141	0.10 [0.02, 0.26]	0.99 [0.96, 1.00]

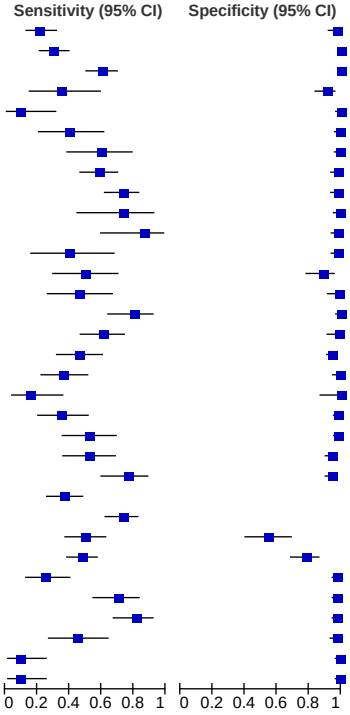


Figure 23: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010 (acute) (serum)	6	1	100	194	0.06 [0.02, 0.12]	0.99 [0.97, 1.00]
Branda 2010 (convalescent) (serum)	12	1	94	194	0.11 [0.06, 0.19]	0.99 [0.97, 1.00]
Branda 2013 (EU) (serum)	7	0	13	100	0.35 [0.15, 0.59]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	2	0	18	100	0.10 [0.01, 0.32]	1.00 [0.96, 1.00]
Dressler 1993 (retrospective (acute) (serum)	0	0	25	125	0.00 [0.00, 0.14]	1.00 [0.97, 1.00]
Dressler 1993 (retrospective) (conval.) (serum)	4	0	21	125	0.16 [0.05, 0.36]	1.00 [0.97, 1.00]
Fung 1994 (acute) (serum)	35	6	40	100	0.47 [0.35, 0.59]	0.94 [0.88, 0.98]
Fung 1994 (convalescent) (serum)	43	6	32	100	0.57 [0.45, 0.69]	0.94 [0.88, 0.98]
Goettner 2005 (line blot) (serum)	7	0	8	110	0.47 [0.21, 0.73]	1.00 [0.97, 1.00]
Goettner 2005 (line plut plus) (serum)	8	1	7	109	0.53 [0.27, 0.79]	0.99 [0.95, 1.00]
Goettner 2005 (WB) (serum)	5	1	10	109	0.33 [0.12, 0.62]	0.99 [0.95, 1.00]
Goossens 2000 (Genzyme Virotech) (serum)	7	11	19	51	0.27 [0.12, 0.48]	0.82 [0.70, 0.91]
Goossens 2000 (MRL) (serum)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]
Lencakova 2008 (serum)	29	0	25	60	0.54 [0.40, 0.67]	1.00 [0.94, 1.00]
Liu 2013 (serum)	35	5	17	287	0.67 [0.53, 0.80]	0.98 [0.96, 0.99]
Mathiesen 1996 (serum)	12	4	35	96	0.26 [0.14, 0.40]	0.96 [0.90, 0.99]
Merljak Skocir 2008 (serum)	8	7	17	19	0.32 [0.15, 0.54]	0.73 [0.52, 0.88]
Molins 2014 (acute) (serum)	8	2	32	201	0.20 [0.09, 0.36]	0.99 [0.96, 1.00]
Molins 2014 (convalescent) (serum)	14	2	24	201	0.37 [0.22, 0.54]	0.99 [0.96, 1.00]
Molins 2016 (acute) (serum)	5	3	35	200	0.13 [0.04, 0.27]	0.99 [0.96, 1.00]
Molins 2016 (convalescent) (serum)	11	3	27	200	0.29 [0.15, 0.46]	0.99 [0.96, 1.00]
Porwancher 2011 (early acute) (serum)	6	0	73	0	0.08 [0.03, 0.16]	Not estimable
Porwancher 2011 (early convalescent) (serum)	17	0	65	0	0.21 [0.13, 0.31]	Not estimable
Ruzic-Sabljic 2002 (culture: pos vs neg) (serum)	20	16	46	35	0.30 [0.20, 0.43]	0.69 [0.54, 0.81]
Ruzic-Sabljic 2002 (serum)	36	26	81	70	0.31 [0.23, 0.40]	0.73 [0.63, 0.81]
Wilske 1993 (OspC-blot) (serum)	3	1	28	141	0.10 [0.02, 0.26]	0.99 [0.96, 1.00]
Wilske 1993 (p100-blot) (serum)	7	9	24	133	0.23 [0.10, 0.41]	0.94 [0.88, 0.97]
Wilske 1993 (p41/i-blot) (serum)	2	6	29	136	0.06 [0.01, 0.21]	0.96 [0.91, 0.98]
Wilske 1999 (recombinant - new) (serum)	7	3	59	136	0.11 [0.04, 0.21]	0.98 [0.94, 1.00]
Wilske 1999 (recombinant - old) (serum)	3	3	63	136	0.05 [0.01, 0.13]	0.98 [0.94, 1.00]
Wilske 1999 (whole-cell) (serum)	22	3	44	136	0.33 [0.22, 0.46]	0.98 [0.94, 1.00]

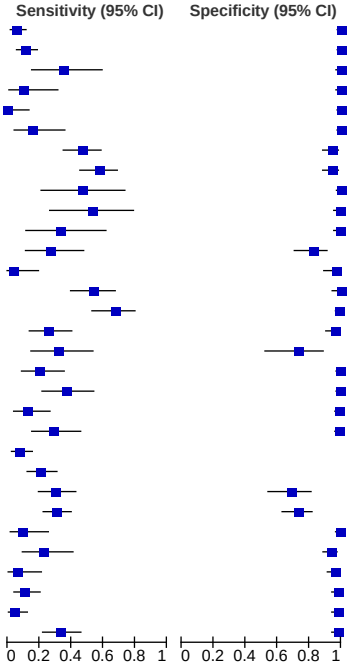


Figure 24: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	66	8	17	96	0.80 [0.69, 0.88]	0.92 [0.85, 0.97]
Branda 2010 (acute) (serum)	36	1	70	194	0.34 [0.25, 0.44]	0.99 [0.97, 1.00]
Branda 2010 (convalescent) (serum)	70	1	36	194	0.66 [0.56, 0.75]	0.99 [0.97, 1.00]
Branda 2013 (EU) (serum)	11	9	9	91	0.55 [0.32, 0.77]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	4	0	16	100	0.20 [0.06, 0.44]	1.00 [0.96, 1.00]
Callister 2002 (multiple ECM) (serum)	10	3	2	31	0.83 [0.52, 0.98]	0.91 [0.76, 0.98]
Callister 2002 (single ECM) (serum)	12	3	10	31	0.55 [0.32, 0.76]	0.91 [0.76, 0.98]
Fung 1994 (acute) (serum)	49	8	26	98	0.65 [0.53, 0.76]	0.92 [0.86, 0.97]
Fung 1994 (convalescent) (serum)	60	8	15	98	0.80 [0.69, 0.88]	0.92 [0.86, 0.97]
Lencakova 2008 (serum)	50	1	4	59	0.93 [0.82, 0.98]	0.98 [0.91, 1.00]
Molins 2014 (acute) (serum)	18	6	0	197	1.00 [0.81, 1.00]	0.97 [0.94, 0.99]
Molins 2014 (convalescent) (serum)	27	6	22	197	0.55 [0.40, 0.69]	0.97 [0.94, 0.99]
Molins 2016 (acute) (serum)	22	15	18	188	0.55 [0.38, 0.71]	0.93 [0.88, 0.96]
Molins 2016 (convalescent) (serum)	30	15	8	188	0.79 [0.63, 0.90]	0.93 [0.88, 0.96]
Porwancher 2011 (early acute) (serum)	31	22	48	428	0.39 [0.28, 0.51]	0.95 [0.93, 0.97]
Porwancher 2011 (early convalescent) (serum)	63	22	19	428	0.77 [0.66, 0.85]	0.95 [0.93, 0.97]
Trevejo 2001 (acute) (serum)	25	1	41	37	0.38 [0.26, 0.51]	0.97 [0.86, 1.00]
Trevejo 2001 (convalescent) (serum)	17	1	39	37	0.30 [0.19, 0.44]	0.97 [0.86, 1.00]

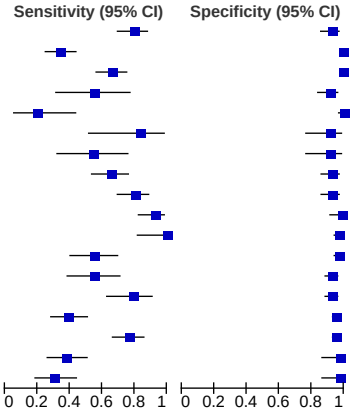


Figure 25: IFA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cerar 2006 (serum)	3	0	73	49	0.04 [0.01, 0.11]	1.00 [0.93, 1.00]
Lencakova 2008 (serum)	20	1	34	59	0.37 [0.24, 0.51]	0.98 [0.91, 1.00]
Mitchell 1994 (multiple ECM) (serum)	32	0	0	16	1.00 [0.89, 1.00]	1.00 [0.79, 1.00]
Mitchell 1994 (single ECM) (serum)	8	0	11	16	0.42 [0.20, 0.67]	1.00 [0.79, 1.00]
Ruzic-Sabljic 2002 (culture: pos vs neg) (serum)	0	2	66	49	0.00 [0.00, 0.05]	0.96 [0.87, 1.00]
Ruzic-Sabljic 2002 (serum)	2	0	115	96	0.02 [0.00, 0.06]	1.00 [0.96, 1.00]
Wilske 1993 (IFA-ABS) (serum)	10	4	21	138	0.32 [0.17, 0.51]	0.97 [0.93, 0.99]

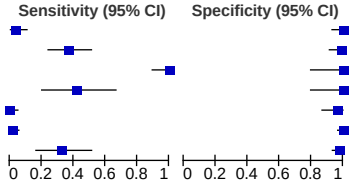


Figure 26: IFA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cerar 2006 (serum)	25	9	51	40	0.33 [0.23, 0.45]	0.82 [0.68, 0.91]
Lencakova 2008 (serum)	24	1	30	59	0.44 [0.31, 0.59]	0.98 [0.91, 1.00]
Ruzic-Sabljic 2002 (culture: pos vs neg) (serum)	1	2	65	49	0.02 [0.00, 0.08]	0.96 [0.87, 1.00]
Ruzic-Sabljic 2002 (serum)	3	2	114	94	0.03 [0.01, 0.07]	0.98 [0.93, 1.00]
Wilske 1993 (IFA-ABS) (serum)	14	4	17	138	0.45 [0.27, 0.64]	0.97 [0.93, 0.99]

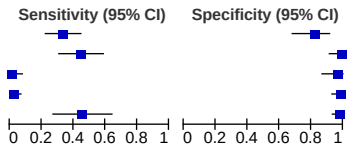


Figure 27: IFA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	36	1	18	59	0.67 [0.53, 0.79]	0.98 [0.91, 1.00]
Russell 1984 (serum)	17	0	17	100	0.50 [0.32, 0.68]	1.00 [0.96, 1.00]

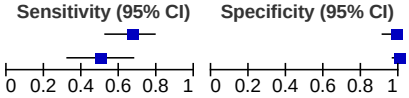


Figure 28: IFA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stiernstedt 1986 (serum)	3	3	22	60	0.12 [0.03, 0.31]	0.95 [0.87, 0.99]

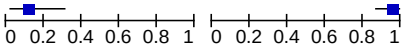


Figure 29: PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lebech 2000 (skin)	22	0	9	38	0.71 [0.52, 0.86]	1.00 [0.91, 1.00]
Molins 2014 (blood and skin)	24	0	15	0	0.62 [0.45, 0.77]	Not estimable
Moter 1994 (skin)	8	0	2	4	0.80 [0.44, 0.97]	1.00 [0.40, 1.00]
Schwartz 1992 (skin)	20	1	15	9	0.57 [0.39, 0.74]	0.90 [0.55, 1.00]
von Stedingk 1995 (skin)	18	0	8	76	0.69 [0.48, 0.86]	1.00 [0.95, 1.00]

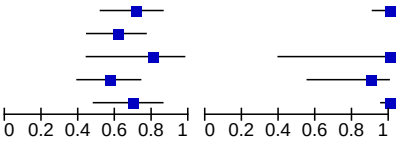
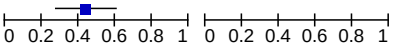


Figure 30: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (blood and skin)	17	0	22	0	0.44 [0.28, 0.60]	Not estimable



1 E.1.2.2 Neuroborreliosis

Figure 31: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	0	0	5	15	0.00 [0.00, 0.52]	1.00 [0.78, 1.00]
Ang 2015 (Enzygnost) (serum)	5	10	45	97	0.10 [0.03, 0.22]	0.91 [0.83, 0.95]
Ang 2015 (Euroimmun) (serum)	0	0	1	14	0.00 [0.00, 0.97]	1.00 [0.77, 1.00]
Ang 2015 (Liaison) (serum)	0	6	54	221	0.00 [0.00, 0.07]	0.97 [0.94, 0.99]
Ang 2015 (Medac) (serum)	1	1	24	91	0.04 [0.00, 0.20]	0.99 [0.94, 1.00]
Ang 2015 (Mikrogen) (serum)	0	0	1	15	0.00 [0.00, 0.97]	1.00 [0.78, 1.00]
Ang 2015 (Serion) (serum)	10	29	16	77	0.38 [0.20, 0.59]	0.73 [0.63, 0.81]
Ang 2015 (Virotech) (serum)	0	0	5	14	0.00 [0.00, 0.52]	1.00 [0.77, 1.00]
Bacon 2003 (conval., neurologic) (rVlsE) (serum)	6	5	5	252	0.55 [0.23, 0.83]	0.98 [0.96, 0.99]
Bacon 2003 (conval., neurologic) (serum)	4	0	7	257	0.36 [0.11, 0.69]	1.00 [0.99, 1.00]
Bacon 2003 (early neurologic) (rVlsE) (serum)	11	5	4	252	0.73 [0.45, 0.92]	0.98 [0.96, 0.99]
Bacon 2003 (early neurologic) (serum)	8	0	7	257	0.53 [0.27, 0.79]	1.00 [0.99, 1.00]
Bacon 2003 (late neurologic) (rVlsE) (serum)	1	5	10	252	0.09 [0.00, 0.41]	0.98 [0.96, 0.99]
Bacon 2003 (late neurologic) (serum)	2	0	9	257	0.18 [0.02, 0.52]	1.00 [0.99, 1.00]
Branda 2013 (EU) (serum)	12	2	3	98	0.80 [0.52, 0.96]	0.98 [0.93, 1.00]
Cerar 2010 (CSF)	7	0	27	32	0.21 [0.09, 0.38]	1.00 [0.89, 1.00]
Cerar 2010 (serum)	16	1	18	31	0.47 [0.30, 0.65]	0.97 [0.84, 1.00]
Dessau 2010 (serum)	64	26	53	789	0.55 [0.45, 0.64]	0.97 [0.95, 0.98]
Flisiak 1996 (flagella) (serum)	12	4	5	23	0.71 [0.44, 0.90]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	12	8	5	19	0.71 [0.44, 0.90]	0.70 [0.50, 0.86]
Fung 1994 (chronic neuroborreliosis) (serum)	5	2	20	104	0.20 [0.07, 0.41]	0.98 [0.93, 1.00]
Fung 1994 (meningitis/facial palsy) (serum)	29	2	11	104	0.72 [0.56, 0.85]	0.98 [0.93, 1.00]
Hansen 1991 (serum)	37	0	63	200	0.37 [0.28, 0.47]	1.00 [0.98, 1.00]
Hunfeld 2002 (serum)	26	87	9	1020	0.74 [0.57, 0.88]	0.92 [0.90, 0.94]
Kaiser 1998 (recombinant) (CSF)	28	0	39	14	0.42 [0.30, 0.54]	1.00 [0.77, 1.00]
Kaiser 1998 (recombinant) (serum)	53	0	14	14	0.79 [0.67, 0.88]	1.00 [0.77, 1.00]
Kaiser 1998 (sonicated) (CSF)	5	0	62	14	0.07 [0.02, 0.17]	1.00 [0.77, 1.00]
Kaiser 1998 (sonicated) (serum)	29	0	38	14	0.43 [0.31, 0.56]	1.00 [0.77, 1.00]
Kaiser 1999 (recombinant) (serum)	81	6	15	74	0.84 [0.76, 0.91]	0.93 [0.84, 0.97]
Kaiser 1999 (whole-cell) (serum)	51	8	45	72	0.53 [0.43, 0.63]	0.90 [0.81, 0.96]
Karlsson 1989 (CSF)	39	1	29	43	0.57 [0.45, 0.69]	0.98 [0.88, 1.00]
Karlsson 1989 (serum)	23	1	45	43	0.34 [0.23, 0.46]	0.98 [0.88, 1.00]
Karlsson 1989a (capture ELISA) (serum)	20	2	17	71	0.54 [0.37, 0.71]	0.97 [0.90, 1.00]
Karlsson 1989a (indirect ELISA) (serum)	14	7	23	66	0.38 [0.22, 0.55]	0.90 [0.81, 0.96]
Lencakova 2008 (serum)	3	1	4	59	0.43 [0.10, 0.82]	0.98 [0.91, 1.00]
Liu 2013 (serum)	40	58	25	234	0.62 [0.49, 0.73]	0.80 [0.75, 0.85]
Mathiesen 1996 (serum)	33	1	17	99	0.66 [0.51, 0.79]	0.99 [0.95, 1.00]
Molins 2017 (serum)	10	23	0	180	1.00 [0.69, 1.00]	0.89 [0.83, 0.93]
Panelius 2001 (serum)	11	0	8	0	0.58 [0.33, 0.80]	Not estimable
Rauer 1995 (recombinant) (serum)	0	3	33	79	0.00 [0.00, 0.11]	0.96 [0.90, 0.99]
Roux 2007 (serum)	7	1	4	15	0.64 [0.31, 0.89]	0.94 [0.70, 1.00]
Widhe 2004 (serum)	11	0	17	23	0.39 [0.22, 0.59]	1.00 [0.85, 1.00]
Wilske 1993 (flagellin) (serum)	30	6	30	136	0.50 [0.37, 0.63]	0.96 [0.91, 0.98]
Wilske 1993 (OGP-ELISA) (serum)	37	4	23	138	0.62 [0.48, 0.74]	0.97 [0.93, 0.99]

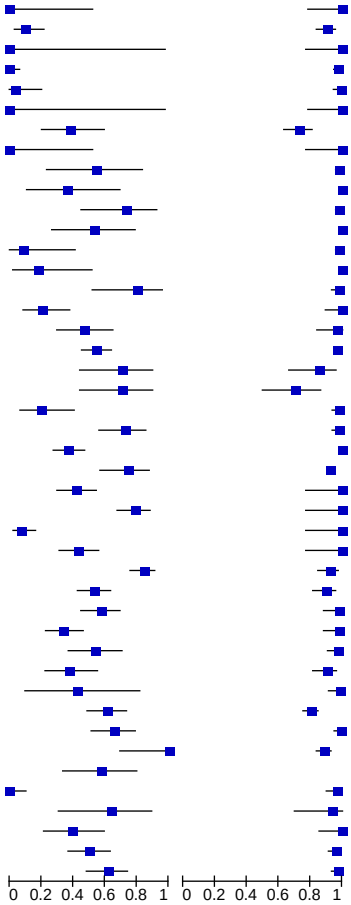


Figure 32: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacon 2003 (conval., neurologic) (rVlsE) (serum)	7	2	4	255	0.64 [0.31, 0.89]	0.99 [0.97, 1.00]
Bacon 2003 (conval., neurologic) (serum)	7	0	4	257	0.64 [0.31, 0.89]	1.00 [0.99, 1.00]
Bacon 2003 (early neurologic) (rVlsE) (serum)	15	2	0	255	1.00 [0.78, 1.00]	0.99 [0.97, 1.00]
Bacon 2003 (early neurologic) (serum)	9	0	6	257	0.60 [0.32, 0.84]	1.00 [0.99, 1.00]
Bacon 2003 (late neurologic) (rVlsE) (serum)	11	2	0	255	1.00 [0.72, 1.00]	0.99 [0.97, 1.00]
Bacon 2003 (late neurologic) (serum)	8	0	3	257	0.73 [0.39, 0.94]	1.00 [0.99, 1.00]
Branda 2013 (EU) (serum)	13	2	2	98	0.87 [0.60, 0.98]	0.98 [0.93, 1.00]
Cerar 2010 (CSF)	14	1	20	31	0.41 [0.25, 0.59]	0.97 [0.84, 1.00]
Cerar 2010 (serum)	24	16	10	16	0.71 [0.53, 0.85]	0.50 [0.32, 0.68]
Dessau 2010 (serum)	51	14	66	801	0.44 [0.34, 0.53]	0.98 [0.97, 0.99]
Dressler 1993 (prospective) (serum)	17	5	12	134	0.59 [0.39, 0.76]	0.96 [0.92, 0.99]
Flisiak 1996 (flagella) (serum)	6	0	11	27	0.35 [0.14, 0.62]	1.00 [0.87, 1.00]
Flisiak 1996 (recombinant) (serum)	5	0	12	27	0.29 [0.10, 0.56]	1.00 [0.87, 1.00]
Fung 1994 (chronic neuroborreliosis) (serum)	9	15	16	91	0.36 [0.18, 0.57]	0.86 [0.78, 0.92]
Fung 1994 (meningitis/facial palsy) (serum)	26	15	14	91	0.65 [0.48, 0.79]	0.86 [0.78, 0.92]
Hansen 1991 (serum)	84	0	16	200	0.84 [0.75, 0.91]	1.00 [0.98, 1.00]
Hunfeld 2002 (serum)	18	60	17	1047	0.51 [0.34, 0.69]	0.95 [0.93, 0.96]
Kaiser 1998 (recombinant) (CSF)	39	0	28	14	0.58 [0.46, 0.70]	1.00 [0.77, 1.00]
Kaiser 1998 (recombinant) (serum)	43	0	24	14	0.64 [0.52, 0.76]	1.00 [0.77, 1.00]
Kaiser 1998 (sonicated) (CSF)	21	10	46	4	0.31 [0.21, 0.44]	0.29 [0.08, 0.58]
Kaiser 1998 (sonicated) (serum)	62	10	5	4	0.93 [0.83, 0.98]	0.29 [0.08, 0.58]
Kaiser 1999 (recombinant) (serum)	77	14	19	66	0.80 [0.71, 0.88]	0.82 [0.72, 0.90]
Kaiser 1999 (whole-cell) (serum)	75	80	21	0	0.78 [0.69, 0.86]	0.00 [0.00, 0.05]
Karlsson 1989 (CSF)	39	2	29	42	0.57 [0.45, 0.69]	0.95 [0.85, 0.99]
Karlsson 1989 (serum)	26	3	42	41	0.38 [0.27, 0.51]	0.93 [0.81, 0.99]
Lencakova 2008 (serum)	4	1	3	59	0.57 [0.18, 0.90]	0.98 [0.91, 1.00]
Liu 2013 (serum)	55	67	10	225	0.85 [0.74, 0.92]	0.77 [0.72, 0.82]
Mathiesen 1996 (serum)	21	0	29	100	0.42 [0.28, 0.57]	1.00 [0.96, 1.00]
Molins 2017 (serum)	9	4	1	199	0.90 [0.55, 1.00]	0.98 [0.95, 0.99]
Panelius 2001 (serum)	14	0	5	0	0.74 [0.49, 0.91]	Not estimable
Panelius 2008 (CSF)	19	0	33	20	0.37 [0.24, 0.51]	1.00 [0.83, 1.00]
Panelius 2008 (serum)	56	0	11	20	0.84 [0.73, 0.92]	1.00 [0.83, 1.00]
Rauer 1995 (recombinant) (serum)	11	0	22	82	0.33 [0.18, 0.52]	1.00 [0.96, 1.00]
Roux 2007 (CSF)	10	4	1	12	0.91 [0.59, 1.00]	0.75 [0.48, 0.93]
Roux 2007 (serum)	7	6	4	10	0.64 [0.31, 0.89]	0.63 [0.35, 0.85]
Sillanpaa 2007 (serum)	14	0	0	83	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]
Widhe 2004 (serum)	23	0	6	23	0.79 [0.60, 0.92]	1.00 [0.85, 1.00]
Wilske 1993 (flagellin) (serum)	45	9	15	133	0.75 [0.62, 0.85]	0.94 [0.88, 0.97]
Wilske 1993 (OGP-ELISA) (serum)	27	4	33	138	0.45 [0.32, 0.58]	0.97 [0.93, 0.99]

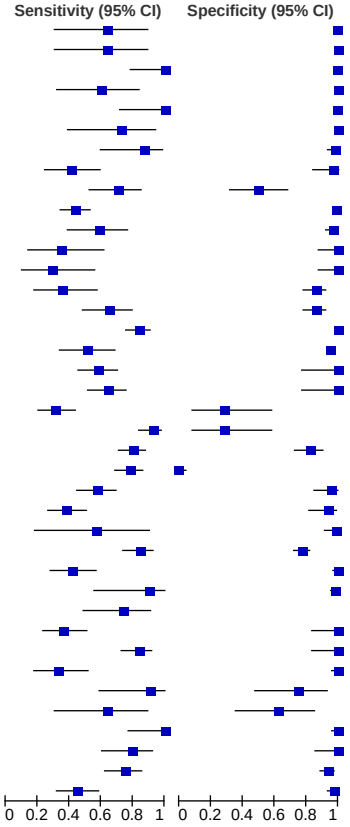


Figure 33: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	4	1	1	14	0.80 [0.28, 0.99]	0.93 [0.68, 1.00]
Ang 2015 (Enzygnost) (serum)	49	13	1	94	0.98 [0.89, 1.00]	0.88 [0.80, 0.93]
Ang 2015 (Euroimmun) (serum)	1	2	0	12	1.00 [0.03, 1.00]	0.86 [0.57, 0.98]
Ang 2015 (Liaison) (serum)	54	19	0	208	1.00 [0.93, 1.00]	0.92 [0.87, 0.95]
Ang 2015 (Medac) (serum)	25	3	0	89	1.00 [0.86, 1.00]	0.97 [0.91, 0.99]
Ang 2015 (Mikrogen) (serum)	1	0	0	15	1.00 [0.03, 1.00]	1.00 [0.78, 1.00]
Ang 2015 (Serion) (serum)	24	30	2	76	0.92 [0.75, 0.99]	0.72 [0.62, 0.80]
Ang 2015 (Virotech) (serum)	5	0	0	14	1.00 [0.48, 1.00]	1.00 [0.77, 1.00]
Branda 2013 (EU) (serum)	15	4	0	96	1.00 [0.78, 1.00]	0.96 [0.90, 0.99]
Branda 2013 (USA) (C6) (serum)	13	0	2	100	0.87 [0.60, 0.98]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	13	3	2	97	0.87 [0.60, 0.98]	0.97 [0.91, 0.99]
Coyle 1993 (CSF)	38	1	39	33	0.49 [0.38, 0.61]	0.97 [0.85, 1.00]
Flisiak 1996 (flagella) (serum)	15	4	2	23	0.88 [0.64, 0.99]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	14	8	3	19	0.82 [0.57, 0.96]	0.70 [0.50, 0.86]
Fung 1994 (chronic neuroborreliosis) (serum)	12	16	13	90	0.48 [0.28, 0.69]	0.85 [0.77, 0.91]
Fung 1994 (meningitis/facial palsy) (serum)	35	16	5	90	0.88 [0.73, 0.96]	0.85 [0.77, 0.91]
Hunfeld 2002 (serum)	30	0	5	0	0.86 [0.70, 0.95]	Not estimable
Johnson 1996 (serum)	16	5	1	108	0.94 [0.71, 1.00]	0.96 [0.90, 0.99]
Karlsson 1989 (CSF)	44	0	24	0	0.65 [0.52, 0.76]	Not estimable
Karlsson 1989 (serum)	40	4	28	40	0.59 [0.46, 0.71]	0.91 [0.78, 0.97]
Lawrenz 1999 (recombinant) (serum)	17	1	0	49	1.00 [0.80, 1.00]	0.98 [0.89, 1.00]
Lawrenz 1999 (whole-cell) (serum)	17	3	0	47	1.00 [0.80, 1.00]	0.94 [0.83, 0.99]
Lencakova 2008 (serum)	7	2	0	58	1.00 [0.59, 1.00]	0.97 [0.88, 1.00]
Molins 2014 (serum)	9	14	1	189	0.90 [0.55, 1.00]	0.93 [0.89, 0.96]
Molins 2016 (serum)	10	5	0	198	1.00 [0.69, 1.00]	0.98 [0.94, 0.99]
Rauer 1995 (recombinant) (serum)	14	3	19	79	0.42 [0.25, 0.61]	0.96 [0.90, 0.99]
Roux 2007 (CSF)	10	4	1	12	0.91 [0.59, 1.00]	0.75 [0.48, 0.93]
Roux 2007 (serum)	10	6	1	10	0.91 [0.59, 1.00]	0.63 [0.35, 0.85]
Russell 1984 (serum)	26	4	0	96	1.00 [0.87, 1.00]	0.96 [0.90, 0.99]
Tjernberg 2007 (Quick C6) (serum)	23	184	3	16	0.88 [0.70, 0.98]	0.08 [0.05, 0.13]
Tjernberg 2007 (Virotech) (serum)	25	152	1	48	0.96 [0.80, 1.00]	0.24 [0.18, 0.31]
van Burgel 2011 (antibody index)	56	5	3	138	0.95 [0.86, 0.99]	0.97 [0.92, 0.99]

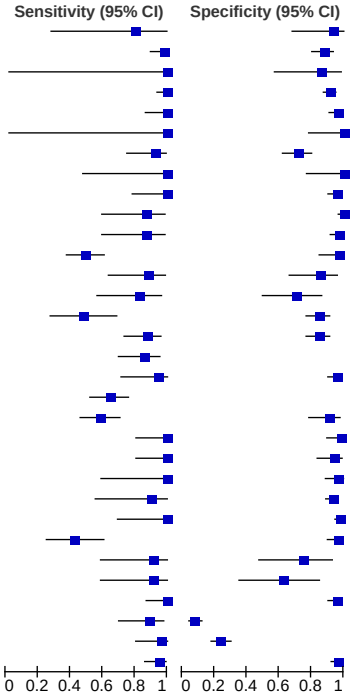


Figure 34: ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cinco 2006 (serum)	6	0	0	24	1.00 [0.54, 1.00]	1.00 [0.86, 1.00]

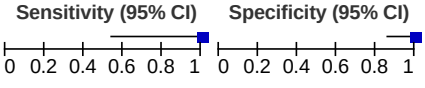


Figure 35: ELFA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (serum)	16	2	1	25	0.94 [0.71, 1.00]	0.93 [0.76, 0.99]

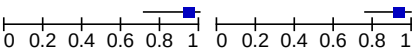


Figure 36: CLIA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Tjernberg 2007 (serum)	22	162	4	38	0.85 [0.65, 0.96]	0.19 [0.14, 0.25]

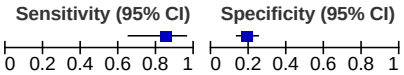


Figure 37: Western blot/Immunoblot (IgM/)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	5	3	62	101	0.07 [0.02, 0.17]	0.97 [0.92, 0.99]
Branda 2013 (EU) (serum)	12	9	3	91	0.80 [0.52, 0.96]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	6	0	9	100	0.40 [0.16, 0.68]	1.00 [0.96, 1.00]
Goettner 2005 (line blot) (serum)	23	1	27	109	0.46 [0.32, 0.61]	0.99 [0.95, 1.00]
Goettner 2005 (line plut plus) (serum)	35	2	15	108	0.70 [0.55, 0.82]	0.98 [0.94, 1.00]
Goettner 2005 (WB) (serum)	20	2	30	108	0.40 [0.26, 0.55]	0.98 [0.94, 1.00]
Karlsson 1989 (serum)	46	5	22	39	0.68 [0.55, 0.78]	0.89 [0.75, 0.96]
Lencakova 2008 (serum)	2	1	5	59	0.29 [0.04, 0.71]	0.98 [0.91, 1.00]
Liu 2013 (serum)	32	17	33	275	0.49 [0.37, 0.62]	0.94 [0.91, 0.97]
Mathiesen 1996 (serum)	30	1	20	99	0.60 [0.45, 0.74]	0.99 [0.95, 1.00]
Molins 2014 (serum)	10	4	0	199	1.00 [0.69, 1.00]	0.98 [0.95, 0.99]
Molins 2016 (serum)	9	12	1	191	0.90 [0.55, 1.00]	0.94 [0.90, 0.97]
Wilske 1993 (OspC-blot) (serum)	26	4	34	138	0.43 [0.31, 0.57]	0.97 [0.93, 0.99]
Wilske 1993 (p100-blot) (serum)	7	1	53	141	0.12 [0.05, 0.23]	0.99 [0.96, 1.00]
Wilske 1993 (p41/i-blot) (serum)	12	1	48	141	0.20 [0.11, 0.32]	0.99 [0.96, 1.00]

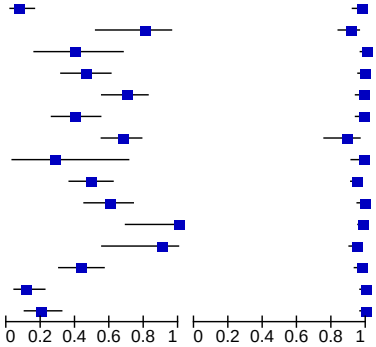


Figure 38: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (EU) (serum)	9	0	6	100	0.60 [0.32, 0.84]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	6	0	9	100	0.40 [0.16, 0.68]	1.00 [0.96, 1.00]
Dressler 1993 (prospective) (serum)	21	7	8	132	0.72 [0.53, 0.87]	0.95 [0.90, 0.98]
Goettner 2005 (line blot) (serum)	43	0	7	110	0.86 [0.73, 0.94]	1.00 [0.97, 1.00]
Goettner 2005 (line plut plus) (serum)	44	1	6	109	0.88 [0.76, 0.95]	0.99 [0.95, 1.00]
Goettner 2005 (WB) (serum)	36	1	14	109	0.72 [0.58, 0.84]	0.99 [0.95, 1.00]
Karlsson 1989 (serum)	44	5	24	39	0.65 [0.52, 0.76]	0.89 [0.75, 0.96]
Lencakova 2008 (serum)	4	0	3	60	0.57 [0.18, 0.90]	1.00 [0.94, 1.00]
Liu 2013 (serum)	45	5	20	287	0.69 [0.57, 0.80]	0.98 [0.96, 0.99]
Mathiesen 1996 (serum)	23	4	27	96	0.46 [0.32, 0.61]	0.96 [0.90, 0.99]
Molins 2014 (serum)	3	2	7	201	0.30 [0.07, 0.65]	0.99 [0.96, 1.00]
Molins 2016 (serum)	4	3	6	200	0.40 [0.12, 0.74]	0.99 [0.96, 1.00]
Panelius 2001 (serum)	10	0	4	0	0.71 [0.42, 0.92]	Not estimable
Peltomaa 2004 (serum)	47	4	0	82	1.00 [0.92, 1.00]	0.95 [0.89, 0.99]
Roux 2007 (CSF)	9	1	2	15	0.82 [0.48, 0.98]	0.94 [0.70, 1.00]
Roux 2007 (serum)	7	6	4	10	0.64 [0.31, 0.89]	0.63 [0.35, 0.85]
Schulte-Spechtel 2004 (recombinant) (serum)	31	0	5	67	0.86 [0.71, 0.95]	1.00 [0.95, 1.00]
Schulte-Spechtel 2004 (whole-cell) (serum)	23	2	13	65	0.64 [0.46, 0.79]	0.97 [0.90, 1.00]
Wilske 1993 (OspC-blot) (serum)	9	1	51	141	0.15 [0.07, 0.27]	0.99 [0.96, 1.00]
Wilske 1993 (p100-blot) (serum)	26	9	34	133	0.43 [0.31, 0.57]	0.94 [0.88, 0.97]
Wilske 1993 (p41/i-blot) (serum)	15	6	45	136	0.25 [0.15, 0.38]	0.96 [0.91, 0.98]
Wilske 1999 (recombinant - new) (serum)	19	3	23	136	0.45 [0.30, 0.61]	0.98 [0.94, 1.00]
Wilske 1999 (recombinant - old) (serum)	12	3	30	136	0.29 [0.16, 0.45]	0.98 [0.94, 1.00]
Wilske 1999 (whole-cell) (serum)	24	3	18	136	0.57 [0.41, 0.72]	0.98 [0.94, 1.00]

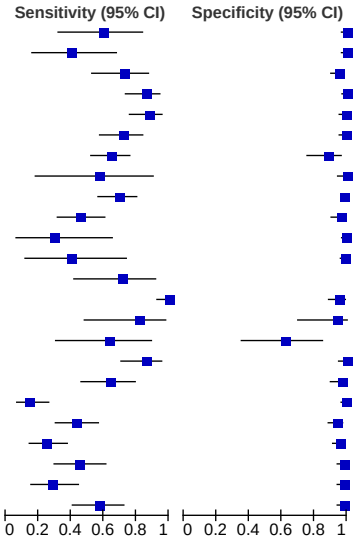


Figure 39: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	65	8	2	96	0.97 [0.90, 1.00]	0.92 [0.85, 0.97]
Branda 2013 (EU) (serum)	13	9	2	91	0.87 [0.60, 0.98]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	8	0	7	100	0.53 [0.27, 0.79]	1.00 [0.96, 1.00]
Karlsson 1989 (serum)	53	8	15	36	0.78 [0.66, 0.87]	0.82 [0.67, 0.92]
Lencakova 2008 (serum)	6	1	1	59	0.86 [0.42, 1.00]	0.98 [0.91, 1.00]
Molins 2014 (serum)	10	6	0	197	1.00 [0.69, 1.00]	0.97 [0.94, 0.99]
Molins 2016 (serum)	9	15	1	188	0.90 [0.55, 1.00]	0.93 [0.88, 0.96]

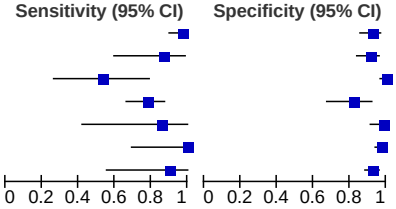


Figure 40: IFA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cerar 2006 (serum)	2	0	26	49	0.07 [0.01, 0.24]	1.00 [0.93, 1.00]
Lencakova 2008 (serum)	1	1	6	59	0.14 [0.00, 0.58]	0.98 [0.91, 1.00]
Wilske 1993 (IFA-ABS) (serum)	18	4	42	138	0.30 [0.19, 0.43]	0.97 [0.93, 0.99]

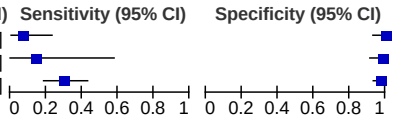


Figure 41: IFA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cerar 2006 (serum)	21	9	7	40	0.75 [0.55, 0.89]	0.82 [0.68, 0.91]
Lencakova 2008 (serum)	1	1	6	59	0.14 [0.00, 0.58]	0.98 [0.91, 1.00]
Wilske 1993 (IFA-ABS) (serum)	45	4	15	138	0.75 [0.62, 0.85]	0.97 [0.93, 0.99]

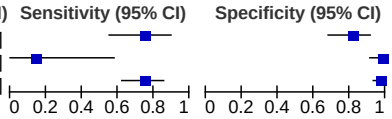


Figure 42: IFA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	2	1	5	59	0.29 [0.04, 0.71]	0.98 [0.91, 1.00]
Russell 1984 (serum)	24	0	2	100	0.92 [0.75, 0.99]	1.00 [0.96, 1.00]

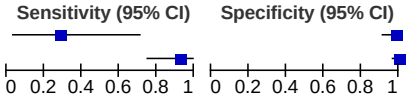


Figure 43: PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lebech 1992 (CSF)	2	0	8	15	0.20 [0.03, 0.56]	1.00 [0.78, 1.00]
Lebech 1992 (urine)	9	0	1	35	0.90 [0.55, 1.00]	1.00 [0.90, 1.00]
Lebech 1998 (CSF)	31	1	119	69	0.21 [0.14, 0.28]	0.99 [0.92, 1.00]
Lebech 2000 (CSF)	5	0	25	20	0.17 [0.06, 0.35]	1.00 [0.83, 1.00]
Molins 2014 (blood and skin)	2	0	6	0	0.25 [0.03, 0.65]	Not estimable
Nocton 1996 (CSF)	17	0	43	42	0.28 [0.17, 0.41]	1.00 [0.92, 1.00]
Priem 1997 (CSF)	15	0	4	33	0.79 [0.54, 0.94]	1.00 [0.89, 1.00]

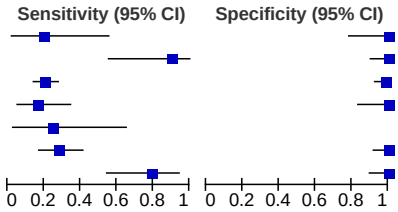


Figure 44: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (blood and skin)	2	0	4	0	0.33 [0.04, 0.78]	Not estimable

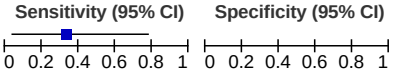
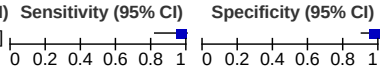


Figure 45: CXCL13

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Senel 2010 (cut-off 337 ng/g) (CSF)	27	2	1	67	0.96 [0.82, 1.00]	0.97 [0.90, 1.00]



1 E.1.2.3 Lyme arthritis

Figure 46: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	0	0	5	15	0.00 [0.00, 0.52]	1.00 [0.78, 1.00]
Ang 2015 (Enzygnost) (serum)	1	10	12	97	0.08 [0.00, 0.36]	0.91 [0.83, 0.95]
Ang 2015 (Liaison) (serum)	0	6	7	221	0.00 [0.00, 0.41]	0.97 [0.94, 0.99]
Ang 2015 (Serion) (serum)	0	29	2	77	0.00 [0.00, 0.84]	0.73 [0.63, 0.81]
Ang 2015 (Virotech) (serum)	1	0	4	14	0.20 [0.01, 0.72]	1.00 [0.77, 1.00]
Bacon 2003 (arthritis) (rVlsE) (serum)	13	5	20	252	0.39 [0.23, 0.58]	0.98 [0.96, 0.99]
Bacon 2003 (arthritis) (serum)	3	0	30	257	0.09 [0.02, 0.24]	1.00 [0.99, 1.00]
Bacon 2003 (conval., arthritis) (rVlsE) (serum)	10	5	14	252	0.42 [0.22, 0.63]	0.98 [0.96, 0.99]
Bacon 2003 (conval., arthritis) (serum)	2	0	22	257	0.08 [0.01, 0.27]	1.00 [0.99, 1.00]
Branda 2013 (EU) (serum)	9	2	6	98	0.60 [0.32, 0.84]	0.98 [0.93, 1.00]
Flisiak 1996 (flagella) (serum)	5	4	2	23	0.71 [0.29, 0.96]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	7	8	0	19	1.00 [0.59, 1.00]	0.70 [0.50, 0.86]
Fung 1994 (arthritis) (serum)	22	2	27	104	0.45 [0.31, 0.60]	0.98 [0.93, 1.00]
Lencakova 2008 (serum)	0	1	13	59	0.00 [0.00, 0.25]	0.98 [0.91, 1.00]
Molins 2017 (serum)	19	23	10	180	0.66 [0.46, 0.82]	0.89 [0.83, 0.93]
Panelius 2001 (serum)	7	0	12	0	0.37 [0.16, 0.62]	Not estimable
Rauer 1995 (recombinant) (serum)	0	3	17	79	0.00 [0.00, 0.20]	0.96 [0.90, 0.99]

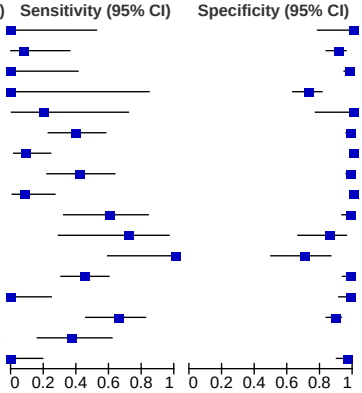


Figure 47: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacon 2003 (arthritis) (rVlsE) (serum)	32	2	1	255	0.97 [0.84, 1.00]	0.99 [0.97, 1.00]
Bacon 2003 (arthritis) (serum)	31	0	2	257	0.94 [0.80, 0.99]	1.00 [0.99, 1.00]
Bacon 2003 (conval., arthritis) (rVlsE) (serum)	21	2	3	255	0.88 [0.68, 0.97]	0.99 [0.97, 1.00]
Bacon 2003 (conval., arthritis) (serum)	21	0	3	257	0.88 [0.68, 0.97]	1.00 [0.99, 1.00]
Branda 2013 (EU) (serum)	15	2	0	98	1.00 [0.78, 1.00]	0.98 [0.93, 1.00]
Dressler 1993 (prospective) (serum)	22	5	3	134	0.88 [0.69, 0.97]	0.96 [0.92, 0.99]
Flisiak 1996 (flagella) (serum)	1	0	6	27	0.14 [0.00, 0.58]	1.00 [0.87, 1.00]
Flisiak 1996 (recombinant) (serum)	0	0	7	27	0.00 [0.00, 0.41]	1.00 [0.87, 1.00]
Fung 1994 (arthritis) (serum)	41	15	8	91	0.84 [0.70, 0.93]	0.86 [0.78, 0.92]
Lencakova 2008 (serum)	12	1	1	59	0.92 [0.64, 1.00]	0.98 [0.91, 1.00]
Molins 2017 (serum)	29	4	0	199	1.00 [0.88, 1.00]	0.98 [0.95, 0.99]
Panelius 2001 (serum)	15	0	4	0	0.79 [0.54, 0.94]	Not estimable
Rauer 1995 (recombinant) (serum)	14	0	3	82	0.82 [0.57, 0.96]	1.00 [0.96, 1.00]
Sillanpaa 2007 (serum)	13	0	1	83	0.93 [0.66, 1.00]	1.00 [0.96, 1.00]

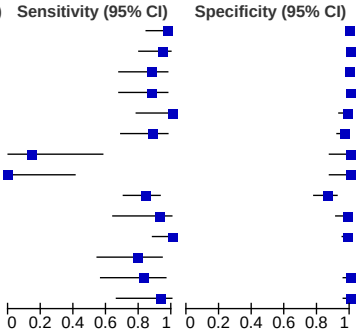


Figure 48: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	4	1	1	14	0.80 [0.28, 0.99]	0.93 [0.68, 1.00]
Ang 2015 (Enzygnost) (serum)	13	13	0	94	1.00 [0.75, 1.00]	0.88 [0.80, 0.93]
Ang 2015 (Liaison) (serum)	7	19	0	208	1.00 [0.59, 1.00]	0.92 [0.87, 0.95]
Ang 2015 (Serion) (serum)	2	30	0	76	1.00 [0.16, 1.00]	0.72 [0.62, 0.80]
Ang 2015 (Virotech) (serum)	5	0	0	14	1.00 [0.48, 1.00]	1.00 [0.77, 1.00]
Branda 2013 (EU) (serum)	15	4	0	96	1.00 [0.78, 1.00]	0.96 [0.90, 0.99]
Branda 2013 (USA) (C6) (serum)	15	0	0	100	1.00 [0.78, 1.00]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	14	3	1	97	0.93 [0.68, 1.00]	0.97 [0.91, 0.99]
Flisiak 1996 (flagella) (serum)	5	4	2	23	0.71 [0.29, 0.96]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	7	8	0	19	1.00 [0.59, 1.00]	0.70 [0.50, 0.86]
Fung 1994 (arthritis) (serum)	43	16	6	90	0.88 [0.75, 0.95]	0.85 [0.77, 0.91]
Johnson 1996 (serum)	32	5	4	108	0.89 [0.74, 0.97]	0.96 [0.90, 0.99]
Lahey 2015 (serum)	5	1	0	25	1.00 [0.48, 1.00]	0.96 [0.80, 1.00]
Lawrenz 1999 (recombinant) (serum)	20	1	3	49	0.87 [0.66, 0.97]	0.98 [0.89, 1.00]
Lawrenz 1999 (whole-cell) (serum)	22	3	1	47	0.96 [0.78, 1.00]	0.94 [0.83, 0.99]
Lencakova 2008 (serum)	12	2	1	58	0.92 [0.64, 1.00]	0.97 [0.88, 1.00]
Molins 2014 (serum)	29	9	0	194	1.00 [0.88, 1.00]	0.96 [0.92, 0.98]
Molins 2016 (serum)	29	5	0	198	1.00 [0.88, 1.00]	0.98 [0.94, 0.99]
Rauer 1995 (recombinant) (serum)	16	3	1	79	0.94 [0.71, 1.00]	0.96 [0.90, 0.99]
Russell 1984 (serum)	38	4	0	96	1.00 [0.91, 1.00]	0.96 [0.90, 0.99]
Tjernberg 2007 (Quick C6) (serum)	2	184	1	16	0.67 [0.09, 0.99]	0.08 [0.05, 0.13]
Tjernberg 2007 (Virotech) (serum)	2	152	1	48	0.67 [0.09, 0.99]	0.24 [0.18, 0.31]

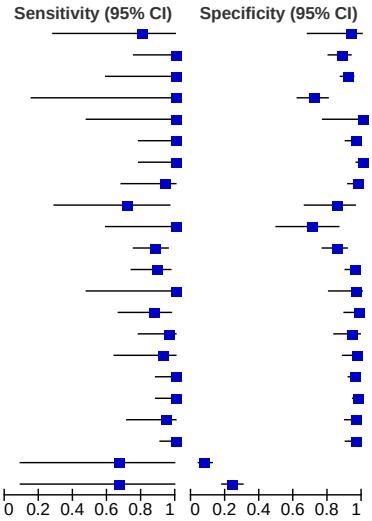


Figure 49: ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cinco 2006 (serum)	16	0	0	24	1.00 [0.79, 1.00]	1.00 [0.86, 1.00]

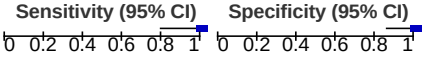


Figure 50: ELISA C6 (IgA)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
D'Arco 2017 (IgA) (serum)	3	2	14	133	0.18 [0.04, 0.43]	0.99 [0.95, 1.00]

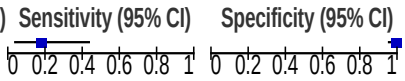


Figure 51: ELFA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (serum)	6	2	1	25	0.86 [0.42, 1.00]	0.93 [0.76, 0.99]

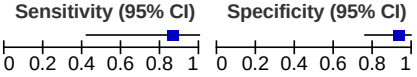


Figure 52: CLIA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Tjernberg 2007 (serum)	2	162	1	38	0.67 [0.09, 0.99]	0.19 [0.14, 0.25]

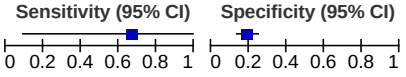


Figure 53: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	0	3	8	101	0.00 [0.00, 0.37]	0.97 [0.92, 0.99]
Branda 2013 (EU) (serum)	10	9	5	91	0.67 [0.38, 0.88]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	4	0	11	100	0.27 [0.08, 0.55]	1.00 [0.96, 1.00]
Lencakova 2008 (serum)	0	1	13	59	0.00 [0.00, 0.25]	0.98 [0.91, 1.00]
Molins 2014 (serum)	9	4	20	199	0.31 [0.15, 0.51]	0.98 [0.95, 0.99]
Molins 2016 (serum)	17	12	12	191	0.59 [0.39, 0.76]	0.94 [0.90, 0.97]
Porwancher 2011 (serum)	19	0	10	0	0.66 [0.46, 0.82]	Not estimable

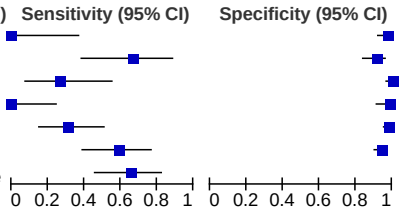


Figure 54: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (EU) (serum)	13	0	2	100	0.87 [0.60, 0.98]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	10	0	5	100	0.67 [0.38, 0.88]	1.00 [0.96, 1.00]
Dressler 1993 (prospective) (serum)	24	7	1	132	0.96 [0.80, 1.00]	0.95 [0.90, 0.98]
Goettner 2005 (line blot) (serum)	9	0	1	110	0.90 [0.55, 1.00]	1.00 [0.97, 1.00]
Goettner 2005 (line plut plus) (serum)	10	1	0	109	1.00 [0.69, 1.00]	0.99 [0.95, 1.00]
Goettner 2005 (WB) (serum)	10	1	0	109	1.00 [0.69, 1.00]	0.99 [0.95, 1.00]
Lencakova 2008 (serum)	13	0	0	60	1.00 [0.75, 1.00]	1.00 [0.94, 1.00]
Molins 2014 (serum)	29	2	0	201	1.00 [0.88, 1.00]	0.99 [0.96, 1.00]
Molins 2016 (serum)	28	3	1	200	0.97 [0.82, 1.00]	0.99 [0.96, 1.00]
Panelius 2001 (serum)	12	0	2	0	0.86 [0.57, 0.98]	Not estimable
Porwancher 2011 (serum)	28	0	54	0	0.34 [0.24, 0.45]	Not estimable

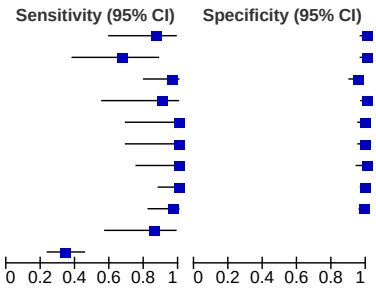


Figure 55: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	8	8	0	96	1.00 [0.63, 1.00]	0.92 [0.85, 0.97]
Branda 2013 (EU) (serum)	14	9	1	91	0.93 [0.68, 1.00]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	11	0	4	100	0.73 [0.45, 0.92]	1.00 [0.96, 1.00]
Lencakova 2008 (serum)	13	1	0	59	1.00 [0.75, 1.00]	0.98 [0.91, 1.00]
Molins 2014 (serum)	29	6	0	197	1.00 [0.88, 1.00]	0.97 [0.94, 0.99]
Molins 2016 (serum)	28	15	1	188	0.97 [0.82, 1.00]	0.93 [0.88, 0.96]
Porwancher 2011 (serum)	29	21	0	429	1.00 [0.88, 1.00]	0.95 [0.93, 0.97]

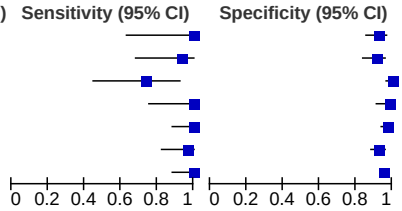


Figure 56: IFA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	0	1	13	59	0.00 [0.00, 0.25]	0.98 [0.91, 1.00]

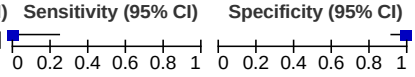


Figure 57: IFA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	10	1	3	59	0.77 [0.46, 0.95]	0.98 [0.91, 1.00]

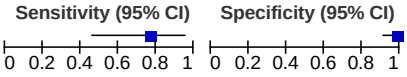


Figure 58: IFA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lencakova 2008 (serum)	10	1	3	59	0.77 [0.46, 0.95]	0.98 [0.91, 1.00]
Russell 1984 (serum)	38	0	0	100	1.00 [0.91, 1.00]	1.00 [0.96, 1.00]

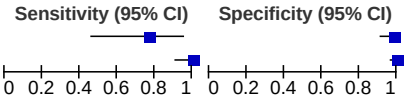
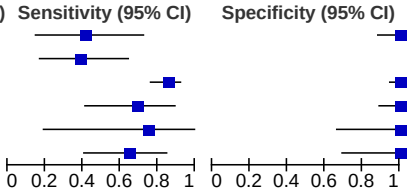


Figure 59: PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaulhac 1996 (SF)	5	0	7	29	0.42 [0.15, 0.72]	1.00 [0.88, 1.00]
Molins 2014 (SF)	7	0	11	0	0.39 [0.17, 0.64]	Not estimable
Nocton 1994 (SF)	75	0	13	64	0.85 [0.76, 0.92]	1.00 [0.94, 1.00]
Schnarr 2011 (SF)	11	0	5	31	0.69 [0.41, 0.89]	1.00 [0.89, 1.00]
van der Heijden 1999 (SF)	3	0	1	9	0.75 [0.19, 0.99]	1.00 [0.66, 1.00]
Vasiliu 1998 (SF)	13	0	7	10	0.65 [0.41, 0.85]	1.00 [0.69, 1.00]



1 E.1.2.4 Lyme carditis

Figure 60: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2017 (serum)	5	23	2	180	0.71 [0.29, 0.96]	0.89 [0.83, 0.93]

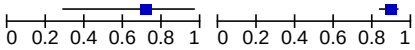


Figure 61: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2017 (serum)	6	4	1	199	0.86 [0.42, 1.00]	0.98 [0.95, 0.99]

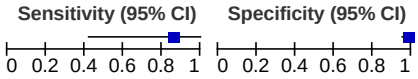


Figure 62: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (serum)	7	9	0	194	1.00 [0.59, 1.00]	0.96 [0.92, 0.98]
Molins 2016 (serum)	6	5	1	198	0.86 [0.42, 1.00]	0.98 [0.94, 0.99]
Russell 1984 (serum)	6	4	0	96	1.00 [0.54, 1.00]	0.96 [0.90, 0.99]

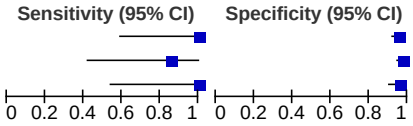


Figure 63: IFA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Russell 1984 (serum)	6	0	0	100	1.00 [0.54, 1.00]	1.00 [0.96, 1.00]

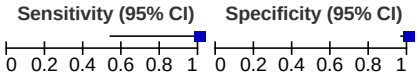


Figure 64: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (serum)	4	4	3	199	0.57 [0.18, 0.90]	0.98 [0.95, 0.99]
Molins 2016 (serum)	5	12	2	191	0.71 [0.29, 0.96]	0.94 [0.90, 0.97]

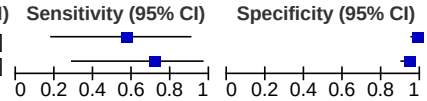


Figure 65: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (serum)	4	2	3	201	0.57 [0.18, 0.90]	0.99 [0.96, 1.00]
Molins 2016 (serum)	5	3	2	200	0.71 [0.29, 0.96]	0.99 [0.96, 1.00]

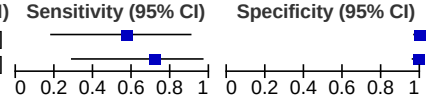


Figure 66: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (serum)	6	6	1	197	0.86 [0.42, 1.00]	0.97 [0.94, 0.99]
Molins 2016 (serum)	7	15	0	188	1.00 [0.59, 1.00]	0.93 [0.88, 0.96]

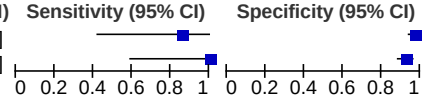


Figure 67: PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (blood, skin and heart)	2	0	5	0	0.29 [0.04, 0.71]	Not estimable

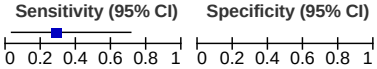
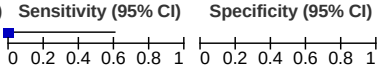


Figure 68: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (blood, skin and heart)	0	0	4	0	0.00 [0.00, 0.60]	Not estimable



1 E.1.2.5 Acrodermatitis chronica atrophicans (ACA)

Figure 69: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	0	0	6	15	0.00 [0.00, 0.46]	1.00 [0.78, 1.00]
Ang 2015 (Enzygnost) (serum)	0	10	14	97	0.00 [0.00, 0.23]	0.91 [0.83, 0.95]
Ang 2015 (Liaison) (serum)	0	6	9	221	0.00 [0.00, 0.34]	0.97 [0.94, 0.99]
Ang 2015 (Medac) (serum)	0	1	2	91	0.00 [0.00, 0.84]	0.99 [0.94, 1.00]
Ang 2015 (Serion) (serum)	0	29	2	77	0.00 [0.00, 0.84]	0.73 [0.63, 0.81]
Ang 2015 (Virotech) (serum)	0	0	6	14	0.00 [0.00, 0.46]	1.00 [0.77, 1.00]
Asbrink 1985 (after treatment) (serum)	4	9	22	176	0.15 [0.04, 0.35]	0.95 [0.91, 0.98]
Asbrink 1985 (before treatment) (serum)	7	9	19	176	0.27 [0.12, 0.48]	0.95 [0.91, 0.98]
Branda 2013 (EU) (serum)	10	4	2	98	0.83 [0.52, 0.98]	0.96 [0.90, 0.99]
Hansen 1989 (flagellum) (serum)	6	10	44	190	0.12 [0.05, 0.24]	0.95 [0.91, 0.98]
Hansen 1989 (sonic) (serum)	11	11	39	189	0.22 [0.12, 0.36]	0.94 [0.90, 0.97]
Hansen 1991 (serum)	5	0	43	200	0.10 [0.03, 0.23]	1.00 [0.98, 1.00]
Karlsson 1989a (capture ELISA) (serum)	0	2	10	71	0.00 [0.00, 0.31]	0.97 [0.90, 1.00]
Karlsson 1989a (indirect ELISA) (serum)	3	7	7	66	0.30 [0.07, 0.65]	0.90 [0.81, 0.96]
Mathiesen 1996 (serum)	3	1	17	99	0.15 [0.03, 0.38]	0.99 [0.95, 1.00]
Rauer 1995 (recombinant) (serum)	0	3	42	79	0.00 [0.00, 0.08]	0.96 [0.90, 0.99]
Widhe 2004 (serum)	3	0	2	23	0.60 [0.15, 0.95]	1.00 [0.85, 1.00]

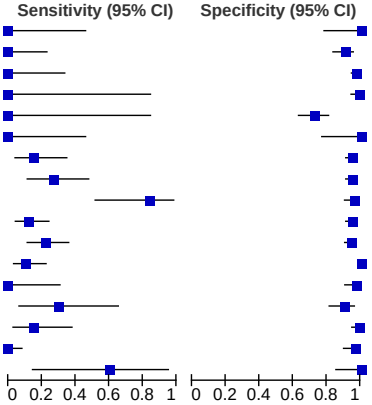


Figure 70: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Asbrink 1985 (after treatment) (serum)	24	9	2	176	0.92 [0.75, 0.99]	0.95 [0.91, 0.98]
Asbrink 1985 (before treatment) (serum)	26	9	0	176	1.00 [0.87, 1.00]	0.95 [0.91, 0.98]
Branda 2013 (EU) (serum)	14	2	0	98	1.00 [0.77, 1.00]	0.98 [0.93, 1.00]
Hansen 1989 (flagellum) (serum)	50	8	0	192	1.00 [0.93, 1.00]	0.96 [0.92, 0.98]
Hansen 1989 (sonic) (serum)	49	12	1	188	0.98 [0.89, 1.00]	0.94 [0.90, 0.97]
Hansen 1991 (serum)	48	0	0	200	1.00 [0.93, 1.00]	1.00 [0.98, 1.00]
Mathiesen 1996 (serum)	20	0	0	100	1.00 [0.83, 1.00]	1.00 [0.96, 1.00]
Panelius 2008 (serum)	8	0	2	20	0.80 [0.44, 0.97]	1.00 [0.83, 1.00]
Rauer 1995 (recombinant) (serum)	14	0	28	82	0.33 [0.20, 0.50]	1.00 [0.96, 1.00]
Widhe 2004 (serum)	5	0	0	23	1.00 [0.48, 1.00]	1.00 [0.85, 1.00]

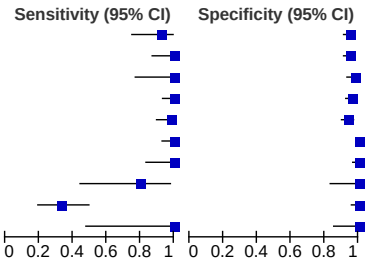


Figure 71: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Diacheck) (serum)	6	1	0	14	1.00 [0.54, 1.00]	0.93 [0.68, 1.00]
Ang 2015 (Enzygnost) (serum)	14	13	0	94	1.00 [0.77, 1.00]	0.88 [0.80, 0.93]
Ang 2015 (Liaison) (serum)	8	19	0	208	1.00 [0.63, 1.00]	0.92 [0.87, 0.95]
Ang 2015 (Medac) (serum)	2	3	0	89	1.00 [0.16, 1.00]	0.97 [0.91, 0.99]
Ang 2015 (Serion) (serum)	2	30	0	76	1.00 [0.16, 1.00]	0.72 [0.62, 0.80]
Ang 2015 (Virotech) (serum)	6	0	0	14	1.00 [0.54, 1.00]	1.00 [0.77, 1.00]
Branda 2013 (EU) (serum)	14	4	0	96	1.00 [0.77, 1.00]	0.96 [0.90, 0.99]
Branda 2013 (USA) (C6) (serum)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	14	3	0	97	1.00 [0.77, 1.00]	0.97 [0.91, 0.99]
Rauer 1995 (recombinant) (serum)	36	3	6	79	0.86 [0.71, 0.95]	0.96 [0.90, 0.99]
Tjernberg 2007 (Quick C6) (serum)	8	184	1	16	0.89 [0.52, 1.00]	0.08 [0.05, 0.13]
Tjernberg 2007 (Virotech) (serum)	9	152	0	48	1.00 [0.66, 1.00]	0.24 [0.18, 0.31]

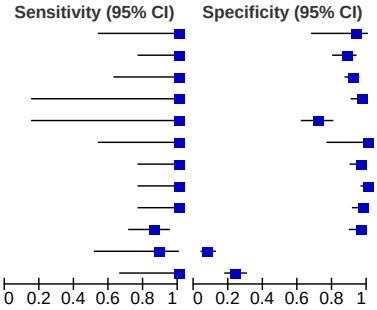


Figure 72: CLIA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Tjernberg 2007 (serum)	6	162	3	38	0.67 [0.30, 0.93]	0.19 [0.14, 0.25]

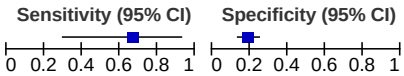


Figure 73: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	0	3	11	101	0.00 [0.00, 0.28]	0.97 [0.92, 0.99]
Branda 2013 (EU) (serum)	5	9	9	91	0.36 [0.13, 0.65]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	4	0	10	100	0.29 [0.08, 0.58]	1.00 [0.96, 1.00]
Mathiesen 1996 (serum)	2	1	18	99	0.10 [0.01, 0.32]	0.99 [0.95, 1.00]

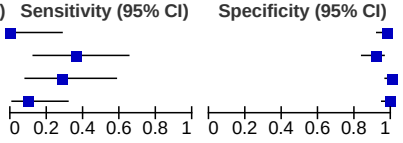


Figure 74: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (EU) (serum)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]
Branda 2013 (USA) (serum)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]
Goettner 2005 (line blot) (serum)	10	0	0	110	1.00 [0.69, 1.00]	1.00 [0.97, 1.00]
Goettner 2005 (line plut plus) (serum)	10	1	0	109	1.00 [0.69, 1.00]	0.99 [0.95, 1.00]
Goettner 2005 (WB) (serum)	9	1	1	109	0.90 [0.55, 1.00]	0.99 [0.95, 1.00]
Mathiesen 1996 (serum)	1	4	19	96	0.05 [0.00, 0.25]	0.96 [0.90, 0.99]

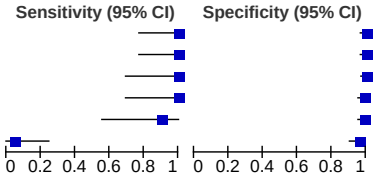


Figure 75: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015 (Mikrogen) (serum)	11	8	0	96	1.00 [0.72, 1.00]	0.92 [0.85, 0.97]
Branda 2013 (EU) (serum)	14	9	0	91	1.00 [0.77, 1.00]	0.91 [0.84, 0.96]
Branda 2013 (USA) (serum)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]

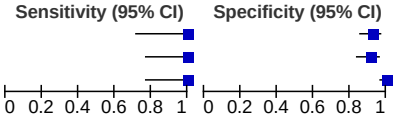
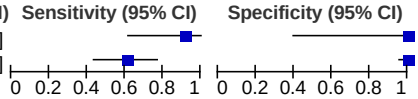


Figure 76: PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Moter 1994 (skin)	11	0	1	4	0.92 [0.62, 1.00]	1.00 [0.40, 1.00]
von Stedingk 1995 (skin)	22	0	14	76	0.61 [0.43, 0.77]	1.00 [0.95, 1.00]



1 **E.1.2.6 Unspecified Lyme disease**

Figure 77: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (flagella) (serum)	27	4	15	23	0.64 [0.48, 0.78]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	25	8	17	19	0.60 [0.43, 0.74]	0.70 [0.50, 0.86]
Flisiak 1998 (serum)	28	3	20	23	0.58 [0.43, 0.72]	0.88 [0.70, 0.98]
Goossens 2000 (late) (Behring) (serum)	8	1	5	61	0.62 [0.32, 0.86]	0.98 [0.91, 1.00]
Goossens 2000 (late) (Boehring) (serum)	6	0	7	62	0.46 [0.19, 0.75]	1.00 [0.94, 1.00]
Goossens 2000 (late) (Dako) (serum)	9	3	4	59	0.69 [0.39, 0.91]	0.95 [0.87, 0.99]
Goossens 2000 (late) (Genzyme Virotech) (serum)	8	1	5	61	0.62 [0.32, 0.86]	0.98 [0.91, 1.00]
Goossens 2000 (late) (IBL) (serum)	8	6	5	56	0.62 [0.32, 0.86]	0.90 [0.80, 0.96]
Hernandez-Novoa 2003 (disseminated) (serum)	12	7	6	122	0.67 [0.41, 0.87]	0.95 [0.89, 0.98]
Hunfeld 2002 (serum)	4	87	39	1020	0.09 [0.03, 0.22]	0.92 [0.90, 0.94]
Karlsson 1989a (capture ELISA) (serum)	30	2	47	71	0.39 [0.28, 0.51]	0.97 [0.90, 1.00]
Karlsson 1989a (indirect ELISA) (serum)	24	7	53	66	0.31 [0.21, 0.43]	0.90 [0.81, 0.96]
Smismans 2006 (purified) (serum)	9	9	4	31	0.69 [0.39, 0.91]	0.78 [0.62, 0.89]
Smismans 2006 (synthetic C6) (serum)	11	3	2	37	0.85 [0.55, 0.98]	0.93 [0.80, 0.98]
Smismans 2006 (whole-cell) (serum)	11	19	2	21	0.85 [0.55, 0.98]	0.53 [0.36, 0.68]
Wilske 1993 (all Lyme) (flagellin) (serum)	48	6	86	136	0.36 [0.28, 0.45]	0.96 [0.91, 0.98]
Wilske 1993 (all Lyme) (OGP-ELISA) (serum)	62	4	72	138	0.46 [0.38, 0.55]	0.97 [0.93, 0.99]
Wilske 1993 (late) (flagellin) (serum)	6	6	37	136	0.14 [0.05, 0.28]	0.96 [0.91, 0.98]
Wilske 1993 (late) (OGP-ELISA) (serum)	10	4	33	138	0.23 [0.12, 0.39]	0.97 [0.93, 0.99]

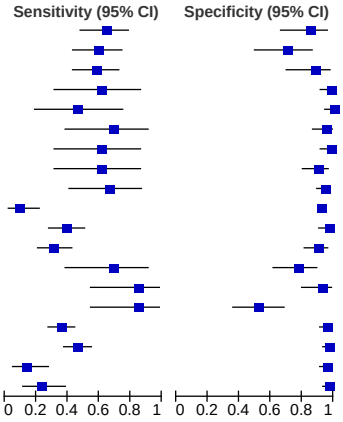


Figure 78: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (flagella) (serum)	10	0	32	27	0.24 [0.12, 0.39]	1.00 [0.87, 1.00]
Flisiak 1996 (recombinant) (serum)	12	0	30	27	0.29 [0.16, 0.45]	1.00 [0.87, 1.00]
Flisiak 1998 (serum)	22	0	26	26	0.46 [0.31, 0.61]	1.00 [0.87, 1.00]
Goossens 2000 (late) (Behring) (serum)	12	9	1	53	0.92 [0.64, 1.00]	0.85 [0.74, 0.93]
Goossens 2000 (late) (Boehring) (serum)	7	7	6	55	0.54 [0.25, 0.81]	0.89 [0.78, 0.95]
Goossens 2000 (late) (Dako) (serum)	10	2	3	60	0.77 [0.46, 0.95]	0.97 [0.89, 1.00]
Goossens 2000 (late) (Genzyme Virotech) (serum)	12	4	1	58	0.92 [0.64, 1.00]	0.94 [0.84, 0.98]
Goossens 2000 (late) (IBL) (serum)	9	8	4	54	0.69 [0.39, 0.91]	0.87 [0.76, 0.94]
Hernandez-Novoa 2003 (disseminated) (serum)	4	55	14	74	0.22 [0.06, 0.48]	0.57 [0.48, 0.66]
Hunfeld 2002 (serum)	40	60	3	1047	0.93 [0.81, 0.99]	0.95 [0.93, 0.96]
Nohlmans 1994 (late) (Dako) (serum)	18	1	3	83	0.86 [0.64, 0.97]	0.99 [0.94, 1.00]
Nohlmans 1994 (late) (Diagast) (serum)	18	0	3	84	0.86 [0.64, 0.97]	1.00 [0.96, 1.00]
Smismans 2006 (purified) (serum)	13	0	9	40	0.59 [0.36, 0.79]	1.00 [0.91, 1.00]
Smismans 2006 (synthetic C6) (serum)	20	3	2	37	0.91 [0.71, 0.99]	0.93 [0.80, 0.98]
Smismans 2006 (whole-cell) (serum)	20	3	2	37	0.91 [0.71, 0.99]	0.93 [0.80, 0.98]
Wilske 1993 (all Lyme) (flagellin) (serum)	95	9	39	133	0.71 [0.62, 0.78]	0.94 [0.88, 0.97]
Wilske 1993 (all Lyme) (OGP-ELISA) (serum)	80	4	54	138	0.60 [0.51, 0.68]	0.97 [0.93, 0.99]
Wilske 1993 (flagellin) (serum)	38	9	5	133	0.88 [0.75, 0.96]	0.94 [0.88, 0.97]
Wilske 1993 (OGP-ELISA) (serum)	43	4	0	138	1.00 [0.92, 1.00]	0.97 [0.93, 0.99]

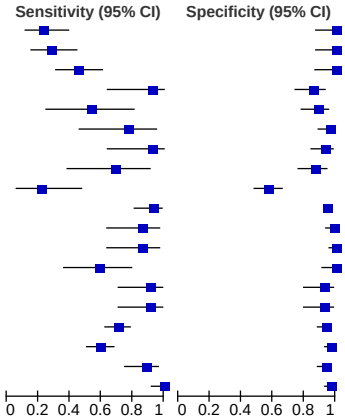


Figure 79: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010 (serum)	56	8	0	187	1.00 [0.94, 1.00]	0.96 [0.92, 0.98]
Branda 2011 (early disseminated) (serum)	26	21	0	1279	1.00 [0.87, 1.00]	0.98 [0.98, 0.99]
Branda 2011 (late) (serum)	29	21	0	1279	1.00 [0.88, 1.00]	0.98 [0.98, 0.99]
Flisiak 1996 (flagella) (serum)	32	4	10	23	0.76 [0.61, 0.88]	0.85 [0.66, 0.96]
Flisiak 1996 (recombinant) (serum)	34	8	8	19	0.81 [0.66, 0.91]	0.70 [0.50, 0.86]
Flisiak 1998 (serum)	37	3	11	23	0.77 [0.63, 0.88]	0.88 [0.70, 0.98]
Gomes-Solecki 2001 (whole-cell) (serum)	85	5	35	95	0.71 [0.62, 0.79]	0.95 [0.89, 0.98]
Goossens 2000 (late) (Milenia) (serum)	9	3	4	59	0.69 [0.39, 0.91]	0.95 [0.87, 0.99]
Hernandez-Novoa 2003 (disseminated) (serum)	14	0	4	0	0.78 [0.52, 0.94]	Not estimable
Hunfeld 2002 (serum)	41	0	2	0	0.95 [0.84, 0.99]	Not estimable
Johnson 1996 (serum)	75	5	36	108	0.68 [0.58, 0.76]	0.96 [0.90, 0.99]
Jovicic 2003 (serum)	63	8	31	112	0.67 [0.57, 0.76]	0.93 [0.87, 0.97]
Ledue 2008 (early disseminated) (serum)	33	17	8	790	0.80 [0.65, 0.91]	0.98 [0.97, 0.99]
Molins 2014 (serum)	106	14	18	189	0.85 [0.78, 0.91]	0.93 [0.89, 0.96]
Molins 2015 (early Lyme) (serum)	101	2	79	156	0.56 [0.49, 0.63]	0.99 [0.96, 1.00]
Molins 2016 (serum)	100	5	24	198	0.81 [0.73, 0.87]	0.98 [0.94, 0.99]
Nohlmans 1994 (late) (Diamedix) (serum)	18	0	3	84	0.86 [0.64, 0.97]	1.00 [0.96, 1.00]
Nohlmans 1994 (late) (Whittaker) (serum)	15	0	6	84	0.71 [0.48, 0.89]	1.00 [0.96, 1.00]
Oksi 1995 (flagella) (serum)	17	5	24	32	0.41 [0.26, 0.58]	0.86 [0.71, 0.95]
Oksi 1995 (recombinant) (serum)	6	2	35	35	0.15 [0.06, 0.29]	0.95 [0.82, 0.99]
Oksi 1995 (sonicated) (serum)	32	4	9	33	0.78 [0.62, 0.89]	0.89 [0.75, 0.97]
Smismans 2006 (purified) (serum)	20	9	2	31	0.91 [0.71, 0.99]	0.78 [0.62, 0.89]
Smismans 2006 (synthetic C6) (serum)	20	3	2	37	0.91 [0.71, 0.99]	0.93 [0.80, 0.98]
Smismans 2006 (whole-cell) (serum)	22	20	0	20	1.00 [0.85, 1.00]	0.50 [0.34, 0.66]
Steere 2008 (acute disseminated) (serum)	13	5	0	131	1.00 [0.75, 1.00]	0.96 [0.92, 0.99]
Steere 2008 (chronic disseminated) (serum)	31	5	0	131	1.00 [0.89, 1.00]	0.96 [0.92, 0.99]

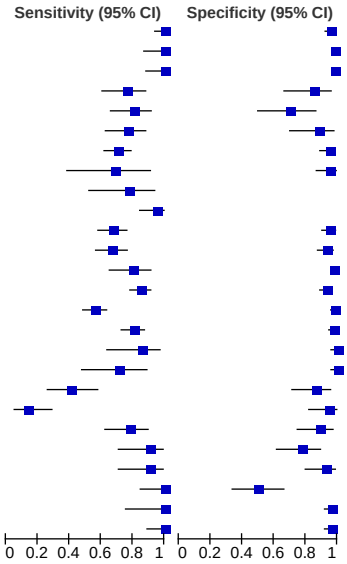


Figure 80: ELFA

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Flisiak 1996 (serum)	33	2	9	25	0.79 [0.63, 0.90]	0.93 [0.76, 0.99]
Flisiak 1998 (serum)	39	2	9	24	0.81 [0.67, 0.91]	0.92 [0.75, 0.99]

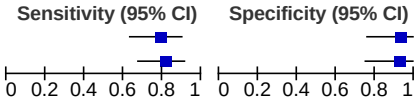


Figure 81: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010 (serum)	28	0	28	195	0.50 [0.36, 0.64]	1.00 [0.98, 1.00]
Goossens 2000 (late) (Genzyme Virotech) (serum)	8	7	5	55	0.62 [0.32, 0.86]	0.89 [0.78, 0.95]
Goossens 2000 (late) (MRL) (serum)	7	1	6	61	0.54 [0.25, 0.81]	0.98 [0.91, 1.00]
Molins 2014 (serum)	57	4	67	199	0.46 [0.37, 0.55]	0.98 [0.95, 0.99]
Molins 2015 (early Lyme) (serum)	60	5	120	153	0.33 [0.26, 0.41]	0.97 [0.93, 0.99]
Molins 2016 (serum)	81	12	43	191	0.65 [0.56, 0.74]	0.94 [0.90, 0.97]
Wilske 1993 (all Lyme) (OspC-blot) (serum)	58	4	76	138	0.43 [0.35, 0.52]	0.97 [0.93, 0.99]
Wilske 1993 (all Lyme) (p100-blot) (serum)	17	1	117	141	0.13 [0.08, 0.20]	0.99 [0.96, 1.00]
Wilske 1993 (all Lyme) (p41/i-blot) (serum)	20	1	114	141	0.15 [0.09, 0.22]	0.99 [0.96, 1.00]
Wilske 1993 (late) (OspC-blot) (serum)	17	4	26	138	0.40 [0.25, 0.56]	0.97 [0.93, 0.99]
Wilske 1993 (late) (p100-blot) (serum)	8	1	35	141	0.19 [0.08, 0.33]	0.99 [0.96, 1.00]
Wilske 1993 (late) (p41/i-blot) (serum)	5	1	38	141	0.12 [0.04, 0.25]	0.99 [0.96, 1.00]

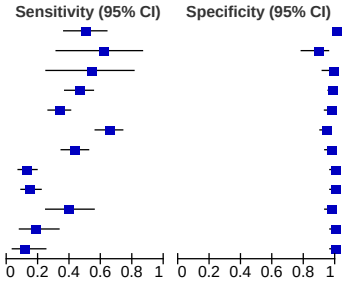


Figure 82: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010 (serum)	48	1	8	194	0.86 [0.74, 0.94]	0.99 [0.97, 1.00]
Flisiak 1998 (serum)	24	0	24	26	0.50 [0.35, 0.65]	1.00 [0.87, 1.00]
Goettner 2005 (line blot) (serum)	69	0	16	110	0.81 [0.71, 0.89]	1.00 [0.97, 1.00]
Goettner 2005 (line plut plus) (serum)	72	1	13	109	0.85 [0.75, 0.92]	0.99 [0.95, 1.00]
Goettner 2005 (WB) (serum)	60	1	25	109	0.71 [0.60, 0.80]	0.99 [0.95, 1.00]
Goossens 2000 (late) (Genzyme Virotech) (serum)	6	11	7	51	0.46 [0.19, 0.75]	0.82 [0.70, 0.91]
Goossens 2000 (late) (MRL) (serum)	6	2	7	60	0.46 [0.19, 0.75]	0.97 [0.89, 1.00]
Klempner 2001 (serum)	14	0	7	10	0.67 [0.43, 0.85]	1.00 [0.69, 1.00]
Molins 2014 (serum)	58	2	66	201	0.47 [0.38, 0.56]	0.99 [0.96, 1.00]
Molins 2015 (early Lyme) (serum)	7	0	173	158	0.04 [0.02, 0.08]	1.00 [0.98, 1.00]
Molins 2016 (serum)	53	3	71	200	0.43 [0.34, 0.52]	0.99 [0.96, 1.00]
Wilske 1993 (all Lyme) (OspC-blot) (serum)	19	1	115	141	0.14 [0.09, 0.21]	0.99 [0.96, 1.00]
Wilske 1993 (all Lyme) (p100-blot) (serum)	68	9	66	133	0.51 [0.42, 0.59]	0.94 [0.88, 0.97]
Wilske 1993 (all Lyme) (p41/i-blot) (serum)	43	6	91	136	0.32 [0.24, 0.41]	0.96 [0.91, 0.98]
Wilske 1993 (late) (OspC-blot) (serum)	7	1	36	141	0.16 [0.07, 0.31]	0.99 [0.96, 1.00]
Wilske 1993 (late) (p100-blot) (serum)	43	9	0	133	1.00 [0.92, 1.00]	0.94 [0.88, 0.97]
Wilske 1993 (late) (p41/i-blot) (serum)	26	6	17	136	0.60 [0.44, 0.75]	0.96 [0.91, 0.98]
Wilske 1999 (late) (recomb - new) (serum)	38	3	1	136	0.97 [0.87, 1.00]	0.98 [0.94, 1.00]
Wilske 1999 (late) (recomb - old) (serum)	29	3	10	136	0.74 [0.58, 0.87]	0.98 [0.94, 1.00]
Wilske 1999 (late) (whole-cell) (serum)	39	3	0	136	1.00 [0.91, 1.00]	0.98 [0.94, 1.00]

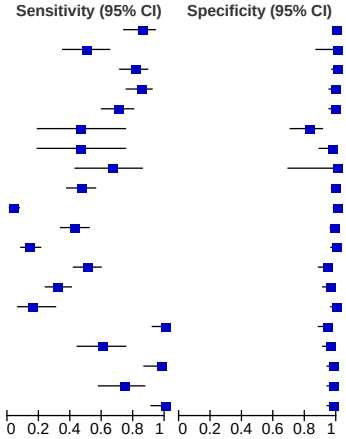


Figure 83: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010 (serum)	55	1	1	194	0.98 [0.90, 1.00]	0.99 [0.97, 1.00]
Grodzicki 1988 (acute) (serum)	16	0	14	20	0.53 [0.34, 0.72]	1.00 [0.83, 1.00]
Grodzicki 1988 (convalescent) (serum)	25	0	5	20	0.83 [0.65, 0.94]	1.00 [0.83, 1.00]
Jovicic 2003 (serum)	87	5	7	115	0.93 [0.85, 0.97]	0.96 [0.91, 0.99]
Molins 2014 (serum)	90	6	34	197	0.73 [0.64, 0.80]	0.97 [0.94, 0.99]
Molins 2015 (early Lyme) (serum)	15	0	165	158	0.08 [0.05, 0.13]	1.00 [0.98, 1.00]
Molins 2016 (serum)	96	15	28	188	0.77 [0.69, 0.84]	0.93 [0.88, 0.96]

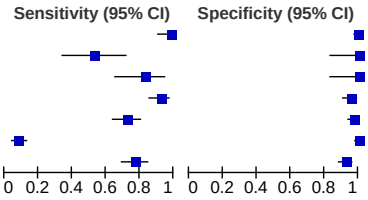


Figure 84: CLIA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ledue 2008 (early disseminated) (serum)	31	16	10	791	0.76 [0.60, 0.88]	0.98 [0.97, 0.99]
Molins 2015 (early Lyme) (serum)	110	14	70	144	0.61 [0.54, 0.68]	0.91 [0.86, 0.95]

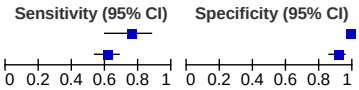


Figure 85: IFA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cerar 2006 (chronic LB over 6mo) (serum)	3	0	18	49	0.14 [0.03, 0.36]	1.00 [0.93, 1.00]
Cerar 2006 (early LB under 6mo) (serum)	6	0	54	49	0.10 [0.04, 0.21]	1.00 [0.93, 1.00]
Wilske 1993 (all Lyme) (IFA-ABS) (serum)	31	4	103	138	0.23 [0.16, 0.31]	0.97 [0.93, 0.99]
Wilske 1993 (late) (IFA-ABS) (serum)	2	4	41	138	0.05 [0.01, 0.16]	0.97 [0.93, 0.99]

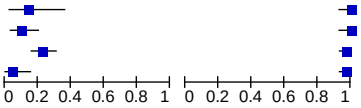


Figure 86: IFA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Cerar 2006 (chronic LB over 6mo) (serum)	21	9	0	40	1.00 [0.84, 1.00]	0.82 [0.68, 0.91]
Cerar 2006 (early LB under 6mo) (serum)	35	9	25	40	0.58 [0.45, 0.71]	0.82 [0.68, 0.91]
Hanrahan 1984 (titer 1:128) (serum)	88	1	72	328	0.55 [0.47, 0.63]	1.00 [0.98, 1.00]
Hanrahan 1984 (titer 1:256) (serum)	57	0	103	329	0.36 [0.28, 0.44]	1.00 [0.99, 1.00]
Hanrahan 1984 (titer 1:64) (serum)	112	10	48	319	0.70 [0.62, 0.77]	0.97 [0.94, 0.99]
Wilske 1993 (all Lyme) (IFA-ABS) (serum)	102	4	32	138	0.76 [0.68, 0.83]	0.97 [0.93, 0.99]
Wilske 1993 (late) (IFA-ABS) (serum)	43	4	0	138	1.00 [0.92, 1.00]	0.97 [0.93, 0.99]

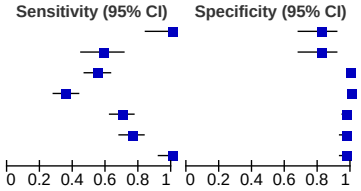


Figure 87: IFA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jovicic 2003 (serum)	34	13	60	107	0.36 [0.27, 0.47]	0.89 [0.82, 0.94]

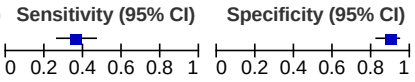


Figure 88: Recombinant Rapid Assay

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gomes-Solecki 2001 (recombinant) (serum)	87	3	33	97	0.72 [0.64, 0.80]	0.97 [0.91, 0.99]

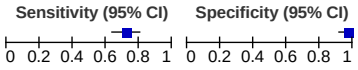


Figure 89: PCR

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Liebling 1993 (CSF)	13	1	0	14	1.00 [0.75, 1.00]	0.93 [0.68, 1.00]
Liebling 1993 (serum)	13	0	9	6	0.59 [0.36, 0.79]	1.00 [0.54, 1.00]
Liebling 1993 (SF)	4	0	1	22	0.80 [0.28, 0.99]	1.00 [0.85, 1.00]
Liebling 1993 (urine)	3	1	0	12	1.00 [0.29, 1.00]	0.92 [0.64, 1.00]

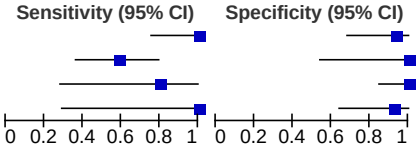


Figure 90: CD57

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Stricker 2001 (acute LD)	0	4	10	18	0.00 [0.00, 0.31]	0.82 [0.60, 0.95]
Stricker 2001 (chronic LD)	31	4	0	18	1.00 [0.89, 1.00]	0.82 [0.60, 0.95]

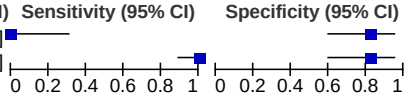


Figure 91: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Phillips 1998 (blood)	43	0	4	23	0.91 [0.80, 0.98]	1.00 [0.85, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

Figure 92: Lymphocyte transformation test

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
von Baehr 2012 (stimulation index 3+) (venous)	84	2	10	158	0.89 [0.81, 0.95]	0.99 [0.96, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

1 E.1.2.7 Post-treatment Lyme Disease Syndrome

Figure 93: ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab) (serum)	25	3	12	37	0.68 [0.50, 0.82]	0.93 [0.80, 0.98]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Fallon 2014 (speciality lab A) (serum)	25	1	12	39	0.68 [0.50, 0.82]	0.97 [0.87, 1.00]		
Fallon 2014 (speciality lab B) (serum)	25	3	12	37	0.68 [0.50, 0.82]	0.93 [0.80, 0.98]		
Fallon 2014 (university reference) (serum)	23	5	14	35	0.62 [0.45, 0.78]	0.88 [0.73, 0.96]		

Figure 94: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab) (serum)	6	0	31	40	0.16 [0.06, 0.32]	1.00 [0.91, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Fallon 2014 (speciality lab A) (serum)	1	1	36	39	0.03 [0.00, 0.14]	0.97 [0.87, 1.00]		
Fallon 2014 (speciality lab B) (serum)	16	8	21	32	0.43 [0.27, 0.61]	0.80 [0.64, 0.91]		
Fallon 2014 (university reference) (serum)	8	5	29	35	0.22 [0.10, 0.38]	0.88 [0.73, 0.96]		
Porwancher 2011 (serum)	13	0	21	0	0.38 [0.22, 0.56]	Not estimable		

Figure 95: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab) (serum)	16	0	21	40	0.43 [0.27, 0.61]	1.00 [0.91, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Fallon 2014 (speciality lab A) (serum)	16	0	21	40	0.43 [0.27, 0.61]	1.00 [0.91, 1.00]		
Fallon 2014 (speciality lab B) (serum)	18	3	19	37	0.49 [0.32, 0.66]	0.93 [0.80, 0.98]		
Fallon 2014 (university reference) (serum)	21	1	16	39	0.57 [0.39, 0.73]	0.97 [0.87, 1.00]		
Porwancher 2011 (serum)	17	0	17	0	0.50 [0.32, 0.68]	Not estimable		

Figure 96: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Porwancher 2011 (serum)	23	21	11	429	0.68 [0.49, 0.83]	0.95 [0.93, 0.97]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1

2 E.1.2.8 Analyses by time point (<6 weeks, 6 weeks to 6 months, >6 months)

Figure 97: Less than 6 weeks – ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1988 (NB) (flagellum) (CSF)	38	0	5	106	0.88 [0.75, 0.96]	1.00 [0.97, 1.00]	0 0.2 0.4 0.6 0.8 1	0 0.2 0.4 0.6 0.8 1
Hansen 1988 (NB) (flagellum) (serum)	22	10	21	305	0.51 [0.35, 0.67]	0.97 [0.94, 0.98]		
Hansen 1988 (NB) (sonic extract) (CSF)	35	0	8	106	0.81 [0.67, 0.92]	1.00 [0.97, 1.00]		
Hansen 1988 (NB) (sonic extract) (serum)	17	10	26	305	0.40 [0.25, 0.56]	0.97 [0.94, 0.98]		
Hansen 1991 (EM) (serum)	13	0	24	200	0.35 [0.20, 0.53]	1.00 [0.98, 1.00]		
Hansen 1991 (NB) (serum)	32	0	38	200	0.46 [0.34, 0.58]	1.00 [0.98, 1.00]		
Hansen 1991a (NB) (CSF)	50	0	20	29	0.71 [0.59, 0.82]	1.00 [0.88, 1.00]		
Hansen 1991a (NB) (serum)	43	0	27	29	0.61 [0.49, 0.73]	1.00 [0.88, 1.00]		
Karlsson 1989 (NB) (serum)	20	1	35	43	0.36 [0.24, 0.50]	0.98 [0.88, 1.00]		
Karlsson 1989a (EM) (capture) (serum)	8	2	20	71	0.29 [0.13, 0.49]	0.97 [0.90, 1.00]		
Karlsson 1989a (EM) (indirect) (serum)	7	7	21	66	0.25 [0.11, 0.45]	0.90 [0.81, 0.96]		
Karlsson 1989a (NB) (capture) (serum)	17	2	10	71	0.63 [0.42, 0.81]	0.97 [0.90, 1.00]		
Karlsson 1989a (NB) (indirect) (serum)	12	7	15	66	0.44 [0.25, 0.65]	0.90 [0.81, 0.96]		
Marangoni 2005 (EM) (Enzygnost) (serum)	52	9	23	225	0.69 [0.58, 0.79]	0.96 [0.93, 0.98]		
Marangoni 2005 (EM) (RecomWell) (serum)	42	0	33	234	0.56 [0.44, 0.67]	1.00 [0.98, 1.00]		
Padula 1994 (EM) (recombinant) (serum)	29	0	10	76	0.74 [0.58, 0.87]	1.00 [0.95, 1.00]		
Padula 1994 (EM) (whole-cell) (serum)	25	0	14	76	0.64 [0.47, 0.79]	1.00 [0.95, 1.00]		

Figure 98: Less than 6 weeks – ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1988 (NB) (flagellum) (CSF)	25	0	18	106	0.58 [0.42, 0.73]	1.00 [0.97, 1.00]
Hansen 1988 (NB) (flagellum) (serum)	30	9	13	306	0.70 [0.54, 0.83]	0.97 [0.95, 0.99]
Hansen 1988 (NB) (sonic extract) (CSF)	22	0	21	106	0.51 [0.35, 0.67]	1.00 [0.97, 1.00]
Hansen 1988 (NB) (sonic extract) (serum)	12	13	31	302	0.28 [0.15, 0.44]	0.96 [0.93, 0.98]
Hansen 1991 (EM) (serum)	8	0	29	200	0.22 [0.10, 0.38]	1.00 [0.98, 1.00]
Hansen 1991 (NB) (serum)	54	0	16	200	0.77 [0.66, 0.86]	1.00 [0.98, 1.00]
Hansen 1991a (NB) (CSF)	59	2	11	27	0.84 [0.74, 0.92]	0.93 [0.77, 0.99]
Hansen 1991a (NB) (serum)	54	1	16	28	0.77 [0.66, 0.86]	0.97 [0.82, 1.00]
Karlsson 1989 (NB) (serum)	15	3	40	41	0.27 [0.16, 0.41]	0.93 [0.81, 0.99]
Marangoni 2005 (EM) (Enzygnost) (serum)	52	27	23	207	0.69 [0.58, 0.79]	0.88 [0.84, 0.92]
Marangoni 2005 (EM) (RecomWell) (serum)	38	7	37	227	0.51 [0.39, 0.62]	0.97 [0.94, 0.99]

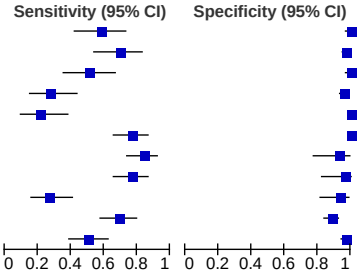


Figure 99: Less than 6 weeks – ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (serum)	28	4	27	40	0.51 [0.37, 0.65]	0.91 [0.78, 0.97]
Marangoni 2005 (EM) (Enzygnost) (serum)	57	36	18	198	0.76 [0.65, 0.85]	0.85 [0.79, 0.89]
Marangoni 2005 (EM) (Quick C6)	43	8	32	226	0.57 [0.45, 0.69]	0.97 [0.93, 0.99]
Marangoni 2005 (EM) (RecomWell) (serum)	51	7	24	227	0.68 [0.56, 0.78]	0.97 [0.94, 0.99]

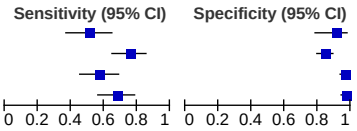


Figure 100: Less than 6 weeks – Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (serum)	37	5	18	39	0.67 [0.53, 0.79]	0.89 [0.75, 0.96]
Padula 1994 (EM) (serum)	28	2	11	74	0.72 [0.55, 0.85]	0.97 [0.91, 1.00]

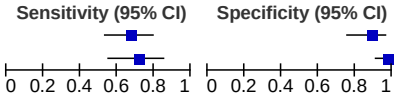


Figure 101: Less than 6 weeks – Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (serum)	32	5	23	39	0.58 [0.44, 0.71]	0.89 [0.75, 0.96]

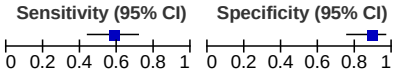


Figure 102: Less than 6 weeks – Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (serum)	41	8	14	36	0.75 [0.61, 0.85]	0.82 [0.67, 0.92]

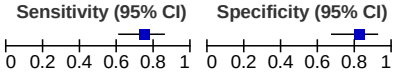


Figure 103: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sapi 2013 (blood)	34	0	38	48	0.47 [0.35, 0.59]	1.00 [0.93, 1.00]

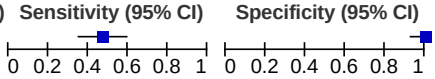


Figure 104: 6 weeks to 6 months – ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1988 (NB) (flagellum) (CSF)	11	0	2	106	0.85 [0.55, 0.98]	1.00 [0.97, 1.00]
Hansen 1988 (NB) (flagellum) (serum)	6	10	7	305	0.46 [0.19, 0.75]	0.97 [0.94, 0.98]
Hansen 1988 (NB) (sonic extract) (CSF)	12	0	1	106	0.92 [0.64, 1.00]	1.00 [0.97, 1.00]
Hansen 1988 (NB) (sonic extract) (serum)	3	10	10	305	0.23 [0.05, 0.54]	0.97 [0.94, 0.98]
Hansen 1991 (EM) (serum)	3	0	10	200	0.23 [0.05, 0.54]	1.00 [0.98, 1.00]
Hansen 1991 (NB) (serum)	5	0	25	200	0.17 [0.06, 0.35]	1.00 [0.98, 1.00]
Hansen 1991a (NB) (CSF)	16	0	3	29	0.84 [0.60, 0.97]	1.00 [0.88, 1.00]
Hansen 1991a (NB) (serum)	11	0	8	29	0.58 [0.33, 0.80]	1.00 [0.88, 1.00]
Kaiser 1999 (NB) (less than 6 months) (serum)	49	8	32	72	0.60 [0.49, 0.71]	0.90 [0.81, 0.96]
Karlsson 1989 (NB) (over 6 weeks) (serum)	3	1	10	43	0.23 [0.05, 0.54]	0.98 [0.88, 1.00]
Karlsson 1989a (EM) (capture) (serum)	2	2	0	71	1.00 [0.16, 1.00]	0.97 [0.90, 1.00]
Karlsson 1989a (EM) (indirect) (serum)	1	7	1	66	0.50 [0.01, 0.99]	0.90 [0.81, 0.96]
Karlsson 1989a (NB) (capture) (serum)	3	2	7	71	0.30 [0.07, 0.65]	0.97 [0.90, 1.00]
Karlsson 1989a (NB) (indirect) (serum)	2	7	8	66	0.20 [0.03, 0.56]	0.90 [0.81, 0.96]
Marangoni 2005 (EM) (Enzygnost) (serum)	15	9	5	225	0.75 [0.51, 0.91]	0.96 [0.93, 0.98]
Marangoni 2005 (EM) (RecomWell) (serum)	11	0	9	234	0.55 [0.32, 0.77]	1.00 [0.98, 1.00]
Padula 1994 (EM) (recombinant) (serum)	10	0	5	76	0.67 [0.38, 0.88]	1.00 [0.95, 1.00]
Padula 1994 (EM) (whole-cell) (serum)	12	0	3	76	0.80 [0.52, 0.96]	1.00 [0.95, 1.00]

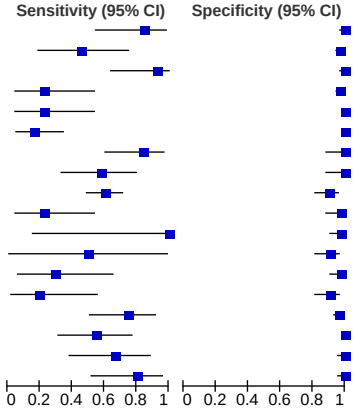


Figure 105: 6 weeks to 6 months – ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1988 (NB) (flagellum) (CSF)	12	0	1	106	0.92 [0.64, 1.00]	1.00 [0.97, 1.00]
Hansen 1988 (NB) (flagellum) (serum)	13	9	0	306	1.00 [0.75, 1.00]	0.97 [0.95, 0.99]
Hansen 1988 (NB) (sonic extract) (CSF)	13	0	0	106	1.00 [0.75, 1.00]	1.00 [0.97, 1.00]
Hansen 1988 (NB) (sonic extract) (serum)	11	13	2	302	0.85 [0.55, 0.98]	0.96 [0.93, 0.98]
Hansen 1991 (EM) (serum)	6	0	7	200	0.46 [0.19, 0.75]	1.00 [0.98, 1.00]
Hansen 1991 (NB) (serum)	30	0	0	200	1.00 [0.88, 1.00]	1.00 [0.98, 1.00]
Hansen 1991a (NB) (CSF)	19	2	0	27	1.00 [0.82, 1.00]	0.93 [0.77, 0.99]
Hansen 1991a (NB) (serum)	19	1	0	28	1.00 [0.82, 1.00]	0.97 [0.82, 1.00]
Kaiser 1999 (NB) (less than 6 months) (serum)	35	26	46	54	0.43 [0.32, 0.55]	0.68 [0.56, 0.78]
Karlsson 1989 (NB) (over 6 weeks) (serum)	11	3	2	41	0.85 [0.55, 0.98]	0.93 [0.81, 0.99]
Marangoni 2005 (EM) (Enzygnost) (serum)	9	27	11	207	0.45 [0.23, 0.68]	0.88 [0.84, 0.92]
Marangoni 2005 (EM) (RecomWell) (serum)	17	7	3	227	0.85 [0.62, 0.97]	0.97 [0.94, 0.99]

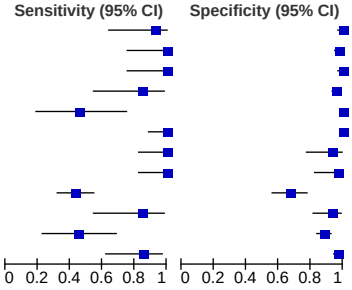


Figure 106: 6 weeks to 6 months – ELISA (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (over 6 weeks) (serum)	12	4	1	40	0.92 [0.64, 1.00]	0.91 [0.78, 0.97]
Marangoni 2005 (EM) (Enzygnost) (serum)	17	36	3	198	0.85 [0.62, 0.97]	0.85 [0.79, 0.89]
Marangoni 2005 (EM) (Quick C6)	16	8	4	226	0.80 [0.56, 0.94]	0.97 [0.93, 0.99]
Marangoni 2005 (EM) (RecomWell) (serum)	19	7	1	227	0.95 [0.75, 1.00]	0.97 [0.94, 0.99]

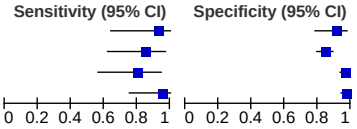


Figure 107: 6 weeks to 6 months – Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (over 6 weeks) (serum)	9	5	4	39	0.69 [0.39, 0.91]	0.89 [0.75, 0.96]
Padula 1994 (EM) (serum)	13	2	2	74	0.87 [0.60, 0.98]	0.97 [0.91, 1.00]

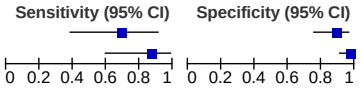


Figure 108: 6 weeks to 6 months – Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (over 6 weeks) (serum)	12	5	1	39	0.92 [0.64, 1.00]	0.89 [0.75, 0.96]

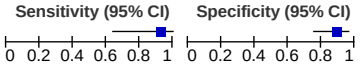


Figure 109: 6 weeks to 6 months – Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Karlsson 1989 (NB) (over 6 weeks) (serum)	12	8	1	36	0.92 [0.64, 1.00]	0.82 [0.67, 0.92]

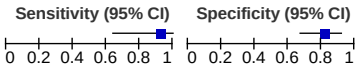


Figure 110: 6 weeks to 6 months: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sapi 2013 (16 weeks) (blood)	68	0	4	48	0.94 [0.86, 0.98]	1.00 [0.93, 1.00]
Sapi 2013 (8 weeks) (blood)	60	0	12	48	0.83 [0.73, 0.91]	1.00 [0.93, 1.00]

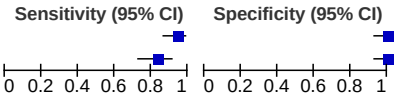


Figure 111: More than 6 months – ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1991a (NB) (CSF)	1	0	10	29	0.09 [0.00, 0.41]	1.00 [0.88, 1.00]
Hansen 1991a (NB) (serum)	2	0	9	29	0.18 [0.02, 0.52]	1.00 [0.88, 1.00]
Kaiser 1999 (NB) (over 6 months) (serum)	2	8	13	72	0.13 [0.02, 0.40]	0.90 [0.81, 0.96]

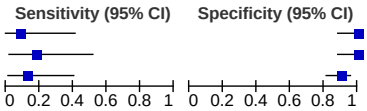
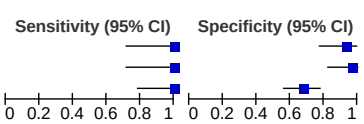


Figure 112: More than 6 months – ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hansen 1991a (NB) (CSF)	11	2	0	27	1.00 [0.72, 1.00]	0.93 [0.77, 0.99]
Hansen 1991a (NB) (serum)	11	1	0	28	1.00 [0.72, 1.00]	0.97 [0.82, 1.00]
Kaiser 1999 (NB) (over 6 months) (serum)	15	26	0	54	1.00 [0.78, 1.00]	0.68 [0.56, 0.78]



E.2 Initial tests: Coupled sensitivity and specificity forest plots for children

E.2.1 Evidence from cross-sectional studies

E.2.1.1 Erythema migrans (EM)

Figure 113: ELISA (IgM)

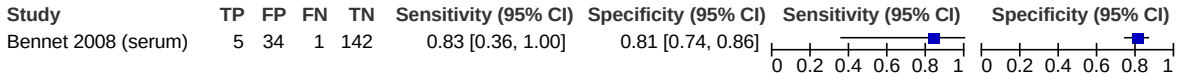
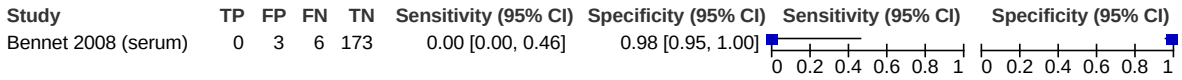


Figure 114: ELISA (IgG)



E.2.1.2 Neuroborreliosis

Figure 115: ELISA (IgM)

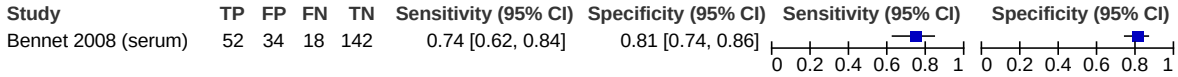


Figure 116: ELISA (IgG)

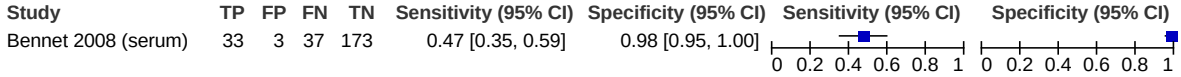


Figure 117: PCR – Lyme meningitis only

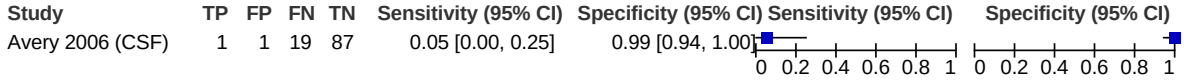


Figure 118: ELISA (IgM) – facial palsy only

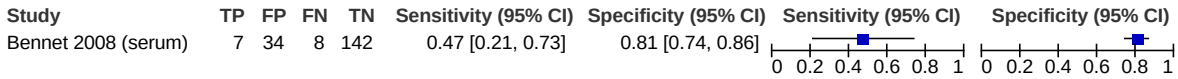


Figure 119: ELISA (IgG) – facial palsy only

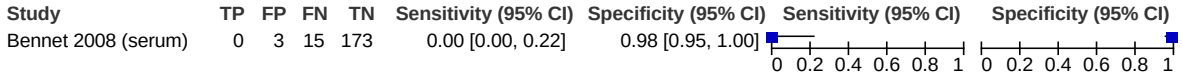
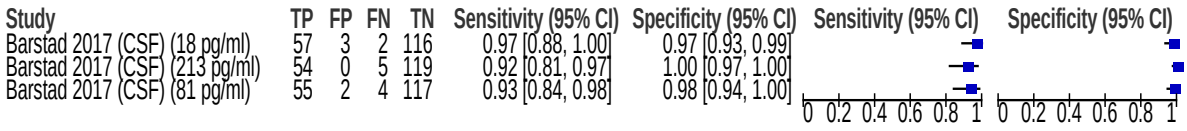


Figure 120: CXCL13



1 E.2.1.3 Unspecified Lyme disease

Figure 121: ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lipsett 2016 (serum)	91	48	23	782	0.80 [0.71, 0.87]	0.94 [0.92, 0.96]

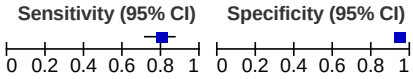
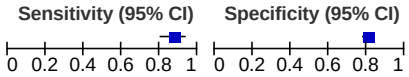


Figure 122: ELISA WCS

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lipsett 2016 (serum)	100	160	14	670	0.88 [0.80, 0.93]	0.81 [0.78, 0.83]



2 E.2.2 Evidence from case-control studies

3 E.2.2.1 Erythema migrans (EM)

Figure 123: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gerber 1995 (rOspC) (serum)	38	1	44	49	0.46 [0.35, 0.58]	0.98 [0.89, 1.00]
Gerber 1995 (whole-cell) (serum)	23	0	59	50	0.28 [0.19, 0.39]	1.00 [0.93, 1.00]

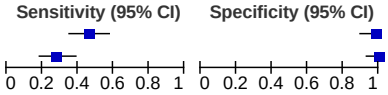
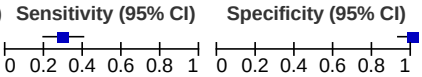


Figure 124: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gerber 1995 (serum)	24	0	58	50	0.29 [0.20, 0.40]	1.00 [0.93, 1.00]



4 E.2.2.2 Neuroborreliosis

Figure 125: ELISA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krbkova 2016 (recombinant) (CSF)	22	0	64	66	0.26 [0.17, 0.36]	1.00 [0.95, 1.00]
Krbkova 2016 (recombinant) (serum)	43	4	43	62	0.50 [0.39, 0.61]	0.94 [0.85, 0.98]
Krbkova 2016 (whole-cell) (CSF)	37	0	49	66	0.43 [0.32, 0.54]	1.00 [0.95, 1.00]
Krbkova 2016 (whole-cell) (serum)	47	11	39	55	0.55 [0.44, 0.65]	0.83 [0.72, 0.91]

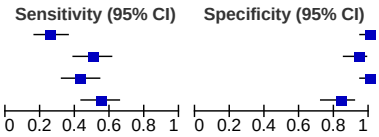


Figure 126: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krbkova 2016 (recombinant) (CSF)	69	2	17	64	0.80 [0.70, 0.88]	0.97 [0.89, 1.00]
Krbkova 2016 (recombinant) (serum)	75	12	11	54	0.87 [0.78, 0.93]	0.82 [0.70, 0.90]
Krbkova 2016 (whole-cell) (CSF)	55	0	31	66	0.64 [0.53, 0.74]	1.00 [0.95, 1.00]
Krbkova 2016 (whole-cell) (serum)	63	13	23	53	0.73 [0.63, 0.82]	0.80 [0.69, 0.89]
Skogman 2008 (recombinant) (CSF)	32	0	8	36	0.80 [0.64, 0.91]	1.00 [0.90, 1.00]

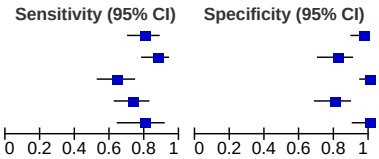


Figure 127: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krbkova 2016 (CSF)	11	0	75	66	0.13 [0.07, 0.22]	1.00 [0.95, 1.00]
Krbkova 2016 (serum)	31	2	55	64	0.36 [0.26, 0.47]	0.97 [0.89, 1.00]

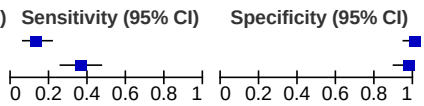


Figure 128: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krbkova 2016 (CSF)	31	2	55	64	0.36 [0.26, 0.47]	0.97 [0.89, 1.00]
Krbkova 2016 (serum)	47	6	39	60	0.55 [0.44, 0.65]	0.91 [0.81, 0.97]

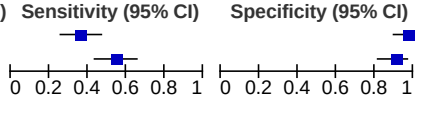
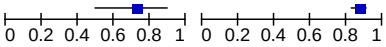


Figure 129: CXCL13

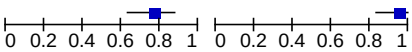
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wutte 2011 (serum) 100 pg/ml	16	39	6	261	0.73 [0.50, 0.89]	0.87 [0.83, 0.91]		



E.2.2.3 Lyme arthritis

Figure 130: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Heikkila 2002 (serum)	40	2	12	38	0.77 [0.63, 0.87]	0.95 [0.83, 0.99]		



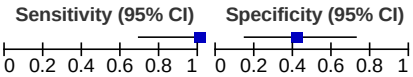
E.3 Confirmatory tests: Coupled sensitivity and specificity forest plots for adults

E.3.1 Evidence from cross-sectional studies

E.3.1.1 Unspecified Lyme Disease

Figure 131: Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Blaauw 1999 (serum)	10	7	0	5	1.00 [0.69, 1.00]	0.42 [0.15, 0.72]		



E.3.2 Evidence from case-control studies

E.3.2.1 Erythema migrans (EM)

Figure 132: ELISA (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Magnarelli 1992 (recombinant) (serum)	16	0	1	40	0.94 [0.71, 1.00]	1.00 [0.91, 1.00]		
Magnarelli 1992 (whole-cell) (serum)	17	0	0	40	1.00 [0.80, 1.00]	1.00 [0.91, 1.00]		

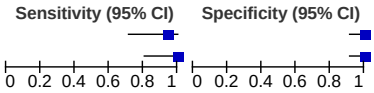


Figure 133: Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Christova 2003 (serum)	36	0	15	90	0.71 [0.56, 0.83]	1.00 [0.96, 1.00]		

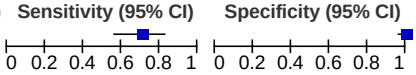


Figure 134: Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Christova 2003 (serum)	12	0	6	90	0.67 [0.41, 0.87]	1.00 [0.96, 1.00]		

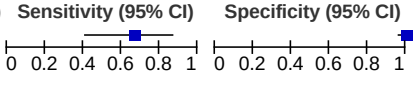


Figure 135: Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Trevejo 2001 (acute) (serum)	21	1	7	37	0.75 [0.55, 0.89]	0.97 [0.86, 1.00]		
Trevejo 2001 (convalescent) (serum)	16	1	27	37	0.37 [0.23, 0.53]	0.97 [0.86, 1.00]		

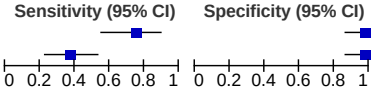


Figure 136: IFA (IgM)

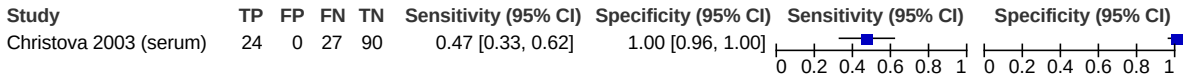
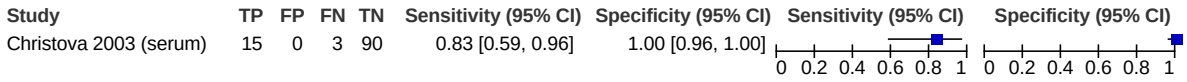
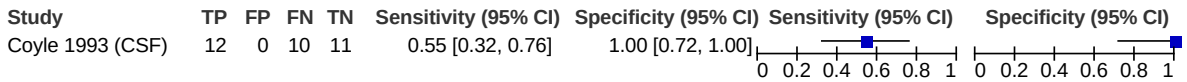


Figure 137: IFA (IgG)



E.3.2.2 Neuroborreliosis

Figure 138: Western blot/Immunoblot (IgG)



E.4 Confirmatory tests: Coupled sensitivity and specificity forest plots for children

E.4.1 Evidence from cross-sectional studies

None.

E.4.2 Evidence from case-control studies

None.

E.5 Combination of tests: Coupled sensitivity and specificity forest plots for adults

E.5.1 Evidence from cross-sectional studies

None.

1 E.5.2 Evidence from case-control studies

2 E.5.2.1 Erythema migrans (EM)

Figure 139: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015	40	0	18	90	0.69 [0.55, 0.80]	1.00 [0.96, 1.00]
Bacon 2003 (acute disseminated EM)	19	0	19	257	0.50 [0.33, 0.67]	1.00 [0.99, 1.00]
Bacon 2003 (acute single EM)	11	0	31	257	0.26 [0.14, 0.42]	1.00 [0.99, 1.00]
Bacon 2003 (early convalescent disseminated EM)	33	0	13	257	0.72 [0.57, 0.84]	1.00 [0.99, 1.00]
Bacon 2003 (early convalescent single EM)	38	0	22	257	0.63 [0.50, 0.75]	1.00 [0.99, 1.00]
Branda 2011	48	7	66	1293	0.42 [0.33, 0.52]	0.99 [0.99, 1.00]
Branda 2013 (European tests)	11	1	9	99	0.55 [0.32, 0.77]	0.99 [0.95, 1.00]
Branda 2013 (US tests)	4	0	16	100	0.20 [0.06, 0.44]	1.00 [0.96, 1.00]
Johnson 1996 (disseminated EM; FLA-ELISA + IB)	8	0	0	113	1.00 [0.63, 1.00]	1.00 [0.97, 1.00]
Johnson 1996 (localised EM; FLA-ELISA + IB)	29	0	21	113	0.58 [0.43, 0.72]	1.00 [0.97, 1.00]
Molins 2014 (EM acute phase)	16	2	24	201	0.40 [0.25, 0.57]	0.99 [0.96, 1.00]
Molins 2014 (EM convalescent phase)	23	2	15	201	0.61 [0.43, 0.76]	0.99 [0.96, 1.00]
Molins 2016 (EM acute)	19	4	21	199	0.47 [0.32, 0.64]	0.98 [0.95, 0.99]
Molins 2016 (EM convalescent)	24	4	14	199	0.63 [0.46, 0.78]	0.98 [0.95, 0.99]
Steere 2008 (EM acute with dissemination)	17	2	23	136	0.42 [0.27, 0.59]	0.99 [0.95, 1.00]
Steere 2008 (EM acute without dissemination)	6	2	30	136	0.17 [0.06, 0.33]	0.99 [0.95, 1.00]
Steere 2008 (EM convalescent no dissemination)	19	2	17	136	0.53 [0.35, 0.70]	0.99 [0.95, 1.00]
Steere 2008 (EM convalescent with dissemination)	30	2	10	136	0.75 [0.59, 0.87]	0.99 [0.95, 1.00]
Tevejo 2001 (acute phase simplified approach)	27	0	39	37	0.41 [0.29, 0.54]	1.00 [0.91, 1.00]
Trevejo 2001 (acute phase; CDC approach)	21	0	45	37	0.32 [0.21, 0.44]	1.00 [0.91, 1.00]
Trevejo 2001 (convalescent phase CDC approach)	16	0	39	37	0.29 [0.18, 0.43]	1.00 [0.91, 1.00]
Trevejo 2001 (convalescent; simplified approach)	39	0	16	37	0.71 [0.57, 0.82]	1.00 [0.91, 1.00]
Weiner 2015 (EM acute phase)	7	0	16	32	0.30 [0.13, 0.53]	1.00 [0.89, 1.00]
Weiner 2015 (EM convalscent phase)	18	0	5	32	0.78 [0.56, 0.93]	1.00 [0.89, 1.00]

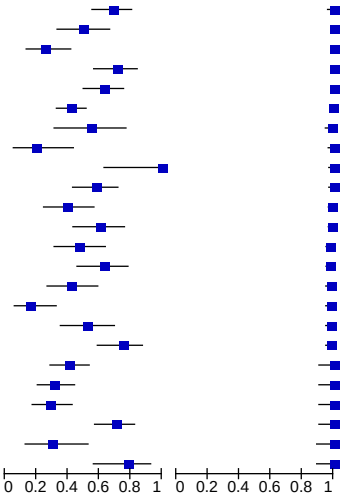


Figure 140: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015	42	0	24	104	0.64 [0.51, 0.75]	1.00 [0.97, 1.00]
Branda 2013 (US tests)	4	0	16	100	0.20 [0.06, 0.44]	1.00 [0.96, 1.00]
Molins 2016 (EM acute C6 + Marblot IB)	16	2	24	201	0.40 [0.25, 0.57]	0.99 [0.96, 1.00]
Molins 2016 (EM acute C6 + ViraStripe IB)	17	1	23	202	0.42 [0.27, 0.59]	1.00 [0.97, 1.00]
Molins 2016 (EM convalescent C6 + Marblot IB)	24	2	14	201	0.63 [0.46, 0.78]	0.99 [0.96, 1.00]
Molins 2016 (EM convalescent C6 + ViraStripe IB)	24	1	14	202	0.63 [0.46, 0.78]	1.00 [0.97, 1.00]

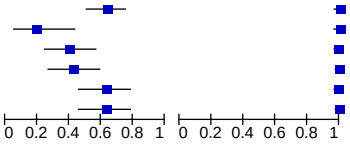


Figure 141: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2011	60	7	54	1293	0.53 [0.43, 0.62]	0.99 [0.99, 1.00]
Branda 2013 (US tests)	13	0	7	100	0.65 [0.41, 0.85]	1.00 [0.96, 1.00]
Molins 2016 (EM acute)	20	1	20	202	0.50 [0.34, 0.66]	1.00 [0.97, 1.00]
Molins 2016 (EM convalescent)	30	1	8	202	0.79 [0.63, 0.90]	1.00 [0.97, 1.00]

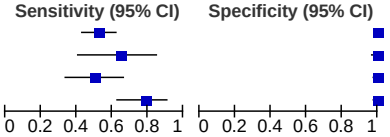


Figure 142: ELISA WCS and Immunoblot (VIsE)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016 (EM acute)	19	1	21	202	0.47 [0.32, 0.64]	1.00 [0.97, 1.00]
Molins 2016 (EM convalescent)	28	1	10	202	0.74 [0.57, 0.87]	1.00 [0.97, 1.00]

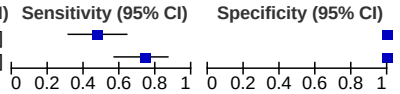


Figure 143: ELISA (IgM/IgG) and Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (EM acute phase)	12	1	28	202	0.30 [0.17, 0.47]	1.00 [0.97, 1.00]
Molins 2014 (EM convalescent phase)	20	1	18	202	0.53 [0.36, 0.69]	1.00 [0.97, 1.00]
Steere 2008 (EM acute with dissemination)	15	1	25	136	0.38 [0.23, 0.54]	0.99 [0.96, 1.00]
Steere 2008 (EM acute without dissemination)	4	1	32	136	0.11 [0.03, 0.26]	0.99 [0.96, 1.00]
Steere 2008 (EM convalescent no dissemination)	14	1	22	136	0.39 [0.23, 0.57]	0.99 [0.96, 1.00]
Steere 2008 (EM convalescent with dissemination)	28	1	12	136	0.70 [0.53, 0.83]	0.99 [0.96, 1.00]
Weiner 2015 (EM acute phase)	7	0	16	0	0.30 [0.13, 0.53]	Not estimable
Weiner 2015 (EM convalscent phase)	16	0	7	32	0.70 [0.47, 0.87]	1.00 [0.89, 1.00]

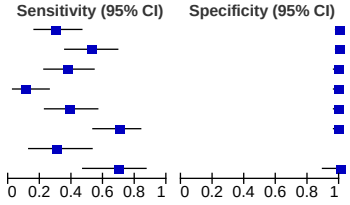
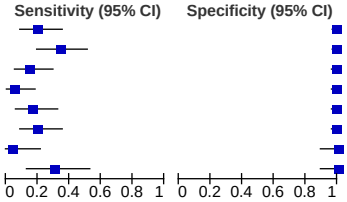


Figure 144: ELISA (IgM/IgG) and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014 (EM acute phase)	8	2	32	201	0.20 [0.09, 0.36]	0.99 [0.96, 1.00]
Molins 2014 (EM convalescent phase)	13	2	25	201	0.34 [0.20, 0.51]	0.99 [0.96, 1.00]
Steere 2008 (EM acute with dissemination)	6	1	34	136	0.15 [0.06, 0.30]	0.99 [0.96, 1.00]
Steere 2008 (EM acute without dissemination)	2	1	34	136	0.06 [0.01, 0.19]	0.99 [0.96, 1.00]
Steere 2008 (EM convalescent no dissemination)	6	1	30	136	0.17 [0.06, 0.33]	0.99 [0.96, 1.00]
Steere 2008 (EM convalescent with dissemination)	8	1	32	136	0.20 [0.09, 0.36]	0.99 [0.96, 1.00]
Weiner 2015 (EM acute phase)	1	0	22	32	0.04 [0.00, 0.22]	1.00 [0.89, 1.00]
Weiner 2015 (EM convalscent phase)	7	0	16	32	0.30 [0.13, 0.53]	1.00 [0.89, 1.00]



1 E.5.2.2 Neuroborreliosis

Figure 145: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015	29	0	1	90	0.97 [0.83, 1.00]	1.00 [0.96, 1.00]
Bacon 2003 (early neurologic convalescent)	9	0	2	257	0.82 [0.48, 0.98]	1.00 [0.99, 1.00]
Bacon 2003 (early neurologic)	13	0	2	257	0.87 [0.60, 0.98]	1.00 [0.99, 1.00]
Bacon 2003 (late neurologic)	11	0	0	257	1.00 [0.72, 1.00]	1.00 [0.99, 1.00]
Branda 2013 (European tests)	13	1	2	99	0.87 [0.60, 0.98]	0.99 [0.95, 1.00]
Branda 2013 (US tests)	6	0	9	100	0.40 [0.16, 0.68]	1.00 [0.96, 1.00]
Johnson 1996 (early neurologic; FLA-ELISA + IB)	3	0	0	113	1.00 [0.29, 1.00]	1.00 [0.97, 1.00]
Johnson 1996 (Late neurologic; FLA-ELISA + IB)	14	0	0	113	1.00 [0.77, 1.00]	1.00 [0.97, 1.00]
Molins 2014	9	2	1	203	0.90 [0.55, 1.00]	0.99 [0.97, 1.00]
Molins 2016	8	4	2	199	0.80 [0.44, 0.97]	0.98 [0.95, 0.99]
Peltomaa 2004 (facial paralysis)	47	2	0	86	1.00 [0.92, 1.00]	0.98 [0.92, 1.00]
Weiner 2015	9	0	1	32	0.90 [0.55, 1.00]	1.00 [0.89, 1.00]

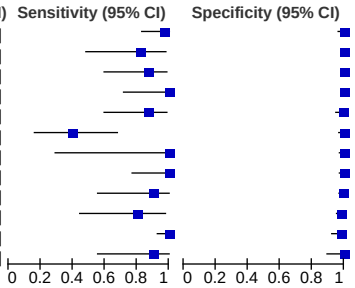


Figure 146: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ang 2015	47	0	4	104	0.92 [0.81, 0.98]	1.00 [0.97, 1.00]
Branda 2013 (US tests)	6	0	9	100	0.40 [0.16, 0.68]	1.00 [0.96, 1.00]
Molins 2016 (C6 + Marblot IB)	9	2	1	201	0.90 [0.55, 1.00]	0.99 [0.96, 1.00]
Molins 2016 (C6 + ViraStripe IB)	9	1	1	202	0.90 [0.55, 1.00]	1.00 [0.97, 1.00]

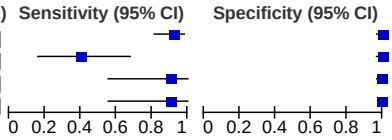


Figure 147: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (US tests)	13	0	2	100	0.87 [0.60, 0.98]	1.00 [0.96, 1.00]
Molins 2016	9	1	1	202	0.90 [0.55, 1.00]	1.00 [0.97, 1.00]

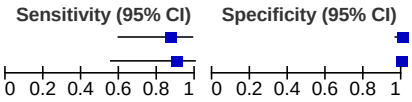


Figure 148: ELISA (IgM/IgG) and Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	9	1	1	202	0.90 [0.55, 1.00]	1.00 [0.97, 1.00]
Weiner 2015	9	0	1	32	0.90 [0.55, 1.00]	1.00 [0.89, 1.00]

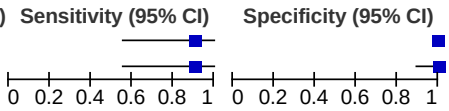


Figure 149: ELISA (IgM/IgG) and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	3	2	7	201	0.30 [0.07, 0.65]	0.99 [0.96, 1.00]
Weiner 2015	4	0	6	32	0.40 [0.12, 0.74]	1.00 [0.89, 1.00]

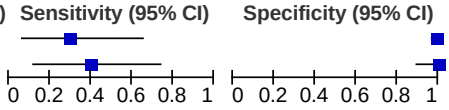
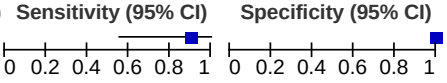


Figure 150: ELISA WCS and Immunoblot (VlsE)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016	9	1	1	202	0.90 [0.55, 1.00]	1.00 [0.97, 1.00]



1 E.5.2.3 Lyme arthritis

Figure 151: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacon 2003 (arthritis convalescent)	23	0	1	257	0.96 [0.79, 1.00]	1.00 [0.99, 1.00]
Bacon 2003 (arthritis)	32	0	1	257	0.97 [0.84, 1.00]	1.00 [0.99, 1.00]
Branda 2013 (European tests)	14	1	1	99	0.93 [0.68, 1.00]	0.99 [0.95, 1.00]
Branda 2013 (US tests)	9	0	6	100	0.60 [0.32, 0.84]	1.00 [0.96, 1.00]
Johnson 1996 (LA; FLA-ELISA + IB)	36	0	0	113	1.00 [0.90, 1.00]	1.00 [0.97, 1.00]
Molins 2014	29	2	0	203	1.00 [0.88, 1.00]	0.99 [0.97, 1.00]
Molins 2016	28	4	1	199	0.97 [0.82, 1.00]	0.98 [0.95, 0.99]
Weiner 2015	8	0	0	32	1.00 [0.63, 1.00]	1.00 [0.89, 1.00]

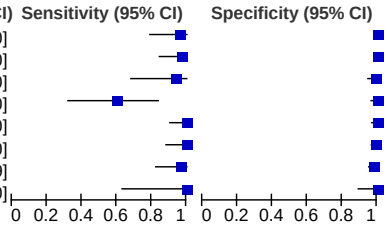


Figure 152: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (US tests)	10	0	5	100	0.67 [0.38, 0.88]	1.00 [0.96, 1.00]
Molins 2016 (C6 + Marblot IB)	29	2	0	201	1.00 [0.88, 1.00]	0.99 [0.96, 1.00]
Molins 2016 (C6 + ViraStripe IB)	28	1	1	202	0.97 [0.82, 1.00]	1.00 [0.97, 1.00]

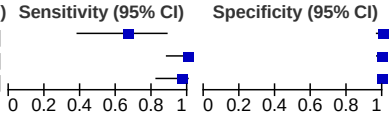


Figure 153: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (US tests)	14	0	1	100	0.93 [0.68, 1.00]	1.00 [0.96, 1.00]
Molins 2016	29	1	0	202	1.00 [0.88, 1.00]	1.00 [0.97, 1.00]

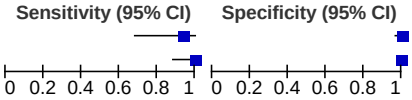


Figure 154: ELISA (IgM/IgG) and Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	9	1	20	202	0.31 [0.15, 0.51]	1.00 [0.97, 1.00]
Weiner 2015	1	0	7	32	0.13 [0.00, 0.53]	1.00 [0.89, 1.00]

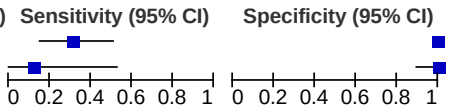


Figure 155: ELISA (IgM/IgG) and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	29	2	0	201	1.00 [0.88, 1.00]	0.99 [0.96, 1.00]
Weiner 2015	8	0	0	32	1.00 [0.63, 1.00]	1.00 [0.89, 1.00]

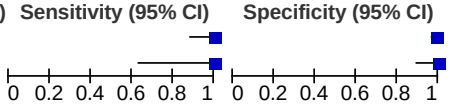
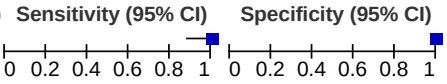


Figure 156: ELISA WCS and Immunoblot (VlsE)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016	29	1	0	202	1.00 [0.88, 1.00]	1.00 [0.97, 1.00]



2 E.5.2.4 Lyme carditis

Figure 157: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	6	2	1	203	0.86 [0.42, 1.00]	0.99 [0.97, 1.00]
Molins 2016	7	4	0	199	1.00 [0.59, 1.00]	0.98 [0.95, 0.99]
Weiner 2015	5	0	1	32	0.83 [0.36, 1.00]	1.00 [0.89, 1.00]

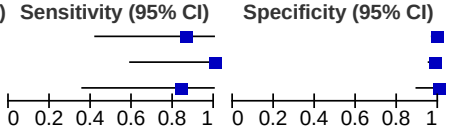


Figure 158: ELISA (IgM/IgG) and Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	4	1	3	202	0.57 [0.18, 0.90]	1.00 [0.97, 1.00]
Weiner 2015	4	0	2	32	0.67 [0.22, 0.96]	1.00 [0.89, 1.00]

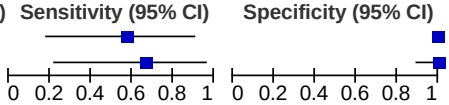


Figure 159: ELISA (IgM/IgG) and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2014	4	2	3	201	0.57 [0.18, 0.90]	0.99 [0.96, 1.00]
Weiner 2015	3	0	3	32	0.50 [0.12, 0.88]	1.00 [0.89, 1.00]

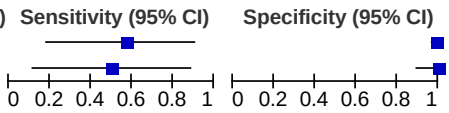


Figure 160: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016	6	1	1	202	0.86 [0.42, 1.00]	1.00 [0.97, 1.00]

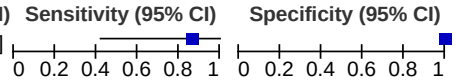


Figure 161: ELISA WCS and Immunoblot (VlsE)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016	6	1	1	202	0.86 [0.42, 1.00]	1.00 [0.97, 1.00]

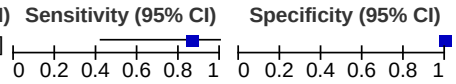
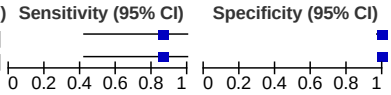


Figure 162: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016 (C6 + Marblot IB)	6	2	1	201	0.86 [0.42, 1.00]	0.99 [0.96, 1.00]
Molins 2016 (C6 + ViraStripe IB)	6	1	1	202	0.86 [0.42, 1.00]	1.00 [0.97, 1.00]



1 E.5.2.5 Acrodermatitis chronica atrophicans (ACA)

Figure 163: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (European tests)	14	1	0	99	1.00 [0.77, 1.00]	0.99 [0.95, 1.00]
Branda 2013 (US tests)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]

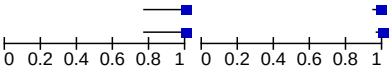


Figure 164: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (US tests)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]

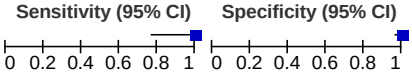
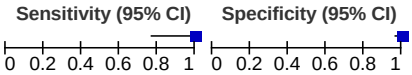


Figure 165: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (US tests)	14	0	0	100	1.00 [0.77, 1.00]	1.00 [0.96, 1.00]



2 E.5.2.6 Unspecified Lyme Disease

Figure 166: ELISA (IgM/IgG) and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bacon 2003	189	0	91	257	0.68 [0.62, 0.73]	1.00 [0.99, 1.00]
Branda 2011	96	7	73	1293	0.57 [0.49, 0.64]	0.99 [0.99, 1.00]
Branda 2013 (European tests)	52	1	12	99	0.81 [0.70, 0.90]	0.99 [0.95, 1.00]
Branda 2013 (US tests)	33	0	31	100	0.52 [0.39, 0.64]	1.00 [0.96, 1.00]
Johnson 1996 (unspecified LD; FLA- ELISA + IB)	90	0	21	113	0.81 [0.73, 0.88]	1.00 [0.97, 1.00]
Molins 2014	83	2	41	201	0.67 [0.58, 0.75]	0.99 [0.96, 1.00]
Molins 2016	86	4	38	199	0.69 [0.60, 0.77]	0.98 [0.95, 0.99]
Weiner 2015	47	0	23	32	0.67 [0.55, 0.78]	1.00 [0.89, 1.00]

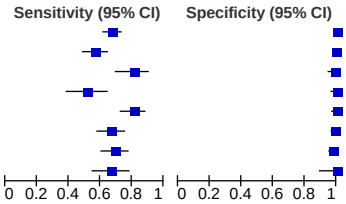


Figure 167: ELISA (IgM/IgG) and Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Weiner 2015	37	0	33	32	0.53 [0.41, 0.65]	1.00 [0.89, 1.00]

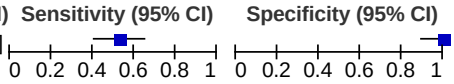


Figure 168: ELISA (IgM/IgG) and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Weiner 2015	23	0	47	32	0.33 [0.22, 0.45]	1.00 [0.89, 1.00]

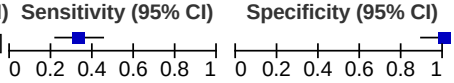


Figure 169: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2013 (US tests)	34	0	30	100	0.53 [0.40, 0.66]	1.00 [0.96, 1.00]
Molins 2016 (C6 + Marblot IB)	84	2	40	201	0.68 [0.59, 0.76]	0.99 [0.96, 1.00]
Molins 2016 (C6 + ViraStripe IB)	84	1	40	202	0.68 [0.59, 0.76]	1.00 [0.97, 1.00]

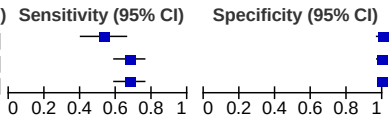


Figure 170: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2011	115	7	54	1293	0.68 [0.60, 0.75]	0.99 [0.99, 1.00]
Branda 2013 (US tests)	54	0	10	100	0.84 [0.73, 0.92]	1.00 [0.96, 1.00]
Molins 2016	94	1	30	202	0.76 [0.67, 0.83]	1.00 [0.97, 1.00]

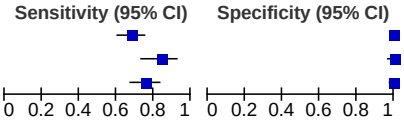


Figure 171: ELISA WCS and Immunoblot (VlsE)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Molins 2016	91	1	33	202	0.73 [0.65, 0.81]	1.00 [0.97, 1.00]

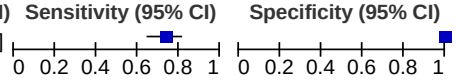


Figure 172: ELISA (IgM) and Immunoblot (IgM) – early Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Behring EIA + Genzyme Virotech IB)	12	0	14	62	0.46 [0.27, 0.67]	1.00 [0.94, 1.00]
Goossens 1999 (Behring EIA + MRL IB)	12	0	14	62	0.46 [0.27, 0.67]	1.00 [0.94, 1.00]
Goossens 1999 (Boehringer + Genzyme Virotech)	8	0	18	62	0.31 [0.14, 0.52]	1.00 [0.94, 1.00]
Goossens 1999 (Boehringer EIA + MRL IB)	9	0	17	62	0.35 [0.17, 0.56]	1.00 [0.94, 1.00]
Goossens 1999 (Dako EIA + Genzyme Virotech IB)	9	0	17	62	0.35 [0.17, 0.56]	1.00 [0.94, 1.00]
Goossens 1999 (Dako EIA + MRL IB)	11	0	15	62	0.42 [0.23, 0.63]	1.00 [0.94, 1.00]
Goossens 1999 (Genzyme Virotech EIA + GV IB)	13	0	13	62	0.50 [0.30, 0.70]	1.00 [0.94, 1.00]
Goossens 1999 (Genzyme Virotech EIA + MRL IB)	12	0	14	62	0.46 [0.27, 0.67]	1.00 [0.94, 1.00]
Goossens 1999 (IBL EIA + Genzyme Virotech IB)	9	2	17	60	0.35 [0.17, 0.56]	0.97 [0.89, 1.00]
Goossens 1999 (IBL EIA + MRL IB)	12	0	14	62	0.46 [0.27, 0.67]	1.00 [0.94, 1.00]

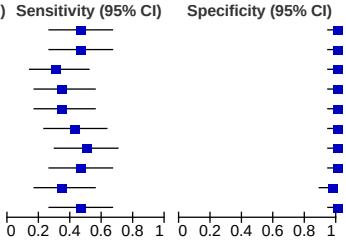


Figure 173: ELISA (IgG) and Immunoblot (IgG) – early Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Behring EIA + Genzyme Virotech IB)	6	4	20	58	0.23 [0.09, 0.44]	0.94 [0.84, 0.98]
Goossens 1999 (Behring EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]
Goossens 1999 (Boehringer + Genzyme Virotech)	4	4	22	58	0.15 [0.04, 0.35]	0.94 [0.84, 0.98]
Goossens 1999 (Boehringer EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]
Goossens 1999 (Dako EIA + Genzyme Virotech IB)	5	2	21	60	0.19 [0.07, 0.39]	0.97 [0.89, 1.00]
Goossens 1999 (Dako EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]
Goossens 1999 (Genzyme Virotech EIA + GV IB)	5	3	21	59	0.19 [0.07, 0.39]	0.95 [0.87, 0.99]
Goossens 1999 (Genzyme Virotech EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]
Goossens 1999 (IBL EIA + Genzyme Virotech IB)	4	4	22	58	0.15 [0.04, 0.35]	0.94 [0.84, 0.98]
Goossens 1999 (IBL EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]

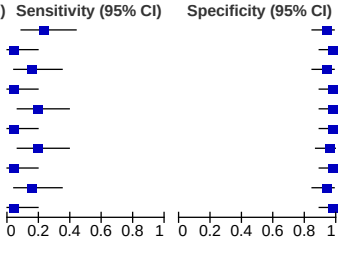


Figure 174: ELISA (IgM/IgG) and Immunoblot (IgM) – early Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Milenia EIA + Genzyme Virotech IB)	3	3	23	59	0.12 [0.02, 0.30]	0.95 [0.87, 0.99]
Goossens 1999 (Milenia EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]

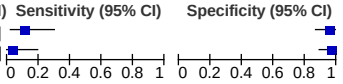


Figure 175: ELISA (IgM/IgG) and Immunoblot (IgG) – early Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Milenia EIA + Genzyme Virotech IB)	3	3	23	59	0.12 [0.02, 0.30]	0.95 [0.87, 0.99]
Goossens 1999 (Milenia EIA + MRL IB)	1	2	25	60	0.04 [0.00, 0.20]	0.97 [0.89, 1.00]

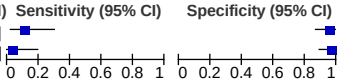


Figure 176: ELISA (IgM) and Immunoblot (IgM) – late Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Behring EIA + Genzyme Virotech IB)	5	0	8	62	0.38 [0.14, 0.68]	1.00 [0.94, 1.00]
Goossens 1999 (Behring EIA + MRL IB)	6	0	7	62	0.46 [0.19, 0.75]	1.00 [0.94, 1.00]
Goossens 1999 (Boehringer + Genzyme Virotech)	4	0	9	62	0.31 [0.09, 0.61]	1.00 [0.94, 1.00]
Goossens 1999 (Boehringer EIA + MRL IB)	6	0	7	62	0.46 [0.19, 0.75]	1.00 [0.94, 1.00]
Goossens 1999 (Dako EIA + Genzyme Virotech IB)	5	0	8	62	0.38 [0.14, 0.68]	1.00 [0.94, 1.00]
Goossens 1999 (Dako EIA + MRL IB)	6	0	7	62	0.46 [0.19, 0.75]	1.00 [0.94, 1.00]
Goossens 1999 (Genzyme Virotech EIA + GV IB)	5	0	8	62	0.38 [0.14, 0.68]	1.00 [0.94, 1.00]
Goossens 1999 (Genzyme Virotech EIA + MRL IB)	6	0	7	62	0.46 [0.19, 0.75]	1.00 [0.94, 1.00]
Goossens 1999 (IBL EIA + Genzyme Virotech IB)	4	2	9	60	0.31 [0.09, 0.61]	0.97 [0.89, 1.00]
Goossens 1999 (IBL EIA + MRL IB)	5	0	8	62	0.38 [0.14, 0.68]	1.00 [0.94, 1.00]

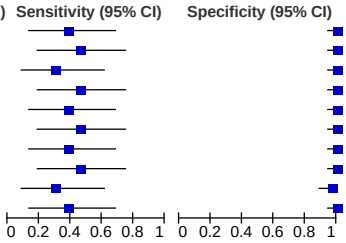


Figure 177: ELISA (IgG) and Immunoblot (IgG) – late Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Behring EIA + Genzyme Virotech IB)	6	4	7	58	0.46 [0.19, 0.75]	0.94 [0.84, 0.98]
Goossens 1999 (Behring EIA + MRL IB)	5	2	8	60	0.38 [0.14, 0.68]	0.97 [0.89, 1.00]
Goossens 1999 (Boehringer + Genzyme Virotech)	6	4	7	58	0.46 [0.19, 0.75]	0.94 [0.84, 0.98]
Goossens 1999 (Boehringer EIA + MRL IB)	5	2	8	60	0.38 [0.14, 0.68]	0.97 [0.89, 1.00]
Goossens 1999 (Dako EIA + Genzyme Virotech IB)	5	2	8	60	0.38 [0.14, 0.68]	0.97 [0.89, 1.00]
Goossens 1999 (Dako EIA + MRL IB)	5	2	8	60	0.38 [0.14, 0.68]	0.97 [0.89, 1.00]
Goossens 1999 (Genzyme Virotech EIA + GV IB)	5	3	8	59	0.38 [0.14, 0.68]	0.95 [0.87, 0.99]
Goossens 1999 (Genzyme Virotech EIA + MRL IB)	5	2	8	60	0.38 [0.14, 0.68]	0.97 [0.89, 1.00]
Goossens 1999 (IBL EIA + Genzyme Virotech IB)	4	4	9	58	0.31 [0.09, 0.61]	0.94 [0.84, 0.98]
Goossens 1999 (IBL EIA + MRL IB)	4	2	9	60	0.31 [0.09, 0.61]	0.97 [0.89, 1.00]

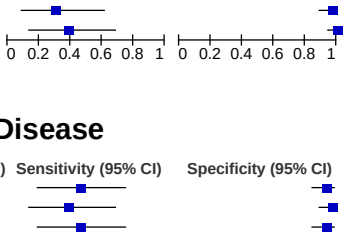


Figure 178: ELISA (IgM/IgG) and Immunoblot (IgM) – late Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Milenia EIA + Genzyme Virotech IB)	2	3	11	59	0.15 [0.02, 0.45]	0.95 [0.87, 0.99]
Goossens 1999 (Milenia EIA + MRL IB)	1	2	12	60	0.08 [0.00, 0.36]	0.97 [0.89, 1.00]

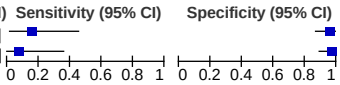


Figure 179: ELISA (IgM/IgG) and Immunoblot (IgG) – late Lyme Disease

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Goossens 1999 (Milenia EIA + Genzyme Virotech IB)	6	3	7	59	0.46 [0.19, 0.75]	0.95 [0.87, 0.99]
Goossens 1999 (Milenia EIA + MRL IB)	6	2	7	60	0.46 [0.19, 0.75]	0.97 [0.89, 1.00]

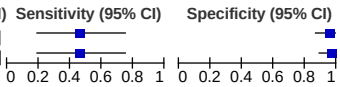


Figure 180: ELISA (IgM/IgG) and Immunoblot (IgM/IgG) – acute neuritis or carditis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010	17	0	10	166	0.63 [0.42, 0.81]	1.00 [0.98, 1.00]
Branda 2011	19	7	7	1293	0.73 [0.52, 0.88]	0.99 [0.99, 1.00]
Steere 2008	13	2	0	136	1.00 [0.75, 1.00]	0.99 [0.95, 1.00]

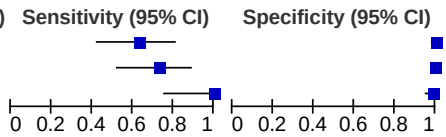


Figure 181: ELISA (IgM/IgG) and Immunoblot (IgG with VlsE band) – acute neuritis or carditis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010	26	0	1	166	0.96 [0.81, 1.00]	1.00 [0.98, 1.00]

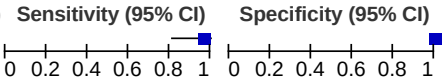


Figure 182: ELISA (IgM/IgG) and VlsE band – acute neuritis or carditis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010	26	0	1	166	0.96 [0.81, 1.00]	1.00 [0.98, 1.00]

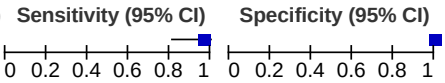


Figure 183: ELISA WCS and ELISA C6 – acute neuritis or carditis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2011	26	7	0	1293	1.00 [0.87, 1.00]	0.99 [0.99, 1.00]

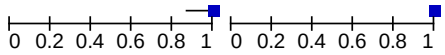


Figure 184: ELISA (IgM/IgG) and Immunoblot (IgM) – acute neuritis or carditis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Steere 2008	11	1	2	136	0.85 [0.55, 0.98]	0.99 [0.96, 1.00]

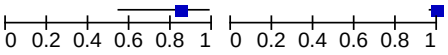


Figure 185: ELISA (IgM/IgG) and Immunoblot (IgG) – acute neuritis or carditis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Steere 2008	11	1	2	136	0.85 [0.55, 0.98]	0.99 [0.96, 1.00]

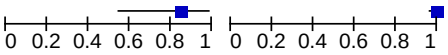


Figure 186: ELISA (IgM/IgG) and Immunoblot (IgM/IgG) – arthritis or late neuritis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010	29	0	0	166	1.00 [0.88, 1.00]	1.00 [0.98, 1.00]
Branda 2011	29	7	0	1293	1.00 [0.88, 1.00]	0.99 [0.99, 1.00]
Steere 2008	31	2	0	136	1.00 [0.89, 1.00]	0.99 [0.95, 1.00]

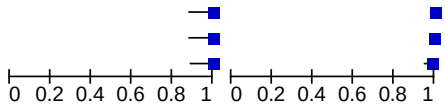


Figure 187: ELISA (IgM/IgG) and Immunoblot (IgG with VlsE band) – arthritis or late neuritis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010	29	0	0	166	1.00 [0.88, 1.00]	1.00 [0.98, 1.00]

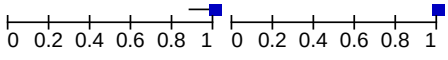


Figure 188: ELISA (IgM/IgG) and VlsE band – arthritis or late neuritis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2010	28	0	1	166	0.97 [0.82, 1.00]	1.00 [0.98, 1.00]

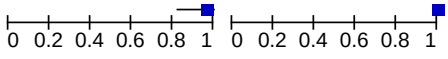


Figure 189: ELISA WCS and ELISA C6 – arthritis or late neuritis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Branda 2011	29	7	0	1293	1.00 [0.88, 1.00]	0.99 [0.99, 1.00]

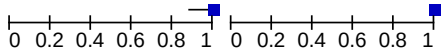


Figure 190: ELISA (IgM/IgG) and Immunoblot (IgM) – arthritis or late neuritis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Steere 2008	7	1	24	136	0.23 [0.10, 0.41]	0.99 [0.96, 1.00]

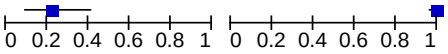
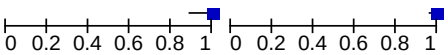


Figure 191: ELISA (IgM/IgG) and Immunoblot (IgG) – arthritis or late neuritis

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Steere 2008	31	1	0	136	1.00 [0.89, 1.00]	0.99 [0.96, 1.00]



E.5.2.7 Post-treatment Lyme Disease Syndrome (PTLDS)

Figure 192: ELISA and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab)	15	0	22	40	0.41 [0.25, 0.58]	1.00 [0.91, 1.00]
Fallon 2014 (speciality lab A)	14	0	23	40	0.38 [0.22, 0.55]	1.00 [0.91, 1.00]
Fallon 2014 (speciality lab B)	16	1	21	39	0.43 [0.27, 0.61]	0.97 [0.87, 1.00]
Fallon 2014 (University reference lab)	18	0	19	40	0.49 [0.32, 0.66]	1.00 [0.91, 1.00]

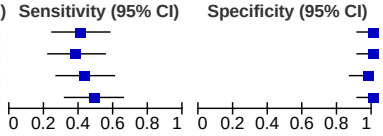


Figure 193: ELISA C6 and Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (speciality lab A)	15	0	22	40	0.41 [0.25, 0.58]	1.00 [0.91, 1.00]
Fallon 2014 (speciality lab B)	17	0	20	40	0.46 [0.29, 0.63]	1.00 [0.91, 1.00]

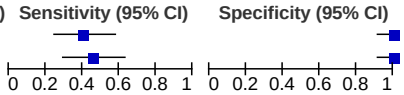
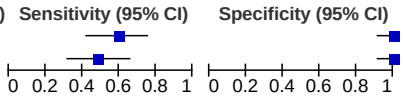


Figure 194: ELISA and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (speciality lab A)	22	0	15	40	0.59 [0.42, 0.75]	1.00 [0.91, 1.00]
Fallon 2014 (speciality lab B)	18	0	19	40	0.49 [0.32, 0.66]	1.00 [0.91, 1.00]



E.6 Combination of tests: Coupled sensitivity and specificity forest plots for children

E.6.1 Evidence from cross-sectional studies

E.6.1.1 Unspecified Lyme Disease

Figure 195: ELISA C6 and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lipsett 2016 (serum)	89	12	25	818	0.78 [0.69, 0.85]	0.99 [0.97, 0.99]

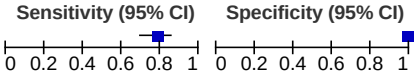


Figure 196: ELISA WCS and ELISA C6

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lipsett 2016 (serum)	91	29	23	801	0.80 [0.71, 0.87]	0.97 [0.95, 0.98]

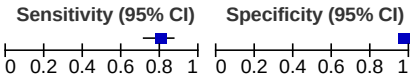
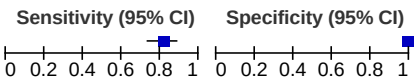


Figure 197: ELISA WCS and Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lipsett 2016 (serum)	93	10	21	820	0.82 [0.73, 0.88]	0.99 [0.98, 0.99]

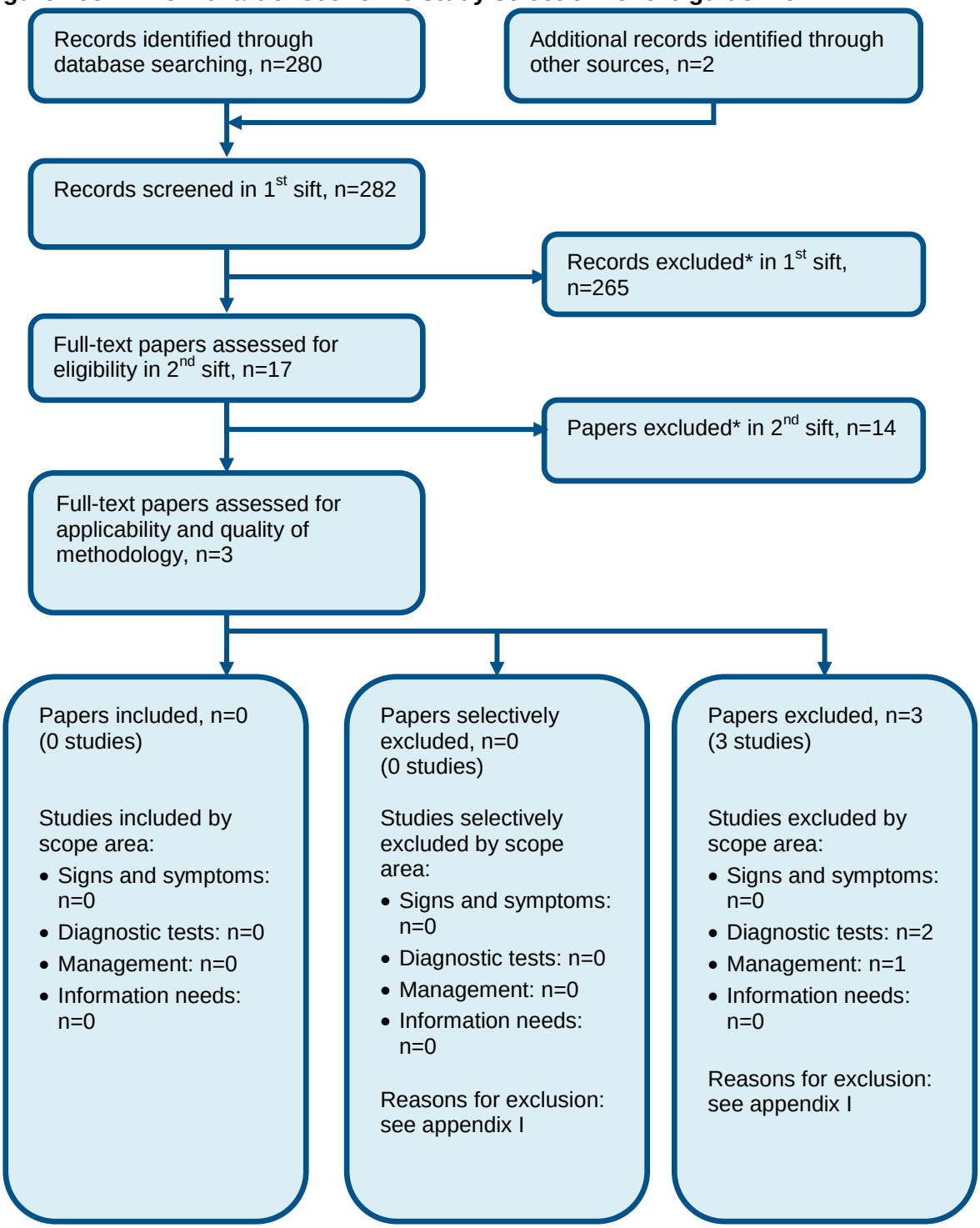


E.6.2 Evidence from case-control studies

None.

Appendix F: Health economic evidence selection

Figure 198: 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: Health economic exploratory analysis

H.1 Exploratory analysis for diagnostic testing for Lyme disease

H.1.1 Introduction

Currently in the NHS, a 2-tier testing strategy is used to diagnose Lyme disease. The first 'initial' test, an ELISA, is done to 'rule out' Lyme disease. Those who test positive or have an equivocal result in this initial test are then given a second 'confirmatory' test, an immunoblot. This confirmatory test aims to 'rule in' people with Lyme disease.

The initial test (ELISA) is the less costly of the 2 tests and can be run, validated and interpreted on automated platforms without too much specialist input in most reasonably sized laboratories. Therefore, currently in the NHS, this is undertaken either in a local laboratory or at the centralised laboratory: the Rare and Imported Pathogens Laboratory (RIPL). The confirmatory test (immunoblot) is more expensive and requires specific expertise for interpretation of results. This test is centralised to RIPL to ensure they are doing enough tests to maintain competence and experience (which is difficult with Lyme disease, as it is relatively rare) and ensure a quality, validated result. As a result, the immunoblot is not considered as a single test but only as a confirmatory test after an initial test.

Clinical and cost-effectiveness evidence was sought for diagnostic tests for Lyme disease. In the planning stages, this area was prioritised for original economic analysis during guideline development due to the potential for a change in practice if evidence was found for additional tests for Lyme disease. No evidence was found to support the use of additional tests, and overall, the committee considered the clinical evidence supportive of continuing with the current 2-tier testing strategy. No economic evaluations were identified.

Testing costs will be higher with a 2-tier testing strategy than with a single initial test (ELISA). However, this may be offset by reduced costs associated with reduced misdiagnosis. The committee highlighted that the main aim of 2-tier testing was to minimise false positive diagnoses. Reducing false positives would be associated with a reduction in antibiotic treatment costs. In addition, where people receive an incorrect diagnosis they may continue to be symptomatic and have further healthcare contacts until a correct diagnosis is made and appropriate treatment is given. Reducing false positives would also be expected to increase QALYs. Conducting an additional test, however, may increase the number of false negatives. A false negative would be associated with increased costs to the NHS, as the person may continue to be symptomatic and have further healthcare contacts until a correct diagnosis is made. By not receiving prompt treatment, these people may develop long-term complications of undiagnosed Lyme disease, which would have a negative impact on QALYs and may be costly to manage.

In the absence of any published economic evidence regarding 2-tier testing compared to a single initial test, an analysis was undertaken to help support committee decision-making.

H.1.2 Approach to analysis

An exploratory analysis was conducted to estimate the additional cost of 2-tier testing (initial ELISA including C6 IgM and IgG followed by confirmatory immunoblot if ELISA is positive) over initial testing only (ELISA including C6 IgM and IgG) in people with suspected Lyme disease and to evaluate the potential for the cost of a misdiagnosis (either false positive or

false negative) for 2-tier testing to be cost-neutral. The committee considered it likely that the costs of 2-tier testing would be offset by cost savings due to reduced false positives; therefore, this analysis aimed to explore this quantitatively.

This analysis was undertaken from an NHS and personal social services perspective, using published costs from 2016/2017. This analysis was conducted in accordance with the NICE reference case; although, this analysis was restricted to costs only and so QALYs were not used. Furthermore, a probabilistic sensitivity analysis was not deemed useful for this exploratory analysis. Uncertainty was considered through multiple scenario sensitivity analyses.

A full cost–utility analysis was considered to be inappropriate for this question, as there is too much uncertainty around model inputs and too many tenuous assumptions would be required. The results would therefore likely be unreliable. The clinical evidence identified for the diagnostic test accuracy was very heterogeneous and assessed as very low quality primarily due to study design (majority case-control studies and some cross-sectional studies) and an imperfect reference standard or different reference standards used across studies. As a result, the evidence was not meta-analysed. The committee was able to see trends in the evidence but was unable to select any 1 study as a 'best estimate'. Many other inputs that would be required, such as true prevalence of Lyme disease and utility values for different presentations of Lyme disease, were also unknown.

This analysis assumes that only those that test positive in the ELISA receive an immunoblot.

The accuracy data does not allow us to estimate the number of equivocal results that would occur following an ELISA; therefore, it is not possible to incorporate those in the analysis. It is assumed that this would be a small proportion and so is unlikely to affect the results substantially.

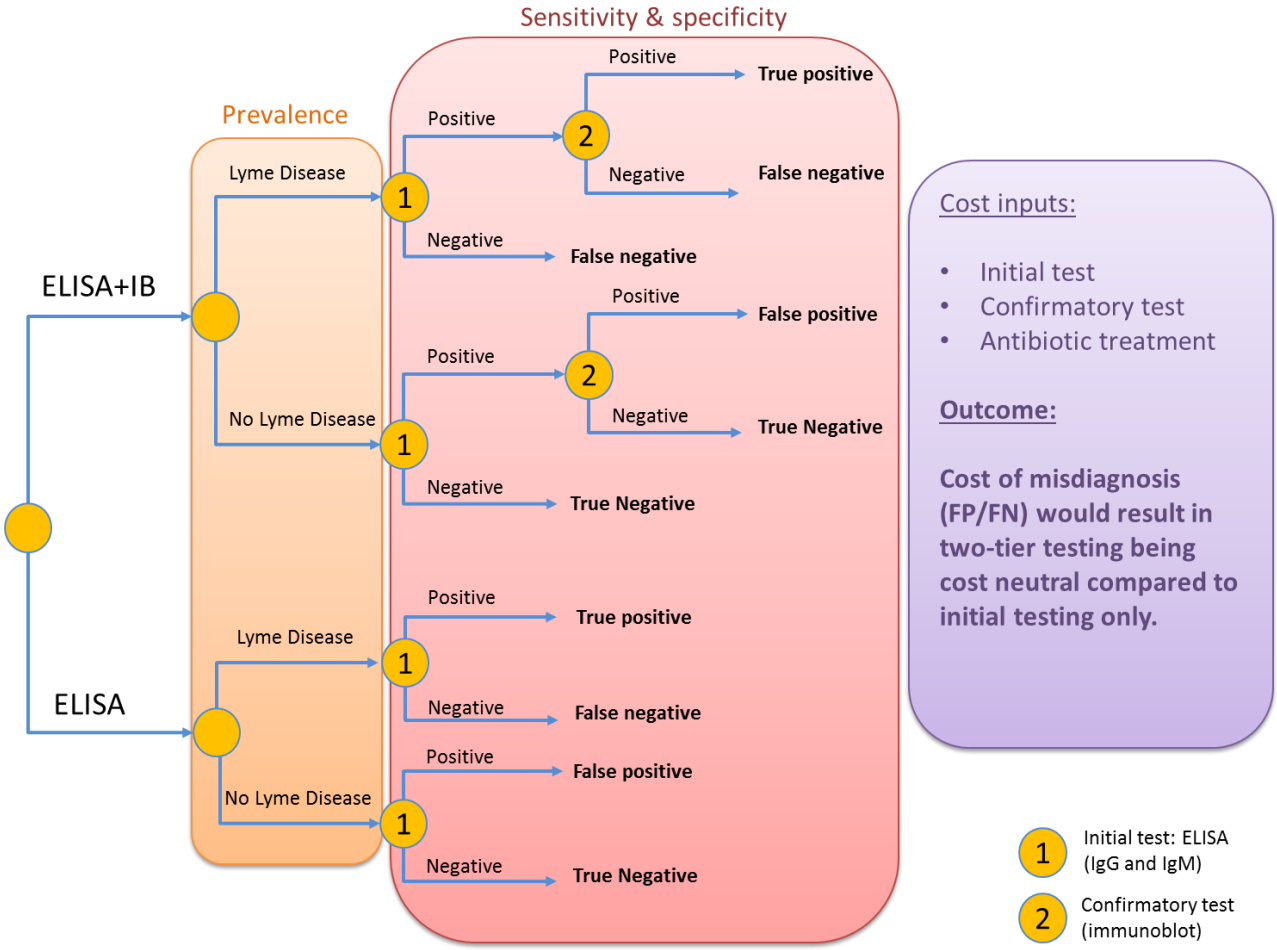
The decision tree is depicted in Figure 199. This analysis includes the following data inputs:

- prevalence of Lyme disease in those being tested
- sensitivity and specificity of the initial test and the confirmatory test
- cost of each test
- cost of treating Lyme disease with antibiotics.

The outcome of this analysis is the unit cost of misdiagnosis (either false negative or false positive) that would result in 2-tier testing being cost neutral compared to initial testing only. It is acknowledged that, in reality, the cost of misdiagnosis for false negatives and false positives may in fact be different. As noted in the introduction, false positives would be associated with potentially unnecessary antibiotic treatment costs. In addition, where people receive an incorrect diagnosis they may continue to be symptomatic and have further healthcare contacts until a correct diagnosis is made and appropriate treatment is given. With false negative there may be increased costs to the NHS, as the person may continue to be symptomatic and have further healthcare contacts until a correct diagnosis is made. By not receiving prompt treatment, these people may develop long-term complications of undiagnosed Lyme disease, which may be costly to manage.

A key limitation of this analysis is that only costs of misdiagnosis, diagnosis and treatment are accounted for, and no health effects are included. It is highlighted that even if costs would not be completely offset by a reduction in costs associated with misdiagnosis, 2-tier testing could still be cost-effective if the benefits to people with suspected Lyme disease can justify any additional cost.

Figure 199: Decision tree



H.1.3 Data inputs

Population

Lyme disease can present with a number of different symptoms depending on the progression of the disease. These include early-localised symptoms such as erythema migrans rash and disseminated symptoms such as arthritis, carditis and neuroborreliosis. The diagnostic accuracy of the tests varies depending on the presenting symptoms. For this exploratory analysis, sensitivity and specificity data were selected for the following different presentations: Lyme carditis, Lyme neuroborreliosis and Lyme arthritis.

Prevalence

RIPL reports approximately 1,000 serologically confirmed cases from approximately 15,000 tested samples per year for England and Wales.[386] Based on these estimates, the prevalence of Lyme disease amongst those tested is 7%. This estimate does not account for those having an ELISA locally and testing negative; therefore, this could be an overestimate. The true prevalence of Lyme disease may vary depending on the presenting symptoms; however, no prevalence estimates were identified for different presenting symptoms. Due to the uncertainty in this estimate, a sensitivity analysis was conducted using a prevalence of 1% and 15%.

Sensitivity and specificity

As no meta-analysis was conducted, a number of different studies were used to explore a range of sensitivities and specificities and their impact on the cost of misdiagnosis. As explained above, accuracy data was selected for different presenting symptoms. For Lyme neuroborreliosis, 3 different sets of data were selected, as there was some variation in the accuracy data identified for this presentation. This was to explore if these different sensitivities and specificities had a significant effect on the outcome of the analysis. More recent studies thought to reflect more accurately the currently available ELISA IgG and IgM C6 tests were selected. A few of the outliers in the data identified in the review were from older studies (for example, Karlsson 1989[204]), studies where the tests were done on cerebrospinal fluid samples rather than serum samples (for example, Coyle 1993[62]) or studies with very few participants (for example, Cinco 2006[54]). As a result, these were not considered to be appropriate for inclusion in the analysis.

For Lyme arthritis and Lyme carditis, only 1 set of sensitivity and specificity outcomes were selected for each presentation. It was not deemed necessary to look at more, as there was less variation in the accuracy estimates. More recent studies with large study populations were chosen.

Only data on the accuracy of the initial test and the combination 2-tier tests was available, not for the confirmatory tests alone. For the 2-tier testing comparator, in order to determine the proportion of people who tested positive in the initial test and who therefore were eligible for the confirmatory test, it was necessary to incorporate the accuracy of both tests separately. The sensitivity and specificity of the confirmatory test was therefore back-calculated using the accuracy of the combined 2-tier testing using the formula below:

$$Sensitivity\ confirmatory\ test = \frac{True\ positive\ from\ 2-tier\ testing}{Total\ number\ of\ people\ with\ Lyme\ disease}$$

$$Specificty\ confirmatory\ test = \frac{True\ negatives\ from\ 2-tier\ testing}{Total\ number\ of\ people\ without\ Lyme\ disease}$$

The accuracy inputs used for each scenario are summarised in Table 31 below.

Table 31: Sensitivity and specificity data inputs

Scenario	Initial test		Confirmatory test (h)		Two-tier test	
Lyme type	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
1 Lyme neuroborreliosis	92% (a)	72% (a)	98%	99%	90% (b)	100% (b)
2. Lyme neuroborreliosis	90% (c)	93% (c)	100%	92%	90% (d)	99% (d)
3. Lyme neuroborreliosis	92% (a)	72% (a)	87%	93%	80% (e)	98% (e)
4. Lyme arthritis	100% (c)	96% (c)	100%	87%	100% (d)	99% (d)
5. Lyme carditis	86% (f)	98% (f)	100%	74%	86% (g)	99% (g)

(a) Henningsson 2014 ELISA IgG and IgM[175]
(b) Molins 2016 C6 and Virastripe immunoblot[307]
(c) Molins 2014 ELISA IgG and IgM[308]
(d) Molins 2014 ELISA IgG and IgM and immunoblot IgG and IgM[308]
(e) Molins 2016 ELISA IgG and IgM and immunoblot IgG and IgM [307]

(f) Molins 2016 ELISA C6[307]
(g) Molins 2016 ELISA C6 and Marblot[307]
(h) Calculated from 2-tier test and initial test data

Costs

The costs of the test were taken from the published costs from RIPL (April 2016-March 2017).[385] The ELISA can be done in local NHS laboratories, but published costs were unavailable. The cost of antibiotic treatment for Lyme neuroborreliosis and Lyme carditis is based on 200mg doxycycline daily for 21 days, as per the recommendations made in this guideline. For Lyme arthritis, the cost is based on 200mg doxycycline daily for 28 days. Amoxicillin and azithromycin are alternative antibiotic treatments recommended in this guideline. The unit costs of these are very similar to doxycycline and so are not expected to impact the results of this exploratory analysis. Therefore, it was not deemed necessary to conduct a sensitivity analysis around the cost of the antibiotics. A sensitivity analysis was conducted for Lyme neuroborreliosis where it is assumed that all people suspected with Lyme neuroborreliosis receive intravenous antibiotics because of their presenting symptoms (for example, meningitis). As a result, in this scenario, the cost of treatment cancels itself out as everyone incurs the treatment cost and so the cost is not included in the analysis.

All cost inputs are summarised in Table 32.

Table 32: Cost inputs

Item	Unit cost	Source
C6 antigen-based ELISA (combined IgG and IgM)	£25.45	RIPL laboratory manual April 2016-March 2017[385]
Immunoblot (separate IgG and IgM line blots)	£70.11	RIPL laboratory manual April 2016-March 2017[385]
Doxycycline 200mg daily, 21 days	£4.57	January 2017 NHS Electronic Drug Tariff[328]
Doxycycline 200mg daily, 28 days	£6.10	January 2017 NHS Electronic Drug Tariff[328]

Additional scenarios

In addition to the 5 scenarios outlined in Table 31, a number of sensitivity analyses were conducted to explore uncertainty in the assumptions and inputs. These are summarised below (scenarios 6-8).

As noted above, there is some uncertainty regarding the true prevalence of Lyme disease in England; thus, 2 sensitivity analyses were completed, 1 with a lower prevalence of 1% (scenario 6) and 1 with a higher prevalence of 15% (scenario 7), in both cases using the test accuracy data and treatment costs of scenario 1.

The cost of Lyme neuroborreliosis antibiotic treatment could be higher if intravenous rather than oral antibiotics were given. As highlighted above, if the population suspected of Lyme disease had symptoms such as meningitis, they would all receive intravenous antibiotics irrespective of the Lyme diagnosis. In this scenario, then the cost of treatment would be the same for all people entering the analysis and would therefore cancel out. A sensitivity analysis (scenario 8) was conducted using the accuracy data for scenario 1 but with no cost of treatment included to reflect all people receiving intravenous antibiotics.

H.1.4 Results

The results in terms of the unit cost of misdiagnosis to the NHS for 2-tier testing to be cost neutral compared to initial testing only of all 8 scenarios are reported in Table 33. The results indicate that the unit cost of a misdiagnosis would need to be between £69 and £381

(depending on data used) for the 2-tier testing to be cost neutral compared to initial testing only.

Table 33: Threshold analysis results: unit cost of misdiagnosis resulting in 2-tier testing being cost neutral compared to initial testing only

Scenario	Unit cost of misdiagnosis resulting in 2-tier testing being cost neutral
1 (Lyme neuroborreliosis)	£83
2 (Lyme neuroborreliosis)	£142
3 (Lyme neuroborreliosis)	£91
4 (Lyme arthritis)	£218
5 (Lyme carditis)	£381
6 (Lyme neuroborreliosis – low prevalence)	£69
7 (Lyme neuroborreliosis – high prevalence)	£109
8 (Lyme neuroborreliosis – intravenous antibiotics)	£88

A breakdown of the mean cost of antibiotics and testing per person is presented in Table 34. This demonstrates that the cost of testing is greater for 2-tier testing on average per person but the cost of treatment is lower compared to initial testing only. Note the cost of treatment is not included for Scenario 8 as explained above under 'Additional Scenarios'.

Table 34: Breakdown of mean cost of testing and antibiotics per person

Test	Mean cost of testing per person	Mean cost of antibiotics per person
Scenario 1 (Lyme neuroborreliosis)		
Initial test only	£25.45	£1.47
Initial and confirmatory test	£48.07	£0.29
Scenario 2 (Lyme neuroborreliosis)		
Initial test only	£25.45	£0.57
Initial and confirmatory test	£34.24	£0.30
Scenario 3 (Lyme neuroborreliosis)		
Initial test only	£25.45	£1.47
Initial and confirmatory test	£48.07	£0.33
Scenario 4 (Lyme arthritis)		
Initial test only	£25.45	£0.63
Initial and confirmatory test	£32.97	£0.44
Scenario 5 (Lyme carditis)		
Initial test only	£25.45	£0.35
Initial and confirmatory test	£30.97	£0.28
Scenario 6 (Lyme neuroborreliosis – low prevalence)		
Initial test only	£25.45	£1.31
Initial and confirmatory test	£45.53	£0.05
Scenario 7 (Lyme neuroborreliosis – high prevalence)		
Initial test only	£25.45	£1.72
Initial and confirmatory test	£51.81	£0.63
Scenario 8 (Lyme neuroborreliosis – intravenous antibiotics)		
Initial test only	£25.45	£0.00
Initial and confirmatory test	£48.07	£0.00

A breakdown of the number of true positives, true negatives, false positives and false negatives for scenarios 1–5 are presented in Table 35. These results demonstrate that for 2-tier testing, there is a small increase in false negatives in some scenarios but a large decrease in false positives compared to the initial testing only. Overall, there are fewer misdiagnoses with 2-tier testing compared to initial testing only.

Table 35: Breakdown of correct and incorrect diagnoses (scenarios 1–5)

Test	TP	TN	FP	FN	Incorrect diagnoses (FP and FN)
Scenario 1 (Lyme neuroborreliosis)					
Initial test only	61	672	261	5	267
Initial and confirmatory test	60	931	3	7	9
Scenario 2 (Lyme neuroborreliosis)					
Initial test only	60	868	65	7	72
Initial and confirmatory test	60	928	5	7	12
Scenario 3 (Lyme neuroborreliosis)					
Initial test only	67	896	261	5	267
Initial and confirmatory test	53	915	18	13	32
Scenario 4 (Lyme arthritis)					
Initial test only	70	893	37	0	37
Initial and confirmatory test	67	928	5	0	5
Scenario 5 (Lyme carditis)					
Initial test only	57	915	19	9	28
Initial and confirmatory test	57	928	5	9	15

Abbreviations: FN: false negative; FP: false positive; TN: true negative; TP: true positive

H.1.5 Discussion

The results of this exploratory analysis indicate that the unit cost of a misdiagnosis would need to be between £69 and £381 (depending on data inputs used) for the 2-tier testing to be cost neutral compared to initial testing only. To aid their consideration of what the unit cost of misdiagnosis might be to the NHS, relevant unit costs were presented to the committee (Table 36).

Table 36: Relevant unit costs

Item	Unit cost	Source
GP appointment	£36	PSSRU 2016[69]
Consultant-led outpatient attendance infectious disease, adult	£240	NHS reference costs 2015-2016[82]
Consultant-led outpatient attendance infectious disease, paediatric	£317	
Consultant-led outpatient attendance rheumatology, adult	£152	
Consultant-led outpatient attendance	£211	

Item	Unit cost	Source
rheumatology, paediatric		
Consultant-led outpatient attendance cardiology, adult	£136	
Consultant-led outpatient attendance cardiology, paediatric	£178	

Overall, the committee considered that a misdiagnosis was very likely to cost at least £381, as these people would have a number of healthcare interactions whether the misdiagnosis was a false positive or a false negative. Therefore, the committee agreed that 2-tier testing is very likely to be at least cost neutral compared to initial testing only and that it may even be cost saving.

A limitation of this analysis is that it did not account for health benefits. If health benefits had been incorporated, then 2-tier testing would likely be cost effective compared to initial testing, as the total number of correct diagnoses is greater in all scenarios for 2-tier testing compared to initial testing only.

Overall, this analysis is considered to be partially applicable with potential serious limitations.

In conclusion, the committee agreed that this analysis supported a recommendation that people suspected of Lyme disease should have an initial ELISA and if they test positive, they should have a confirmatory immunoblot.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 37: Studies excluded from the clinical reviews on initial tests, confirmatory tests and combination of tests for Lyme disease

Reference	Reason for exclusion
Aberer 2007[1]	Excluded due to an incorrect diagnostic test
Aberer 2012[2]	Excluded due to an incorrect study design
Aguero-Rosenfeld 2003[3]	Excluded due to an incorrect study design
Ai 1994[4]	Excluded due to an incorrect population
Albisetti 1997[6]	Excluded due to an incorrect analysis
al-Sharif 2011[5]	Excluded due to an incorrect analysis
Ananjeva 1995[7]	Excluded due to an incorrect analysis
Ang 2011[9]	Excluded due to an incorrect analysis
Arnez 2002[10]	Excluded due to an incorrect analysis
Arteaga 1998[11]	Excluded due to an incorrect population
Artsob 1993[12]	Excluded due to an incorrect study design
Artsob 1991[13]	Excluded due to an incorrect population
Aucott 2016[15]	Excluded due to an incorrect outcome
Bazovska 2001[19]	Excluded due to an incorrect analysis
Bednarova 2006[20]	Excluded due to an incorrect diagnostic test
Bergstrom 1991[22]	Excluded due to an incorrect analysis
Berti 2016[23]	Conference abstract
Bil-Lula 2015[24]	Excluded due to an incorrect population
Binnicker 2008[25]	Excluded due to an incorrect analysis
Bizzaro 2001[26]	Excluded due to an incorrect population
Blaauw 1993[28]	Excluded due to an incorrect analysis
Blanc 2007[29]	Excluded due to an incorrect analysis
Borde 2012[30]	Excluded due to an incorrect study design
Bounas-Pyrros 2016[31]	Conference abstract
Bremell 2013[35]	Excluded due to an incorrect analysis
Brettschneider 1998[36]	Excluded due to an incorrect analysis
Bretz 2001[37]	Excluded due to an incorrect analysis
Brissette 2010[38]	Excluded due to an incorrect diagnostic test
Brunner 1998[40]	Excluded due to an incorrect population
Bucak 2016[41]	Excluded due to an incorrect analysis
Buffrini 2000[42]	Excluded due to an incorrect analysis
Burbelo 2010[43]	Excluded due to an incorrect diagnostic test
Busson 2012[44]	Excluded due to an incorrect population
Callister 1996[46]	Excluded due to an incorrect analysis
Cerar 2008[50]	Excluded due to an incorrect study design
Cerar 2008[47]	Excluded due to an incorrect population
Cermakova 2005[51]	Excluded due to an incorrect analysis
Chan 1996[52]	Excluded due to an incorrect analysis
Coleman 2011[55]	Excluded due to an incorrect diagnostic test
Commins 2011[56]	Excluded due to an incorrect population
Cook 2016[57]	Systematic review (references checked)
Cook 2017[58]	Excluded due to an incorrect study design
Cooke 1994[59]	Excluded due to an incorrect analysis
Cottle 2012[60]	Excluded due to an incorrect analysis
Coulter 2005[61]	Excluded due to an incorrect population
Coyle 1990[64]	Excluded due to an incorrect analysis
Coyle 1994[63]	Excluded due to an incorrect population
Coyle 1995[65]	Excluded due to an incorrect population

Reference	Reason for exclusion
Craft 1984[66]	Excluded due to an incorrect analysis
Cretella 1995[67]	Excluded due to an incorrect analysis
Cruz 1991[68]	Excluded due to an incorrect analysis
Cutler 1990[70]	Excluded due to an incorrect analysis
Cutler 1994[71]	Excluded due to an incorrect analysis
Cutler 1989[72]	Excluded due to an incorrect analysis
Cyr 2005[73]	Excluded due to an incorrect analysis
Dattwyler 1999[75]	Excluded due to an incorrect study design
Dattwyler 1988[76]	Excluded due to an incorrect analysis
Davidson 1996[77]	Excluded due to an incorrect analysis
Davidson 1999[78]	Excluded due to an incorrect analysis
Deanehan 2014[79]	Excluded due to an incorrect analysis
Dehnert 2012[80]	Excluded due to an incorrect analysis
Demaerschalck 1995[81]	Excluded due to an incorrect analysis
Dessau 2010[84]	Excluded due to an incorrect study design
Dessau 2015[86]	Excluded due to an incorrect analysis
Dessau 2013[83]	Excluded due to an incorrect analysis
Dessau 2015[87]	Excluded due to an incorrect analysis
Dh te 2000[88]	Excluded due to an incorrect analysis
Dickeson 2016[89]	Excluded due to an incorrect analysis
Dressler 1991[91]	Excluded due to an incorrect population
Du 2007[92]	Excluded due to an incorrect analysis
Dumler 2001[93]	Excluded due to an incorrect study design
Dunaj 2013[94]	Excluded due to an incorrect study design
Durovska 2010[95]	Excluded due to an incorrect population
Eichenfield 1986[96]	Excluded due to an incorrect study design
Eisendle 2007[97]	Excluded due to an incorrect population
Ekerfelt 2004[98]	No reference standard
Embers 2016[99]	Excluded due to an incorrect population
Embers 2007[100]	Excluded due to an incorrect study design
Engstrom 1995[101]	Excluded due to an incorrect analysis
Eshoo 2012[102]	Excluded due to an incorrect analysis
Evans 2010[104]	Excluded due to an incorrect analysis
Evans 2005[103]	Excluded due to an incorrect analysis
Exner 2003[105]	Excluded due to an incorrect analysis
Fahrer 1998[106]	Excluded due to an incorrect study design
Fahrer 1991[107]	Excluded due to an incorrect analysis
Fawcett 1998[111]	Excluded due to an incorrect analysis
Fawcett 1992[109]	Excluded due to an incorrect analysis
Fawcett 1993[110]	Excluded due to an incorrect analysis
Feder 1992[112]	Excluded due to an incorrect analysis
Feder 1995[113]	Excluded due to an incorrect study design
Felz 1999[114]	Excluded due to an incorrect study design
Fidelus-Gort 1993[115]	Excluded due to an incorrect population
Figueroa 1996[116]	Excluded due to an incorrect study design
Fikrig 2004[117]	Excluded due to an incorrect analysis
Fikrig 1992[118]	Excluded due to an incorrect study type
Fister 1989[119]	Excluded due to an incorrect study design
Fix 1998[120]	Excluded due to an incorrect study type
Fleming 2004[121]	Excluded due to an incorrect analysis
Flisiak 1999[122]	Excluded due to an incorrect study design
Fujita 1991[125]	Excluded due to an incorrect study type
Furuta 2001[127]	Excluded due to an incorrect population
Garro 2009[128]	Excluded due to an incorrect analysis
Ghayad 2012[130]	Excluded due to an incorrect study design
Glatz 2006[131]	Excluded due to an incorrect study design
Gomes-Solecki 2007[134]	Excluded due to an incorrect analysis

Reference	Reason for exclusion
Gomes-Solecki 2000[133]	Excluded due to an incorrect study design
Gomes-Solecki 2002[136]	Excluded due to an incorrect population
Goodlad 2002[137]	Excluded due to an incorrect study type
Gooskens 2006[138]	Excluded due to an incorrect analysis
Goossens 2001[141]	Not available
Gordillo 1999[142]	Excluded due to an incorrect analysis
Gospodinova 2010[143]	Excluded due to an incorrect analysis
Grabe 2008[144]	Excluded due to an incorrect analysis
Gross 1998[146]	Excluded due to an incorrect analysis
Grusell 2002[147]	Excluded due to an incorrect analysis
Grygorczuk 2007[148]	Excluded due to an incorrect diagnostic test
Guellec 2016[149]	Excluded due to an incorrect population
Gutierrez 1995[151]	Excluded due to an incorrect population
Gutierrez 2000[150]	Excluded due to an incorrect analysis
Guy 1991[153]	Excluded due to an incorrect study design
Guy 1989[152]	Excluded due to an incorrect population
Halpern 2014[155]	Excluded due to an incorrect analysis
Hamann-Brand 1994[156]	Excluded due to an incorrect population
Hammers-Berggren 1994[158]	Excluded due to an incorrect study design
Hammers-Berggren 1994[157]	Excluded due to an incorrect study design
Hammouda 1995[159]	Excluded due to an incorrect population
Hanner 1993[160]	Excluded due to an incorrect analysis
Hansen 1992[166]	Excluded due to an incorrect analysis
Hansen 1990[163]	Excluded due to an incorrect analysis
Hauser 1998[169]	Excluded due to an incorrect analysis
Hauser 1998[168]	Excluded due to an incorrect analysis
Hauser 1999[170]	Excluded due to an incorrect analysis
Hauser 1997[171]	Excluded due to an incorrect analysis
Heikkila 2002[173]	Excluded due to an incorrect analysis
Heikkila 2002[174]	Excluded due to an incorrect analysis
Hilton 1996[178]	Excluded due to an incorrect study design
Hjetland 2014[179]	Excluded due to an incorrect population
Hofmann 1996[180]	Excluded due to an incorrect study design
Hofstad 1987[181]	Excluded due to an incorrect population
Huppertz 1993[183]	Excluded due to an incorrect study design
Jansson 2005[184]	Excluded due to an incorrect population
Jarefors 2006[185]	Excluded due to an incorrect diagnostic test
Jiang 2005[187]	Not in English
Jin 2013[188]	Excluded due to an incorrect analysis
Jobe 2008[189]	Excluded due to an incorrect analysis
Johnston 1992[191]	Excluded due to an incorrect analysis
Jones 2009[192]	Excluded due to an incorrect analysis
Jonsson 1990[193]	Excluded due to an incorrect study design
Kaiser 2000[197]	Excluded due to an incorrect analysis
Kaiser 1994[195]	Excluded due to an incorrect study design
Kaiser 1995[196]	Excluded due to an incorrect analysis
Kaiser 1993[198]	Excluded due to an incorrect analysis
Kalish 2001[201]	Excluded due to an incorrect study design
Karlsson 1994[203]	Excluded due to an incorrect population
Keller 1992[205]	Excluded due to an incorrect population
Kepa 2015[206]	Excluded due to an incorrect analysis
Kolmel 1992[208]	Excluded due to an incorrect analysis
Kondrusik 2007[209]	Excluded due to an incorrect study design
Kowarik 2012[210]	Excluded due to an incorrect population
Kuiper 1994[212]	Excluded due to an incorrect analysis
Lahdenne 2003[213]	Excluded due to an incorrect analysis
Lahdenne 2006[214]	Excluded due to an incorrect analysis

Reference	Reason for exclusion
Lakos 2012[218]	Excluded due to an incorrect population
Lakos 2010[219]	Excluded due to an incorrect analysis
Lakos 2005[217]	Excluded due to an incorrect analysis
Lakos 1990[216]	Excluded due to an incorrect analysis
Lane 1990[220]	Excluded due to an incorrect analysis
Lange 1991[222]	Not in English
Lantos 2015[223]	Excluded due to an incorrect analysis
Lantos 2016[224]	Excluded due to an incorrect analysis
Lebech 2002[227]	Excluded due to an incorrect study design
Ledue 1996[230]	Excluded due to an incorrect analysis
Lee 2014[232]	Excluded due to an incorrect analysis
Lee 2010[233]	Excluded due to an incorrect analysis
Leeflang 2016[234]	Excluded due to an incorrect study design
Leinweber 2004[235]	Excluded due to an incorrect diagnostic test
Lencakova 2007[237]	Excluded due to an incorrect analysis
Li 2011[239]	Excluded due to an incorrect analysis
Liang 1999[240]	Excluded due to an incorrect analysis
Lin 1991[242]	Excluded due to an incorrect analysis
Lipsett 2015[244]	Excluded due to an incorrect analysis
Liu 2016[245]	Excluded due to an incorrect analysis
Liu 2016[246]	Excluded due to an incorrect analysis
Liveris 2012[249]	Excluded due to an incorrect analysis
Liveris 2012[250]	Excluded due to an incorrect analysis
Liveris 2011[248]	Excluded due to an incorrect analysis
Liveris 2002[251]	Excluded due to an incorrect analysis
Livermore 2016[252]	Conference abstract
Ljostad 2007[255]	Excluded due to an incorrect analysis
Ljostad 2005[254]	Excluded due to an incorrect study design
Londono 2014[256]	Excluded due to an incorrect analysis
Lotric-Furlan 1999[257]	Excluded due to an incorrect analysis
Luft 1992[259]	Excluded due to an incorrect analysis
Luft 1993[258]	Excluded due to an incorrect analysis
Luger 1990[260]	Excluded due to an incorrect analysis
Lukac 2006[261]	Excluded due to an incorrect analysis
Ma 1992[262]	Excluded due to an incorrect analysis
Mackensen 2011[263]	Excluded due to an incorrect analysis
Mackworth-Young 1990[264]	Excluded due to an incorrect diagnostic test
Maes 2017[265]	Excluded due to an incorrect analysis
Magnarelli 1991[268]	Excluded due to an incorrect analysis
Magnarelli 1995[271]	Excluded due to an incorrect analysis
Magnarelli 1996[273]	Excluded due to an incorrect analysis
Magnarelli 2000[274]	Excluded due to an incorrect analysis
Magnarelli 1984[276]	Excluded due to an incorrect analysis
Magnarelli 1990[277]	Excluded due to an incorrect analysis
Magnarelli 1989[269]	Excluded due to an incorrect analysis
Magnarelli 1987[270]	Excluded due to an incorrect analysis
Magnarelli 2002[275]	Excluded due to an incorrect analysis
Magnarelli 1987[266]	Excluded due to an incorrect analysis
Mansy 1996[278]	Excluded due to an incorrect population
Marangoni 2006[280]	Excluded due to an incorrect analysis
Marangoni 2005[282]	Excluded due to an incorrect analysis
Markowicz 2015[283]	Excluded due to an incorrect analysis
Marques 2005[285]	Excluded due to an incorrect analysis
Marques 2009[284]	Excluded due to an incorrect analysis
Marques 2000[286]	Excluded due to an incorrect analysis
Mathiesen 1998[287]	Excluded due to an incorrect analysis
Mavin 2014[292]	Excluded due to an incorrect analysis

Reference	Reason for exclusion
Mavin 2011[290]	Excluded due to an incorrect analysis
Mavin 2009[289]	Excluded due to an incorrect analysis
Mavin 2007[291]	Excluded due to an incorrect analysis
Mayne 2014[293]	Excluded due to an incorrect analysis
Melby 1990[294]	Excluded due to an incorrect population
Melchers 1991[295]	Excluded due to an incorrect study design
Melski 1993[296]	Excluded due to an incorrect study design
Mikkila 1997[298]	Excluded due to an incorrect analysis
Milewski 2011[299]	Excluded due to an incorrect analysis
Millner 1989[300]	Excluded due to an incorrect analysis
Millner 1991[301]	Excluded due to an incorrect analysis
Mogilyansky 2004[303]	Excluded due to an incorrect population
Molins 2016[306]	Duplicate
Moniuszko 2012[311]	Excluded due to an incorrect analysis
Moniuszko 2014[309]	Excluded due to an incorrect analysis
Moniuszko 2015[310]	Excluded due to an incorrect study design
Moravcova 2005[375]	Excluded due to an incorrect analysis
Moravcova 2001[312]	Not in English
Mouritsen 1996[314]	Excluded due to an incorrect analysis
Mueller 2006[315]	Excluded due to an incorrect analysis
Mullegger 2007[316]	Excluded due to an incorrect analysis
Murray 1986[317]	Excluded due to an incorrect analysis
Nachamkin 1996[318]	Excluded due to an incorrect analysis
Nadal 1989[319]	Excluded due to an incorrect analysis
Nadelman 1996[320]	Excluded due to an incorrect analysis
Nadelman 1990[321]	Excluded due to an incorrect study design
Nagel 2008[322]	Excluded due to an incorrect analysis
Naktin 2017[323]	Excluded due to an incorrect study type
Nayak 2016[325]	Excluded due to an incorrect analysis
Neubert 1986[326]	Excluded due to an incorrect diagnostic test
Neumann 1989[327]	Excluded due to an incorrect analysis
Nichol 1998[329]	Excluded due to an incorrect analysis
Nigrovic 2013[330]	Excluded due to an incorrect analysis
Nilsson 1996[331]	Excluded due to an incorrect analysis
Norman 1996[336]	Excluded due to an incorrect analysis
Nowakowski 2009[337]	Excluded due to an incorrect analysis
Nowakowski 2001[338]	Excluded due to an incorrect analysis
Ogden 2017[339]	Excluded due to an incorrect analysis
Ogrinc 2013[341]	Excluded due to an incorrect analysis
Ogrinc 2002[340]	Excluded due to an incorrect analysis
Oksi 1999[342]	Excluded due to an incorrect study design
Oksi 2001[343]	Excluded due to an incorrect analysis
Olsson 1991[345]	Excluded due to an incorrect analysis
Oschmann 1997[346]	Excluded due to an incorrect analysis
Pachner 1993[347]	Excluded due to an incorrect analysis
Pachner 1992[348]	Excluded due to an incorrect diagnostic test
Palacios 1999[350]	Excluded due to an incorrect analysis
Palecek 2010[351]	Excluded due to an incorrect analysis
Paluchowska 1996[352]	Excluded due to an incorrect analysis
Panelius 2002[353]	Excluded due to an incorrect analysis
Panelius 2003[354]	Excluded due to an incorrect analysis
Panelius 2007[357]	Excluded due to an incorrect analysis
Pappas 1985[358]	Excluded due to an incorrect population
Park 2011[359]	Excluded due to an incorrect analysis
Patriquin 2016[360]	Excluded due to an incorrect analysis
Paul 1987[361]	Excluded due to an incorrect analysis
Pavia 2000[362]	Excluded due to an incorrect analysis

Reference	Reason for exclusion
Pavlickova 2004[363]	Excluded due to an incorrect study design
Peltomaa 1998[365]	Excluded due to an incorrect analysis
Pennell 1987[366]	Excluded due to an incorrect analysis
Peter 1997[367]	Excluded due to an incorrect analysis
Petersen 2008[368]	Excluded due to an incorrect analysis
Pfluger 1989[369]	Excluded due to an incorrect diagnostic test
Philipp 2006[370]	Excluded due to an incorrect analysis
Picha 2014[374]	Excluded due to an incorrect analysis
Picha 2008[372]	Excluded due to an incorrect study design
Picha 2016[373]	Excluded due to an incorrect population
Picken 1997[376]	Excluded due to an incorrect study design
Pierer 1999[377]	Excluded due to an incorrect study design
Pietikainen 2016[378]	Excluded due to an incorrect analysis
Pietruczuk 2006[379]	Excluded due to an incorrect analysis
Pleyer 2001[380]	Excluded due to an incorrect analysis
Plorer 1993[381]	Excluded due to an incorrect analysis
Puri 2014[387]	Excluded due to an incorrect analysis
Qiu 2000[388]	Excluded due to an incorrect population
Ranki 1994[389]	Excluded due to an incorrect analysis
Rasiah 1994[390]	Excluded due to an incorrect analysis
Rauer 2001[391]	Excluded due to an incorrect analysis
Rebman 2015[394]	Excluded due to an incorrect analysis
Rehse-Kupper 1987[395]	Excluded due to an incorrect analysis
Reiber 2013[396]	Excluded due to an incorrect population
Riesbeck 2007[397]	Excluded due to an incorrect analysis
Rijpkema 1997[399]	Excluded due to an incorrect analysis
Rijpkema 1994[398]	Excluded due to an incorrect analysis
Robertson 2000[400]	Excluded due to an incorrect analysis
Rodiger 2013[401]	Excluded due to an incorrect study design
Rose 1994[402]	Excluded due to an incorrect analysis
Rose 1991[403]	Excluded due to an incorrect analysis
Rosslhuber 2012[404]	Excluded due to an incorrect study design
Rossmann 2009[405]	Excluded due to an incorrect study design
Rudenko 2005[407]	Excluded due to an incorrect analysis
Rupprecht 2005[408]	Excluded due to an incorrect analysis
Rutkowski 1997[410]	Excluded due to an incorrect analysis
Ruzic-Sabljic 2017[412]	Excluded due to an incorrect analysis
Ryffel 1998[413]	Excluded due to an incorrect analysis
Salazar 2005[414]	Excluded due to an incorrect diagnostic test
Santino 2008[415]	Excluded due to an incorrect analysis
Schempp 1993[417]	Excluded due to an incorrect analysis
Schenk 2015[418]	Excluded due to an incorrect analysis
Schmidt 2011[420]	Excluded due to an incorrect analysis
Schmidt 1995[419]	Excluded due to an incorrect study design
Schmitz 1993[421]	Excluded due to an incorrect analysis
Schutzer 1997[426]	Excluded due to an incorrect analysis
Schutzer 1999[427]	Excluded due to an incorrect analysis
Schutzer 1990[425]	Excluded due to an incorrect analysis
Schwaiger 2001[428]	Excluded due to an incorrect analysis
Schwartz 1993[429]	Excluded due to an incorrect analysis
Schwartz 1993[430]	Excluded due to an incorrect analysis
Schwarzova 2009[432]	Excluded due to an incorrect analysis
Seppala 1994[434]	Excluded due to an incorrect population
Seriburi 2012[435]	Excluded due to an incorrect analysis
Shrestha 1985[436]	Excluded due to an incorrect study design
Sieper 1993[437]	Excluded due to an incorrect analysis
Sikand 1999[438]	Excluded due to an incorrect diagnostic test

Reference	Reason for exclusion
Sillanpaa 2014[440]	Excluded due to an incorrect analysis
Sillanpaa 2013[441]	Excluded due to an incorrect analysis
Simpson 1990[442]	Excluded due to an incorrect analysis
Sjostedt 1994[444]	Excluded due to an incorrect analysis
Skarpaas 2007[445]	Excluded due to an incorrect analysis
Skogman 2010[447]	Excluded due to an incorrect analysis
Smit 2015[449]	Excluded due to an incorrect analysis
Smouha 1997[450]	Excluded due to an incorrect study design
Soloski 2014[451]	Excluded due to an incorrect analysis
Sood 1993[452]	Excluded due to an incorrect study design
Sood 1995[453]	Excluded due to an incorrect analysis
Sroka-Oleksiak 2016[454]	Not in English
Steere 1993[459]	Excluded due to an incorrect diagnostic test
Steere 1983[456]	Excluded due to an incorrect analysis
Steere 1977[457]	Excluded due to an incorrect study design
Stefancikova 2001[460]	Excluded due to an incorrect analysis
Steinberg 1996[461]	Excluded due to an incorrect study design
Stiernstedt 1985[465]	Excluded due to an incorrect population
Stiernstedt 1986[464]	Excluded due to an incorrect analysis
Strle 2014[467]	Excluded due to an incorrect analysis
Strle 2017[468]	Excluded due to an incorrect analysis
Stubs 2009[469]	Excluded due to an incorrect diagnostic test
Sundin 2012[470]	Excluded due to an incorrect analysis
Tammemagi 1995[471]	Excluded due to an incorrect analysis
Thompson 2009[472]	Excluded due to an incorrect analysis
Tilton 1997[473]	Excluded due to an incorrect population
Tjernberg 2008[476]	Excluded due to an incorrect analysis
Tokarska-Rodak 2010[478]	Excluded due to an incorrect analysis
Tokarska-Rodak 2008[479]	Excluded due to an incorrect study design
Treib 1998[480]	Excluded due to an incorrect analysis
Trevejo 1999[482]	Excluded due to an incorrect analysis
Trevisan 1996[483]	Excluded due to an incorrect population
Trnovcova 2007[484]	Excluded due to an incorrect study design
Tuuminen 2011[486]	Excluded due to an incorrect analysis
Tveitnes 2012[487]	Excluded due to an incorrect population
Tylewska-Wierzbanowska 2002[488]	Excluded due to an incorrect analysis
Ulvestad 2001[489]	Excluded due to an incorrect analysis
Valentine-Thon 2007[490]	Excluded due to an incorrect analysis
van Burgel 2011[491]	Excluded due to an incorrect population
Vermeersch 2009[495]	Excluded due to an incorrect analysis
Vienecke 1995[496]	Excluded due to an incorrect analysis
von Wissmann 2015[499]	Excluded due to an incorrect analysis
Vrethem 2011[500]	Excluded due to an incorrect analysis
Waddell 2016[501]	Excluded due to an incorrect study design
Wang 1996[503]	Excluded due to an incorrect diagnostic test
Wang 2000[502]	Excluded due to an incorrect analysis
Wang 1993[504]	Excluded due to an incorrect analysis
Weber 1986[505]	Excluded due to an incorrect study design
Weiss 1995[507]	Excluded due to an incorrect population
Weller 1991[508]	Excluded due to an incorrect diagnostic test
Werner 2001[509]	Excluded due to an incorrect analysis
Widhe 2005[511]	Excluded due to an incorrect analysis
Wienecke 1993[512]	Excluded due to an incorrect analysis
Wienecke 1995[513]	Excluded due to an incorrect population
Wieneke 2000[514]	Excluded due to an incorrect population
Wilhelmsson 2016[515]	Excluded due to an incorrect analysis

Reference	Reason for exclusion
Wilkinson 1984[516]	Excluded due to an incorrect analysis
Wilske 1984[520]	Excluded due to an incorrect population
Wilske 1994[518]	Excluded due to an incorrect analysis
Wise 1991[521]	Excluded due to an incorrect study design
Wojciechowska-Koszko 2011[522]	Excluded due to an incorrect analysis
Wokke 1988[523]	Excluded due to an incorrect population
Wormser 2013[526]	Excluded due to an incorrect analysis
Wormser 2000[525]	Excluded due to an incorrect analysis
Wormser 2013[529]	Excluded due to an incorrect analysis
Wormser 2014[530]	Excluded due to an incorrect analysis
Wormser 2000[524]	Excluded due to an incorrect study design
Wormser 1998[528]	Excluded due to an incorrect study design
Wormser 2008[527]	Excluded due to an incorrect study design
Wutte 2014[531]	Excluded due to an incorrect analysis
Ye 2016[534]	Excluded due to an incorrect diagnostic test
Ye 2017[533]	Excluded due to an incorrect analysis
Yu 1996[535]	Excluded due to an incorrect study design
Yu 1996[536]	Excluded due to an incorrect analysis
Zajkowska 2015[538]	Excluded due to an incorrect analysis
Zajkowska 2001[537]	Excluded due to an incorrect diagnostic test
Zajkowska 2000[539]	Excluded due to an incorrect analysis
Zbinden 1994[540]	Excluded due to an incorrect analysis
Zhang 2015[541]	Excluded due to an incorrect analysis
Zhang 1997[542]	Excluded due to an incorrect analysis
Zhioua 1998[543]	Excluded due to an incorrect analysis
Ziemer 2008[544]	Excluded due to an incorrect population
Zoller 1991[545]	Excluded due to an incorrect analysis
Zoller 1990[546]	Not in English
Zweitzig 2016[547]	Not available

I.2 Excluded health economic studies

Table 38: Studies excluded from the health economic review

Reference	Reason for exclusion
Mavin 2014[292]	This study was excluded due to a combination of limited applicability and very serious methodological limitations. QALYs were not used as the health outcome measure. The analysis is based on a study that was not included in the clinical review for the guideline due to a lack of reference standard. Furthermore, only costs of the reagents are included in the analysis. Costs of other tests, staffing and downstream costs are not reported. The source of unit costs is unclear. No analysis of uncertainty is reported.
Jansson 2005[184]	This study was excluded due to a combination of limited applicability and very serious methodological limitations. Finnish resource use data and unit costs (2004) may not reflect current NHS context. QALYs were not used as the health outcome measure. The analysis is based on a study that was not included in the clinical review for the guideline due to a lack of reference standard and an unclear population. A cost saving is presented in the discussion of paper with no detail provided as to how this was calculated. Unclear what unit costs are incorporated into this analysis. The source of unit costs not reported. No analysis of uncertainty is reported.

Appendix J: Research recommendations

J.1 What are the best laboratory tests to diagnose initial and ongoing infection and determine reinfection in the different presentations of Lyme disease

Research question: What is the most clinically and cost effective serological antibody-based test, biomarker (such as CXCL13), lymphocyte transformation and ELISPOT for diagnosing Lyme disease in the UK at all stages, including reinfection?

Why this is important:

Determining the most clinically and cost effective diagnostic tests for Lyme disease will improve patient care and is of high priority. The clinical presentation of Lyme disease is very variable, with diagnosis of all presentations except erythema migrans relying in part on laboratory testing. Current literature suggests that a combined IgG/IgM ELISA based on the C6 peptide and immunoblot are useful but published evidence is of either low or very low quality and is not UK based. There is evidence of variation in the C6 peptide between the principal Borrelia genospecies in UK ticks and a combination of ELISAs may improve sensitivity. Determining the most clinically and cost effective diagnostic tests for Lyme disease will improve patient care and is of high priority.

A “test of cure” for Lyme disease does not exist and, consistent with most other infectious diseases, positive serology is likely to remain positive following successful treatment of acute infection in the majority of patients. However, we know little about the evolution of antibody titres over time in those who have been treated successfully and in those who have persisting symptoms. It is frequently stated that early antibiotic treatment of Lyme disease abrogates the immune response, so that serology remains or becomes negative. The evidence base for this is minimal and this is not a common occurrence in other infections. Understanding the natural course of Lyme disease serology and non-serological tests over time may assist in the interpretation of test results in patients who remain symptomatic and in those who are high risk for re-infection, such as those with occupational exposure

In particular, further research into the value of CXCL13 and other biomarkers including, ELISPOT testing and lymphocyte transformation tests may be helpful to support the current low quality evidence.

Criteria for selecting high-priority research recommendations:

PICO question	Population: children, young people and adults with Lyme disease Intervention(s): 2-tier testing (IgM/IgG ELISA based on the C6 antigen followed by an immunoblot) Comparison: CXCL13 (for Neuroborreliosis), ELISPOT (for Neuroborreliosis), lymphocyte transformation (for any Lyme disease presentation), immunoblot alone (for any presentation of Lyme disease) Outcome(s): core outcome set
Importance to patients or the population	None of the diagnostic tests currently available for Lyme disease are 100% accurate and therefore people with Lyme disease are missed or people without Lyme disease are falsely diagnosed with Lyme disease and receive treatment. For people with suspected Lyme disease, it is important to receive a correct diagnosis and appropriate treatment. Determining the most clinically and cost-effective test will ensure the best possible outcome for the highest number of people.
Relevance to NICE guidance	Due to a lack of an accurate reference standard, diagnostic test accuracy studies will always provide an overestimate or underestimate of the true accuracy of a test. A diagnostic randomised controlled trial will provide

	evidence on whether one test results in better outcomes compared to another test, rather than aiming to determine which test is more accurate in diagnosing Lyme disease without taking treatment options and therefore patient outcomes into account.
Relevance to the NHS	Determining the most clinically and cost effective test for Lyme disease will improve diagnostic accuracy and patient care as well as reduce the misuse of costly services.
National priorities	No
Current evidence base	The evidence on the accuracy of diagnostic tests for Lyme disease is generally of very low quality. No diagnostic RCTs were identified for this guideline.
Equality	None relevant
Study design	Diagnostic RCT Diagnostic test accuracy studies should be conducted for novel tests of limited availability.
Feasibility	Inaccurate tests can result in a missed diagnosis of Lyme disease or in people being falsely diagnosed with the disease. As a result, people might receive inappropriate treatment and repeat testing. Some people might develop long-term morbidity, which can result in high costs for the NHS and social services. The high costs of such research are therefore justified by the potentially high reduction in costs for the NHS.
Other comments	The study may attract commercial funders in the diagnostics arena including companies developing novel assays or biomarkers.
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

J.2 Seroprevalence of Lyme disease specific antibodies (and other tick borne infections in the UK population)

Research question: What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections (such as babesiosis, ehrlichiosis, anaplasmosis, bartonellosis or Q fever) in people in the UK when performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?

Why this is important:

This information is not currently available and is of high priority. Without understanding the underlying population seroprevalence of Lyme disease-specific antibodies in the UK, it is impossible to interpret incidence data accurately or to understand fully the epidemiology of Lyme disease in the UK. The available data suggests there are areas of higher and lower prevalence in the UK but with many gaps in knowledge. The information is will help to interpret serology of individuals living in endemic areas where positive serological results may be more common and may not always indicate an acute or recent infection. This will be of benefit to patients and healthcare workers in the UK treating or affected by Lyme disease. Many people are concerned about the possible presence of co-infections transmitted by ticks: these are thought to be rare in the UK (compared to, for example, the east coast of the US) but we have no data to confirm or refute this. Better evidence may improve diagnostic and treatment decisions.

Criteria for selecting high-priority research recommendations:

PICO question	The questions that should be answered are: • What is the seroprevalence of Lyme disease specific antibodies in the UK using UK accredited assays? • What is the prevalence of co-infections with other tick-borne infections in people who acquired Lyme disease in the UK?

	The focus of this research will be people with a positive serology for Lyme disease, babesiosis, ehrlichiosis, anaplasmosis, bartonellosis and Q fever in the UK. People do not have to have active disease to be eligible for this study.
Importance to patients or the population	Currently, tests cannot distinguish between active or past infection of Lyme disease. People who are seropositive for Lyme disease-specific antibodies and who have signs and symptoms indicative of Lyme disease will receive appropriate treatment. Understanding the epidemiology and regional prevalence of Lyme disease in the UK will help in the interpretation of serological test results. Distinguishing between active disease and seropositivity following successfully treated disease will improve patient outcomes. This research will also provide physicians with the knowledge of co-infection transmitted by ticks so that appropriate treatment, if required, can be offered.
Relevance to NICE guidance	This guideline recommends that people who are seropositive but do not have any signs and symptoms indicative of Lyme disease should not receive treatment. Research on the seroprevalence of Lyme disease specific antibodies in the UK population will provide a more robust evidence base for recommendations on the appropriate course of action for seropositive people.
Relevance to the NHS	Distinguishing between active disease and seropositivity following successfully treated disease will provide physicians with the knowledge to provide treatment only when required. People who are seropositive but do not have any signs and symptoms suggestive of active Lyme disease do not require treatment. This research can help save costs by not providing treatment when it is not indicated and by reducing adverse events following inappropriate treatment.
National priorities	No
Current evidence base	There is a general lack of evidence on the seroprevalence of Lyme disease in the UK and the epidemiology of tick-borne co-infections, such as ehrlichiosis or babesiosis. Currently, tests cannot distinguish between active disease and seropositivity following successful treatment.
Equality	None relevant
Study design	Epidemiological study in a UK population. A routine-data-based study is the most beneficial study design, although appropriate data collection systems will have to be implemented first.
Feasibility	This research will help reduce costs due to avoiding treatment when it is not indicated. Well-defined disease criteria and a highly accurate reference standard are essential to ensure reliable study results.
Other comments	
Importance	High: the research is essential to inform future updates of key recommendations in the guideline.

1