NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health and social care directorate

Quality standards and indicators

Briefing paper

Quality standard topic: Lyme disease

Output: Prioritised quality improvement areas for development.

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1 Introduction

This briefing paper presents a structured overview of potential quality improvement areas for Lyme disease. It provides the committee with a basis for discussing and prioritising quality improvement areas for development into draft quality statements and measures for public consultation.

1.1 Structure

This briefing paper includes a brief description of the topic, a summary of each of the suggested quality improvement areas and supporting information.

If relevant, recommendations selected from the key development source below are included to help the committee in considering potential statements and measures.

1.2 Development source

The key development source referenced in this briefing paper is:

Lyme disease (2018) NICE guideline NG95

2 Overview

2.1 Focus of quality standard

This quality standard will cover the diagnosis and management of Lyme disease in people of all ages.

2.2 Definition

Lyme disease is a tick-borne infectious disease caused by a group of bacteria called Borrelia burgdorferi. There are different types of Borrelia burgdorferi, and these cause different patterns of illness.

Ticks live in grassy and wooded areas in both rural and urban locations. They become infected with bacteria by biting certain animals such as rodents, some birds and other small animals. Infected ticks then transmit the bacteria to humans by attaching themselves to a person via long grass or foliage.

Tick bites are usually painless. Infection is more likely if the tick remains attached to the skin for more than 24 hours. There is a variable incubation period, which generally ranges from a few days to 1 month. The first and most common symptom is a single, circular, target-like rash usually centred on the bite, known as erythema migrans. Without treatment, it typically fades within 3 to 4 weeks.

Early symptoms are non-specific and similar to the symptoms of flu. These include aching, fever, headache, fatigue, join pain, abnormal skin conditions and a stiff neck. In some people, the infection may not progress further, even if untreated. In some cases that are not treated, the disease spreads away from the site of the original infection.

Different manifestations of Lyme disease infection, which typically occur weeks or months after the bite, include:

- joint problems of varying severity
- nerve and brain problems, such as inflammation of the nerves, particularly those around the face and inflammation around the brain
- inflammation of the heart and other heart problems
- rashes on the skin, but not necessarily at the site of the tick bite. These tend to be smaller than the rashes that appear sooner after infection. Occasionally, blue-red nodules (called lymphocytoma) may develop
- the eyes, kidneys and liver may be affected, but this occurs more rarely.[1]

2.3 Incidence and prevalence

The true incidence of Lyme disease in England and Wales is unknown. It is estimated that there are around 2,000-3,000 new cases of Lyme disease a year. Public Health England (PHE) reports there were 1,579 laboratory-confirmed cases of Lyme disease in 2017. This figure doesn't include cases that are diagnosed and treated based on clinical presentation (such as erythema migrans), without laboratory testing. It is estimated there are between 1,000 and 2,000 additional such cases each year.[2]

Confirmed cases vary by geographical location, with around half of cases being diagnosed in the South East and South West of England. The incidence of Lyme disease is believed to be increasing as ticks spread to new areas and higher altitudes. Statistics from PHE show that the number of cases diagnosed through laboratory testing in England Wales has been rising since the 1980s from 0.38 per 100,000 population between 1997 and 2000, to 1.64 in 2010, and 2.70 in 2017.[3] This is thought to be linked to better reporting, improved diagnostic testing, and increased awareness among the public and healthcare professionals.

2.4 Diagnosis and management

Diagnosis of Lyme disease is made through clinical assessment, or clinical assessment supported by laboratory testing. People presenting with an erythema

[1] Lyme disease (2018) NICE guideline NG95, final scope. Patient Info (2018). Lyme disease
[2] Public Health England (2018) Lyme disease epidemiology and surveillance, 3.1
[3] Public Health England (2018) Lyme disease epidemiology and surveillance, 3

migrans rash are diagnosed with Lyme disease without laboratory investigations (serology tests), and treated with antibiotics.

People who don't develop a rash, but have symptoms suggesting Lyme disease, and are at risk of tick exposure, have blood tests. Laboratory investigations help to identify cases caused by Lyme disease, so that appropriate treatment can be given, and that other diseases are not misdiagnosed as Lyme disease. If tests are negative but symptoms persist, repeat samples are sent.

Antibiotic treatment is the main treatment for Lyme disease. People who have had initial treatment for Lyme disease and continue to experience symptoms may be considered for a second course of antibiotics if the infection hasn't been cleared.

If symptoms persist after treatment, the test is repeated to test for relapse and other causes are considered. Specialist advice may be sought especially if there are neurological, rheumatological, cardiac or ophthalmic complications. Practitioners can liaise with staff at the Rare and Imported Pathogens Laboratory (RIPL) for advice.

Early treatment helps reduce the risk of later symptoms developing. Although early treatment is almost always successful, there is uncertainty regarding the best treatment for late-diagnosed cases, and some people may not recover completely following recommended antibiotic treatment. Persistent symptoms can affect a person's ability to continue day-to-day life, and they may need time to gradually return to usual activities.

2.5 Resource impact

No resource impact is anticipated from NG95. This is because it is considered that where clinical practice changes, as a result of this guidance, there will not be a significant change to resource impact, due to small numbers of people affected by Lyme disease.

3 Summary of suggestions

3.1 Responses

In total 10 stakeholders responded to the 2-week engagement exercise 09/10/2018-23/10/2018.

Stakeholders were asked to suggest up to 5 areas for quality improvement. Specialist committee members were also invited to provide suggestions. The responses have been merged and summarised in table 1 for further consideration by the committee.

Full details of all the suggestions provided are given in appendix 5 for information.

Table 1 Summary of suggested quality improvement areas

Suggested area for improvement	Stakeholders
Diagnosis and assessment	
• Clinical assessment	CLC, LDA, LDUK, RCGP, SCM
• Laboratory investigations to support diagnosis	LDA, RCPhys, SCM
• Testing standards	RCPath, RCPhys, SCM
Antibiotic management	
• Standardised antibiotic treatment	CLC, LDUK, RCGP, RCPath, RCPhys, SCM
• Doxycycline and pregnancy	RCGP
Non-antibiotic management	
• Reassessment	CLC, ILADS, LDUK, SCM
• Specialist advice and referral	CLC, LDA, LDUK, RCGP, SCM
Awareness and information	
• Raising awareness	ILADS, LDA, LDUK, RCGP, SCM
• Information about diagnosis, management and follow-up	SCM
Additional areas	
• Clinical epidemiology and research	CLC, RCGP, SCM
• Improving laboratory investigations	ILADS, LDUK, RCGP, SCM
BSAC, British Society for Antimicrobial Chemotherapy – submitted a response (no comments) CLC, Caudwell LymeCo Charity ILADS, International Lyme and Associated Diseases Society LDA, Lyme Disease Action LDUK, Lyme Disease UK RCGP, Royal College of General Practitioners RCN, Royal College of Nursing – submitted a response (no comments) RCPCH, Royal College of Paediatrics and Child Health – submitted a response (no comments) RCPath, Royal College of Pathologists RCPhys, Royal College of Physicians, England SCM, Specialist Committee Members (1-7)	

3.2 Identification of current practice evidence

Bibliographic databases were searched to identify examples of current practice in UK health and social care settings; 49 papers were identified for Lyme disease. In addition, 34 papers were suggested by stakeholders at topic engagement and 26 papers internally at project scoping.

Of these papers, 7 have been included in this report and are included in the current practice sections where relevant. Appendix 3 outlines the search process.

4 Suggested improvement areas

4.1 Diagnosis and assessment

4.1.1 Summary of suggestions

Clinical assessment

Stakeholders highlighted that clinical assessment should play an important role in the diagnosis of Lyme disease. Stakeholders identified prompt recognition of erythema migrans, which is very specific to Lyme disease and doesn't need laboratory investigations as a priority. Stakeholders also suggested recognising atypical forms of the rash as a specific area.

Stakeholders commented that over-reliance on laboratory investigations could lead to cases being missed. Alternative diagnoses may also be overlooked, as non-specific (non-focal) symptoms are similar to those of other conditions. Knowledge of the limitations of laboratory investigations and applying clinical judgement when interpreting the results were also suggested.

Stakeholders suggested offering laboratory investigations to people presenting with Bell's palsy is a priority especially children presenting with this symptom.

Laboratory investigations to support diagnosis

Stakeholders suggested that a consistent approach to routine testing for Lyme disease is a priority in terms of both an overall strategy, and the sequencing of laboratory investigations. Offering an ELISA test as a first (screening) test, and repeating it if the result is negative (to take account, for example, of variable timings of a person's particular immune response) is a quality improvement area.

Stakeholders highlighted interpretation of results as another quality improvement area. They commented that tests shouldn't be repeated to demonstrate that treatment has 'cured' the infection. Stakeholders stated that results from confirmatory immunoblot tests, even when offered in accordance with the recommended timescale (after 12 weeks if symptoms are ongoing), may be misinterpreted to support cessation of treatment. It was also suggested people with ongoing symptoms that may suggest Lyme disease should have access to the relevant laboratory investigations, regardless of whether they remember a tick bite.

Stakeholders highlighted the importance of lumbar puncture cerebrospinal fluid (CSF) analysis in the early diagnosis and prompt management of Lyme disease infection affecting the nervous system ('neuroborreliosis'). Symptoms and clinical examination alone may not be sufficient to support a diagnosis. They also commented that access to CSF tests may be limited or delayed. Concerns were also

raised regarding the quality of samples, and questioned whether appropriate samples (paired CSF and serum samples) are being sent to laboratories.

Testing standards

Stakeholders emphasised the importance of sending samples for testing to UKAS-accredited laboratories, to support accurate diagnosis of Lyme disease. Stakeholders also suggested that samples that tested positive for Lyme disease antibodies in local laboratory services should be sent to a reference laboratory for confirmation. The impact of inaccurate test results were identified as over-diagnosis of Lyme disease, associated inappropriate antibiotic prescribing, and failure to diagnose of a different condition.

4.1.2 Selected recommendations from development source

Table 2 below highlights recommendations that have been provisionally selected from the development source(s) that may support potential statement development. These are presented in full after table 2 to help inform the committee's discussion.

Table 2 Specific areas for quality improvement

Suggested quality improvement area	Selected source guidance recommendations
Clinical assessment	**Diagnosis - clinical assessment** NICE NG95 Recommendations 1.2.1, 1.2.3, 1.2.4 and 1.2.12
Laboratory investigations to support diagnosis	**Diagnosis - laboratory investigations to support diagnosis** NICE NG95 Recommendations 1.2.13-1.2.20
Testing standards	**Diagnosis - laboratory investigations to support diagnosis** NICE NG95 Recommendations 1.2.22, 1.2.23 and 1.2.26

Clinical assessment

Diagnosis – clinical assessment

NICE NG95 – Recommendation 1.2.1

Diagnose Lyme disease in people with erythema migrans, a red rash that:

- increases in size and may sometimes have a central clearing
- is not usually itchy, hot or painful
- usually becomes visible from 1 to 4 weeks (but can appear from 3 days to 3 months) after a tick bite and lasts for several weeks
- is usually at the site of a tick bite.

NICE NG95 – Recommendation 1.2.3

Consider the possibility of Lyme disease in people presenting with several of the following symptoms, because Lyme disease is a possible but uncommon cause of:

- fever and sweats
- swollen glands
- malaise
- fatigue
- neck pain or stiffness
- migratory joint or muscle aches and pain
- cognitive impairment, such as memory problems and difficulty concentrating (sometimes described as 'brain fog')
- headache
- paraesthesia.

NICE NG95 – Recommendation 1.2.4

Consider the possibility of Lyme disease in people presenting with symptoms and signs relating to 1 or more organ systems (focal symptoms) because Lyme disease is a possible but uncommon cause of:

- neurological symptoms, such as facial palsy or other unexplained cranial nerve palsies, meningitis, mononeuritis multiplex or other unexplained radiculopathy; or rarely encephalitis, neuropsychiatric presentations or unexplained white matter changes on brain imaging
- inflammatory arthritis affecting 1 or more joints that may be fluctuating and migratory
- cardiac problems, such as heart block or pericarditis
- eye symptoms, such as uveitis or keratitis
- skin rashes such as acrodermatitis chronica atrophicans or lymphocytoma.

NICE NG95 – Recommendation 1.2.12

Use a combination of clinical presentation and laboratory testing to guide diagnosis and treatment in people without erythema migrans. Do not rule out diagnosis if tests are negative but there is high clinical suspicion of Lyme disease.

Laboratory investigations to support diagnosis

Diagnosis - laboratory investigations to support diagnosis

NICE NG95 – Recommendation 1.2.13

If there is a clinical suspicion of Lyme disease in people without erythema migrans:

- offer an enzyme-linked immunosorbent assay (ELISA) test for Lyme disease and
- consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion.

NICE NG95 – Recommendation 1.2.14

Test for both IgM and IgG antibodies using ELISAs based on purified or recombinant antigens derived from the VlsE protein or its IR6 domain peptide (such as C6 ELISA).

NICE NG95 – Recommendation 1.2.15

If the ELISA is positive or equivocal:

- perform an immunoblot test for Lyme disease **and**
- consider starting treatment with antibiotics while waiting for the results if there is a high clinical suspicion of Lyme disease.

NICE NG95 – Recommendation 1.2.16

If the ELISA for Lyme disease is negative and the person still has symptoms, review their history and symptoms, and think about the possibility of an alternative diagnosis.

NICE NG95 – Recommendation 1.2.17

If Lyme disease is still suspected in people with a negative ELISA who were tested within 4 weeks from symptom onset, repeat the ELISA 4 to 6 weeks after the first ELISA test.

NICE NG95 – Recommendation 1.2.18

If Lyme disease is still suspected in people with a negative ELISA who have had symptoms for 12 weeks or more, perform an immunoblot test.

NICE NG95 – Recommendation 1.2.19

Diagnose Lyme disease in people with symptoms of Lyme disease and a positive immunoblot test.

NICE NG95 – Recommendation 1.2.20 (excerpt)

If the immunoblot test for Lyme disease is negative (regardless of the ELISA result) but symptoms persist, consider a discussion with or referral to a specialist, to:

- review whether further tests may be needed for suspected Lyme disease, for example, synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis **or**
- consider alternative diagnoses (both infectious, including other tick-borne diseases, and non-infectious diseases).

Testing standards

Diagnosis - laboratory investigations to support diagnosis

NICE NG95 – Recommendation 1.2.22

Carry out tests for Lyme disease only at laboratories that:

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

NICE NG95 – Recommendation 1.2.23 (excerpt)

Do not routinely diagnose Lyme disease based only on tests done outside the NHS, unless the laboratory used is accredited, participates in formal external quality assurance programmes and uses validated tests (see recommendation 1.2.22). If there is any doubt about tests:

- carry out testing again using a UKAS-accredited laboratory and/or seek advice from a national reference laboratory.

NICE NG95 – Recommendation 1.2.26

Advise people that tests from non-UKAS laboratories may not have been fully evaluated to diagnose Lyme disease.

Current UK practice

Clinical assessment

A small study funded by Lyme Research UK which retrospectively surveyed 152 people in the UK and Ireland diagnosed with Lyme disease about their experiences of access to care in 2011.

Participants were self-selecting and so the findings may not be representative of other groups. Nearly half had an initial diagnosis from a private consultant, and 9 with an NHS diagnosis were not tested using NHS services. In terms of diagnosis based on clinical presentation, relevant findings include:

- 40% had a distinctly circular (bull's eye) rash near the time of being bitten
- 17% had an 'atypical non-circular rash'
- 43% didn't have a rash, or weren't sure
- Of those with a rash 67% (87) mentioned or showed the rash to a doctor
- More than 70% of 120 people reported that diagnosis took longer than 6 months. Reported causes of delays (reported by 143 people in the study) included:
    - 41% felt their symptoms had been ignored
    - 22% reported their symptoms had taken a long time to develop
    - 20% reported their symptoms were not specific to Lyme disease
    - 20% reported additional tests and investigations had taken time
    - 18% reported they didn't visit a doctor immediately
    - 9% reported their symptoms as 'complex' and 'non-classic'

The study also reported (shown below) the most common reasons people reported for a delayed diagnosis, regardless of whether they tested positive or negative for Lyme disease:

	Tested positive (%)	**Tested negative (%)**
Symptoms were ignored	23%	57%
Did not receive timely testing	21%	35%
Referred to the wrong specialist	15%	37%

78% of those who tested negatively for Lyme disease reported being misdiagnosed as the reason for the delay.[4]

[4] Bloor K and Hale V (2013) An internet survey of Lyme patients' experience of access to care

500 people diagnosed with Lyme disease in the UK were recruited by social media and surveyed online in 2016. 20% reported they had been diagnosed on the basis of having an erythema migrans rash.

Respondents also reported on time taken to diagnosis. Relevant findings include:

- around 70% reported they had symptoms for over 2 years prior to diagnosis
- around 30% waited more than 10 years for a diagnosis. [5]

120 people from online patient support groups completed a survey published in 2014 about their symptoms, tests and experiences of medical investigations carried out by the NHS. It was not clear when the survey was run or to what extent the responses reflect the experiences of people diagnosed with Lyme disease. 25 conditions, including Lyme disease, were listed among the list of diagnoses reported by respondents. Relevant findings include:

- around 50% were diagnosed with chronic fatigue syndrome
- around 40% were diagnosed with Lyme borreliosis
- around 40% were diagnosed with ME.[6]

Stakeholders highlighted the results of a forthcoming report of a local audit carried out in an area associated with incidence of Lyme disease (Southampton). The study reports that around 45% of children diagnosed with Bell's palsy also had positive test results for Lyme disease.

Laboratory investigations to support diagnosis

The most recent quarterly statistics (July – September 2018) of laboratory-confirmed Lyme disease in England and Wales from the Rare Imported Pathogens Laboratory (RIPL, Porton Down) show that of 816 cases, 187 were identified as 'long-standing'.[7] The statistics for the first quarter (January – March 2018) reported that of 133 cases, 69 were 'long-standing'.[8]

The online patient support group survey (2014) of 120 people found that:

- 88% had an ELISA test
- 35% had a Western blot (immunoblot) test
- 6% had a positive ELISA and Western blot test.

[5] Cauldwell Lyme Disease Charity a (2016) Lyme disease on the NHS
[6] Vector-Borne Infection Research, Analysis and Strategy (VIRAS) (2014) NHS Testing and Investigation of Lyme Borreliosis – Patient Experiences Survey
[7] PHE (2018) Common animal associated infections quarterly report (England and Wales): third quarter 2018 – Lyme disease.
[8] PHE (2018) Common animal associated infections quarterly report (England and Wales): first quarter 2018 – Lyme disease.
[9] Vector-Borne Infection Research, Analysis and Strategy (VIRAS) (2014) NHS Testing and investigation of Lyme Borreliosis – Patient Experiences Survey.

90% of people reported they felt ‘dissatisfied’ or ‘very dissatisfied’ with their assessment for Lyme disease in NHS settings.[9]

Testing standards

The small study funded by Lyme Research UK of 152 people diagnosed with Lyme disease found that based on clinical presentation:

- 77% reported they were tested on the NHS using standard tests
- 18% reported they weren’t tested on the NHS using standard tests
- 5% weren’t sure.[10]

More than half (56%) of 500 people diagnosed with Lyme disease in the UK surveyed online in 2016 reported they weren’t diagnosed by NHS doctors or NHS testing labs.[11]

[10] Bloor K and Hale V (2013) An internet survey of Lyme patients’ experience of access to care
[11] Cauldwell Lyme Disease Charity a (2016) Lyme disease on the NHS

4.2 Antibiotic management

4.2.1 Summary of suggestions

Standardised antibiotic treatment

Stakeholders suggested a standardised approach to antibiotic management in accordance with NICE's guideline on Lyme disease to avoid under-treatment as a quality improvement area. Prompt treatment of erythema migrans using a standard antibiotic regimen was highlighted as a specific area.

Suggestions relate to the choice of drug, dosage and duration of treatment. Prescribing doxycycline as first-line treatment, with amoxicillin as an alternative, for 21 days (28 days for Lyme arthritis) at the correct dosage was highlighted as a specific area for quality improvement. Stakeholders also suggested that people may be referred to a specialist rather than being prescribed a second course of antibiotics. Stakeholders commented that clarithromycin was prescribed in preference to the recommended first-line drug, amoxicillin, particularly to children.

Stakeholders also commented that monitoring the proportion of antibiotics prescribed for certain forms of Lyme disease that are administered orally, compared to the proportion administered intravenously, is a further area for quality improvement. Stakeholders also suggested people should attend outpatient clinics in preference to being admitted to hospital if they are prescribed non-oral antibiotics.

Doxycycline and pregnancy

It was suggested that women are asked about the possibility of pregnancy prior to prescribing doxycycline.

4.2.2 Selected recommendations from development source

Table 3 below highlights recommendations that have been provisionally selected from the development source(s) that may support potential statement development. These are presented in full after table 3 to help inform the committee's discussion.

Table 3 Specific areas for quality improvement

Suggested quality improvement area	Selected source guidance recommendations
Standardised antibiotic treatment	**Management - antibiotic treatment** NICE NG95 Recommendations 1.3.4 and 1.3.5 **Ongoing symptoms after a course of antibiotics** NICE NG95 Recommendations 1.3.11
Doxycycline and pregnancy	**Management - antibiotic treatment** NICE NG95 Recommendation 1.3.6 **Management - management for women with Lyme disease during pregnancy and their babies** NICE NG95 Recommendations 1.3.18 and 1.3.19

Standardised antibiotic treatment

Management - antibiotic treatment

NICE NG95 Recommendation 1.3.4

For adults and young people (aged 12 and over) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in table 1 (see Appendix 2).

NICE NG95 Recommendation 1.3.5

For children (under 12) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in table 2 (see Appendix 2).

Ongoing symptoms after a course of antibiotics

NICE NG95 Recommendation 1.3.11

Consider a second course of antibiotics for people with ongoing symptoms if treatment may have failed. Use an alternative antibiotic to the initial course, for example, for adults with Lyme disease and arthritis, offer amoxicillin if the person has completed an initial course of doxycycline.

Doxycycline and pregnancy

Management – management for women with Lyme disease during pregnancy and their babies

NICE NG95 Recommendation 1.3.6

Ask women (including young women under 18) if they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation 1.3.18 on treatment in pregnancy).

NICE NG95 Recommendation 1.3.18

Assess and diagnose Lyme disease during pregnancy in the same way as for people who are not pregnant. Treat Lyme disease in pregnant women using appropriate antibiotics for the stage of pregnancy [1].

NICE NG95 Recommendation 1.3.19

Tell women with Lyme disease during pregnancy that they are unlikely to pass the infection to their baby and emphasise the importance of completing the full course of antibiotic treatment.

4.2.3 Current UK practice

Standardised antibiotic treatment

More than a third of 500 people diagnosed with Lyme disease in the UK surveyed in 2016 reported that they hadn't been prescribed any antibiotics by NHS doctors. Other relevant findings include:

- 17% reported receiving more than 8 weeks' worth of antibiotics
- around 10% (each) were prescribed 2 and 4 weeks of antibiotics, consistent with the then-current PHE treatment guidelines
- 5% had been prescribed antibiotics for 1 year or more.[12]

Doxycycline and pregnancy

No current practice data was identified for this area; the suggestion is based on stakeholders' knowledge and experience.

[12] Cauldwell Lyme Disease Charity (2016) Lyme disease on the NHS

4.3 Non-antibiotic management

4.3.1 Summary of suggestions

Reassessment

Stakeholders felt that identifying alternatives to antibiotic treatment for the management of ongoing symptoms is a quality improvement area. They also highlighted reassessment following treatment failure. Stakeholder suggested that delays to a second course of antibiotics being prescribed can occur if a reassessment appointment has not been booked. This risks the symptoms spreading beyond the original site of infection. Stakeholders also suggested clinical review and reassessment for people without a confirmed diagnosis of Lyme disease is a priority, and that clinical review would also support diagnosis of other conditions.

Specialist advice and referral

Stakeholders suggested that people who continue to experience symptoms after 2 courses of antibiotics are referred to an infectious disease specialist. People with certain neurological, cardiac or rheumatological symptoms should have their case discussed with a specialist in secondary or tertiary care, this should be on an urgent basis, to improve referral routes for people with complex forms of Lyme disease. It was highlighted that diagnosis may be delayed by multiple referrals to different specialities. Stakeholders highlighted that specialists and microbiologists in the Rare and Imported Pathogens Laboratory (RIPL, Porton Down) need to provide advice (through discussion and referral) that is consistent with the NICE guideline.

4.3.2 Selected recommendations from development source

Table 4 below highlights recommendations that have been provisionally selected from the development source(s) that may support potential statement development. These are presented in full after table 4 to help inform the committee's discussion.

Table 4 Specific areas for quality improvement

Suggested quality improvement area	Selected source guidance recommendations
Reassessment	**Management – antibiotic treatment** NICE NG95 Recommendation 1.3.8 **Management – ongoing symptoms after a course of antibiotics** NICE NG95 Recommendation 1.3.9 **Management – non-antibiotic management of ongoing symptoms** NICE NG95 Recommendations 1.3.14 and 1.3.15
Specialist advice and referral	**Diagnosis - laboratory investigations to support diagnosis** NICE NG95 Recommendation 1.2.20 **Management - specialist advice** NICE NG95 Recommendations 1.3.2 and 1.3.3 **Management – ongoing symptoms after a course of antibiotics** NICE NG95 Recommendation 1.3.12 **Management – management for women with Lyme disease during pregnancy and their babies** NICE NG95 Recommendation 1.3.20

Reassessment

Management – antibiotic treatment

NICE NG95 Recommendation 1.3.8

Consider clinical review during or after treatment for Lyme disease to assess for possible side effects and response to treatment.

Management – ongoing symptoms after a course of antibiotics

NICE NG95 Recommendation 1.3.9

If symptoms that may be related to Lyme disease persist, do not continue to improve or worsen after antibiotic treatment, review the person's history and symptoms to explore:

- possible alternative causes of the symptoms
- if re infection may have occurred
- if treatment may have failed
- details of any previous treatment, including whether the course of antibiotics was completed without interruption
- if symptoms may be related to organ damage caused by Lyme disease, for example, nerve palsy.

Management – non-antibiotic management of ongoing symptoms

NICE NG95 Recommendation 1.3.14

Offer regular clinical review and reassessment to people with ongoing symptoms, including people who have no confirmed diagnosis.

NICE NG95 Recommendation 1.3.15

Explore any ongoing symptoms with the person and offer additional treatment if needed following usual clinical practice.

Specialist advice and referral

Diagnosis - laboratory investigations to support diagnosis

NICE NG95 Recommendation 1.2.20 (excerpt)

If the immunoblot test for Lyme disease is negative (regardless of the ELISA result) but symptoms persist, consider a discussion with or referral to a specialist, to:

Choose a specialist appropriate for the person's history or symptoms, for example, an adult or paediatric infection specialist, rheumatologist or neurologist.

Management - specialist advice

NICE NG95 – Recommendation 1.3.2

Discuss the diagnosis and management of Lyme disease in children and young people under 18 years with a specialist, unless they have a single erythema migrans lesion and no other symptoms. Choose a specialist appropriate for the child or young person's symptoms dependent on availability, for example, a paediatrician, paediatric infectious disease specialist or a paediatric neurologist.

NICE NG95 – Recommendation 1.3.3

If an adult with Lyme disease has focal symptoms, consider a discussion with or referral to a specialist, without delaying treatment. Choose a specialist appropriate for the person's symptoms, for example, an adult infection specialist, rheumatologist or neurologist.

Management – ongoing symptoms after a course of antibiotics

NICE NG95 – Recommendation 1.3.12

If a person has ongoing symptoms following 2 completed courses of antibiotics for Lyme disease:

- do not routinely offer further antibiotics **and**
- consider discussion with a national reference laboratory or discussion or referral to a specialist as outlined in recommendation 1.2.20.

Management – management for women with Lyme disease during pregnancy and their babies

NICE NG95 – Recommendation 1.3.20

Advise women who had Lyme disease during pregnancy to tell this to their healthcare professional if they have any concerns about their baby. In this situation, healthcare professionals should discuss the history with a paediatric infectious disease specialist and seek advice on what investigations to perform.

4.3.3 Current UK practice

A small study funded by Lyme Research UK which retrospectively surveyed 152 people in the UK and Ireland diagnosed with Lyme disease about their experiences of access to care in 2011. A specific limitation in relation to this topic is that it isn't clear in what circumstances the diagnosis was made (for example, through reassessment).

Relevant findings include:

- 15% (of 120) were diagnosed within 6 months
- around 30% waited more than 1 year and up to 6 years
- 15% waited 15 years or more for a diagnosis
- Reported reasons for delays (information provided by 143 people) included:
    - referral to the 'wrong' specialist – around 25%
    - slow referral times – 4%.

The survey also reported that being referred to the wrong specialist was a key reason for delay. This was reported among people who tested positive and negative for Lyme disease – 15% and 37% respectively.[13]

[13] Bloor K and Hale V (2013) An internet survey of Lyme patients' experience of access to care

4.4 Awareness and information

4.4.1 Summary of suggestions

Raising awareness

Stakeholders suggested that improving awareness of Lyme disease among the public is a priority. Giving people advice on avoiding ticks, how to remove them correctly from their body and targeting high-risk groups were further suggestions. Stakeholders highlighted that awareness that risk of infection isn't limited to areas of the UK typically associated with tick incidence is a priority. They also commented that many people don't remember tick bites. It was felt that absence of a tick bite history may restrict access to diagnostic tests.

Stakeholders highlighted greater awareness of Lyme disease in primary care would support early diagnosis and treatment on the basis of an erythema migrans rash. Stakeholders felt that greater awareness among secondary care specialties could support a more streamlined diagnostic process, potentially avoiding repeating investigations for suspected Lyme disease across different specialties. More widespread knowledge of recommended methods of removing ticks in A&E departments was suggested as a specific area. Stakeholders observed that people who've found a tick on their skin may initially present at A&E; correct and prompt removal help reduce the risk of the transmission of Lyme disease.

Stakeholders also suggested that an evidence base for tick removal and other preventative strategies could be developed.

Information about diagnosis, management and follow-up

Stakeholders highlighted that providing adequate and complete information about the diagnostic process is a priority. It was suggested that failure to do this, coupled with low satisfaction with discussion in consultations, may lead to people arranging tests at laboratories which aren't accredited/externally-validated for performing laboratory investigations for Lyme disease. This may result in inaccurate diagnoses of Lyme disease, or missed diagnoses of other conditions.

Stakeholders suggested providing information about the management and prognosis of Lyme disease is a quality improvement area. Giving information to people about favourable outcomes identified in research for specific forms of Lyme disease was also proposed.

4.4.2 Selected recommendations from development source

Table 5 below highlights recommendations that have been provisionally selected from the development source(s) that may support potential statement development. These are presented in full after table 5 to help inform the committee's discussion.

Table 5 Specific areas for quality improvement

Suggested quality improvement area	Selected source guidance recommendations
Raising awareness	**Awareness of Lyme disease** NICE NG95 Recommendations 1.1.1 and 1.1.2 NICE NG95 Recommendation 1.1.3 **Diagnosis – clinical assessment** NICE NG95 Recommendations 1.2.5 and 1.2.6
Information about diagnosis, management and follow-up	**Diagnosis - information for people being tested for Lyme disease** NICE NG95 Recommendations 1.2.26 and 1.2.27 **Management - ongoing symptoms after a course of antibiotics** NICE NG95 Recommendation 1.3.13 **Information for people with Lyme disease** NICE NG95 Recommendations 1.4.1 and 1.4.3

Raising awareness

Awareness of Lyme disease

NICE NG95 – Recommendation 1.1.1

Be aware that:

- ticks are mainly found in grassy and wooded areas, including urban gardens and parks
- tick bites may not always be noticed
- infected ticks are found throughout the UK and Ireland, and although some areas appear to have a higher prevalence of infected ticks, prevalence data are incomplete
- particularly high-risk areas are the South of England and Scottish Highlands but infection can occur in many areas
- Lyme disease may be more prevalent in parts of central, eastern and northern Europe (including Scandinavia) and parts of Asia, the US and Canada.

NICE NG95 – Recommendation 1.1.2

Be aware that most tick bites do not transmit Lyme disease and that prompt, correct removal of the tick reduces the risk of transmission.

NICE NG95 Recommendation 1.1.3

Give people advice about:

- where ticks are commonly found (such as grassy and wooded areas, including urban gardens and parks)
- the importance of prompt, correct tick removal and how to do this (see the Public Health England website for information on removing ticks)
- covering exposed skin and using insect repellents that protect against ticks
- how to check themselves and their children for ticks on the skin
- sources of information on Lyme disease, such as Public Health England, and organisations providing information and support, such as patient charities.

Diagnosis – clinical assessment

NICE NG95 – Recommendation 1.2.5

If a person presents with symptoms that suggest the possibility of Lyme disease, explore how long the person has had symptoms and their history of possible tick exposure, for example, ask about:

- activities that might have exposed them to ticks
- travel to areas where Lyme disease is known to be highly prevalent.

NICE NG95 – Recommendation 1.2.6

Do not rule out the possibility of Lyme disease in people with symptoms but no clear history of tick exposure.

Information about diagnosis, management and follow-up

Diagnosis - information for people being tested for Lyme disease

NICE NG95 – Recommendation 1.2.26

Advise people that tests from non-UKAS laboratories may not have been fully evaluated to diagnose Lyme disease.

NICE NG95 – Recommendation 1.2.27

Explain to people that:

- the symptoms and signs associated with Lyme disease overlap with those of other conditions
- they will be assessed for alternative diagnoses if their tests are negative and their symptoms have not resolved
- symptoms such as tiredness, headache and muscle pain are common, and a specific medical cause is often not found.

Ongoing symptoms after a course of antibiotics

NICE NG95 – Recommendation 1.3.13

Explain to people with ongoing symptoms following antibiotic treatment for Lyme disease that:

- continuing symptoms may not mean they still have an active infection
- symptoms of Lyme disease may take months or years to resolve even after treatment
- some symptoms may be a consequence of permanent damage from infection
- there is no test to assess for active infection and an alternative diagnosis may explain their symptoms.

Information for people with Lyme disease

NICE NG95 – Recommendation 1.4.1

Explain to people diagnosed with Lyme disease that:

- Lyme disease is a bacterial infection treated with antibiotics
- most people recover completely
- prompt antibiotic treatment reduces the risk of further symptoms developing and increases the chance of complete recovery
- it may take time to get better, but their symptoms should continue to improve in the months after antibiotic treatment
- they may need additional treatment for symptom relief.

NICE NG95 – Recommendation 1.4.3

Advise people with Lyme disease to talk to their doctor if their symptoms have not improved or if symptoms return after completing treatment.

4.4.3 Current UK practice

Raising awareness

A UK study in 2011 surveyed the tick bite avoidance behaviours of 343 people aged 18 and over who lived in an urban area but travelled to areas with known incidence of ticks.[14] Of those surveyed the majority were aged between 18 and 44 years, 72% were female and 80% were white. Participants were recruited via a London-based outdoor group. Their tick bite avoidance behaviours were investigated in reference to the New Forest, Scottish Highlands, Dartmoor, Exmoor, the South Downs, Thetford Forest, the Lake District, the Yorkshire Moors and Richmond Park. Relevant findings include:

- wearing long trousers and sticking to clear pathways were the only 2 tick bite avoidance (primary prevention) behaviours practised at least half the time
- 15% reported checking for ticks on their clothes while walking at least half the time in a tick-affected area
- 15% reported checking for ticks on their bodies while walking at least half the time
- around 20% reported checking for ticks after walking at least half the time; around 40% identified forgetting as the most common reason for not checking
- 15% could identify an adult and a nymph tick[15]
- 30% knew how to correctly remove a tick;
    - incorrect methods mentioned were: waiting for the tick to drop off by itself, covering it in Vaseline, or burning it off with a cigarette lighter.
    - a low level of disgust about the process of removing a tick was among the strongest predictors of engaging in tick checking behaviour.

A small study funded by Lyme Research UK which retrospectively surveyed 152 people in the UK and Ireland diagnosed with Lyme disease about their experiences of access to care in 2011. The findings highlighted around 50% remembered a tick bite had caused their illness.

- around 50% couldn't remember, or were unsure how the disease was transmitted
- around 50% weren't being 'regularly bitten' at the time they became ill
- around 25% didn't know if they were regularly bitten when they became ill
- 14% felt their GP was fully informed about ticks when they became ill (4% responded they didn't know)

[14] Mowbary, F, Armlot, R and Rubin JG (2014) Predictors of protective behaviour against ticks in the UK: a mixed methods study. Ticks and tick-borne diseases 5 (4): 392-400. doi: 10.1016/j.ttbdis.2014.01.006

[15] Nymph ticks are smaller than adult ticks and are most likely to transmit infection; they can remain very small, even after feeding (about the size of a poppy seed). Due to these factors they are more likely to be missed and remain on the skin longer. Source: Lyme disease (2018) Clinical Knowledge Summaries topic – background information.

- 8% felt their main NHS consultant was fully-equipped to deal with their health problems (14% responded they didn't know, or that the question didn't apply)
- 50% felt the delay in being given a diagnosis was due to 'not knowing about Lyme disease and its signs'
- of 66 people who had a negative diagnosis via the NHS, 76% were subsequently 'diagnosed by a private doctor'
- 24% of people with negative diagnoses were diagnosed by the NHS.[16]

Information about diagnosis, management and follow-up

The online patient support group survey (2014) of 120 people found that in relation to what people were told by doctors about laboratory investigations for Lyme disease:

- 40% were told an ELISA test result ruled out a diagnosis of Lyme disease
- 18% were told a Western blot (immunoblot) test ruled out a diagnosis of Lyme disease
- 14% were told tests weren't completely reliable
- 49% were told NHS tests are reliable.[17]

[16] Bloor K and Hale V (2013) An internet survey of Lyme patients' experience of access to care
[17] Vector-Borne Infection Research, Analysis and Strategy (VIRAS) (2014) NHS Testing and Investigation of Lyme Borreliosis – Patient Experiences Survey

4.5 Additional areas

Summary of suggestions

The improvement areas below were suggested as part of the stakeholder engagement exercise. However they were felt to be either unsuitable for development as quality statements, outside the remit of this particular quality standard referral or require further discussion by the committee to establish potential for statement development.

There will be an opportunity for the committee to discuss these areas at the end of the session on 6 December 2018.

Clinical epidemiology and research

Stakeholders highlighted that developing additional methods for establishing the incidence of Lyme disease in the UK is an area for quality improvement. Creating a surveillance scheme via the RCGP Research surveillance Centre (RSC), and categorising Lyme disease as a notifiable disease were suggested as clinically diagnosed Lyme disease is not recorded in official statistics. Systematic follow-up of people with a diagnosis of Lyme disease was also suggested, to enhance clinical practice through sharing expertise, and support research. Identifying consistent end-points for measuring treatment success was suggested as a specific area.

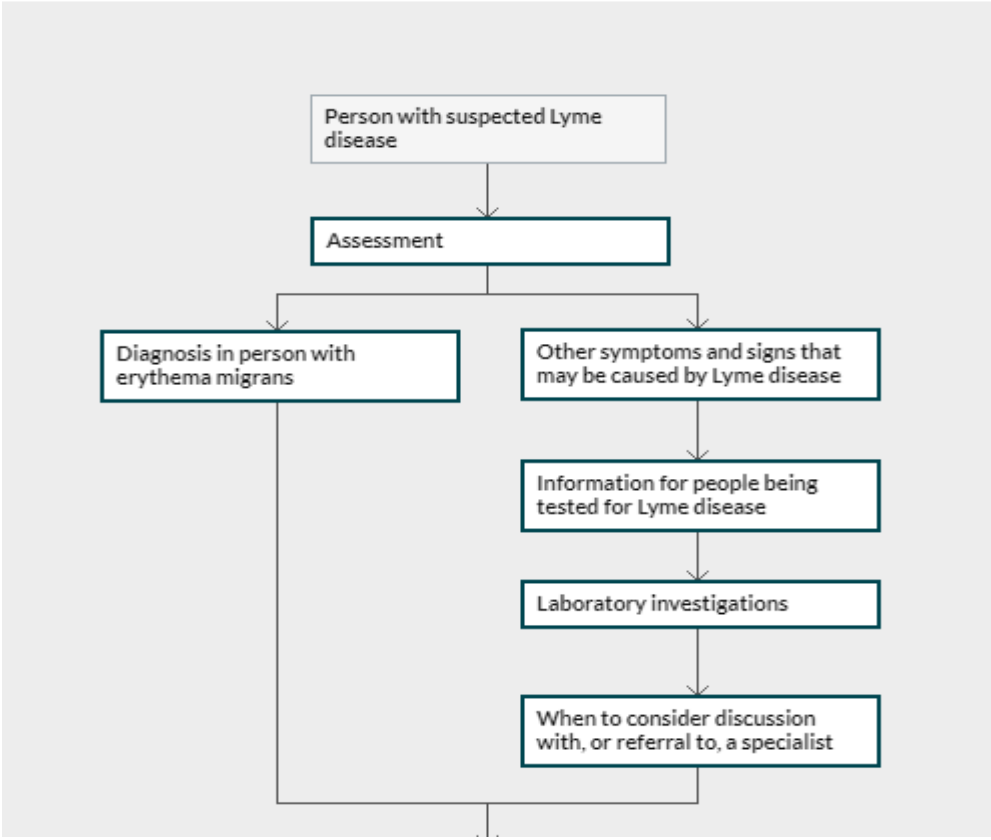
Quality statements focus on actions that demonstrate high quality care or support, not the methods by which evidence is collated. Suggested methods of data collection may be referred to in the data sources for quality measures. A statement in this area cannot be progressed.

Improving laboratory investigations

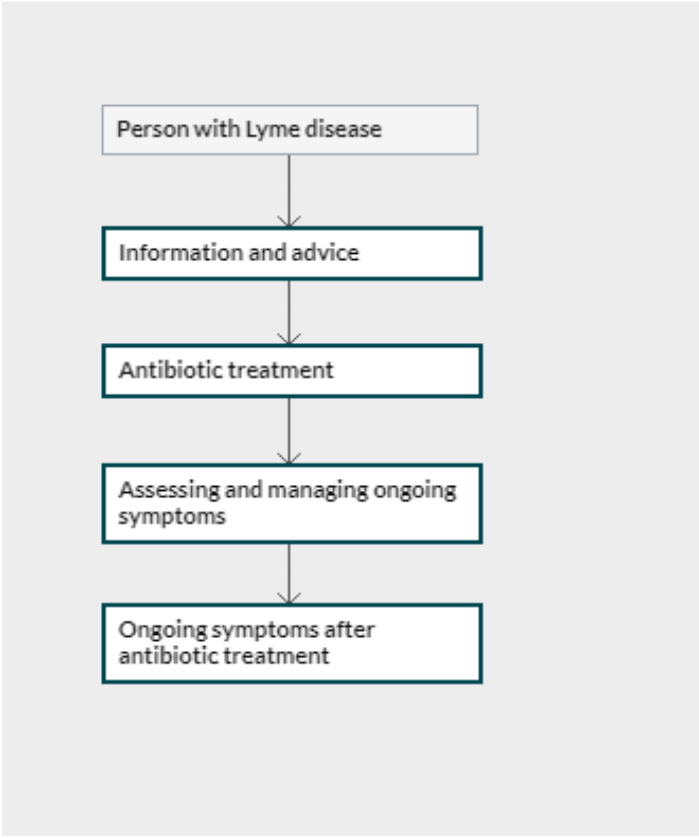
Stakeholders highlighted that improving laboratory investigations (blood tests) used to test for Lyme disease is a priority. This suggestion is beyond the scope of a quality standard. Stakeholders suggested that knowledge and testing methods for other tick-borne infections (such as babesia and bartonella) that may be coinfections of Lyme disease is a quality improvement area. A stakeholder also commented that people may test for coinfections without experiencing symptoms of Lyme disease, which they suggested was a separate issue from experiencing self-limiting infection with Lyme disease. Improving the characterisation of Lyme disease where ongoing symptoms are linked with active infection was suggested as another specific area. This is not supported by the source recommendations; a statement in this area cannot be progressed.

Appendix 1: Additional information – Lyme disease pathway and visual summary of laboratory investigations and diagnosis of Lyme disease.

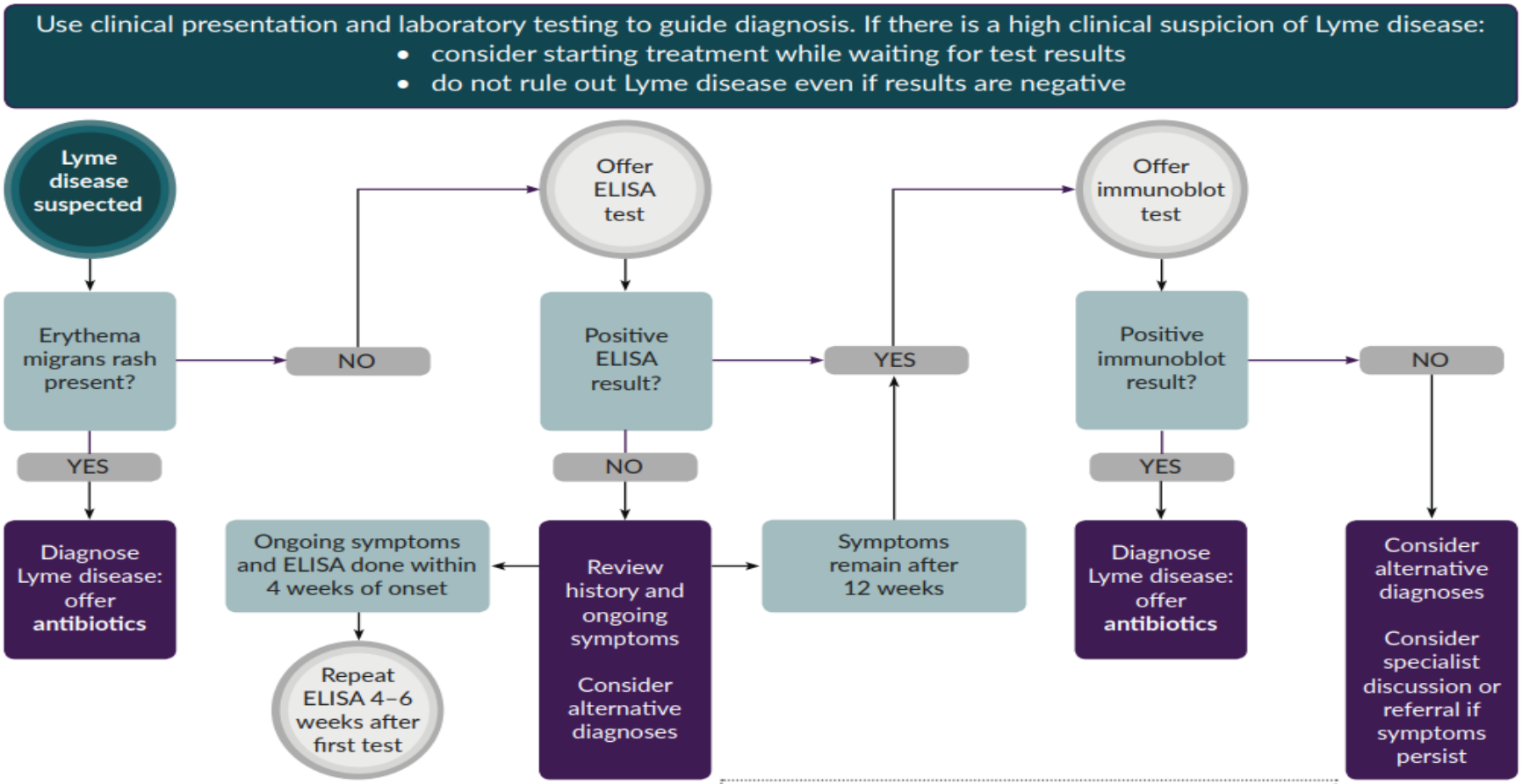
Diagnosing Lyme disease



Managing Lyme disease



Lyme disease: laboratory investigations and diagnosis



NICE National Institute for Health and Care Excellence

This is a summary of the recommendations on tests for Lyme disease from NICE's guideline on Lyme disease. The guideline also covers clinical assessment and management, including antibiotic treatment. See www.nice.org.uk/guidance/NG95

Appendix 2: Additional information – antibiotic treatment

Table 1 Antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) according to symptoms – relates to recommendation 1.3.4[a]

Symptoms	Treatment	First alternative	Second alternative
Lyme disease without focal symptoms			
Erythema migrans **and/or** Non-focal symptoms	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 21 days	Oral amoxicillin: 1 g 3 times per day for 21 days	Oral azithromycin[b]: 500 mg daily for 17 days
Lyme disease with focal symptoms			
Lyme disease affecting the cranial nerves or peripheral nervous system	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 21 days	Oral amoxicillin: 1 g 3 times per day for 21 days	–
Lyme disease affecting the central nervous system	Intravenous ceftriaxone: 2 g twice per day or 4 g once per day for 21 days (when an oral switch is being considered, use doxycycline)	Oral doxycycline: 200 mg twice per day or 400 mg once per day for 21 days	–
Lyme disease arthritis	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 28 days	Oral amoxicillin: 1 g 3 times per day for 28 days	Intravenous ceftriaxone: 2 g once per day for 28 days
Acrodermatitis chronica atrophicans			
Lyme carditis[b]	Oral doxycycline: 100 mg twice per day or 200 mg once per day for 21 days	Intravenous ceftriaxone: 2 g once per day for 21 days	–
Lyme carditis and haemodynamically unstable[b]	Intravenous ceftriaxone: 2 g once per day for 21 days (when an oral switch is being considered, use doxycycline)	–	–

[a] For Lyme disease suspected during pregnancy, use appropriate antibiotics for stage of pregnancy.

[b] Do not use azithromycin to treat people with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.

Table 2 Antibiotic treatment for Lyme disease in children (under 12) according to symptoms – relates to recommendation 1.3.5 [a, b, c]

Symptoms	Age	Treatment	First alternative	Second alternative
Lyme disease without focal symptoms				
Erythema migrans **and/or** Non-focal symptoms	9–12 years	Oral doxycycline[a] for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily for 21 days[d]	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	Oral azithromycin[e, f] for children 50 kg and under: 10 mg/kg daily for 17 days
	Under 9	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	Oral azithromycin[e, f] for children 50 kg and under: 10 mg/kg daily for 17 days	–
Lyme disease with focal symptoms				
Lyme disease affecting the cranial nerves or peripheral nervous system	9–12 years	Oral doxycycline[a] for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	–

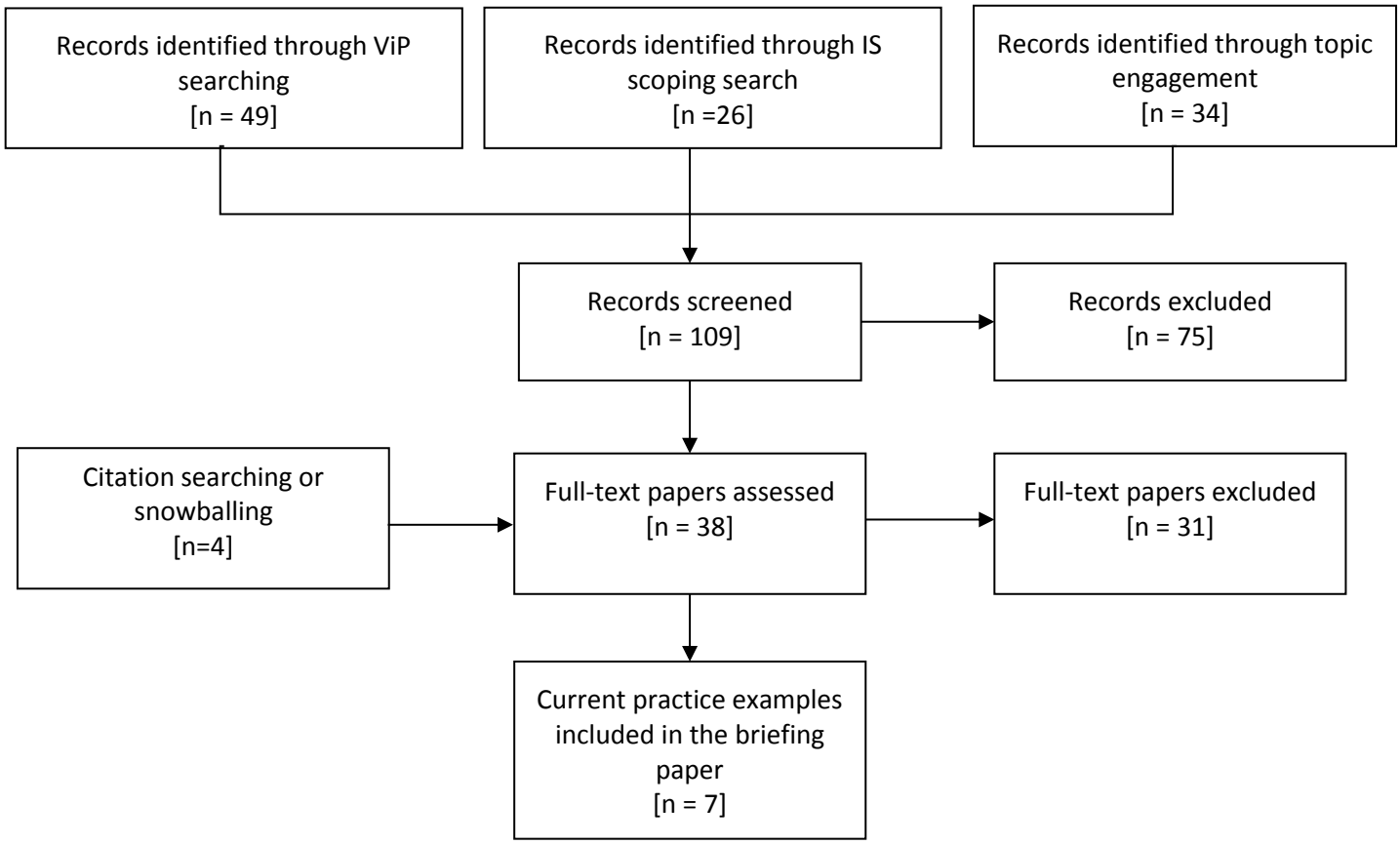
		5 mg/kg daily for 21 days[d]		
	Under 9	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day for 21 days	–	–
Lyme disease affecting the central nervous system	9–12 years	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 4 g) once per day for 21 days	Oral doxycycline[a]for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily[d]	–
	Under 9	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 4 g) once per day for 21 days	–	–
Lyme arthritis **or** Acrodermatitis chronica atrophicans	9–12 years	Oral doxycycline[a] for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 28 days For severe infections, up to 5 mg/kg daily for 28 days[d]	Oral amoxicillin for children 33 kg and under: 30 mg/kg 3 times per day 28 days	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 2 g) once per day for 28 days

	Under 9	Oral amoxicillin for children, 33 kg and under: 30 mg/kg 3 times per day for 28 days	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 2 g) once per day for 28 days	–
Lyme carditis and haemodynamically stable[f]	9–12 years	Oral doxycycline[a] for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily for 21 days[d]	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 2 g) once per day for 21 days	–
	Under 9	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 2 g) once per day for 21 days	–	–
Lyme carditis and haemodynamically unstable[f]	9–12 years	Intravenous ceftriaxone for children under 50 kg: 80 mg/kg (up to 2 g) once per day for 21 days	Oral doxycycline[a]for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days For severe infections, up to 5 mg/kg daily for 21 days[d]	–
	Under 9	Intravenous ceftriaxone for		

		children under 50 kg: 80 mg/kg (up to 2 g) once per day for 21 days		

[a] At the time of publication (April 2018), doxycycline did not have a UK marketing authorisation for this indication in children under 12 years and is contraindicated. The use of doxycycline for children aged 9 years and above in infections where doxycycline is considered first line in adult practice is accepted specialist practice. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
[b] Discuss management of Lyme disease in children and young people with a specialist, unless they have a single erythema migrans lesion with no other symptoms, see recommendation 1.3.2.
[c] Children weighing more than the amounts specified should be treated according to table 1.
[d] Use clinical judgement to determine doses of doxycycline for children under 12 years with severe infections.
[e] At the time of publication (April 2018), azithromycin did not have a UK marketing authorisation for this indication in children under 12 years. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Prescribing guidance: prescribing unlicensed medicines for further information.
[f] Do not use azithromycin to treat people with cardiac abnormalities associated with Lyme disease because of its effect on QT interval.

Appendix 3: Review flowchart



Appendix 4: Glossary

ELISA (enzyme-linked immunosorbent assay): One of the blood tests looking for antibodies to Borrelia burgdorferi. A positive result is followed by a confirmatory **immunoblot** test. The timing of the initial ELISA test is 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.

Immunoblot: Confirmatory test that follows an ELISA test as part of 2-tier testing.

Rare and Imported Pathogens Laboratory (RIPL, PHE): The RIPL (Porton Down) specialises in unusual and hazardous pathogens, including imported fever, Lyme borreliosis, Q fever, anthrax and leptospirosis. It provides medical and laboratory specialist services to the NHS and other healthcare providers, including Lyme borreliosis.

RIPL is the National Reference Laboratory for Lyme disease testing. First line laboratory testing for suspected Lyme disease may be available through local NHS service providers. Where this is not available, and for all confirmatory testing, RIPL provides a Lyme disease diagnostic service. There is a separate reference laboratory for Scotland.[18]

UKAS (United Kingdom Accreditation Service): UK's National Accreditation Body, responsible for determining the technical competence and integrity of organisations such as those offering testing, calibration and certification services.

UKAS provides accreditation to the internationally recognised standard ISO 15189 Medical Laboratories – requirements for quality and competence.[19]

[18] Source: PHE (2018) Lyme disease services - diagnostic and advisory services for Lyme disease
[19] For further information, see: UKAS Medical Laboratory Accreditation, Transition from CPA to ISO 15189 is completed.

Appendix 5: Suggestions from stakeholder engagement exercise – registered stakeholders

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
Diagnosis and assessment					
	Clinical assessment				
01	CLC	3: Diagnosis should involve both serological testing and clinical diagnosis, without inappropriate reliance on serology results, and doctors should be enabled to give confident clinical judgements, especially on erythema migrans rashes, by means of widely available training and well-publicised comprehensive resources	We do not currently have a gold-standard test for Lyme. Serology tests, properly used, have value, but over-reliance on serology is leading to mistakes which are damaging for patients. Clinical evidence is also very important. Lyme disease presents with common symptoms in characteristic patterns and doctors need to be able to use these symptom constellations to diagnose Lyme disease. Some aspects of clinical Lyme diagnosis are difficult and doctors need resources to guide them which are well-publicised, easy to use in the consultation room and comprehensive. This particularly applies to the differential diagnosis of the erythema migrans rash. When clinical symptoms are ignored in preference to tests which patients know to be	Some doctors lack confidence to diagnose Lyme disease from signs, symptoms and history, so there is over-reliance on serology. Doctors seem unaware of the limitations of the tests (low sensitivity compared to many other tests). Patients are often told, even those who have previously had an EM rash diagnosed, that they don't have Lyme disease because the tests are negative. Statements on results sheets from PHE apparently encourage this (according to patient statements). Some GPs lack confidence to diagnose against negative lab results. Some doctors order tests a) too early b) in patients with an erythema rash c) to assess for "cure" after treatment. RASHES: from patients, evidently doctors often rely on whether a rash looks like a "typical bull's eye", unaware that rashes are often atypical. Rashes which don't	Sources: Personal daily contact with patients in support groups. Patient testimonies. NICE 2018 Guideline for Lyme Disease The guideline states: "Do not rule out Lyme disease even if tests are negative"

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
			unreliable, this damages the trust patients have in their doctors and encourages them to turn to other methods of diagnosis.	look classic with rings are not diagnosed as EM, while conversely some doctors treat ringed or angry insect bites as EM. Consideration of EM may take days/weeks as alternatives are treated with anti-histamines, steroid creams, anti-fungals and flucloxacillin. Doctors need a flow-chart, key of questions to pose about a rash, and characteristics to look for. This should be created by clinicians with extensive experience in identifying Lyme rashes, which may mean accessing the assistance of doctors in areas where Lyme has been historically more prevalent. In my experience of patients' reports it is not common for a doctor to ask questions about the appearance time of the rash, how it feels, whether it is spreading, whether its characteristics have changed since the bite event or other questions which could help distinguish between an insect bite, cellulitis or ringworm.	
01 cont'd	**Why is this a key area for quality improvement cont'd** Examples**:**				

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
	Patient A: Previously healthy mother of two, with an unidentified bite camping in Cornwall, followed by 5-6cm rash, not seen by doctor, developed typical Lyme symptoms over the next few months (severe fatigue, aching muscles, tingling limbs, joint pain, cognitive issues, dizziness). Blood test for Lyme in July was negative and doctor ruled out Lyme disease. Patient E: had 18 ticks removed and ~10 days later had some of them with bruise-like rashes, and symptoms of muscle pain. Tests taken at 11 days after bites, and 5 weeks after bites, both overall negative and patient is told she does not have Lyme disease. Patient B: 4 year old child presented to GP with clear EM rash. Blood tests ordered immediately and (inadequate) treatment is prescribed. Patient C: with 13cm EM rash tested just 2 weeks after bites are noticed. Not re-tested at correct time.				
02	CLC	5: Patients with possible late disease, who may include those who were never treated, those who were under-treated, and those in whom treatment failed, should receive full investigation by doctors aware of the symptom constellation of late Lyme disease	Serological tests are known to be unreliable in Lyme disease - anecdotally, more so in patients who have been ill for several years. Diagnosis of late disease needs to rely more on examining the pattern and symptom progression by doctors familiar with the possible symptom patterns and manifestations. Thorough clinical investigation, with awareness that tick bites are often unnoticed and can occur anywhere in the UK, is necessary. 1) Doctors who rely on serology will miss the diagnosis in some patients. 2) When patients know they have not been assessed thoroughly for Lyme disease, they are less likely to trust	Diagnosis of late disease relies on serological tests known to have limitations. Doctors are hesitant to make diagnoses without lab results. Practice is based on assumptions, not on evidence. The UK is caught in a vicious circle of ignorance. We diagnose little late disease, because doctors are inexpert in clinical diagnosis. Because figures for late Lyme disease are low, doctors do not believe that the patient in front of them can have it. The numbers of patients receiving diagnoses of Lyme disease from private sources and non-UK testing methods, is seen as evidence of poor practice by independent Lyme doctors, without evidence that all such diagnoses are flawed. In other diseases, trial treatment is sometimes used as part of the	Sources: Personal daily contact with patients in support groups. NICE 2018 Guideline for Lyme Disease.

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
			their doctors and co-operate with investigations for alternative diagnoses. These may then be missed. 3) When patients lose confidence in their doctors, they are more likely to try to find alternative sources of medical help. Patients do not willingly spend money where it is not necessary, but inadequate evaluation of a possible diagnosis, and/or dismissal on grounds of possibly flawed serology, in a situation of continued disabling illness, drives them to private investigations	diagnosis process. This would be appropriate also in late Lyme disease. It is common for charities and online support groups to see patients who have been told such things as: Lyme disease is rare in the UK/this part of the UK. You cannot have had Lyme disease for all this time – it would have resolved or you would have died. You cannot have a test because you cannot recall a tick bite.You cannot have Lyme disease because you have a negative ELISA test. Your positive ELISA test is a false positive. You had treatment so you cannot still have Lyme disease. It is more likely that you have (all of) fibromyalgia, and ME/CFS, and Postural Orthostatic Tachycardia Syndrome, and depression, than that you have Lyme disease, because Lyme disease is rare. While doctors are reluctant, for whatever reason, to make clinical diagnoses of Lyme disease, the	

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
				UK is also losing the opportunity to learn more about the late manifestations of the disease.	
03	Lyme Disease Action	Raising awareness of the limitations of Lyme serology testing.	1. There is well documented evidence of limited accuracy with regard to Lyme serology tests, both ELISAs and immunoblots due to inherent factors related to test design and implementation. 2. There is also well documented evidence of variability in the adaptive immune response to Borrelia in humans. Some people may fail to mount a robust enough antibody response, and for others there may be a failure of isotype switching from IgM to IgG which would affect interpretation of the immunoblot. NICE states that a negative result should not be used to exclude a diagnosis of Lyme disease. Numerous case reports of seronegative Lyme disease are well-documented in the scientific literature, as	Lyme Disease Action (LDA) has concerns for the quality of patient care and safety in this area. Lyme Disease Action has encountered limited awareness, knowledge and clinical experience of this particular area of the medical and scientific evidence base regarding Lyme disease amongst specialists. LDA is aware of a number of cases with a high pre-test probability of Lyme disease, where patient safety has been compromised with very negative outcomes, where clinical decisions have relied heavily on serology test results, at the expense of the clinical context. Some have included assumptions based mainly on both positive and negative results. The pre-test probability of Lyme disease is not always included in the Lyme serology request, which may lack clinical and contextual detail. The Lyme Reference Laboratory has a high throughput of automated serology tests and interpretation	NICE CG95 Lyme disease 2018 https://www.nice.org.uk/guidance/ng95/ References: 1. Leeflang et al. The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. BMCInfect Dis 2016; 16: 140. doi: 10.1186/s12879-016-1468-4. 2. Ang et al. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. Eur J Clin Microbiol 2011. 30(8):1027-32. doi: 10.1007/s10096-011-1157-6. 3. Preac-Mursic et al. Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection. 1989 Nov-Dec;17(6):355-9.

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
			well as cases with equivocal results from Lyme serology or cerebrospinal fluid. This scientific evidence was not reviewed in the NICE clinical guidance CG 95. At the individual patient level, it will therefore be possible for some patients with seronegative Lyme disease to go through the whole NICE testing algorithm and be referred on for specialist assessment, with alternative diagnoses excluded as part of that process. It is important in such cases for specialists to be aware of the limitations of Lyme serology testing and the medical and scientific evidence base demonstrating diagnostic challenges for some cases of Lyme disease.	follows the manufacturer's algorithm. UK doctors, both specialists and GPs generally have insufficient experience and understanding of Lyme disease two-tier serology testing to adequately apply clinical judgement to the results where necessary. Lyme Disease Action is aware of cases where a reasonable request for Lyme disease testing, or re-testing as per the NICE testing algorithm has been refused by the clinician.	
04	Lyme Disease UK	1: Diagnosis: Recognition and treatment of EM rashes	An EM rash is diagnostic of Lyme disease without the need for a blood test. If this rash is missed, the opportunity for prompt treatment is also missed. EM rashes appear to be missed due to poor	Photographic examples of EM rashes are posted in LDUK's Online Community which have been dismissed by doctors as not being related to Lyme disease despite following the timings and characteristics of an EM rash.	The rash examples in the 'Tools and Resources' section of the guideline need to include more images of atypical rashes. Doctors need to be made more aware that not all rashes look like the first example that comes up in a Google search which is of a 'classic' bull's-eye rash. The

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
			recognition by medical professionals. Many are not aware that EM rashes can be atypical in appearance and are not always the classic bull's-eye shape.	Patients also share stories of being sent for blood tests when they have a clear EM rash. According to the guideline, this scenario does not require a blood test as the rash is diagnostic in itself and antibodies are unlikely to have formed at this point. Doctors seem unaware of the guideline's existence.	guideline simply states that the rash 'may sometimes have a central clearing'. There is not enough written guidance on the atypical nature of rashes and doctors need training in this area. The NICE guideline states, in section 1.2.11, 'Diagnose and treat Lyme disease without laboratory testing in people with erythema migrans.'
05	Lyme Disease UK	4: Education: Awareness of the guideline's existence	It is important that medical professionals are aware of the existence of the NICE Lyme disease guideline so that they are diagnosing and treating using up to date information. Doctors should also be taking the online e-learning module on Lyme disease created by the RCGP and Lyme Disease Action.	… We hear many reports from patients of doctors being seemingly confident in their understanding of Lyme disease and confident in dismissing the possibility of a Lyme infection. This is happening even in clear cases involving an EM rash, a history of tick exposure and a constellation of Lyme disease symptoms. We make this point to illustrate that some doctors are unaware of their own lack of awareness of the information in the new NICE guideline and this is unacceptable …	In LDUK's 'Online Community', we see people sharing that their doctors were unaware of the NICE Lyme disease guideline and instead, were using old referral pathways. These must be removed or updated. Even when the existence of the guideline has been pointed out, it appears as though many doctors are still unable to follow it thoroughly resulting in misdiagnoses and inadequate treatment. …
06	Lyme Disease UK	2: Testing and Clinical Diagnosis: Reducing the over-reliance on serology	A negative test cannot rule out the disease and we do not have a test for cure. If	The guideline highlights the pitfalls of Lyme disease serology. In LDUK's Online Community, we	In the NICE guideline, section 1.2.12, it states, 'Use a combination of clinical

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		and increasing doctors' confidence in making a clinical diagnosis of Lyme disease	doctors rely solely on serology and do not consider clinical symptoms and signs, a Lyme disease diagnosis can be easily missed. This can have devastating effects on a patient's life. Doctors are struggling to understand and implicate guidance on Lyme disease but other tick-borne infections may be at play and these appear to be frequently dismissed due to a lack of knowledge. Many doctors don't appear to have heard of Babesiosis or Bartonellosis, for example and testing for these infections is also highly problematic.	see many patients being told that their NHS blood tests are negative or falsely positive which is not in line with the test manufacturer's guidance. There is a lack of acknowledgement or awareness of persistence of positive IgM positive test results in long term infection. Therefore, doctors dispute the possibility of ongoing infection, despite patients displaying symptoms of the disease and having a history of a tick bite, rash and/or tick exposure. The ruling out of a Lyme disease diagnosis using serological results alone effectively blocks patients' access to any antibiotic treatment and often leads to a misdiagnosis of CFS, fibromyalgia or mental illness to name a few or to being discharged and being told to get on with life. This needs to change and doctors need to be trained to recognise the clinical signs of the disease so that they don't dismiss patients. Many are told, 'it's all in your head.' There is a whole section on 'Clinical Assessment' in the	presentation and laboratory testing in people with erythema migrans. Do not rule out Lyme disease if tests are negative but there is a high clinical suspicion of Lyme disease.' In section 1.2.27, the guideline states, 'Tell people that tests for Lyme disease have limitations.' In section 5 in the 'Recommendations for Research' section regarding laboratory testing, it says 'published evidence is of either low or very low quality and is not UK based. A 'test of cure' for Lyme disease does not exist. In the Rationale and Impact section of the NICE guideline, it states, 'A discussion with a UK national reference laboratory might be helpful, for example, if a different tick-borne disease is possible. The NICE guideline, in section 5 says, 'Little is known about the evolution of antibody titres over time in those who have been

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				guideline and yet it appears as though doctors are not confident when it comes to making a clinical diagnosis of Lyme disease, even with this guidance. Examples in our Online Community include an anecdotal report of a doctor being prepared to treat a patient who had multiple tick bites but who was then overruled by a scientist at Porton Down because of negative test results, even though this person had never met the patient. It is very wrong that doctors' clinical opinions are being overruled in this way even though the NICE guideline does recommend 'a discussion with a UK national reference laboratory' if someone has ongoing symptoms.' The over-reliance of serology prevails and patients are frequently sent for a wide range of expensive testing and diagnostic imaging for other conditions, costing the NHS dearly. Patients are also being re-tested for Lyme disease to 'prove' that	treated successfully and those who have ongoing symptoms.' Course of Antibody Response in Lyme Borreliosis Patients before and after Therapy - Arberer et al https://www.hindawi.com/journals/isrn/2012/719821/ The guideline recognises that Lyme disease can persist. For example in section 1.2.18 and 1.3.9 it mentions symptoms can persist beyond 12 weeks, however suggests the patient is referred to a specialist, of which there are non within the NHS. People who have ongoing symptoms from Lyme disease who improve on longer term (private) treatment. There is still outdated information on official sites that doctors may use. For example here https://bnf.nice.org.uk/treatment-summary/lyme-disease.html. Limitations of the test and how to interpret are given in the manufacturer's instruction leaflet,

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				treatment has been effective. This is not possible as there is no test for cure. It is our experience that the guidance to offer a second test at the end of 12 weeks or if a patient is still symptomatic is being misused. Even if the test result is positive, people are being told that the tests can remain this way for a while but they no longer have active Lyme disease. If the result is negative, it is being used as 'evidence' that someone is no longer infected. This is a waste of money and results in a cessation of treatment.	for example we believe the Western Blot currently in use to be this test. http://www.viramed.de/images/stories/pdf/Arbeitsanleitungen_EN/2551_Borrelia_ViraStripe_IgM_AL_en.pdf
07	RCGP	Training and educational materials on Lyme disease - for GPs and other primary care clinicians All Primary Care Clinicians can identify Erythema Migrans (This includes GPs, Practice Nurses, Advanced Nurse Practitioners)	NICE guidance highlights the importance of raising awareness of Lyme disease in primary care. Early diagnosis and adequate treatment of Lyme disease reduces the risk of developing chronic health problems. Improved education will reduce the risk of missed diagnoses and inadequate treatment.	Many GPs report a lack of confidence in diagnosing and treating Lyme disease. Improved education would empower GP and other primary care clinicians to provide reassurance when appropriate and treatment when clinically indicated. Patients regularly contact patient charities with concerns relating to the management of Lyme disease by their General Practitioners.	NICE CG95 Lyme Disease 2018 https://www.nice.org.uk/guidance/ng95/
08	RCGP	Clinicians assessing patients who have a history of unexplained symptoms	See comment 07		

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		consider arranging a blood test for Lyme's Disease			
09	SCM	2: Doctors should diagnose patients based appropriately on both symptoms and serology, without placing undue emphasis on test results.	Evidence shows serology testing for Lyme disease has low sensitivity. Signs and symptoms are very important and in some presentations more reliable for diagnosis than serology.	The charity receives queries regularly from patients with convincing symptoms of Lyme disease having a clinical diagnosis of Lyme disease reversed on the basis of test results from RIPL, sometimes even in cases with EM rash. The guideline states prominently that false negatives can occur but this seems to be having little or no impact so far on GPs' reasoning.	The NICE guideline states that the diagnostic test for Lyme "has limitations" and that patients should be told this. Also stated in the guideline: 1. the tests can produce false negative and false positive results. 2. The sensitivity of the two-tier test is not validated on a UK population. 3. Some patients can be seropositive without symptomatic Lyme disease.
10	SCM	Additional developmental areas of emergent practice Better EM Rash recognition and resources for help GPs	Diagnosis based on recognition of the EM rash is more reliable than serology, provided the doctor recognises the rash	Doctors where Lyme disease is rarer may see very few EM rashes and fail to recognise them easily. Doctors seem to be more worried about EM rashes and I suspect some bad insect bites and other rashes may be receiving inappropriate Lyme disease treatment.	The photo resource that accompanies the guideline could be enhanced. Perhaps additional, detailed advice on rash differentiation could be created?
11	SCM	1: People with clinically suspected Lyme disease (LD), without erythema migrans, are offered a	A diagnosis of LD, other than when Erythema Migrans (EM) only is suspected, should be made from a combination of clinical assessment and	Awareness of ticks and tick-borne infections such as LD is low in many parts of the UK.	Public Health England (PHE) guidance ''Be tick aware' – Toolkit for raising awareness of the potential risk posed by ticks and

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		laboratory based screening test (ELISA)	laboratory testing, as recommended in NICE guideline (NG95). ….	Patients with LD can present with unspecific symptoms, similar to many other conditions and laboratories may be reluctant to perform tests for LD for cost and other concerns if symptoms are not considered typical of LD	tick-borne disease in England', March 2018 NICE guideline on Lyme disease, NG95, April 2018
12	SCM	People presenting with acute facial palsy should be offered an approved test for Lyme disease.	This is an important presentation, particularly in children, where Lyme might be forgotten and the patient treated for Bell's palsy without the necessary antibiotics		
13	SCM	Practitioners in primary, secondary or tertiary care should consider Lyme Disease (as per NICE guideline) and send blood tests (as per NICE guideline) if no EM is present".	This would generate counts of how many tests are done/refused/results – part of the public perception/political issues is patient groups suggesting that some practitioners do not consider Lyme or do tests when symptoms are present. EM doesn't have tests, so tests should be done as per guideline when no EM is present		
14	SCM	Management	Could say "Do tests for Lyme disease in people (children or adults) presenting with facial palsy". A local audit of data in children in Southampton (known high incidence area) has shown approx. 45% Bells Palsy have Lyme positive tests – this is currently being prepared for submission for publication.		
15	SCM	4: [Evaluate persisting symptoms after first treatment course and during second course of antibiotics. Treat ongoing infection and/or seek additional professional opinions].	Evaluating the progression of symptoms under treatment in patients diagnosed by serology is therefore essential information to confirm or re-think the diagnosis …	A 6-week or more delay in starting treatment makes treatment failure more likely and these delays often happen because … 4. Children without visible symptoms (EM rash or Bell's palsy) are particularly vulnerable to delayed treatment as their	… The charity repeatedly receives pleas to advise patients (among whom children are heavily over-represented) who have had delayed diagnosis, 3 or 6 weeks antibiotics (or less) and are then refused further treatment despite continuing symptoms suggestive of active infection ..

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				symptoms are attributed to all kinds of other causes.	
Laboratory investigations to support diagnosis					
16	Lyme Disease Action	See comment 03			
17	RCPhys	We have liaised with our experts in Immunology and Infectious Disease and would like to make the following suggestions: … Ensure there are paired CSF and serum samples send for suspect neurological Lyme			
18	SCM	Correct the prevailing misconceptions about Lyme disease amongst health professionals	Patients are sometimes denied a blood test for Lyme disease and so critical early treatment is delayed.	Lyme Disease Action help desk has documented cases where patients have been told “It is just a fashionable disease” or “everyone thinks they have Lyme disease”. In the past doctors were led to believe that Lyme disease is easy to diagnose and easy to cure. This has led to a patient backlash with patients using overseas testing and treatment clinics. Only by acknowledging the clinical and diagnostic uncertainties will the conflict this has caused be reduced.	Lyme Disease Action helpdesk data.
19	SCM	People with symptoms suggestive of ongoing or chronic Lyme disease and who have had possible exposures to ticks anywhere in the UK (or overseas)	This emphasises the need to recognise that people can be exposed to ticks anywhere in the UK (not just the New Forest etc) and that 30% of Lyme patients cannot ever recall a tick bite. Some labs will not process samples unless a tick bite history is provided		

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		should be offered an approved test for Lyme disease, irrespective of whether they remember a tick bite.			
20	SCM	5: Order serology testing for all symptomatic suspected Lyme patients 6 weeks after possible tick bite, or 6 weeks after first test, even if first test result was negative. Do not delay treatment in cases of high clinical suspicion by awaiting test results.	Antibodies to Borrelia Burgdorferi take up to 6 weeks to develop, therefore testing too early after initial infection has high likelihood of producing a false negative result.	The need for a second test at the correct time is explained in the guideline but many doctors only order one test, with inappropriate timing.	Please see NICE guideline for Lyme disease diagnosis flow chart and accompanying recommendations
21	SCM	1: People with clinically suspected Lyme disease (LD), without erythema migrans, are offered a laboratory based screening test (ELISA)	See comment 11		
22	SCM	Re-assessment of serology test interpretation	Serology tests are the only ones currently available and it is clear that they miss some patients. These patients receive no treatment.	Care for patients with negative serology is non-existent and they face multiple, expensive referrals, being bounced back to their GP each time.	There are many scientific papers documenting cases of Lyme disease with negative serology. The test kits used in the UK specifically warn that early inadequate treatment, or treatment with steroids can abrogate the immune response and lead to a negative test result.

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23	SCM	See comment 15	There is no test of cure …	… Some doctors order repeat antibody tests after treatment (as a "test for cure" or checking if the first, positive test was correct.) …	
24	SCM	Diagnostic tests - ensure NICE guidance on strategy and hierarchy of tests applied across all parts of NHS England.	Are confirmatory tests as recommended in the document used? Does some of the distrust of results come from inadequate interpretation of results in the clinic room. Can these factors be improved.		
25	SCM	2: People with clinically suspected Neuro borreliosis (or Lyme disease affecting the peripheral or central nervous system) are offered lumbar puncture and CSF analysis	Lyme disease that affects the central nervous system, or Lyme Neuro Borreliosis (LNB), can have catastrophic consequences for the patient if left undiagnosed and untreated. Symptoms of LNB can be similar to many other conditions. It can be difficult to diagnose LNB based on symptoms and clinical examination only. Ruling out other differential diagnosis to LNB is important	CSF analysis requires lumbar puncture to be carried out, in hospital in the majority of cases. Access to specialist review and lumbar puncture, sometimes accompanied with imaging of the brain (CT or MRI) can be delayed or limited unless specific guidance recommending this diagnostic pathway is available. I am not aware of any audit in the NHS regarding this issue	European Federation of Neurological Societies (EFNS) guideline (2010) Cerebrospinal fluid findings in adults with acute Lyme Neuroborreliosis. Djukic et al. J Neurol (2012) 259:630–636 Suspected early Lyme neuroborreliosis in patients with erythema migrans. Ogrinc K et al. Clin Infect Dis. 2013;57(4):501
26	SCM	Cerebrospinal fluid examination	Is this performed as per recommendations? Are appropriate samples sent to the correct reference laboratories?		
Testing standards					
27	RCPath	NHS clinical microbiology laboratories should ensure that they have protocols in place that support the provision of a quality assured lyme serology diagnostic pathway.	The diagnosis of Lyme disease in patients without confirmed erythema migrans depends on reliable serological screening and confirmatory testing. Commissioners of healthcare	There is abundant anecdotal evidence of British patients who have been tested by commercial laboratories in the UK and abroad using incomplete or inaccurate tests for Lyme disease. This has led to missed alternative diagnoses and/or inappropriate and occasionally harmful treatment (e.g. Clostridium difficile disease from ceftriaxone). In addition, over diagnosis of lyme infection leads to inappropriate use of antibiotics and is an avoidable driver of antibiotic resistance	

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		Serological testing, whether locally provided or through a reference laboratory, should be UKAS accredited and reports to clinicians should highlight the need for any repeat testing in line with NICE guideline NG95, to ensure patients receive appropriate investigation of suspected infection.	services should be aware of laboratories that offer unaccredited diagnostic tests that can lead to wrong diagnoses and inappropriate, potentially dangerous treatment. Commissioners should only commission laboratory services from laboratories who offer UKAS accredited tests or who refer to accredited reference laboratories.		
28	RCPhys	We have liaised with our experts in Immunology and Infectious Disease and would like to make the following suggestions: • Ensure that all Lyme tests are done in CPA accredited laboratories • All positive tests done locally are referred to RIPL for confirmation …			
29	SCM	1: People with clinically suspected Lyme disease (LD), without erythema migrans, are offered a laboratory based screening test (ELISA)	… Only laboratories that are accredited by the UK accreditation service (UKAS), use validated tests and participate in a formal external quality assurance programme should be used in diagnosing LD.		
30	SCM	3: Information provision (verbal and in writing)	It is well recognized from clinical experience that patients who are concerned with having LD, may seek assessment from doctors and laboratories that are not recommended by national guidelines	From experience in seeing patients in clinic and from speaking to patient support groups on LD, as well as having been a member of the last NICE guideline (NG95) committee, it is clear that some patients feel	NICE guideline on Lyme disease, NG95, April 2018 Various publications, including third party sector guidance

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			These assessments and tests that are not carried out in centres that are accredited or validated for the diagnosis of LD, may falsely suggest a diagnosis of LD, as well as falsely ruling out the diagnosis of LD …	unsatisfied with the information and care given to them …	
Antibiotic management					
	Standardised antibiotic treatment				
31	CLC	1: GPs and A&E doctors should prescribe the correct antibiotics, without delay, at the correct dosage and duration for Lyme disease in all cases of Lyme disease diagnosis	Treatment failure is more common when the initial treatment is inadequate. Delay in treatment, low dosages and short courses all contribute to increasing the risk of treatment failure. Treatment failure is not always immediately obvious so complete routine initial treatment is critical.	In engagement with patients I encounter patient under-treatment several times per week - this is bound to be the tip of the iceberg. Doctors often appear to use the BNF and outdated sources. Frequently, correct antibiotic doses need to be worked out by charity and support group volunteers like myself (a retired pediatric specialist nurse practitioner helps with this) and parents advised to return, with the guideline, and ask for the correct dosage to be prescribed. Parents join the support group for general information and discover their children have been incorrectly treated.	Personal daily contact with patients in support groups. Patient testimonies. NICE 2018 Guideline for Lyme Disease treatment tables

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				Imagine if this happened to cancer patients? Examples: (Patient A) Mother of 2 who became increasingly ill after a bite with rash in February, prescribed 500mg amoxicillin 3x per day in June for symptoms consistent with Lyme disease. (Patient B) 18kg child with clear EM rash prescribed 250mg amoxicillin 3x per day. (Patient C) Woman with ~2 weeks history of 13cm EM rash, fatigue, fevers and concentration difficulty initially prescribed 10 days of doxycycline 200mg per day. (Patient E) Woman who had had 18 ticks removed by a hospital and who developed several EM rashes, was given 2 weeks doxycycline 200mg per day by a locum doctor. A&E departments more often give NICE dosages, but often only 1 week with the remainder to be prescribed by the GP. This is not always satisfied by the GP. Fairly often doctors prescribe clarithromycin, especially for	

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				children, at BNF dosages. They appear to do this when faced with the amoxicillin dosages which they think are “too high”. (Patient B) 18kg child with confirmed EM was prescribed 135mg clarithromycin 2x per day, after the mother complained that previous amoxicillin dose (see above) was below NICE guideline dose. Clarithromycin is not recommended by NICE, as not efficacious. (Patient F) 3 year old with an embedded tick bite on the head given a 4 day course of phenoxymethylpenicillin as a prophylactic.	
32	Lyme Disease UK	See comment 04			
33	Lyme Disease UK	3: Treatment: Antibiotic Choice, Duration and Dosage	Although evidence on effective antibiotic protocols is minimal, it is important for all doctors to follow the NICE guideline treatment recommendations to give newly infected patients the best chance of recovery and to try to prevent them from going on to develop chronic illness. The costs of missing early diagnosis and	In LDUK’s Online Community, we see many examples of people receiving inadequate treatment despite the existence of the guideline. People are either receiving too short a course of antibiotics or the dosage being prescribed is too low, particularly in the case of children. There seems to be resistance to prescribe a second course if a patient is still symptomatic	Doctors should be following the antibiotic tables in the NICE guideline for both adults and children. The NICE guideline states, in section 1.3.8, ‘Consider clinical review during or after treatment for Lyme disease to assess for possible side effects and response to treatment.’

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			treatment, to both patient and the NHS, are considerable. The guideline supports doctors when it comes to making an early diagnosis and administering prompt treatment and so they should feel confident following the guideline rather than holding back, especially when it comes to making a clinical diagnosis based on the symptom list and patient's history.	whereas the guideline recommends a second course. It appears as though people are not being told that they need to book in for a review with their doctor shortly prior to the course of antibiotics finishing even though the guideline recommends a clinical review. In some cases, there is a lag between the cessation of a first course of antibiotics and the prescription of a second course which could jeopardise recovery. Babies born to mothers with Lyme disease should also be closely monitored post- birth by the parents and medical professionals in case symptoms develop. Additionally, if people are still symptomatic after a second course of antibiotics, some are being told that it is impossible that they have an ongoing infection and further treatment is then denied. It is not possible to say with any certainty that ongoing infection is impossible as we do not have a test for cure for Lyme disease.	The NICE guideline states, in section 1.3.9, 'If symptoms that may be related to Lyme disease persist, do not continue to improve or worsen after antibiotic treatment, review the person's history and symptoms to explore: - if treatment may have failed' In Section 1.3.11, the NICE guideline states, 'Consider a second course of antibiotics for people with ongoing symptoms if treatment may have failed.' In Section 1.3.12, the NICE guideline states, 'Do not routinely offer further antibiotics' but this should not mean it is impossible to offer a further course if someone is improving on treatment and then relapses when it's withdrawn. In section 1.3.18-21 pregnant mothers are discussed. There is no mention of how the baby should be monitored to see if 'there is any suspicion of infection'. It also mentioned transmission is unlikely, however there is no research to support this.

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					In Section 1.4, the guideline states that 'Most people recover completely.' This statement is based on a piece of research where approximately 50% people recovered and this statement is therefore unsatisfactory and not very reassuring at all.
34	Lyme Disease UK	Additional developmental areas of emergent practice	From our Online Community, we know that some people do recover as a result of longer term antibiotics. For those people who see improvement after two courses of antibiotics but who then decline when treatment is stopped, doctors should not feel under threat by extending treatment as although the guideline says not to routinely offer further antibiotics, we believe in some cases it may be appropriate, for example where the start of treatment is delayed or treatment response is seen.		Research backing up effective antibiotic regimens for acute Lyme disease is lacking, let alone for chronic cases. There have been many studies showing persistence of the bacteria beyond short courses of antibiotics, even if this evidence is not in the scope of the NICE guideline process due to being older research or research on persistence which does not disclose a remedy. The lack of evidence encountered by the committee throughout the construction of the guideline only becomes obvious when reading the evidence reviews in the full version and is only briefly stated in the explanatory pages of the short version of the guideline. There are large gaps in critical areas, especially around Lyme disease prevalence, testing and treatment.

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					Yet, recommendations have been made in the face of this lack of evidence, often based on the experience of the committee members rather than science. This shows the clear and urgent need for more research. This lack of evidence is not obvious to doctors quickly scanning the guideline, during a 10 minute appointment. The weak evidence base should be clear at the top of the document and all patients should be made aware of how much research still needs to be done. We see plenty of anecdotal evidence in our Online Community of people recovering with longer term treatment. The guideline acknowledges the possibility of treatment failure and with no test for cure, it is not possible to be certain that after two courses of antibiotics, the bacteria has definitely been eradicated, especially if someone is still symptomatic. We have seen examples of people starting to improve after two courses of antibiotics but then

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					when treatment is withdrawn as per the NICE guideline, their health declines again. It therefore seems illogical, not to mention costly, for doctors to start chasing other diagnoses rather than extending antibiotic treatment with the aim of restoring the patient's health completely. We recognise that this goes against what the guideline says to do 'routinely', but doctors need to be able to use their clinical judgment in individual cases, especially as the guideline acknowledges treatment failure. NICE Guideline Section 1.3.9 states, 'If symptoms that may be related to Lyme disease persist, do not continue to improve or worsen after antibiotic treatment, review the person's history and symptoms to explore:..if treatment may have failed.' NICE Guideline section 1.3.13 states, 'Do not routinely offer further antibiotics and consider discussion with a national reference laboratory or referral to a specialist'. Perhaps if GPs, the laboratory and specialists hear

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					enough of people not recovering from two courses of treatment, there may be more of an argument for urgent research and extended courses of treatment, particularly as according to the NICE guideline, 'the evidence of the effectiveness of antimicrobial regimens used in different presentations of Lyme disease is of poor quality, outdated and often based on small studies.' It is not right that doctors who are using longer courses of treatment and who are getting chronically ill patients better are being labelled as 'charlatans.'

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35	RCGP	All patients who have a diagnosis of Lyme Disease are treated with 3 weeks (4 weeks for Lyme Arthritis) of doxycycline or amoxicillin at the correct dose	See comment 07		
36	RCPath	Patients with lyme disease requiring intravenous antibiotic treatment should be offered access to out-patient parenteral antibiotic treatment (OPAT) in order to avoid the need for admission to hospital.	Treatment of carditis or neurological lyme disease can necessitate up to 21 days of intravenous therapy with ceftriaxone. In patients who are minimally unwell, this should be given through an OPAT service to avoid unnecessary admission and to support patient convenience.	OPAT services are established in a growing number of secondary care settings in the UK. They benefit healthcare economies because they avoid the cost of admission. They also provide the benefit of convenience to patients. OPAT should now be seen as the standard of care for this and similar clinical scenarios.	
37	RCPhys	We have liaised with our experts in Immunology and Infectious Disease and would like to make the following suggestions: … Monitor the balance between oral versus IV therapy given for non-neurological Lyme …			
38	SCM	Patients who attend with a single erythema migrans (EM) lesion should be offered first line antibiotics for Lyme Disease without specific blood tests for Lyme disease	recognition and early management of illness without delaying for blood tests which may be negative		

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39	SCM	1: Treat Lyme disease with correct antibiotic, dosage and duration, as recommended in the NICE guideline	The evidence shows high treatment failure rates at lower doses and shorter durations. The need to prescribe the correct antibiotic for any infection is obvious.	Based on enquiries to the charity (which is a NICE recommended source of patient information on the guideline): 1. Some GPs prescribe the standard BNF dose of amoxycillin rather than the Lyme disease guideline dose which is roughly double this. 2. Some GPs prescribe 14 days instead of 21 days of doxycycline as first line treatment. 3. Some GPs prescribe clarithromycin, especially for children - which has no known efficacy for Lyme disease. 4. Some patients go to A&E with severe symptoms where there seems to be a policy of only prescribing 1 week of treatment with the intention that the GP prescribes the following 2 weeks - however some GPs then refuse to prescribe the rest of the course for various incorrect reasons. 5. Some patients with ongoing signs of infection after 21 days of doxycycline are referred to specialists, with treatment suspended, without being prescribed the second course of antibiotics recommended in the guideline.	1. Sources: NICE guideline for Lyme disease treatment tables & BNF
40	SCM	4: [Evaluate persisting symptoms after first treatment course and during	In Lyme disease, treatment failure is common and well documented. There is no	A 6-week or more delay in starting treatment makes treatment failure	[The charity repeatedly receives pleas to advise patients (among whom children are heavily over-

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		second course of antibiotics. Treat ongoing infection and/or seek additional professional opinions]	quantitative evidence on the failure rate of the protocols recommended in the NICE guideline…	more likely and these delays often happen because: … Doctors un unsure about EM rash and investigate by trial and error eg. steriod cream & antihistamines for a week, then flucloxacillin for a week, before Lyme is properly investigated. (During this time the EM may subside naturally and confuse diagnosis further)	represented) who have had delayed diagnosis, 3 or 6 weeks antibiotics (or less) and are then refused further treatment despite continuing symptoms suggestive of active infection].
41	SCM	See comment 13			
42	SCM	Management	Could say “People with single EM lesion with or without history of tick bite should be offered first line antibiotics for Lyme Disease without blood tests”. This is the most straightforward: if you have a rash diagnostic of Lyme then the NICE guidelines says treat with no tests. It would be good for the NHS to be able to count these.		
	Doxycycline and pregnancy				
43	RCGP	All women of childbearing age are asked about the possibility of being pregnant before treatment with doxycycline	See comment 07		
Non-antibiotic management					
	Reassessment				
44	CLC	2: Patients should be evaluated routinely and immediately at the end of antibiotic courses, in the knowledge that treatment failure happens and should	“Further antibiotic treatment is now recommended as an option if persisting infection is a possibility.” (NICE Guideline)	Doctors frequently make non-evidence-based statements that Lyme disease cannot persist past initial treatment, often when the initial treatment has not itself been	Sources: Personal daily contact with patients, including in support groups. Patient testimonies. NICE 2018 Guideline for Lyme Disease

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		be addressed with further antibiotics without delay	The committee acknowledged treatment failure. There is currently no test for cure or eradication of the infection. Allowing infection to persist at the end of the initial treatment is highly undesirable, as Lyme disease is known to be able to invade deeper tissues such as nerves and joints. It is important that doctors assess patients for clinical signs of treatment success or failure around the time the course of antibiotics finishes as a gap in treatment will reduce efficacy of the antibiotics. The guideline notes that this is an area with a dearth of relevant evidence and much uncertainty.	adequate as defined by the NICE guideline. Some doctors refer patients with ongoing symptoms after one course of antibiotics - the guideline says a second course of antibiotics is recommended. Thus it is common for patients to be left for weeks without treatment beyond the first course, with active infection. Patients are told by doctors that no further treatment is necessary but do not know that their fevers, fatigue, swollen glands and pains probably indicate ongoing infection. Often after weeks/months they ask their doctors/ our charity / Lyme Disease UK online patient forum for advice and find out. Delays in treatment mean that initial 21 day treatment is less likely to be adequate. Examples: Patient comment: “My almost 10 year old son was diagnosed with Lyme a week ago due to bullseye rash. GP has prescribed 21 days of doxycycline and doesn’t want to see him again.”	

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				Patient C: Patient with 13cm EM rash, treated with 21 days doxycycline (prescribed as 10 days, then 11 days) still has neck stiffness, swollen glands, fever, all-over aches, severe fatigue and concentration difficulties, but doctor does not prescribe a repeat course of antibiotics, instead consults ID clinic. ID clinic advises that patient has had recommended course so should not have more. GP refers patient to the clinic. Appointment is over 11 weeks later.	
45	ILADS	3: Better management of chronic infection with the potential need for long term antibiotics	Once identified above, we need better treatment strategies to improve outcomes and minimize antibiotic exposure	Supported by the literature (importance) **Supporting information:** 1. Dvorakova J, Celer V. [Pharmacological aspects of Lyme borreliosis]Ceska Slov Farm. 2004 Jul;53(4):159-64. 2. Kaiser R. Clinical courses of acute and chronic neuroborreliosis following treatment with ceftriaxone.Nervenarzt.2004 Jun;75(6):553-7. 3. Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infect Dis. 2002;34(6):421-5. 4. Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996 Jan-Feb;24(1):98-102. 5. Rohácová H, Hancil J, Hulinská D, Mailer H, Havlík J. Ceftriaxone in the treatment of Lyme neuroborreliosis. Infection. 1996 Jan-Feb;24(1):88-90.	

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				6. Embers ME, Barthold SW, Borda JT, Bowers L, Doyle L, Hodzic E, Jacobs MB, Hasenkampf NR, Martin DS, Narasimhan S, Phillippi-Falkenstein KM, Purcell JE, Ratterree MS, Philipp MT. Persistence of Borrelia burgdorferi in rhesus macaques following antibiotic treatment of disseminated infection. PLoS One. 2012;7(1):e29914. Epub 2012 Jan 11.	
46	Lyme Disease UK	See comment 6			
47	Lyme Disease UK	5: Diagnosis: Patients are assessed and evaluated for Lyme disease if they feel they have been infected for some time and are experiencing symptoms of the illness	The NICE guideline is useful for those who are newly infected with the disease but there is no guidance available for those who were bitten years ago and who were never treated promptly. It cannot be assumed that these patients will respond to the same treatment as acute cases.	In LDUK's Online Community, we hear of people, who have been ill for many years, going to their doctor with a wide range of Lyme disease symptoms and in some cases, a memory or photo of an EM rash, explaining that they were never treated at the time of the bite. Some are told that even if they had Lyme disease, it is likely to have gone away now. Others receive an IgM positive result and are told that there is no way they can have a chronic infection whereas Lyme behaves differently to other infectious diseases and IgM positives can occur later on in the illness. So, these patients are left with little choice but to seek out help from private doctors with experience of treating late stage Lyme disease, especially as there are no Lyme disease specialists	The NICE guideline states in section 1.3.13 that, 'Continuing symptoms may not mean they still have an active infection' and 'symptoms of Lyme disease may take months or years to resolve'. In the absence of a test for cure, it is not possible to give out this advice confidently. It is also hard to distinguish which symptoms are due to 'permanent damage from infection' when again, there is no test for cure to be certain that the infection has been eradicated. For those who were never treated, the prejudice around their choice to seek private treatment should stop when no other help is on offer. As the guideline states, 'the studies published on the management of Lyme disease use differing outcomes, which are often poorly defined' and 'the evidence of antimicrobial treatment

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				within the NHS. There needs to awareness and acceptance that Lyme disease can become a complex condition if left untreated and that some people are chronically ill with the disease. These patients should still be eligible for treatment or at least not be criticised for exploring other options when they are receiving no help on the NHS.	regimens used in different presentations of Lyme disease is of poor quality, outdated and often based on small studies.' The fact that some people recover with long term private treatment is evidence that more is needed to be done for those who are chronically ill, as this current guideline is not serving these patients. It is built on a very weak evidence base which is made clear in the recommendations for research which are extensive. At the very least, patients should feel able to make informed decisions about their care and be supported by their GP, for example their private Lyme doctor may recommend with routine blood tests that the NHS can offer.
48	SCM	3: Evaluate thoroughly for Lyme disease in symptomatic patients regardless of how long symptoms have been suffered.	Lyme disease is not usually (or ever) self limiting in symptomatic patients. Active disease (symptoms and positive serology) can be found after years of illness. Cure can be achieved in these people and they should be treated.	Some doctors mistakenly state that Lyme disease is self-limiting. The NICE guideline applies to all patients, regardless of the duration of symptoms prior to seeking help. Since the guideline has come out, I have not heard from any patient, with long-term prior symptoms, that they have	NICE Guideline

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			Some people (an unknown percentage) have Borrelia burgdorferi antibodies without having ever experienced Lyme disease symptoms - this is a separate issue from the assumption (without evidence) by some doctors that symptomatic Lyme disease is self-limiting.	been properly evaluated for Lyme disease by their GP. This leads to breakdown in doctor-patient trust which is damaging for all patients, including those who don't have Lyme disease. Because their case has not been properly evaluated they may: • Pay for lengthy antibiotic treatment pointlessly, • Cease to collaborate with NHS investigations seeking alternative diagnoses, • Avoid consulting their GP about other problems (including contagious ones)	
49	SCM	4: Evaluate persisting symptoms after first treatment course and during second course of antibiotics. Treat ongoing infection and/or seek additional professional opinions.	There is no test of cure. In Lyme disease, treatment failure is common and well documented. There is no quantitative evidence on the failure rate of the protocols recommended in the NICE guideline. Clinical evaluation of the patient and extension of treatment if necessary is the	The guideline intended doctors (mainly consultants) to make clinical decisions on when treatment should stop but it is almost always stopped after 6 weeks regardless of the outcome. There is often a wit of weeks or months before the specialist appointment, with the risk that an active infection may remain untreated for this time interval. Some doctors tell patients Lyme cannot persist beyond one	Unacceptably high treatment failure rates, from 25% to 49% in some papers, were reported in the research on 14-day treatment courses examined by the NICE guideline committee. Higher doses and longer treatment lengths were considered essential. The charity repeatedly receives pleas to advise patients (among whom children are heavily over-represented) who have had delayed diagnosis, 3 or 6 weeks

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			only way to improve outcomes. Antibody testing can produce positive results in some people for whom Lyme disease is not the cause of the current symptoms. Evaluating the progression of symptoms under treatment in patients diagnosed by serology is therefore essential information to confirm or re-think the diagnosis.	treatment course (contrary to the guideline) or two courses of treatment, despite evidence to the contrary. Some doctors order repeat antibody tests after treatment (as a "test for cure" or checking if the first, positive test was correct). Some doctors tell patients their ongoing and unchanged symptoms cannot be Lyme disease any more, they now have a different illness, and they are investigated for other illnesses, including TB/ types of cancer. A 6-week or more delay in starting treatment makes treatment failure more likely and these delays often happen because 1. the incubation period is up to 3 months. 2. Initial symptoms are often mild and slow to develop, 3. tick bites that people DON'T notice are more likely to pass on disease, because these ticks remain attached longer …	antibiotics (or less) and are then refused further treatment despite continuing symptoms suggestive of active infection. The BIA expressed its resistance to some areas of the NICE guideline, notably the 21-day courses instead of 14 days, and the higher dosing of amoxicillin, and the use of a second course of antibiotics. this may be influencing some doctors. These patients - I repeat most are children - are now undergoing extensive NHS testing for tuberculosis/cancers/autoimmune diseases/psychological analyses to seek a cause of their ongoing symptoms.
50	SCM	See comment 19			
	Specialist advice and referral				

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51	CLC	4: Specialists and microbiologists, who may give advice to GPs or accept patient referrals from them, should, except in exceptional circumstances, implement and support the NICE guideline recommendations rather than contradicting and over-ruling them	It is important that there is continuity of theory and practice at different levels and areas of the NHS. GPs, hospital specialists, laboratory staff and Public Health England scientists should be operating from the same evidence-based principles. It is inconsistent and undermines the belief that the NHS is competent to deal with Lyme disease if different parts of the system manifest different attitudes and practices. When patients encounter this situation they lose confidence in those treating them and it encourages them to seek help outside the NHS. Fundamentally, the NICE guideline is understood to represent the recommendations of a group of highly qualified professionals and lay-people who have reviewed the currently-available high-standard research and consulted with stakeholders.	Patients frequently see different practitioners within the NHS and PHE not implementing the guideline. Patients are being mis-treated/ under-treated, for an infection that can cause them permanent - sometimes life-altering - tissue injury including neurological / brain injury. Patients perceive the disagreement between doctors, lose faith and turn to other providers. Other diagnoses may be missed. Among GPs this is frequently lack of awareness, among specialists it is a "difference of opinion" from the guideline. The BIA commented on the draft guideline. “The length of the ‘short’ draft guideline makes it difficult to read even for specialists. The BIA position statement 2011 is a helpful short document.” “We recommend that the suggestion to consider referral of such cases with negative serology to an infectious disease specialist be removed.” Examples:	Sources: Personal daily contact with patients in support groups. Patient testimonies. NICE 2018 Guideline for Lyme Disease. NICE Draft consultation and comments published 11th April 2018

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			This is called into doubt when specialists in various fields contradict or refuse to implement it. There will always be a need for variation in medical practice according the situation of individual patients, but it is highly undesirable when different parts of the NHS are working to different principles.	(Patient D) ID specialist in renowned teaching hospital told suspected Lyme patient a) They would not prescribe a second course of antibiotics to any Lyme patient, b) Only 2 weeks of doxycycline are needed if a person has Lyme disease, c) An EM rash does not necessarily mean Lyme infection and is often caused by something else, d) They have no qualms about ignoring the NICE guideline, e) The ELISA test is very accurate, but the Western Blot is too general and therefore inaccurate, f) Anyone with Lyme will test positive at 8 weeks with an ELISA and if they do not, then they cannot have Lyme disease. (Patient A) Patient discharged from hospital with diagnosis of Post Lyme Disease Syndrome and recommending no further treatment. This term is not defined in research nor recognised in the NICE guideline. Patient had severe symptoms consistent with Lyme disease, with a history of EM rash a few months earlier, and had not received prompt or adequate treatment.	

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				(Patient B) Paediatrician at local hospital advised GP against giving full guideline dosage to a 4 year old with an EM rash, and recommended half the correct dose. (Patient C) ID clinic at Cambridge, told GP not to prescribe second course of antibiotics to a patient they had not seen. Patient had "had enough antibiotics". Patient had history of EM rash, had had 21 days treatment and still had clear, disabling non-focal symptoms. (Patient E) Senior scientist at PHE advised GP not to prescribe second course of antibiotics to a patient who had had 18 tick bites, several EM rashes, other Lyme disease symptoms, who had had 2 weeks doxycycline and 2 negative test results within 6 weeks of the bite.	
52	Lyme Disease Action	The development of a specialist Lyme disease service.	Specialist advice and possible referral is recommended within NICE guidance where the presentation is focal and complex. This is also recommended for all children and young people under the	This would help develop multi-disciplinary clinical expertise in secondary care and facilitate implementation of key research recommendations made by NICE. This would help develop case definitions specific for the UK and help record treatment outcomes.	NICE CG95 Lyme disease 2018 https://www.nice.org.uk/guidance/ng95/ Cottle et al (1) reported that the Liverpool Infectious Diseases Unit saw only 16 people with positive blood tests and 11 with confirmed

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			age of 18 who present with symptoms other than a single erythema migrans rash.	There would also be the facility to develop a bio-bank of patient samples for use in evaluating new tests.	erythema migrans during the 5-year period studied. Lyme disease in a British referral clinic Cottle, Mekonnen, Beadsworth, Miller & Beeching. QJM: Monthly Journal of the Association of Physicians June 2012
53	Lyme Disease Action	Development of regional specialist GPs whom colleagues could consult or refer to. This could be for confirmation of a rash, or other clinical presentations.	Most cases of early Lyme disease can be dealt with at primary care level. A delay in referring to secondary care can lead to serious complications.	The incidence of Lyme disease is such that GPs in some areas may not have experience. For example, in the W Midlands there were only 58 acute cases confirmed during 2017.	https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports#zoonoses
54	Lyme Disease UK	4: Education: Awareness of the guideline's existence	It is important that medical professionals are aware of the existence of the NICE Lyme disease guideline so that they are diagnosing and treating using up to date information. Doctors should also be taking the online e-learning module on Lyme disease created by the RCGP and Lyme Disease Action.	The NICE guideline along with the RCGP e-learning module on Lyme disease need to be more widely publicised as it appears as though many doctors are using outdated advice and are not aware of the guideline or the course's existence. It should not be up to patients to point out that the new guideline exists. We hear many reports from patients of doctors being seemingly confident in their understanding of Lyme disease and confident in dismissing the	In LDUK's 'Online Community', we see people sharing that their doctors were unaware of the NICE Lyme disease guideline and instead, were using old referral pathways. These must be removed or updated. Even when the existence of the guideline has been pointed out, it appears as though many doctors are still unable to follow it thoroughly resulting in misdiagnoses and inadequate treatment. The severity of the disease is downplayed in many areas of the

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				possibility of a Lyme infection. This is happening even in clear cases involving an EM rash, a history of tick exposure and a constellation of Lyme disease symptoms. We make this point to illustrate that some doctors are unaware of their own lack of awareness of the information in the new NICE guideline and this is unacceptable. This situation is compounded by the downplaying of the seriousness of Lyme disease in many aspects of the guideline, the reluctance of Infectious Diseases consultants to treat Lyme patients and the current lack of awareness from doctors in other disciplines including neurology, rheumatology and cardiology. Patients are falling through the cracks and being passed from specialist to specialist, often collecting numerous misdiagnoses and inappropriate treatment along the way. There are long-standing and common misconceptions about Lyme disease amongst medical	guideline, for example 'most tick bites do not transmit Lyme disease', 'tell women with Lyme during pregnancy that they are unlikely to pass the infection to their baby', 'most other symptoms associated with Lyme disease have other more common causes', 'continuing symptoms may not mean they still have an active infection' and 'most people recover completely.' This is at odds with the research used to create the guideline in which approximately 50% recovered and the horrendous suffering we see daily in our Online Community.

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				professionals and the general public that will be difficult to change without a concerted effort to communicate and to educate. The content of the new guideline must be thoroughly understood by all doctors. Patients also report that they were met with a hostile and emotional response from their doctors when they raised the possibility of Lyme disease. The politics and public perception of the disease is seeping into medical consultations and affecting patient care. The stigma surrounding the disease must come to an end. Leaving patients at best offended, and at worst misdiagnosed, under-treated or untreated, has severe consequences. Misinformation and lack of clarity must be a source of frustration for doctors and better education and awareness would aid the doctor/patient relationship and allow better conversations and care to take place.	
55	RCGP	All patients who have had 2 courses of antibiotics and	See comment 07		

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		are still symptomatic are referred to an Infectious Disease Consultant			
56	RCGP	Development of a specialist Lyme disease service	Specialist advice and possible referral is recommended within NICE guidance where the presentation is focal and complex. This is also recommended for all children and young people under the age of 18 who present with symptoms other than a single erythema migrans rash. GPs often report difficulty in accessing secondary care support when managing Lyme disease patients with chronic health problems.	There are no recognised specialist services for patients suffering from the long term consequences of Lyme disease. This would help to develop multi-disciplinary clinical expertise in secondary care and facilitate implementation of key research recommendations made by NICE. It would also allow audit of treatment outcomes.	NICE CG95 Lyme disease 2018 https://www.nice.org.uk/guidance/ng95/
57	SCM	Pathways for expert advice	Are these in place within the different regions of the UK? Would more formal pathways result in better and more speedier outcomes for the patient?		
58	SCM	Could say “People with neurological, cardiac or rheumatological features of Lyme disease should be discussed with and/or referred to an appropriate specialist (adult or paediatric care)”			

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59	SCM	Establishment of a specialist clinic for referral of complex Lyme disease cases	Patients undergo multiple referrals to different specialists and the diagnosis is often reached very late, if at all. NICE Guideline NG95 recommends referral to a specialist under certain circumstances but UK specialists have no experience of complex cases and this expertise needs to be developed.	Because this is an emerging disease in the UK (first reported case 1986) there is no specialist expertise. There is evidence from 2 retrospective studies (1,2) that infectious diseases clinics only consider sero positive cases. 1) Cottle, Mekonnen, Beadsworth, Miller & Beeching. Lyme disease in a British referral clinic QJM: Monthly Journal of the Association of Physicians June 2012 2) Dryden M, Saeed K, Ogborn S, Swales P. Lyme borreliosis in southern United Kingdom and a case for a new syndrome, chronic arthropod-borne neuropathy. Epidemiol Infect. 2014 May 9;1–12.	Quarterly figures show that between 22-47% of reported cases are late diagnoses. (1) There is no data on outcomes of late diagnosed cases. Lyme Disease Action help desk has documented cases of treatment failure. 1. https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports#zoonoses

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60	SCM	…. Treat ongoing infection and/or seek additional professional opinions.	In Lyme disease, treatment failure is common and well documented. There is no quantitative evidence on the failure rate of the protocols recommended in the NICE guideline … … Clinical evaluation of the patient and extension of treatment if necessary is the only way to improve outcomes. … Antibody testing can produce positive results in some people for whom Lyme disease is not the cause of the current symptoms. Evaluating the progression of symptoms under treatment in patients diagnosed by serology is therefore essential information to confirm or re-think the diagnosis	The guideline intended doctors (mainly consultants) to make clinical decisions on when treatment should stop but it is almost always stopped after 6 weeks regardless of the outcome. There is often a wit of weeks or months before the specialist appointment, with the risk that an active infection may remain untreated for this time interval …	The charity repeatedly receives pleas to advise patients (among whom children are heavily over-represented) who have had delayed diagnosis, 3 or 6 weeks antibiotics (or less) and are then refused further treatment despite continuing symptoms suggestive of active infection …. These patients - I repeat most are children - are now undergoing extensive NHS testing for tuberculosis/cancers/autoimmune diseases/psychological analyses to seek a cause of their ongoing symptoms.

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61	SCM	Patients with possible or probable complicated Lyme disease, especially those with neurological, cardiac or rheumatological features, should be discussed with and/or referred to an appropriate secondary or tertiary care specialist urgently [the urgency and its quantification could be for discussion]	This reinforces the need to have referral routes available, and to use them, for complex Lyme disease patients		
Awareness and information					
	Raising awareness				
62	ILADS	4: Better prevention of tick borne infections	PREVENTION is better than needing to treat		
63	Lyme Disease Action	Raising awareness generally with the pubic and healthcare professionals about ticks and the risk of Lyme disease	There is evidence that early tick removal reduces the risk of infection. NICE, PHE and voluntary sector organisations emphasise the importance of tick awareness and tick bite avoidance in the primary prevention of Lyme disease. This is important because currently there is no vaccine available for use in humans. It is also important to avoid prophylactic antibiotic treatment of simple	Lyme Disease Action is aware of limited knowledge in this area in the UK, including ignorance of correct methods of tick removal in NHS facilities, including emergency departments where patients may attend with ticks attached. Lyme disease is an emerging infection in the UK and other tick-borne diseases are likely to also become more common. A concerted public health approach in the Netherlands over many years shows a reduction in	Public Health England (2018) Tick awareness and the tick surveillance scheme. https://www.gov.uk/guidance/tick-surveillance-scheme Department of Health (2013) The UK 5 year anti-microbial strategy https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

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			tick bites as this would result in overuse of antibiotics.	GP consultations for tick bites and suggests stabilisation of early Lyme disease.	Decrease in tick bite consultations and stabilization of early Lyme borreliosis in the Netherlands in 2014 after 15 years of continuous increase. Hofhuis et al, BMC Public Health, May 2016; 16:425 doi: 10.1186/s12889-016-3105-y
64	Lyme Disease Action	Training and education about Lyme disease in primary care.	It is internationally acknowledged that early treatment is more likely to lead to complete recovery than late treatment. NICE guidance highlights the importance of raising awareness of Lyme disease in primary care in order to improve recognition and early diagnosis and treatment.	Lyme Disease Action has been contacted for help and support by a large number of patients in whose cases awareness of Lyme disease, recognition and the importance of early diagnosis and treatment in primary care appears to have been inadequate.	NICE CG95 Lyme disease 2018 https://www.nice.org.uk/guidance/ng95/ Unfortunately, there is no nationally collected data on outcomes. Quarterly reports on laboratory confirmed cases show that between 20% and 60% of cases in any one quarter are recorded as late diagnoses. https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports#zoonoses
65	Lyme Disease UK	4: Education: Awareness of the guideline's existence	See comment 05		
66	RCGP	Training and educational materials on Lyme disease - for GPs and other primary care clinicians All Primary Care Clinicians can identify Erythema Migrans (This includes	See comment 07		

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		GPs, Practice Nurses, Advanced Nurse Practitioners) NB The RCGP Clinical Innovation and Research Centre (CIRC) is presently engaged in a Spotlight Project - Raising Awareness of Lyme Disease in General Practice			
67	RCGP	Raising awareness of Lyme disease within all secondary care specialties	Lyme disease - The New Great Imitator may present with symptoms affecting any system at any age.	Lyme disease hospital diagnosis was recorded as having increased by 42% per year between 2011 and 2015 in England. Delayed or missed diagnosis may result in multiple clinical investigations with consequent health and social cost implications.	https://bjgp.org/content/early/2017/04/11/bjgp17X690497
68	RCGP	Additional developmental areas of emergent practice.	Evidence base for prevention and tick removal.		
69	RCGP	Raising awareness of the risk of ticks and Lyme disease within the general population and high risk groups.	The importance of tick-bite avoidance has been acknowledged by NICE, PHE and voluntary groups. Individuals have a vested interest in protecting themselves and their families.	Appropriate advice on tick-avoidance and correct tick removal should decrease the risk of an individual contracting Lyme disease. An awareness of the early signs and symptoms of lyme disease will increase the	Public Health England (2018) Tick awareness and the tick surveillance scheme. https://www.gov.uk/guidance/tick-surveillance-scheme

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			Simple information and advice would have significant beneficial outcomes and increase public confidence in the **self-management of asymptomatic tick bites.**	likelihood of early presentation of the disease in primary care.	
70	SCM	Prevention	Is the right preventative information reaching the at risk population?		
71	SCM	I cannot think of a suitable wording around patients with and without Lyme disease receiving appropriate educational literature but hope someone else can come up with a realistic and quantifiable suggestion			
72	SCM	Correct the prevailing misconceptions about Lyme disease amongst health professionals	See comment 18		
Information about diagnosis, management and follow-up					
73	SCM	Consultation:	Can quality of consultation be improved where there is patient concern caused by divergence between rest results from NHS approved laboratories and those that are not accredited. This is a major concern to many patients and as a consequence a burden for health providers		
74	SCM	Follow-up	Could say “People who have been diagnosed with Lyme Disease should be offered information regarding good outcomes following treatment” (following recent Danish BMJ publication – post NICE publication – showing excellent outcomes at 10 years in people of all ages with confirmed Lyme Disease in their central nervous system)		

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75	SCM	Information provision (verbal and in writing)	… Providing clear and easy to understand information for patients regarding the diagnosis and management of LD, and its pitfalls, at the time of assessment by the health care provider, is crucial so that patients can make an informed decision about their health.	From experience in seeing patients in clinic and from speaking to patient support groups on LD, as well as having been a member of the last NICE guideline (NG95) committee, it is clear that some patients feel unsatisfied with the information and care given to them. In patients who have been assessed as not having LD it is important to further investigate other causes and to continue to treat their symptoms. In patients who have been adequately treated for LD but still are symptomatic it is important to explain that symptoms may take time to resolve, and to continue to treat their symptoms Giving assurance and clear information can go some way to avoid the patient feeling let down by the health care system and hopefully avoid further unnecessary and potentially harmful practices. Verbal information by the health care provider, should be coupled with written information, such as patient information leaflets or advice on relevant websites for further information **Supporting information:** NICE guideline on Lyme disease, NG95, April 2018	
Additional areas					
Clinical epidemiology and research					

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76	CLC	Additional Developmental areas of emergent practice Systematic follow up of all patients with a Lyme disease diagnosis, with records made available for epidemiological and other research	There is currently no centralised database of Lyme disease patients' diagnoses, symptoms, treatment or long term outcomes. The experience base of UK doctors dealing with Lyme disease is too thinly spread over many doctors. A pooled data set could create a resource for doctors as well as researchers. Data of this kind would provide "real world" information which has been neglected in research projects, which have focused on non-representative patient samples (noted as "high risk of bias" in research quality evaluations using QUADAS.)		
77	RCGP	Development of a clinical epidemiological data base for Lyme disease in the UK - via 1) Review of long term outcomes in patients with PHE laboratory confirmed Lyme disease. 2) development of prospective studies via specialist Lyme disease clinics. 3) Use of the RCGP Research surveillance Centre (RSC) Data set in conjunction with PHE data to monitor numbers of patients with Erythema Migrans treated in primary care. http://www.rcgp.org.uk/clinical-and-research/our-programmes/research-and-surveillance-centre.aspx	NICE acknowledges the lack of robust epidemiological data on Lyme disease in the UK.	It is clear that a significant number of Lyme disease patients report chronic symptoms following treatment for Lyme disease. NICE guidance advocates a large clinico-epidemiological study on UK Lyme disease. However, this would take a considerable amount of time to develop. In the short term, follow up of PHE laboratory confirmed cases via regular questionnaires, over a two year period may assist in assessing the incidence of long term sequelae and the effectiveness of the present guidelines.	https://www.nice.org.uk/guidance/ng95/chapter/Recommendations-for-research#2-clinical-epidemiology-of-lyme-disease-in-the-uk

ID	Stakeholder	Suggested key area for quality improvement	Why is this important?	Why is this a key area for quality improvement?	Supporting information
78	SCM	1	Developing core outcomes for clinical trials	Poor evidence in general for managing lyme disease, evidence present often of poor quality and hard to reproduce. No one has a consistent 'end point' for which to measure success of treatment for example	Please refer to the NICE guidelines where this is referred to in more detail
79	SCM	2	Becoming a notifiable disease	I feel that it is hard to work out the incidence of lyme disease in the uk due to the fact it is not notifiable. We rely on numbers on confirmed laboratory testing – this does not take into account the treated cases of erythema migrans, or the cases where the diagnosis has not been tested for or missed. We need accurate figures especially as the incidence seems to be rising	See public health annual info re incidence of zoonoses
80	SCM	3: Evaluate thoroughly for Lyme disease in symptomatic patients regardless of how long symptoms have been suffered.	… Some people (an unknown percentage) have Borrelia burgdorferi antibodies without having ever experienced Lyme disease symptoms - this is a separate issue from the assumption (without evidence) by some doctors that symptomatic Lyme disease is self-limiting.	Some doctors mistakenly state that Lyme disease is self-limiting ...	NICE guideline

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Improving laboratory investigations					
81	ILADS	1: Improved lab sensitivity/specificity to better characterize ACTIVE infection of Bb infection and common co-infections: Babesia, Mycoplasma, Ehrlichia, Bartonella, Anaplasmosis, other	The present testing options are inadequate	Fundamental need	
81 cont'd	ILADS	**Supporting information:** Cameron DJ, Johnson, LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Review of Anti-Infective Therapy September 2014, Vol. 12, No. 9 , Pages 1103-1135 Treib J, Fernandez A, Haass A, Grauer MT, Holzer G, Woessner R. Clinical and serologic follow-up in patients with neuroborreliosis. Neurology. 1998 Nov;51(5):1489-91. Steere AC, Berardi VP, Weeks KE, Logigian EL, Ackermann R. Evaluation of the intrathecal antibody response to Borrelia burgdorferi as a diagnostic test for Lyme neuroborreliosis. J Infect Dis 1990 Jun;161(6):1203-9. Dvorakova J, Celer V. [Pharmacological aspects of Lyme borreliosis]Ceska Slov Farm. 2004 Jul;53(4):159-64. Kaiser R. Clinical courses of acute and chronic neuroborreliosis following treatment with ceftriaxone.Nervenarzt.2004 Jun;75(6):553-7. Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infect Dis. 2002;34(6):421-5. Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996 Jan-Feb;24(1):98-102. Rohácová H, Hancil J, Hulinská D, Mailer H, Havlík J. Ceftriaxone in the treatment of Lyme neuroborreliosis. Infection. 1996 Jan-Feb;24(1):88-90. Yrjänäinen H, Hytönen J, Hartiala P, Oksi J, Viljanen MK. Persistence of borrelial DNA in the joints of Borrelia burgdorferi-infected mice after ceftriaxone treatment. APMIS. 2010 Sep 1;118(9):665-73.			

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82	ILADS	2: Improved characterization of chronic active Lyme: Delays in diagnosis and Post treatment"	Failure to adequately characterize this cohort leaves MANY individual inadequately treated and often disabled		Supporting information: 1. Cameron DJ, Johnson, LB and Maloney EL Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease Expert Review of Anti-Infective Therapy September 2014, Vol. 12, No. 9 , Pages 1103-1135 2. Shor, S Retrospective analysis of a cohort of Internationally Case Defined Chronic Fatigue Syndrome patients in a Lyme endemic area Bulletin of the IACFS/ME.2011;18(4):109-123 3. Magni et al., Application of Nanotrap technology for high sensitivity measurement of urinary outer surface protein A carboxyl-terminus domain in early stage Lyme borreliosis Journal of Translational Medicine, doi:10.1186/s12967-015-0701-z http://translational-medicine.biomedcentral.com/articles/10.1186/s12967-015-0701-z
83	ILADS	5: Better dissemination of these BALANCED insights to: The medical community; Government agencies; the public			

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84	Lyme Disease UK	2: Testing and Clinical Diagnosis: Reducing the over-reliance on serology and increasing doctors' confidence in making a clinical diagnosis of Lyme disease …	…Many doctors don't appear to have heard of Babesiosis or Bartonellosis, for example and testing for these infections is also highly problematic …		There is a lack of acknowledgement or awareness of persistence of positive IgM positive test results in long term infection. Therefore, doctors dispute the possibility of ongoing infection, despite patients displaying symptoms of the disease and having a history of a tick bite, rash and/or tick exposure ..
85	RCGP	Additional developmental areas of emergent practice	Diagnostics of Lyme Disease by blood testing		
86	SCM	4	Improvement to laboratory tests	We have no specific test for active infection and no test of 'cure'. As the test is looking for an antibody response this can be mitigated by other factors and we also don't normal what sero-prevalence is in endemic areas	
87	SCM	3	Improving education for medical staff	Early diagnosis is the key, and considering this disease as part of your differential diagnosis. The knowledge base is still low	
88	BSAC	Responded. No comments submitted.			
89	RCN	Responded. No comments submitted.			
90	RCPCH	Responded. No comments submitted.			

List of stakeholders who responded at topic engagement:

- BSAC, British Society for Antimicrobial Chemotherapy
- CLC, Caudwell LymeCo Charity
- ILADS, International Lyme and Associated Diseases Society
- LDA, Lyme Disease Action
- LDUK, Lyme Disease UK

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• RCGP, Royal College of General Practitioners • RCN, Royal College of Nursing • RCPath, Royal College of Pathologists • RCPhys, Royal College of Physicians, England • RCPCH, Royal College of Paediatrics and Child Health					