Lyme disease

NICE National Institute for Health and Care Excellence

Consultation on draft guideline – deadline for comments 5pm on 6 November 2017 **email:** Lymedisease@nice.org.uk

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. We would like to hear your views on the draft recommendations presented in the short version and any comments you may have on the evidence presented in the full version. We would also welcome views on the Equality Impact Assessment. **We would like to hear your views on these questions**: 1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. 2. Would implementation of any of the draft recommendations have significant cost implications? 3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) 4. Do you agree with the committee's proposed recommendations to standardise dosage and duration of treatment across different presentations? 5. Based on explanations in the evidence reviews for the management of Lyme disease, is it appropriate for specialists to consider the use of doxycycline in children under 12? If so, should this be limited to children aged 9 and above or available for consideration in any child aged 2 or above? See section 3.9 of Developing NICE guidance: how to get involved for suggestions of general points to think about when commenting.

Lyme disease

NICE National Institute for Health and Care Excellence

Consultation on draft guideline – deadline for comments 5pm on 6 November 2017 **email:** Lymedisease@nice.org.uk

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Lyme Disease Action
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Comment number	**Document** (**full** version, **short** version or the **appendices**	**Page number** Or **'general'** for comments on the whole document	**Line number** Or **'general'** for comments on the whole document	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1.	Short	7	17	**Question 1.** **The recommendation to refer to a specialist for advice on seronegative cases** will have a big impact on primary care, secondary care and patients. As current practice is for a GP to tell a patient "Your test is negative, so you don't have Lyme disease" or "You have had adequate treatment, you cannot have the disease any more", this recommendation will lead to an increase in referrals and potentially long distressing delays for patients. Document 3, p186 l6 recognises the limitations of the tests, but there is an unjustified assumption that a specialist has the experience to help. Currently there are no specialists with the knowledge or experience of seronegative cases in the absence of erythema migrans, current infectious diseases consultants only treat those with positive Lyme serology. Although useful in some cases, synovial fluid and CSF analysis are not sensitive enough to rule out Lyme disease. Similarly the prevailing view among specialists is that re-treatment is neither necessary nor beneficial. If the guideline makes GPs feel unable to use their clinical judgement to prescribe, either in seronegative cases or in cases of relapse - section 1.3.10 - the decision passes to secondary care which is currently unable to help. This leaves the patient in a distressing situation.

Please return to: **Lymedisease@nice.org.uk**

				This will therefore be challenging to implement effectively and logically requires development of specialised clinics for Lyme disease with accompanying training and educational material. See answers to question 3.
2.	Short	22	11	**Question 1** **The recommendation to refer to a paediatric specialist.** Where is the evidence that paediatric specialists would know how to respond in this area of uncertainty as a result of absent evidence, and without understanding of the nature of the infection they are dealing with? If they extrapolate from existing knowledge about other bacterial infections, this is problematic. This comment applies to specialists dealing with all age groups. We note that one of the papers referenced as evidence for treatment of erythema migrans (Luft 1996) reported that suboptimal therapy with azithromycin was more likely to lead to patients being seronegative after treatment further complicating reliance on a serology- based diagnosis. As children with neurological Lyme disease often present with non specific symptoms there is a risk of compromised patient safety if specialists are not made more aware. It is reasonably clear from reading the draft guideline that the committee sought access to an expert with specialist knowledge of central nervous system infections, mainly bacterial encephalitis and meningitis in the acute medical setting, rather than specific expertise in the management of neurological Lyme disease as it typically presents and affects patients. This probably reflects the dearth of specialist expertise in the UK, dealing with all age groups, that Lyme Disease Action and patients encounter. It may be helpful for UK paediatricians to engage with the several paediatric specialists in Europe with considerably more experience of dealing with Lyme borreliosis.
3.	Short	20	16	**Question 1** **The recommendation that Lyme disease tests "need careful interpretation alongside clinical information**". Currently immunoblot results are automatically interpreted by machine, according to the manufacturer's algorithm, which applies an overall result of "positive" or "negative" according to pre-set criteria. The only interpretation that currently takes place is that laboratory staff will perhaps assess which scripted comment to apply depending on whether the result appears to indicate an early or late infection - either "if early in infection suggest re-test in 3 weeks" or "if late infection no further action necessary". The lab receives minimal clinical information and doctors who have both the patient and their medical records do not receive the full test results. See answer to question 3.
4.	short	general	general	**Question 3.** This charity Lyme Disease Action has developed a project brief for development of pilot specialised clinics for Lyme disease, using co-production methods as recommended by NHS England, the Kings Fund and the Health

				Foundation. This proposal is based on resources and experience, developed over several years working on case studies with Public Health England and clinicians, and involves careful interpretation of the detailed test results together with detailed patient history as recommended in Section 1.2.5 of the short guideline. These would help in the development of a working protocol for new specialised clinics to support complex Lyme disease patients and act as a resource for health professionals. See also the comment on document 13 page 6 line 12
5.	short	general	general	**Question 4** This seems sensible and allows for potentially more effective treatment in early cases which are sometimes currently treated with a sub-curative shorter courses, resulting in complications both in further testing and treatment. However, Lyme Disease Action has some concern that 21 days treatment may be insufficient in cases of late diagnosis of disseminated disease as the evidence shows a very low recovery rate together with incomplete recovery in a proportion of cases. Unfortunately data is not available to see whether those with poor outcomes have longer disease duration, although that is the published opinion of many experienced experts across Europe.
6.	3	52	15ff	**Question 5**. This seems appropriate, but we would suggest that a review is carried out to see whether staining of developing teeth is a consequence of exposure to sunlight during treatment, so that appropriate cautions can be issued if necessary. Treatment of Lyme disease is more likely to be during months when children will have greater exposure to sunlight. Lyme Disease Action does not have access to the information used by the committee to consider whether doxycycline should be extended to all children over 2. However we would like to caution that, as the committee noted, amoxicillin does not have such good penetration to the spinal fluid and so if doxycycline is contraindicated then IV ceftriaxone should be considered as first line treatment in cases of disseminated disease. This is in line with the committee's majority view of the rationale for giving doxycycline as first line treatment over amoxicillin for adults. Arnez et al 2002 reported that 25.7% of 214 children with multiple EM had abnormal CSF findings. Young children with neurological Lyme disease may present with non-specific systemic symptoms which may now be classified as "non-focal" (Broekhuijsen-van Henten et al 2011).
7.	Short	general	general	Because of the lack of current awareness of Lyme disease in doctors in the UK, many will refer to this guideline for diagnostic and treatment recommendations. It is important that the poor quality of evidence found by the review is highlighted in the short guideline so doctors are able to use their clinical judgement in the full light of the facts. There is otherwise a risk that doctors will assume that recommendations are based on good evidence, and will act accordingly. This will not help either patients or the NHS. The only place the limited evidence base is mentioned in the short guideline is in the Rationale and Impact section

				and the Research Recommendations. In a short appointment with a patient, doctors will not look there for treatment recommendations: they will simply refer to the tables.
8.	Short	1	3 (box)	2 other groups should be included in "Who is it for?" Change to- " **All** healthcare professionals, **for example** GPs, nurses**, physiotherapists**, specialists, microbiologists and **public health."**
9.	Short	3	6	amend to - including **urban** parks and gardens.
10.	Short	3	15	add bullet - Peak incidence occurs in June with a smaller peak in September but tick bites can occur throughout the year.
11.	Short	3	17	If someone picks the tick off with fingers or flat tweezers, thus squashing it, it may possibly increase the risk of transmission, so amend to ".. prompt, **correct** removal of the tick…"
12.	Short	3	21	add "**correctly**" at the end of the sentence
13.	Short	4	14	add bullet - "Erythema migrans can be challenging to diagnose on a dark skin and also when the appearance is atypical, such as a solid red rash, bruise-like and multiple EM rashes that may not be at the bite-site."
14.	Short	4	15	Sentence is difficult to understand. Suggest amend to - "Be aware that a rash which is not an erythema migrans can develop as a reaction to a tick bite. This: "(and then follow the bullets)
15.	Short	4	19	Change to "Is more likely to be hot, itchy or painful"
16.	Short	5	1	replace fatigue with "general malaise"
17.	Short	5	2	add new bullet "fatigue" because fatigue is pronounced in Lyme disease
18.	Short	5	4	Although doctors use the term "pain" patients will often talk about aches, so suggest re-phrase this bullet to "joint and muscle aches and pain"
19.	Short	5	15	insert "stroke-like symptoms" after neuropsychiatric presentations
20.	Short	5	16	cardiac problems are less common than arthritis, so for clarity, suggest move this bullet below arthritis. It may also be helpful to indicate that this may be an early complication, possibly the presenting problem, because although rare this is "red flag" territory and has been associated with Lyme-related deaths in a small number of young adults in the USA and at least one case in the UK.
21.	Short	5	17	add to the end of this "or multiple unexplained connective tissue inflammation"
22.	Short	5	20	Lyme disease usually affects more than one focal system. To help with clinical decision making, add at the end of this section "Bear in mind that Lyme disease is a multi system disorder".
23.	Short	5	24	after activities add "recreational or occupational"
24.	Short	6	2	To be clear, this should say "..or positive **NHS** testing.."
25.	Short	6	13	Amend algorithm: • After "No erythema migrans" insert a box "If high probability of Lyme disease, start antibiotic treatment according to symptoms as in section 1.2.17 • after "Offer Immunoblot test" on path "-ve immunoblot" insert box "Carefully interpret detailed test results alongside clinical history to assess probability of Lyme disease"
26.	Short	6	13	The committee noted in document 3 page 189 line 13-15 that "No studies were on UK populations. There is a strong potential of the results being an overestimate of the true sensitivity and specificity values due to the way case-control

				studies are conducted." and that the evidence was low or very low quality. As in our comment on the short guideline p 9 line 10, doctors need to know the limitations of the evidence base. We would suggest that this is pointed out at the top of the algorithm and at the beginning of this section.
27.	Short	6	20	Remove "to confirm diagnosis of Lyme disease" and replace with "for further testing". The immunoblot does not do this and to state that it will confirm or rule out gives a false impression of the accuracy of the test
28.	Short	6	24	Replace "likely" with "possible". The current wording appears to foreclose on Lyme disease and there is a danger this may lead to a considerable delay in treatment. Treatment of Lyme disease is less effective when late.
29.	Short	7	15	Insert "If ELISA or C6 EIA is positive, but immunoblot is negative, review clinical history and detailed immunoblot, to enable a clinical decision on the probability of Lyme disease." This is as recommended on page 20 line 16 that tests "need careful interpretation alongside clinical information". The review (document 3 p190 l3 states "there was no clear advantage of ELISA tests over immunoblots and vice versa." In addition an ECDC review found there is evidence that commercial ELISAs are as sensitive as and more specific than immunoblots. (Leeflang et al The diagnostic accuracy of serological tests for Lyme borreliosis in Europe : a systematic review and meta-analysis . BMC Infect Dis. BMC Infectious Diseases; 2016;16.) This important review also called into question the presumed accuracy of Lyme serology tests both in early localised Lyme disease and later stages, as well as the general low quality of such studies and the need for further research in a clinical "real-world" setting in which the tests are used.
30.	Short	7	23	Add a new bullet " - consider pragmatic treatment." This is an important point to maintain patient safety because of the known limitations of serology (page 8 line 21). Tests should not be used beyond their limitations and beyond their intended purpose.
31.	Short	7	24	change 1.2.20 to "Be aware that because antibodies can be detectable for some years, positive serology does not necessarily mean that Lyme disease is the cause of current symptoms."
32.	Short	8	16	add bullet: "the person has received inadequate antibiotic treatment very early in infection as this may cause a temporary inhibition of antibody production."
33.	Short	9	3	After "central nervous system infection" add "ophthalmic involvement eg uveitis" as uveitis is considered a "red flag" symptom.
34.	Short	9	4	replace "is likely to be the underlying cause" with "suspected" - to reflect wording on p22 line 6
35.	Short	9	10	It is important that it is clear to clinicians that there are significant limitations to the evidence base as this will help inform clinical decisions. Suggest insert "Evidence for treatment recommendations was all of low quality and particularly in Lyme neuroborreliosis showed low rates of cure. Clinical judgement of treatment response is important and clinicians should discuss with a specialist if in doubt." The committee has stated in the evidence documents that "*There is currently insufficient quality evidence on the most effective drug and dose, and the effectiveness of extended treatment or retreatment regimens in those with continuing symptoms remains uncertain*". Treating clinicians, who are unlikely to look at the long documents, need to be aware of this.
36.	Short	9	18	A Jarisch-Herxheimer reaction in Lyme disease often (unlike in syphilis) will take place later in treatment - Oksi et al 2007 DOI: 10.1007/s10096-007-0340-2 and it is important that clinicians and patients are aware of this and do not

				terminate treatment. Amend this bullet to "If symptoms worsen during treatment…"
37.	Short	10	table 1	It is not clear whether "Erythema migrans" means "erythema migrans in the absence of other symptoms"
38.	Short	10	table 1	Lyme disease affecting the central nervous system. Suggest course completion of intravenous ceftriaxone 21 days rather than switching to oral doxycycline. Continued recovery from Lyme disease, which may cause chronic infection cannot be assumed after swapping over to oral antibiotics, as used with acute bacterial infections. In the case of acute infections, relapse would be quickly apparent but this could well be over a longer time-frame for Lyme disease, and although possibly more subtle would have serious consequences for the patient.
39.	Short	10	table 1	Patients with Acrodermatitis chronic atrophicans often have not only a peripheral neuropathy but abnormalities within the cerebrospinal fluid, implying central nervous system involvement. In this case, intravenous ceftriaxone 4g daily for 28 days should be the "Treatment" with doxycycline 200-400mg per day as first alternative, amoxicillin 1g 3 times daily for 28 days as second alternative.
40.	Short	10	table 1	Carditis and haemodynamically unstable: Suggest course completion rather than switching to oral doxycycline when haemodynamically stable. Continued recovery from Lyme disease, which may cause chronic infection cannot be assumed after swapping over to oral antibiotics, as used with acute bacterial infections. In the case of acute infections, relapse would be quickly apparent but this could well be over a longer time-frame for Lyme disease, and although possibly more subtle would have serious consequences for the patient
41.	Short	10	table 1	If 28 days recommended for arthritis, because of the reduced penetration of antibiotics to synovium & synovial fluid (page 25 line 26) the same recommendation should apply to those with evidence of connective tissue inflammation as these tissues pose the same constraints.
42.	Short	10	table 1	See comment on page 14 line 2 and consider altering footnote on pregnancy:
43.	Short	11	table 2	31 Reliance on focal vs non focal symptoms in children may be particularly problematic. Young children with neurological Lyme disease may present with non-specific systemic symptoms ie "non-focal" (Broekhuijsen-van Henten et al 2011).
44.	Short	11	table 2	Intravenous ceftriaxone should be included as an option for early Lyme disease affecting the cranial and peripheral nervous system which has failed to respond to treatment with 21 days of amoxicillin treatment. The aim would be to maximise the chance of cure, and prevent progression of early to late-stage disease.
45.	Short	12	10	Suggest two additional bullets • "if relapse may have occurred". ie relapse of symptoms of Lyme disease before resolution and recovery have been achieved. This is relevant for a significant sub-group of patients as the evidence has shown. The uncertainty about relapse and treatment-failure was one of the top 10 priorities for research in the Priority Setting Partnership conducted by Lyme Disease Action and the James Lind Alliance http://www.jla.nihr.ac.uk/priority-setting-partnerships/lyme-disease/downloads/Lyme-Disease-PSP-spreadsheet-of-data.pdf • "if symptoms may be caused by autoimmunity related to Lyme disease." As stated in this document, page 6, line 8. Research into the prevalence of relapse and into autoimmunity should be included in **research recommendation** 2.
46.	Short	12	11	Suggest change "If the person's history suggests re-infection" to "if a person's history suggests re-infection or relapse

				of infection."
47.	Short	12	16	Within the context of persisting symptoms related to Lyme disease, Lyme arthritis would normally not just be considered as a "focal" symptom, but referred to as either early, late (duration greater than 6 months) or even refractory Lyme arthritis. It is important to recognise that late Lyme arthritis may be associated with neurological Lyme disease with neurological symptoms and abnormalities on lumbar puncture. In this case it would be important to recommend treatment with intravenous ceftriaxone.
48.	Short	12	17	Add "use clinical judgement to consider the higher dose of doxycycline or the use of IV ceftriaxone if neurological symptoms are present"
49.	Short	12	20	The recommendation to refer to a specialist will not currently be useful unless a specialised service is established. In the absence of erythema migrans, current infectious diseases consultants only treat those with positive Lyme serology.
50.	Short	13	2	add bullet as further explanation "there is currently no test which will differentiate"
51.	Short	13	4-7	For comment on social care and social services see comment on document 13 page 6 line 12
52.	Short	13	15	This list should contain another bullet referring to NICE Clinical Guideline 91: 'Depression in adults with a chronic physical health problem: recognition and management'.
53.	Short	13	19	add bullet "referral to physiotherapy for management of joint and neurological symptoms to assist in prevention of disability"
54.	Short	14	2	Recommendations for pregnant women should recognise that they will have an altered immune response, tending to be more immune tolerant. Also the pregnancy itself may be compromised by Lyme disease and this is thought to be a greater risk in the first trimester than in later stages. This together with the difficulty of using oral doxycycline means European experts tend to use ceftriaxone for disseminated early and late-stage Lyme disease in pregnancy (Poster presentation International Tick-borne Disease Conference, Vienna, September 2017, Franc Strle et al "Management of multiple erythema migrans in pregnancy ".)
55.	Short	14	17	alter to "most people recover if treated appropriately and promptly" (some trials on disseminated disease showed less than 50% response rate so "most recover completely" is false.)
56.	Short	14	18	move above previous bullet and replace "developing and increases the chance of complete recovery" with "and persistent infection"
57.	Short	15	3	move section 1.4.3 forward to after 1.4.1 as a more logical place
58.	Short	15	20	Suggest including some assessment of immune function in clinical assessments and outcome measures eg T-cell subsets. Also suggest consideration for assessment of autonomic function and cognitive neuropsychological testing to further investigate so-called "subjective symptoms". Suggest a long term follow up of late diagnosed cases. See comment on Short guideline page 35 lines 15-17 and document 6 page 15 line 21.
59.	Short	15	22	There is a need for further research into how best to treat autoimmune aspects of Lyme neuroborreliosis as there are hardly any studies in this area. There has been a tendency to concentrate on autoimmunity within the context of Lyme

				arthritis, possibly because this is more easily visible and accessible clinically. **A research recommendation** in this area would help address uncertainty about treatment and validate that patients suffering such symptoms are worthy of recognition and further study. See comment re document 7 page 23 line 18.
60.	Short	16	2	Document 13 page 7 line 5/6 states "The review question on the management of non-specific symptoms related to Lyme disease did not identify any studies in people with non-specific symptoms in the early stages of Lyme disease". The lack of recognition and documentation of non-specific symptoms in early Lyme disease is a problem and would warrant further study as part of **research recommendation** 2. This could help with case definitions for early Lyme disease, especially those without an erythema migrans rash who were previously fit and well prior to onset of the "non-specific symptoms", and for whom diagnostic tests in current use may lack sufficient sensitivity (Leeflang et al 2016). This was of the top 10 priorities from the Priority Setting Partnership organised by Lyme Disease Action with the James Lind Alliance which have been identified for further research and submitted to the National Institute for Health Research (NIHR): http://www.jla.nihr.ac.uk/priority-setting-partnerships/lyme-disease/downloads/Lyme-Disease-PSP-spreadsheet-of-data.pdf The possibility that persisting symptoms may be caused by autoimmunity should also be considered under this **research recommendation**. (Document 13 page 6 line 8)
61.	Short	17	16	See comments on • document 7 page 19 line 4, with research recommendation into treatment of people with persisting symptoms • document 7 page 24 lines 28,29 on research into neuroborreliosis treatment. • document 8 page 18 line 16 - Lyme arthritis follow up and treatment • document 13 general - treatment in relapse or persisting symptoms
62.	Short	18	10	Possible abrogation of the immune response is an important area for investigation as it has a potential impact on diagnosis. We would suggest that this formed a separate **research recommendation**. Core outcome sets (currently R 1) could be devised as part of research recommendation R 4.
63.	Short	19	8	As significant uncertainties in epidemiology, change this to "Furthermore the number of people diagnosed with Lyme disease is currently relatively low, although true numbers are unknown."
64.	Short	19	13	As reported elsewhere the true epidemiology is not known. Change this to "Lyme disease has a varied presentation with symptoms overlapping those of other diseases and conditions so it may sometimes be difficult to identify" - it is this aspect which makes it difficult to identify.
65.	Short	20	16	"Careful interpretation" is often needed but there is no evidence that this happens in clinical practice. Immunoblot results are interpreted by the machine and given an overall result of "positive" or "negative". The only interpretation that currently takes place is that lab staff will perhaps assess which scripted comment to apply depending on whether the result indicates an early or late infection - either "if early in infection suggest re-test in 3 weeks" or "if late infection no further action necessary". The lab receives minimal clinical information and doctors who have both the patient and their medical records do not receive the full test results.

				Question1: This will be challenging to implement as in neither case is "careful interpretation alongside clinical assessment" currently carried out and this will be a change in practice. As it is needed, we would suggest working with Lyme Disease Action, which has successfully used careful interpretation of the detailed test results together with detailed patient history, working with PHE and clinicians to achieve a good outcome.
66.	Short	21	6	An immunoblot cannot "rule out or confirm diagnosis". Rephrase to "..and an immunoblot should be carried out to further look for evidence of an immune response to the disease." This applies to all other documents where this phrase is used.
67.	Short	22	5	insert uveitis
68.	Short	25	3, 20	Doxycycline 100mg does not come in weekly packs. It is available in packs of 8 or 50. If the requirement to make prescriptions efficient overrules the requirement to provide the evidence based treatment of 30 days, then 29 days can be achieved with a pack of 50 plus a pack of 8. This also minimises packaging
69.	Short	29	30	The evidence on neuroborreliosis showed a significant percentage of patients with recurrent symptoms - eg Ljostad et al 2008 59% did not reach total recovery. Given the lack of information on UK epidemiology it is probably not possible to be certain there will be no resource impact.
70.	Short	29	9	It is more correct to say "because of lack of data available in existing trials and lack of trials on repeat treatment". Several trials, with less than 100% recovery rate, report that some patients were re-treated, but detail is unavailable. So it is apparent that re-treatment works, but the detail of re-treatment is unavailable.
71.	Short	29	30	There is no information on the number of people with recurrent symptoms. Suggest rephrase to ". would be unlikely to result in a significant resource impact."
72.	Short	34	9	There is no evidence that infection with B burgdorferi can go unnoticed. This assumption, which has no place in an evidence based guideline, is based on some people having antibodies to the bacteria but never having been diagnosed with Lyme disease. Given that symptoms can simply be 'flu like and that people can recover without treatment, this is not surprising but cannot be used to infer that their undiagnosed illness was "unnoticed". This sentence and the next should be deleted, as it has already been stated in this section that Lyme disease is caused by *B burgdorferi*.
73.	Short	34	15-17	We appreciate the need to avoid poorly defined terms, however, localised v disseminated and early v late are terms well used and agreed upon. This matters because it is this as much as the organ system affected which influences treatment choice and prognosis. The BNF uses the term "disseminated" so adopting this term would avoid confusion in a clinical setting where the BNF is a key source of information for prescribers. Consideration needs to be given to a **research recommendation** to follow up diagnosed cases of late disease.
74.	Short	34	20	The statement about "evidence-based advice" needs qualification by acknowledging the limitations of the available evidence. Suggest adding to the end of this sentence "…, but the guideline committee recognises the poor quality of the available evidence."
75.	Short	34	25	add to the end of the sentence ".., and to investigate diagnostic tests and treatment options."
76.	1	6	2	It might be helpful to state "…cases of laboratory-confirmed Lyme disease have increased since the first report in the

				medical literature in 1986." Williams et al Lyme disease in a Hampshire child- medical curiosity or beginning of an epidemic? Br Med J. 1986;292(June):1560–1.
77.	2	6	19	Is there a reason why the classic triad composing Bannwarth's syndrome was not included in the PICO characteristics? Some of the symptoms that were used are either extremely non-specific on their own (eg arrhythmias) or very rare (lymphocytoma).
78.	2	23	9	The NeBoP score showed high sensitivity and high specificity. Consideration should be given to exploring the use of this in children in the UK given the difficulties of diagnosing neuroborreliosis in children. Young children with neurological Lyme disease may present with non-specific systemic symptoms and there is the danger they may not be treated appropriately if doxycycline is contraindicated. See also our comments 2 and 6.
79.	3	142, 152	general	Index tests on CSF are not included in the PICO for confirmatory tests except for PCR and CXCL13. What about white cell count, protein, and immunoblots as applied to CSF. Also what about the antibody index as used widely in Europe?
80.	3	186	4	A repeat immunoblot cannot "rule out or confirm diagnosis". No test can currently rule out Lyme disease and the only test which can confirm it is culture and this is not used for diagnostic purposes in the UK.
81.	5	51	38-41	As azithromycin does not penetrate the spinal fluid, caution should be used with children who may not appear to have neurological symptoms. See comment 2.
82.	5	52	29	A Jarisch-Herxheimer reaction can also occur late in treatment (Oksi 2007). To say "It is an unusual reaction" is perhaps unsafe and may lead doctors to discontinue treatment when this happens. The evidence in the papers included in this document show Jarisch-herxheimer reactions occurring in between 16% and 24% of people. It might be safer to explicitly provide these figures so a GP can decide on fact rather than a subjective word like "unusual". The aim is to ensure that treatment is not terminated unnecessarily.
83.	6	15	31	Given the past and current lack of awareness in the UK, there are many patients who present with late Lyme disease a long time after an erythema migrans which was not recognised as such by either patient or GP. These patients are likely to have been through many investigations and referrals to find the cause of multi-system non-specific symptoms. This guideline aims to prevent future cases, but there are likely to be many existing cases. It is widely accepted that late diagnosed cases have a poorer outcome. Investigation of these patients should be the subject of a **research recommendation** with recruitment into a trial to include assessment of serology evolution, response to treatment, immune dysfunction etc.
84.	6	16	13	Re azithromycin use: see comment 2 re. concerns on use of azithromycin in children with non specific / "non-focal" symptoms. It was noted in document 5 page 46, line 19 that azithromycin does not penetrate the spinal fluid and this is clearly important if a child, diagnosed with "non focal" symptoms, has neuroborreliosis.
85.	7	6	7	Suggest "a wide range of possible neurological presentations" instead of "number of" as the latter could be interpreted as restricted to the examples given.
86.	7	6	8	Suggest "painful sensory and motor radiculopathy" to explicitly state that sensory changes and weakness may occur in addition to pain.
87.	7	6	11	Instead of "type of neuroborreliosis" which is vague, we would suggest specifying the "site and stage of infection ie

				whether early Lyme neuroborreliosis or late-stage Lyme neuroborreliosis, in each case specifying whether the peripheral or central nervous system is affected."
88.	7	18	9	Patients and carers may be trained in safe administration of OPAT which may reduce the need for day patient attendance to 5 days during commencement of therapy and the initial training period, followed by once weekly attendance. There is evidence this reduces the risk of hospital acquired infection and it would reduce the cost of OPAT and be more convenient for the patient.
89.	7	19	4	Only 7 studies, low and very low quality are eligible for inclusion for this important section of the guideline. This represents a very small total population of only 368 patients over 30 years of Lyme disease research worldwide. Included studies show marked differences in inclusion/exclusion criteria and outcome measures, and marked heterogeneity of selected study populations on important aspects such as age, early vs late Lyme neuroborreliosis (duration longer than 6 months) and site of infection. They mainly include subjects with early Lyme neuroborreliosis or that involving the peripheral nervous system. Outcome measures show that response rates vary with low rates of cure, and are particularly poor in those who are diagnosed late; in many of the studies some patients were retreated. It is clear that the best treatment requires a **research recommendation** as a priority. It may be risky to extrapolate from treatment studies of mainly early Lyme neuroborreliosis to late-stage disease.
90.	7	22	7	Extrapolating data and clinical experience of treatment from syphilis to Lyme disease may be useful but should come with a caveat with regard to the prospect of bacterial clearance. Antibiotics do not completely eradicate all bacteria but rely on immune clearance, especially doxycycline which is bacteriostatic. As a vector-borne zoonotic infection, Borrelia has successfully evolved a wide range of extremely effective responses to immune attack by means of differential gene transcription in order to survive in the tick vector and a wide range of potential animal hosts. Phenotypic antibiotic tolerance which has been demonstrated as a feature of Borrelia, has been proposed as a clinically important side-effect of evolutionary fitness. (Cabello et al 2017)
91.	7	22	2	Children with Lyme disease affecting the nervous system may not present with neurological symptoms.
92.	7	22	24	See comment on Short guideline page 22 line 11
93.	7	23	17	Antibiotics do not completely eradicate all bacteria but rely on immune clearance, especially doxycycline which is bacteriostatic. As a vector-borne zoonotic infection, Borrelia has successfully evolved a wide range of extremely effective responses to immune attack by means of differential gene transcription in order to survive in the tick vector and a wide range of potential animal hosts. Phenotypic antibiotic tolerance which has been demonstrated as a feature of Borrelia, has been proposed as a clinically important side-effect of evolutionary fitness. (Cabello et al 2017) So treatment may not eliminate the bacteria and there is emerging scientific evidence for phenotypic persister cells being a possible cause of persistent symptoms. Immune dysfunction and autoimmunity, as a result of inflammation and damage to nervous tissue has been well-documented. It is currently not possible to know for any one patient how far symptoms are related to bacterial persistence, immune dysfunction or tissue damage. This leads to heterogeneity in clinical cohorts, methodological difficulties in a research setting and problems extrapolating from this to a clinical setting.

94.	7	23	18	Re: “nerve damage taking an extended period to improve or resolve” This is a repeated theme, with the committee not appearing to fully recognise the potential profound impact of inflammation in peripheral and central nervous tissue resulting in demyelination and a vicious circle of autoimmunity as a result. Whilst early Lyme neuroborreliosis, once effectively treated may take time to resolve, it does not necessarily follow that it will continue to do so if the burden of inflammation is too high. Patients whose symptoms do not improve or resolve following treatment for Lyme disease need better care and treatment but currently may face stigma, prejudice and discrimination, often associated with a dismissive response from doctors. There is a need for further research into how best to treat autoimmune aspects of Lyme neuroborreliosis - see comment on research recommendation R2
95.	7	23	27-33	Studies with experimentally induced acute Lyme neuroborreliosis in Rhesus macaques show marked reduction in inflammation with dexamethasone (Ramesh et al 2015). This may warrant **further research** at some stage rather than being foreclosed.
96.	7	24	22	See comment on page 18 line 9 re. reduced OPAT costs.
97.	7	24	28,29	With such a limited low quality evidence base including so few patients in total, it is not possible to absolutely conclude that intravenous antibiotics are not superior, and whether they may be superior for certain cohorts eg late-stage and pregnant patients. Only 3 out of the 7 selected studies compare intravenous with oral antibiotics and only 1 compares the recommended intravenous antibiotic, ceftriaxone 2g daily with oral doxycycline 200mg daily and that has a very poor outcome. It is not possible to come conclude that there is “no evidence” that intravenous ceftriaxone is more effective from this one small study. The study population is Norwegian which may not be applicable to the UK as Norway has different prevailing genospecies of Borrelia: a higher prevalence of Borrelia afzelii compared to B. garinii, whereas the reverse is true for the UK, as far as is known. The mean study age is 54 and 52 years for doxycycline and ceftriaxone respectively, and so may not be applicable to younger adults, paediatric or pregnant sub-groups. There was a high rate of “coexisting diseases” in each group (41% for doxycycline 29% for ceftriaxone) and the clinical scoring system devised has not been validated for use in Lyme disease. This scoring system was self-assessed as appropriate by the study authors and hence prone to bias. Both antibiotics are known to have a range of other pharmacological effects eg. immune-modulatory effects, and so there is the possibility of improvement of some other coexisting disease, particularly in the doxycycline group where 41% had coexisting disease of some form. The recommended dose of ceftriaxone used in the study by Ljøstad at al is 2g daily, which is half that recommended by NICE for patients with central nervous system symptoms. Treatment duration was 14 days and outcomes were generally poor and did not achieve cure in 59%. This issue requires **further research** and verification within a UK setting. Absence of evidence is not evidence of

				absence.
98.	7	24	44	Continued recovery from Lyme disease, which may cause chronic infection cannot be assumed after swapping over to oral antibiotics, as used with acute bacterial infections. In the case of acute infections, relapse would be quickly apparent but this could well be over a longer time-frame for Lyme disease, and although possibly more subtle would have serious consequences for the patient.
99.	7	24	45	Re: "bioavailability of doxycycline" This is not the only issue to be taken into account with doxycycline and may not be the main factor involved in doxycycline failure. There is evidence of phenotypic tolerance to some antibiotics.
100.	7	24	46	The risk of line infection, although serious may be over-rated in terms of frequency of occurrence.
101.	7	24	48	Re "non-compliance". This sounds judgmental and narrow. It is more acceptably stated as "non-adherence". People stop medication for a variety of reasons, not necessarily through non-compliance with medical advice.
102.	7	25	37-40	Re: "the potential to be catastrophic" This not only applies to clearly demonstrable central nervous system involvement with Lyme disease as the patient representatives on the committee will have testified. Significant pain, fatigue, a relapsing remitting pattern of multi-system symptoms, which may or may not be subjective; the nature of which are poorly understood, are a key feature of the chronic illness state. The end result is experienced by Lyme disease patients and their families as "catastrophic". This has not been given sufficient recognition in this draft guideline. There is a risk that Lyme disease will be seen as only to be taken seriously if it involves the central nervous system, which according to some sources is said to be rare. There is an opportunity and a duty to address this issue in this guideline in order to reduce the stigma and address the potential for iatrogenic harm as a result of complacency and ignorance, which adds to the burden of trauma for patients seeking medical care.
103.	7	26	1/2	Re: "Non-compliance or intolerance with doxycycline may be a justification for switching to intravenous ceftriaxone" Suggest a key reason would be also doxycycline failure which is well-documented and has a scientific basis
104.	8	6	9	mis-spelling of poly-arthritis.
105.	8	18	16	It is notable that the 3 included studies all included patients who had received prior oral antibiotic treatment; in the Caperton study, nearly half of them. There must therefore be some doubt about the efficacy of oral treatment, and we suggest that long term follow up of patients treated under this guideline is included in a **research recommendation**. The medical literature on Lyme disease includes many references to refractory Lyme arthritis, and this is not acknowledged in this guideline. Arthritis has not been included in the evidence review document 13 on the management of persisting symptoms.
106.	9	6	12	It is important in any summary of Acrodermatitis chronica atrophicans to mention that it is almost always associated with peripheral neuropathy and often with arthralgia and abnormal findings in the spinal fluid. It is not simply a skin condition.
107.	9	19	13	See comment above: Acrodermatitis chronica atrophicans is not just a skin rash.
108.	9	20	3	The document states that doxycycline and IV ceftriaxone were both given for 30 days. This is not reflected in the abstract which states "Of the 46 patients suffering from acrodermatitis chronica atrophicans, 14 were treated with

				ceftriaxone 2g for 15 days. The remaining patients received either oral penicillin V 1.5 million IU t.i.d. or doxycycline 100 mg b.i.d. for 20 to 30 days.". Because acrodermatitis chronica atrophicans is associated with neuropathy and arthralgia, and some cases have spinal fluid abnormalities, it is possible that an equivalent course of IV ceftriaxone (ie 30 days) might be more efficacious. **We suggest this recommendation is reviewed.**
109.	9	20	6	Doxycycline is available in packs of 8 or 50 - ie 4 days or 25 days. A 29 day course is therefore easily achievable and would at least be closer to what the evidence shows is best.
110.	10	6	19	Add at end of sentence "…and there has been one case of fatal Lyme carditis in the UK." (Cary et al 1990)
111.	13	6	3/4	The word "seropositive" should be removed as the title is inconsistent with the PICO question which is "people with Lyme disease determined by diagnostic tests or clinical diagnosis". One of the included studies, Klempner 2001 included seronegative patients.
112.	13	6	9	Add "There is no test of disease activity" which is also true. This is why it is unsafe to restrict this part of the guideline to seropositive patients only. There is an extensive literature on seronegative Lyme disease in humans, confirmed by culture or PCR even after antibiotic treatment, when the bacteria may become more difficult to culture.
113.	13	6	12	What does the committee mean here by "social services"? • This is vague and potentially misleading. Recovering patients and those with persistent symptoms unresponsive to treatment may need access to continuing medical care, mental health services (as per NICE Clinical Guideline 91 'Depression in adults with a chronic physical health problem: recognition and management'), physiotherapy, occupational therapy, a range of rehabilitation services, pain clinics, counselling for themselves and their carers, carer support, educational welfare officers (for children and adolescents), voluntary sector support, and only if they were extremely disabled would they receive a package of care organised by social services via a complex care team. • Perhaps the committee was referring to the current system of benefits such as Personal Independence Payments or Employment and Support Allowance? This important point needs to be made clear, as patients do suffer significant financial hardship as a result of loss of earnings and in some cases costs of care related to travel to regional centres of expertise which may be at some distance. • Parents of children recovering from Lyme disease might experience unnecessary worry that "Social Services" implies that there would be a referral to "Children and Families Social Services" if their child were slow to recover from Lyme disease.
114.	13	6	12	Re: "consider these". Please see previous comment for suggestions for what clinical practitioners may need to consider when constructing a suitable care plan aimed at addressing a patient's recovery needs. There also needs to be consideration for who takes charge of and coordinates such care if multiple practitioners, disciplines and agencies are involved. This is a strong argument for a multidisciplinary specialist service to address the unmet need of complex Lyme disease patients at secondary and tertiary care level. These patients currently may access NHS care in an uncoordinated way, with a sense that no one is in charge of their over-all care and treatment.

				This is frustrating for the patient and probably inefficient and costly for the NHS. There is an opportunity for the guideline to make a recommendation which would improve the delivery of care to complex Lyme patients. See answers to Question 3.
115.	13	6	19	Arthritis has not been included in the PICO question, despite the fact that refractory arthritis is a term well recognised in the medical literature. The 3 studies included in the review of Lyme arthritis (document 8) all included patients who were re-treated. One of these papers is not considered here (Caperton 1990) and neither of the two on the list (Steere 1985 and Steere 1994) are in the list of excluded papers. Persisting Lyme arthritis appears to have been unconsidered by the committee. See comment on document 8 page 18 line 16.
116.	13	7	8	Note that the Klempner study excluded not only those with active synovitis but also those with positive PCR tests. It did not exclude those with other objective signs of Lyme disease such as measurable cognitive dysfunction, intrathecal antibody production or raised protein in the cerebrospinal fluid. The seronegative group had a higher baseline score than the seropositive group and the potential effect of this on treatment outcomes was not taken into account. This meant that both the seronegative and seropositive showed some degree of uncontrolled heterogeneity. The distribution may have included some patients who had such low levels of impairment that a treatment effect would have been hard to demonstrate even with an effective treatment. This study is statistically underpowered as a result of Type II error. The results of this study should be interpreted with caution in this area of particular medical uncertainty, as outlined in Section 13, page 6, line 8 of this draft guideline.
117.	13	16	16	See comment on document 7 page 18 line 9 re. reduced OPAT costs.
118.	13	19	25	The rationale for research recommendation RR3 is not in appendix J of evidence report D.
119.	13	164	Appendix I	Re excluded studies: Fallon 2008[68] should be included because it is a randomised controlled trial which includes a primary outcome measure of neurocognitive function across 6 domains, using well-validated methods to assess any reduction of cognitive clinical symptoms. • It includes a secondary outcome of pain and fatigue which were assessed using a wide range of well-validated methods including the Fatigue Severity Scale–111(FSS-11), McGill pain questionnaire, Short Form–36 Physical Component Scale (SF36), all well-validated tools for assessing symptom reduction and quality of life. Similar outcomes and methods were used in the 3 studies included in this guideline. In addition, depression was assessed using the Beck Depression Inventory, anxiety by the Zung Anxiety Scale and mental functioning by the SF-36 MCS, and global symptoms by the SCL-90 Global Symptom Index. • The outcomes studied in Fallon 2008 have high value for patients, especially any improvement in pain and fatigue, and the results from Fallon are consistent with those of Krupp 2003. • Fallon 2008 therefore satisfies PICO critical criteria. It is difficult to see why this important study was excluded on the grounds of “incorrect outcomes” as these include measures of symptoms reduction and quality of life in primary and secondary outcomes. Chronic pain and fatigue are highlighted in this guideline as particularly challenging for Lyme disease patients and their treating clinicians, so inappropriate exclusion of Fallon 2008 which provides valuable outcome data in this area will adversely affect the utility and safety of any recommendations, especially when there are only 3 studies left from

				which to make key recommendations. Two of these studies are graded low to very low quality in most areas. See also comment on page 7 line 8.
120.	13	General	General	Section 13 relates to 4 of the top 10 priorities from the Priority Setting Partnership organised by Lyme Disease Action with the James Lind Alliance which have been identified for further research and submitted to the National Institute for Health Research (NIHR): http://www.jla.nihr.ac.uk/priority-setting-partnerships/lyme-disease/downloads/Lyme-Disease-PSP-spreadsheet-of-data.pdf • Are continuing symptoms of Lyme disease following conventional recommended treatment due to continued infection, or an immune response or other process? • How common is relapse and treatment failure in Lyme disease? • What is the optimal course of action for Lyme disease if symptoms relapse after a treatment course is finished? • What is the optimal course of action if symptoms persist in Lyme disease after initial treatment? NICE has the opportunity to acknowledge and validate these key areas of uncertainty by making appropriate research recommendations.
121.	14	26	26	
122.	15	14	17	The committee agreed on the importance of providing quality information about Lyme disease. There is wide variation in the quality of advice on official websites which a normal person might reasonably assume is reliable: eg those of Hospital Trusts, Local Authorities, Councils and public parks. For example Bradgate Park (Leicester City Council) website has useful information about how not to get bitten but also says usually disease is not transmitted unless the tick has been attached for more than 36 hours. Even PHE and NHS web pages have conflicting advice / information: sometimes subtle, sometimes significant. For example, on the question of the erythema migrans rash some say "not all get one", some say "not all see one" and some even guess a percentage. It would be helpful if NICE would make a recommendation that public information providers review their own published information and align it with the guideline (or remove it) as necessary.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Where commenting on one of the 15 guideline chapters, please enter the number only in the document column (essential so we know which document you are commenting on), and the page and line numbers.
- Complete the disclosure about links with, or funding from, the tobacco industry.

Please return to: **Lymedisease@nice.org.uk**

Lyme disease

NICE National Institute for Health and Care Excellence

Consultation on draft guideline – deadline for comments 5pm on 6 November 2017 **email:** Lymedisease@nice.org.uk

- Include page and line number (not section number) of the text each comment is about.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 response from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Underline and highlight any confidential information or other material that you do not wish to be made public.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Spell out any abbreviations you use
- For copyright reasons, comment forms do not include attachments such as research articles, letters or leaflets (for copyright reasons). We return comments forms that have attachments without reading them. The stakeholder may resubmit the form without attachments, but it must be received by the deadline.

You can see any guidance that we have produced on topics related to this guideline by checking NICE Pathways.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory Committees.