National Institute for Health and Care Excellence

Final

Lyme disease: diagnosis and management

[M] Evidence review for person-to-person transmission

NICE guideline 95

Intervention evidence review

April 2018

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-2919-1

Contents

1 Person-to-person transmission

1.1 Review question: What are the patterns of person-to-person transmission of Lyme disease?

1.2 Introduction

Lyme disease (Lyme borreliosis) is a tick-borne infectious disease. It is caused by a specific group of *Borrelia burgdorferi sensu lato* (*Borrelia burgdorferi s.l.*) bacteria, which can be transmitted to humans through a bite from an infected tick. The possibility of person-to-person spread has been raised, and developing Lyme disease during pregnancy is of concern to women who are pregnant. Person-to-person transmission was therefore included in the scope to assess what evidence was available.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years), children (under 12 years), neonates or new-borns (under 28 days old) and stillbirths with suspected (or under investigation for) Lyme disease.
Study design	Observational studies that report an incidence or prevalence estimate of Lyme disease through 1 of the following ways of transmission: • vertical transmission • sexual transmission • transmission through blood products
Statistical measures	Transmission risk of Lyme disease, defined as the number of effective contacts per unit of time (that is, people infected through the contact measured) divided by the total number of contacts between infectious and susceptible individuals per time unit. In the absence of reliable transmission risk data, incidence and prevalence data will be included in this review. Incidence of Lyme disease (any clinical presentation related to Lyme disease), defined as the number of new cases within a specified time period divided by the size of the population initially at risk. The prevalence of Lyme disease (any clinical presentation related to Lyme disease) is defined as the number of individuals with the disease divided by the number of individuals tested in the population at risk.
Review strategy	Titles and abstracts will be reviewed to identify papers that mention transmission of Lyme disease, transmission risk or any models used to generate such estimates. The full text of the identified articles will then be assessed and studies on vector-borne transmission (that is, infections through a tick bite) will be excluded from the review. Stratum: • By way of transmission Appraisal of methodological quality: • The methodological quality of each study will be assessed using an adaptation of a checklist for prevalence and incidence studies published by the Joanna Briggs Institute

Synthesis of data:

- Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for studies reporting a transmission risk, incidence or prevalence estimate of Lyme disease through vertical transmission, sexual transmission, or transmission through blood products. No such studies were identified. In the absence of studies reporting a transmission risk, incidence or prevalence estimate, any observational studies reporting person-to-person transmission excluding case reports were reviewed.

Eight cohort studies, 2 case-control studies and 2 case series that reported outcomes related to vertical transmission were included in the review.[6,17,21,22,24-27,33,50,51,58] The definition of transmission differed across the studies and included outcomes such as pregnancy complications or seropositive test results in new-borns. Included studies are summarised in Table 2 below. Other study limitations are listed in the quality assessment below (Table 3).

No observational studies reporting sexual transmission or transmission via blood products were found.

Vertical transmission of an infectious pathogen refers to the transmission of the pathogen directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth. The term ‘transmission’ is, however, often used in a much wider context and can refer to a number of different clinical scenarios. For example, *Borrelia burgdorferi sensu lato* could be transmitted from mother to child during pregnancy or childbirth and result in an asymptomatic infection of the child; alternatively, pregnancy complications or birth defects could be a direct result of the maternal infection rather than a vertical transmission of the pathogen to the child. As there is uncertainty about how vertical transmission of Lyme disease would present, we included all of these definitions.

The majority of the included studies reported pregnancy complications potentially resulting from maternal Lyme disease whereas some studies reported laboratory evidence of contracted fetal or infant Lyme disease. In order to determine if *Borrelia burgdorferi sensu lato* was transmitted from mother to child, both the mother and the child would have to be tested for the bacteria.

See also the study selection flow chart in appendix C.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Study design	Population	Setting	Results	Comments
Carlomagno 1988[6]	Retrospective case-control study	n=98 (49 cases of spontaneous abortion, 49 cases of normal term pregnancy)	Endemic area of Italy	6/49 spontaneous abortion people group had specific antibodies to *Borrelia burgdorferi s.l.*: • 4 reported a tick bite 6-36 months prior to the abortion (1 with skin lesions and symptoms, 1 reported antimicrobial treatment) 3/49 term pregnancy group had specific antibodies to *Borrelia burgdorferi s.l.*: • none remembered a tick bite/EM rash and all delivered healthy infants	No direct evidence of cause and effect
Lakos 2010[17]	Retrospective cohort study	n=95 gestational Lyme disease people Inclusion criteria: EM rash during pregnancy (CDC and EUCALB criteria); visited the centre after delivery, with EM that had commenced before or during pregnancy; clinically diagnosed ACA with signs of inflammation still present after delivery, which had commenced before or during the pregnancy; facial palsy beginning during	Single centre Hungary	20/95 (21.1%) had adverse pregnancy outcomes; cavernous haemangioma was the only outcome which was higher in the study population than expected as compared with the average frequency in Hungary: • cavernous haemangioma 4/95 (4.2% 95% CI 1.2-10.4); average incidence in Hungary 0.11% (0.08-0.14) None of the tested new-borns showed an IgM reaction. All new-borns born to mothers who were IgG positive at delivery were IgG positive (unclear how many new-born were	10 people were untreated, 9 people received penicillin IV 2x10 MU, 57 received ceftriaxone IV 2 g/day for 15 days, oral treatment applied in 19 people None of the participants used illicit drugs, smoked cigarettes or regularly drank alcohol during their pregnancies No direct evidence of cause and effect

Study	Study design	Population	Setting	Results	Comments
		pregnancy with preceding EM or with the presence of intrathecal *Borrelia burgdorferi s.l.* antibody production Age, mean (SD) 29.7 (4.3) years Family origin: White		tested)	
MacDonald 1986[21]	Prospective case series	n=4 still born fetuses	USA	• Spirochetes were cultured from fetal liver tissue in all 4 cases • Spirochetes were cultured from the heart in 1 case • By immunofluorescence, spirochetes were detected in fetal liver, heart, adrenal, brain, kidney, meninges and in the subarachnoid space in 1 case and in the liver or placenta in the remaining cases	No infections had been diagnosed in the mothers during pregnancy
MacDonald 1989[22]	Retrospective cohort study	n=24 perinatal autopsies	Single hospital in a hyper-endemic area, USA	4/24 (17%) showed evidence of Lyme borreliosis	
	Prospective case series	n=14 perinatal deaths attributed to Lyme disease		Evidence of *Borrelia burgdorferi s.l.* found in 13/14 fetuses/babies (culture [2], immunofluorescence [6], immunohistochemistry [2], placenta immunofluorescence [1], placenta Warthin–S tarry silver impregnation [1], placenta culture [1])	4/14 babies survived, but were reported as cases
Maraspin 1996[24] Maraspin 1999[25]	Prospective cohort study	n=105 pregnant women with typical EM (diagnosed using CDC criteria)	Single centre, Slovenia	12/105 (11.4%) had adverse pregnancy outcomes: • 6 pre-term deliveries (2 deaths), no causal relationship between pre-	36 people were asymptomatic, 69 reported local or mild constitutional symptoms 25 acquired infection during first

Study	Study design	Population	Setting	Results	Comments
		Age median, 29 years (range 17-42 years)		term birth and *Borrelia burgdorferi s.l.* infection found, no spirochetes found in Warthin–Starry silver impregnated tissues during autopsy • 5 babies with congenital abnormalities, no causal relationship between abnormalities and *Borrelia burgdorferi s.l.* infection found • 2 pregnancies ended with an abortion (1 missed, 1 spontaneous), incidence of abortion was lower than national level	trimester, 43 in the second trimester, 37 in the third trimester People treated with phenoxymethylpenicillin (1 million IU t.i.dd), Benzylpenicillin (10 million IU 2 times per day) or ceftriaxone (2 g daily) for 14 days – outcome was favourable in all women
Maraspin 2011[26]	Prospective cohort study	n=7 pregnant women diagnosed with previously untreated typical EM with *Borrelia burgdorferi s.l.* isolated from blood culture	Department of infectious disease, Slovenia	1/7 pregnancies ended with preterm birth at week 37, all 7 infants were healthy	May include a subset of people included in Maraspin 1996/1999 (182 blood cultures were performed in a total of 187 pregnant women with previously untreated typical EM between 1994 and 2006, 7 were positive) EM developed in the first trimester in 1 person, second trimester in 2 people and third trimester in 4 people People treated with ceftriaxone IV 2 g daily for 14 days – outcome favourable in all 7 women
Markowitz 1986[27]	Prospective and retrospective cohort study	n=19 pregnant women with EM or if no history of EM, onset of neurologic, cardiac, or joint	CDC surveillance system, USA	5/19 (26%) had abnormal pregnancy outcomes: • 1 intrauterine fetal death, culture and IFA of placenta and fetal	Only cases in which the outcome of pregnancy was not known at the time of enrolment were enrolled in the study

Study	Study design	Population	Setting	Results	Comments
		involvement of Lyme disease during pregnancy and an antibody titre of 1:256 or higher by immunofluorescence assay or 1:200 or higher by ELISA, or onset of manifestations in 2 of 3 organ systems (neurologic, cardiac or joint) during pregnancy Age median, 30 years (range 21-37)		tissues negative for *B. burgdorferi* • 1 premature labour at 36 weeks, infant was normal • 1 infant with syndactyly (type 1) of the second and third toes • 1 infant who was born healthy but later diagnosed with cortical blindness and developmental delay, child had no serum antibodies to *B. burgdorferi* • 1 infant who was born healthy except for a generalised, petechial, vesicular rash and hyperbilirubinemia, viral and bacterial blood and skin cultures were negative Umbilical cord blood from 5 normal infants was tested – 4 tested for IgM to *B. burgdorferi* none had an elevated titre, 1 infant had an antibody titre of 1:512 at birth but no detectable antibody 7 months later	13 people received penicillin
Nadal 1989[33]	Prospective cohort study	n= 12 pregnant women with elevated titres out of 1,416 pregnant women tested serologically for *B. burgdorferi* Age, mean 28.3 years (range 21-40)	Department of obstetrics, Switzerland	• Delayed adaptation in 1 pre-term infant and 1 post-term infant • 2 infants had hyperbilirubinemia • 1 infant had muscle hypotonia • 1 post-term infant was underweight for age as a consequence of chronic placental insufficiency • 1 infant had macrocephaly • 1 infant had supraventricular extrasystoles • 1 infant had a ventricular septal	Only 1/12 women showed evidence of clinically active Lyme disease during pregnancy No direct evidence of cause and effect

Study	Study design	Population	Setting	Results	Comments
				defect 11/12 children examined at mean age 13 months – 1 infant born to a mother with clinical symptoms had a cardiac defect, the other 10 were healthy, 1 infant had a borderline titre of 1:64 but no specific IgM could be detected	
Strobino 1993[51]	Prospective cohort study	n=2,014 women identified from the first prenatal visit	2 hospitals, USA	All birth defects • Lyme disease ever: OR 1.68 (95% CI 0.91-3.13) • Lyme disease during pregnancy: OR 0.53 (95% CI 0.07-4.16) • <1 year before: OR 1.65 (95% CI 0.60-4.57) • >1 year before: OR 2.94 (95% CI 0.98-8.86) • Timing unknown: OR 1.76 (95% CI 0.47-6.57) Major defects • Lyme disease ever: OR 1.43 (95% CI 0.50-4.09) • Lyme disease during pregnancy: - • <1 year before: OR 0.98 (95% CI 0.13-7.52) • >1 year before: OR 3.49 (95% CI 0.74-16.49) • Timing unknown: OR 1.75 (95% CI 0.22-13.99) Minor defects	Lyme disease measured by self-reported questionnaire given to mothers at first prenatal visit Follow-up data on pregnancy outcome came from 1 or more of the following: mid-pregnancy interview by phone, contact at delivery in the hospital, baby's discharge summary, mailed questionnaire 6 months after expected delivery date, paediatric and obstetric records Pregnancy outcome was obtained for 96% of participants Major defects: defects in structure or function that were considered serious, required treatment at birth or thereafter and were not due to known chromosome anomalies Minor defects: defects in structure or function that were not serious and did not usually require

Study	Study design	Population	Setting	Results	Comments
				• Lyme disease ever: OR 1.81 (95% CI 0.89-3.69) • Lyme disease during pregnancy: OR 0.80 (95% CI 0.10-6.28) • <1 year before: OR 1.99 (95% CI 0.66-6.05) • >1 year before: OR 2.66 (95% CI 0.71-9.94) • Timing unknown: OR 1.77 (95% CI 0.38-8.29) Fetal deaths • Lyme disease ever: 7.6% • Lyme disease during pregnancy: 0% • Lyme disease <1 year before: 13.8% • Lyme disease >1 year before: 9.5% • No Lyme disease: 8%	treatment. Defects were categorised a priori and classification was carried out without knowledge of exposure status No direct evidence of cause and effect
Strobino 1999[50]	Retrospective case-control study	n=796 children diagnosed with congenital cardiac anomaly (cases) and 704 children with innocent heart murmur, benign rhythm pattern or non-cardiac chest pain (controls) Inclusion (cases): <7 years with a diagnosis of an anatomic or physiologic cardiac abnormality not	Lyme disease endemic area, USA	Mothers of control subjects were more likely than those of case patients to have had Lyme disease during pregnancy or within 3 months before conception OR 0.89 (95% CI 0.22-3.61) Within 1 year before conception: OR 1.00 (95% CI 0.38-2.63) Any time before conception: OR 0.85 (95% CI 0.39-1.89)	Odds ratios adjusted for maternal age, number of live births, current county of residence, year of birth of study child, occupational x-ray exposure, maternal high blood pressure, and characteristics of residence at the time of birth Possible Lyme disease cases (20% of total Lyme disease cases) were excluded from the analysis, but results did not change when they were included

Study	Study design	Population	Setting	Results	Comments
		associated with documented chromosomal abnormality, genetic syndrome, prematurity, or a defined postnatal cause (controls): <12 years evaluated because of a heart murmur, rhythm irregularity, or chest pain and found to have no cardiac pathology			
Williams 1995[58]	Prospective cohort study	n=5,011 infants (2,504 endemic area, 2,507 non-endemic area)	1 community hospital in an endemic area, 1 community hospital in a non-endemic area, USA	All malformations (endemic area) • Lyme before pregnancy: 8.7% • Lyme during pregnancy: 16.7% • Cord blood IgG positive: 5% • Total endemic cohort: 7.8% Major malformations (endemic area) • Lyme before pregnancy: 8.7% • Lyme during pregnancy: 16.7% • Cord blood IgG positive: 0% • Total endemic cohort: 2.9% Minor malformations (endemic area) • Lyme before pregnancy: 0% • Lyme during pregnancy: 0% • Cord blood IgG positive: 5% • Total endemic cohort: 4.8%	Study reports Lyme disease and malformation rates in both endemic and control cohorts but malformation rates as a percentage of Lyme disease pregnancies are only reported for the endemic area No direct evidence of cause and effect

1.4.4 Narrative summary

There was an absence of good quality evidence in relation to vertical transmission. The main body of evidence came from cohort studies that reported the rates of adverse pregnancy outcomes, with no direct evidence of a causal link with maternal Lyme disease. Rates of adverse outcomes varied from 11.4% (12 out of 105) in women with a typical EM rash during pregnancy to 35.7% (6 out of 17) in women who had Lyme disease more than 1 year before pregnancy. Evidence from 1 cohort study suggested that the risk of cavernous haemangioma was higher in infants born to mothers with Lyme disease than in the general population and another cohort study suggested that the risk of birth defects was higher in infants born to women who had had Lyme disease before pregnancy but not during, compared with women who had never had Lyme disease. However, neither of these studies included a multivariable analysis to control for confounding factors. In 1 of the studies, the confidence intervals were very wide and included a risk reduction.

Evidence from 2 case-control studies suggested an increased risk of spontaneous abortion but no increased risk of congenital cardiac defects.

Issues that limited confidence in the evidence included heterogeneity in the study populations. Populations varied within and between studies in clinical presentations and treatment regimens. The stage at which Lyme disease developed also varied from before conception to the third trimester of pregnancy. None of the studies reported a case definition for Lyme disease in infants or children, and several of the studies did not report a case definition for Lyme disease in mothers. Serology or self-reported Lyme disease, which may not be reliable measures, was often used to identify Lyme disease cases.

Direct evidence of vertical transmission came from 1 retrospective analysis of autopsies performed at a single centre and from 2 case series. None of these studies provided an incidence or prevalence estimate of Lyme disease through vertical transmission.

1.4.5 Quality assessment of clinical studies included in the evidence review

Table 3: Study limitations [adapted from the Joanna Briggs Institute[31]]

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
Carlomagno 1988[6]	Yes	Unclear – sampling not described	No	Yes	Fetus: no acceptable case definition (spontaneous abortion) Mother: presence of specific antibodies to *Borrelia burgdorferi s.l.* and self-report tick bite/EM rash	Serology testing by indirect immunofluorescence, titre of specific IgG ≥1:64 considered positive Tick bite/EM rash measured by self-report in a retrospective interview - only reported for those with positive serology	No – number of mothers with positive serology and tick bite/EM rash out of total number of spontaneous abortions and normal pregnancies	No direct evidence of cause and effect relationship between spontaneous abortion and maternal Lyme disease
Lakos 2010[17]	Yes	Yes	Yes	Yes	Infant: no acceptable case definition (adverse	Homemade immunoblot using *Borrelia afzelii* as an	No – number of adverse pregnancy outcomes out	No direct evidence of cause and effect

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					pregnancy outcomes, IgG and IgM for a subset of infants) Mother: EM rash during pregnancy (CDC and EUCALB criteria); clinically diagnosed ACA; facial palsy with preceding EM or with the presence of intrathecal *Borrelia burgdorferi s.l.* antibody production	antigen Examination of infants by 1 of the authors (a paediatrician who specialises in infectious diseases) or a medical report registered by the family paediatrician, mothers asked to report any later problems of suspected congenital origin	of total number of mothers with Lyme disease, number of infants with IgG/IgM antibodies out of total number of those tested	relationship between adverse pregnancy outcomes and maternal Lyme disease People received different treatment regimens
MacDonald 1986[21]	Yes	No	Yes	Yes	No case definition reported	Culture of autopsy tissue Indirect immunofluores	No – cases selected on the basis of evidence of Lyme disease	N/A

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
						cence of tissue sections and positive culture specimens		
MacDonald 1989[22]	Yes	No	Yes	Yes	No case definition reported	Culture, immunofluorescence, immunohistochemistry, Warthin–Starry silver impregnation	No – number of fetuses/infants with evidence of Lyme disease out of total number of perinatal deaths (does not include mothers with Lyme disease who delivered healthy babies)	N/A
Maraspin 1996[24] Maraspin 1999[25]	Yes	Yes	Yes	Yes	Fetuses/infants: no case definition reported Mother: typical EM (diagnosed using CDC	Adverse pregnancy outcome measured by clinical evaluation	No – number of adverse pregnancy outcomes out of total number of mothers with Lyme disease but no causal	Clinical presentations varied between people, and people received different treatment

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					criteria)		association with Lyme disease identified	regimens
Maraspin 2011[26]	Yes	Yes	Yes	Yes	Infants: no case definition reported Mother: typical EM (CDC criteria) with *Borrelia burgdorferi s.l.* isolated from blood culture	Clinical evaluation	No – number of adverse pregnancy outcomes out of total number of mothers with Lyme disease	No direct evidence of cause and effect relationship between adverse pregnancy outcomes and maternal Lyme disease
Markowitz 1986[27]	Yes	Yes	Yes	Yes	Fetus/infant: no case definition reported Mother: EM or if no history of EM, onset of neurologic, cardiac, or joint involvement of Lyme disease during	Physicians contacted or medical records reviewed to document adverse pregnancy outcomes Available serum samples tested by IFA	No – number of adverse pregnancy outcomes out of total number of mothers with Lyme disease but no causal association with Lyme disease identified	13/19 people received treatment

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					pregnancy and an antibody titre of 1:256 or higher by immunofluorescence assay or 1:200 or higher by ELISA, or onset of manifestations in 2 of 3 organ systems (neurologic, cardiac or joint) during pregnancy	or ELISA; if possible, cord blood obtained at delivery; placental and fetal tissue, if obtained, cultured and examined by dark-field microscopy and IFA		
Nadal 1989[33]	Yes	Yes	No	Yes	No case definition reported	Antibody titres determined by IFA (threshold for IgG 1:64 and titres above were examined for IgM) Records of mothers with titres >1:64	No – number of adverse pregnancy outcomes out of total number of mothers with elevated titres	Only mothers with elevated titres were examined further Only 1/12 women showed evidence of clinically active Lyme disease during

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
						reviewed for signs and symptoms compatible with Lyme disease Clinical evaluation by a paediatrician/study authors		pregnancy No direct evidence of cause and effect relationship between adverse pregnancy outcomes and maternal Lyme disease
Strobino 1993[51]	Yes	Yes	Yes	Yes	Fetus/infant: no case definition reported Mother: IgG antibodies to *B. burgdorferi* by fluorescence immunoassay test, positive sera tested for IgM (titres >75 considered positive), self-	Questionnaire about Lyme disease history and data on characteristics related to possible Lyme exposure Data on pregnancy outcome, 1 or more of the following: mid-pregnancy	No – number of adverse pregnancy outcomes out of total number of mothers with Lyme disease	No direct evidence of cause and effect relationship between adverse pregnancy outcomes and maternal Lyme disease

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					reported Lyme disease history	interview by phone, contact at delivery in the hospital, baby's discharge summary, mailed questionnaire 6 months after expected delivery date, paediatric and obstetric records Prenatal blood test and maternal or cord blood samples taken at delivery – tested by fluorescence immunoassay		
Strobino 1999[50]	Yes	Yes	Yes	No – only 39% returned questionnaire	Children: no case definition reported	Questionnaire including Lyme disease and potential	No – number of mothers with a history of Lyme	N/A

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
					Mother: Definite Lyme disease – characteristic Lyme symptoms (rash, joint pain or swelling, fever, headache, stiff neck) and diagnosis and treatment by a physician Possible Lyme disease – treated for Lyme disease but there was some question about the diagnosis or inconsistencies in their history or they were never treated for Lyme disease	exposure to *B. burgdorferi* during pregnancy (Lyme disease diagnosis by a physician, dates of occurrence, symptoms, treatment, dates and results of all Lyme disease blood tests)	disease out of total congenital heart defect cases compared with number of mothers with a history of Lyme disease out of total controls	
Williams	Yes	Yes	Yes	No –	Infant: no case	Questionnaire	No – number	No direct

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
1995[58]				questionnaire data available for 82% of endemic area mothers and 71% of non-endemic area mothers	definition reported Mother: self-reported history of Lyme disease	including items on exposure to tick bites, symptoms and diagnosis of Lyme disease Samples of cord blood taken at delivery and analysed by ELISA Discharge summary with admission and discharge diagnoses for infants, follow up from the child's paediatrician via mailed questionnaire at 6 months and from the mother at periodic	of infants with malformations out of total number of pregnancies in different Lyme disease exposure groups	evidence of cause and effect relationship between malformations and maternal Lyme disease

Study	Was the sample frame appropriate to address the target population?	Were the study participants sampled in an appropriate way?	Were the study subjects and setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for the identification of the condition?	Was the condition measured in a standard, reliable way for all people?	Was there appropriate statistical analysis?	Other limitations
						intervals		

1.5 Economic evidence

Health economic evidence was not relevant to this question and so a health economic evidence review was not conducted.

1.6 Resource impact

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

1.7 Evidence statements

1.7.1 Clinical evidence statements

This review did not identify any evidence for sexual transmission of Lyme disease or transmission of Lyme disease through blood products.

In relation to vertical transmission, no studies reporting incidence or prevalence figures were identified. Cohort studies reported adverse pregnancy outcome rates ranging from 11.4% to 35.7% with no direct evidence of a causal link with maternal Lyme disease. Evidence from 2 cohort studies comparing the rates of adverse pregnancy outcomes in women with and without Lyme disease suggested a trend towards an increased risk of adverse outcomes but the data was not adjusted for confounding factors. Evidence from 2 case-control studies was conflicting. Direct evidence of vertical transmission came from 1 retrospective analysis of autopsies and from 2 small case series showing cultivation of spirochetes and detection by immunofluorescence of autopsied tissue and placentas of stillborn fetuses, but the studies did not provide an incidence or prevalence estimate of Lyme disease through vertical transmission. All studies were at high risk of bias due to issues with the study populations, case definitions and methods of data collection.

1.7.2 Health economic evidence statements

Not applicable.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The key outcome of interest was a transmission risk, incidence or prevalence estimate of Lyme disease through vertical transmission, sexual transmission or transmission through blood products. Transmission risk was defined as the number of effective contacts per unit of time (that is, people infected through the contact measured) divided by the total number of contacts between infectious and susceptible individuals per time unit. In the absence of studies reporting a transmission risk, incidence or prevalence estimate, any observational study excluding case reports reporting a person-to-person transmission was included in this review.

No evidence was found for transmission of Lyme disease through sexual contact or blood products. For vertical transmission only cohort studies, case-control studies and case series reporting

1.8.1.2 The quality of the evidence

Indirect evidence came from 11 studies reporting outcomes related to vertical transmission. Quality assessment of the individual studies was carried out according to an adapted version of The Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence and Incidence Data. Although none of the included studies reported incidence or prevalence data, the Joanna Briggs Institute checklist was chosen because of the type of evidence identified for this review.

Specific issues that limited our confidence in the evidence in general were heterogeneity among the study populations in clinical presentation, treatment regimens and stage at which Lyme disease developed in the mother; lack of adequate case definitions of both the mothers and offspring; methodological limitations in Lyme disease measurement and indirectness of study outcomes (adverse pregnancy outcomes could not be definitively attributed to transmission of Lyme disease). There was also the issue of high risk of selection bias and small sample size associated with the case series.

None of the included studies carried out a multivariable analysis to control for confounding factors, and in 1 of the studies, the confidence intervals were very wide and included a risk reduction.

1.8.1.3 Benefits and harms

The main body of evidence came from cohort studies that reported rates of adverse pregnancy outcomes, with no direct evidence of a causal link with maternal Lyme disease. Rates of adverse outcomes varied from 11.4% (12 out of 105) in women with a typical EM rash during pregnancy to 35.7% (6 out of 17) in women who had had Lyme disease more than 1 year before pregnancy.

Evidence from 1 cohort study suggested that the risk of cavernous haemangioma was higher in infants born to mothers with Lyme disease than in the general population and another cohort study suggested that the risk of birth defects was higher in infants born to women who had had Lyme disease before pregnancy but not during, compared with women who had never had Lyme disease.

Evidence from 1 case-control study suggested an increased risk of spontaneous abortion, although the numbers were relatively low. Evidence from another case control study showed no increased risk of congenital cardiac defects.

Laboratory evidence of vertical transmission came from 1 retrospective analysis of autopsies reporting evidence of Lyme disease in 4 out of 24 perinatal autopsies performed at a single centre and from 2 small case series of autopsied fetal tissue. The guideline committee discussed the limitations of the techniques used in the studies. In particular, the immunofluorescent test is based on an antibody to *Borrelia burgdorferi sensu lato* that cross-reacts with basement membranes, so immunofluorescence staining can attach to normal parts of human tissue and cross-react. Warthin Starry staining is not specific for Lyme disease and the spirochetes detected may in fact be saprophytes, and there is the possibility of culture contamination. In 1 study, no diagnosis of Lyme disease was reported in any of the mothers. The committee agreed that this evidence should be interpreted with caution.

Overall, the guideline committee considered the evidence inconclusive in terms of identifying a risk of vertical transmission of Lyme disease. The committee considered that vertical transmission is not impossible, although no strong causal link between a maternal Lyme disease infection and adverse pregnancy outcomes could be found. There was also no evidence that a maternal infection resulted in a transmission of *Borrelia spirochaete* to the child. Therefore, the guideline committee decided to recommend that women diagnosed with Lyme disease during pregnancy follow the same clinical pathway as the rest of the population, except for the choice of antibiotic treatment (using amoxicillin as first line rather

than doxycycline) and an individualised discussion about the potential risks of vertical transmission. It should be emphasised that there is a lack of good quality evidence in the area, but that the risk appears to be very low.

Symptoms of Lyme disease in infants are not known, and there was no specific cluster of adverse pregnancy outcomes that was consistent across the studies. Therefore, mothers and clinicians should monitor the infant for any symptoms after birth. The guideline committee recommended that babies born to mothers who have been treated for symptomatic Lyme disease during pregnancy be clinically assessed and discussed with a paediatric infectious diseases specialist.

The guideline committee acknowledged the overall lack of good quality evidence in the area of person-to-person transmission and therefore decided to make a recommendation for further research on the incidence, presenting features, management and outcome of Lyme disease, including in women with Lyme disease who are pregnant.

1.8.2 Cost effectiveness and resource use

No health economic evidence was identified. The clinical evidence suggests that vertical transmission is very unlikely but not impossible. No clinical evidence of sexual transmission was identified. As highlighted above, the committee agreed to recommend that women diagnosed with Lyme disease during pregnancy follow the same clinical pathway as the rest of the population, except for the choice of antibiotic treatment and an individualised discussion about the potential risks of vertical transmission. Neither of these recommendations is likely to have a significant resource impact.

A recommendation was made that babies born to mothers who have been treated for Lyme disease during pregnancy be clinically assessed and discussed with a paediatric infectious diseases specialist. This may require additional healthcare resources; however, it is considered to be best practice, is already part of the remit of NHSE commissioned paediatric infectious diseases services, and is likely to be done already in most settings.

1.8.3 Other factors the committee took into account

The guideline committee discussed the possibility of serological testing on all babies born to mothers who have been diagnosed with Lyme disease during pregnancy. If a mother who has had Lyme disease is IgG positive, her baby may also be IgG positive because the antibodies may have been passed directly from mother to baby. However, it is not known definitively whether IgG antibodies are an indication of placental transmission only. It is unlikely that babies would be exposed to ticks in the first weeks after being born, so if infants develop an IgM response during this time then this may be evidence of vertical transmission. However, differences in babies' immune response mean that routine testing may not be useful in establishing a diagnosis of Lyme disease. It was agreed that clinical assessment and discussion with a specialist was a more appropriate method of monitoring infants for potential adverse effects of maternal Lyme disease.

The guideline committee also explored the scenario of an engorged tick attached to a pregnant woman and discussed the risks and benefits of sending the tick for analysis in view of treating prophylactically in the case of a positive result. Tick testing is not always accurate and the woman may have unknowingly been bitten by more than 1 tick. A negative result could therefore lead to a false sense of security, which, in the event of her developing symptoms, may prevent her from seeking further medical help or her GP from investigating for Lyme disease. The committee decided that as for people who are not pregnant treatment should only be given if Lyme disease is diagnosed.

The guideline committee did not include an obstetrician so the obstetric advisor to the National Guideline Alliance at the Royal College of Obstetricians and Gynaecologists was

asked to review the evidence report and draft recommendations and advise on any issues of interpretation of clarity. No changes were suggested from her review.

The committee developed a research recommendation to improve clinical epidemiology of Lyme disease in the UK to include the follow up of women who have Lyme disease when pregnant. This would provide essential information for both health care professionals and the public and allow appropriate advice and management.

References

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

2. Alexander JM, Cox SM. Lyme disease and pregnancy. Infectious Diseases in Obstetrics and Gynecology. 1995; 3(6):256-261

3. Anonymous. Update: Lyme disease and cases occurring during pregnancy--United States. Morbidity and Mortality Weekly Report. 1985; 34(25):376-378, 383-384

4. Anonymous. Lyme disease occurring during pregnancy. Clinical Pediatrics. 1986; 25(4):204

5. Bale JF, Jr., Murph JR. Congenital infections and the nervous system. Pediatric Clinics of North America. 1992; 39(4):669-690

6. Carlomagno G, Luksa V, Candussi G, Rizzi GM, Trevisan G. Lyme borrelia positive serology associated with spontaneous abortion in an endemic Italian area. Acta Europaea Fertilitatis. 1988; 19(5):279-281

7. Dlesk A, Broste SK, Harkins PG, McCarty PA, Mitchell PD. Lyme seropositivity and pregnancy outcome in the absence of symptoms of Lyme disease. Arthritis and Rheumatism. 1989; 32:S46

8. Edly SJ. Lyme disease during pregnancy. New Jersey Medicine. 1990; 87(7):557-560

9. Elliott DJ, Eppes SC, Klein JD. Teratogen update: Lyme disease. Teratology. 2001; 64(5):276-281

10. Gerber MA, Zalneraitis EL. Childhood neurologic disorders and Lyme disease during pregnancy. Pediatric Neurology. 1994; 11(1):41-43

11. Gibbs RS, Roberts DJ. Case 27-2007: a 30-year-old pregnant woman with intrauterine fetal death. New England Journal of Medicine. 2007; 357(9):918-925

12. Goldenberg RL, Thompson C. The infectious origins of stillbirth. American Journal of Obstetrics and Gynecology. 2003; 189(3):861-873

13. Grandsaerd MJG, Meulenbroeks AA. Lyme borreliosis as a cause of facial palsy during pregnancy. European Journal of Obstetrics Gynecology and Reproductive Biology. 2000; 91(1):99-101

14. Hercogova J, Tomankova M, Frosslova D, Janovska D. Early-stage Lyme borreliosis during pregnancy: treatment in 15 women with erythema migrans. Ceskoslovenska Gynekologie. 1993; 58(5):229-232

15. Jasik KP, Okla H, Slodki J, Rozwadowska B, Slodki A, Rupik W. Congenital tick-borne diseases: is this an alternative route of transmission of tick-borne pathogens in mammals? Vector Borne and Zoonotic Diseases. 2015; 15(11):637-644

16. Joseph JT, Purtill K, Wong SJ, Munoz J, Teal A, Madison-Antenucci S et al. Vertical transmission of Babesia microti, United States. Emerging Infectious Diseases. 2012; 18(8):1318-1321

17. Lakos A, Solymosi N. Maternal Lyme borreliosis and pregnancy outcome. International Journal of Infectious Diseases. 2010; 14(6):e494-e498

18. Lavoie PE, Lattner BP, Duray PH, Malawista SE, Barbour AG, Johnson RC. Culture positive, seronegative transplacental Lyme borreliosis infant mortality. Arthritis and Rheumatology. 1987; 30(4 Suppl 3):S50

19. Lawrence RM, Lawrence RA. Breast milk and infection. Clinics in Perinatology. 2004; 31(3):501-528

20. Leiby DA, Gill JE. Transfusion-transmitted tick-borne infections: a cornucopia of threats. Transfusion Medicine Reviews. 2004; 18(4):293-306

21. MacDonald AB. Human fetal borreliosis, toxemia of pregnancy, and fetal death. Zentralblatt fur Bakteriologie, Mikrobiologie, und Hygiene - Series A, Medical Microbiology, Infectious Diseases, Virology, Parasitology. 1986; 263(1-2):189-200

22. MacDonald AB. Gestational Lyme borreliosis. Implications for the fetus. Rheumatic Diseases Clinics of North America. 1989; 15(4):657-677

23. MacDonald AB, Benach JL, Burgdorfer W. Stillbirth following maternal Lyme disease. New York State Journal of Medicine. 1987; 87(11):615-616

24. Maraspin V, Cimperman J, Lotric-Furlan S, Pleterski-Rigler D, Strle F. Treatment of erythema migrans in pregnancy. Clinical Infectious Diseases. 1996; 22(5):788-793

25. Maraspin V, Cimperman J, Lotric-Furlan S, Pleterski-Rigler D, Strle F. Erythema migrans in pregnancy. Wiener Klinische Wochenschrift. 1999; 111(22-23):933-940

26. Maraspin V, Ruzic-Sabljic E, Pleterski-Rigler D, Strle F. Pregnant women with erythema migrans and isolation of borreliae from blood: course and outcome after treatment with ceftriaxone. Diagnostic Microbiology and Infectious Disease. 2011; 71(4):446-448

27. Markowitz LE, Steere AC, Benach JL, Slade JD, Broome CV. Lyme disease during pregnancy. JAMA. 1986; 255(24):3394-3396

28. McQuiston JH, Childs J, Chamberland ME, Tabor E. Transmission of tick-borne agents of disease by blood transfusion: a review of known and potential risks in the United States. Transfusion. 2000; 40(3):274-284

29. Menitove JE. Transfusion-transmitted infections: update. Seminars in Hematology. 1996; 33(4):290-301

30. Mikkelsen AL, Palle C. Lyme disease during pregnancy. Acta Obstetricia et Gynecologica Scandinavica. 1987; 66(5):477-478

31. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. International Journal of Evidence-Based Healthcare. 2015; 13(3):147-153

32. Mylonas I. Borreliosis during pregnancy: a risk for the unborn child? Vector Borne and Zoonotic Diseases. 2011; 11(7):891-898

33. Nadal D, Hunziker UA, Bucher HU, Hitzig WH, Duc G. Infants born to mothers with antibodies against Borrelia burgdorferi at delivery. European Journal of Pediatrics. 1989; 148(5):426-427

34. Piesman J. Transmission of Lyme disease spirochetes (Borrelia burgdorferi). Experimental and Applied Acarology. 1989; 7(1):71-80

35. Relic M, Relic G. Lyme borreliosis and pregnancy. Vojnosanitetski Pregled. 2012; 69(11):994-998

36. Salzman MB, Rubin LG. Lyme disease during pregnancy. Children's Hospital Quarterly. 1991; 3(3):175-177

37. Schaumann R, Fingerle V, Buchholz K, Spencker FB, Rodloff AC. Facial palsy caused by Borrelia infection in a twin pregnancy in an area of nonendemicity. Clinical Infectious Diseases. 1999; 29(4):955-956

38. Schlesinger PA, Duray PH, Burke BA, Steere AC, Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, Borrelia burgdorferi. Annals of Internal Medicine. 1985; 103(1):67-68

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

40. Schmidt M, Geilenkeuser WJ, Sireis W, Seifried E, Hourfar K. Emerging pathogens - how safe is blood? Transfusion Medicine and Hemotherapy. 2014; 41(1):10-17

41. Schutzer SE, Janniger CK, Schwartz RA. Lyme disease during pregnancy. Cutis. 1991; 47(4):267-268

42. Shirts SR, Brown MS, Bobitt JR. Listeriosis and borreliosis as causes of antepartum fever. Obstetrics and Gynecology. 1983; 62(2):256-261

43. Silver HM. Lyme disease during pregnancy. Infectious Disease Clinics of North America. 1997; 11(1):93-97

44. Smith GN, Gemmill I, Moore KM. Management of tick bites and lyme disease during pregnancy. Journal of Obstetrics and Gynaecology Canada. 2012; 34(11):1087-1091

45. Smith LG, Jr., Pearlman M, Smith LG, Faro S. Lyme disease: a review with emphasis on the pregnant woman. Obstetrical and Gynecological Survey. 1991; 46(3):125-130

46. Stiernstedt G. Lyme borreliosis during pregnancy. Scandinavian Journal of Infectious Diseases, Supplement. 1990; 22(71):99-100

47. Stramer SL. Current perspectives in transfusion-transmitted infectious diseases: emerging and re-emerging infections. ISBT Science Series. 2014; 9(1):30-36

48. Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR et al. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009; 49(Suppl 2):1S-29S

49. Stray-Pedersen B. New aspects of perinatal infections. Annals of Medicine. 1993; 25(3):295-299

50. Strobino B, Abid S, Gewitz M. Maternal Lyme disease and congenital heart disease: a case-control study in an endemic area. American Journal of Obstetrics and Gynecology. 1999; 180(3 Pt 1):711-716

51. Strobino BA, Williams CL, Abid S, Chalson R, Spierling P. Lyme disease and pregnancy outcome: a prospective study of two thousand prenatal patients. American Journal of Obstetrics and Gynecology. 1993; 169(2 Pt 1):367-374

52. Sultan P, Green C, Riley E, Carvalho B. Spinal anaesthesia for caesarean delivery in a parturient with babesiosis and Lyme disease. Anaesthesia. 2012; 67(2):180-183

53. Trevisan G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? International Journal of Dermatology. 1997; 36(9):677-680

54. Walsh CA, Mayer EW, Baxi LV. Lyme disease in pregnancy: case report and review of the literature. Obstetrical and Gynecological Survey. 2007; 62(1):41-50

55. Weber K, Bratzke HJ, Neubert U, Wilske B, Harrison Duray P. Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatric Infectious Disease Journal. 1988; 7(4):286-289

56. Wendel S. Current concepts on transmission of bacteria and parasites by blood components. Vox Sanguinis. 1994; 67(Suppl 3):161-174

57. Williams CL, Strobino B, Lee A, Curran AS, Benach JL, Inamdar S et al. Lyme disease in childhood: clinical and epidemiologic features of ninety cases. Pediatric Infectious Disease Journal. 1990; 9(1):10-14

58. Williams CL, Strobino B, Weinstein A, Spierling P, Medici F. Maternal Lyme disease and congenital malformations: a cord blood serosurvey in endemic and control areas. Paediatric and Perinatal Epidemiology. 1995; 9(3):320-330

59. Wylie BR. Transfusion transmitted infection: viral and exotic diseases. Anaesthesia and Intensive Care. 1993; 21(1):24-30

Appendices

Appendix A: Review protocols

Table 4: Review protocol for the transmission of Lyme disease

Question number: 7

Relevant section of Scope: transmission

Field	Content
Review question	What are the patterns of person-to-person transmission of Lyme disease?
Type of review question	Epidemiological Health economic evidence was not relevant for this review question.
Objective of the review	To identify if and how Lyme disease can be transmitted from person to person. This includes vertical (mother-to-child transmission during pregnancy or childbirth or through breastfeeding), sexual transmission, and transmission through blood products.
Eligibility criteria – population / disease / condition / issue / domain	Adults (18 years and over), young people (12 to 17 years), children (under 12 years), neonates and newborns (under 28 days old) and stillbirths with suspected (or under investigation for) Lyme disease. Lyme disease (specifically, conditions caused by *Borrelia burgdorferi sensu lato*)
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Not applicable
Eligibility criteria – comparator(s) / control or reference (gold) standard	Not applicable
Outcomes and prioritisation	Transmission risk of Lyme disease, defined as the number of effective contacts per unit of time (that is, people infected through the contact measured) divided by the total number of contacts between infectious and susceptible individuals per time unit. In the absence of reliable transmission risk data, incidence and prevalence data will be included in this review. Incidence of Lyme disease (any clinical presentation related to Lyme disease), defined as the number of new cases within a specified time period divided by the size of the population initially at risk. The prevalence of Lyme disease (any clinical presentation related to Lyme disease) is defined as the number of individuals with the disease divided by the number of individuals tested in the population at risk. The following ways of transmissions will be considered: • vertical transmission • sexual transmission • transmission through blood products
Eligibility criteria – study design	All studies that report an incidence or prevalence estimate of Lyme disease through 1 of the following ways of transmission:

Field	Content
	• vertical transmission • sexual transmission • transmission through blood products
Other inclusion exclusion criteria	Date limits for search: none Language: English only
Proposed sensitivity / subgroup analysis, or meta-regression	Stratum: • By way of transmission
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)	Bibliographies, citations, study sifting and reference management will be managed using EndNote.
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library all years Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	Identified evidence for this review question will be presented in a table in the evidence report.
Data items – define all variables to be collected	Not applicable
Methods for assessing bias at outcome / study level	Study limitations for each study will be assessed using an adaptation of a checklist for prevalence and incidence studies published by the Joanna Briggs Institute.
Criteria for quantitative synthesis	No quantitative synthesis will be performed. The evidence will be presented as a list or, if applicable, range of values.
Methods for quantitative analysis – combining studies and exploring (in)consistency	No quantitative synthesis will be performed. The evidence will be presented as a list or, if applicable, range of values.
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	No quantitative synthesis will be performed.
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

Field	Content
	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

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 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 03 July 201	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 6: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/

9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocyctic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	(letter or comment*).ti.
19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	11 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	exp models, economic/
49.	*Models, Theoretical/

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

Embase (Ovid) search terms

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

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

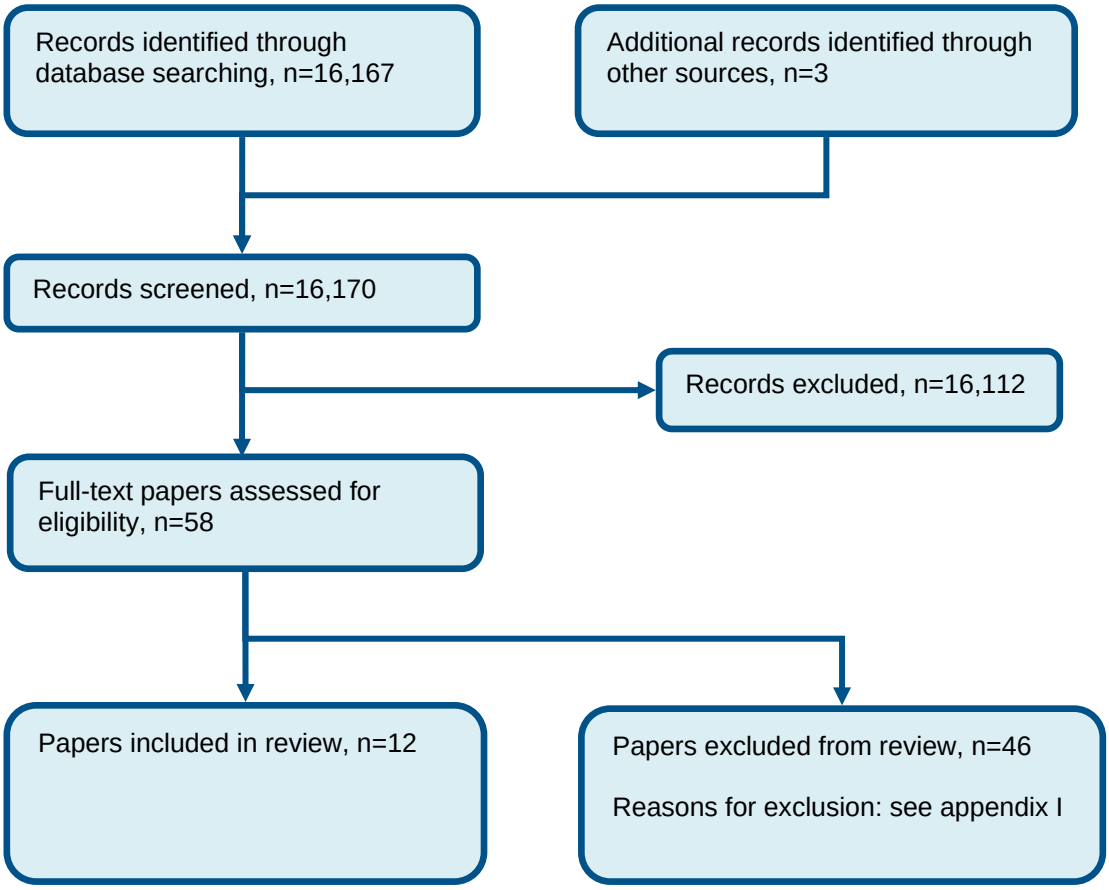
52.	monte carlo method/
53.	(markov* or monte carlo).ti,ab.
54.	econom* model*.ti,ab.
55.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
56.	or/46-55
57.	quality adjusted life year/
58.	"quality of life index"/
59.	short form 12/ or short form 20/ or short form 36/ or short form 8/
60.	sickness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

NHS EED and HTA (CRD) search terms

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of person-to-person transmission



Appendix D: Clinical evidence tables

Reference	Carlomagno 1988[6]
Study design	Retrospective case-control study
Number of participants and characteristics	n=98 49 cases of spontaneous abortion, 49 normal-term pregnancies
Sampling method	Not reported
Case definition	Mother: presence of specific antibodies to *Borrelia burgdorferi s.l.* and self-report tick bite/EM rash Fetus: no acceptable case definition (spontaneous abortion)
Country and setting	Endemic area of Italy
Study duration	1 year
Outcomes and effect sizes	6/49 people who had a spontaneous abortion had specific antibodies to *Borrelia burgdorferi s.l.*: 4 reported a tick bite 6-36 months prior to the abortion (1 with skin lesions and symptoms, 1 reported antimicrobial treatment) 3/49 term pregnancy group had specific antibodies to *Borrelia burgdorferi s.l.*: none remembered a tick bite/EM rash and all delivered healthy infants
Quality assessment	Sampling method not described; study subjects and setting not described in detail; valid methods for the identification of the condition not used; condition not measured in a standard reliable way for all people; appropriate statistical analysis not used; no direct evidence of cause and effect

Reference	Lakos 2010[17]
Study design	Retrospective cohort study
Number of participants and characteristics	n=95 people with gestational Lyme disease Inclusion criteria: EM rash during pregnancy (CDC and EUCALB criteria); visited the centre after delivery, with EM that had commenced before or during pregnancy; clinically diagnosed ACA with signs of inflammation still present after delivery, which had commenced before or during the pregnancy; facial palsy beginning during pregnancy with preceding EM or with the presence of intrathecal *Borrelia* antibody production

Reference	Lakos 2010[17]
	Age, mean (SD) 29.7 (4.3) years Family origin: White
Sampling method	Retrospective review of registered cases
Case definition	Mother: EM rash during pregnancy (CDC and EUCALB criteria); clinically diagnosed ACA; facial palsy with preceding EM or with the presence of intrathecal *Borrelia* antibody production Fetus: no acceptable case definition (adverse pregnancy outcomes, IgG and IgM for a subset of infants)
Country and setting	Single centre, Hungary
Study duration	22 years
Outcomes and effect sizes	20/95 (21.1%) had adverse pregnancy outcomes; cavernous haemangioma was the only outcome which was higher in the study population than expected as compared with the average frequency in Hungary: cavernous haemangioma 4/95 (4.2% 95% CI 1.2-10.4); average incidence in Hungary 0.11% (0.08-0.14) None of the tested new-borns showed an IgM reaction. All new-borns born to mothers who were IgG positive at delivery were IgG positive (unclear how many new-born were tested)
Quality assessment	Valid methods for the identification of the condition not used; condition not measured in a standard reliable way for all people; appropriate statistical analysis not used; no direct evidence of cause and effect; people received different treatment regimens

Reference	MacDonald 1986[21]
Study design	Prospective case series
Number of participants and characteristics	n=4 still born fetuses
Sampling method	Not reported
Case definition	Not reported
Country and setting	USA

Reference	MacDonald 1986[21]
Study duration	Not reported
Outcomes and effect sizes	Spirochetes were cultured from fetal liver tissue in all 4 cases Spirochetes were cultured from the heart in 1 case By immunofluorescence, spirochetes were detected in fetal liver, heart, adrenal, brain, kidney, meninges and in the subarachnoid space in 1 case and in the liver or placenta in the remaining cases
Quality assessment	Sampling method not described; setting not described; appropriate statistical analysis not used; no infections diagnosed in the mothers during pregnancy

Reference	MacDonald 1989[22]
Study design	Retrospective cohort study Prospective case series
Number of participants and characteristics	Cohort study: n=24 perinatal autopsies Case series: n=14 perinatal deaths due to Lyme disease
Sampling method	Not reported
Case definition	Not reported
Country and setting	Single hospital in a hyper-endemic area, USA
Study duration	Cohort study: 7 years Case series: 3 years
Outcomes and effect sizes	Cohort study: 4/24 (17%) showed evidence of Lyme borreliosis Case series: Evidence of *Borrelia burgdorferi s.l.* found in 13/14 fetuses/babies (culture [2], immunofluorescence [6], immunohistochemistry [2], placenta immunofluorescence [1], placenta Warthin–Starry silver impregnation [1], placenta culture [1])
Quality assessment	Sampling method not described; valid methods for the identification of the condition not used in mothers; condition not measured in a standard reliable way for mothers, appropriate statistical analysis not used

Reference	Maraspin 1996[24] Maraspin 1999[25]
Study design	Prospective cohort study

Reference	Maraspin 1996[24] Maraspin 1999[25]
Number of participants and characteristics	n=105 pregnant women with typical EM (diagnosed using CDC criteria) Age median, 29 years (range 17-42 years)
Sampling method	Consecutive pregnant women presenting at a medical centre with erythema migrans
Case definition	Mother: typical EM (diagnosed using CDC criteria) Fetuses/infants: no case definition reported
Country and setting	Single centre, Slovenia
Study duration	4 years
Outcomes and effect sizes	12/105 (11.4%) had adverse pregnancy outcomes: 6 pre-term deliveries (2 deaths), no causal relationship between pre-term birth and *Borrelia burgdorferi s.l.* infection found, no spirochetes found in Warthin–Starry silver impregnated tissues during autopsy 5 babies with congenital abnormalities, no causal relationship between abnormalities and *Borrelia burgdorferi s.l.* infection found 2 pregnancies ended with an abortion (1 missed, 1 spontaneous), incidence of abortion was lower than national level
Quality assessment	Valid methods for the identification of the condition not used in fetuses or infants; appropriate statistical analysis not used; variation in clinical presentations and treatment regimens

Reference	Maraspin 2011[26]
Study design	Prospective cohort study
Number of participants and characteristics	n=7 pregnant women diagnosed with previously untreated typical EM with *Borrelia burgdorferi s.l.* isolated from blood culture selected from 182 blood cultures performed in a total of 187 pregnant women
Sampling method	Pregnant women presenting with erythema migrans at the study centre selected from 182 blood cultures performed in a total of 187 pregnant women
Case definition	Mother: typical EM (CDC criteria) with *Borrelia burgdorferi s.l.* isolated from blood culture Infants: no case definition reported
Country and setting	Single centre, Slovenia

Reference	Maraspin 2011[26]
Study duration	12 years
Outcomes and effect sizes	1/7 pregnancies ended with preterm birth at week 37, all 7 infants were healthy
Quality assessment	Valid methods for the identification of the condition not used in infants; condition not measured in a standard reliable way for infants, appropriate statistical analysis not used; no direct evidence of cause and effect

Reference	Markowitz 1986[27]
Study design	Prospective and retrospective cohort study
Number of participants and characteristics	n=19 pregnant women with EM or if no history of EM, onset of neurologic, cardiac, or joint involvement of Lyme disease during pregnancy and an antibody titre of 1:256 or higher by immunofluorescence assay or 1:200 or higher by ELISA, or onset of manifestations in 2 of 3 organ systems (neurologic, cardiac or joint) during pregnancy Age median, 30 years (range 21-37)
Sampling method	Review of records through the CDC surveillance system
Case definition	Mother: EM or if no history of EM, onset of neurologic, cardiac, or joint involvement of Lyme disease during pregnancy and an antibody titre of 1:256 or higher by immunofluorescence assay or 1:200 or higher by ELISA, or onset of manifestations in 2 of 3 organ systems (neurologic, cardiac or joint) during pregnancy Fetus or infant: no case definition reported
Country and setting	CDC surveillance system, USA
Study duration	8 years
Outcomes and effect sizes	5/19 (26%) had abnormal pregnancy outcomes: 1 intrauterine fetal death, culture and IFA of placenta and fetal tissues negative for *B. burgdorferi* 1 premature labour at 36 weeks, infant was normal 1 infant with syndactyly (type 1) of the second and third toes 1 infant who was born healthy but later diagnosed with cortical blindness and developmental delay, child had no serum antibodies to *B. burgdorferi* 1 infant who was born healthy except for a generalised, petechial, vesicular rash and hyperbilirubinemia, viral and bacterial blood and skin cultures were negative Umbilical cord blood from 5 normal infants was tested – 4 tested for IgM to *B. burgdorferi*, none had an elevated titre, 1 infant had an

Reference	Markowitz 1986[27]
	antibody titre of 1:512 at birth but no detectable antibody 7 months later
Quality assessment	Valid methods for the identification of the condition not used in infants; condition not measured in a standard reliable way for all infants; appropriate statistical analysis not used

Reference	Nadal 1989[33]
Study design	Prospective cohort study
Number of participants and characteristics	n= 12 pregnant women with elevated titres out of 1,416 pregnant women tested serologically for *B. burgdorferi* Age, mean 28.3 years (range 21-40)
Sampling method	Blood samples from pregnant women and cord blood specimens from their offspring at a single centre
Case definition	Not reported
Country and setting	Single centre, Switzerland
Study duration	1 year
Outcomes and effect sizes	Delayed adaptation in 1 pre-term infant and 1 post-term infant 2 infants had hyperbilirubinemia 1 infant had muscle hypotonia 1 post-term infant was underweight for age as a consequence of chronic placental insufficiency 1 infant had macrocephaly 1 infant had supraventricular extrasystoles 1 infant had a ventricular septal defect 11/12 children examined at mean age 13 months – 1 infant born to a mother with clinical symptoms had a cardiac defect, the other 10 were healthy, 1 infant had a borderline titre of 1:64 but no specific IgM could be detected
Quality assessment	Study subjects not described in detail; valid methods for the identification of the condition not used; condition not measured in a standard reliable way for all people; appropriate statistical analysis not used; no direct evidence of cause and effect

Reference	Strobino 1993[51]
Study design	Prospective cohort study

Reference	Strobino 1993[51]
Number of participants and characteristics	n=2,014 women identified from the first prenatal visit
Sampling method	Consecutive pregnant women attending their first prenatal visit
Case definition	Mother: IgG antibodies to *B. burgdorferi* by fluorescence immunoassay test, positive sera tested for IgM (titres >75 considered positive), self-reported Lyme disease history Fetus/infant: no case definition reported
Country and setting	2 hospitals, endemic area USA
Study duration	2 years
Outcomes and effect sizes	All birth defects Lyme disease ever: OR 1.68 (95% CI 0.91-3.13) Lyme disease during pregnancy: OR 0.53 (95% CI 0.07-4.16) <1 year before: OR 1.65 (95% CI 0.60-4.57) >1 year before: OR 2.94 (95% CI 0.98-8.86) Timing unknown: OR 1.76 (95% CI 0.47-6.57) Major defects Lyme disease ever: OR 1.43 (95% CI 0.50-4.09) Lyme disease during pregnancy: - <1 year before: OR 0.98 (95% CI 0.13-7.52) >1 year before: OR 3.49 (95% CI 0.74-16.49) Timing unknown: OR 1.75 (95% CI 0.22-13.99) Minor defects Lyme disease ever: OR 1.81 (95% CI 0.89-3.69) Lyme disease during pregnancy: OR 0.80 (95% CI 0.10-6.28) <1 year before: OR 1.99 (95% CI 0.66-6.05) >1 year before: OR 2.66 (95% CI 0.71-9.94) Timing unknown: OR 1.77 (95% CI 0.38-8.29)

Reference	Strobino 1993[51]
	Fetal deaths Lyme disease ever: 7.6% Lyme disease during pregnancy: 0% Lyme disease <1 year before: 13.8% Lyme disease >1 year before: 9.5% No Lyme disease: 8%
Quality assessment	Valid methods for the identification of the condition not used for infants; condition not measured in a standard reliable way for all people; appropriate statistical analysis not used; no direct evidence of cause and effect

Reference	Strobino 1999[50]
Study design	Retrospective case-control study
Number of participants and characteristics	n=796 children diagnosed with congenital cardiac anomaly (cases) and 704 children with innocent heart murmur, benign rhythm pattern or non-cardiac chest pain (controls) Inclusion (cases): <7 years with a diagnosis of an anatomic or physiologic cardiac abnormality not associated with documented chromosomal abnormality, genetic syndrome, prematurity, or a defined postnatal cause (controls): <12 years evaluated because of a heart murmur, rhythm irregularity, or chest pain and found to have no cardiac pathology
Sampling method	Patient records from a single centre
Case definition	Mother: Definite Lyme disease – characteristic Lyme symptoms (rash, joint pain or swelling, fever, headache, stiff neck) and diagnosis and treatment by a physician Possible Lyme disease – treated for Lyme disease but there was some question about the diagnosis or inconsistencies in their history or they were never treated for Lyme disease Children: no case definition reported
Country and setting	Paediatric cardiology service of a single centre in a Lyme disease endemic area, USA
Study duration	1.5 years
Outcomes and effect sizes	Mothers of control subjects were more likely than those of case patients to have had Lyme disease during pregnancy or within 3 months before conception OR 0.89 (95% CI 0.22-3.61) Within 1 year before conception: OR 1.00 (95% CI 0.38-2.63)

Reference	Strobino 1999[50]
	Any time before conception: OR 0.85 (95% CI 0.39-1.89)
Quality assessment	Analysis not conducted with sufficient coverage of study sample; valid methods for the identification of the condition not used for children; condition not measured in a standard reliable way for all people; appropriate statistical analysis not used

Reference	Williams 1995[58]
Study design	Prospective cohort study
Number of participants and characteristics	n=5,011 infants (2,504 endemic area; 2,507 non-endemic area)
Sampling method	Consecutive infants born during the study period
Case definition	Mother: self-reported history of Lyme disease Infant: no case definition reported
Country and setting	1 community hospital in an endemic area, 1 community hospital in a non-endemic area, USA
Study duration	2.5 years
Outcomes and effect sizes	All malformations (endemic area) Lyme before pregnancy: 8.7% Lyme during pregnancy: 16.7% Cord blood IgG positive: 5% Total endemic cohort: 7.8% Major malformations (endemic area) Lyme before pregnancy: 8.7% Lyme during pregnancy: 16.7% Cord blood IgG positive: 0% Total endemic cohort: 2.9% Minor malformations (endemic area)

Reference	Williams 1995[58]
	Lyme before pregnancy: 0% Lyme during pregnancy: 0% Cord blood IgG positive: 5% Total endemic cohort: 4.8%
Quality assessment	Analysis not conducted with sufficient coverage of study sample; valid methods for the identification of the condition not used for children; condition not measured in a standard reliable way for all people; appropriate statistical analysis not used; no direct evidence of cause and effect

Appendix E: Forest plots

None.

Appendix F:GRADE tables

None.

Appendix G: Health economic evidence selection

Not applicable.

Appendix H: Health economic evidence tables

Not applicable.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Reference	Reason for exclusion
Ai 1994[1]	Excluded due to an incorrect outcome
Alexander 1995[2]	Excluded due to an incorrect study design
Anonymous 1985[3]	Excluded due to an incorrect study design
Anonymous 1986[4]	Excluded due to an incorrect study design
Bale 1992[5]	Excluded due to an incorrect study design
Dlesk 1989[7]	Excluded due to an incorrect study design
Edly 1990[8]	Excluded due to an incorrect study design
Elliott 2001[9]	Excluded due to an incorrect study design
Gerber 1994[10]	Excluded due to an incorrect study design
Gibbs 2007[11]	Excluded due to an incorrect condition
Goldenberg 2003[12]	Excluded due to an incorrect study design
Grandsaerd 2000[13]	Excluded due to an incorrect study design
Hercogova1993[14]	Not in English
Jasik 2015[15]	Excluded due to an incorrect study design
Joseph 2012[16]	Excluded due to an incorrect condition
Lavoie 1987[18]	Excluded due to an incorrect study design
Lawrence 2004[19]	Excluded due to an incorrect study design
Leiby 2004[20]	Excluded due to an incorrect study design
MacDonald 1987[23]	Excluded due to an incorrect study design
McQuiston 2000[28]	Excluded due to an incorrect study design
Menitove 1996[29]	Excluded due to an incorrect study design
Mikkelsen 1987[30]	Excluded due to an incorrect study design
Mylonas 2011[32]	Excluded due to an incorrect study design
Piesman 1989[34]	Excluded due to an incorrect study design
Relic 2012[35]	Not in English
Salzman 1991[36]	Excluded due to an incorrect study design
Schaumann 1999[37]	Excluded due to an incorrect study design
Schlesinger 1985[38]	Excluded due to an incorrect study design
Schmidt 1995[39]	Excluded due to an incorrect outcome
Schmidt 2014[40]	Excluded due to an incorrect study design
Schutzer 1991[41]	Excluded due to an incorrect study design
Shirts 1983[42]	Excluded due to an incorrect study design
Silver 1997[43]	Excluded due to an incorrect study design
Smith 1991[45]	Excluded due to an incorrect study design
Smith 2012[44]	Excluded due to an incorrect study design
Stiernstedt 1990[46]	Excluded due to an incorrect study design
Stramer 2009[48]	Excluded due to an incorrect study design
Stramer 2014[47]	Excluded due to an incorrect study design
Stray-Pedersen 1993[49]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Sultan 2012[52]	Excluded due to an incorrect study design
Trevisan 1997[53]	Excluded due to an incorrect study design
Walsh 2007[54]	Excluded due to an incorrect study design
Weber 1988[55]	Excluded due to an incorrect study design
Wendel 1994[56]	Excluded due to an incorrect study design
Williams 1990[57]	Excluded due to an incorrect population
Wylie 1993[59]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Not applicable.