National Institute for Health and Care Excellence

Final

Lyme disease: diagnosis and management

[C] Evidence reviews for diagnostic tests

NICE guideline 95

Diagnostic evidence review

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Final

This evidence review was developed by the National Guideline Centre

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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 help 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 sensu lato* (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 DNA; 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 *Borrelia burgdorferi sensu lato* (*Borrelia burgdorferi s.l.*).

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 burgdorferi s.l.* 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 burgdorferi s.l.* culture, polymerase chain reaction (PCR) and clinical diagnosis. *Borrelia burgdorferi s.l.* 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 burgdorferi s.l.* 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* ELISA 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 *Borrelia burgdorferi s.l.* 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 *Borrelia burgdorferi s.l.* 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 s.l.* 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)	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	Influenza 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)	n=27 Healthy	EIA	*IgM and IgG* <u>ELISA:</u>	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Arthritis (n=7) Neuroborreliosis (n=17) Age: not reported	volunteers		Lyme borreliosis Dako, Denmark Borrelio Recombinant Biomedica, Austria VIDAS Lyme Screen II bioMerieux, France		CDC 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* <u>ELISA:</u> Lyme borreliosis Dako, Denmark VIDAS Lyme Screen II bioMerieux, France <u>Western blot:</u> 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	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Goettner 2005[132]	n=85 EM (n=15) Neuroborreliosis (n=50) ACA (n=10) Lyme arthritis (n=10)	n=110 Healthy blood donors (n=60) Syphilis (n=10) Rheumatoid factor positive (n=10) Fever of unknown origin (n=30)	WB Lineblot	*IgG*	Serum	Clinical 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	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
				Dako EIA 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	Serum (n=315):	ELISA	IgM and IgG	Serum CSF	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Lymphocytic meningoradiculitis following Lyme disease Age (median): 51 years (6-74)	Healthy controls (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)		Sonic extract ELISA Flagellum ELISA			
Hansen	n=157	n=200	ELISA	*IgM and IgG*	Serum	Clinical	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
1989[162]	EM (n=107) ACA (n=50) Age (median): EM: 54 years (6-83) ACA: 61 years (28-89)	Healthy controls		Sonic extract ELISA Flagellum ELISA		diagnosis 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)	n=129 Healthy	Immunoblot	*IgM and IgG* BAG-*Borrelia* Blot	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Disseminated (disseminated EM or neuroborreliosis, n=18) Age: not reported	controls (n=53) Other infectious diseases (n=76)		Germany		CDC definition	
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)	n=113 Healthy	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
	Early neurologic (n=3) Lyme arthritis (n=36) Late neurologic (n=14) Age: not reported	blood donors					
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)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
							Total protein in 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

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
							symptoms
Klempner 2001[207]	n=21 Acute Lyme disease Age: not reported	n=10 Healthy persons	Western blot or Immunoblot	IgG MarDX Diagnostics, USA	Serum	Clinical 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	n=50	PCR	PCR	CSF	Clinical diagnosis	Previous neuroborreliosi

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Neuroborreliosis Age: 41.5 years (SD 24)	Healthy controls (n=25) Urinary tract infections (n=10) Multiple sclerosis (n=5) Central nervous system infections (n=10)			Urine		s group not included in 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)	PCR	PCR	Skin biopsy CSF	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
		High-dose antibiotic treatment 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	n=29 Syphilis (n=14)	ELISA	*IgM and IgG* Colorimetric ELISA (Lyme STAT Test Kit Whittaker	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Age: not reported	Infectious mononucleosis (n=4) Rheumatoid factor (n=11)		Bioproducts) FASTLYME			
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	n=77 Syphilis (n=15) Yaws (n=8)	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
	Age: not reported	Louse-borne relapsing 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	n=234 Healthy blood donors	ELISA	*IgM and IgG* RecomWell *Borrelia* test (Mikrogen; IgG and IgM)	Serum	Culture	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Age: 42.8 years (29-65)			Enzygnost Borreliosis (DADE Behring; IgG and 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

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
							years after onset of 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	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)	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
	neuroborreliosis (n=10) Late Lyme disease, LA (29)			Culture 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* <u>CLIA:</u> VIDAS Lyme IgM and IgG assay (bioMerieux) <u>ELISA:</u> C6 EIA (Immunetics) <u>Western blot:</u> 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* <u>ELISA:</u> C6 *B. burgdorferi* Lyme ELISA (Immunetics) <u>Western blot:</u> 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	n=203	ELISA	*IgM/IgG*	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Acute EM (n=40), convalescent EM (n=38), Neuroborreliosis (n=10), Lyme carditis (n=7), Lyme arthritis (n29) Age: not reported	Healthy controls		VIDAS Lyme (IgM/IgG),bioMerieux, 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	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
						and exclusion of other known 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	n=37 Healthy controls	ELISA	*IgM and IgG* In house sonicate antigen ELISA (IgM, IgG, or both)	Serum	Diagnosis based on clinical symptoms	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	Age: 37.6 years (4-76)			41-kDa flagellin ELISA (IgM, IgG, or both; DAKO) Recombinant P39 protein ELISA (ImmunoWeLL)		and positive culture or PCR	
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	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
		(n=20)					
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)	n=794 Healthy blood donors from New Mexico (n=300) Healthy blood donors from New England (n=300)	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
	Age: not reported	People undergoing 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	n=82	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
	EM (n=118) Lyme neuroborreliosis (n=33) LA (n=17) ACA (n=42) Age: not reported	No current symptoms/history 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	n=96	IF WB	*IgM and IgG*	Serum	Clinical diagnosis	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
	EM Age: not reported	Healthy persons		In-house indirect IF test (IgG and IgM) 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

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Senel 2010[433]	n=37 Definite neuroborreliosis (n=28) Systemic borreliosis (n=9) Age: 58 years (32-70)	n=89 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	ELISA (Quantikine, R&D Systems) for detection of CXCL13	CSF	Clinical diagnosis	CSF/serum albumin 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)	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
		Anti-nuclear 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	

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Stanek 1999[455]	n=99 EM Age: Female: (n=55): median 49 years (10-80) Male (n=44): median 51 (18-77)	n=100 Blood donors	EIA	In-house EIA (IgG and IgM)	Serum	Clinical 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%)

Study	Population and target condition	Control group	Type of index test	Index test	Sample	Reference standard	Comments
Stricker 2001[466]	n=83 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)	n=22 People with AIDS	CD57	CD57	Not reported	Clinical 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-	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
	84)						
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	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
						meningitis, 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)	n=208 Blood donors (n=120) Autoimmun	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
	Migrating arthromyalgias (n=34) Facial palsy (n=5) Acute neuroborreliosis (n=7)	e diseases (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 disseminatio n), previous Lyme disease (successfull y 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	Neuroborr eliosis	CXCL13	CXCL13	CSF	Definite neuroborreli osis: CSF pleocytosis and *Borrelia*-specific antibodies in CSF Possible neuroborreli osis: 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 burgdorferi s.l.* 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 burgdorferi s.l.* 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 burgdorferi s.l.* 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 burgdorferi s.l.* 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 *Borrelia burgdorferi s.l.* 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 burgdorferi s.l.* 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 burgdorferi s.l.* 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 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 burgdorferi s.l.* 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 burgdorferi s.l.* 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
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 EM)	303	VERY LOW[1] due to very serious risk of bias	0.72 [0.57-0.84]	1.00 [0.99-1.00]
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]	0.40 [0.25-0.57]	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		
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]
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)				

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
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]
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]	0.30 [0.17-0.47]	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		
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 serious imprecision	0.30 [0.13-0.53]	Not estimable
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]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
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 serious imprecision	0.87 [0.60-0.98]	1.00 [0.99-1.00]
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	0.90 [0.55-1.00]	0.99 [0.97-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		serious imprecision		
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]
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]	0.90 [0.55-1.00]	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 and serious imprecision		
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)				
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]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
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] due to very serious risk of bias	0.97 [0.82-1.00]	1.00 [0.97-1.00]
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]	1.00 [0.63-1.00]	1.00 [0.89-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		due to very serious risk of bias and serious imprecision		
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]
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]	0.86 [0.42-1.00]	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 and very serious imprecision		
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 very serious imprecision	0.86 [0.42-1.00]	1.00 [0.97-1.00]
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	0.63 [0.42-0.81]	1.00 [0.98-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		serious imprecision		
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] due to very serious risk of bias	0.96 [0.81-1.00]	1.00 [0.98-1.00]
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]	1.00 [0.89-1.00]	0.99 [0.95-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		due to very serious risk of bias		
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)				
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	88	VERY LOW[1,3]	0.35 [0.17-0.56]	1.00 [0.94-1.00]

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 (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 IB)	88	VERY LOW[1,3] due to very serious risk of bias and serious imprecision	0.35 [0.17-0.56]	0.97]0.89-1.00]
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]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
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]
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	75	VERY LOW[1,3]	0.31 [0.09-0.61]	1.00 [0.94-1.00]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Virotech)		due to very serious risk of bias and serious imprecision		
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 serious imprecision	0.38 [0.14-0.68]	1.00 [0.94-1.00]
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	0.46 [0.19-0.75]	0.94 [0.84-0.98]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
		serious imprecision		
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]
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	75	VERY LOW[1,3]	0.46 [0.19-0.75]	0.95 [0.87-0.99]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
Virotech IB)		due to very serious risk of bias and serious imprecision		
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] due to very serious risk of bias	0.52 [0.39-0.64]	1.00 [0.96-1.00]
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]	0.53 [0.40-0.66]	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		
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]
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]

Index Test (Threshold)	n	Quality[4]	Sensitivity % (95% CI)	Specificity % (95% CI)
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.

3.7 The committee's discussion of the evidence

3.7.1 Interpreting the evidence

3.7.1.1 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 burgdorferi s.l.* 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 burgdorferi s.l*.

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 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.

3.7.1.2 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. Similar 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.

3.7.1.3 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 burgdorferi s.l. 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 when compared with clinical diagnosis. The committee noted that the relatively low sensitivity 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 burgdorferi s.l.* as the organisms may be localised to the synovium.

3.7.2 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 an immunoblot should be considered. The committee noted that although this would be more costly, as these people would be receiving an additional test, 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 immunoblot despite an initial negative ELISA to be considered to have a significant resource impact, it would need to be applicable to over 14,000 people based on the current cost of this test. 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 or other diagnoses, 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.

3.7.3 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 while waiting for test results to 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 recognised the need to ensure that health care professionals and people are aware of the limitations of tests, in particular of false negative results and the importance of clinical judgement.

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, many of whom 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 burgdorferi s.l.* is ongoing.

The committee also discussed that different tests use different antigens from the main pathogenic genospecies of *Borrelia burgdorferi s. l*. 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. Immunoblots for IgM and IgG antibodies designed to detect all three main species of the *Borrelia burgdorferi s. l.* complex should be used for confirmation tests. Testing should be carried out for both IgM and IgG antibodies in acute cases and on CSF samples; IgG blots alone may be used for cases with a prolonged history of symptoms, or if no IgM blot is available and the small lag in IgG antibody appearance is taken into account in interpretation.

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 the confirmatory immunoblot be considered. The rationale behind this approach was that the overwhelming majority of these people would not have Lyme disease and the additional test 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 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 burgdorferi s.l*.

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 burgdorferi s.l.* 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 burgdorferi s.l.* 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.

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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 burgdorferi s.l.* 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 burgdorferi s.l.* 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 burgdorferi s.l.* 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

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.

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

Embase (Ovid) search terms

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

Cochrane Library (Wiley) search terms

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

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

B.2 Health Economics literature search strategy

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

Table 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

Embase (Ovid) search terms

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

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

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

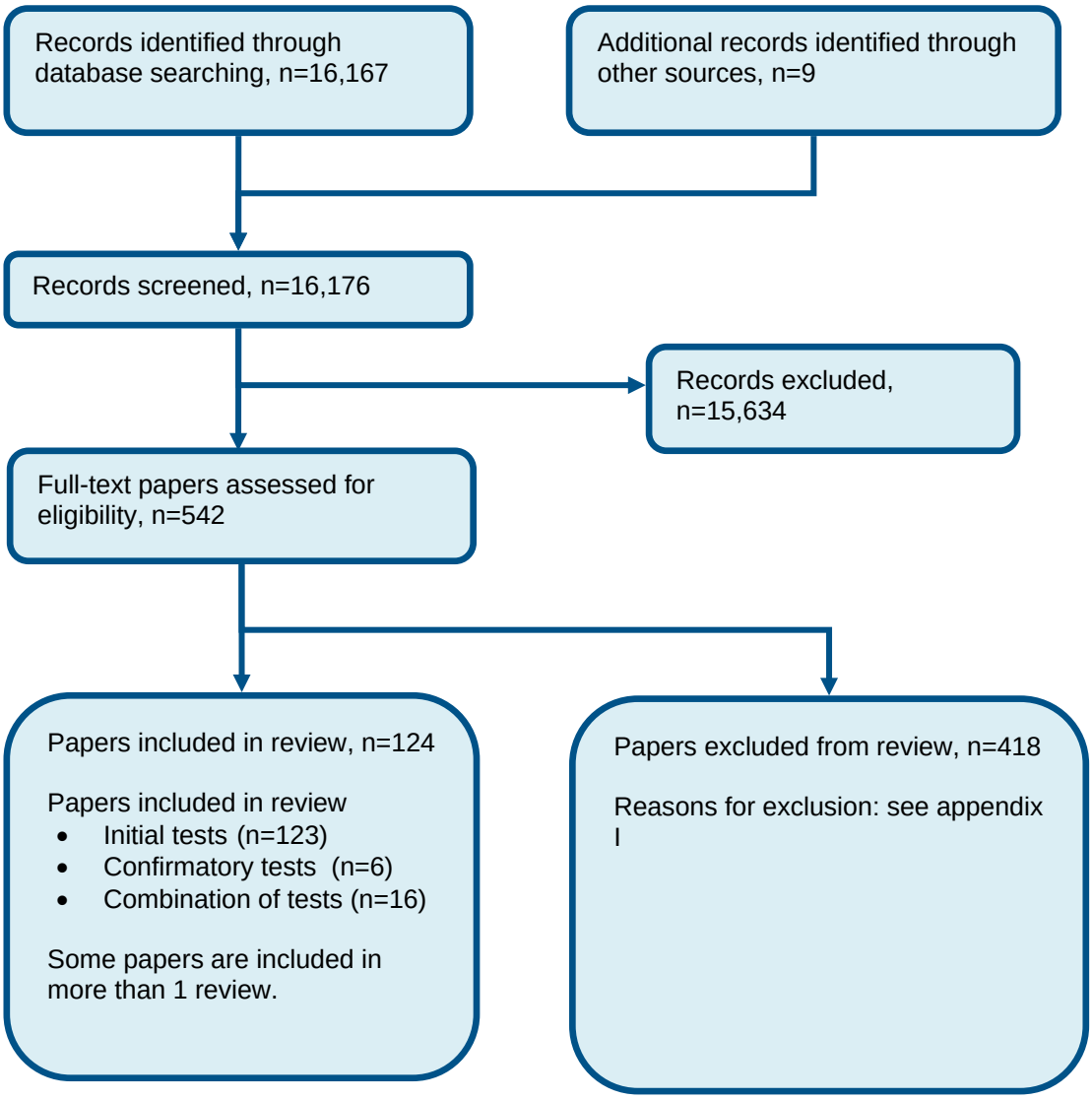
NHS EED and HTA (CRD) search terms

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

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the reviews of 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]

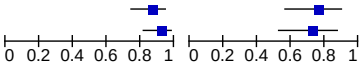


Figure 3: ELISA (IgG) – antibody index

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]

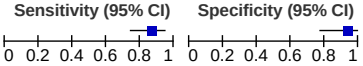


Figure 4: ELISA (IgM/IgG) – antibody index

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]

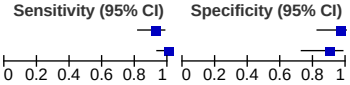


Figure 5: ELISA C6

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]

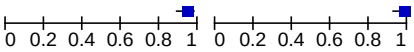


Figure 6: ELISPOT

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]

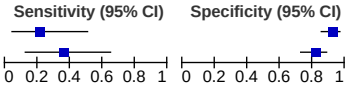
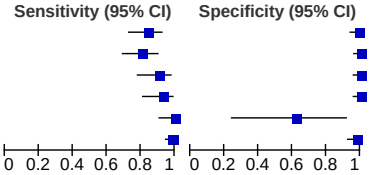


Figure 7: CXCL13

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]



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]

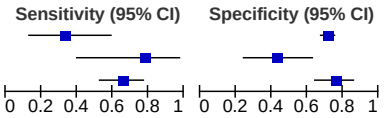


Figure 9: ELISA (IgG)

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]

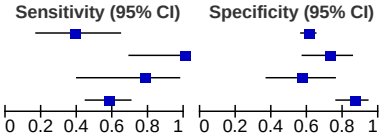


Figure 10: ELISA (IgM/IgG)

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]

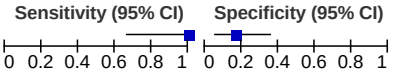
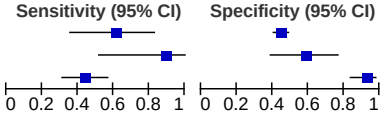


Figure 11: Immunoblot (IgM)

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]

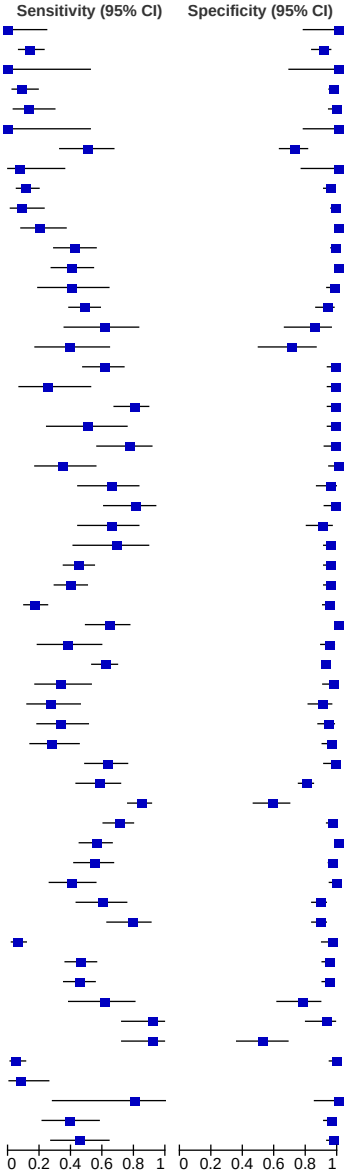


Figure 14: ELISA (IgG)

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]

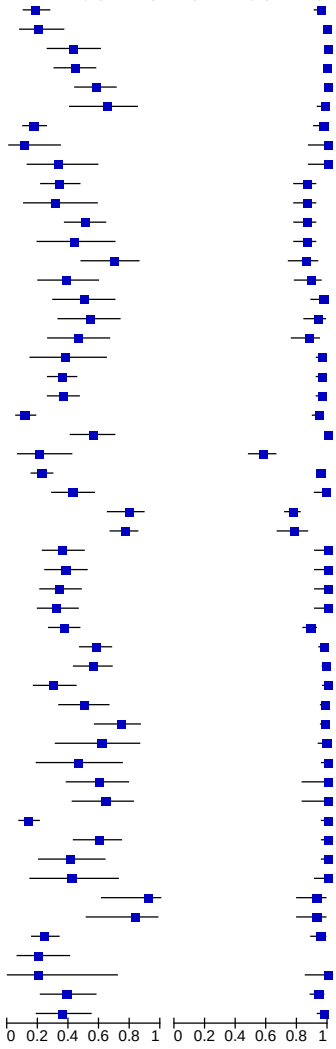


Figure 15: ELISA (IgM/IgG)

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]

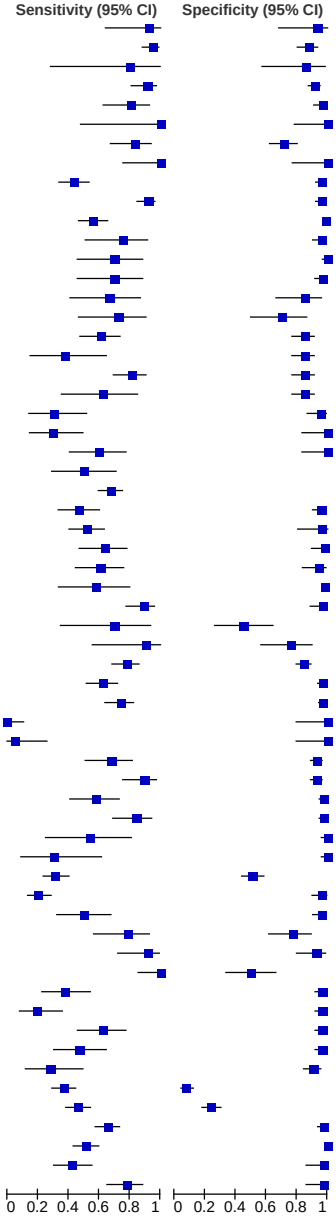


Figure 16: ELISA C6

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]

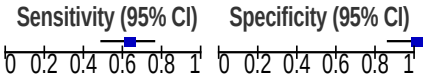


Figure 17: ELISA C6 (IgA)

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]

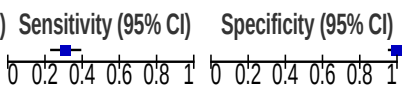


Figure 18: ELFA

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]

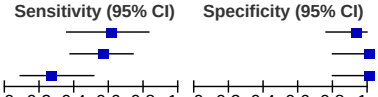


Figure 19: CLIA (IgM)

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]

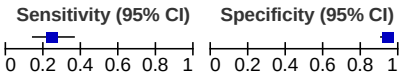


Figure 20: CLIA (IgG)

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]

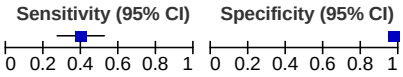


Figure 21: CLIA (IgM/IgG)

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]

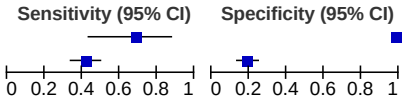


Figure 22: Western blot/Immunoblot (IgM)

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]

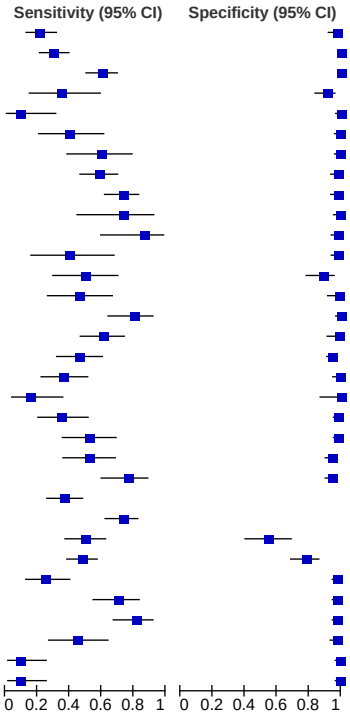


Figure 23: Western blot/Immunoblot (IgG)

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]

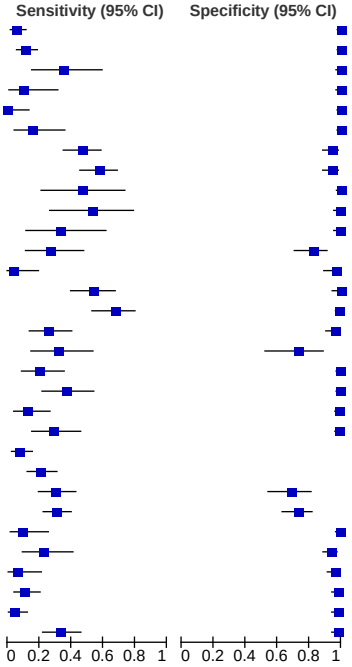


Figure 24: Western blot/Immunoblot (IgM/IgG)

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]

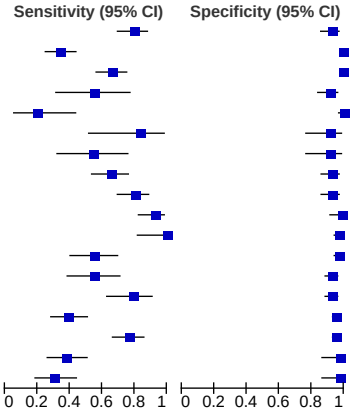


Figure 25: IFA (IgM)

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]

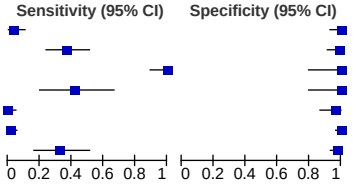


Figure 26: IFA (IgG)

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]

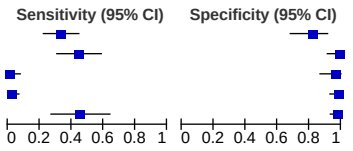


Figure 27: IFA (IgM/IgG)

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]

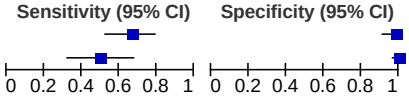


Figure 28: IFA

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]

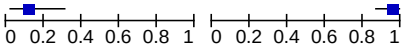


Figure 29: PCR

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]

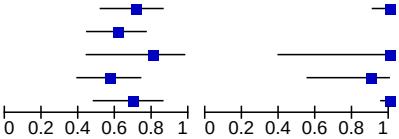
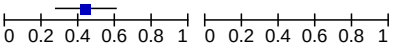


Figure 30: Culture

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



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]

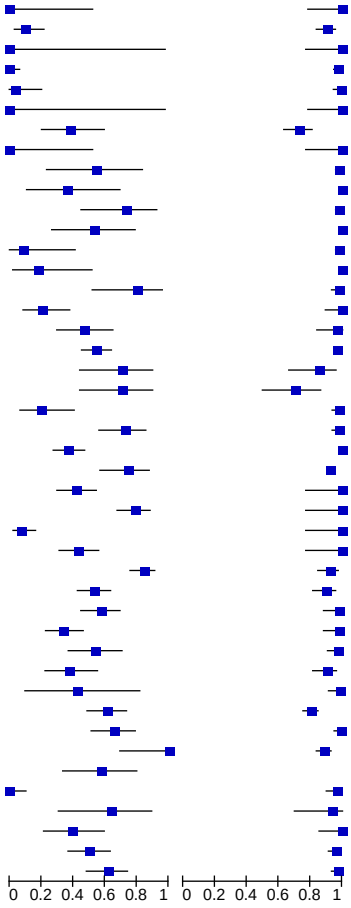


Figure 32: ELISA (IgG)

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]

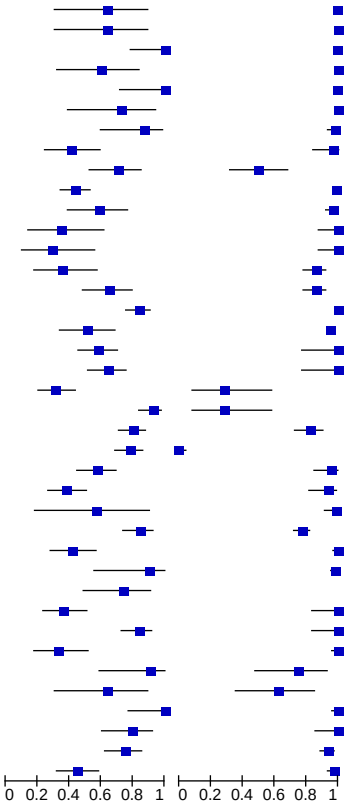


Figure 33: ELISA (IgM/IgG)

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]

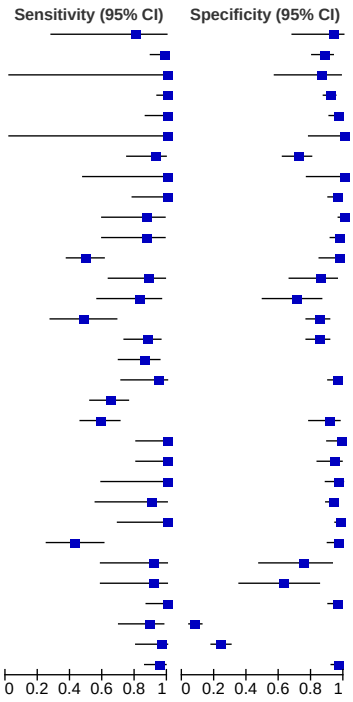


Figure 34: ELISA C6

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]

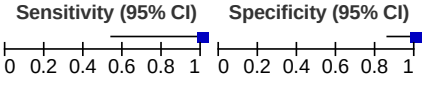


Figure 35: ELFA

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]

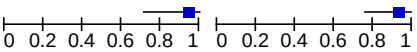


Figure 36: CLIA (IgM/IgG)

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]

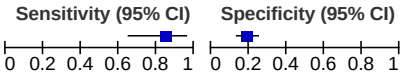


Figure 37: Western blot/Immunoblot (IgM/)

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]

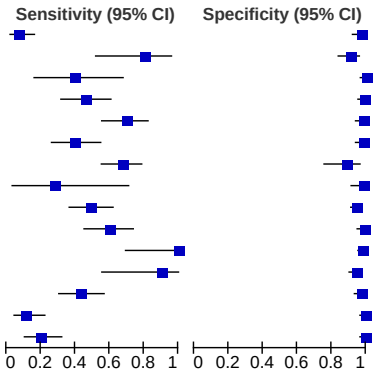


Figure 38: Western blot/Immunoblot (IgG)

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]

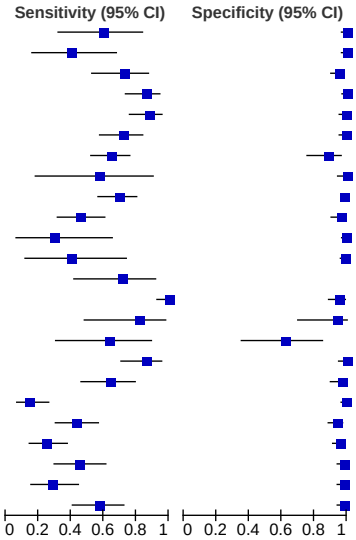


Figure 39: Western blot/Immunoblot (IgM/IgG)

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]

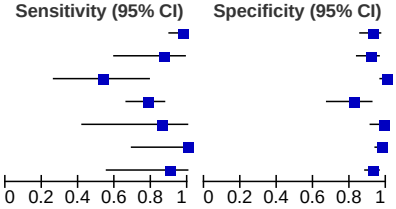


Figure 40: IFA (IgM)

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]

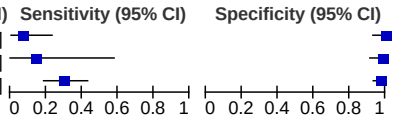


Figure 41: IFA (IgG)

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]

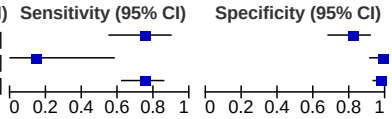


Figure 42: IFA (IgM/IgG)

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]

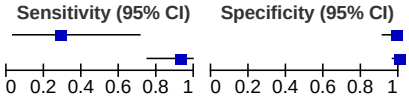


Figure 43: PCR

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]

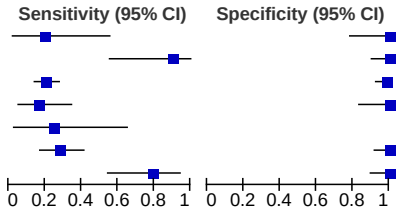


Figure 44: Culture

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

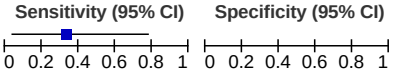
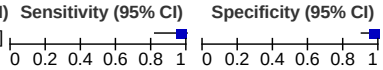


Figure 45: CXCL13

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]



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]

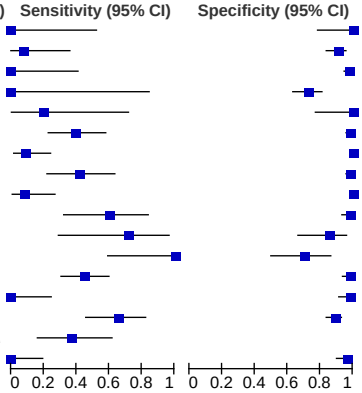


Figure 47: ELISA (IgG)

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]

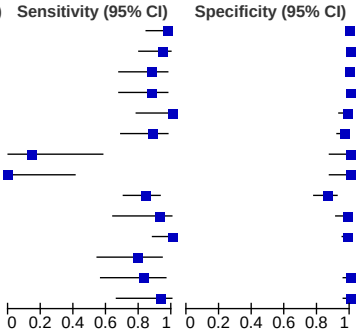


Figure 48: ELISA (IgM/IgG)

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]

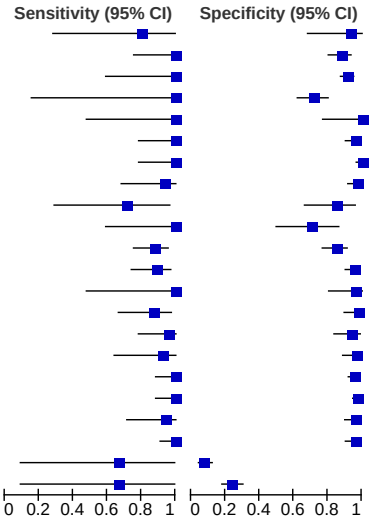


Figure 49: ELISA C6

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]

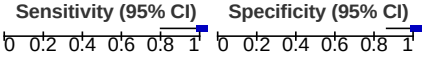


Figure 50: ELISA C6 (IgA)

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]

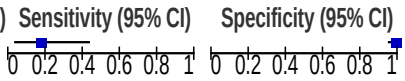


Figure 51: ELFA

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]

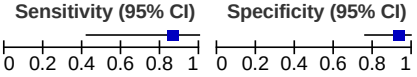


Figure 52: CLIA (IgM/IgG)

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]

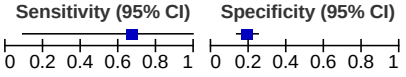


Figure 53: Western blot/Immunoblot (IgM)

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

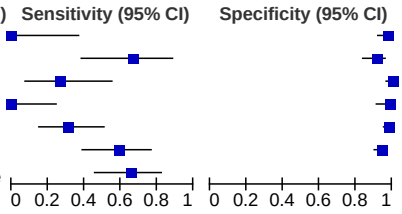


Figure 54: Western blot/Immunoblot (IgG)

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

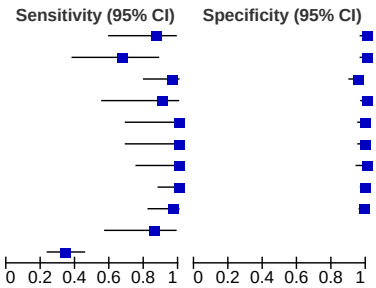


Figure 55: Western blot/Immunoblot (IgM/IgG)

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]

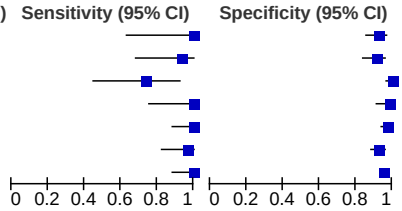


Figure 56: IFA (IgM)

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]

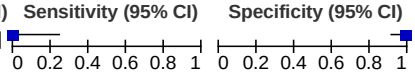


Figure 57: IFA (IgG)

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]

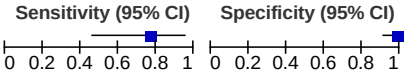


Figure 58: IFA (IgM/IgG)

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]

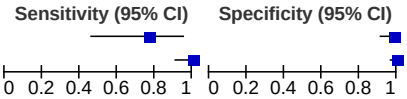
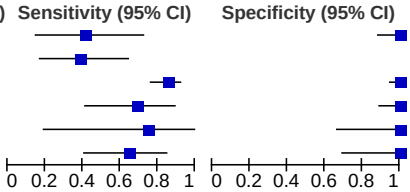


Figure 59: PCR

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]



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]

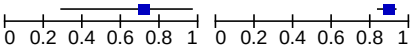


Figure 61: ELISA (IgG)

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]

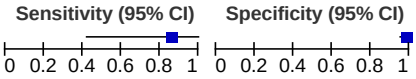


Figure 62: ELISA (IgM/IgG)

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]

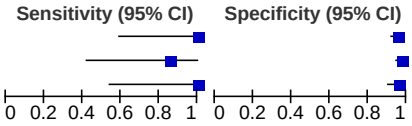


Figure 63: IFA (IgM/IgG)

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]

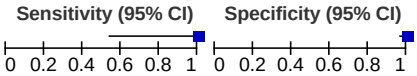


Figure 64: Western blot/Immunoblot (IgM)

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]

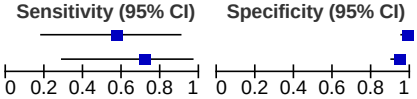


Figure 65: Western blot/Immunoblot (IgG)

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]

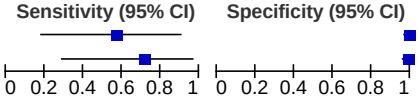


Figure 66: Western blot/Immunoblot (IgM/IgG)

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]

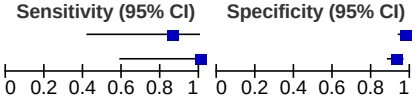


Figure 67: PCR

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

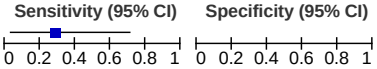
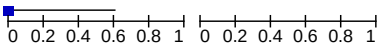


Figure 68: Culture

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



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]

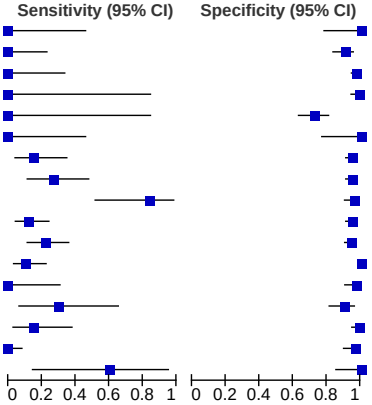


Figure 70: ELISA (IgG)

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]

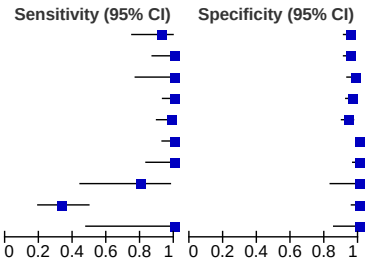


Figure 71: ELISA (IgM/IgG)

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]

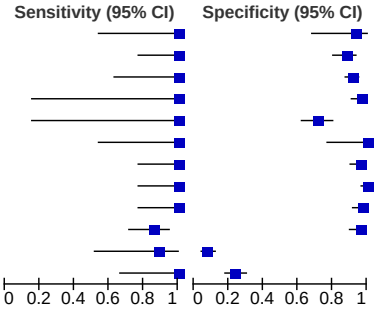


Figure 72: CLIA (IgM/IgG)

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]

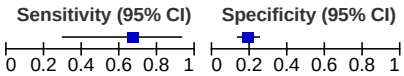


Figure 73: Western blot/Immunoblot (IgM)

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]

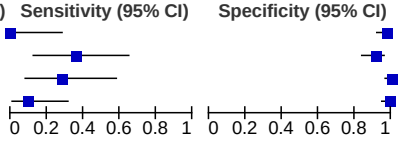


Figure 74: Western blot/Immunoblot (IgG)

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]

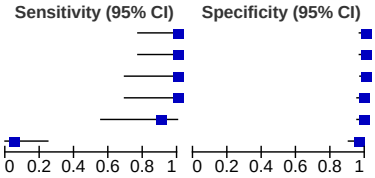


Figure 75: Western blot/Immunoblot (IgM/IgG)

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]

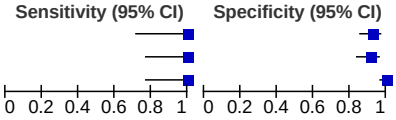
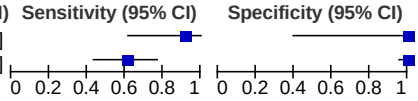


Figure 76: PCR

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]



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]

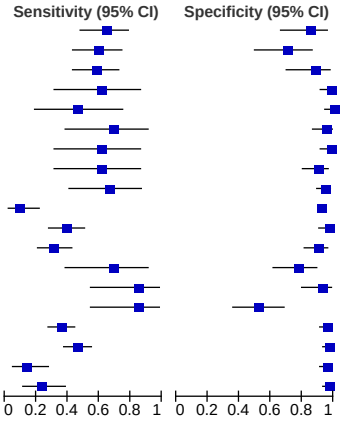


Figure 78: ELISA (IgG)

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]

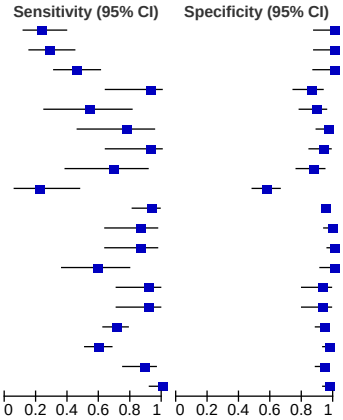


Figure 79: ELISA (IgM/IgG)

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]

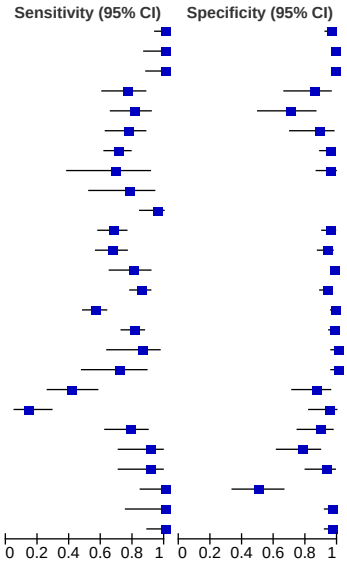


Figure 80: ELFA

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]

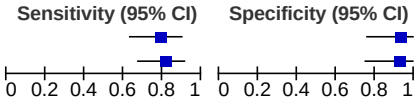


Figure 81: Western blot/Immunoblot (IgM)

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]

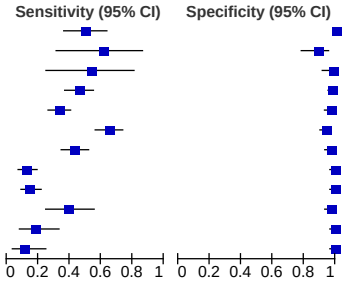


Figure 82: Western blot/Immunoblot (IgG)

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]

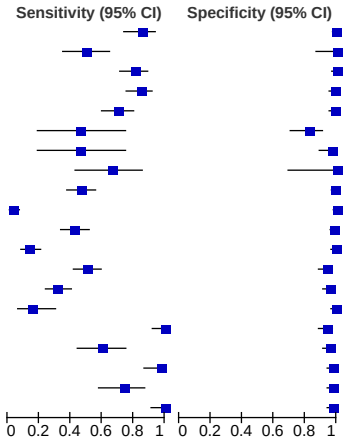


Figure 83: Western blot/Immunoblot (IgM/IgG)

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]

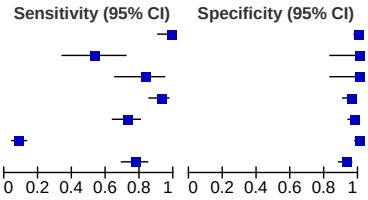


Figure 84: CLIA (IgM/IgG)

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]

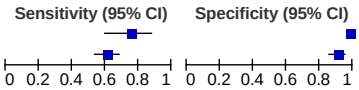


Figure 85: IFA (IgM)

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]

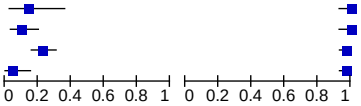


Figure 86: IFA (IgG)

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]

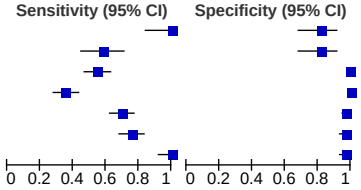


Figure 87: IFA (IgM/IgG)

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]

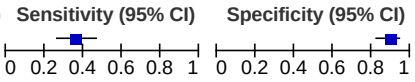


Figure 88: Recombinant Rapid Assay

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]

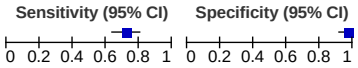


Figure 89: PCR

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]

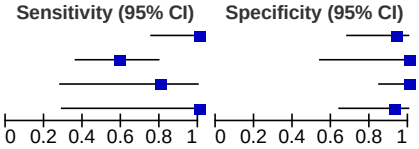


Figure 90: CD57

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]

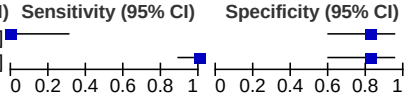


Figure 91: Culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Phillips 1998 (blood)	43	0	4	23	0.91 [0.80, 0.98]	1.00 [0.85, 1.00]

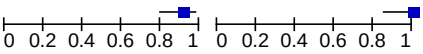
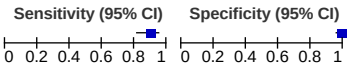


Figure 92: Lymphocyte transformation test

Study	TP	FP	FN	TN	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]



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)
Fallon 2014 (commercial lab) (serum)	25	3	12	37	0.68 [0.50, 0.82]	0.93 [0.80, 0.98]
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]

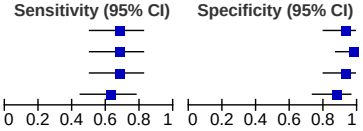


Figure 94: Western blot/Immunoblot (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab) (serum)	6	0	31	40	0.16 [0.06, 0.32]	1.00 [0.91, 1.00]
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

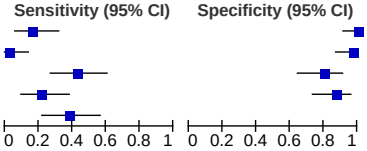


Figure 95: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Fallon 2014 (commercial lab) (serum)	16	0	21	40	0.43 [0.27, 0.61]	1.00 [0.91, 1.00]
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

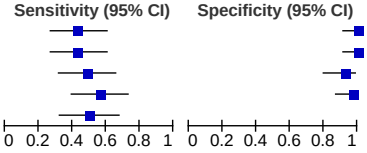
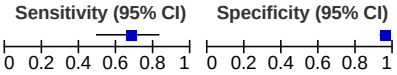


Figure 96: Western blot/Immunoblot (IgM/IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Porwancher 2011 (serum)	23	21	11	429	0.68 [0.49, 0.83]	0.95 [0.93, 0.97]



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)
Hansen 1988 (NB) (flagellum) (CSF)	38	0	5	106	0.88 [0.75, 0.96]	1.00 [0.97, 1.00]
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]

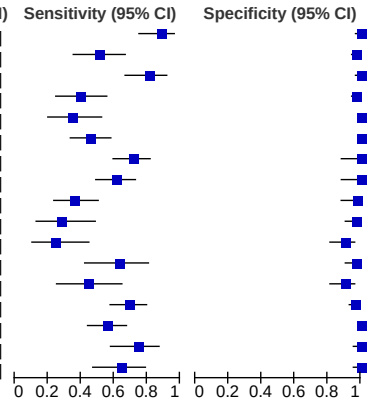


Figure 98: Less than 6 weeks – ELISA (IgG)

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]

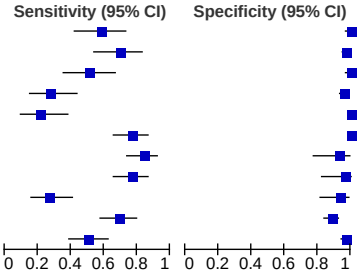


Figure 99: Less than 6 weeks – ELISA (IgM/IgG)

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]

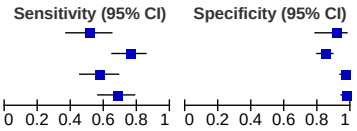


Figure 100: Less than 6 weeks – Western blot/Immunoblot (IgM)

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]

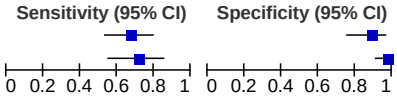


Figure 101: Less than 6 weeks – Western blot/Immunoblot (IgG)

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]

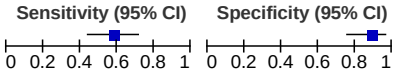


Figure 102: Less than 6 weeks – Western blot/Immunoblot (IgM/IgG)

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]

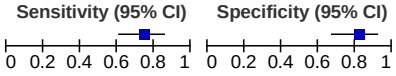


Figure 103: Culture

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]

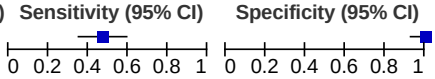


Figure 104: 6 weeks to 6 months – ELISA (IgM)

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]

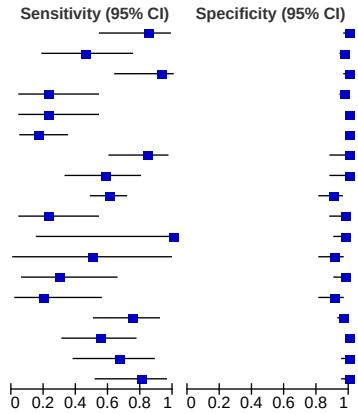


Figure 105: 6 weeks to 6 months – ELISA (IgG)

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]

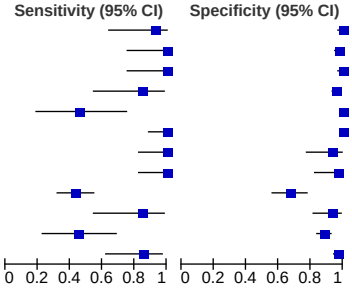


Figure 106: 6 weeks to 6 months – ELISA (IgM/IgG)

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]

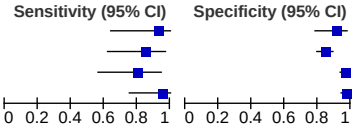


Figure 107: 6 weeks to 6 months – Western blot/Immunoblot (IgM)

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]

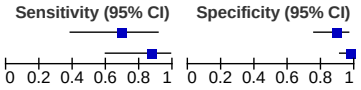


Figure 108: 6 weeks to 6 months – Western blot/Immunoblot (IgG)

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]

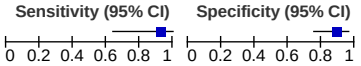


Figure 109: 6 weeks to 6 months – Western blot/Immunoblot (IgM/IgG)

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]

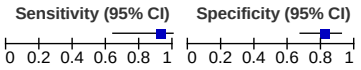


Figure 110: 6 weeks to 6 months: Culture

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]

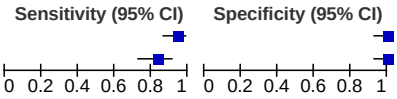


Figure 111: More than 6 months – ELISA (IgM)

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]

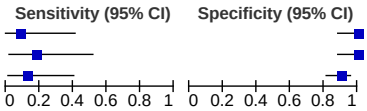
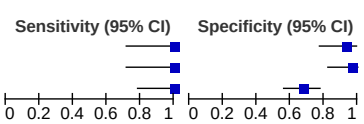


Figure 112: More than 6 months – ELISA (IgG)

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)

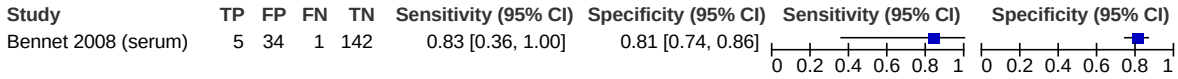
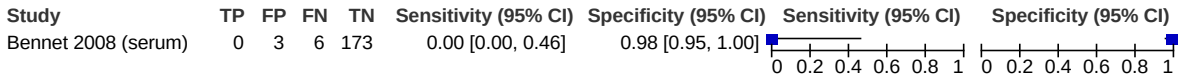


Figure 114: ELISA (IgG)



E.2.1.2 Neuroborreliosis

Figure 115: ELISA (IgM)

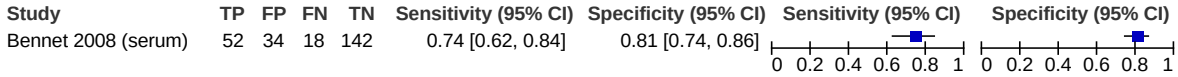


Figure 116: ELISA (IgG)

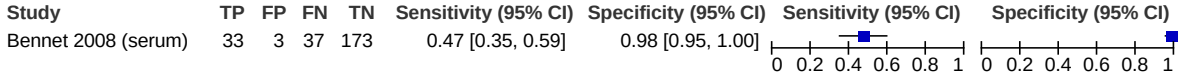


Figure 117: PCR – Lyme meningitis only

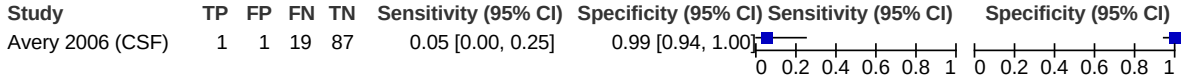


Figure 118: ELISA (IgM) – facial palsy only

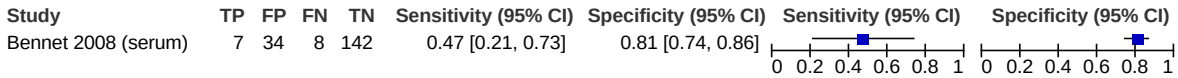


Figure 119: ELISA (IgG) – facial palsy only

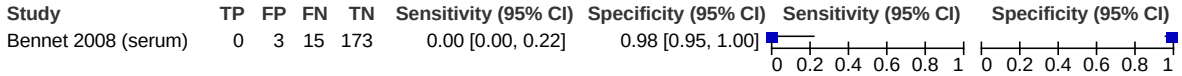
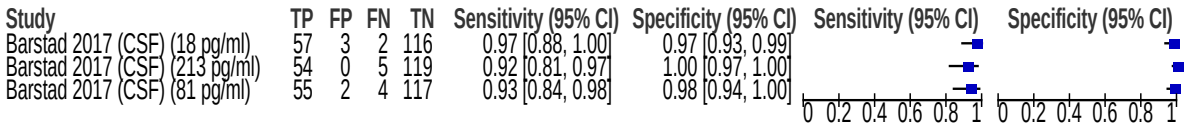


Figure 120: CXCL13



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]

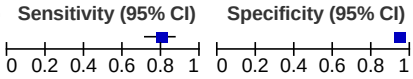
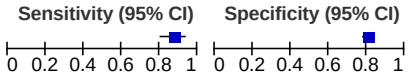


Figure 122: ELISA WCS

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]



E.2.2 Evidence from case-control studies

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]

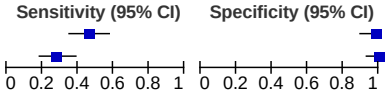
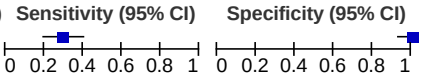


Figure 124: Western blot/Immunoblot (IgM)

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]



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]

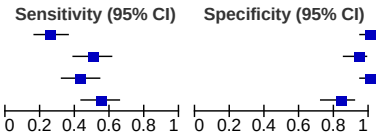


Figure 126: ELISA (IgG)

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]

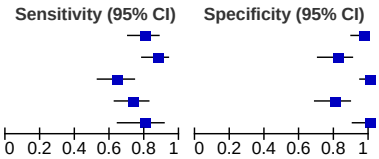


Figure 127: Western blot/Immunoblot (IgM)

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]

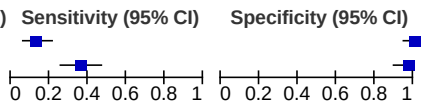


Figure 128: Western blot/Immunoblot (IgG)

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]

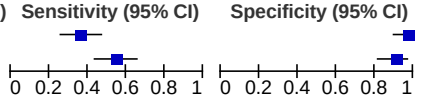
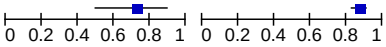


Figure 129: CXCL13

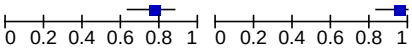
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Wutte 2011 (serum) 100 pg/ml	16	39	6	261	0.73 [0.50, 0.89]	0.87 [0.83, 0.91]		



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]		



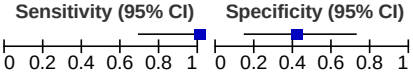
E.3 Confirmatory tests: Coupled sensitivity and specificity forest plots for adults

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]		

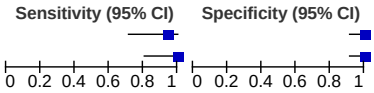


Figure 133: Immunoblot (IgM)

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]		

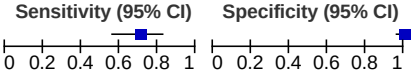


Figure 134: Immunoblot (IgG)

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]		

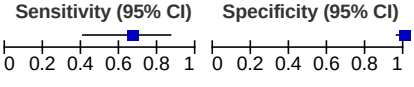


Figure 135: Immunoblot (IgM/IgG)

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]		

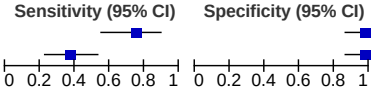


Figure 136: IFA (IgM)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christova 2003 (serum)	24	0	27	90	0.47 [0.33, 0.62]	1.00 [0.96, 1.00]

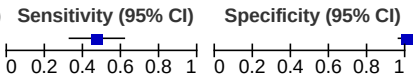
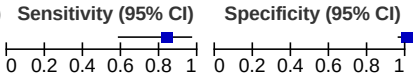


Figure 137: IFA (IgG)

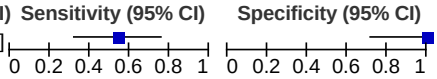
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christova 2003 (serum)	15	0	3	90	0.83 [0.59, 0.96]	1.00 [0.96, 1.00]



E.3.2.2 Neuroborreliosis

Figure 138: Western blot/Immunoblot (IgG)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Coyle 1993 (CSF)	12	0	10	11	0.55 [0.32, 0.76]	1.00 [0.72, 1.00]



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.

E.5.2 Evidence from case-control studies

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]

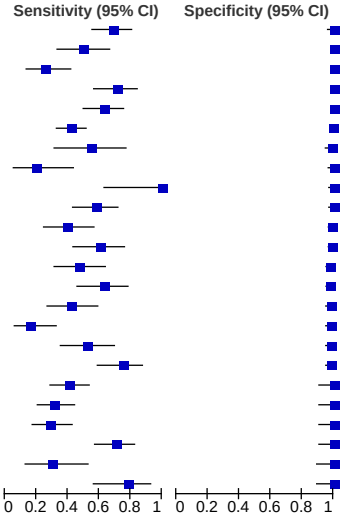


Figure 140: ELISA C6 and Immunoblot (IgM/IgG)

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]

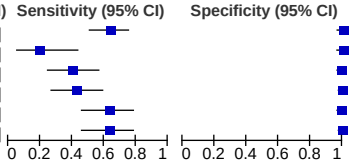


Figure 141: ELISA WCS and ELISA C6

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]

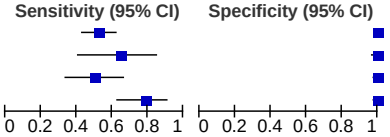


Figure 142: ELISA WCS and Immunoblot (VlsE)

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]

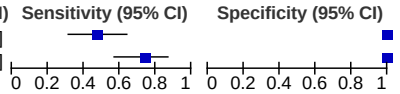


Figure 143: ELISA (IgM/IgG) and Immunoblot (IgM)

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]

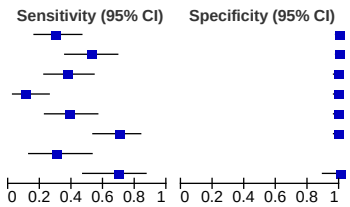
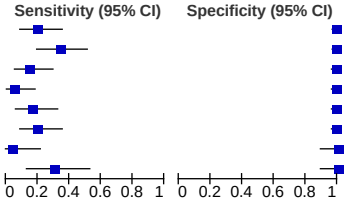


Figure 144: ELISA (IgM/IgG) and Immunoblot (IgG)

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]



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]

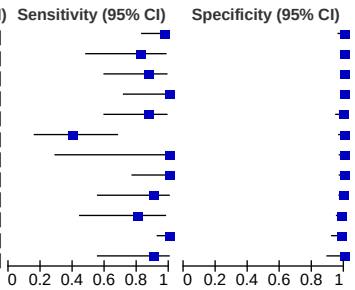


Figure 146: ELISA C6 and Immunoblot (IgM/IgG)

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]

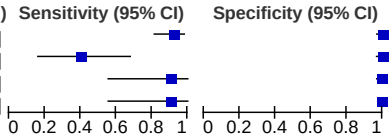


Figure 147: ELISA WCS and ELISA C6

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]

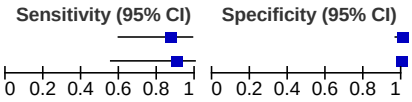


Figure 148: ELISA (IgM/IgG) and Immunoblot (IgM)

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]

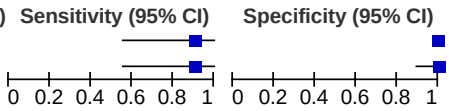


Figure 149: ELISA (IgM/IgG) and Immunoblot (IgG)

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]

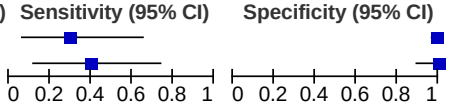
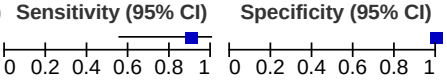


Figure 150: ELISA WCS and Immunoblot (VlsE)

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]



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]

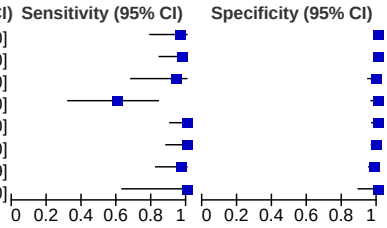


Figure 152: ELISA C6 and Immunoblot (IgM/IgG)

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]

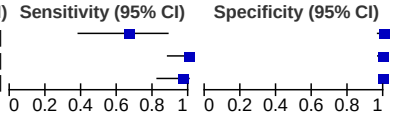


Figure 153: ELISA WCS and ELISA C6

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]

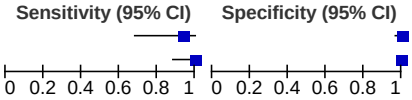


Figure 154: ELISA (IgM/IgG) and Immunoblot (IgM)

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]

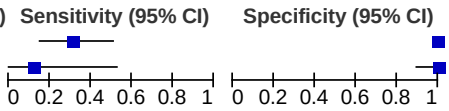


Figure 155: ELISA (IgM/IgG) and Immunoblot (IgG)

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]

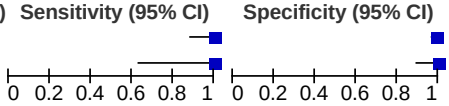
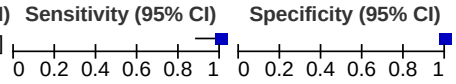


Figure 156: ELISA WCS and Immunoblot (VlsE)

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]



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]

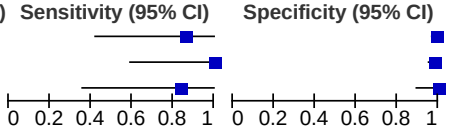


Figure 158: ELISA (IgM/IgG) and Immunoblot (IgM)

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]

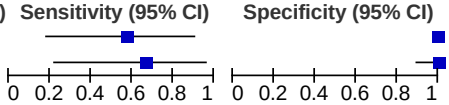


Figure 159: ELISA (IgM/IgG) and Immunoblot (IgG)

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]

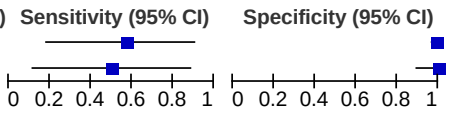


Figure 160: ELISA WCS and ELISA C6

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]

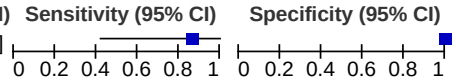


Figure 161: ELISA WCS and Immunoblot (VlsE)

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]

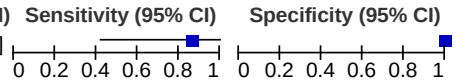
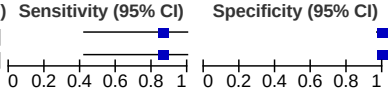


Figure 162: ELISA C6 and Immunoblot (IgM/IgG)

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]



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]

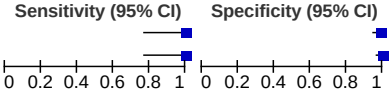


Figure 164: ELISA WCS and ELISA C6

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]

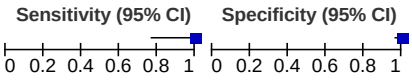
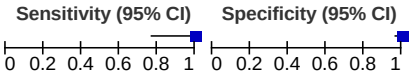


Figure 165: ELISA C6 and Immunoblot (IgM/IgG)

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]



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]

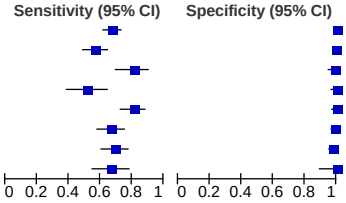


Figure 167: ELISA (IgM/IgG) and Immunoblot (IgM)

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]

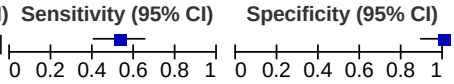


Figure 168: ELISA (IgM/IgG) and Immunoblot (IgG)

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]

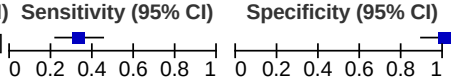


Figure 169: ELISA C6 and Immunoblot (IgM/IgG)

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]

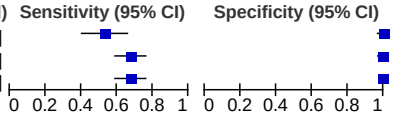


Figure 170: ELISA WCS and ELISA C6

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]

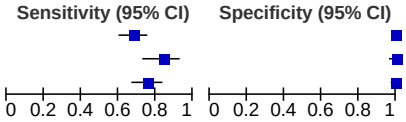


Figure 171: ELISA WCS and Immunoblot (VlsE)

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]

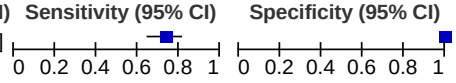


Figure 172: ELISA (IgM) and Immunoblot (IgM) – early Lyme Disease

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]

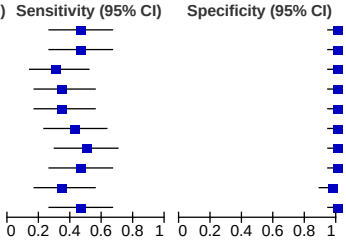


Figure 173: ELISA (IgG) and Immunoblot (IgG) – early Lyme Disease

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]

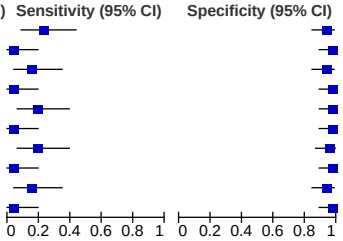


Figure 174: ELISA (IgM/IgG) and Immunoblot (IgM) – early Lyme Disease

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]

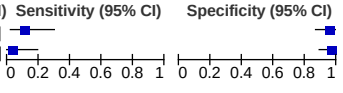


Figure 175: ELISA (IgM/IgG) and Immunoblot (IgG) – early Lyme Disease

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]

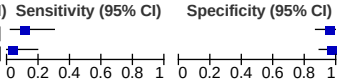


Figure 176: ELISA (IgM) and Immunoblot (IgM) – late Lyme Disease

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]

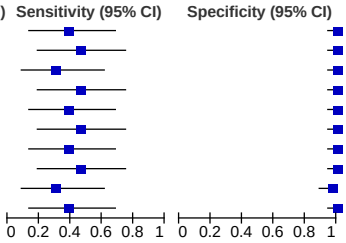


Figure 177: ELISA (IgG) and Immunoblot (IgG) – late Lyme Disease

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]

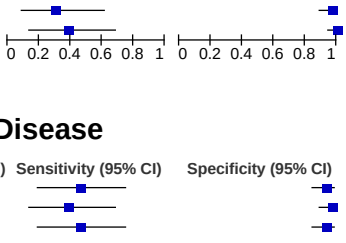


Figure 178: ELISA (IgM/IgG) and Immunoblot (IgM) – late Lyme Disease

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]

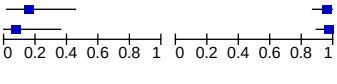


Figure 179: ELISA (IgM/IgG) and Immunoblot (IgG) – late Lyme Disease

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]

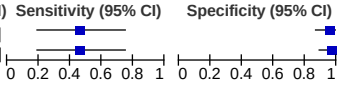


Figure 180: ELISA (IgM/IgG) and Immunoblot (IgM/IgG) – acute neuritis or carditis

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]

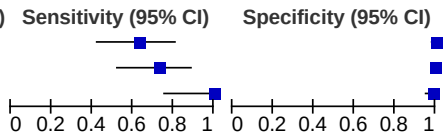


Figure 181: ELISA (IgM/IgG) and Immunoblot (IgG with VlsE band) – acute neuritis or carditis

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]

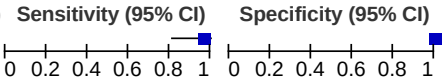


Figure 182: ELISA (IgM/IgG) and VlsE band – acute neuritis or carditis

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]

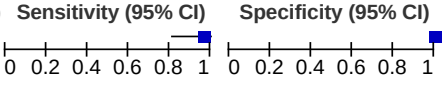


Figure 183: ELISA WCS and ELISA C6 – acute neuritis or carditis

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]

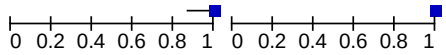


Figure 184: ELISA (IgM/IgG) and Immunoblot (IgM) – acute neuritis or carditis

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]

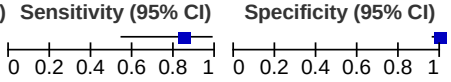


Figure 185: ELISA (IgM/IgG) and Immunoblot (IgG) – acute neuritis or carditis

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]

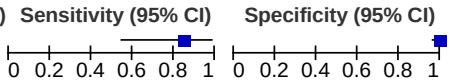


Figure 186: ELISA (IgM/IgG) and Immunoblot (IgM/IgG) – arthritis or late neuritis

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]

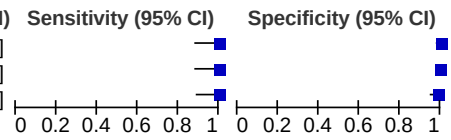


Figure 187: ELISA (IgM/IgG) and Immunoblot (IgG with VlsE band) – arthritis or late neuritis

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]

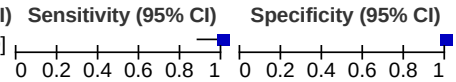


Figure 188: ELISA (IgM/IgG) and VlsE band – arthritis or late neuritis

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]

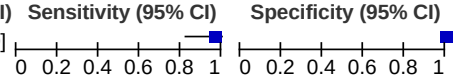


Figure 189: ELISA WCS and ELISA C6 – arthritis or late neuritis

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]

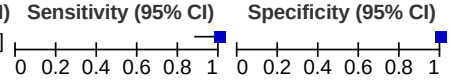


Figure 190: ELISA (IgM/IgG) and Immunoblot (IgM) – arthritis or late neuritis

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]

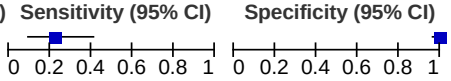
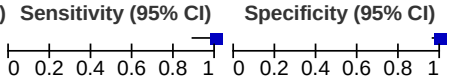


Figure 191: ELISA (IgM/IgG) and Immunoblot (IgG) – arthritis or late neuritis

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]

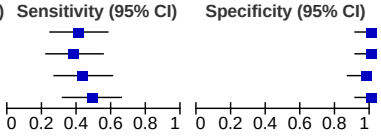


Figure 193: ELISA C6 and Immunoblot (IgG)

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]

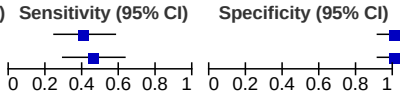
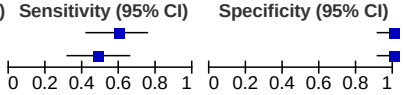


Figure 194: ELISA and ELISA C6

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]

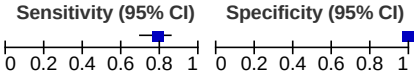


Figure 196: ELISA WCS and ELISA C6

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]

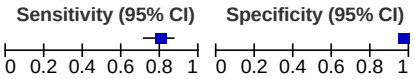
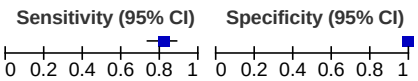


Figure 197: ELISA WCS and Immunoblot (IgM/IgG)

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]

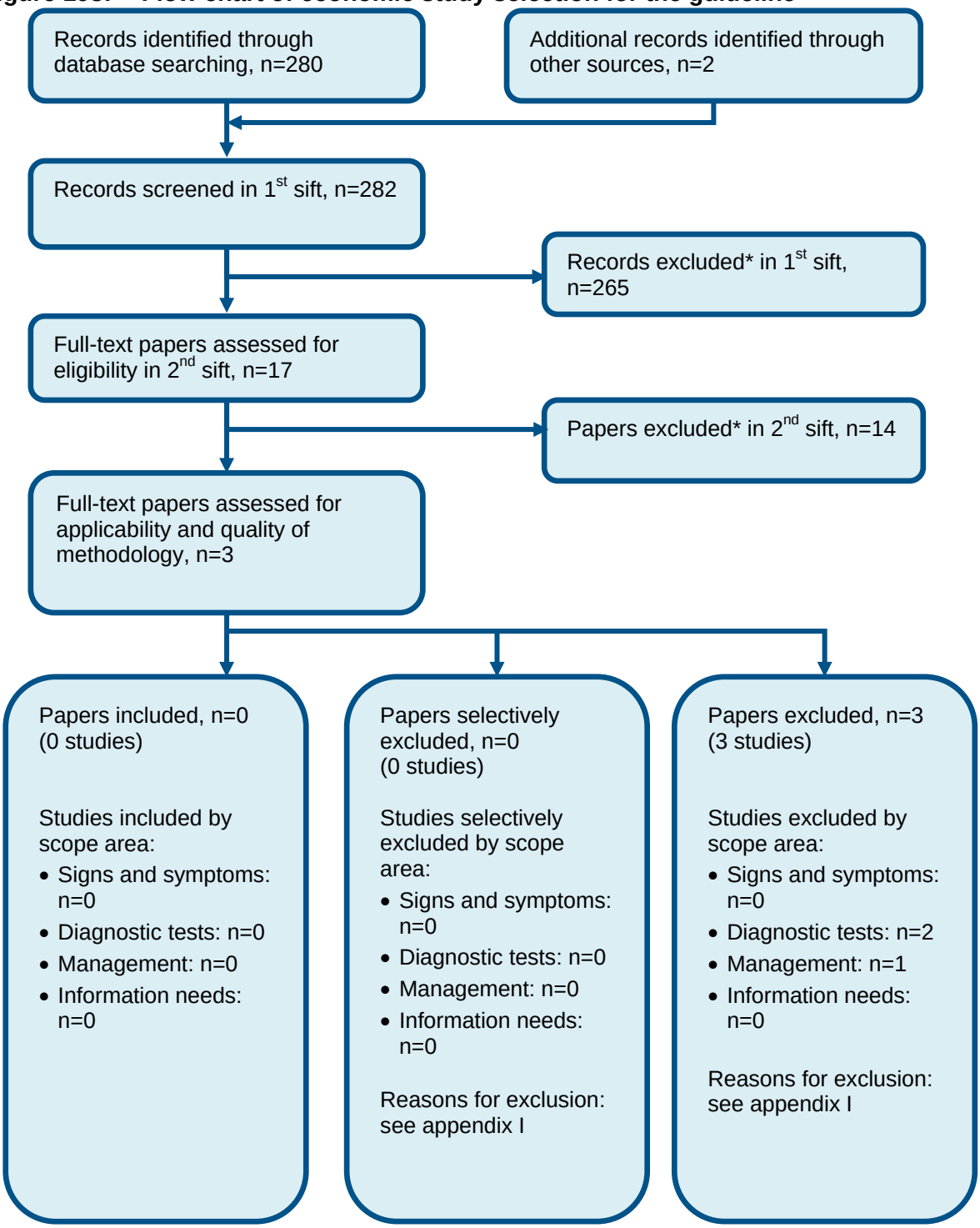


E.6.2 Evidence from case-control studies

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.

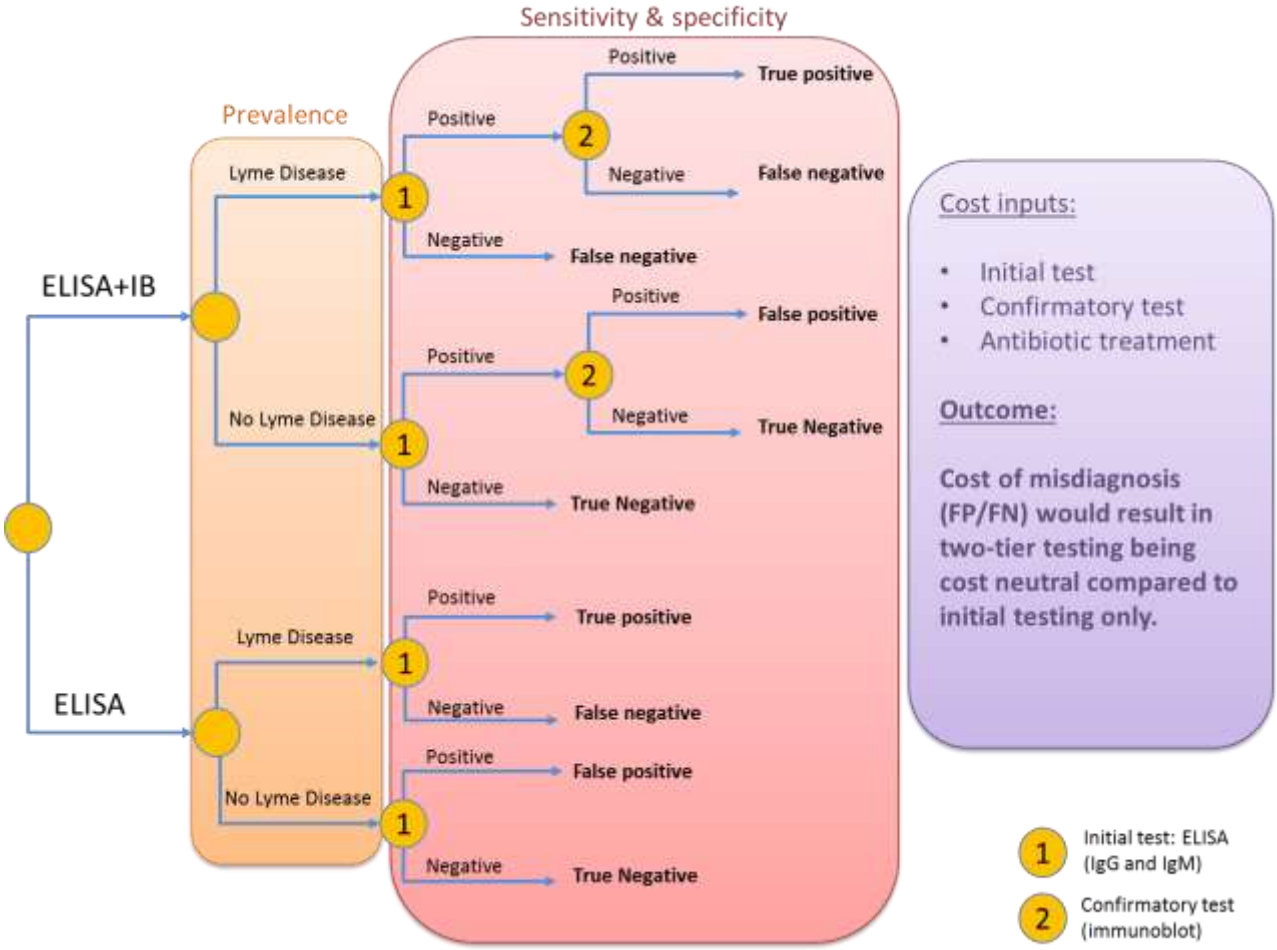
The decision tree is depicted in Figure 199. This analysis includes the following data inputs:

- 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	61.3	672.0	261.3	5.3	266.7
Initial and confirmatory test	60.1	930.7	2.6	6.6	9.2
Scenario 2 (Lyme neuroborreliosis)					
Initial test only	60.0	868.0	65.3	6.7	72.0
Initial and confirmatory test	60.0	928.1	5.2	6.7	11.9
Scenario 3 (Lyme neuroborreliosis)					
Initial test only	66.7	896.0	261.3	5.3	266.7
Initial and confirmatory test	53.4	915.0	18.3	13.3	31.6
Scenario 4 (Lyme arthritis)					
Initial test only	70.0	893.0	37.3	0.0	37.3
Initial and confirmatory test	66.7	928.5	4.9	0.0	4.9
Scenario 5 (Lyme carditis)					
Initial test only	57.3	914.7	18.7	9.3	28.0
Initial and confirmatory test	57.3	928.5	4.9	9.3	14.2

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 or other test 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 a high priority. The clinical presentation of Lyme disease is variable with the 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 IR6 peptide and immunoblot are useful; however, published evidence is of either low or very low quality and is not UK based. There is evidence of variation in the IR6 peptide between the principal *Borrelia* genospecies in UK ticks and a combination of ELISAs may improve sensitivity.

A 'test of cure' for Lyme disease does not exist and, consistent with most other infectious diseases, serology is likely to remain positive following successful treatment of infection in the majority of patients. However, little is known about the evolution of antibody titres over time in those who have been treated successfully and in those who have ongoing symptoms. It is frequently stated that early antibiotic treatment of Lyme disease abrogates the immune response, so that serology remains or becomes negative. This is not a common occurrence in other infections but there are inadequate prospective data on whether it occurs in people with Lyme disease. Observational studies to clarify this would be helpful. In addition, 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 novel biomarkers (for example, CXCL13 and others) and other types of tests may be helpful to support the current low quality evidence. The examples of tests included in this research recommendation reflect those included in this guideline. However, other novel biomarkers are likely to be developed and require similar assessment.

Criteria for selecting high-priority Criteria for selecting high-priority research recommendations:

PICO question	Population: all people and patient groups with Lyme disease Intervention(s): 2-tier testing (IgM/IgG ELISA based on the IR6 antigen followed by an immunoblot) Comparison (exemplar tests provided): CXCL13 and/or other cytokine biomarkers, T-cell tests (for Neuroborreliosis and any Lyme disease presentation), ELISPOT (for Neuroborreliosis and any Lyme disease presentation), 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 is 100% accurate. People with Lyme disease are therefore 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 both in terms of personal health outcomes and ensuring better cost-effectiveness.
National priorities	No.
Current evidence base	The evidence on the accuracy of diagnostic tests for Lyme disease is generally of very low quality and no tests have been formally validated on the UK population. 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. • Observational study: An observational study is needed on possible effects of treatment at different times after infection on the evolution of antibodies against Lyme disease.
Feasibility	Studies will be able to include primary, secondary and tertiary care settings using NIHR speciality networks. 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 not receive treatment or 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. False negative antibody tests early after infection may lead to underestimation of people at risk of later complications of infection.
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 in people in the UK?

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 there are many gaps in knowledge. This study is needed to act as a basis for future studies. The information may also help 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. Data now may also act as a baseline to help determine whether Lyme disease is spreading and becoming more common. 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 other parts of the world) but there are insufficient 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 assays currently available in UK accredited laboratories? • 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. Understanding the epidemiology and regional prevalence of Lyme disease in the UK will help in the interpretation of serological test results. Knowledge about the prevalence of coinfection with other tick borne infections will provide patients and physicians with better evidence to guide more appropriate investigation of patients with Lyme disease for coinfections and their treatment if required.
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 and patients with confidence that their illness is being managed correctly. 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. Possible approaches are to systematically include tests for co-infection when testing people for Lyme disease.
Feasibility	This research will help reduce costs due to avoiding treatment when it is not indicated and better managing definitely positive cases. 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.