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SH	Breakspear Medical Group	General	General	General	We are an organisation who has treated around 3000 Lyme and other infectious diseases patients and feel that our comments should be considered. We have large number of audits for your committee to consider we would like you to take into an account the following recent publications and also the ILADs guide lines which are available on their web site. Cook, M. J. and Puri, B. K. (2017) Application of Bayesian decision-making to laboratory testing for Lyme disease and comparison with testing for HIV. *International Journal of General Medicine,* 10, 113-123. Cook, M. J. and Puri, B. P. (2016) Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. *International Journal of General Medicine*, 9, 427-440. Feng, J., Auwaerter, P. G. and Zhang, Y. (2015) Drug combinations against Borrelia burgdorferi persisters in vitro: eradication achieved by using daptomycin, cefoperazone and doxycycline. *PLoS One*, 10 (3). Horowitz, R., Lacout, A., Marcy, P. Y. and Perronne, C. (2017) To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis. *Clinical Microbiology and Infection,* article in press. Puri, B. K., Segal, D. R. M. and Monro, J. A. (2014) Diagnostic use of the lymphocyte transformation test-memory lymphocyte immunostimulation assay in confirming active Lyme borreliosis in clinically and serologically ambiguous cases. *International Journal of Clinical and Experimental Medicine*, 7, 5890-5892.	Thank you for your comment and for your information. We respond to individual points raised in relevant sections. The references quoted here were excluded as follows: Cook 2017 was excluded from the diagnostic review because it is not a clinical diagnostic study; Cook 2016 was excluded because NICE methodology is to do our own systematic review if the systematic review identified is not the same as the guideline review protocol, although we do check references included in other reviews to ensure no studies are missed; Feng 2015 was not ordered because it is an in vitro study and therefore excluded when examining clinical outcomes; Horowitz 2017 (actually Dessau 2017) is listed as in press and not available; Puri 2014 was excluded from diagnostic review because there was no reference standard.

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SH	British Infection Association	General	General	General	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.	Thank you for your comment. The guideline has been developed in line with NICE standard processes and formats.
SH	British Infection Association	General	General	General	The document does not include the word ECG in the summary or the Lyme carditis evidence review. Our members wish to understand if the committee feels that a patient with localised erythema marginatum would require a routine ECG with all the burden on the GPs and anxiety that may be associated? In disseminated disease we would expect an ECG to be required.	Thank you for your comment. We presume that you are referring to erythema migrans rather than erythema marginatum The committee do not consider that people with localised EM should have an ECG and that clinical assessment should dictate appropriate investigations.
SH	British Infection Association	General	General	General	A statement on the handling and interpretation of ELISA positive immunoblot negative results would be useful and is not included in the current document.	Thank you for your comment. Following stakeholder comments, the recommendations have been altered to cover this scenario.
SH	British Infection Association	General	General	General	A statement on testing for alleged 'co-infection' ie Ehrlichia, Anaplasma, Rickettsia would be helpful and is not included in the document.	Thank you for your comment. Following stakeholder comments, the committee considered how best to indicate that other tick-borne infections might need to be considered. It was agreed to add a recommendation to consider discussion with the appropriate reference laboratory if people's symptoms are not improving following antibiotic treatment to cover this possibility.
SH	British Infection Association	Short			"Consider the possibility of Lyme' in people presenting with several of the following symptoms…" This statement is confusing due to lack of specificity. Please see later comments on 1.2.19. In particular the use of the term 'brain fog' is unhelpful and will encourage confusion with non-Lyme related chronic fatigue syndrome	Thank you for your comment. The recommendation needs to be considered in the context of the recommendation about possible tick bite and clinical judgement of other likely causes of these symptoms.
SH	British Infection Association	Short			For people with a negative ELISA who have had symptoms for 12 weeks 4 or more and Lyme disease is still suspected:	Thank you for your comment.

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					• repeat the ELISA and • perform an immunoblot test." The authors suggest that this "is not likely to have a significant resource impact". One of our members has completed an audit to assess this. In one unit over one year approximately 280 requests submitted to a single laboratory for Lyme serology had only tiredness/fatigue/malaise/viral symptoms (with or without non-specific symptoms e.g. headache/myalgia/arthralgia and with or without a history of a tick bite) as the clinical details. The overwhelming majority of these were negative. Some of these patients will have an alternative cause identified for symptoms, and some patients' symptoms will resolve, but this still has the potential to lead to a significant number of immunoblots at significant expense and for what may be limited benefit. Do the committee have a clear view as to how much additional testing will be required and how what the yield of this additional testing will be?	Following stakeholder comment repeating the ELISA has been removed. NICE defines a significant resource impact as a recommendation that leads to an additional £1million pounds in NHS spending in a year. As detailed in evidence report C, For this recommendation of an immunoblot to be considered to have a significant resource impact, it would need to be applicable to over 10,000 people based on the current cost of these tests. Based on the details of your audit and committee experience it is not anticipated that 10,000 people in England would meet the requirements outlined in this recommendation in a year. The committee do not anticipate that a large proportion of those who test negative will have ongoing symptoms beyond 12 weeks and therefore need additional testing. The yield is expected to be small, but the committee considered that the reassurance it would provide to be invaluable. In addition, it may identify Lyme disease in those who had not yet developed an immune response or had a false negative result the first time.

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SH	British Infection Association	Short			The recommendation that patients with negative serology be referred to an Infectious Diseases specialist "to consider an alternative diagnosis" (section 1.2.19). Lyme disease is unlikely in a patient with non-specific symptoms and negative Lyme serology (although negative serology may occur when treated early and effectively in which case onward referral may not be required). Some people believe that they have Lyme disease despite a negative test and without an illness associated with erythema migrans. We recommend that the suggestion to consider referral of such cases with negative serology to an infectious disease specialist be removed. Those with otherwise unexplained symptoms should be referred to the appropriate specialist clinic such as neurology, rheumatology, psychiatry or perhaps in some cases a chronic fatigue clinic specifically and not an infectious diseases specialist in general. Infectious diseases clinic referral should be reserved for where there is concern of active current infection (usually not Lyme in the context of negative serology but if there is concern of an alternative infection) and onward referral made accordingly.	Thank you for your comment. This is a 'consider' recommendation for discussion or referral to an appropriate specialist. This includes neurologists, rheumatologists, psychiatrists etc. The wording of this recommendation has now been amended to 'a specialist appropriate for the person's history or symptoms (for example, an adult or paediatric infection specialist, or rheumatologist or neurologist)' for clarity. There are cases with negative serology where referral to an infection specialist may be appropriate, for example to investigate alternative infections.
SH	British Infection Association	Short	Table 1		Our members do not all support a duration of 21 days, particularly in erythema migrans. The attached evidence review does not clearly support this duration and studies included in the review show no benefit over shorter courses. The recommendation may restrict future clinical studies to evaluate the best duration of treatment.	Thank you for your comment. The recommendations for antibiotic management were reviewed following consultation and the decisions made by the committee clarified. The evidence for length of treatment is weak and the committee decided to recommend longer courses of 21 days of treatment as standard because of their concern at low cure rates in some studies and the lack of clear evidence for shorter

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					The azithromycin regime is complicated & does not appear to make sense from a pharmacokinetics point of view. We suggest once a day for 10 days. This would be simpler for patient and prescribers.	courses. They considered it important that people being treated for Lyme could be reassured that that they are have had the longer course if they continue to have symptoms. The committee were reassured that adverse rates were not increased for longer courses. Due to the pharmacology of azithromycin specifically (long half-life), treatment courses are 4 days less than doxycycline or beta lactam equivalents. So the treatment regimen for azithromycin is 17 days, which provides 21 days of effective drug levels in vivo. Also, the recommendation for azithromycin has been altered to a daily dose (not 3 consecutive days per week) in similar fashion as for routine use in other slow-growing bacterial conditions such as atypical mycobacterial infection. In these conditions, azithromycin is used daily for the treatment course, reaching higher steady state than if 3 consecutive days/week is used. The committee decided on this regime for the same reason as the higher dose regimens for doxycycline and amoxicillin have been recommended.
SH	British Infection Association	Short	1.3.7 and 1.3.9		1.3.7 Persistent symptoms after a course of antibiotics 1.3.9 Consider a second course of antibiotics for people with persisting symptoms… There is no evidence to support this practice and furthermore, published studies show no benefit from additional or extended duration of antibiotics for those with persistent symptoms. We would advise removal of the recommendation to retreat. There is evidence of	Thank you for your comment. The committee consider that in this small group of patients the second course of antibiotics is unlikely to do individual or community harm and will be reassuring that Lyme has been definitively treated if present (regardless of test results). This is pragmatic, and will be beneficial to patients who would otherwise have considerable doubt

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					harm from antibiotics, e.g. adverse effects, selection of resistance organisms, and there are cost implications. Whilst reinfection could occur and genuine treatment failure is not impossible, available evidence suggests both these circumstances are very rare. We have serious concerns about this statement which may lead to over treatment, over use of antibiotics and an increased rate of referral of patients with persistent undiagnosed symptoms seeking additional courses of antibiotics or even parenteral antibiotics with high associated risks.	and often feel the need to then consult wider in the private sector. The committee agreed that this approach was the most likely approach to provide such reassurance to the majority of patients who could then seek alternative diagnoses.
SH	British Society for Antimicrobial Chemotherapy (BSAC)	General			We have no comments for this Draft Guideline consultation for Lyme Disease.	Thank you.
SH	Cochrane - Neuromuscular	Evidence Review C		C	Not clear to me how this relates to the text. The last box contains 34 selected papers. 7 are neuroborreliosis. Only 6 papers are included in this evidence review for Chapter F. I presume appendix C might apply to all chapters bbut if that is the case there is inconsistency between 7 identified and 6 included. If it only applies to neuroborreliosis it is not clear why the others (eg erythema *chronicum* (?more correct term?) migrans are there. Perhaps there ought to be another series of parallel boxes under the included to indicate which go in which section?	Thank you for your comment that appears to apply to the study selection flow chart in appendix C, evidence review F. This shows the clinical evidence selection for the whole management question and the box at the bottom shows the number of papers included for each clinical presentation. For neuroborreliosis, there were 6 studies reported across 7 papers. The numbers of papers and studies included in each clinical presentation review have now been added to the clinical evidence selection diagram for clarity.
SH	Cochrane - Neuromuscular	Short		I	It is not clear what the criteria are for 'due to an incorrect study design', 'due to an incorrect outcome' or the occasional meaningless '*due to an incorrect not available'* (!) (Gasser 1996). Given that the LDA will be all over this, definitions and criteria are key, both in the	Thank you for your comment. Studies are assessed for eligibility against the review protocols (appendix A of the evidence reviews). For example, if the review protocol specified randomised controlled trials, then any study design other than an RCT would be 'excluded

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					text and in the table (clearly without making it unreadable)	due to an incorrect study design'. Gasser 1996 was excluded because the full text paper was not available. The reason for exclusion in the excluded studies table has now been amended.
SH	Cochrane - Neuromuscular	Short	General	General	In general I think the recommendations are pretty fair given the above	Thank you.
SH	Cochrane - Neuromuscular	Short		1.3 and general	I have never yet seen a case of Lyme Neuropathy – it causes a radiculitis. Neuropathy is not relevant. I am also not entirely convinced by Lyme Myopathy; there is a case report of orbital myositis in a dog, amyopathic dermatomyositis in a human (is that possible?) and occasional case reports of associated inflammatory myopathy and positive Lyme serologies of various qualities. I am not sure it happens. The other tissues do	Thank you for this information. The wording was agreed by the committee and a co-opted expert in adult neurology.
SH	Cochrane - Neuromuscular	Short		1.10.3	There is a recommendation that CNS and PNS disease should be treated differently because of reduced CSF penetration. There is little material difference in the Blood Brain Barrier and Blood Nerve Barrier penetration as far as we know, despite the difference in structure with astrocytic foot processes in the the CNS (see Poduslo). Therefore to recommend higher doses of Abs for CNS disease and not PNS (root) disease is perhaps only half logical?. Since there are so few studies and clearly no studies on dose in the PNS one might make a sensible recommendation based on analogy and BBB/BNB known science?	Thank you for your comment. Overall, the guideline approach is to use higher doses to be certain of likely effective treatment. This is in keeping with treatments for all causes of bacterial meningitis, which is also in many manufacturers SPCs. Other PNS diseases are not generally treated with as high doses of antimicrobials as meningitis or encephalitis (for example the treatment of herpes virus infections), so while we agree the science/evidence is weak the recommendations are in keeping with treatments for other types of infection.
SH	Department of Health	General	General	General	I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you.

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SH	Fight Lyme Now	Evidence Review C	General	General	FIGHT LYME NOW: TECHNICAL RECOMMENDATIONS FOR THE DETECTION OF LYME DISEASE BY LABORATORY TESTS As a science-based lobby group for Lyme disease, a fundamental concern of Fight Lyme Now has been the laboratory testing for the organism that characterises Lyme disease, namely, Borrelia burgdorferi sensu lato (*Borrelia)*. As a first draft of guidelines, we are pleased to read that the NICE committee has established a fundamental baseline for laboratory testing in the UK. We would suggest, however, that a number of technical and clinical factors must still be taken into consideration. From the information that has appeared in the literature over the past 10 years (and also from a recent Fight Lyme Now survey), it is clear the sensitivity of the test system rises as the symptom complex better fits the diagnosis of Lyme disease. With respect to current test systems, it must be noted that they are validated using samples from clinically well-characterised subjects-often those with symptoms consistent with neuroborreliosis or Lyme arthritis. A corollary these two statements is that 1), the antibody titre likely rises as the symptom complex most closely mirrors 'classical' Lyme disease and 2), the test manufacturer (as most tests are from commercial organizations) establishes the cutoff for positivity on samples from patients where the humoural arm (antibody-producing arm) of their immune system has been the most highly activated (by *Borrelia*).	Thank you for your supportive comment regarding the recommendations and research recommendations. The issues you raise were discussed by the committee, which recognised the limitations of ways in which tests are developed. The committee agree that the lack of a gold standard and use of clinical presentations has consequences for development of tests. This contributed to the low to very low quality rating of the evidence for diagnostic tests and is discussed in section 4.4.1.2 of evidence review C. The committee also recognise that testing positive for Lyme disease does not mean Lyme disease is the cause of symptoms that are present. The guideline makes recommendations to ensure that those who remain symptomatic should have an immunoblot performed if clinically appropriate. The committee support your interest in ensuring tests used in UK are appropriate for the UK population and we have now emphasised this in the research recommendations. The research recommendations are developed from the gaps in the evidence that the committee considered most important to answer. Our remit however does not allow us to specify who should develop the tests.

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					Although not scientifically rigorous, our survey has identified a significant number of individuals for whom the initial diagnosis was not Lyme, yet these individuals subsequently tested positive for Lyme disease. So the sensitivity of testing for individuals who obtained an initial diagnosis of, for example, chronic fatigue, was around 16%. From the above discussion, one has to question the rational of establishing the cut-off (or the point at which the assay is considered negative), using samples from individuals with very well characterised Lyme disease and applying the this test to other groups of individuals where it is likely that if infected, the antibody titre will be low. A major problem here is that the cut-off for positivity will be slightly different between different assay systems. This above poses two fundamental concerns. The first is that the current assay systems will have a detection bias for 'classical Lyme disease' at the expense of conditions such as chronic fatigue or a psychiatric condition (where a significant proportion of individuals may have been infected with *Borrelia*) and also where Lyme disease symptoms persist. The second problem is that NHS regional laboratories apparently test patient samples for Lyme disease with a different assay system to that used in the reference laboratory at Porton Down. Whilst this may not pose problems with samples from clinically well-characterised patients (ie high clinical suspicion of Lyme disease at first diagnosis), it may indeed be a problem for patients for whom the diagnosis of Lyme disease is not initially suspected. If these individuals are able to obtain a test on a blood sample and it is negative, one assumes	

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					they will not have the opportunity to be re-tested by the reference laboratory. Also, using this 'three-tier-system' (regional laboratory test- RIPL ELISA- RIPL Immunoblot), different samples are being tested on different occasions. The titre of antibody may vary significantly between these testing occasions and the relative cut-off of the different assays may have a significant influence on the test result. It should be reiterated at this point that an assay system is validated using samples selected from individuals for whom the diagnosis of Lyme disease is the most likely. So a cut-off for positivity is established on a clinical basis. This is not the same as the sensitivity of the assay system at a technical level. To establish the 'technical limit of detection' of an assay, one must analyse serum samples from 'control individuals' where symptoms of Lyme disease are absent and where the region of the world is not know to have a high incidence of Lyme disease. These samples are processed and by statistical means, one can then calculate the 'technical limit of sensitivity'. This is the absolute 'bottom line' for the assay system. The problem here is that manufacturers impose their own 'bottom line' depending on the algorithm they use to determine the clinical significance of the assay value (an amount of antibody that may be above the 'technical limit of sensitivity') they have obtained. The overall fundamental problem is that serology assays (in fact all immunological techniques) are semi-quantitative at best. So one currently determines the amount of antibody in the blood by using antigen immobilised to some kind of substrate (such as well-	

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					bottom of a 96 well plastic plate). Antibody is 'captured' from the blood, but the amount of the antibody captured cannot be quantitated in terms of an amount per/ml of blood. So, the amount of antibody captured will depend on the exact way the assay system has been established-in other words, the 'technical sensitivity' will vary. As discussed in previous paragraphs, this may not be a problem when comparing serum samples (with different assay systems) obtained form patients with neuroborreliosis, but it will be a problem for individuals who, for whatever reason, produce low amounts of antibody in response to infection with *Borrelia*. These individuals will be characterised as seronegative, despite having part of the symptom complex of Lyme disease. The above discussion clearly places a great deal of emphasis on Research. As an organisation, we are heartened to read that the research objectives are: *RR1. What is the most clinically and cost effective serological antibody-based test, biomarker (such as CXCL13), lymphocyte transformation and ELISPOT for diagnosing Lyme in the UK at all stages, including reinfection?* *RR2. What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections (such as babesiosis, ehrlichiosis, anaplasmosis, bartonellosis or Q fever) in people in the UK when performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?*	

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					However, despite our overall approval, we don't feel that these research objectives go far enough. For this reason we have a number of *further recommendations for research*: 1) We believe that the NHS must stop relying on commercial systems for the diagnosis of Lyme disease. Whilst we understand the financial constraints, it is our opinion that the NHS must develop its own serology diagnostic system that takes into consideration the technical issues around serology assay development. We believe that an assay system must be developed where the amount of antibody captured by the particular antigen (or group of antigens used in the ELISA system) is quantitated to achieve an absolute 'technical sensitivity' - in other words, the minimum amount of antibody that can be detected. This does not need to be done for the routine use of the assay system; this procedure must be performed as apart of the development of the assay system (validation). If this is not possible for technical reasons, then the assay system must be optimised using know positive samples to give the highest possible technical sensitivity. This assay system must then be used to re-address the issue of *Borrelia* antibody positivity in relation to the symptom complexes in the UK (the seroprevalence issue of the above). 2) In particular, we are pleased to see that the issue of LTT assay use for Lyme disease detection is to be considered as a research priority. The immune system is highly complex and in order for a response to be made to the organism (*Borrelia* or co-infecting agents), tissue conditions must be favourable. In other words,	

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					whether T cells receive stimulation to direct the innate immune system/cytotoxic T cells or whether they receive stimulation to up-regulate the humoural response (antibody response) may (will) depend on signals received at a particular tissue site. Whilst Th1 and Th17 cells are very much involved in antibody production from B cells (IgG class antibodies), for some reason, there may be circumstances where the B cell response to T-helper-cell-priming is poor. This, one assumes, is a major rationale for using a T-cell test, such as the EliSpot, in cases where despite seronegativity, the patient has some of the symptoms that suggest *Borrelia* infection. 3) Major recommendations with respect to 2) above are for the NHS again to develop its own LTT-type assay system, where careful attention is paid to the type of antigen(s) used and to the particular cytokine that is detected. Currently assay systems such as the EliSpot detect the Th1 cytokine, IFNgamma. This excludes other responses, such as Th17, that are known to occur following *Borrelia* infection. 4) If it is not possible for the NHS to develop its own LTT system, we would suggest that at the very least, a thorough investigation is performed on assay specificity. Just as for the suggestion on seroprevalence (a parameter that is highly dependent on the assay 'technical sensitivity'), the T-cell response will very much depend on the way the LTT system is established. For example the MELISA looks at total T-cell responses in around 1 million peripheral blood mononuclear cells (PBMCs); the EliSpot, by contrast, only uses 100,000 PBMCs per antigen(s). This will mean that the assay sensitivity of the MELISA is 10	

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					fold greater than that of the EliSpot; inversely, however, a value obtained as an stimulation index by the EliSpot will be of greater significance than a value obtained using the MELISA. 5) Fight Lyme Now believe that not enough work has been done to develop a sensitive direct test for *Borrelia*. We believe that most of the current direct testing strategies fail to take into consideration the particular fraction of whole blood in which *Borrelia* may reside. We are aware that the RIPL are working on a system to use whole blood with a PCR-based approach, however, careful consideration must be paid to the methodology used for determining assay sensitivity. Many of the procedures currently employed 'spike' blood fractions with a plasmid containing a *Borrelia* DNA sequence. This is not adequate to determine 'technical sensitivity' and blood fractions must be 'spiked' with a known quantity of the (live) test organism. This allows for the internal control (the spike), to be taken (in its native live form) throughout the whole of the assay procedure. Often a plasmid will be added to DNA that has been extracted from blood samples-this is entirely incorrect. 6) As an extension of 5) above, there are problems when using a PCR system where the majority of the DNA comes from immune cells present in a whole blood sample. For this reason, other techniques such as 'droplet digital PCR' might be considered where the ratio of DNA from the organism to DNA from the 'patient' (immune cells), is more favourable (ie. a higher proportion of *Borrelia* DNA). By this means, PCR inhibition will be reduced. As an extension of the above, there are techniques being developed for the	

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					early signs of sepsis and these are approaching a sensitivity of 1 microorganisms per ml of blood. These techniques should be considered for the direct detection of *Borrelia* in samples of blood from seronegative patients who have persistent symptoms of Lyme disease.	
SH	International Lyme and Associated Diseases Society	General	General	General	As a registered stakeholder in the management of Lyme disease and other tick-borne infections, ILADS has presented evidence-based recommendations we hope will provide support to amend your present guidelines. These concepts include inadequate sensitivities to the present 2-tiered diagnostic system, including the need to include IgM analysis even in the setting of chronic disease. The concept of chronic active *Borrelial* infection, with or without the presence of co-infections was described. We provided evidence for active infection being a plausible explanation for persistent symptoms in the setting of what was felt to otherwise represent adequate antimicrobial therapy. Lastly, evidence was provided for the benefit of longer course therapies in the setting of persistent symptoms. We hope that these recommendations will be incorporated in your final draft. In so doing, better	Thank you for your comment and this information.

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					reflecting the full biologic complexity of Lyme disease. As a result of incorporating our recommendations we believe that citizens of the United Kingdom can receive the optimal care they deserved. Thank you in advance for your considerations	
SH	International Lyme and Associated Diseases Society	General	General	General	REFERENCES 1. Aguero-Rosenfeld ME, Wang G, Schwartz I, Wormser GP. Diagnosis of Lyme borreliosis. Clin Microbiol *Rev*. *2005* Jul;*18*(3):*484-509*. 2. Marangoni A, Sparacino M, Cavrini F, Storni E, Mondardini V, et al. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed Lyme disease in Italy. J Med Microbiol. 2005 (54):361-7. 3. Lahey LJ, Panas MW, Mao R, Delanoy M, Flanagan JJ, et al. Development of a Multiantigen Panel for Improved Detection of Borrelia burgdorferi Infection in Early Lyme Disease. Clin Microbiol. 2015 Dec;53(12):3834-41. doi: 10.1128/JCM.02111-15. Epub 2015 Oct 7. 4. Cook MJ and Puri BK Commercial test kits for detection of Lyme borreliosis: a meta-analysis of test accuracy. Int J Gen Med 2016 Nov 18;9:427-440. eCollection 2016 5. Smith JL, Israel CW. The presence of spirochetes in late seronegative syphilis.JAMA. 1967 Mar 27;199(13):126-30. PMID:5336423 6. Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Seronegative Lyme Disease. Dissociation of T- and B-Lymphocyte Responses to Borrelia burgdorferi. N Engl J Med 1988;319:1441-6	Thank you for providing these references for your comments. We have reviewed the references to ensure that those that are relevant to the review questions were considered for inclusion.

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SH	International Lyme and Associated Diseases Society	Short	6 and 7 of 35	1.2.12 -16 and 19:	1.2.12 Offer testing if there is a clinical suspicion of Lyme disease, using an enzyme-linked immunosorbent assay (ELISA) for Lyme disease that tests for both IgM and IgG antibodies and is based on C6 peptide or an equivalent purified or synthetic VIsE antigen and IgM and IgG immunoblots. *If ELISA and Immunoblots are negative consider testing serum and whole blood by PCR.* 1.2.13 For people with a negative ELISA and Immunoblot who were tested within 4 weeks from symptom onset, consider repeating the ELISA and Immunoblot 4 to 6 weeks later if Lyme disease is still suspect. *Consider alternative direct measurement*	Thank you for these suggestions. The recommendations are recognised to reflect current practice and we would not usually include tests, which are not currently available or not validated. We are unable therefore to add tests such as the urine antigen test to the recommendation. We do have a research recommendation for tests and this includes mention of novel tests. The guideline does include a suggestion to discuss the presentation with the reference lab to consider whether testing for other tick borne infections is required.

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					technologies such as urine antigen test, as they become available. 1.2.14 If ELISA, immunoblot and PCR tests are negative but unexplained symptoms persist, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or pediatric rheumatologist) to review: whether further tests may be needed for suspected Lyme disease, for example synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis, *urine antigen test, T-cell test or consider alternative diagnoses. Include Tick-borne Relapsing Fever (TBRF) Borreliosis in your differential diagnosis because a lot of patients infected with TBRF Borrelia have Lyme-like symptoms.* 1.2.1715 Consider treatment with antibiotics (see section 1.3) before test results become available if there is a high probability that the person has Lyme disease.	

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					1.2.186 If Lyme disease is confirmed with ELISA and immunoblot tests, and the person has focal symptoms, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or pediatric rheumatologist), without delaying treatment. 1.2.19 If ELISA and immunoblot tests are negative but unexplained symptoms persist, consider a discussion with or referral to an infectious disease specialist or a specialist appropriate for the person's symptoms (for example, an adult or pediatric rheumatologist) to: □ review whether further tests may be needed for suspected Lyme disease, for example, synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis or □ consider alternative diagnoses. 1.2.2017 Be aware that some people, particularly those living in high-prevalence areas may have positive serology but do not have Lyme disease because antibodies can remain in the body for some years.	

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SH	International Lyme and Associated Diseases Society	short	10 and 11 of 35	Table 1 and 2	Persistent symptoms after a course of antibiotics Culture of spirochetes is still the gold standard to diagnose active infection (24) However, due to the low numbers of viable spirochaetes usually present in patient biopsies and the fastidious nature of the B. burgdorferi s.l. strains the sensitivity of culture is highly variable, ranging from less than 1% in Lyme arthritis to 70% in EM skin lesions. Negative results, therefore, do not exclude active infections (24) Nucleic acid amplification testing using polymerase chain reaction (PCR) technology is an alternative technology used to detect this fastidious organism. However, in European LB the spirochaetemia is transient and spirochaetes are relatively difficult to sample from tissues. Furthermore, detection of DNA by conventional PCR cannot unequivocally establish whether infections are active or not. (24) Thus, we presently lack the tools to confidently generate a "test of cure.". Given the reality that there exist significant deficiencies in diagnostic biomarkers for this condition, over-reliance on testing needs to be weighed against, the importance of clinical judgment.	Thank you for your comment and this information. The guideline is a clinical guideline and the evidence reviews for treatment are directed to look for evidence of benefit of treatment. The committee members were familiar with the animal studies you quoted, but these are inadequate in themselves to presume that prolonged antibiotic treatment is required or beneficial. Looking for benefit from an intervention in the form of patient outcomes is a useful approach. In cases such as this where the cause of persistent symptoms is contested, improved patient outcomes would suggest prolonged antibiotic treatment was helpful despite an inability to demonstrate a deep-seated infection. Following stakeholder comments, studies including those by Fallon, as you describe, have been added. These can be seen in evidence report L. The committee disagreed that these provided adequate evidence to recommend prolonged antibiotics. The committee conclusions and recommendations were unchanged by the additional studies. The recommendations do allow for referral to a specialist where additional treatment can of course be considered according to clinical judgement but there is no robust evidence to allow us to recommend such a course of action.

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					Further, the literature supports the inadequacy of standard treatment protocols in the management of this condition. Evidence is provided for the persistence of *Borrelia burgdorferi (Bb) active* infection, such that recommended short-term antibiotics fail in 25%-71% of patients with late-stage disease (25-40) In the 2012 Embers trial on nonhuman primates, (25) 12 Rhesus monkeys treated with the equivalent regimen as the Klempner human study (41) showed evidence of adequate MICs of ceftriaxone and doxycycline. Their findings were significant for 12/12 sacrificed study patients revealed positive skin cultures 4 weeks after treatment. Their conclusion was that "These results demonstrate that *B. burgdorferi* can withstand antibiotic treatment, administered post dissemination, in a primate host." Hodzic (26) designed a murine study, such that *Bb* infected animals were treated with IV ceftriaxone, also achieving peak serum ceftriaxone levels exceeding the *Bb* MIC and MBC. The findings were significant for all antibiotic-treated mice being PCR positive at 12	

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					months. Further, the infectivity of these mice was confirmed by xenodiagnosis. In essence, *Bb* naïve ticks feeding on the PCR positive treated mice were able to transmit infection to *Bb* naïve mice at a rate of 100% Thus, reflecting viability and infectivity of spirochetes post-treatment. Supporting this concept of post-treatment persistence is evidence in the literature describing multiple *Bb* forms that are felt to likely perpetuate this phenomenon (42-52) Thus, given the aforementioned evidence of persistence, we argue that a potentially substantive cohort of post-treatment patients presenting with persistent symptoms associated with their Lyme disease represent active infection. The corollary to this is that these individuals may benefit from longer than standard courses of antimicrobials. In fact, the literature supports value of prolonged antimicrobial therapy in the setting of Lyme disease and persistent symptoms. In two of the 4, NIH funded retreatment trials (9,29), sub-cohort analysis revealed clinical benefit. Specifically, in the Fallon study (10),	

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					Pain and physical functioning improved at to a statistically significant and sustainable degree, that was not felt by the authors to represent placebo effects. In the Krupp study (53) sustainable, statistically significant improvement in fatigue was noted. Further, there were four studies that independently provided evidence for clinical benefit in the setting of prolonged antimicrobials and persistent Lyme disease symptoms (54-57) Further, concomitant exposure to tick-borne "co-infections" are well established. Potential co-infecting pathogens include *Babesia* (58-64), Bartonella species (65-66) nd Rickettsia (67) (including *Ehrlichia/Anaplasma*) (59,60,63) These "co-infections" may not have the same sensitivities to antimicrobials as does *Borrelia* infection, and thus may not have the anticipated clinical response. Thus, the recommendations provided on antibiotic treatment tables are arguably arbitrary. In most deep-seated infections, once an individual has received a recommended course of antimicrobials if they have had only a partial but incomplete response, is their	

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					treatment stopped? In general, patients are followed clinically to determine adequacy of treatment. If additional courses of treatment are felt to be clinically warranted at the point of care, extensions to this treatment are generally provided. Why should infection with *Borrelia* be any different? (68-70) Our recommendations: Tables 1 and 2 referable to antibiotic regimen: That there be a qualifier for each regimen to include language such as "at the end of each course of therapy, clinically reassess. If the patient clinically has a partial response, consider extending their course and/or introduce an alternate treatment protocol. This would also be the case if there is a clinical deterioration consistent with the initial presentation soon after cessation of said treatment regimen.	
SH	International Lyme and Associated Diseases Society	Short	6 of 35 to 8 of 35	1.2.12 to 1.2.22	CDC's Two-Step Laboratory Testing Process for Lyme Disease (CDC) Currently in the UK, the CDC's two-tire serological testing for evidence of antibodies against the Lyme disease bacteria is recommended. Both steps should be done using the same blood sample. a. The first step uses a testing procedure called "EIA" (enzyme immunoassay) or rarely, an "IFA" (indirect immunofluorescence assay). b. If this first step is negative, no further testing of the specimen is recommended. If the first step	Thank you for this information. Following stakeholder consultation, we have added recommendations to clarify the importance of clinical diagnosis and to increase awareness of false positives and false negatives.

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					is positive or indeterminate (sometimes called "equivocal"), the second step should be performed. The second step uses a test called an immunoblot test, commonly, a "Western blot" test. Results are considered positive only if the EIA/IFA and the immunoblot are both positive. Problem: The two-step test for Lyme Disease has excellent specificity (almost 100%) but poor sensitivity. 1. Two-tiered serologic testing has a reported sensitivity of 30 to 40% the first week after presentation of EM rash and 29-78% in convalescent stages after treatment. Antibody response increases over time and the reported sensitivity in patients with neurological involvement or Lyme disease arthritis is 87% and 97% respectively (1). Reason: Although some screening tests have excellent specificity, overall the sensitivity of these tests is poor, especially early or late in disease when the levels of antibodies are low- 62-73% at best (2,3). According to the Cook meta-analysis (4), "The weighted mean sensitivity for all tests and for all samples was 59.5%. Individual study means varied from 30.6 to 86.2%. Sensitivity for each test technology varied from 62.4% for Western blot kits, and 62.3% for enzyme-linked immunosorbent assay tests, to 53.9% for synthetic C6 peptide ELISA tests and 53.7% when the two-tier methodology was used." Hence, over-reliance on the two-tier testing method as the *sine qua non* of a diagnosis of Lyme disease	

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					excludes the possibility of seronegative disease, an entity well established in syphilis (5) and reported to occur in Lyme disease 6-9). In fact, in the 2007 Fallon study (10) only 1 of 100 candidates or 5% (many of whom had strong histories supporting the clinical diagnosis of Lyme disease) had positive ELISA and fully diagnostic IgG Western blots which were required for entrance into the study. 2. According to CDC, IgM Western blot should only be used early in the disease. However, it is well documented that IgM specific antibodies can be present late in Lyme (11, 12). Generally, in late disease, ELISA or C6 is usually negative. Thus this group of patients would be missed by two-tier testing. 3. CDC does not include bands 31kDa (Osp A) and 34kDa (OspB) in their Western blots. Antibodies to these antigens are present in late disease (12-14), demonstrated that including Osp A improved sensitivity. 4. The standard kits for Lyme disease generally use antigen from *Borrelia burgdorferi* strain B31, recommended worldwide. However, there are different regional strains such as the European strain *Borrelia afzelii* (15) . In fact, inclusion of these regional strains improves serological diagnosis in Scotland (16,17). Further, there have been established other species of *Borrelia* involved in Lyme disease: several species in the *Borrelia burgdorferi sensu lato* complex and also *Borrelia*	

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					*miyamoto*i for which there is little or no cross-reactivity (18,19) It is well documented that about 20% of patients never make antibodies (20). Also early in the disease, the amount of antibodies is very low to detect by serological methods. Thus, in these patients that do not make antibodies or early in the disease, PCR (21), urine antigen tests (22) and T-cell tests (23) would be useful.	
SH	International Lyme and Associated Diseases Society	short	12 of 35 to 13 of 35	1.3.7 to 1.3.11	1.3.7 If symptoms that may be related to Lyme disease persist or worsen after 2 antibiotic treatment, review the person's history and examination to 3 explore: 4 - any possible alternative causes of the symptoms 5 - if re-infection may have occurred 6 - details of any previous treatment, including whether the course of 7 antibiotics was completed without interruption 8 - if symptoms may be related to organ damage caused by Lyme disease, 9 for example, nerve palsy.	Thank you for these suggestions. We have responded to your rationale for these amendments to the recommendations in our response to comment 80. We are unable to accept your suggestions as explained in that response.

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					Consider an additional or alternate antimicrobial regimen (whether for *Borrelia* and or potential co-infection present) 1.3.8 If the person's history suggests re-infection, offer antibiotic treatment 11 according to their symptoms (see tables 1 and 2). 12 1.3.9 Consider a second course of antibiotics for people with persisting 13 symptoms if treatment may have failed. Use an alternative antibiotic to 14 that used for initial treatment, for example for adults with Lyme disease 15 and arthritis, offer amoxicillin if the person has completed an initial course 16 of doxycycline. 17 Remove 1.3.10 1.3.11 Explain to people with persisting symptoms following antibiotic treatment that symptoms of Lyme disease may take months to resolve even after treatment	

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					□ continuing symptoms does not necessarily mean they still have an active infection □ symptoms may be a consequence of damage from infection □ there may be an alternative diagnosis. Yet symptoms may still be due to an active infection by *Borrelia* and/or any one of a number of co-infections that may not have been adequately managed by the intervention employed.	
SH	Lyme Disease Action	Evidence Review A	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.	Thank you for your comment and this information. We do not think it is necessary to add this. We did not review any historical data.
SH	Lyme Disease Action	Evidence Review B	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).	Thank you for your comment. The review question was targeted to presentations the committee thought would have high sensitivity and specificity for a diagnosis of Lyme disease. The committee agreed a limited number of presentations. Bannwarth's syndrome was not specifically included in the list chosen by the committee. The evidence search was reviewed following stakeholder comment and would have identified any studies if available.
SH	Lyme Disease Action	Evidence Review B	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.	Thank you for your comment. The committee agreed that the NeBoP score showed promise, given the relatively high sensitivity and specificity.

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					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.	However, there was not sufficient or strong enough evidence to support a recommendation.
SH	Lyme Disease Action	Evidence Review C, Appendix D	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).	Thank you for your supportive comment. The committee did not discuss any possible association between teeth staining and exposure to sun. This is a general issue in regard to use of doxycycline and not specific to this guideline.

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SH	Lyme Disease Action	Evidence Review C, Appendix D	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.	Thank you for your comment. The wording of the review questions allowed us to identify evidence for the diagnostic accuracy of different tests. The committee were aware that in clinical practice, serology tests are used to support a diagnosis rather than diagnose Lyme disease. However, in clinical practice the terminology is used in this way. Clarification of how the terms are used has been added to the guideline.
SH	Lyme Disease Action	Evidence Review C, Appendix D	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?	Thank you for your comment. ELISAs and immunoblots as applied to CSF and CSF/serum antibody index was included in the evidence review. No evidence for white cell count and protein in CSF was identified. Index tests were listed in the review protocol by name of the test to allow us to capture all relevant evidence for their diagnostic accuracy, including different markers and sample types. The clinical evidence summary (tables 7-10), forest plots (appendix E) and clinical evidence tables (appendix D) provide more detail on the specific markers and sample types used in each study.
SH	Lyme Disease Action	Evidence Review D	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.	Thank you for your comment. We have added this to the text.
SH	Lyme Disease Action	Evidence Review D	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	Thank you for your comment. We have changed the wording of the recommendations for healthcare professionals and for information for patients to reflect that this may occur more widely. We have detail to the short guideline in the 'terms used in this guideline' to provide additional information.

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					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.	
SH	Lyme Disease Action	Evidence Review E	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.	Thank you for your comment. We have clarified in the research recommendations (both epidemiology and for management) that this population needs to be included.
SH	Lyme Disease Action	Evidence Review E	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.	Thank you for your comment. The guideline recommends that all children with presentations other than EM are discussed with a specialist who should be able to advise on this.
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for your comment. This has now been reworded according to your suggestion.
SH	Lyme Disease Action	Evidence Review F	6	8	Suggest "painful sensory and motor radiculopathy" to explicitly state that sensory changes and weakness may occur in addition to pain.	Thank you for your comment. We have made this change as you suggested.
SH	Lyme Disease Action	Evidence Review F	6	11	Instead of "type of neuroborreliosis" which is vague, we would suggest specifying the "site and stage of	Thank you for your comment. This sentence has now been amended for clarity to say 'site of

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					infection ie whether early Lyme neuroborreliosis or late-stage Lyme neuroborreliosis, in each case specifying whether the peripheral or central nervous system is affected."	infection'. This section is intended as a short introduction only.
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for your comment. This guideline is not intended to review the best methods of delivering OPAT and therefore we did not review evidence for this specifically. As a result, we are unable to comment specifically on evidence for patient and carer-led OPAT.
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for your comment. We have clarified in the research recommendations that research is required for the different presentations of Lyme and suspected Lyme.

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SH	Lyme Disease Action	Evidence Review F	22	2	Children with Lyme disease affecting the nervous system may not present with neurological symptoms.	Thank you for your comment. Clinical judgement is required when assessing children and any people who cannot articulate symptoms.
SH	Lyme Disease Action	Evidence Review F	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)	Thank you for this background information.
SH	Lyme Disease Action	Evidence Review F	22	24	See comment on Short guideline page 22 line 11	Thank you for your comment. We have responded to your comment on short guideline (comment ID 195)
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for your comment. This section is referring to the available evidence for management of facial palsy only. As per NICE process, we do not consider animal studies.
SH	Lyme Disease Action	Evidence Review F	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	Thank you for this background information.

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					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.	
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for this comment. The guideline does include recommendations for continued follow up and support for people with persisting symptoms. The guideline does not consider underlying pathophysiology and management of any autoimmune aspects was not prioritised at scoping of the guideline.

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					There is a need for further research into how best to treat autoimmune aspects of Lyme neuroborreliosis - see comment on research recommendation R2	
SH	Lyme Disease Action	Evidence Review F	24	22	See comment on page 18 line 9 re. reduced OPAT costs.	Thank you for your comment. This guideline is not intended to review the best methods of delivering OPAT and therefore we did not review evidence for this specifically. As a result, we are unable to comment specifically on evidence for patient and carer-led OPAT.
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for your comment. The review recognises that there is no direct evidence for this in Lyme disease and following stakeholder comments the wording in the recommendation has been changed so that a change to oral treatment is less prominent.
SH	Lyme Disease Action	Evidence Review F	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.	Thank you for this information.
SH	Lyme Disease Action	Evidence Review F	24	46	The risk of line infection, although serious may be over-rated in terms of frequency of occurrence.	Thank you for your comment. We have altered the wording to indicate that a switch to oral medication is not specifically recommended in the guideline although the committee recognised that healthcare professionals may consider this option.

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SH	Lyme Disease Action	Evidence Review F	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.	Thank you for your comment. We have now amended this wording in accordance with your suggestion.
SH	Lyme Disease Action	Evidence Review F	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	Thank you for your comment. This sentence has now been reworded to better reflect the uncertainty due to the lack of evidence. We've included this in our research recommendation. The committee decided to recommend 4g ceftriaxone, as this is the recommended dose for bacterial meningitis.

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					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.	
SH	Lyme Disease Action	Evidence Review F	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	Thank you for your comment. This section is specifically referring to potential neurological disability caused by damage to the nervous system. It does not diminish the problems you describe that can be associated with chronic illness.

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					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.	
SH	Lyme Disease Action	Evidence Review F	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	Thank you for your comment. This possibility is covered in the recommendations to offer a second course of antibiotics to people with persisting symptoms if treatment may have failed using an alternative antibiotic to that used for initial treatment.
SH	Lyme Disease Action	Evidence Review G	6	9	mis-spelling of poly-arthritis.	Thank you for your comment. This has now been amended.
SH	Lyme Disease Action	Evidence Review G	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.	Thank you for your comment. The committee agreed that long-term follow up of patients treated for Lyme disease is important and this has been clarified in the research recommendation. People who had received previous treatment with antibiotics were a subgroup identified by the committee, which would be analysed separately if heterogeneity in the evidence was identified, in order to determine whether this was the cause. As there was no meta-analysis in this review, no subgroup analysis was conducted. People who had received previous antibiotics did not form the majority of people included in the 3 arthritis studies.
SH	Lyme Disease Action	Evidence Review H	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.	Thank you for your comment. We have added to the text that sensory peripheral neuropathy has been described in association with acrodermatitis chronica atrophicans.

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SH	Lyme Disease Action	Evidence Review H	19	13	See comment above: Acrodermatitis chronica atrophicans is not just a skin rash.	Thank you. We have added to the introduction.
SH	Lyme Disease Action	Evidence Review H	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.	Thank you for your comment. The recommendations were reviewed by the committee and have now been amended.
SH	Lyme Disease Action	Evidence Review H	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.	Thank you for your comment. The evidence is of very low quality and does not justify prescription of an unusual dose length.
SH	Lyme Disease Action	Evidence Review I	6	19	Add at end of sentence "…and there has been one case of fatal Lyme carditis in the UK." (Cary et al 1990)	Thank you for your comment. As per NICE methodology, we do not consider case reports as we consider evidence from the best available study designs appropriate for the review questions. We therefore did not look at this evidence.
SH	Lyme Disease Action	Evidence Review L	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-	Thank you for this information. NICE research recommendations are developed from the specific evidence reviews that were carried out in guideline development and do not include details of underlying pathophysiology. The research recommendations in the guideline relating to

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					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.	treatment and follow up do have considerable overlap with those you describe.
SH	Lyme Disease Action	Evidence Review L	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.	Thank you for your comment. The word 'seropositive' has now been removed from the title.
SH	Lyme Disease Action	Evidence Review L	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.	Thank you for your comment. This point is already captured in the sentence 'There is currently no test that helps determine this.' This evidence review and the associated recommendations are not restricted to seropositive cases only.

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SH	Lyme Disease Action	Evidence Review L	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.	Thank you for your comment. This sentence has now been amended with wider examples for clarity.
SH	Lyme Disease Action	Evidence Review L	6	12	Re: "consider these". Please see previous comment for suggestions for what clinical practitioners may need to	Thank you for your comment

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					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.	The NICE guideline on Patient Experience (CG138) includes consideration of the importance of co-ordination of care for people in contact with multiple services. This guideline will be linked to the Patient Experience guideline on the NICE website.
SH	Lyme Disease Action	Evidence Review L	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.	Thank you for your comment. People who had received previous antibiotics did not form the majority of people included in the 3 arthritis studies listed and these studies therefore did not inform this review. The review protocols in the guideline were for different clinical presentations and people in whom a previous course of antibiotic treatment had failed were specified as a subgroup. Following stakeholder comments, we have added further studies to this review.
SH	Lyme Disease Action	Evidence Review L	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	Thank you for your comment. These issues are reflected in the quality assessment of the outcomes; the evidence was downgraded for risk

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					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.	of bias and imprecision and the guideline committee took account of this in their interpretation.
SH	Lyme Disease Action	Evidence Review L	16	16	See comment on document 7 page 18 line 9 re. reduced OPAT costs.	Thank you for your comment. We did not review evidence for who should deliver OPAT specifically as this was not in our scope or specified in our protocols. As a result, we are unable to comment specifically on evidence for patient and carer-led OPAT.
SH	Lyme Disease Action	Evidence Review L	19	25	The rationale for research recommendation RR3 is not in appendix J of evidence report D.	Thank you for your comment. It is unclear which research recommendation your comment refers to. The guideline committee made 2 research recommendations relating to evidence review D, the rationales for which are included in appendix J of evidence report D. Research recommendation 3 in the short guideline relates to evidence review C and the rationale can be found in appendix J of evidence report C.
SH	Lyme Disease Action	Evidence Review L	164	Appendix I	Re excluded studies:	Thank you for your comment. This study has now been included in the evidence review and the

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					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	committee reviewed the evidence again following stakeholder consultation. The conclusions were not affected by the additional evidence.

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					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.	
SH	Lyme Disease Action	Evidence Review N	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.	Thank you for your comment. This is a clinical guideline whose remit is to make recommendation for healthcare professionals. We are unable therefore to make recommendations to public information providers.
SH	Lyme Disease Action	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	Thank you for this information.

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					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	
SH	Lyme Disease Action	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.	Thank you for your response to this question.
SH	Lyme Disease Action	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	Thank you for your comment. The quality of the evidence identified is not usually mentioned in the short guideline, but discussed fully in the evidence reviews. The recommendations provide

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					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.	a pragmatic pathway based on the limited clinical evidence and committee consensus informed by their clinical experience, as discussed in the rationale and impact sections. The recommendations have also been amended following stakeholder consultation to clarify the importance of clinical acumen in diagnosis and treatment in the absence of high quality evidence.
SH	Lyme Disease Action	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."	Thank you for your comment. The current wording is standard NICE wording.
SH	Lyme Disease Action	Short	3	6	amend to - including urban parks and gardens.	Thank you for your comment. This has now been amended to include the word 'urban'.
SH	Lyme Disease Action	Short	3	15	add bullet - Peak incidence occurs in June with a smaller peak in September but tick bites can occur throughout the year.	Thank you for your comment. The recommendation wording was reviewed following stakeholder comments and the committee considered that further detail was unhelpful in raising general awareness.
SH	Lyme Disease Action	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…"	Thank you for your comment. This recommendation has now been amended to include the word 'correct' as per your suggestion.
SH	Lyme Disease Action	Short	3	21	add "correctly" at the end of the sentence	Thank you for your comment. We have changed the wording to include 'correct'' and a link to PHE guidance on how to remove a tick has now been added

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SH	Lyme Disease Action	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."	Thank you for your comment. The committee have agreed a number of images of typical and atypical EM to accompany the guideline, as providing images was considered clearer than attempting descriptions of these.
SH	Lyme Disease Action	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)	Thank you for your comment. The recommendation wording has been changed as you suggest.
SH	Lyme Disease Action	Short	4	19	Change to "Is more likely to be hot, itchy or painful"	Thank you for your comment. The wording has been changed as you suggest.
SH	Lyme Disease Action	Short	5	1	replace fatigue with "general malaise"	Thank you for your comment. The word 'fatigue' has now been replaced with 'malaise'.
SH	Lyme Disease Action	Short	5	2	add new bullet "fatigue" because fatigue is pronounced in Lyme disease	Thank you for your comment. There is now a separate bullet point for 'fatigue'.
SH	Lyme Disease Action	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"	Thank you for your comment. The word 'aches' has now been added to this bullet point.
SH	Lyme Disease Action	Short	5	15	insert "stroke-like symptoms" after neuropsychiatric presentations	Thank you for your comment. The committee reviewed the recommendation and did not consider your suggested wording would be helpful.
SH	Lyme Disease Action	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.	Thank you for your comment. The order of the symptoms and signs has now been amended.
SH	Lyme Disease Action	Short	5	17	add to the end of this "or multiple unexplained connective tissue inflammation"	Thank you for your comment. The committee reviewed the recommendation and discussed this

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						possible addition but considered it was not specific enough to be helpful.
SH	Lyme Disease Action	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".	Thank you for your comment. The wording of this recommendation has been amended following stakeholder consultation to 'people presenting with symptoms and signs relating to 1 or more organ systems'.
SH	Lyme Disease Action	Short	5	24	after activities add "recreational or occupational"	Thank you for your comment. We try to make the recommendations as concise as possible without losing any information; therefore, we did not elaborate on the different types of activities because the word 'activities' covers for both recreational and occupational activities more succinctly.
SH	Lyme Disease Action	Short	6	2	To be clear, this should say "..or positive NHS testing.."	Thank you for your comment. Following stakeholder consultation, recommendation 1.2.24 has been amended to 'UK accreditation service accredited laboratories' and describes the validation process that tests should have met.
SH	Lyme Disease Action	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"	Thank you for your comment. The recommendations have been altered to indicate the limitations of the tests and the algorithm reflects the new recommendations.
SH	Lyme Disease Action	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	Thank you for your comment. The recommendations have been altered to indicate the limitations of the tests and the algorithm reflects the new recommendations.

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					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.	
SH	Lyme Disease Action	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	Thank you for your comment. The wording of this recommendation has been revised following stakeholder consultation to reflect that the immunoblot test does not definitively confirm diagnosis.
SH	Lyme Disease Action	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.	Thank you for your comment. The wording was reviewed and is consistent with NICE style,
SH	Lyme Disease Action	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	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests.

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					studies and the need for further research in a clinical "real-world" setting in which the tests are used.	
SH	Lyme Disease Action	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. This will therefore be challenging to implement effectively and logically requires development of	Thank you for your comment. The recommendations have been amended to put more emphasis on clinical judgement and the limitations of tests and consideration of treatment despite negative results. It is hoped that this will result in improved care for patients. The guideline did not examine service delivery issues and cannot comment specifically on Lyme disease clinics.

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					specialised clinics for Lyme disease with accompanying training and educational material. See answers to question 3.	
SH	Lyme Disease Action	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.	. Thank you for your comment. The recommendation has been amended to put more emphasis on clinical judgement and the limitations of tests and consideration of treatment despite negative results.
SH	Lyme Disease Action	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."	Thank you for your comment. Following stakeholder comments, the committee decided to remove this recommendation.
SH	Lyme Disease Action	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."	Thank you for your comment. The committee discussed this issue and considered it an important issue but did not agree that there was enough evidence to include this information in a recommendation. It is included in the research recommendations.
SH	Lyme Disease Action	Short	9	3	After "central nervous system infection" add "ophthalmic involvement eg uveitis" as uveitis is considered a "red flag" symptom.	Thank you for your comment. The committee reviewed the recommendation and made changes to it as suggested.
SH	Lyme Disease Action	Short	9	4	replace "is likely to be the underlying cause" with "suspected" - to reflect wording on p22 line 6	Thank you for your comment. The committee reviewed the recommendation and made changes to it as you suggest.
SH	Lyme Disease Action	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	Thank you for your comment. The quality of the evidence identified is not usually mentioned in the recommendations but is included in the rationale section of the short version as well as in the evidence reviews.

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					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.	
SH	Lyme Disease Action	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…"	Thank you for your comment. The recommendation has been altered to clarify that the reaction can occur during treatment.
SH	Lyme Disease Action	Short	10	table 1	It is not clear whether "Erythema migrans" means "erythema migrans in the absence of other symptoms"	Thank you- the wording of the table has now been changed.
SH	Lyme Disease Action	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.	Thank you for your comment. The wording has been changed to clarify that a switch to oral treatment is not being recommended. However if switch from IV to oral treatment is being considered then doxycycline is the preferred oral treatment.
SH	Lyme Disease Action	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	Thank you for your comment. The committee made the recommendation by consensus. The recommendation for IV ceftriaxone 4g for 28 days was informed by the use of ceftriaxone for bacterial meningitis. The available evidence indicated that oral treatment with doxycycline for

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					as first alternative, amoxicillin 1g 3 times daily for 28 days as second alternative.	30 days was of clinical benefit although the evidence is of very low quality.
SH	Lyme Disease Action	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	Thank you for your comment. The wording has been changed to clarify that a switch to oral treatment is not being recommended. However, if a switch from IV to oral treatment is being considered, then doxycycline is the preferred oral treatment
SH	Lyme Disease Action	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.	Thank you for your comment. The recommendations for Acrodermatitis chronic atrophicans is for 28 days on that basis.
SH	Lyme Disease Action	Short	10	table 1	See comment on page 14 line 2 and consider altering footnote on pregnancy:	Thank you for your comment (comment number 180)
SH	Lyme Disease Action	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).	Thank you for your comment. The recommendations indicate the importance of discussing diagnosis and treatment in children with non EM Lyme disease with a paediatric specialist.
SH	Lyme Disease Action	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.	Thank you for your comment. The committee recognised that IV ceftriaxone or oral doxycycline might be considered by a specialist in discussion with parents and carers and so decided not to add this detail here.

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SH	Lyme Disease Action	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.	Thank you for your comment. Treatment failure is already included in the recommendation, and it is unclear how the addition of relapse as an option would be helpful to the healthcare practitioner assessing the patient. Similarly, autoimmunity related to Lyme is a possible mechanism of action and it is unclear how including it here would help. A clinical epidemiological study with appropriate follow up should describe symptom patterns but would not be able to provide information on cause such as auto-immunity.
SH	Lyme Disease Action	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."	Thank you for your comment. Treatment failure is already include in the recommendation and it is unclear how the addition of relapse as an option would be helpful to the healthcare practitioner assessing the patient.
SH	Lyme Disease Action	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	Thank you for your comment. In this guideline the committee preferred to avoid contested definitions of the stages of Lyme disease and instead to make recommendations for treatment according to clinical presentation. IV ceftriaxone is the recommended treatment for central nervous system involvement.

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					this case it would be important to recommend treatment with intravenous ceftriaxone.	
SH	Lyme Disease Action	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"	Thank you for your comment. IV ceftriaxone is the recommended treatment for central nervous system involvement.
SH	Lyme Disease Action	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.	Thank you for your comment. The guideline makes clear the limitations of tests and the committee hope that the implementation of this guideline will improve knowledge of healthcare professionals.
SH	Lyme Disease Action	Short	13	4-7	For comment on social care and social services see comment on document 13 page 6 line 12	Thank you for your comment. This recommendation has now been reworded for clarity.
SH	Lyme Disease Action	Short	13	2	add bullet as further explanation "there is currently no test which will differentiate"	Thank you for your comment. An additional bullet to this effect has now been added to the recommendation.
SH	Lyme Disease Action	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'.	Thank you for your comment. While NICE clinical guideline 91 is relevant, NICE guideline on common mental disorders covers more than just depression and provides reference to more specific NICE guidelines.
SH	Lyme Disease Action	Short	13	19	add bullet "referral to physiotherapy for management of joint and neurological symptoms to assist in prevention of disability"	Thank you for your comment. This list is not intended to be exhaustive, but to give some examples of symptoms that may require assessment and management.
SH	Lyme Disease Action	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	Thank you for this information and the very recent reference. As per NICE process, we do not consider poster presentations for inclusion in evidence reviews. Published full text studies are preferred to ensure there is adequate information to carry out full critical appraisal of the study and outcomes.

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					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 ".)	
SH	Lyme Disease Action	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.)	Thank you for your comment. The recommendation is covering the wide range of presentations of Lyme disease and the committee considered that from that perspective most people do recover completely.
SH	Lyme Disease Action	Short	14	18	move above previous bullet and replace "developing and increases the chance of complete recovery" with "and persistent infection"	Thank you for your comment. The committee reviewed the wording of this recommendation and considered information in bullet points about the nature of Lyme disease was more important. We have added that most people recover completely when treated early.
SH	Lyme Disease Action	Short	15	3	move section 1.4.3 forward to after 1.4.1 as a more logical place	Thank you for your comment. The committee reviewed the order of the recommendations and did not consider the suggested move was required.
SH	Lyme Disease Action	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.	Thank you for these suggestions, which we have added to detail of the research recommendation, which can be found in the evidence reports.
SH	Lyme Disease Action	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	Thank you for your comment. NICE research recommendations are developed from the specific evidence reviews that were carried out in

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					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.	guideline. The guideline did not examine these areas and therefore cannot make a research recommendation.
SH	Lyme Disease Action	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	Thank you for your comment. We agree that this research would help inform case definitions. Comprehensive information about symptoms and other factors might give some insights into causes of ongoing symptoms but this study design is unlikely to be definitive in assessing the underlying pathophysiology.

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					The possibility that persisting symptoms may be caused by autoimmunity should also be considered under this research recommendation. (Document 13 page 6 line 8)	
SH	Lyme Disease Action	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	Thank you for your comment. We have replied to these comments in the relevant sections.
SH	Lyme Disease Action	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.	Thank you for your comment. The committee reviewed this suggestion and considered that core outcome set is an important research recommendation and it would not be appropriate to merge this with treatment recommendation. Abrogation of the immune response is included in research recommendation 5.
SH	Lyme Disease Action	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."	Thank you for your comment. We have removed this phrase as it was unhelpful.
SH	Lyme Disease Action	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.	Thank you for your comment. We have amended the sentence as suggested.
SH	Lyme Disease Action	Short	20	16	Question 1	Thank you for this information.

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					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.	
SH	Lyme Disease Action	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.	Thank you for your comment and your suggestion of a way forward. Your comments will be considered by NICE where relevant support activity is being planned'

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					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.	
SH	Lyme Disease Action	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.	Thank you for your comment. The wording has been retained. The committee recognised that tests assess immune response rather than 'diagnose' but they are an aid to diagnosis, which is how the sentence is worded.
SH	Lyme Disease Action	Short	22	5	insert uveitis	Thank you for your comment. Uveitis has been added to the recommendation but is not repeated in the rationale.
SH	Lyme Disease Action	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	Thank you for your comment. The aim of the guideline is to make generalists and specialists more aware of Lyme disease. The role of a specialist is to consider an alternate diagnosis and advise about treatment. In areas of uncertainty, healthcare professionals are expected to confer with colleagues and more specialised centres. This could include international contacts.

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					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.	
SH	Lyme Disease Action	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	Thank you for your comment. The committee discussed this and while accepting your point considered that courses in weeks were more easily understood.
SH	Lyme Disease Action	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.	Thank you for your comment. The section does say 'available' evidence that we believe captures the important points.

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SH	Lyme Disease Action	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.	Thank you for your comment. A significant resource impact is defined by NICE as a recommendation that leads to an additional £1million pounds or more in NHS spending in a year in England. The committee did not anticipate that additional antibiotic prescribing for those with persisting symptoms would exceed this annual cost.
SH	Lyme Disease Action	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."	Thank you for your comment. A significant resource impact is defined by NICE as a recommendation that leads to an additional £1million pounds or more in NHS spending in a year in England. The committee did not anticipate that additional antibiotic prescribing for those with persisting symptoms would exceed this annual cost.
SH	Lyme Disease Action	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.	Thank you for your comment. The evidence reviews were based on symptoms with timing as possible strata if evidence indicated differences according to time points. The evidence did not fit into early or late definitions so the recommendations remain based on symptoms and signs. The research recommendation for a clinical epidemiological study of Lyme disease in the UK should follow up all cases.
SH	Lyme Disease Action	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	Thank you for your comment. This sentence has now been amended to 'Infection with Borrelia

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					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*.	burgdorferi can go unremarked, with mild symptoms that are ignored by the person'.
SH	Lyme Disease Action	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."	Thank you for your comment. The context section is designed to give a brief overview of the guideline. The limitations of the evidence are discussed fully in the evidence reviews. However, the statement to which you refer has now been amended to 'based on the available evidence' to better reflect the overall lack of evidence.
SH	Lyme Disease Action	Short	34	25	add to the end of the sentence ".., and to investigate diagnostic tests and treatment options."	Thank you. This has been added.
SH	Lyme Disease UK	Evidence Review B	24	17-26	Special comment on Evidence Review B, page 24 lines 17-26, on signs and symptoms in children*; 'Signs and symptoms of Lyme disease in children were considered, but the committee did not think separate recommendations were warranted. Fever in children during the summer months when respiratory infections are less common was identified as a circumstance when Lyme disease in children might be more likely when associated with a relevant clinical history. While the committee wished all clinicians to be aware of possible presentations of Lyme disease they considered that children and young people (younger than 18 years) who are presenting with possible Lyme disease and non-EM, for example facial palsy, should*	Thank you for your comment. The section does not rule out the possibility that children may present differently from adults. For clarity, we have added this to the detail in this section. The recommendations were reviewed following stakeholder comment and the committee did not consider a change to the recommendations was warranted. The committee considered that children's inability to articulate their symptoms is common to all assessment of children and not specific to Lyme disease. Similarly, the assessment of children who have had congenital infection will not usually rely on an account by the

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					have their diagnosis and management discussed with a specialist, as these presentations are unusual and the importance of accurate diagnosis and treatment is essential. This is discussed further in evidence report D'. Patient experience, observations from out group of over 8000 members and the approach of independent Lyme disease experts disagrees with this conclusion. Experience is that children do present differently in some respects to adults, very often because they are unable to articulate clearly how they feel and may express their subjective symptoms by way of behaviour and mood, which may be interpreted as unexplained social and psychological problems rather than the outcome of non-verbalised physical symptoms. True psychological impact from the disease is also observed. It must also be borne in mind that in the case of congenital Lyme, which is acknowledged by the guideline, a child will never have been fully well, and may not know how what they feel diverges from what is "normal" for others. This has not been adequately considered. The view of the committee has been derived from much evidence on studies involving children but could be considered as limited in two ways. A) the studies were observing the reliability of certain symptoms, such as EM and facial palsy, rather than asking the open question of what manifestations of disease are seen in children with Lyme disease B) understandably the studies included children with clear diagnoses of	child but from clinical observation and assessment and parents or carers reports. The limitations you describe of diagnostic studies are recognised and reflected in the very low quality rating given to the evidence included. The committee have made a research recommendation on clinical epidemiology that we hope will improve knowledge of clinical presentations.

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					Lyme disease, therefore children whose perhaps diffuse and unclear symptoms had not led to diagnosis were not included. Therefore the very population which is at risk, those who have Lyme disease but who have not been diagnosed, were not studied. As a way of discovering whether Lyme disease presentation may differ in children and lead to misdiagnosis, the evidence base is unavoidably lacking. For this reason, the evidence searched for should have looked to the clinicians' experience. There is an underlying understanding that publication of clinical experience by practising paediatric Lyme specialists for example in the US will have been affected by the political situation that has affected Lyme disease for several decades. Before drawing conclusions simply based on limited studies, the committee should be prepared to acknowledge that the evidence about manifestation of Lyme disease in children is dangerously incomplete, that research is needed urgently and that doctors should be aware that children may demonstrate Lyme symptoms differently from adults. We would suggest a comment to this effect in the short guideline around section 1.2.6 *'The evidence for possible different manifestation of Lyme disease in children, especially young children, is scarce. Children, especially those with congenital Lyme, may express physical symptoms through unexplained mood and behaviour differences, being unable always to articulate symptoms as do adults.'*	

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SH	Lyme Disease UK	Evidence Review C	192	32-34	If the committee did not systematically review this area and recognised that the immune response to Borrelia is still being studied, how is it possible to make a judgement on the effect of antibiotic treatment on testing?	Thank you for your comment. The committee chose not to make a statement or recommendation about this because of the lack of evidence.
SH	Lyme Disease UK	Evidence Review C	192	28-29	Why is the view of test manufacturers ignored? Where is the evidence supporting this view?	Thank you for your comment. The committee were not aware of any evidence provided by the manufacturers with the only reference available outlining a series of case studies published in 1989.
SH	Lyme Disease UK	Evidence Review C	192	27	Immune-suppressants are mentioned in passing but subsequent discussion only considers antibiotics and does not discuss at all whether or how immune-suppressants may affect testing if, for example, given for facial palsy suspected at first as being Bell's palsy. Steroids may affect the immune response but are also contraindicated in Lyme disease. The committee should reconsider the effect of immune-suppressants on testing and the further impact on Lyme disease, and offer advice to doctors on this issue.	Thank you for your comment. The recommendations do include information that antibody response may be affected by immunosuppressant treatment. The recommendations have also been changed to put more emphasis on clinical presentation with recognition of limitations of testing. The committee reviewed the recommendations following stakeholder comment and did not feel able to add further advice to the recommendations other than emphasising the importance of clinical judgement on decisions about treatment and not basing decisions on testing only. The vast majority of the studies included in this review did not report detail of previous or concurrent treatment with steroids or any other immunosuppressant. One study (Evidence Report F) in people with facial palsy found that antibiotics alone resulted in a greater reduction of symptoms compared to antibiotics plus steroids for facial palsy but this was a retrospective observational study and outcomes of very low quality.

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						Steroids can have a role in the treatment of infection such as bacterial meningitis and uveitis.
SH	Lyme Disease UK	Evidence Review C	192	30	Who is *'the medical community'*? Many independent Lyme disease experts regard testing after antibiotic use to be compromised, so this can only mean "some" of *'the medical community'.*	Thank you for your comment. The phrase 'not widely accepted' was used here to imply that not every member of the medical community accepts the lack of response after antibiotics. It is not intended to suggest that the entire medical community agree. However, we agree that this could be clarified and 'the medical community who consider' has now been amended to 'the medical community, many of whom consider'.
SH	Lyme Disease UK	Evidence Review C	192	32	Patients are sometimes tested directly after finishing a course of antibiotics, prescribed for an erythema migrans rash, to "show" that the infection has been cured. Evidence Review C states here that *'if the patient was inadequately treated the organism would go on replicating after a recovery period and an antibody response would develop',* which suggests that if the patient is testing during this recovery period then a false negative is a danger. Even if the antibiotics do not permanently abrogate the immune response, a temporary effect at a time when testing may be offered involves a risk of a false result.	Thank you for your comment. The guideline does not recommend any testing for people with EM.
SH	Lyme Disease UK	General	First Row	Question 1:	Response: Overall the guidelines are vague and will mislead both clinicians and patients. This will make them challenging to implement and put into practice. One practical point to note is the in our experience the majority of doctors are not familiar with how to order a 2-tier test and do not have time in a consultation to work it out. The guidance on the PHE website is not clear enough, with reference to 2 forms when there is only one. Nurses often struggle to find the correct test on their computer system because of naming	Thank you for your comment. We acknowledge the lack of good quality evidence but consider that the recommendations will provide some guidance while further research is awaited. We will pass your concerns about ordering tests to PHE.

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					conventions, and labs often refuse tests because doctors do not know that the clinical history may be important. Bias and prejudice from clinicians is likely to impede progress in implementation. Constructing guidelines on a highly complex disease with a very poor evidence-base has resulted in over-simplification and lack of clarity which will give little useful guidance.	
SH	Lyme Disease UK	General	First Row	Question 2:	Response: We are not qualified to do cost analysis, and our expertise is all about what we see happening in patients' lives. What we see indicates that poor awareness and diagnosis and inadequate treatment result in people becoming permanently ill with multi-system disease, often at a young age. The costs to the country in terms of lost productivity, lost taxes, and NHS and Benefits spend must be enormous. There is further cost borne by patients in private treatment (which may be abroad, taking money out of the UK economy) as well as the incalculable loss of destroyed lives. Were this to be properly acknowledged the cost of effective treatment would be placed in a right perspective.	Thank you for your comment. NICE guidelines include clinical and cost effectiveness evaluation of interventions when recommendations are made. NICE guidelines do not incorporate broader costs such as productivity costs or personal costs although it is recognised financial and non-financial costs extend beyond the health system. In this guideline, no treatment has received a negative recommendation based on economic grounds alone.
SH	Lyme Disease UK	General	First Row	Question 3:	Response: National initiatives to spread information amongst doctors all grades are needed. Note the extremely low uptake of the RCGP course – much more than this is needed.	Thank you for your comment and this information. When completed all of the material used to develop the guideline will be publicly available on the NICE website. The development of web

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					There needs to be an extensive resource of validated information linked to the guideline and given much publicity. (Where are doctors currently supposed to go to find validated information about Lyme disease?) It would be good to have a web resource where there are linked doctor and patient areas, each visible to the other but with audience-appropriate language and detail, to enable doctors and patients to have the same view of the authorised material and to enable them to be reasonable in their expectations of each other. A public awareness campaign to ensure that people in key areas, such as pharmacists and teachers as well as medical staff, understand more about Lyme disease is essential. There is more information about Zika and Malaria in doctors' surgeries and chemists than there is about Tick-borne infections which can be contracted in a garden. Clear guidance on how to order tests, how to assess validity of non-NHS tests, a system of pre-defined statements giving test results, in accordance with manufacturers' instructions, so that labs, doctors and patients all understand all the communications, would further ease implementation. The progress being made in France, which is covered in this article, would be an interesting and useful case-study as they implement an extensive public education campaign. Undertaking the necessary research is key.	resources and public awareness campaigns are out of the scope of this guideline.

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					Reference: The Telegraph, 17th July 2017 http://www.telegraph.co.uk/news/2017/07/17/france-launches-tick-alert-app-frantic-bid-map-lyme-disease/	
SH	Lyme Disease UK	General	First Row	Question 4:	No. This is completely inappropriate for treating different people at different stages with different manifestations of a highly variable disease. It completely underestimates the sophistication of the bacterium and the course of disease. Dosage and duration should be based on patients' clinical response to treatment, bearing in mind there is no currently available test of cure.	Thank you for your response.
SH	Lyme Disease UK	General	First Row	Question 5:	This is a clinical judgement but we would draw attention to the suitability of doxycycline as an antibiotic against rickettsial infections which may travel with Lyme disease infection.	Thank you for your response.
SH	Lyme Disease UK	Short	General	General	Abbreviations used in the comments: ACA: Acrodermatitis chronica atrophicans A&E: Accident and Emergency Hospital Department CFS: Chronic Fatigue Syndrome CMT: Core Medical Training DEET: N,N-diethyl-meta-toluamide EBV: Epstein–Barr virus ELISA: Enzyme-linked immunosorbent assay GP: General Practitioner HIV: Human immunodeficiency virus	Thank you.

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					ME: Myalgic Encephalomyelitis PCR: Polymerase chain-reaction RIPL: Rare and Imported Pathogens Laboratory TB: Tuberculosis	
SH	Lyme Disease UK	Short	General Comment	N/a	Lyme Disease UK's online support group has over 8000 members. We have a daily overview of the intense suffering as well as the pervasive lack of knowledge about Lyme disease amongst GPs and NHS specialists. Our members found much of the guideline misleading and ambiguous. Doctors reading this guideline are likely to come away with the message that Lyme disease is rare, easy to treat and that it cannot persist beyond two short courses of antibiotics. Symptoms which we see as common in our community are played down severely and so a representative picture of a Lyme disease patient is missing from the guideline as is how serious a disease this is. Patients and doctors need to be well informed about the reality of the situation which is that - due to a major lack of evidence, a desperate need for research, unreliable testing and no test to tell us when the disease has been eradicated - this guideline is drawn up on a very shaky foundation. Unfortunately, the guideline is built on biased, incomplete evidence and hidden assumptions. 1) The impact of lack of evidence on the content of the guidelines	We have reviewed the recommendations following stakeholder comments and have worked to increase clarity. The committee were aware of the limitations of the evidence base and have drafted research recommendations, which they hope will inform future research priorities for Lyme disease. Where there was an absence of evidence, the committee agreed recommendations based on their experience.

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					The lack of evidence encountered by the committee throughout the preparation of the guideline is only obvious on reading the evidence reviews in the full version, and only briefly stated in the explanatory pages of the short version. This must be made clearer throughout the short version document to encourage experienced doctors to use their clinical judgement where appropriate. We had expected that this guideline would better equip doctors to make a confident clinical diagnosis of Lyme disease, using serology as a tool, not a master. Most GPs will deal with the first 15 pages of the short version, in which lack of evidence is rarely made clear. Not only is the lack of evidence on which the guideline is built not clear, but the default response to areas particularly lacking in evidence seems to be a combination of complacency, reassurance and the status quo, as represented by the American IDSA approach to Lyme disease. Reverting to this attitude as the default, is irresponsible as this is what has partly led to the burgeoning problem in existence today. The attitude in the absence of evidence seems to be that there is no cause for concern, rather than taking a precautionary approach until it is shown, by proper research, to be unnecessary. This approach runs	(1) The format of NICE short guidelines is to separate recommendations from more detailed evidence reviews. The reasons the recommendations were made are also included in a section called rationale and impact, which provides some background to the recommendations including quality of evidence. The purpose of the guideline is to better equip healthcare professionals and the committee are confident that this guideline provides a useful tool for healthcare professionals. The committee discussed at length all the areas in the guideline to make the best recommendations possible. A precautionary approach is taken in areas where the committee considers this warranted such as review of infants potentially at risk and the use of a second course of antibiotics and longer courses of antibiotics.

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					throughout the guideline. This is particularly the case with treatment recommendations, where the evidence is especially lacking, but where the average GP would be reasonable to assume that treatment recommendations are based on good evidence that these protocols work. The fact that in some areas, the guideline has been drawn up by the committee relying on their own experience, surely demonstrates how severe the lack of evidence is. 2) Reluctance to make explicit acknowledgement of implied limitations There are some issues which are implicit within the guideline which are never stated explicitly. This has two important effects i) the majority of GPs, unaware of the complexities of Lyme, will entirely miss these points and ii) the guideline has not addressed the further ramifications of these issues. These are: a. Testing – Whilst it is <u>implicit</u> throughout the guideline that testing is not absolutely reliable and accurate, nowhere is it <u>explicitly</u> stated in the guideline that serology tests are not reliable and nowhere is there any consideration of sensitivity and specificity data (or explanation of these terms) of the tests routinely used by RIPL. There are many	(2) Following stakeholder comments we have added recommendation explicitly stating that false positives and false negatives occur and to emphasise the importance of clinical judgement as well as testing.

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					places where this is implied - e.g. where test results are at odds with clinical symptoms and history and quite correctly, Lyme is still considered as a possible diagnosis. But, the truth is that this is a situation where some with positive serology do not have Lyme disease, and some with negative serology do have Lyme disease. Many people in our group have history of tick bite, rash, summer-flu, untreated, still have symptoms but are seronegative. This, as well as manufacturers' data, pours doubt on the usefulness of serology which is nowhere addressed openly. We doubt this situation would be accepted in other serious infections. The implications of missing a case is grave. People end up with long lasting debilitating symptoms, unable to work and care for themselves. Whilst overuse of antibiotics is a consideration, the impact of undertreating or not treating is too grave to ignore. Doctors must be given information on the lack of evidence to allow them to take this into account as part of a clinical diagnosis. As the guidelines stand, a patient could present with a known tick bite, multiple Lyme disease symptoms, no other alternative diagnosis and	The format of NICE guideline recommendations is that the background information is not repeated in the short version but is easily available. The recommendations are based on actions and these do include information that symptoms can continue and that there is no test of cure. The information on majority of ticks not transmitting Lyme is from PHE.

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					yet, with a false negative test result. The over-reliance on serology, encouraged by the guideline, could mean that the GP could discount Lyme disease and miss the vital opportunity to treat early and reduce the chance of the patient experiencing long-term debilitating symptoms. b. Treatment failure – it is <u>implicit</u> from the instruction to repeat courses of antibiotics and/or refer to specialists, that treatment failure occurs, however this is not <u>explicitly</u> stated. Further, the full guideline shows how incomplete is the evidence on which treatment recommendations are built. Neither of these is clear in the short guideline which is all that most GPs will read. They are given no information about the insubstantial evidence nor of the level of treatment failures that are observed. The scientific paper which is used as evidence and on which much in the guideline depends, had nearly half the subjects failing to recover. Doctors are being encouraged to give reassurance that is not based on evidence - eg telling people that most ticks do not transmit Lyme disease, that most people recover from Lyme disease following short courses of treatment, that once	We have added that recovery can take 'months or years'. The committee were reassured that the evidence failed to show maternal transmission. The recommendations are developed from review questions and centred on actions and not on pathophysiological background. The evidence review examined the need for prolonged antibiotics and found no benefit of this. The recommendations therefore are about information and support. The persistence of symptoms is mentioned in the guideline and the uncertainty about cause is clear. (3) These points are addressed in responses above.

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					treatment has ceased, recovery can take months and that it is unlikely that a mother has passed on the infection to her baby. c. Persistence – related to the above point, persistence after antibiotic therapy is implicit but not stated explicitly as a possible outcome. The acknowledgement of ACA makes it clear that untreated Lyme can also persist for years without self-resolving. Many doctors believe that Lyme cannot persist and this guideline reinforces this blinkered view. The persistence of Lyme disease should be stated explicitly as well as being implied in the guideline. 3) Failure to address issues which are only implied, not stated Lack of explicit recognition of the aspects noted above, means that failure to address the problems is also hidden. a. With regard to testing, it is not made clear to doctors that testing is not reliable and therefore the question of what to do in the face of conflicts between test results and clinical evidence is not properly addressed. GPs clearly, from patient experience, regard the	

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					tests as definitive and regularly exclude Lyme disease in the face of overwhelming clinical evidence, solely on the basis of laboratory tests. The guideline fails to address this problem and dissuades doctors from using their clinical judgment. b. By not explicitly acknowledging the possibility of treatment failure beyond two courses of antibiotics, the guideline avoids the need to give guidance on how to help patients for whom this is the reality. This fails patients, their doctors and the taxpayer. c. Failure to acknowledge explicitly the persistence of Lyme disease in some cases, has enabled the guideline quietly to fail to address questions such as some aspects of person to person transmission and treatment of those who have been misdiagnosed or who have had Lyme disease for many years. If blood transmission does prove to be possible, implications of getting this wrong are severe. The implications of not treating people who have been misdiagnosed or who have had Lyme disease for many years, is already severe.	(4) The guideline does not refer to Lyme specialists but to specialists in infectious disease and to other specialists such as cardiologists and rheumatologists. The committee considered that people who need specialist input are more likely to be people for whom a diagnosis is difficult or who do not improve with treatment. The requirement of a specialist is to re-assess the patient and review the diagnosis and treatment and whether alternative diagnoses should be considered. Much of this is based on judgement and experience and not easily the subject of a guideline. As you indicate above, the evidence base is poor and specialist expertise needs to be developed. The committee hope that the guideline and its dissemination will improve awareness and knowledge among all specialists.

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					d. Many people in our 8000+ strong online support group who have been left untreated for years, some of whom have benefited from private treatment, look at this guideline and do not believe that it would have had any effect on their own history. The failures that led to their own descent into chronic illness have not been corrected. The most important of these is the denial of active Lyme disease after recommended treatment, even though there exists no 'test of cure' and research clearly demonstrates persistence. 4) References to Lyme 'specialists' – are there any in the UK? Referral to specialists is used in many sections as a kind of "back-stop" or "catch-all" solution for difficult situations that have no answer or ones which the guideline appears not to acknowledge openly. We would question how many fully competent NHS specialists in Lyme disease actually exist in the UK, given that few have experience of treating many Lyme patients and there appears to be no Lyme-specific instruction in Infectious Disease specialist training. Until there are demonstrable and identifiable Lyme specialists in the UK, who truly represent an expert degree of understanding in the complexities of Lyme	(5) The symptoms studies in the diagnostic accuracy review (evidence report B) were not chosen as key markers of the disease but as possible markers where a diagnosis could be confidently made and acted on. The recommendations do list a much broader range of symptoms associated with Lyme disease. Following stakeholder comment the importance of clinical assessment has been added and acknowledgement of the limitations of tests. It is difficult to make clear recommendations on symptoms, which you state are difficult to describe and feature less in the literature. It is hoped that research recommendations will provide improved clinical epidemiology and information on testing which will improve clinical care.

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					disease, the use of referral to a specialist as a "catch-all" end-point for problems is inadequate and irresponsible. This guideline does not provide a sufficient basis or specialist knowledge. There is an additional problem involved in referral to multiple specialisms in that the various constellations of signs and symptoms found in Lyme disease patients may be missed because specialists hone in on one area of medicine rather than seeing the overall patient picture. NHS referrals take time and GPs need guidance as to what to do during this period to ensure there is not a treatment gap. 5) A misplaced focus on uncommon symptoms and circular logic There is a disturbing level of circular logic hidden in the development of the guideline. In particular this is shown around the symptoms that have been chosen as key markers of Lyme disease. Aside from the erythema migrans, which is a relatively well-understood symptom, the other symptoms, looked at in Evidence Review B, were; lymphocytoma, cardiac symptoms such as heart block, facial palsy and ACA. Of these, there is some anecdotal but general understanding, largely demonstrated in the NICE CKS, that lymphocytoma is uncommon in Europe, cardiac	

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					symptoms are rare in the UK and usually present early, ACA is very uncommon, and facial palsy, although associated with children, is something that in our large patient group, we do not see commonly. Facial palsy is associated with seropositivity which may enhance its prevalence in the statistics. European Lyme disease is generally regarded as having more general neurological symptoms whilst US Lyme disease is more associated with Lyme arthritis, possibly because of the geographical distribution of different Borrelia species. There is little consideration of symptoms which we see frequently in UK patients, such as fatigue, general neurological issues, cognitive dysfunction and autonomic dysfunction. So far as the impact on testing is concerned, we see on page 20, lines 27-30 of the Short Version that '*The evidence suggested that the combination of initial IgM and IgG ELISA and confirmatory IgM and IgG immunoblot testing had a high sensitivity and specificity, particularly for Lyme arthritis, Lyme carditis and acrodermatitis chronica atrophicans',* these being less common manifestations of Lyme disease in the UK. This suggests that this testing regime had a lower specificity and sensitivity for other, more common, manifestations of Lyme disease.	

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					Evidence Review B, page 18, section 1.7.1, makes it clear that these symptoms (ACA, facial palsy, cardiac problems and lymphocytoma) are very poor predictors of Lyme disease, with generally low sensitivity, although they presumably score well on testing as they show high specificity as predictors. The one predictor that showed well for sensitivity was the NeBoP combination score which significantly brings fatigue into the equation. The evidence quality is low but the implication important. Evidence Review B, page 23, lines 35-37 Section 1.10.3, states that *'The committee used the evidence review and their knowledge of presentations of Lyme disease to develop recommendations for possible presentations associated with Lyme disease'.* This shows that in a situation where evidence is lamentably poor, the guideline has relied heavily on the experience and knowledge of a small group of people, none of whom is a noted Lyme specialist with extensive experience of treating Lyme disease. This section also notes in Lines 37-38, that *'The committee acknowledged that some non-specific symptoms associated with Lyme disease are difficult to describe'* and it is these symptoms which receive scant attention. Whilst this is completely understandable in some ways, it is unacknowledged that it is these very symptoms, notably cognitive dysfunction, pain and fatigue, which	(6) No evidence was found on blood products, organ donation and sexual transmission and this is explained in the evidence review. (7) The committee are hopeful that the guideline will increase awareness of Lyme disease and provide a framework for healthcare professionals to improve diagnosis and management. The guideline development process involves a rigorous search for and assessment of the literature so treatment is based on best available evidence.

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					most disrupt the lives of Lyme patients and which appear to be least associated with good response to testing. As a whole, there is a concern that a large part of this guideline is built around consideration of a few symptoms which are uncommon, but observable, more reliably identified by the current testing regime and feature more in the research literature. In contrast, some more common and disabling symptoms, which are difficult to describe, feature less in the literature and may well be associated with testing failure, have been given less prominence. This means that the status quo is enhanced and infected patients are pushed towards a misdiagnosis of CFS/ME or fibromyalgia, for example. The reasons underlying this bias may be understandable but the bias, and its implications, have not been acknowledged. 6) Person to person transmission Person to person transmission, listed in the Scope, was not fully addressed. In the short guideline, there is no mention of blood products, organ donation or sexual transmission. Absence of solid evidence is not absence of proof and as studies exist to suggest person to person transmission is possible, if not proven, caution should be advised until proper	(8) The format of a NICE guideline is that it emphasises actions and does not provide general and background information about a condition. The guideline recommendations do indicate that people may need long-term support including help with education and work settings. NHS England's commissioning of the Lyme guideline acknowledges in part the burden of this disease on patients, their families and carers. Following stakeholder consultation a recommendation for discussion with the reference laboratory or a specialist has been added, for those whose symptoms are not improving, in case testing for other tick borne disease is required.

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					research is completed. We discuss this further in specific comments. 7) Failure to tackle common misconceptions directly or challenge bias Lyme disease is currently receiving a lot of media attention and publicity. Misinformation, common myths and assumptions believed by either the patient or medical professionals can quite easily spill into, and influence, the outcome of medical consultations. Particularly so, with a disease that doctors are not familiar with and which can often be perceived as an unlikely or controversial diagnosis. For this reason, it is important that key messages in the guideline are clear and that they directly challenge long-held misbeliefs and misconceptions. The overall vagueness of the guideline does not achieve this and will have a negative impact on patients in terms of timely diagnosis, effective treatment and potential for recovery. As a result, patients will continue to feel the need to seek private and potentially risky treatment options. The offensive and uncompassionate responses to a recent Pulse online article about these draft guidelines (see here) coupled with the low take up rate of the free RCGP course, which was co-created by the charity Lyme	(9) The level of the evidence is explicitly discussed in the evidence reports and included in the rationale sections. The guideline also has a number of research recommendations developed following the search for evidence. The wording used is standard NICE wording that is used for all guidelines.

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					Disease Action, reflects the experiences of many of our members. Whilst there are some front line medical staff who have experience and understanding of Lyme disease, many fail to identify even clear-cut cases and treat patients in a derogatory and unsympathetic way. We fear that this guideline will do nothing to challenge these biases and misconceptions and in places, reinforce them. 8) The serious nature of Lyme disease There is nothing in the short guideline which indicates the very serious and disabling effects which are experienced by some patients. Nowhere is there an indication that some people with late Lyme disease are unable to work, need to be cared for, and cannot socialise at all or take part in any recreational activities. For some, even reading and watching television are impossible due to light and sound sensitivity. The acute emergency of heart block is referenced, but there is no material that suggests why suicide is a relatively common cause of death amongst Lyme patients. Responses to a Lyme disease infection range from total unaided recovery (producing the phenomenon of healthy seropositive people) to permanent disability and sometimes death. The guideline only refers to possible slow recovery (eg	(10) Following stakeholder consultation, recommendations have been added to emphasise the importance of clinical assessment and to recognise the limitations of tests.

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					page 13 line 3) and misleadingly informs patients and doctors that "most people recover completely", rather than that some patients never recover and are disabled, long-term. This is important because doctors routinely treat patients as though Lyme disease is a trivial illness from which they will recover without problems. It is also important because people do not take tick-bite prevention measures, or prompt action in response to signs and symptoms after a tick-bite, as seriously as they would if this awareness was widespread. This lack of clarity about the possible long-term implications of a Lyme disease infection is negligent. We believe that the exclusion of co-infections from the Scope was a serious mistake, which we contested at the time. Ticks can transmit a number of diseases, which may, in part, explain why patient response to treatment varies and is not as predictable or successful as this guideline suggests. 9) The lack of clarity with which the guideline communicates the insecure nature of the evidence-base The guideline uses key phrases to communicate the level of certainty provided by evidence, including variations of directives such as "offer", "consider",	The guideline does not specify how long a person has had symptoms for and health care professionals will need to use clinical judgement in assessment of people who may have had symptoms for some time.

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					"think about". (Ref section 9.2 *Developing NICE guidelines: the manual*) We consider that there are two problems associated with this aspect. One is the presumed familiarity of busy GPs with this subtle but important use of wording. How many doctors actually understand the difference implied by these words? The other applies specifically to this guideline. There is a discrepancy between the almost universal scarcity of good quality evidence found by the committee and the confident language used in the guideline. There are many areas where words indicating a good level of evidence are used where in fact the evidence is of low quality. Eg in section 1.3.15-17, the verbs are *Manage*, *Inform*, and *Advise* being applied to Lyme disease in pregnancy where the evidence is extremely unclear. Hesitant "consider" directives seem to be more applied to situations where Lyme disease may be diagnosed or considered to have persisted and more confident language is used to direct reassurance towards patients. This is unjustified and paints a falsely certain picture. This use of language may be difficult to avoid in a disease like Lyme disease, where there is more uncertainty and less good evidence than is usual. However, accurate communication of the level of certainty in the recommendations can simply be stated explicitly. It would be relevant to cite the James Lind	

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					Alliance Top 10 uncertainties in Lyme disease as a demonstration of the understanding and knowledge on which this guideline is based. 10) Only a specific subset of patients are covered Whilst this guideline may provide some improvement for newly infected patients with a EM rash or who are seropositive, there is no help for those patient who are sero-negative or those who don't respond to two courses of antibiotics. There is no acceptance of the need for clinical diagnosis nor acknowledgement of the large percentage of people for whom treatment is likely to fail. It also fails to cover how a clinician should approach patients who may have been mis-diagnosed in the past or who have no diagnosis prior to the guideline, but who are symptomatic - should they be re-assessing existing patients who show Lyme disease signs and symptoms? How many patients will be left suffering from long term disabling symptoms? How much will this cost the taxpayer in unnecessary NHS costs, lost taxes and benefits? Overall	

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					The committee must consider whether the guidelines as a whole are fit for purpose in their current form. As they stand they are implicitly accepting that a large percentage of cases will either be missed or not recover. References: NICE CKS https://cks.nice.org.uk/lyme-disease#!diagnosissub Pulse*: "GPs advised not to rule out Lyme disease despite lack of tick bite",* 25th September 2017 http://www.pulsetoday.co.uk/news/clinical-news/gps-advised-not-to-rule-out-lyme-disease-despite-lack-of-tick-bite/1/20035346.article?PageNo=1&SortOrder=dateadded&PageSize=10#comments James Lind Alliance, *Lyme Disease Top 10* http://www.jla.nihr.ac.uk/priority-setting-partnerships/lyme-disease/top-10-priorities/	
SH	Lyme Disease UK	Short	1	Paragraph 1	We are very concerned about the use of the term "specialist" throughout the guideline and we have expressed this in our comments below. The recommendation to consider referral to a specialist assumes that the specialist will have good knowledge of Lyme disease and be competent to treat the person. We are not aware that UK NHS specialists, either in Infectious Disease, or in other specialties, have such expertise.	Thank you for your comment. The referral to the specialist is to consider alternative diagnoses as well as provide treatment for Lyme disease. In areas of uncertainty, healthcare professionals are expected to confer with colleagues and more specialised centres. This would include international contacts.

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					See our further discussion on the referral to 'specialists' in the comment referring to page 7 lines 11-14.	
SH	Lyme Disease UK	Short	1	Paragraph 1	People who suspect they have Lyme disease should be added to this list as they need to be aware of what pathway of care can be expected.	Thank you for your comment. The terminology is intended to include people on any part of Lyme pathway included suspected Lyme disease.
SH	Lyme Disease UK	Short	3	13-15	This may be misleading. In the 'Context' section on page 35, it states; *'Lyme disease occurs mainly in the northern hemisphere and travellers to specific areas of Europe, North America and elsewhere may be at risk'* without any indication of which regions are considered *'specific'* and where *'elsewhere'* may refer to. Asia is mentioned in the 'Context' section on page 33, but not here. Which parts of Asia, for example? Statements about prevalence carry the risk that assumptions are made about areas not mentioned. Therefore, the guideline should not make statements which may lead a GP erroneously to rule out Lyme as a possibility. In the case of the individual person, it is not possible to use geography to rule out a consideration of a Lyme infection. Suggest a much broader statement. *'Lyme disease should be considered endemic throughout the Northern Hemisphere.'*	Thank you for your comment. The committee discussed the wording of this recommendation at length, with a view to alerting healthcare professionals of areas of higher prevalence yet not confining their concerns to those areas. We have removed the word 'specific' from the context section as we agree it was unhelpful.
SH	Lyme Disease UK	Short	3	13-15	Additionally, the statement *'more prevalent'* is misleading. More prevalent than where? What evidence supports this statement? There doesn't appear to be any usefulness of comparison, therefore for clarity we suggest *'is also prevalent in…'*	Thank you for the comment. The committee considered that wording indicated that there are areas of different prevalence and the bullet point needs to be taken in the context of the other recommendations.

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SH	Lyme Disease UK	Short	3	18-20	Did you mean to say this? The sentence structure implies that gardens and parks are overgrown and it doesn't cover the fact that ticks are also found in urban areas. We suggest changing this to *'ticks are found in grassy and wooded areas but also in urban and peri-urban parks and gardens'. 'Overgrown'* should be removed as it creates bias away from well-tended areas which may still harbour ticks. urban parks and gardens as shown in this 2016 study. Many of our 8000+ members have reported being infected in such areas including back gardens and whilst sitting on mown lawns. Reference: Hansford et al *Ticks and Borrelia in urban and peri-urban green space habitats in a city in southern England.* Ticks Tick Borne Dis. 2017 Mar;8(3):353-361. doi: 10.1016/j.ttbdis.2016.12.009. Epub 2016 Dec 21 https://www.ncbi.nlm.nih.gov/pubmed/?term=Hansford%2C+K.M.%2C+et+al.%2C+Ticks+and+Borrelia+in+urban+and+peri-urban+green+space+habitats+in+a+city+in+southern+England.+Ticks+Tick+Borne+Dis%2C+2016.	Thank you for your comment. The wording of this bullet point has now been amended to 'where ticks are commonly found (such as grassy and wooded areas, including urban gardens and parks).
SH	Lyme Disease UK	Short	3	5-6	Did you mean to say this? The sentence structure implies that gardens and parks are overgrown and it doesn't cover the fact that ticks are also found in urban areas, as shown in this 2016 study. Many of our 8000+ members have reported being infected in such areas including back gardens and whilst sitting on mown lawns. One member shared; "I was sitting on a picnic rug on a manicured lawn when I was bitten"	Thank you for your comment. The wording of this bullet point has now been amended to 'where ticks are commonly found (such as grassy and wooded areas, including urban gardens and parks).

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					Another says; "my next door neighbour was bitten and infected in his back garden in London. Fortunately his doctor was familiar with Lyme disease and he was tested promptly". Another says; "My friend came to ask me for advice as their school newsletter mentioned a number of children had been bitten in the playground and they were recommending tick checks, however they hadn't suggested prevention techniques". This member's thoughts are in common with many others'; "I had no idea there were ticks in my area and even if I did I didn't know what prevention techniques I could have employed". We suggest changing this to *'ticks are found in grassy and wooded areas but also in urban and peri-urban parks and gardens.'* The word *'overgrown'* should be removed as it creates bias away from well-tended areas which may still harbour ticks. Reference: Hansford et al *Ticks and Borrelia in urban and peri-urban green space habitats in a city in southern England.* Ticks Tick Borne Dis. 2017 Mar;8(3):353-361. doi: 10.1016/j.ttbdis.2016.12.009. Epub 2016 Dec 21 https://www.ncbi.nlm.nih.gov/pubmed/?term=Hansford%2C+K.M.%2C+et+al.%2C+Ticks+and+Borrelia+in+urban+and+peri-urban+green+space+habitats+in+a+city+in+southern+England.+Ticks+Tick+Borne+Dis%2C+2016..	

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SH	Lyme Disease UK	Short	3	5-6	A mention of pets, wild animals and birds need to be inserted somewhere - e.g. *'ticks can be found anywhere where there are pets, wild mammals or birds.'* One of our 8000 members shared; "My dog and cats have regularly been bitten. I never thought to check myself as well as them. There is so much information in the vets about Lyme disease in animals, but until joining this group I had never seen anything about the risk to humans. It also didn't occur to me that an unnoticed partially fed tick could transfer from one of my pets to me".	Thank you for your comment. The recommendations on awareness are not meant to be exhaustive and include all risks. The committee considered that detailed lists were more likely to cause people to think they could not have Lyme if they did not have those risks and therefore chose not to add further detail.
SH	Lyme Disease UK	Short	3	11-12	*'In many areas'* suggests that there are some areas where Lyme infection does not occur. There is no evidence for this. In addition, because prevalence data has not been collected for the whole country, it could be misleading to highlight just the South of England and Scotland. Prevalence doesn't necessarily correlate with infection rates. People travelling may not notice a tick bite when away or relate it to symptoms experienced some weeks later when home. We suggest; *'in any area of the UK, therefore location and travel history within the UK should not influence clinical assessment'*.	Thank you for your comment. The committee tried to find a balance between indicating that Lyme disease can occur anywhere and recognising that there appear to be higher areas of prevalence.
SH	Lyme Disease UK	Short	3	16-17	For the statement; *'Be aware that most tick bites do not transmit Lyme disease',* what evidence supports this, especially as prevalence and infection rate data is	Thank you for your comment and information. The information is from Public Health England who operates a tick surveillance scheme. The

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					not complete? Why is it necessary to say this? What is the desired understanding? There is a risk that a doctor will interpret this as a reason not to suspect Lyme disease in the person in front of him, instead of looking at the evidence objectively. This statement is biased and may reduce use of prevention methods and vigilance. The possible result of this statement is at odds with the committee's expressed concern in Evidence Review A, Page 20, lines 13-15; *'The committee considered that one of the most important issues in the diagnosis and management of Lyme disease is that the healthcare professional considers Lyme disease as a possible diagnosis. This is a particular issue in areas where Lyme disease is less prevalent.'* The same information in Evidence Review A supports these statements; *'Some tick bites do transmit Lyme disease', and 'prompt removal of the tick reduces the risk of transmission'.* It is important to encourage prompt removal but care should be taken that wording does not imply that attachment time can be used to rule out risk of transmission. No lower limit for transmission time has been established: - anecdotal evidence (from humans) challenges the accepted assumptions (based on animal studies), - attachment time is sometimes hard to establish, - the observed tick may not be the only tick which has bitten, another may have bitten unobserved, the	reason to include this is to reassure people who are bitten. The committee acknowledge that there is no lower limit for transmission.

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					presence of one tick being adequate to demonstrate exposure to others, - This study by MJ Cook, reviews the evidence on transmission time. Reference: Cook, MJ. *Lyme borreliosis: a review of data on transmission time after tick attachment.* Int J Gen Med. 2014 Dec 19;8:1-8. doi: 10.2147/IJGM.S73791 https://www.ncbi.nlm.nih.gov/pubmed/?term=transmission+time+borrelia+cook	
SH	Lyme Disease UK	Short	3	16-17	Patients in our support group have experienced doctors ruling out a Lyme infection on the basis of tick attachment time; "I was told that this tick had not been attached for 48 hours therefore I couldn't have Lyme disease. When I started getting symptoms I didn't relate them to the bite as I believed the doctor". Statistically, prompt removal of the tick may reduce transmission time, but in an individual case, transmission will either have occurred before, or not occurred, before removal, so *'may reduce'* is more accurate. We would suggest; *'Be aware not all tick bites transmit Lyme disease. Prompt removal of the tick may reduce the risk of transmission, but no lower limit for transmission time has been established; prompt removal should not prevent consideration of Lyme disease.'*	Thank you for your comment. The committee acknowledge that there is no lower limit for transmission time and are not implying this in the recommendation.
SH	Lyme Disease UK	Short	3	4	Add an additional bullet to make people aware of the lack of research into Lyme disease and hence limitations of these guidelines.	Thank you for your comment. The quality of the evidence is not usually mentioned in the recommendations, but is discussed fully in the

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					e.g. Be aware that... *'There is limited research on many aspects of Lyme disease. This guideline is based on the currently available evidence.'*	individual evidence reviews and the rationale sections.
SH	Lyme Disease UK	Short	3	4	Also add additional bullet to cover congenital Lyme (and if the committee decides to add concern about blood products to section 1.3, that should also be included here) e.g. '*Congenital transmission is possible. (Transmission through blood products or organ donation is theoretically possible and has not been disproved.) Lack of a history of tick bite is never an exclusion criterion for Lyme disease.'*	Thank you for your comment. Information for women with Lyme disease during pregnancy is covered by recommendation 1.3.18. No evidence for transmission of Lyme disease through blood products was identified; therefore, the committee did not make any recommendation on this. Recommendation 1.2.6 states 'Do not rule out the possibility of Lyme disease in people with symptoms but no clear history of tick exposure.'
SH	Lyme Disease UK	Short	3	7	To aid doctors and patients, it could be useful to expand this sentence to explain why - e.g. *'because nymph ticks can be as small as poppy seeds and as the bites are normally painless, the tick can feed and drop off without being noticed, particularly if attached to areas such as the hairline, behind the ears and behind the knees.'* One of our 8000 members shared; "If I didn't know what I was looking for I would have missed the bite. It was tiny and behind her ear".	Thank you for your comment. Recommendations do not usually include explanations. This has now been added in section 1.11.3 of the awareness of Lyme disease report.
SH	Lyme Disease UK	Short	3	21	Add in information about how to do this safely, using an appropriate tick removal tool, following the manufacturer's instructions as they can differ. Also note that all surgeries, pharmacies and A&E departments should be able to safely remove a tick. It is very important to include some examples of what NOT to do: e.g. burn them off, smother them in vaseline, use household tweezer, wipe the tick with	Thank you for your comment. A hyperlink to PHE guidance on how to remove a tick has now been added.

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					anti bacterial wipe, put a plaster over the tick and send people away. In our support group we have seen reports of medical staff, in GP surgeries and A&E departments, regularly making these mistakes or being unable to remove a tick at all. "I went to the GP and they were unable to remove the tick and suggested I went to the vet to buy a tool" "I was sent to A&E, but had to wait for 4 hours before being seen. When I was seen they didn't know what to do. They wiped the tick and after much discussion removed it with a pair of blunt plastic tweezers" "I didn't know it was sensible to own a tick removal tool. I now have a card which I take everywhere with me and fine tick remover tweezers at home. I have given all my friends tick removal tools and none of them realised the risks"	
SH	Lyme Disease UK	Short	4	3-5	It would be helpful to tell patients how to find patient charities and other forms of support.	Thank you for this suggestion. Information about patient charities and support groups will be available via NICE website
SH	Lyme Disease UK	Short	4	22-24	Careful expression is needed here to ensure doctors understand that while there are many causes of these symptoms individually, in combination they point to Lyme disease. We would recommend that the words *'but uncommon'* are removed. Thought should be given to a better description of the diagnostic situation. Although Lyme may be an uncommon cause of these symptoms individually, when seen in combination, we would argue that a Lyme disease infection is highly	Thank you for your comment. This statement is not intended to suggest that Lyme disease is uncommon, but that it is an uncommon cause of the symptoms outlined in the bullet points. The term 'migratory' has been added to the recommendation. The importance of reviewing the history and the context of the presentation is included in other recommendations.

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					possible. Pattern recognition in Lyme disease is key. There is a tension here about the severity of symptoms and there needs to be some attempt to express this. In early disease many of these symptoms are likely to be present, but they will appear at different times and at first will not be severe. Since Lyme disease is significantly easier to treat the earlier it is caught, it is very important that the pattern of the combination of symptoms receives attention, even if the severity is not great. Migratory symptoms are common. A tick bite/exposure which is associated with an accumulation of several symptoms including neck pain, fatigue, headache, muscular and joint pain and paraesthesia should prompt consideration of Lyme disease. However, in later disease, the severity of the symptoms is much more marked and is likely to disrupt normal life. Patients may have the same combination of symptoms, but their severity and disruption of normal life will mark this out as an identifiable disease. Suggest replacing text with; *'Consider the possibility of Lyme disease in people presenting with several of the following symptoms, because 1/3 people will not show a rash and, when seen in combination, Lyme disease may be the cause of:'*	
SH	Lyme Disease UK	Short	4	12 - 13	For this statement; *'usually becomes visible from 1 to 4 weeks (but can appear from 3 days to 3 months) after exposure and lasts for several weeks',* where is the evidence that the rash lasts for several weeks? If there is none, then this should read *'can last for'. We recommend adding; 'Be aware that ticks may have been attached for 2+ days before discovery, so*	Thank you for your comment. We have changed the wording as you suggest.

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					timescale is not always clear and erythema migrans should not be ruled out solely on the basis that it is too early to develop one.'	
SH	Lyme Disease UK	Short	4	15-16	Because of the structure and wording, section 1.2.2 appears only to deal with other rashes developed after a tick bite. It does not deal helpfully with other rashes which may be confused with an erythema migrans rash and may or may not develop in association with a previous tick bite. Tinea and cellulitis frequently cause diagnostic uncertainty, the former not being related to any bite, and the latter being related either to a tick bite, another type of bite, or no bite. The section needs to be restructured to give GPs guidance on how to distinguish between erythema migrans and tinea, infection (including cellulitis) or local reaction. This could be done in a number of ways, but is vital to give a GP the best chance of making the right diagnosis. One of our 8000 members states "my mum's' neighbour came to me to ask about my experience of being diagnosed. She had an awful migrating rash on her ankle after a bite. Her GP didn't know if it was Lyme disease or cellulitis"	Thank you for your comment. The committee discussed whether it would be helpful to add more detailed information on possible causes of rash but agreed that this was beyond the scope of the guideline.
SH	Lyme Disease UK	Short	4	1	It would be helpful to mention which repellents are effective against ticks or at least provide a link to useful information. The typical recommendation to look for DEET based products should be investigated and in our experience, it is important to look for picaridin/icaridin or citriodiol as shown here. Reference: Dr Nicola Seal, *Tick Repellents; Literature Review and Tips*	Thank you for your comment. As prevention of tick bites was outside the scope of the guideline, no evidence review was undertaken on insect repellents. However, the recommendation now says to use a repellent that repels ticks.

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					http://lymediseaseuk.com/2016/03/27/literature-review-of-tick-repellents-nicola-seal/	
SH	Lyme Disease UK	Short	4	2	Explain that ticks can often go unnoticed and that nymph ticks can be incredibly small (poppy seed size). Tell people to take photos of any attached ticks found as well as any rashes which appear and keep a diary of any symptoms which develop following a bite, as symptoms can have a delayed onset. Drawing around the bite site or any rashes with a biro can be useful to monitor a rash's migration.	Thank you for these suggestions. We have added more detail in the evidence review.
SH	Lyme Disease UK	Short	4	7	Clinical assessment It is essential that diagnosis by erythema migrans rash is as accurate as possible because treatment at this stage offers best hope of a resolution. We understand that some doctors, faced with lack of knowledge, a rash and a concerned patient, will offer ineffective courses of antibiotics - e.g. 1 week of 100mg per day of doxycycline, "just in case". One member shares; "I was bitten by a tick told the rash which later appears probably was nothing to worry about, but I was given 1 week of doxycycline 50mg a day" This type of prescribing is regrettable. It is also the case that patients will sometimes present with a rash they believe to be Lyme, but may not be recognised by the doctor as erythema migrans, and we recognise this puts pressure on doctors. More clinician knowledge is the answer to these problems.	Thank you for your comment. The recommendation for treatment of a person with erythema migrans have been made with a view to ensuring adequate treatment is given. The committee have worked with NICE to provide images of typical and atypical EM to support health care professionals.

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					Doctors also need to be aware that resolution of a rash during a course of antibiotics does not mean that the underlying infection has cleared. The erythema migrans rash is pathognomonic for Lyme disease but may resolve while systemic infection continues. Our strong overall recommendation is that clinicians need a readily-accessed, excellent resource to enable confident and accurate diagnosis of an erythema migrans rash. Doctors should not be relying on a Google image search which regularly brings up a 'perfect' bull's-eye shaped erythema migrans rash on fair skin.	
SH	Lyme Disease UK	Short	4	8	There should be images, as part of the text of this guideline, which give an idea of the range of possible appearance of erythema migrans, because doctors will not always have time or ability to access an online database. There should also be a weblink to a comprehensive resource of pictures and guidance on characteristics of erythema migrans rashes, with a guide to important questions to ask to aid diagnosis of erythema migrans rash as distinct from local reaction, and skin infections such as cellulitis and tinea. This should include target rashes, uniform rashes, rashes on dark skin, rashes which are not circular, multiple rashes and rare forms such as blistering rashes. This resource should also include photos of lymphocytoma. Important questions include the time of rash appearance, any spreading nature of the rash, the presence/absence of swelling/heat/itching, the awareness that if tick exposure time is unclear, then so is the timing of the rash, the awareness that local	Thank you for your comment and information. The committee have worked with NICE to provide images of typical and atypical EM to support health care professionals.

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					reaction and erythema migrans rash may occur together and so must be disambiguated, the awareness that erythema migrans may be multiple and not around the bite site, any response to antifungal/antihistamines as well as awareness of equally serious differential diagnoses. Our support group's experience is that most GPs try to identify the rash from sight only without asking any of the questions above. Elizabeth Maloney MD co-authored the current Lyme American Lyme disease guidelines. The presentation found here. The section, *'Diagnosing Lyme Disease: Clinical Strategies for Disease Detection'*, has a useful section on erythema migrans diagnosis and some relevant photographs. Perhaps US doctors like Dr Elizabeth Maloney could be approached for sources of representative images. Dr Petra Hopf-Seidel of Ansbach also has a collection of erythema migrans photos. Lyme Disease UK has its own collection of erythema migrans rash photos, which can be provided on request. Examples of comprehensive EM resources: https://winonalyme.com/2014/10/02/lyme-rash-photos http://lymediseaseguide.net/lyme-rash-photos-and-pictures https://phpa.health.maryland.gov/OIDEOR/CZVBD/Shared%20Documents/Lyme_MD_poster_FINAL.pdf https://www.cdc.gov/lyme/signs_symptoms/rashes.html http://www.medicalacademiccenter.com/presentations/	

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					Reference: Elizabeth Maloney, Diagnosing Lyme Disease: Clinical Strategies for Disease Detection, http://www.medicalacademiccenter.com/presentations	
SH	Lyme Disease UK	Short	4	9	Suggest rewording and extending bullet point to include; *'a usually red rash, that increases in size and may sometimes have a central clearing. Be aware that rashes can be varied in colour and shape especially where there is skin tension and where skin tones vary. Increasing in size is key feature.'*	Thank you for your comment. The committee have agreed a number of images of typical and atypical EM to accompany the guideline, as providing images was considered clearer than attempting descriptions of these.
SH	Lyme Disease UK	Short	4	11	Suggest rewording and extending bullet point to include; *'not usually itchy, hot, painful or swollen, although it is possible for erythema migrans to develop over a local reaction to the same bite, which could be itchy, hot, painful or swollen.'*	Thank you for your comment. The committee reviewed the wording of the recommendation describing EM and considered that while the occurrence you mention can happen the time course makes it less likely and all eventualities could not be covered in the recommendation.
SH	Lyme Disease UK	Short	4	14	Suggest extending bullet point to include; *'usually at site of the tick bite, but may occur elsewhere.'* Add an extra bullet point here: '*multiple erythema migrans rashes are possible, from multiple or single bites'* (indicating systemic spread). Also, consider the addition of lymphocytoma to the erythema migrans section as diagnostic of Lyme disease, most often in children but sometimes in adults. If not here, lymphocytoma should be added to other signs of Lyme disease in section 1.2.3	Thank you for your comment. We have altered the wording as you suggest.
SH	Lyme Disease UK	Short	4	17	We believe the committee meant the development and receding of a local reaction would typically happen within or during about two days, not that it will happen more than two days later. *'Over'* could mean "more	Thank you for your comment. The wording of the recommendation has been changed in line with your comment.

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					than" or "after". We would suggest that *'during the 48 hours'* is less ambiguous.	
SH	Lyme Disease UK	Short	4	20	This statement is not clear, but will be improved if the recommendation above about restructuring is followed. GPs who are genuinely unable to distinguish between two possibilities need guidance on the correct treatment. In our experience the most likely situations are: - Is this erythema migrans rash or ringworm – should the doctor provide doxycycline, antifungal medication or both? - Is this erythema migrans rash or cellulitis – which antibiotic is recommended to cover both conditions? In uncertain cases, there should be a recommendation that a follow-up appointment is made at the time, as in many practices this is not happening and this may lead to a delay in further consideration, with poor consequences.	Thank you for your comment. The committee discussed whether adding a recommendation for review was useful but considered that this is usual clinical practice. The committee agreed that it was beyond the scope of the guideline to provide detailed description of possible other causes of skin rash.
SH	Lyme Disease UK	Short	5	1-20	All cases of palsy should be clinically assessed and tested for Lyme disease. As Lyme disease is a common cause of facial palsy. Given it is easy to miss a bite from a tiny tick, early treatment is crucial a test and clinical assessment would seem logical here.	Thank you for your comment. The committee were not aware of evidence that Lyme disease is a common cause of facial palsy. In the evidence review for incidence one study using Hospital Episode Statistics looked at people coded for Lyme disease and facial palsy and found 11 finished hospital consultation episodes in 2014/15. The data is obviously very limited as discussed in evidence review A but does not support that Lyme disease is a common cause of facial palsy.

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SH	Lyme Disease UK	Short	5	1-20	Gut symptoms have not been listed but are commonly seen in members of our support group. There is also scientific literature on gut palsy. Has this been considered by the committee and if it has been rejected, on what basis?	Thank you for your comment. This was not raised in scoping or by the committee as a specific area to be included.
SH	Lyme Disease UK	Short	5	12-20	Add a section following 1.2.4. Many patients who are subsequently found to have Lyme disease are misdiagnosed with a predictable set of other conditions. The Caudwell Lyme Charity completed a survey involving 500 patients, in which 209 patients had additional diagnoses. We would recommend you mention these conditions so that a doctor seeing a combination of diagnoses from various specialists starts to consider Lyme disease as a cause. There are also many diverse symptoms noted as characteristic of Lyme disease by experienced doctors whose knowledge remains solely in the clinical sphere. Is it not possible to draw attention to these symptoms so that the constellation sparks suspicion in the mind of the alert doctor? Be aware that patients with Lyme disease are often diagnosed with depression, chronic fatigue syndrome, fibromyalgia, autoimmune conditions such as Hashimoto's thyroid disease, atypical MS, IBS and may display seemingly unusual symptoms such as hair loss, changed intolerance to alcohol, fasciculations, weight gain OR loss, dysautonomias (especially Postural Orthostatic Tachycardia), ear problems such as tinnitus and vertigo, chest/rib pain, urological disorders, sleep disturbance.	Thank you for your comment and this information. The committee acknowledge that people can be misdiagnosed and that people who have Lyme may have co-morbidities. However there is a lack of robust epidemiological evidence in this area and the committee have therefore made a research recommendation to improve this. At this stage additional recommendations about this would be pre-mature.

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					These patterns are noted by experienced, independent Lyme disease experts such as Dr Burrascano, Dr Horowitz, Dr Hopf-Seidel and Dr Maloney. Doctors should be alerted to these patterns and combinations. References: Caudwell LymeCo Charity, *Lyme Disease on the NHS, Patient Survey Results*, Q5, '*Additional Diagnoses: Do you have any additional diagnoses (according to the NHS?)*, 2016. www.lymediseaseuk.com/wp-content/uploads/2017/11/Q5-Additional-diagnoses.pdf Dr. Maloney (modified version of Dr. Joseph Burrascano's original checklist (with his permission), Symptom Checklist: Lyme disease https://www.partnershipfortick-bornediseaseseducation.org/wp-content/uploads/2016/06/Symptom-Checklist-with-References.pdf	
SH	Lyme Disease UK	Short	5	1-8	*'Malaise'* is a way to describe how many Lyme disease patients feel after being infected and we suggest including this as a separate point. We feel *'malaise'* a better term than *'flu-like*'. '*Flu-like*' may be problematic because of the habit of patients generally to use "flu" too liberally? Malaise is a more useful term to express the general ill feeling of people with early Lyme? In children, for example, this can present as unexplained mood or behavioural changes as they can be unable to articulate how they are feeling.	Thank you for your comment. The wording of this recommendation has now been revised in line with your comment with the removal of 'flu-like' symptoms and the inclusion of malaise. Migratory has also been added. The committee considered that aspects such a varying of symptoms is part of individual clinical assessment and common in people with ongoing symptoms from different infectious causes.

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					It would also be useful to add *'which may be migratory'* after *'muscle and joint pain'.* Suggest adding a section*:* *'In patients suspected of having Lyme disease for months or years, symptoms may be profoundly disabling, but also may vary from day to day and week to week. This is a characteristic of Lyme disease, not of the unreliability of the patient. Some symptoms, such as joint pain, are commonly migratory in Lyme.'* We suggest starting with fatigue and have bullets as follows, lines 1 – 8, extending to 13 *• Fatigue, malaise and exhaustion with little exertion* *• Swollen lymph glands* *• Neck pain or stiffness* *• Joint or muscle pain* *• Cognitive impairment such as memory problems, word finding problems and difficulty concentrating (sometimes described as "brain-fog")* *• Headache* *• Paraesthesia especially numbness and tingling* *• Insomnia* *• Palpitations* *• Sweats* *• Fever, which may be high, low or absent* *Focal symptoms may be more marked around the bite area, if known. Symptoms may be mild at first, but the pattern should prompt consideration of Lyme disease'*	

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SH	Lyme Disease UK	Short	5	21-25	*'and'* suggests that how long the person has had symptoms is, in itself, informative. However, it is knowing whether the history of the symptoms tallies with the possible exposure, which is important. Suggest *'in conjunction with'* instead of *'and'* e.g. having symptoms for 4 years is of itself not suggestive, but having had symptoms for 4 years and having been on a walking holiday in Devon 4.5 years ago, is suggestive. It is worth asking people what their occupation is - e.g. gardeners, farmers etc may be more at risk. However, given that ticks have even been found in urban parks and gardens, it is important to include a reminder that any outdoor activity poses a risk of tick exposure.	Thank you for your comment. The committee considered your suggestion; however, it is not in line with NICE style.
					Prevalence data is incomplete and so *'travel to areas where Lyme disease is known to be prevalent'* could be misleading and result in someone not receiving a Lyme disease diagnosis if they haven't travelled to an area where prevalence is considered to be high. Consider replacing text with '*If a person presents with symptoms that suggest the possibility of Lyme disease, explore how long the person has had symptoms in conjunction with their history of possible tick exposure. For example, ask about:* (Consider adding bullet point) *'Have there been any unusual responses to unconnected courses of antibiotics during the time when symptoms have been present? In someone suffering from Lyme disease, prescription of antibiotics for other reasons may have given a "bad reaction" or unexpected temporary resolution of currently suspected Lyme symptoms.'*	The recommendations mention some areas of apparent higher prevalence and asking about travel is important while acknowledging that it is possible to encounter ticks in all areas of UK.

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SH	Lyme Disease UK	Short	5	9-11	The word *'uncommon'* should be removed as it could lead to the possibility of a Lyme disease diagnosis being dismissed. Where is the evidence that these symptoms are uncommon? Lyme disease may be an uncommon cause of each of these symptoms when considered individually, but when several of them occur at once, especially in the context of systemic symptoms and/or history of tick bite/exposure to tick bite, Lyme disease is a logical and not uncommon cause. In our support group of more than 8000 people, we frequently see Lyme patients who carry several separate misdiagnoses before going on to be diagnosed with Lyme disease because the implications of the combination of symptoms has not been recognised. We suggest replacing text with; *'Consider the possibility of Lyme disease in people presenting with symptoms and signs relating to an organ system (focal symptoms), especially when seen in combination with each other, in the context of systemic signs and symptoms and/or history of tick-bite or exposure. Lyme disease is a possible cause of:'*	Thank you for your comment. This statement is not intended to suggest that the symptoms are uncommon, but that Lyme disease is an uncommon cause. For example, Lyme disease is unlikely to be the cause of the majority of cardiac problems. Following stakeholder consultation, the wording of the recommendation has been amended to '1 or more organ systems' to clarify that Lyme disease can be the cause of symptoms relating to multiple organ systems.
SH	Lyme Disease UK	Short	5	1-2	*'Flu-like symptoms'* are problematic because they are the ones most likely to be associated with many infections, probably the least good indicator, not found in all patients, and yet at the head of the list. Unusual fatigue is common but fever is very variable – further, '*fever'* is an ambiguous term. Doctors may interpret fever to mean "only with a high temperature" and we have known patients not given a Lyme diagnosis on that basis. We ran a poll in our support group of over 8000 people to find out about people's experiences	Thank you for your comment. We have removed the term 'flu like symptoms'.

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					with fevers. This revealed that fever may be clear (above 38 C) in some, but low-grade in many and absent in a significant number. In later disease, it is more common to feel feverish but not have a measurable temperature. Fever is therefore a poor indicator and *'flu-like symptoms'* should not be at the top of the list.	
SH	Lyme Disease UK	Short	5	26-27	How will *'no clear history of tick exposure'* be defined, given that ticks have even been found in urban parks and gardens as shown in this 2016 study? Many of our 8000+ members have reported being infected in such areas including back gardens and whilst sitting on mown lawns. Any outdoor activity poses a risk of tick exposure. Consider adding, for information; *'Be aware that patients may not present until some considerable time after infection with a history of slowly developing symptoms. The disease is variable in progression.'* Reference: Hansford et al *Ticks and Borrelia in urban and peri-urban green space habitats in a city in southern England.* Ticks Tick Borne Dis. 2017 Mar;8(3):353-361. doi: 10.1016/j.ttbdis.2016.12.009. Epub 2016 Dec 21 https://www.ncbi.nlm.nih.gov/pubmed/?term=Hansford%2C+K.M.%2C+et+al.%2C+Ticks+and+Borrelia+in+urban+and+peri-urban+green+space+habitats+in+a+city+in+southern+England.+Ticks+Tick+Borne+Dis%2C+2016	Thank you for your comment. The committee wished to ensure that Lyme disease might be considered even if the history of tick exposure is poor. The wording you suggest does not convey this.
SH	Lyme Disease UK	Short	5	28-29	How long is this applicable for? What if people develop symptoms 3 weeks after the tick bite? Will this then be deemed unrelated? People need to be encouraged to keep a symptom diary following a tick bite and be warned to look out for any unusual symptoms in the	Thank you for your comment. People without symptoms do not have Lyme disease regardless of time since bite.

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					coming weeks and months. Other illnesses that might cause additional weakness e.g. cancer, diabetes and heart disease should be taken into account, should Lyme disease start manifesting. This is ambiguous in terms of whether past or current symptoms are being referred to; i.e. will doctors be asking the person if they ever had any symptoms following an old tick bite, even if they don't feel symptomatic now? If they did feel symptomatic, a possible, retrospective diagnosis of Lyme disease should go on their records. There is a clear difference between making a note on people's record and actively treating Lyme disease. Consider replacing text with; *'Do not diagnose Lyme disease in people who have never had symptoms, even if they have had a tick bite. In those who have had tick bite and have had clear symptoms in the past but have no current symptoms, consider recording possible Lyme disease, but do not treat while asymptomatic.'*	The committee accepted that people might have a diagnosis made in retrospect if they have a convincing history but this would still require the person to have been symptomatic. This is similar to the clinical approach to other infections.
SH	Lyme Disease UK	Short	5	17	Lyme arthritis is commonly fluctuating and migratory according to Lyme clinician experience and patient experience. Anecdotal UK patient experience suggests sore, swollen knees that come and go is common for example. Consider adding a point about the migratory and fluctuating nature so that this important symptom is not rejected because it is not consistent. Add *'inflammatory arthritis affecting 1 or several joints which may be fluctuating and migratory in nature'*.	Thank you for your comment. We have clarified the recommendation to include that inflammatory arthritis can be fluctuating and migratory.
SH	Lyme Disease UK	Short	5	18	We would query the use of the words *'(less commonly)'* in a section which already begins with *'uncommon'.* Less commonly than what? Where is the	Thank you for your comment and the useful information. The words 'less commonly' have now been removed.

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					evidence for this? Only in the context of reliable diagnosis of all Lyme patients would it be possible to state that this symptom is less common than others. *'Less commonly'* may communicate "less importantly or less significantly" and this is presumably not the intended message. A less common symptom does not make it less significant in the case of the individual patient. Dr Petra Hopf-Seidel finds eye problems to be common features of Lyme disease. The familiarity with which independent Lyme experts see eye problems is demonstrated, sufficient to question the basis for the committee's use of *'less commonly',* by quotations found in the 2017 edition of *"Borreliose Wissen"* No. 36, selected quotes from doctors, in translation, read: p26: *'I find indications of visual disturbance in about 30 per cent of my Borreliosis patients, either blurred vision or double vision. Symptoms are usually not constant but instead are particularly intensive on some days, then again sometimes not at all. I find that with systematic long-term antibiotic treatment the visual disturbances reduce to the same extent as the general clinical findings, such as exhaustion, muscle pain and established symptoms.' 'The proportion of my Borreliosis patients that complain of eye problems: approximately 40 per cent.'* *'I estimate the proportion of patients in my practice with eye problems at around five to ten per cent.'* *'…There is no literature on the incidence of ocular symptoms with Lyme Borreliosis. Among my clientele eye diseases occur roughly on a scale of five per cent.'*	

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					'Approximately 30 per cent, who report on a progressive worsening of their eyesight – however only in the chronic form' *p27: 'More than 70 per cent of our patients state in the initial anamnesis and also in follow-up discussions that they suffer from eye problems. Since, in addition to borrelia, many of the other co-infections (bacteria, viruses and parasites) can also have an impact on the eye, this organ is very frequently affected.'* *'Eye symptoms are very often among the early symptoms of the chronic form of Borreliosis. Light sensitivity in particular is reported by many patients. In general, one can observe that eye symptoms are encountered very early on in the chronic form, however they respond only very slowly to corresponding therapies.'* In the light of such testimony from treating Lyme doctors it would seem reasonable for the committee to remove the bracketed qualification of eye symptoms as *'less commonly'* unless they have good evidence to demonstrate otherwise. One of our 8000+ members states; "My optometrist knew more about Lyme disease than any other doctor I had seen. He said my eye symptoms would only improve if Lyme disease was treated and went as far as to suggest I go abroad for treatment".	
SH	Lyme Disease UK	Short	6	1-4	This is a spurious and confusing statement. How can a *'supportive history'* be defined when any outdoor	Thank you for your comment. The recommendations have been changed following

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					activity poses a risk of tick exposure, as ticks have even been found in urban parks and gardens and Lyme disease is endemic in the UK? If this is left in, what is meant by an "unsupportive" history needs to be clarified here so that doctors can distinguish between a "supportive" and "unsupportive" history. This statement also encourages an over-reliance on positive serology. The risk of missing a Lyme disease diagnosis should be weighed up against treating someone with short term antibiotic therapy. *'Inappropriate treatment'* also includes other treatments which do not target Lyme disease but which could be contraindicated, such as steroids. Subjective alternative diagnoses/labels like CFS/ME and Functional disorders (for which there are no serological tests), should not be classed as alternative diagnoses which could be *'missed'*. The risk of missing Lyme disease is too great. Additionally, exploring additional diagnoses could take many months, missing an early treatment opportunity for Lyme disease. It must be clear that doctors can and should make a clinical diagnosis and only use serology as part of their assessment. A negative test can never rule out Lyme disease. One of our members shares their experience; "I was told my test was a false positive, but I was given no treatment. My health deteriorated to such a point I was unable to work or care for myself. I later was tested by RIPL privately and tested positive for another tick-borne infection - anaplasmosis. I was given a clinical	stakeholder comments to emphasise the importance of clinical assessment and to recognise the limitations of tests. The committee did consider that healthcare professionals have to make a judgement on probability and this is part of usual clinical care. The judgement involves exploring a supportive history for Lyme disease but also alternative diagnoses.

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					diagnosis on the basis of my symptoms, history and test results. 12+ months of private treatment has improved my health by around 80%. After 4 years I am now discussing a phased return to work with my employer and look forward to being able to contribute to society again. I know I am one of the lucky ones as I had the means to seek private diagnosis and treatment".	
SH	Lyme Disease UK	Short	6	8-11	Cognitive impairment needs to be expanded upon here to include the examples given on page 5 (line 5-6). It is our experience from our support group of over 8000 people, that this is a common symptom and yet above, it is listed as *'uncommon'* in Lyme disease, which is highly misleading. Patients may be thought unreliable when suffering from cognitive impairment. The same effect may occur because patients describe symptoms fluctuating over days and weeks, and affecting different parts of the body. This is especially true of joint and muscle pain where the migratory nature is recognised by experienced independent Lyme experts as being a sign of the disease. For this reason consider adding; *'Be aware that fluctuating and migratory symptoms are a feature of Lyme disease.'*	Thank you for your comment. The recommendation does not indicate that cognitive impairment is uncommon in Lyme disease, rather in all the people with cognitive impairment Lyme disease is a relatively uncommon cause.
SH	Lyme Disease UK	Short	6	5-7	It is important to be aware that these symptoms may be caused by Lyme disease and that symptom management must not be a substitute for Lyme disease treatment. The management of insomnia also needs to be included.	Thank you for your comment. We agree that symptoms management and Lyme disease treatment are not mutually exclusive. The areas included are examples only.

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SH	Lyme Disease UK	Short	6	22-24	Note that this statement makes the implicit point that it is possible to have Lyme disease and a negative test. If typical Lyme disease symptoms are present, searching for another diagnosis is a waste of resources as patients are often referred to many different specialists, none of whom are able to treat the patient's individual symptoms successfully. This is because individual specialists are not looking at the overview of the many symptoms caused by Lyme disease. Subjective diagnoses such as CFS/ME and fibromyalgia should not count when there is no serological testing for these conditions. These diagnoses can leave patients feeling abandoned and on the scrap heap.	Thank you for your comment. The recommendation has been amended to clarify the limitations of tests.
SH	Lyme Disease UK	Short	6	14-15	Current guidance already says this, and yet we very often have patients joining our support group whose doctors have tested for Lyme disease in the presence of erythema migrans rash. This endorses the previously made point about the difficulty doctors have and the help they need diagnosing erythema migrans rash (section 1.2.1) as it seems immediate testing is often the response to an uncertainty around rash. Given that the current guidance is not being followed and that testing at this stage represents a waste of NHS resources, and at best will result in treatment delay for the patient, and most probably a false negative result. We suggest; *'Do not test a person with an erythema migrans rash. If uncertain, seek advice.'* Although this raises the question of whom the GP can and should consult for an experienced view.	Thank you for your comment. The committee felt that if erythema migrans was present, then it is Lyme disease and should be treated with antibiotics; thus, the recommendation to treat without testing.

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SH	Lyme Disease UK	Short	6	20-21	Immunoblot testing cannot confirm or rule out Lyme disease. Therefore the statement on line 20-21 is misleading; contradicts the limitations of the tests described in this guideline and places too much emphasis on the ability of current serology to rule out Lyme disease. 1) We frequently see patients being denied further testing or treatment on the basis that a positive ELISA test is a "false positive", often explained as cross-reactivity with EBV. Table 8 in the Immunetics information about the C6 ELISA used at RIPL seems to make clear that the test is specific and there is no evidence of cross-reaction with EBV. Where is the evidence that every Lyme patient will test positive on current testing? A similar thing occurs with a positive Western Blot. The test manufacturer's instructions state: "*An acute EBV infection can cause a polyclonal stimulation of Borrelia antibodies. If IgM antibodies against OspC or p41 are detected without clinical symptoms for borreliosis an EBV infection needs to be tested*	Thank you for your comment. This recommendation has been revised following stakeholder consultation to emphasise the limitations of tests. The committee considered that the majority of immunoblot tests are currently conducted at reference laboratories and expert advice on interpretation is therefore available from these.

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					for". Explaining a positive test result as a cross-reaction to EBV, when a patient has clinical symptoms for borreliosis and EBV has not been tested for is an incorrect use of the manufacturer's guidelines. Is the committee aware that this happens? One of our 8,000 members sums up the experience of many "I was told my test result was a false positive and would be caused by EBV, however I had many symptoms of Lyme disease. The doctor didn't suggest testing for EBV" Is there any justification for clinicians not to follow manufacturers guidelines? We suggest the committee explicitly warns against unjustified labelling of "false positive" results. The Scope did not address the possibility that testing might not be shown to be reliable and yet this guideline seems to show in many places that there is no test which is completely	

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					accurate. Nowhere is there evidence that all testing is without false negatives. This raises the issue that there must be an adequate response for the patient who does have Lyme disease but appears as seronegative on testing. This is a gap in the guideline provision that must be addressed. 2) The following applies to all Lyme testing that remarks on IgM and IgG antibodies. There is evidence that the IgM and IgG responses in Lyme are unusual and that, in particular, the responses may be slow and unpredictable, and that IgM antibodies may be produced throughout infection, even in late disease. - Course of Antibody Response in Lyme Borreliosis Patients before and after Therapy. Elisabeth Aberer and Gerold Schwantzer "*Previous studies showed that the immune response to Borrelia burgdorferi appears to lack robust T-dependent B cell responses, as neither long-lived plasma cells nor memory B cells form for months after infection, and nonswitched IgM*	

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					antibodies are produced continuously during this chronic disease" - CD4+ T Cells Promote Antibody Production but Not Sustained Affinity Maturation during Borrelia burgdorferi Infection Rebecca A. Elsner, Christine J. Hastey and Nicole Baumgarth - From the manufacturer's information on the Viramed Borrelia Virastripe IgM test kit: page 4 point 2 *"IgM antibodies usually appear 2-3 weeks after onset of the disease for the first time (22). Antibody titers often decline several weeks to months after convalescence. But they may also persist up to several years (7,11,20)".* We frequently see patients being tested for late Lyme disease who register a positive IgM result and a negative IgG result and have Lyme excluded on the basis that IgM indicates recent infection even though the test kit says that IgM can persist. It is probably the case that most doctors are not aware of the atypical course of antibody response in Lyme, but test	

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					results should make this clear. The committee needs to address this aspect and give advice, especially on the unpredictable antibody response and the atypical IgM behaviour. 3) From our members experience it is clear there are huge inconsistencies in the way in which test results are interpreted. We don't know if this stems from the advice given by the laboratory, the doctors' ability to interpret the advice or the doctors' bias, however we recommend that the committee review this and provide clear, repeatable statements that are in line with manufacturers' guidelines. Clinicians must be advised to share these statements with patients. <u>References:</u> Elisabeth Aberer and Gerold Schwantzer, "*Course of Antibody Response in Lyme Borreliosis Patients before and after Therapy,"* ISRN Immunology, vol. 2012, Article ID 719821, 4 pages, 2012. doi:10.5402/2012/719821	

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					https://www.hindawi.com/journals/isrn/2012/719821/ Elsner RA, Hastey CJ, Baumgarth N. CD4+ T Cells Promote Antibody Production but Not Sustained Affinity Maturation during Borrelia burgdorferi Infection. Ehrt S, ed. *Infection and Immunity*. 2015;83(1):48-56. doi:10.1128/IAI.02471-14. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288900/ Viramed: Borrelia ViraStripe IgM Test Kit www.viramed.de/images/stories/pdf/Arbeitsanleitungen_EN/2551_Borrelia_ViraStripe_IgM_AL_en.pdf Immunetics, Immunetics® C6 Lyme ELISA™ Kit, Cat. No.: DK-E601-096-A, 96 Tests, For In Vitro Diagnostic Use http://www.oxfordimmunotec.com/international/wp-content/uploads/sites/3/CF-E601-905_Automatic.pdf	
SH	Lyme Disease UK	Short	6	18	These guidelines leave little room for clinical suspicion as symptoms are played down and listed as uncommon in Lyme disease and rare. This approach of using a gateway test presumes that all infected individuals will give a positive result to the C6 test. Where is the evidence for this? If there is insufficient evidence, then how can this test be used as the gateway to further testing? A knowledgeable doctor may query a negative result in the face of high clinical suspicion, but there is nothing explicit in the guideline that suggests to the doctor with no previous experience that the test is not 100% reliable.	Thank you for your comment. The recommendation has been amended to clarify the limitations of tests. We have added consideration of other tick borne infections and discussion with the reference

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					This suggests that the committee is tolerant of the possibility that patients may be given an incorrect exclusion of Lyme disease. Is this the case? For a serious bacterial infection, is this acceptable? Whilst co-infections were excluded from these guidelines, when faced with a patient who has a known tick bite, is symptomatic but is seronegative, doctors should be advised to consider a RIPL co-infection panel. Whilst the NHS are not currently able to test for all coinfections, if a patient is infected with another tick borne infection this may help to inform a clinical diagnosis or explain an alternative diagnosis. We can't find evidence to suggest these are rare. This guideline should acknowledge that ticks can transmit other infections at the same time as Lyme disease however this was excluded from the scope of these guidelines and clinicians should follow existing guidance for other infections. The C6 ELISA test used at RIPL is by Immunetics, manufacturer information here. This reference contains information about the sensitivity of the test (false negative rate). This is given as 74.9% for a range of Lyme disease patients, 67.5% for erythema migrans patients (note that some GPs still test patients with erythema migrans and withhold treatment if test is negative), 82.8% for neurological manifestations and 79.2% after 30 days' infection and longer.	laboratory for people with ongoing symptoms despite treatment.

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					Further the information states that *'a negative result does not exclude the possibility of infection with B. burgdorferi s.l.. Patients in early stages of Lyme disease and those who have been treated with antibiotics may not exhibit detectable antibody titers. Patients with clinical history, signs or symptoms suggestive of Lyme disease should be re-tested in 2-4 weeks in the event that the initial test result is negative.'* Is the committee happy with this level of sensitivity as a gateway test? Reference: Immunetics, Immunetics® C6 Lyme ELISA™ Kit, Cat. No.: DK-E601-096-A, 96 Tests, For In Vitro Diagnostic Use http://www.oxfordimmunotec.com/international/wp-content/uploads/sites/3/CF-E601-905_Automatic.pdf	
SH	Lyme Disease UK	Short	7	11-14	This recommendation to consider referral to a specialist assumes that the specialist will have good knowledge of Lyme disease and be competent to treat the person. We are not aware that UK specialists, either in Infectious Disease, or in other specialties, have such expertise. We have a general but deep concern about the situation with regard to 'specialists'. Referral to an *'appropriate specialist'* is mentioned several times in the guideline (e.g. 1.2.18, 1.2.19, 1.3.2, 1.3.10, 1.3.18), usually as the top authority and often final arbiter on diagnosis or treatment. The concern is that	Thank you for your comment. The aim of the guideline is to make generalists and specialists more aware of Lyme disease. The role of a specialist is to consider alternate diagnosis and advise about treatment. In areas of uncertainty healthcare professionals are expected to confer with colleagues and more specialised centres. This could include international contacts. NICE does not advise on contents of curricula.

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					few, if any, specialists in the UK qualify as "Lyme specialists". As we understand it, to be considered as a specialist under the 1983 Medical Act and listed on the specialist register one must have completed training which meets the requirements of the GMC. Consulting the Curriculum for Specialty Training in Infectious Diseases, it seems that doctors will encounter some training in Lyme if they take the Core Medical Training route but not if they achieve their MRCP via the Acute Care Common Stem. Thereafter it is not possible to find mention of Lyme disease in Combined Infection Training or Higher Infectious Disease Training via any of the modules from Medical Microbiology through to Infectious Diseases. What training on Lyme is received in the CMT needs to be transparent and any training on Lyme which is in the later parts of ID specialty training needs to be identified because it appears that Lyme disease does not feature in Specialty training. Rheumatologists and Neurologists (and any of the other specialties in whose care Lyme patients may be) do possibly have the same degree of training in Lyme as Infectious Disease specialists – i.e. a minimal level. Lyme disease is rarely diagnosed in the UK and Infectious Disease specialists seen by our members routinely describe it as such, so it seems unlikely that doctors are acquiring expertise through the experience of treating many patients. Given the above, on what basis can any NHS specialist in the UK be reasonably described as a	

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					"Specialist in Lyme disease"? The only consultant who has described himself as such has published very few papers on Lyme and one of these effectively proposed a new definition and description of late Lyme disease. If there are NHS specialists who are considered by some route other than specialist training to be experts in Lyme disease, then these need to be clearly identified so that GPs are aware of which specialists have the requisite knowledge and experience to be considered as a specialist for Lyme disease referral. The lack of training also raises the question of where NHS specialists working with Lyme disease patients are currently acquiring their information. What resources are doctors using? In reality there is clearly a lamentable shortage of Lyme NHS specialists and the committee should a) be open about the situation and b) consider recommendations to remedy the situation. For example, a dedicated centre of excellence (real or virtual) for the treatment of Lyme disease would allow developing NHS specialists to be exposed to large numbers of patients rather than the small numbers the average consultant might otherwise see. Being open about the lack of NHS specialists would mean that NICE has to consider realistic alternative options for care of patients who have confounded the normal pathway. Three of our 8,000 members share their experiences encountered by many:	

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					"I have been sent back and forth to numerous specialists with so many conflicting ideas. I have been under 8 specialists in the last couple of months and have just been referred to a further 4. None of them communicate with each other, their input causes confusion and gives no pathway towards a clear diagnosis" "I was tested, scanned, x-rayed and biopsied from head to toe by every specialist imaginable. Gastroenterologists, cardiologists, a neurosurgeon, urologist, endocrinologists, allergist, rheumatologist - they all wrote letters to myself and my GP to reassure me of conditions that they had ruled out but not one put together all the symptoms and diagnosed Lyme. My independent Lyme specialist says that my symptoms are that of a 'classic case'" "I was passed from pillar to post with no specialist knowing being able to identify what the root cause was. If so many experts can't find anything then surely with a supportive testing, symptoms and history the most obvious answer is being ignored" Reference: Joint Royal Colleges of Physicians Training Board, *Curriculum for Specialty Training in Infectious Diseases* http://www.gmc-uk.org/2014_Infectious_Diseases.pdf_61354066.pdf	

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SH	Lyme Disease UK	Short	7	16-19	Note again, implied concern about reliability of testing, but not explicit. Surely in the current system ELISA and blot cannot both be negative as the blot is not done unless the ELISA is positive/equivocal? This section should include explicit awareness that also an immunoblot is not infallible. Different blots can produce different results on the same sample due to differences in antigens used and differences in interpretation between manufacturers (Dr. A. Garritsen (Innatoss) personal communication). Thus immunoblots may return incorrect results. How does the Virastripe immunoblot perform on samples compared to tests from for example, Mikrogen and Euroimmun?	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests.
SH	Lyme Disease UK	Short	7	1-3	This suggests that testing too early may be the cause of a negative ELISA in the context of a Lyme disease infection. It does not mention that a patient given treatment before testing may also produce a false negative result. We note page 18, lines 8-11 but point out that information provided by Immunetics on C6 ELISA test mentions this phenomenon: *'Patients in early stages of Lyme disease and those who have been treated with antibiotics may not exhibit detectable antibody titers.'* This possibility should be included in this point - e.g. *'For people with a negative ELISA who were tested within 4 weeks from symptom onset, consider repeating the ELISA 4-6 weeks after the first ELISA test if Lyme disease is still suspected. Also be aware that antibiotic treatment may affect the test result.'* Has the committee taken into account that in cases where there is a high level of clinical suspicion, waiting	Thank you for your comment. The committee were not aware of any evidence provided by the manufacturers with the only reference available outlining a series of case studies published in 1989. This potential effect on antibody response has been included in a research recommendation. The recommendations have been amended to put more emphasis on the importance of clinical suspicion of Lyme and proceeding with treatment in these circumstances.

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					for another blood test may result in a delay in treatment which has long-term consequences? For example, in a patient with tick bite and systemic symptoms but no erythema migrans, a negative test at 4 weeks and a positive re-test at 6 weeks, this means treatment starts 10 weeks after infection with the consequent reduction in chances of a good outcome. This is covered in section 1.2.17 but should be brought up above section 1.2.16 because it is directly concerned with actions at 1.2.15. The link should be made clearer. Consider that the GP discusses the options at this point with the patient i.e. treatment which may be precautionary and unnecessary, versus delay which could risk a worse outcome if treatment is necessary. This is a situation about relative risk and one in which the patient should be informed and consulted. Reference: Immunetics, Immunetics® C6 Lyme ELISA™ Kit, Cat. No.: DK-E601-096-A, 96 Tests, For In Vitro Diagnostic Use http://www.oxfordimmunotec.com/international/wp-content/uploads/sites/3/CF-E601-905_Automatic.pdf	
SH	Lyme Disease UK	Short	7	8-10	How will a *'high probability'* be assessed and how will doctors distinguish between instructions to wait for 12 weeks to repeat tests and starting treatment straight away? There is a concern that waiting for 12 weeks is too much of a delay and an early treatment window will be missed. This instruction allows for clinical diagnosis whereas waiting for weeks to repeat blood tests, does not.	Thank you for your comment. The recommendation does not suggest waiting for 12 weeks to repeat tests, but described the actions if symptoms are already present for 12 weeks or more. The recommendations have been amended to emphasise that treatment should be considered if there is high clinical suspicion without waiting for test results. The committee recognise that a precise definition of high

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						probability or high clinical suspicion cannot be given.
SH	Lyme Disease UK	Short	7	20-22	Where is the evidence that these tests will pick up Lyme disease instead of the two-tiered testing? We understand that synovial fluid or CSF analysis has high specificity, but with a patient in this situation, a high sensitivity is required. What is the evidence for sensitivity, not just of the test, but of the sampling technique + test as a unit? Lumbar punctures come with their own risks. Do you treat/not treat on results these tests? Guidance is required for NHS specialists and there is concern that Lyme disease will be ruled out at this stage, based on a CSF test. If a CSF is required for another reason it may be appropriate to test for Lyme disease, but with such low sensitivity, it would seem the risks outweigh the potential benefit. *The evidence review seems to imply that the evidence is difficult to interpret - e.g. 'Overall, the committee found the evidence difficult to interpret', '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.'* *Regarding PCR and Culture tests:* *'The committee noted that the relatively low-test accuracy could be due to a sampling error, as the bacteria may not exist in the entirety of the sample taken; for example, an aspirate of joint fluid may not grow Borrelia as the organisms may be localised to the*	Thank you for your comment. This recommendation highlights the actions suggested if a person has negative serology but is still symptomatic. The appropriate test will be need to be appropriate to presentation so the decision on test and risk benefits will need to be made by the investigating clinician with the patient. The text is not saying that synovial fluid is not an appropriate test but that care is required about the choice of test and its interpretation.

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					synovium.' This statement in Document [C] 4.4.3, page 193, line 37-42, in part, contradicts the statement in 1.2.19, in that 4.4.3 suggests that referral to a NHS specialist is because bacteria may not exist in sample taken, whereas 1.2.19 suggests a referral is to have these additional tests carried out; *"The committee also agreed that for persons with unexplained symptoms and negative test results, a referral to a specialist appropriate for the symptoms or an infectious diseases specialist should be considered. This is because in certain cases the bacteria may not exist in the sample taken. For example, in persons with Lyme arthritis, an aspirate of joint fluid may not contain Borrelia detectable by PCR as the organisms may be localised to the synovium."* For 1.2.19, clarity is required for the whole section.	
SH	Lyme Disease UK	Short	7	24-26	What is the evidence for this statement and what is a doctor supposed to do with this information? This is a comment about the physiological and immunological status of people; what effect does living in a high prevalence area have on this? Should where a patient currently lives affect the view a doctor takes of their serological status? What does "because" mean in this sentence? Is there a suggestion that antibodies in the system of a person after some years must of necessity be past, resolved infection? Is there an assumption here that resolution happens after a given time but antibodies persist for longer? And is the doctor being encouraged to make the judgement that positive serology must be of past, resolved Lyme disease	Thank you for your comment. This recommendation has been removed following stakeholder comments.

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					because the patient lives in a high prevalence area? Surely the doctor should be judging each case on its medical merits alone? Positive serology without any symptoms may well be indicative of past, resolved infection but that is because the serology and lack of symptoms suggest this; but this might be the case in a high or low prevalence area. What would be the reaction to positive serology in syphilis or TB? Positive serology should always be considered carefully with a level of suspicion for active disease. If the committee means that evidence from high prevalence areas suggests this is sometimes the case, then they should say that and cite the evidence. Additionally, those with positive serology may have been treated in the past, or might have been recently bitten and the symptoms of Lyme disease have yet to develop so again, this comment is misleading.	
SH	Lyme Disease UK	Short	7	4-5	Please note once again implicit acceptance that test is not 100% sensitive. This should be explicit somewhere. This implies that not everyone gets a positive on the C6 ELISA.	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests.
SH	Lyme Disease UK	Short	7	6-7	Repeating both tiers of the test at the same time raises the possibility of contradiction between tiers which is not addressed. If here, the patient with symptoms gets a negative ELISA and a positive immunoblot, what is the clinician to do? Similarly if at 1.2.13 the result is positive ELISA and negative immunoblot, what is the clinician to do? If the C6 ELISA has high specificity then should the clinician regard the positive ELISA above the negative immunoblot, and if that is the case, why test with the immunoblot if the ELISA is negative? The unspoken basis of all the complexity here is that	Thank you for your comment. Following stakeholder comments, the committee reviewed the recommendations and amended them to clarify the limitations of tests and the importance of clinical diagnosis.

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					none of the tests is completely reliable and that some patients may be seronegative. Clinicians need this to be explicit and need support in forming clinical diagnoses in the face of conflicting evidence.	
SH	Lyme Disease UK	Short	7	14-15	The instruction not to delay treatment is appropriate. However, what happens if the treatment is a 3 or 4 week course of antibiotics, perhaps extended to 6 weeks, but the referral takes 3 months? This would result in a treatment break and the patient may still be showing symptoms and worse, deteriorating. This does not fully take into account NHS referral times and is therefore not realistic advice.	Thank you for your comment. We have added a recommendation to ensure the person is reviewed during treatment to ensure response can be monitored. It would be expected that discussion/referral can include over the telephone if necessary. The committee considered this is usual practice.
SH	Lyme Disease UK	Short	7	16	We repeat our concern about the ability of NHS specialists to make informed and expert consideration of what is now "a difficult case". In most cases, referral would be made to a NHS specialist who would be considered such because of specialist training and would have experience of many past patients. Who are the NHS specialists in the UK who have these qualifications? What will happen to the patient whilst they are waiting for the long referral times?	The role of a specialist is to consider alternate diagnosis and advise about treatment. In areas of uncertainty, healthcare professionals are expected to confer with colleagues and more specialised centres. This would include international contacts.
SH	Lyme Disease UK	Short	7	23	Although we agree that alternative diagnoses should be considered at all stages, we have great concern that if patients are sent to NHS specialists who are insufficiently qualified to make expert clinical judgements about Lyme disease, they will be given the default 'negative-on-all-tests' diagnoses, relevant to the specialist i.e. functional neurological disorder from neurologists, fibromyalgia from rheumatologists and CFS from infectious disease consultants. This is, to an extent, understandable from doctors who simply do not have the experience of Lyme disease to be able to make an informed judgement. It should be noted that	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests, which we hope will increase knowledge in this area. Competencies for specialists are not part of NICE's remit.

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					this observation is born of experience with patients and that all of these diagnoses are clinical diagnoses. The committee needs to discuss and address the lack of availability of suitably qualified NHS specialists in the UK.	
SH	Lyme Disease UK	Short	8	11-16	This section does not describe adequately the limitations of antibody testing. Line 11, *'most tests for Lyme disease'*: either the context needs to be defined or the word '*most'* needs to be justified. The insertion of *'NHS'* is suggested. … *'most NHS tests for Lyme disease assess for*'… Although on page 18, lines 10 and 11 cast doubt on the concept that early antibiotic treatment can abrogate the immune response and affect testing, there is no demonstration of a level of confidence about this sufficient for it not to be mentioned. In Evidence Review C page 192 lines 22-35, the committee notes that some manufacturers of tests state this. This is the case with the Viramed Virastripe used at RIPL, where the supporting study has not been included in the evidence review (Preac-Mursic, V., Wilske, B., Gross, B. et al. Infection (1989) 17: 355. https://doi.org/10.1007/BF01645543). The Immunetics C6 ELISA test states this also, but without citing a reference. *"Not widely accepted among the medical community"* is vague and not robust. It is possible that after treatment the organism would go on replicating after a recovery period but doctors often test shortly after antibiotics as a method of confirming "cure" by	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests. The committee were not aware of any evidence provided by the manufacturers in relation to antibody abrogation other than the reference you also provide outline a series of case studies published in 1989 only. The committee discussed this issue and considered it an important issue but did not agree that there was enough evidence to include this information in a recommendation. It is included it in the research recommendations.

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					treatment prompted by erythema migrans. Guideline needs to respond to what actually happens in treatment of real patients. It is reported in Evidence Review C, lines 33 and 34, that *'this area was not systematically examined in the guideline and the committee recognised that further investigation on immunological response to exposure to Borrelia is ongoing'* and yet the committee has chosen not to alert doctors to possible effect on testing by antibiotic treatment. This needs reconsideration and we would recommend insertion of another bullet point after line 16; '*The effect of early courses of antibiotics on the immune response is unclear, but they may abrogate the immune response and cause negative results in the presence of infection.'*	
SH	Lyme Disease UK	Short	8	20-24	Where is the evidence for this? Shared symptoms with other conditions does not mean Lyme disease is not the cause. This statement suggests that the doctors are unaware that there are characteristic patterns of symptoms which can point to Lyme disease. In the following statement, "often" needs to be defined, "a specific medical cause is often not found". Why is it considered useful to tell patients this? It suggests to both doctor and patient that this is an acceptable outcome. Note that in later disease patients may be suffering from levels of tiredness, headache and muscle pain that are life-changing.	Thank you for your comment. The recommendation is not suggesting that Lyme disease is not the cause. However many of the symptoms associated with Lyme disease do occur in other conditions and may be self-limiting. The committee agreed that it is an important part of clinical practice to inform and educate people about their symptoms.
SH	Lyme Disease UK	Short	8	1-3	Validated by whom?	Thank you for your comment. Validation is a process, which is described in the

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						recommendation and requires published evidence on the performance of a test.
SH	Lyme Disease UK	Short	8	5-7	This statement implies that serology is the deciding factor and detracts from the importance of a clinical diagnosis, using tests as a supportive measure. It implies that the NHS tests are never wrong which contradicts manufacturers' instructions.	Thank you for your comment. We disagree with your interpretation of this statement. Following stakeholder consultation, we have revised the recommendations to clarify the importance of clinical judgement in diagnosis and to emphasise the limitations of the tests.
SH	Lyme Disease UK	Short	8	5-7	Doctors are unlikely to know which laboratories fulfil the required criteria and so this needs to be made much clearer here. This statement may be interpreted to mean all private and foreign laboratories are using tests which have not been validated. Sweeping statements are not helpful, in the same way that it would be incorrect to imply that all private hospitals, laboratories and clinicians are 'unscrupulous'. With a membership of over 8000 people, it is our experience that people are able to intelligently review the pros and cons of various options. Many are cases missed by their GPs and therefore people lose faith and chose to seek private diagnosis and treatment. Our approach has always been to share information about the various options both in the UK and abroad, but never to make recommendations. It is critical that patients are given advice on how to assess whether a test is validated rather than simply given a blanket statement about all non-NHS labs.	Thank you for your comment. It is not the intention to suggest all private and foreign laboratories are using tests that have not been validated. The recommendations do indicate what is required for validation of a test i.e.' validation should include published evidence on the test methodology, its relation to Lyme disease and independent reports of performance'.
SH	Lyme Disease UK	Short	8	17-19	Unhelpful comment without detail. Casts slur on all such tests, with no indication as to whether any is acceptable and if so how to determine which. Suggest: *'Advise people how to assess whether private tests are*	Thank you for your comment. The wording of the recommendation has been altered following consultation to clarify the level of validation required.

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					validated as some may not yet have been fully evaluated' and provide details.	
SH	Lyme Disease UK	Short	8	9-10	Are doctors enabled to do this? Can they discuss in layman's terms the concepts of sensitivity and specificity and explain to patients the difference between false positives and false negatives? Are doctors aware of the limitations of the various tests? Our experience is that doctors advising patients in our group do not communicate beyond an assumption that the tests are broadly accurate and that a negative result rules out Lyme disease. They are not encouraged to think otherwise by the communications that they receive from laboratories and doctors are not familiar with the test kit manufacturers' guidance. What resources to doctors have access to, in order to find out and then communicate information about the accuracy and limitations of Lyme disease testing? Agreed and validated information on all types of tests and individual brands should be available centrally and publicly. It is very important that this includes the fact that there is no 'test of cure' (page 18 line 4) as in our experience doctors frequently test for exactly this purpose.	Thank you for your comment. Following stakeholder consultation, more detail has been added to indicate the limitations of tests. The issues you raise are important and will be considered by NICE where relevant support activity is being planned'
SH	Lyme Disease UK	Short	8	15-16	Whilst the evidence section states that the evidence base to support the idea that early antibiotic treatment of Lyme disease abrogates the immune response, so that serology remains or becomes negative this is not in line with the manufacturer's guidance. Any evidence-base used by the NICE committee to support the idea that early antibiotic treatment of Lyme disease is unlikely to abrogate the immune response	The committee were not aware of any evidence provided by the manufacturers in relation to antibody abrogation other than the reference you also provide which outlines a series of case studies published in 1989 only. The committee discussed this issue and considered it an important issue but did not agree that there was enough evidence to include this information in a

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					(so that serology remains or becomes negative) is at odds with the test kit manufacturer's guidelines. Virastripe's guidance states: - '*An early antibiotic therapy can suppress the development of antibodies'* and cite: PREAC-MURSIC, V.: Infect. 355-359 (1989); Marangoni, A. M., V. Sambri, S. Accardo, F. Cavrini, V. Mondardini, A. Moroni, E. Storni, and R. Cevenini. (2006). - A decrease in the immunoglobulin G antibody response against the VlsE protein of Borrelia burgdorferi sensu lato correlates with the resolution of clinical signs in antibiotic-treated patients with early Lyme disease; Clin. Vaccine Immunol. 13:525–529. 14. The same concept is mentioned in this study and various others. Unless there is evidence to clearly demonstrate that the manufacturers are incorrect then the possibility such be added that early antibiotic treatment can potentially result in a false negative test result. Reference: Viramed: Borrelia ViraStripe IgM Test Kit www.viramed.de/images/stories/pdf/Arbeitsanleitungen_EN/2551_Borrelia_ViraStripe_IgM_AL_en.pdf Dattwyler et al, *Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to Borrelia burgdorferi.* N Engl J Med. 1988	recommendation. It is included in the research recommendations.

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					Dec 1;319(22):1441-6. https://www.ncbi.nlm.nih.gov/pubmed/3054554	
SH	Lyme Disease UK	Short	8	15-16	This makes a clinical diagnosis even more important at this stage. This should be emphasised. Serology cannot even be used as a supportive tool in these situations and it contradicts the over-reliance of serology in previous sections of the guideline. This comment fails to recognise that the disease itself impairs immunity, especially in the seriously ill, calling into question detection methods relying on an immune response.	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests.
SH	Lyme Disease UK	Short	9	10-14	The recommendations for treatment are based around an assumption that 3 weeks of doxycycline, delivered at 200mg per day, is the basic unit of treatment. It is understood that there is little evidence supporting longer courses of treatment and yet there are many independent Lyme disease experts whose experience leads them to prescribe longer courses of treatment. What evidence does the committee have that 3 weeks of doxycycline at 200mg per day achieves an acceptable long-term recovery rate, especially when there is no 'test for cure'? If the evidence for this also is lacking, then the situation should be made clear to GPs that this may not be robust treatment as further research is required. We understand there is a paucity of evidence but the contrast between those courses and those used by independent Lyme disease experts (who deal with Lyme on a daily basis) is stark and disturbing. We regularly see people who do not recover from these short courses who go on to do so after more comprehensive treatment. Clinicians and patients need	Thank you for your comment. The evidence for length of treatment is weak and the committee decided to err on the side of caution and recommend longer courses of 21 days of treatment as standard because of their concern at low cure rates in some studies, the lack of clear evidence for shorter courses and concern that people being treated for Lyme may be concerned that they are undertreated if they continue to have symptoms and have received a shorter course. They were reassured that adverse rates were not increased for longer courses. While the evidence for courses over several weeks was limited no evidence was found treatment over many months. The committee made a research recommendation for treatment and longer courses as you describe need to be assessed robustly.

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					to be clear that the research is lacking and there is not yet one known approach to tackling Lyme disease. Not all patients will recover from the courses of antibiotics being suggested in this guideline, even if prescribed in the early stages. This is even less likely when diagnosis is delayed. Looking at the evidence (Evidence Review 7, page 21 lines 14-15 and pages 59-60) it appears that approximately 50% of cases did not recover in the study used. This is unacceptable. One of our 8000+ members shares; "After 18 months of treatment I am finally getting my life back. I can take my children to school again and am hoping to soon be able to return to work." Another says; "After treatment for Lyme disease I recovered my health, however after 12 months the symptoms returned. I am now back on treatment and making good progress." One member states; "I am retired from the medical profession and I recognise that I am lucky that I was living abroad when diagnosed. I received IV antibiotics and longer treatment than I would have done if I had have been at home." Sadly many of our members are so sick that whilst they understand the issues attached to 'experimental' treatment, the potential benefits outweigh the costs. This study looks at how poor the quality of life of a Lyme disease patient is in comparison to other chronic illnesses. This cost can unfortunately be their lives	

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					which this study highlight and which we have seen occur in our support group. For many, the opportunity to talk to others who have sought private treatment is a life line. Whilst unscrupulous clinics no doubt exist, we see our members seeking out clinics, which have a track record of success. Seeing fellow patients going from bed bound, in a wheelchair or having daily seizures to recovering a living normal life is often enough to give people hope to continue. Whilst these treatments may not have yet undergone rigorous clinical trials there are clinicians who have years of clinical experience and success in treating complex cases we are not yet able to do so. References: Johnson, Lorraine et al. "Severity of Chronic Lyme Disease Compared to Other Chronic Conditions: A Quality of Life Survey." Ed. Claus Wilke. *PeerJ* 2 (2014): e322. *PMC*. Web. 6 Nov. 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3976119/ Suicide and Lyme and associated diseases. Bransfield, RC. Neuropsychiatr Dis Treat. 2017 Jun 16;13:1575-1587. doi: 10.2147/NDT.S136137. eCollection 2017. https://www.ncbi.nlm.nih.gov/pubmed/28670127	
SH	Lyme Disease UK	Short	9	6-8	This implies that the same testing procedures may not be applicable to children - there needs to be some indication of whether this is the case here. This also implies that every time a GP sees a patient under 18, with suspected Lyme disease, that they need to	Thank you for your comment. The guideline allows for treatment before test results are available. However, the committee considered that children with, for example, focal neurological symptoms would benefit from having their

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					discuss this with a NHS specialist. This will create more work for the GP. There is no diagnosis guidance for the specialist in the guideline and therefore, this creates a dead end.	management discussed with a specialist as focal neurological symptoms are uncommon in children.
SH	Lyme Disease UK	Short	9	18-19	What evidence is there that the Jarisch-Herxheimer reaction occurs within the first day of treatment? Our experience with members of our support group is that reactions within the first day are likely to be drug side-effects or reactions, whilst a flare of symptoms later than that, typically several days later, are more likely to be a Jarisch-Herxheimer reaction. What evidence did the committee consider on the reaction? Doctors need advice to be able to distinguish a Jarisch-Herxheimer reaction from a drug reaction and they need to be told that the reaction can occur repeatedly through treatment. They need to know how to help patients manage and reduce the reaction. Is this information available elsewhere in NHS resources?	Thank you for your comment. The recommendation has been altered to be less specific about time and additional information has been added to the 'terms used in the guideline' section of the short guideline. The recommendation was developed by consensus based on committee knowledge.
SH	Lyme Disease UK	Short	9	following line 19	There are some other important points which should be noted in advance of the antibiotic prescribing information, which should be inserted after section 1.3.6 1) It is our experience that patients are rarely given the necessary advice on how to take doxycycline. This is important because it can make the patient give up on the course and/or be misinterpreted as a reaction. This is common enough in our experience to warrant inclusion in the guideline. Patients must be told to take the dose with sufficient water and/or food, to stay upright for at least an hour after an evening dose, and to protect the skin from even mild sunlight. This is disappointing negligence which needs addressing.	Thank you for your comment. (1) This recommendation was not included in the guideline as it is not specific to Lyme disease. It is the responsibility of clinicians to follow best practice when prescribing doxycycline to patients. (2) a recommendation has been added following stakeholder consultation to include a review during treatment to assess response.

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					2) If the course of antibiotics needs to be repeated it is very important that the repeat course is continuous with the first if all the benefit from repeating is to be gained, and make best use of the various costs of a repeat course. Continuity is put at risk if it is left to the patient to decide they need to return to the doctor and especially if it takes many days to arrange an appointment as it does in many areas. For this reason, we would recommend that it becomes normal practice for a follow-up appointment to be made at the point of first prescribing, to happen at the end of the course. It is then a medical professional who judges the adequacy of the treatment and if repeating the course is necessary, maximum benefit will be achieved. 3) For inclusion in table. The most common serious conflict a GP will face in prescribing for an erythema migrans rash is if it is not clear whether it is an erythema migrans rash or cellulitis. GPs need clear advice on correct prescribing to cover both conditions. It is not acceptable that GPs treat one but not the other, both are serious conditions needing prompt treatment.	(3) The committee discussed the challenges in diagnosing erythema migrans, which is why they decided to include a description in recommendation 1.2.1. The committee have also worked with NICE to provide images of typical and less typical rashes and these are linked to from guideline in the tools and resources section on the NICE website. It is not possible to provide detail on different possible diagnoses in a short guideline.
SH	Lyme Disease UK	Short	9	2-5	Contraindications should be made clear e.g. steroid use if Lyme disease is underlying cause. If steroids are administered, doctors carrying out emergency procedures should be aware of their potential effects on Lyme disease test results.	Thank you for your comment. Steroid treatment can have a place in treatment of severe infection such as meningitis and uveitis. The guideline does note that antibody responses may be affected if people are on immunosuppressant. The committee considered that it was not possible to make a general comment on steroid effect as this will vary by dose and duration

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SH	Lyme Disease UK	Short	10	Table	The doses of amoxicillin for adults and young people (aged 12 and over) do not match up with the manufacturer's guidance which states; '*Adults, elderly patients and children weighing 40kg or more, 4g-6g per day. Adults, elderly patients and children weighing 40kg or more -Lyme disease (an infection spread by parasites called ticks): Isolated erythema migrans (early stage - red or pink circular rash): 4g a day, Systemic manifestations (late stage - for more serious symptoms or when the disease spreads around the body): up to 6g a day'*. Why does this guidance differ from the guideline? It is important to note that the manufacturer distinguishes between different stages of the disease whereas the guideline does not.	Thank you for your comment. In this guideline the committee preferred to avoid contested definitions of the stages of Lyme disease and instead to make recommendations for treatment according to clinical presentation. The British National Formulary recommends 500 mg 3 times a day for 14–21 days (for 28 days in Lyme arthritis). The committee recommended a higher dose of amoxicillin compared to that listed in the BNF because the included studies used probenecid to increase the concentration of amoxicillin.
SH	Lyme Disease UK	Short	10	Table	For *'Lyme disease affecting the central nervous system'* and *'Carditis and haemodynamically unstable'*, IV ceftriaxone is recommended. Then doctors are being told to '*consider switching to oral doxycycline when no longer acutely unwell'*. What happens if someone remains acutely unwell following the IV ceftriaxone? What does the doctor prescribe then? Additionally, what dose and treatment duration of doxycycline is recommended after IV ceftriaxone if people are switched over? Doctors and patients need to know what this course should be.	Thank you for your comment. The wording has been changed to clarify that a switch to oral treatment is not being recommended. However if switch from IV to oral treatment is being considered then doxycycline is the preferred oral treatment.
SH	Lyme Disease UK	Short	12	1-26	Where is the evidence that Lyme disease cannot persist beyond two courses of antibiotics? There are many studies demonstrating persistence, including the ones below, some of which we have quoted excerpts from:	Thank you for your comment. The guideline does not state that Lyme disease cannot persist beyond 2 courses of antibiotics, but there was no evidence of benefit from additional antibiotic treatment following 2 courses of antibiotics. The guideline does include recommendation to consider referral to specialist for people with

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					- *'These results extended previous studies with ceftriaxone, indicating that antibiotic treatment is unable to clear persisting spirochetes, which remain viable and infectious, but are nondividing or slowly dividing'* Barthold, Stephen W. et al. 2010. "Ineffectiveness of Tigecycline against Persistent Borrelia Burgdorferi." Antimicrobial Agents and Chemotherapy 54(2):643–51. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2812145&tool=pmcentrez&rendertype=abstract).https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2812145/?tool=pmcentrez - *'The agent of Lyme borreliosis, Borrelia burgdorferi, evades host immunity and establishes persistent infections in its varied mammalian hosts'*. Hodzic, Emir, Denise Imai, Sunlian Feng, and Stephen W. Barthold. 2014. "Resurgence of Persisting Non-Cultivable Borrelia Burgdorferi Following Antibiotic Treatment in Mice" edited by R. M. Wooten. PLoS ONE 9(1):e86907. http://dx.plos.org/10.1371/journal.pone.0086907. - *'Results indicated that following antibiotic treatment, mice remained infected with nondividing but infectious spirochetes, particularly when antibiotic treatment was commenced during the chronic stage of infection.'* Hodzic, Emir, Sunlian Feng, Kevin Holden, Kimberly J. Freet, and Stephen W. Barthold. 2008.	ongoing symptoms who can decide on appropriate course of action. The committee developed recommendations for people with ongoing symptoms to ensure that they receive continued support, non-antibiotic management where appropriate and referral for further investigation where required. There was no specific evidence review on risk of persistent/ongoing infection. We reviewed the references to ensure that those that are relevant to the review questions were considered for inclusion. We do not consider in vitro or animal studies in evidence reviews as per NICE process.

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					- "Persistence of Borrelia Burgdorferi Following Antibiotic Treatment in Mice." Antimicrobial agents and chemotherapy 52(5):1728–36. Retrieved November 7, 2010 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2346637&tool=pmcentrez&rendertype=abstract) - *We demonstrated that B. burgdorferi treated in the stationary phase has a higher probability of regrowth following removal of antibiotic.'* Caskey, John R. and Monica E. Embers. 2015. "Persister Development by Borrelia Burgdorferi Populations In Vitro." *Antimicrobial agents and chemotherapy 59(10):6288–95. http://aac.asm.org/content/early/2015/07/21/AAC.00883-15* - *Our study substantiates borrelial persistence in some erythema migrans patients at the site of the infectious lesion despite antibiotic treatment over a reasonable time period' '*Hunfeld KP et al 2005 "In Vitro Susceptibility Testing of Borrelia burgdorferi Sensu Lato Isolates Cultured from Patients with Erythema Migrans before and after Antimicrobial Chemotherapy." *'* - *Finally* this is a list of 700+ peer reviewed papers, which has been compiled by ILADS to demonstrate persistence. In the absence of any sufficient good research into treatment options why have these not been considered and used to inform treatment? Why are experienced doctors not able to use their clinical judgement,	

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					especially where treatment response is seen and the consequences of undertreating so grave? In the absence of such evidence doctors must be able to use clinical judgement, taking into account patient response to treatment, when assessing cases for resolution. Where necessary, doctors must be allowed to use their clinical judgement to continue treatment. We are talking about established drugs, which are used in other conditions for long periods of time, we are not talking about a new experimental entrant to the market.	
SH	Lyme Disease UK	Short	12	2-17	Does the committee have any evidence to suggest that persistent infection is NOT the most likely reason for persisting symptoms other than the historical convention that 3 weeks of antibiotic treatment is sufficient? The possibility of persistent infection should be at the top of the list of possible explorations rather than omitted completely. (For the possibility of re-infection of a "rare" disease during the 3 week treatment period to be considered more likely that persistent infection of a known persisting infection is strange.) Given the possible consequences of delay and treatment interruption in a persistent infection, and given the cost to the NHS of exploring all of the other possibilities, the most logical course is first consideration of persistent infection and re-prescribing. For this reason, it would be logical for the information in section 1.3.9 to come before section 1.3.7 to avoid waste of NHS resources, waste of critical time and maximal effectiveness of the use of antibiotics.	Thank you for your comment. The possible explorations are not listed in order of likelihood. This recommendation is intended to encourage clinicians to consider all possible reasons for ongoing symptoms, so that they can be managed appropriately. Treatment failure has now been added to the list.
SH	Lyme Disease UK	Short	12	13-17	The material here should appear earlier.	Thank you for your comment. The decision to use a different antibiotic was a consensus decision by

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					Where is the evidence that a new antibiotic should be used for the second course? It is vital that consecutive courses of antibiotics run without break to maximise the effectiveness of the full course and to minimise giving either Borrelia or other opportunistic infections the time to recover and strengthen. This is especially important if starting a different antibiotic so that tissue levels of the new one can rise before the tissue levels of the first decline. Assuming the evidence is correct we would suggest wording: *'Persistent symptoms after a course of antibiotics:* ● *At the review consultation, consider a second course of antibiotics for people with persisting symptoms, if treatment may have failed. Use an alternative antibiotic to that used for initial treatment, for example for adults with Lyme disease and arthritis, offer amoxicillin if the person has completed an initial course of doxycycline. Ensure that consecutive courses of antibiotics run without interruption.* ● *If symptoms, that may be related to or caused by Lyme disease, persist or worsen after antibiotic treatment, review the person's history and examination to explore:* ○ *continued persistent infection* ○ *details of any previous treatment, including whether the course of antibiotics was completed without interruption*	the committee. This is common practice in infectious disease treatment. The wording and order of bullet points in the recommendations were changed following stakeholder comments.

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					○ *any possible alternative causes of the symptoms* ○ *if re-infection may have occurred* *if symptoms may be related to organ damage caused by Lyme disease, for example, nerve palsy. ·*	
SH	Lyme Disease UK	Short	12	21-24	Where is the evidence that symptoms can take months to resolve, especially when there is no 'test for cure'? How many months? Has the committee seen studies showing treatment cessation with residual symptoms which resulted in a successful outcome? In those cases how was success measured and defined? Where is the evidence for this? From the evidence review it appears that the main study used results in approx 50% of people recovering, therefore is it not more likely to be treatment failure? This statement cannot be valid without evidence to substantiate it.	Thank you for your comment. The wording has been changed to 'months to years' and does indicate that some damage may be permanent. One of the difficulties in interpreting the studies is that it is not clear what is meant by 'cure' or ongoing symptoms.
SH	Lyme Disease UK	Short	12	18-20	This assumes that infection is proven not to continue beyond two courses of antibiotics. What is the evidence for this assumption? Does the committee have evidence to show that 6 weeks doxycycline treatment at 200mg per day always cures Lyme disease?	Thank you for your comment. The recommendation not to routinely offer further antibiotics following two courses of antibiotics is not based on the assumption that infection is proven not to continue beyond two courses, but there was insufficient evidence to suggest that further treatment is beneficial. The recommendation to consider discussion with or referral to a specialist allows the possibility for a specialist to offer further antibiotic treatment.
SH	Lyme Disease UK	Short	12	9-10	How will organ damage be distinguished from ongoing infection if there is no 'test for cure'?	Thank you for your comment. The committee expect that an evaluation of history and presentation with clinical assessment and judgement will be required and suggest a second

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						course of antibiotics in part because of this difficulty.
SH	Lyme Disease UK	Short	12	11-12	How will reinfection be distinguished from ongoing infection, particularly if someone has not noticed a tick bite and there is no 'test for cure' to determine that previous infection has been eradicated?	Thank you for your comment. The committee expect that an evaluation of history and presentation with clinical assessment and judgement will be required and suggest a second course of antibiotics in part because of this difficulty.
SH	Lyme Disease UK	Short	12	25-26	This statement is biased in normal English usage towards implying that most people with continuing symptoms do not have active infection. Even if this is not what the committee meant, the sentence is ambiguous in that some may pick up an inference not intended to be there. If the committee has evidence for this they should use clear language to say it. If they do not have evidence one way or the other but believe that in some cases continuing symptoms do mean active infection and in some cases they do not, then the language should be clear and not open to interpretation. We would suggest: *'Continuing symptoms may or may not mean they still have an active infection.'*	Thank you for your comment. The wording of the recommendation was reviewed with the committee and NICE editor and now says 'may not mean' they have an infection.
SH	Lyme Disease UK	Short	12	5	Alternative causes should go at the bottom of the list so that Lyme disease related treatment possibilities come above this. Additionally, a Herxheimer reaction may continue to occur after an initial course of antibiotics and so this should be included in the list. Tick-borne co-infections should have been listed here and their exclusion makes the guidelines very restrictive. If alternative conditions include CFS/ME and fibromyalgia, this is problematic as they are subjective conditions for which there are no serological tests.	Thank you for your comment. We have moved alternative diagnoses to the last bullet point.

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SH	Lyme Disease UK	Short	12	20	The purpose of recommending discussion or referral to a NHS specialist would normally be to access the greater experience of difficult cases owned by specialists. Which NHS specialists in the UK have experience of treating treatment failures in Lyme disease such that they can distinguish which cases have persistent infection and which do not?	Thank you for your comment. The role of a specialist is to consider alternate diagnoses and advise about treatment. In areas of uncertainty, healthcare professionals are expected to confer with colleagues and more specialised centres. This could include international contacts as required. Infectious disease consultants have experience and training in Lyme, but depending on the symptoms, the best person might be a general paediatrician, rheumatologist, neurologist or other specialist as appropriate.
SH	Lyme Disease UK	Short	13	15-19	Be aware that depression, anxiety, pain, sleep disturbance and fatigue are all symptoms of Lyme disease. Care needs to be taken to ensure that doctors don't miss a Lyme disease diagnosis because of focusing too greatly on one symptom or another the diagnosis of another condition. For example, depression and anxiety can be stand alone conditions, however they can also be a symptom of Lyme disease or as a result of being unwell with Lyme disease. Of course it is important to help to alleviate these symptoms alongside proper treatment for Lyme disease. They should also be recognised as symptoms of the disease rather than simply *'related to'.* When treating Lyme disease with antibiotic therapy, resolution of these symptoms is the desired treatment outcome. One of our 8000 members shared; "Despite having symptoms, a positive Western blot and weakly positive C6 ELISA, I wasn't diagnosed with Lyme disease. I have a referral to the Chronic Fatigue Clinic, which	Thank you for your comment. The recommendation is not intended to replace antibiotic treatment of Lyme disease but recognises that individual symptoms may benefit from specific treatments.

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					would be welcome in addition to treatment, but I don't understand why it is instead of treatment"	
SH	Lyme Disease UK	Short	13	11-12	It is important that it is made clear that management of symptoms is in addition to proper treatment for Lyme disease. Consider rewording to make this explicit. Also be aware of possible contra-indications. We suggest: *'Assess and if necessary offer treatment, in addition to antibiotic therapy, for symptoms of Lyme disease following usual clinical practice (for example, heart block). Be aware that some treatments may be contra-indicated, such as immune-suppressing drugs, requiring careful judgement.'*	Thank you for your comment. The wording was reviewed and we consider it is clear that this is not an alternative to antibiotic treatment.
SH	Lyme Disease UK	Short	13	13-14	Is untreated Lyme disease being referred to here, undertreated Lyme disease or possible damage from infection? Once again it must be very clear that managing symptoms is separate from, and additional to, treatment of the disease. Recognition of need for symptom control is welcome providing it is within the this context of being in addition to proper treatment. Here, these symptoms are acknowledged as being *'related'* to Lyme disease. Does the committee mean they are symptoms of Lyme disease itself or that these symptoms occur as a result of being unwell? This is unclear. The list implies that these symptoms are commonly associated with the condition whereas in section 1.2, Lyme disease is described as an '*uncommon'* cause of these symptoms. What is meant by a *'related symptom'* is unclear Suggest additional wording for lines 13 and 14: *'Be alert to the possibility of symptoms related to, or*	Thank you for your comment. Symptom management is intended alongside antibiotic treatment. We have used the word 'related' too, as it does not require proof of causation yet recognises associations and patient need.

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					caused by, Lyme disease that may need assessment and management, in addition to treatment of the disease. Management of these symptoms during treatment will support antibiotic therapy but these are all are primary symptoms of Lyme disease, and full resolution is the desired outcome.'	
SH	Lyme Disease UK	Short	13	1	No indication of what is generally believed to be true - that persisting symptoms may be a combination of issues, including lasting damage and continuing infection. We suggest *'persisting symptoms may be a combination of issues including ongoing infection and lasting damage*'. When there is no 'test for cure', how will the two be distinguished?	Thank you for your comment. It is not known whether ongoing symptoms are due to persisting infection, tissue damage, autoimmune reaction or some other process and there is currently no test that helps determine this. The wording was reviewed following stakeholder consultation and has been left in bullet points in keeping with NICE style. The committee recognise that clinical judgement has to be used in patient assessment and history.
SH	Lyme Disease UK	Short	13	3	How can it be certain that recovery is happening and what is meant by the term *'slow'*? Is there any kind of timeframe attached to this statement, to guide doctors? How is recovery being quantified, especially in the absence of a test for cure? We agree that a range support is very necessary in Lyme disease cases but deciding that someone is definitely recovering is problematic, if they are still symptomatic.	Thank you for your comment. The wording has been changed to 'ongoing symptoms'.
SH	Lyme Disease UK	Short	13	10	It is unclear whether *'non-antibiotic management'* is a substitute for antibiotic therapy or whether this is symptom management which should run alongside treatment or "after" treatment. As we are not aware of any evidence to suggest that *'non-antibiotic management'* can cure an infection, it should be made clear that these treatments are in addition to appropriate antibiotic treatment.	Thank you for your comment. The recommendations do not suggest that symptomatic treatments are substitutes for antibiotic treatment.

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SH	Lyme Disease UK	Short	14	5-7	Why give this assurance when on Page 30, Line 11 *'The Committee acknowledged that mother-to-baby transmission of Lyme disease is possible in theory'?* The wording is ambiguous. It could mean that we think that the risk is low but that this probably does happen or that we aren't sure whether this happens but think it probably doesn't. The intended message is that it can happen but the risk is probably small, but some doctors may believe that it is unlikely that it happens at all, so the wording needs to be clear and capable of unambiguous transfer from guideline to doctor to woman. The risk for the child is binary – either it is or is not infected. It would be better to make clear that we believe the risk is small but real. We suggest: *'Inform women with Lyme disease during pregnancy that the evidence is not clear, but it is believed that there is a small but real risk of passing the infection to their baby. Emphasise the importance of completing the full course of antibiotic treatment.'*	Thank you for your comment. The wording of the recommendations was reviewed and the committee considered the information in the recommendation was clear in that the transmission is unlikely.
SH	Lyme Disease UK	Short	14	8-9	This is not consistent with telling people it is unlikely they have passed on the infection. Will women expressing concerns then be told it is unlikely they have passed it on? What is the guidance for people who do express concerns and inform doctors that they had Lyme disease during pregnancy and what about people who have had Lyme disease in the past, especially when there is no 'test for cure'? Doctors and patients both need clarity around this. One of our 8000+ members says "I asked my doctor if it was ok for me to be trying for a baby. Despite having	Thank you for your comment. The committee considered that women should be informed it is unlikely they have passed Lyme on. The committee however considered that assessment and treatment with full discussion was likely to be most reassuring approach if there are concerns.

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					clinical symptoms I was told yes it was, before even being tested".	
SH	Lyme Disease UK	Short	14	10-11	If infectious disease doctors are being told that it is unlikely, will management actually occur? Two papers on the possible appearance of Borrelia in breast milk were excluded from the evidence review on the basis of incorrect study design. There were no other studies. Since this was included in the review protocol (page 34 evidence review M), it was considered to be a relevant question which has not been answered. It should not therefore be ignored in the guideline. We suggest it should be added to the bullet points in 1.3.18. Add bullet: *'There was no evidence to show that Borrelia is not found in breast milk.* As per previous comment about NHS specialists, if there is a paediatric infectious disease NHS specialist qualified to advise on Lyme disease by virtue of training, experience or research the guideline should tell doctors to whom such cases should be referred. If there is not, then this bullet should be omitted or the situation made explicit.	Thank you for your comment. Paediatric infectious disease specialists commonly see women and children who are concerned about congenital infection and who decide on the necessity of treatment based on individual assessment and judgement. The committee considered that because Borrelia cannot survive adverse conditions, the infant's stomach acid would kill any bacteria present."
SH	Lyme Disease UK	Short	14	12-13	Looking for IgM antibodies in the baby, as evidence of infection, assumes that introduction of the pathogen happened after the development of self-nonself discrimination in the foetus. This paper, states *'For instance, foreign antigens presented during foetal life are considered self because adaptative immunity learns to discriminate self from nonself during their maturation in primary lymphoid organs and any antigen present during this selection process is consider as self.'*	Thank you for your comment. The recommendation suggests consideration of treatment if IgM is found or if there is clinical suspicion.

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					Has the committee considered this problem in recommending use of IgM to identify infected babies? What is the evidence that IgM testing is able to overcome this problem in babies potentially infected at the very start of gestation? If this testing is flawed in this respect, the committee should consider a case for clinical diagnosis in these babies. The issue is further extended by the possibility of a mother with persistent or late infection. In a mother showing undiagnosed ACA previous to and during pregnancy, what is the evidence that the embryo will not have been exposed to active infection? Reference: Segundo Gonzalez et al *Conceptual aspects of self and nonself discrimination*, Self Nonself: 2011 Jan-Mar; 2(1): 19–25 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136900/	
SH	Lyme Disease UK	Short	14	18-19	*'Complete recovery'* needs to be defined and where is the evidence for this? Have any follow up/longitudinal studies been done? If not, this needs to be added as an area for research.	Thank you for your comment. The committee considered this did not need further defining and people know subjectively when they are well. The research recommendation on clinical epidemiology should lead to more detailed evidence for this.
SH	Lyme Disease UK	Short	14	20-21	Where is the evidence for this statement, especially in the absence of a test for cure? How many months? Are there any studies which show this? Is the	Thank you for your comment. The information is general information about Lyme disease. As with most infections, cure and recovery are subjectively defined without the need for testing.

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					committee suggesting that any such improvement will be permanent?	The committee did consider that improvement is permanent for many patients.
SH	Lyme Disease UK	Short	14	1	This comment relates to the title and organisation of this section, which should properly be on Person to Person transmission, as itemised in the Scoping Document. Pregnancy should be a subsection of the Person to Person transmission section, with other potential transmission routes covered. Comment follows with suggestion given at the end of the comment: Line 102, Page 4 of the Scoping Document asks *'What is the evidence for person-to-person transmission of Lyme disease?'* That this should include the consideration of sexual transmission, transmission through blood products and organ donation, is confirmed in the Evidence Review by some references e.g. page 27 line 30 & 31, page 7 lines 4 & 5, Evidence Review B. Which surmise that the committee looked but found no research with evidence for these processes. However, the committee also did not find evidence to show these processes do NOT happen. Where is the evidence for safety of these processes (sexual activity and blood/organ donation), with regard to Lyme disease transmission? Absence of evidence is not evidence of absence. In assessing the probability or even possibility of any danger in these circumstances, there should be two strategies; a) could this happen and b) has this been shown to	Thank you for your comment. No evidence was identified for transmission through blood products or sexual transmission and no specific action is therefore required to mitigate any risk. The committee decided it would not be helpful to make any statement regarding the possibility of these types of person-to-person transmission. Therefore your suggested additional section has not been added. The title of the section is designed for ease of reading the recommendations and not by areas in the scope. We have added information to the rationale section to indicate that no evidence was found for sexual or blood transmission. NICE clinical guidelines do not generally examine underlying pathophysiological processes but look for clinical evidence and outcomes as these are more robust and meaningful. No evidence for sexual transmission or transmission from blood donation was found in the evidence review, known to the guideline committee or identified from stakeholder consultation. The lack of

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					happen? If you find evidence that b) it has happened, then you do not need to research (a) which has already been demonstrated by (b). However, if you find no evidence for (b), then logically, you must look back and answer question (a), i.e. could this happen, because the absence of evidence for (b) may just be because no-one has looked hard enough or widely enough for it to have been observed in a quality study. It does not appear as though the committee has made any attempt to answer question (a). If only question (b) has been addressed, then this is a lower order of confidence and must be reflected in the guideline. Where is the evidence that sexual transmission and transmission through blood products and organs cannot happen? If this can be demonstrated, then the need to look for evidence that it has happened is removed but, while it remains unanswered, transmission in these ways is still a possibility, although as yet, unobserved in research. There are studies which show that different parts of the pathways of these possible transmission methods do exist: Johnson et al, *Borrelia burgdorferi: survival in experimentally infected human blood processed for transfusion.* J Infect Dis 1990 Aug;162(2):557-9 https://www.ncbi.nlm.nih.gov/pubmed/2373880 Nadelman et al, *Survival of Borrelia burgdorferi in human blood stored under blood banking conditions.*	evidence of transmission is a useful finding in itself. The committee considered it would be unhelpful to include recommendations on sexual transmission without some evidence and the papers you cite do not provide evidence sufficient to do this. The blood transfusion papers are experimental studies from 1990 and the study indicating the presence of Borrelia in semen and vaginal secretions is explicit that it is not showing sexual transmission.

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					Transfusion. 1990 May;30(4):298-301. https://www.ncbi.nlm.nih.gov/pubmed/2349627 Middelveen et al, *Culture and identification of Borrelia spirochetes in human vaginal and seminal secretions. Version 3. F1000Res. 2014; 3: 309.* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5482345/ Whilst these studies may not reach the NICE research standard, they do indicate that these transmission methods cannot be ruled impossible and there don't appear to be any studies which do reach the NICE research standard which definitely show these transmission methods are impossible. Furthermore, it is generally known that the less complex spirochete, *Treponema pallidum* is known to be transmitted sexually and through blood products. In the absence of research and clear evidence, the question remains of what should appear in the guideline. Doctors speaking with patients need to be enabled to give honest answers to questions about person to person transmission and this guideline does not equip them to do this. The guideline should recommend this subject for urgent research. There is also an impact here on diagnosis – if person to person transmission is possible, then Lyme disease exposure questions should include issues such as whether the person has had a sexual relationship with	

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					a Lyme sufferer or received a blood transfusion or organ donation. Has the committee discussed and considered this aspect? A further issue is that the guideline accepts that not every patient will be cured by a standard 3 week course, nor yet two courses, and so the guideline assumes that patients may still be infected after 6 weeks antibiotic treatment. However, whilst there are sections (contested) which also state that symptoms of Lyme disease may take months to resolve even after treatment (section 1.3.11) there is a real risk that there will be situations where doctors sign off a patient as cured, in spite of telling but apparently minor residual symptoms, and that patient will be eligible to give blood, may have unprotected sex or even donate an organ. Slow diagnosis of Lyme disease by GPs unfamiliar with the variations of rash, or of patients without rash, also raises the possibility that patients with acute, undiagnosed Lyme disease, probably the most easily transmitted, are donating blood. This aspect needs referral to the NHSBT as a matter of urgency. One of our 8000+ members shared; "I donated blood before I was diagnosed. I was already feeling slightly unwell, but put it down to stress and lack of sleep. I didn't deteriorate rapidly until after the blood donation. To this day I feel so much guilt knowing I could have inflicted this on other people". We would strongly recommend that the guideline section is renamed to reflect the demands of the Scoping Document so as not to hide the fact that	

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					sexual transmission and blood products transmission was included in the committee's consideration. This section should be named Person to Person Transmission, and include a section on Lyme disease during and after pregnancy. The guideline should then include an extra section 1.3.19 worded something along the lines of: *'Studies show that transmission via sexual contact and blood transfusion may be possible although they have not been proven. People may wish to take a precautionary approach to these aspects of personal behaviour'.* Not to mention an area with such important implications, which was included in the Scope, would be negligent.	
SH	Lyme Disease UK	Short	14	16	1.4.1 Insert the word *'serious'*. It is important that patients understand that the disease is potentially serious i.e. you don't give up on the course of antibiotics because you feel better and you are frustrated by the effects on your tolerance to sunlight. We suggest: *'Lyme disease is a serious bacterial infection treated with antibiotics.'*	Thank you for your comment. The addition of the word serious was not considered to add to the recommendation and the preference is to keep the wording as simple as possible.
SH	Lyme Disease UK	Short	14	17	We have grave concerns about this statement and consider it to be grossly misleading and possibly dangerous in its effect on the way patients and doctors will approach infection. How do people understand this statement? Nearly all people asked about this statement (large numbers of patients in LDUK asked friends, family and	Thank you for your comment. The recommendation is covering the wide range of presentations of Lyme disease and the committee considered that from that perspective most people do recover. Recommendations in relation to people with ongoing symptoms are present in 1.3.12.

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					random contacts) will say that they think *'most'* means 70-80% although some will then say that they recognise that technically *'most'* only means 50%+ but indicate they think that use would be deliberately misleading. Nearly all people asked about this statement think that *'people'* refers to all patients, whenever the disease is diagnosed and that *'recover completely'* means getting back to the same state of health the person had before the infection. This did not appear to be a statement which people understood in a wide range of ways, there was great unanimity. In addition, NHS employees from retired consultants to nurses understood the statement in the same way. Retired cardiologist, Dr Ronald W. Strachan, MBChB, FRCP, past-president of the Scottish Society of Physicians, said he was happy to put on record that this statement would mean at least 80% patients would be symptom-free for at least 5 years. Is this what the committee wished to be understood by this statement? If so, where is the evidence? Looking through the studies considered by the committee we can see only one study that gives evidence of recovery rates. The study which the committee seems to have based guideline treatment recommendations on is Ljostad 2008 (2010) which compares doxycycline and ceftriaxone treatment and this also gives rates of recovery for 1 year follow-up. However in Evidence Review F page 21 line 15 the committee says *'However, both treatments showed low rates of cure (full resolution of neurological symptoms).'* The resolution rate at 1 year was 50%	

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					and 54% respectively but by this stage numbers were missing from the original cohort, meaning that 44 confirmed recovered after one year represents 37%. If this is the study on which treatment is based then a recovery rate of ~52% (or lower) after 1 year is a poor basis for a statement which is popularly understood to mean 70-80% recover for longer than 5 years or indefinitely. Evidence Review N page 14-15, lines 43-4 states *'The guideline committee considered how best to inform people with Lyme disease on the likely prognosis, while acknowledging the uncertainty regarding treatment success. The guideline committee considered evidence identified in the management review and their clinical experience to form information recommendations for people diagnosed with Lyme disease. It was agreed that people with Lyme disease should be informed that most people recover completely, that prompt antibiotic treatment reduces the risk of further symptoms developing, that it may take time to get better but symptoms should continue to improve in the months after antibiotic treatment and that additional treatment may be needed for their symptoms.'* This states that there is uncertainty regarding treatment success. It says that the committee based their recommendation on the evidence, which has been summarised above, and their clinical experience. What clinical experience does the committee have of treating Lyme disease? Is it extensive enough to be able to demonstrate recovery probability that overrides what has been found in research for an evidence-based guideline?	

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					The committee must take into account how a statement is likely to be understood and consider whether that is consistent with the evidence supporting the statement. In this case the consistency appears to be very low. The statement *'most people recover completely'* will affect the way both doctor and patient see the severity of the disease. What are the outcomes that the committee judged to constitute "complete recovery"? For how long did the committee consider the recovery needed to be maintained? Is there any evidence of recovery to both this extent and for this long? The guideline makes a positive statement that implies that the evidence is clear. Is it? Our recommendation is that this statement needs to be withdrawn and replaced by one which states: *'Recovery from Lyme disease is variable and not well understood'.*	
SH	Lyme Disease UK	Short	14	22	Where is the evidence to suggest treatment for symptom relief is successful in Lyme disease patients? We agree that supportive treatment should be on offer, but this must be in addition to proper Lyme disease treatment. Painkillers and antidepressants are not going to cure a bacterial infection.	Thank you for your comment. Symptomatic treatment is not recommended instead of appropriate antibiotic treatment.
SH	Lyme Disease UK	Short	15	14-20	We welcome and endorse the idea of a patient focused method being used.	Thank you for your comment
SH	Lyme Disease UK	Short	15	3-4	Advise people to talk to their doctor if their symptoms have not improved or if symptoms return after completing treatment.	Thank you for your comment. A recommendation has been added to consider review when people are treated to assess response.
SH	Lyme Disease UK	Short	15	8-9	Two aspects of person to person transmission were omitted from the guideline although the committee clearly felt they were relevant to the Scope demand.	Thank you for your comment. Evidence report M outlines the search for evidence for person to person to transmission

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					They were omitted because of lack of research studies and yet there is no call for research in this area. The possible extension of a vector-borne disease to a disease capable of person to person transmission would have serious ramifications and a call for research is the only responsible response. Concern here that this depends on definition of Lyme disease which incorporates issues around both persistence and testing. Any study should be carefully constructed so that its conclusions aren't limited by these current questions, and is open to re-examination in the light of better testing or changed views on persistence. 1. The lack of research should appear clearly throughout the guideline in each relevant section so that people are fully aware of the guideline is not built on a solid foundation of good quality research 2. This topic should be added as an area where research is urgently required.	and the lack of evidence for sexual transmission or transmission via blood. The evidence available is described in all evidence reports including lack of evidence where appropriate. The research recommendations outlined arise from the specific evidence reviews which were carried out in guideline development and include those areas prioritised by the committee.
SH	Lyme Disease UK	Short	7,8	27, 1-4	Are there NHS-accredited laboratories which do not use validated tests and participate in formal external quality assurance programmes? If so, which are they? Similarly, are there NO foreign laboratories which fulfil these criteria? Or, are tests from foreign laboratories which also conform to these criteria acceptable? If so, how will doctors be made aware of these foreign laboratories? What happens with other diseases - e.g. if someone is diagnosed with HIV in the US, is a re-test	Thank you for your comment. It was not the intention to imply that all private or foreign laboratories are not accredited or perform tests that are not validated. The committee considered that in clinical practice tests might be repeated if there was uncertainty about the laboratory or test performed abroad. The wording of the recommendations have been changed.

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					always required in the UK? Line 27 appears to say that only NHS-accredited labs are capable of performing reliable Lyme disease tests. This section needs to be made much clearer for doctors, especially if some foreign tests are acceptable and others are not.	
SH	Lyme Disease UK	Short	16	2-14	There is wide acceptance among independent Lyme disease experts, but without research evidence, for a collection of unusual, varied and often minor symptoms to be associated with Lyme infection. Any study should include recording the incidence of these symptoms as being possible future indicators of those with Lyme infection. These include: a change in alcohol tolerance, hair loss, fasciculations, light/dark accommodation, etc etc. Any such clinico-epidemiological study should also include sero-negative patients who have a high suspicion of Lyme disease, so that it can become clear whether they have symptoms in common with seropositive Lyme disease patients. Much previous research has concentrated only on sero-positive patients, ruling out the possibility of learning about the postulated sero-negative Lyme patient population. Are you suggesting here that there is morbidity associated with seeking care outside the NHS which is not a problem with care inside the NHS? What do you mean by this and where is the evidence?	Thank you for your comment. The research recommendation is not prescriptive about what information is collected. We agree that sero-negative patients with high suspicion of Lyme disease should also be included. We have removed the last sentence from this section as we agree it did not quite make sense.
SH	Lyme Disease UK	Short	16	22-30	Is the committee accepting that seropositivity is not necessarily associated with disease? If that is the case, and if some diseased patients test negative, then surely this shows that serology is a blunt tool? Given this lack of information, how is it possible to make sweeping statements in the guideline such as	Thank you for your comment. Following stakeholder comments we have reviewed the wording of the recommendations to ensure that the limitations of tests are recognised. The information about ticks is from PHE who have a tick surveillance scheme.

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					'most tick bites do not transmit Lyme disease'? (Page 3 line 16) With the regular movement of people around the country, why are there mentions of seroprevalence in endemic and "other" areas as though they are dealing with different populations of people? Is the committee suggesting that the person's geographical location will be used to assess infection status? Does this happen in any other disease?	It is usual clinical practice to consider the pre-test probability of a disease or condition when deciding on testing or treatment and factors increasing risk of infection is relevant to that.
SH	Lyme Disease UK	Short	16	17-20	It is imperative to establish that the best tests are being used before they are used to determine prevalence. There's an implicit belief that seroprevalence = prevalence and this may not be true if your antibody tests are poor or not all infected people mount a detectable immune response. This is based on a lot of assumptions.	Thank you for your comment.
SH	Lyme Disease UK	Short	16	30-32, 1-2	Thought by who? If there's no data, then there's no data, don't give a "thought to be" without mentioning that this is speculation which is not backed by evidence. Throughout the guideline, comments are made which indicate a default position even though there is frequent acknowledgement of lack of data.	Thank you for your comment. The committee considered that there is some data and specialist experience but more comprehensive research is required. The wording has been altered.
SH	Lyme Disease UK	Short	17	7-18	Any such studies, desperately needed, should take into account best practice from across the experience of Lyme treating clinicians. Studies which genuinely looked at outcomes from a range of treatments would be world-leading.	Thank you for your comment.
SH	Lyme Disease UK	Short	17	22-24	We are pleased that the committee is recommending research into tests including those not currently performed in the UK. We note that ELISPOT is a type	Thank you for your comment. NICE research recommendations are developed from the specific evidence reviews that were carried out in

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					of Lymphocyte Transformation Test and wonder, from the grammar, whether the committee sees them as different tests. Perhaps, by Lymphocyte Transformation Test, the committee means MELISA tests, which are another type of Lymphocyte Transformation Test? We would like to see a nano-trap urine test, which involves an easily collected sample, direct rather than indirect test and which is effective during antibiotic treatment, included in any list of tests to be evaluated. Innatoss laboratories currently market one such test, and DNA Connexions in the US a similar one which uses PCR. We would like to see the committee recommend consideration of the production of a list of tests which, although not offered by the NHS, will be considered as acceptable when validated versions are performed by accredited laboratories outside the UK. The assumption that only tests offered by the NHS, which will be subject to economic arguments, are valid scientifically, is difficult to justify.	guideline development, which is why some tests that looked promising were included. We have however amended the recommendation to indicate the assessment of novel tests as appropriate.
SH	Lyme Disease UK	Short	18	4-14	"Successful treatment" needs to be defined throughout the guideline in the absence of a 'test for cure' - e.g. people need to be monitored and remain symptom free for a specific period of time in order to conclude that Lyme disease treatment has been successful.	Thank you for your suggestion. The committee considered that for clinical purposes this is currently decided by healthcare professional and patient. The development of a core outcome set would be the appropriate way to agree such a definition formally.
SH	Lyme Disease UK	Short	18	24-27	The guideline needs to encourage the GP to consider Lyme more strongly because of the prejudice of many doctors who believe evidence of a tick bite is necessary. The usual situation is the patient saying "I	Thank you for your comment. It is hoped that the guideline and the recommendations will increase awareness and knowledge of Lyme disease.

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					had exposure, I could have been bitten by a tick" and the doctor saying "you were in an area of low prevalence and Lyme is rare, with no tick bite, Lyme is unlikely".	
SH	Lyme Disease UK	Short	19	22-28	This is good but nowhere is the concept of the unusual combination of otherwise common symptoms mentioned as a key characteristic.	Thank you for your comment. The guideline does include reference to a scoring system in children where several symptoms are included but the evidence was not strong enough to recommend this. The recommendation does suggest that the presence of several symptoms should make Lyme disease a consideration.
SH	Lyme Disease UK	Short	19	5-8	This statement is unclear. Do you mean that assuming that although the guidelines encourage doctors to consider Lyme disease, it will normally not result in testing because it will be ruled out before that? This needs to be clarified, especially when the guidelines encourage a high reliance on serology and dissuade doctors from making a clinical diagnosis unless an erythema migrans is present. This statement is grossly misleading; *'the number of people with Lyme disease is generally low'.* Added to the already documented, inadequate testing, we cannot know how prevalent Lyme disease is in the UK and whether it could be responsible for cases of "Medically Unexplained Diseases", like ME/CFS and fibromyalgia.	Thank you for your comment. We have changed the wording to make it clear that improved awareness should result in increased recognition and early treatment. We have removed the reference to 'resource impact', which is a term used by NICE to refer to recommendations whose implementation will cost £1million or more per recommendation per year.
SH	Lyme Disease UK	Short	19	19-21	Included description of rash and characteristics are inadequate.	Thank you for your comment. The description and characteristics in the recommendations were reviewed by the committee following stakeholder comments and some minor changes made. The committee hope that the images presented with the guideline will be particularly helpful in allowing healthcare professionals to recognise erythema migrans.

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SH	Lyme Disease UK	Short	19	13-14	Where is the evidence that it is *'uncommon"*? The lack of ability to recognise the disease may account for multiple misdiagnoses and therefore lack of numbers.	Thank you for your comment. We agree that this was unhelpful and have removed this phrase.
SH	Lyme Disease UK	Short	20	17-25	'Relatively high degree of sensitivity' implies some false negatives. And yet this will debar patients from the second tier of testing (line 26). So it is accepted that there will be false negatives from testing alone, but clinical diagnosis in face of negative tests is not mentioned.	Thank you for your comment. Recommendations on treating in the basis of clinical suspicion have been added and these and the rationale are included in the section on diagnostic tests.
SH	Lyme Disease UK	Short	20	1-8	History and presentation are not clearly defined throughout the guidelines. Everyone who sets foot outside is at risk of Lyme disease, tick bites go unnoticed and many of the characteristic symptoms and signs of Lyme disease (excluding erythema migrans) are being dismissed as being rare and uncommon. The exploration of other diagnoses is actively encouraged. This sentence; 'Those who present without erythema migrans, but whose history and presentation is consistent with Lyme disease, receive diagnostic testing' is an implication of absolute reliance on tests. Furthermore, 'In areas where Lyme disease is less common', is problematic when prevalence data is incomplete.	Thank you for your comment. This section does not imply that treatment cannot take place without testing, and this is discussed later in the guideline in the section on testing. However, the committee did consider that when Lyme disease is considered a possibility, testing will be carried out.

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SH	Lyme Disease UK	Short	20	26-30	High sensitivity (not absolute), particularly for some strains of Borrelia. So in the others it is accepted that there will be a level of false negatives? Would this be accepted for cancer or HIV? NICE CKS says that Lyme arthritis, Lyme carditis and ACA are rare, rare, and uncommon respectively. If the 2-tier test has high sensitivity and specificity particularly for these manifestations of Lyme disease, what does that imply of the sensitivity and specificity for other, more common, manifestations of the disease, such as neuroborreliosis and patient suffering fatigue and cognitive dysfunction, largely ignored in this guideline. What is the sensitivity and specificity for ALL manifestations of Lyme disease? Is a lower testing performance tolerable for these patients? The committee is in danger of condoning a circular argument which sees easily tested manifestations of Lyme disease becoming the measures of Lyme testing. This will lead to continued lack of identification of the more common and currently often seronegative manifestations of Lyme disease and continuation of the unacceptable status quo. We note, and we believe that the committee should also note, that these more successfully tested-for Lyme manifestations, especially arthritis and ACA, are associated with B. burgdorferi ss and B. afzelii, which feature specifically in the antigen mix for the Virastripe used at RIPL. Neuroborreliosis, where we see a lot of very sick but seronegative patients, is believed to be	Thank you for your comment. This section has been changed following stakeholder comment and the addition of recommendations highlighting the importance of treatment if there is high clinical suspicion both while waiting for test results and if results are negative.

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					associated with B. garinii which does not specifically feature in the Virastripe test.	
SH	Lyme Disease UK	Short	20	13-14	Where is the evidence for this? Which symptoms have more common causes? An over-reliance on serology is also highlighted here - we do not have a test that can rule out Lyme disease so how is testing 'helpful to ensure accurate diagnosis'? Here testing is "helpful" but nowhere is there any indication that you can actually make a diagnosis without a positive test result.	Thank you for your comment. Following stakeholder consultation, this sentence has been reworded to 'with symptoms that overlap with those of other disease and conditions'. The recommendations have also been revised to emphasise the importance of clinical assessment in guiding diagnosis and treatment decisions.
SH	Lyme Disease UK	Short	20	15-16	Clinical assessment is not encouraged throughout this guideline and there is an over-reliance on serology. Symptoms are dismissed as uncommon or attributed to other causes and so doctors are not being equipped to make a clinical diagnosis of Lyme disease. Clinical	Thank you for your comment. This section has been changed following stakeholder comment and the addition of recommendations highlighting the importance of treatment if there is high

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					assessment is mentioned frequently but nowhere does it appear that clinical assessment can override a negative test result. What is the point of interpretation of test results alongside clinical assessment if the latter cannot override a negative test? Or does this mean that clinical assessment can be used to override a positive test? The way that tests and clinical assessment relate to each other is NOT clear in the guideline.	clinical suspicion both while waiting for test results and if results are negative.
SH	Lyme Disease UK	Short	21	22-29	The immunoblot cannot be *'confirmatory'* due to its limitations. This recommendation to repeat the ELISA depends on an understanding that any failure of the test must be transient or random. It assumes that there is no reason that the test can produce a false negative which is permanent. Is there evidence for this? There is a paper (see figures 2 and 3) which shows that the response is undulatory. If you test say 3 times over 1 year, you may hit a negative response period each time. Reference: Elisabeth Aberer and Gerold Schwantzer, "Course of Antibody Response in Lyme Borreliosis Patients before and after Therapy," ISRN Immunology, vol. 2012, Article ID 719821, 4 pages, 2012. doi:10.5402/2012/719821 https://www.hindawi.com/journals/isrn/2012/719821/	Thank you for your comment. This section is explaining the rationale for the recommendations, which is explained in more detail in the evidence report (C). The limitations of the tests have been added to the guideline and the earlier section of the rationale altered.
SH	Lyme Disease UK	Short	21	1-7	Alternative diagnoses such as what? If these include conditions such as CFS/ME and fibromyalgia, this is problematic as they are conditions which cannot be objectively proven. This sentence is completely add odds with information provided in the rest of the	Thank you for your comment. Symptoms of Lyme disease can overlap with several other conditions and it was decided not to list them in the guideline, as inevitably some would be missed. We agree that some of these conditions

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					guideline; "If symptoms have been present for weeks, the committee agreed that the ELISA may be repeated and an immunoblot should be carried out, which will help rule out or confirm diagnosis where uncertainty still remains". These tests CANNOT rule out or confirm diagnosis. This wording should be removed.	are difficult to diagnose. The test may help rule out or confirm diagnosis but results need to be used in conjunction with clinical presentation.
SH	Lyme Disease UK	Short	21	8-12	Referral to specialist in the face of conflicting test and clinical indications is normally to benefit from the specialist's knowledge or experience. Which specialists exist within the NHS who have extensive familiarity with current research on Lyme (e.g. visiting conferences regularly) or with genuine experience of seeing and treating Lyme disease patients? Our experience indicates many NHS specialists rule out Lyme disease on the basis of negative serology tests. All the way through this guideline, the response to negative serology is retesting, waiting, focusing on alternative diagnoses. Nowhere does the guideline say explicitly that sometimes tests do not pick up Lyme cases and therefore careful clinical diagnosis may result in proceeding with a Lyme disease diagnosis. Since nowhere does the evidence suggest that serology is 100% effective, where does this leave the false negatives? We need two things: a) acknowledgement that with anything less than 100% sensitivity there will be false negatives and b) to allow for those false negatives, careful clinical assessment may result in provisional diagnosis of Lyme disease leading to treatment.	Thank you for your comment. Following stakeholder consultation recommendations have been added to clarify the limitations of the tests and the rationale section has been amended to reflect this.

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					There also needs to be an awareness that the risk of untreated Lyme disease (both to the patient and NHS budget) is higher than the risk of an exploratory course of antibiotics (again, both to the patient and the NHS budget).	
SH	Lyme Disease UK	Short	21	13-16	Validated by whom? It is also important to point out that testing used by the NHS can be misleading and result in misdiagnosis as well, particularly given the over-reliance on serology, endorsed by this guideline. Clarity is needed on the acceptability of foreign tests. Are there really no accredited laboratories abroad or are all tests done in foreign labs deemed 'unreliable'	Thank you for your comment. Validation is a process that is described in the recommendation and requires published evidence on the performance of a test. The recommendation on use of tests from foreign labs has been altered to clarify meaning.
SH	Lyme Disease UK	Short	22	3-8	There should be concern in this section that particularly with presentations of facial palsy and arthritis. Steroids may be used in treatment of non-Lyme causes of symptoms which is contraindicated. There should be an indication here of the importance of correct diagnosis as it may determine the treatment administered. What about antibiotics following any necessary surgery? There is no guidance about this if a patient is already on an antibiotic protocol for Lyme disease.	Thank you for your comment. The committee considered that steroids could have a place in disease caused by infection particularly if there is a strong inflammatory response. The committee were not aware of specific issues in relation to people on treatment for Lyme and antibiotics following surgery.
SH	Lyme Disease UK	Short	22	9-12	Where is the evidence for facial palsy being "uncommon"? How can the NHS specialist "ensure the diagnosis is correct" when current serology cannot rule out Lyme disease? Lyme disease would still be a potential cause and as such, any "specialist" would need training in how to adequately recognise and differentiate Lyme disease from other conditions. If NICE are drawing distinctions here about differing symptoms in adult and child cases of Lyme disease, there needs to be clear guidance on which symptoms are associated with which age groups.	Thank you for your comment. The committee considered that focal neurological symptoms are more uncommon in children than in adults, and it was important to ensure sinister causes such as brain tumours were ruled out. An evidence review was not done for this as it was not included in the scope, but it was informed by experience of the committee, which included a paediatric neurologist. Lyme disease could still be a potential cause.

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SH	Lyme Disease UK	Short	22	17-20	We would like to draw attention again to the issue of what experience NHS specialists have of Lyme disease, and how likely a paediatrician is to assess for Lyme disease. For both these situations Lyme disease should have a high index of suspicion.	Thank you for your comment. We hope that this guideline will raise awareness of Lyme disease among NHS specialists, paediatricians and all healthcare professionals and encourage consideration of Lyme disease in these types of clinical scenarios.
SH	Lyme Disease UK	Short	22	25-27	People react differently, which is a key characteristic of Lyme disease. So one person may have sudden neurological severe symptoms and another may have slower onset, one person may be treated within a week of the bite and another after 6 weeks. I think we should query the wisdom of standardising response across different presentations of a highly variable illness known to have several strains.	Thank you for your comment. This sentence has been removed. The aim was less to standardise treatment and more about reduction of ambiguity in treatment regimens and this is now explained in the rationale and the evidence reports.
SH	Lyme Disease UK	Short	22	23	Regarding antibiotic treatment, there are no treatment recommendations for the common but subjective symptoms of cognitive dysfunction, fatigue and dysautonomias. Does the committee recognise these as symptoms, which are severely disabling for patients and which need treatment? There is barely a mention of these symptoms in the guideline, either with respect to diagnosis or treatment, and yet they are the most common symptoms we encounter and the most disabling for our members.	Thank you for your comment. These types of symptoms are included in the treatment recommendations for non-focal symptoms.
SH	Lyme Disease UK	Short	23	5-16	Where is the evidence to support the effectiveness of a single daily dose of doxycycline?	Thank you for your comment. The evidence and the committee discussion can be found in evidence reports D,E,F,G, H,I,J,K and L
SH	Lyme Disease UK	Short	24	5-9	This good but the guideline is not actively encouraging clinical diagnosis of Lyme disease, with symptoms being played down and cited as uncommon.	Thank you for your comment. Following stakeholder consultation, the recommendations have been revised emphasise to more clearly the importance of clinical assessment in diagnosing and treating Lyme disease.

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SH	Lyme Disease UK	Short	24	17-20	Addition of 1 week of a low dose of antibiotics seems disproportionate to the symptoms of neurological dysfunction. There seems to be more fear of antibiotics in the guideline than of permanent neurological damage.	Thank you for your comment. This is for treatment of peripheral or cranial nerve problems such as facial palsy. The BNF currently recommends 10-14 days for non-arthritis Lyme disease so 21 days is considerably longer.
SH	Lyme Disease UK	Short	24	21-24	If headaches, a stiff neck and cognitive dysfunction are listed as rare symptoms of Lyme disease, how will people with a diagnosis of meningitis and encephalitis subsequently achieve a diagnosis of Lyme disease and IV antibiotics if clinical diagnosis is not encouraged and serology is negative? What other prior diagnoses should qualify for a consideration of Lyme disease? ME/CFS, fibromyalgia, arthritic conditions? Why is encephalitis being singled out here?	Thank you for your comment. The symptoms listed overlap with many other conditions, which are more common than Lyme disease as a cause. Following stakeholder comments, more emphasis has been put on clinical diagnosis. Other symptoms are considered in other sections.
SH	Lyme Disease UK	Short	24	25-28	Will central nervous system symptoms be diagnosed clinically or only with positive serology? According to the NHS Choices website, Syphilis is treated with a 28 day course - so why is the suggestion for neuro Lyme only 21 days? Reference: NHS Choices, Syphilis http://www.nhs.uk/Conditions/Syphilis/Pages/Treatmentpg.aspx	Thank you for your comment. Diagnosis will be made clinically with support of laboratory testing/ Following stakeholder comments more emphasis has been put on clinical diagnosis and this is reflected in recommendations and rationale on diagnosis and testing. The NHS site for syphilis says intramuscular antibiotics is suggested for 2 weeks for people with syphilis affecting the brain.
SH	Lyme Disease UK	Short	24	2-4	*'People diagnosed with Lyme disease often have symptoms that are not specific to an organ system'.* We would agree with this but throughout the guideline these symptoms are being described as uncommon, where here it says people often have these symptoms. This needs to be clarified so that doctors do not overlook symptoms of Lyme disease.Also included in	Thank you for your comment. The committee did not intend to imply that non-focal symptoms are uncommon, but that Lyme disease is an uncommon cause of these non-focal symptoms. The list of symptoms in the brackets is intended to provide examples rather than an exhaustive list. The committee considered these the most important to list.

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					the brackets should be the non-focal symptoms of later disease, such as chronic fatigue and dysautonomias.	
SH	Lyme Disease UK	Short	25	4-11	This is a common thread throughout the guideline. The fear over prescribing a few too many days antibiotics seems to outweigh concerns over under-treatment. Given that there is no evidence which shows what treatment is effective, surely more flexibility should be given to individual doctors to assess patients' progress and treat according to their best judgement.	Thank you for your comment. The recommendations are based on the best available evidence and recommend longer courses of antibiotics than many guidelines and a repeated course if necessary. Referral to a specialist is an option and a specialist may consider a different course of action. However, in the absence of evidence of effect of prolonged courses of antibiotics it would not be appropriate to recommend these.
SH	Lyme Disease UK	Short	25	21-24	There is a worrying indication here that treatment is endeavouring to cure symptoms, not the infection. Resolution is seen as solving the arthritis with no mention of whether the underlying infection is cured. There is a complete disregard for the theory held to be true by many researchers, that Borrelia is persistent in a number of forms.	Thank you for your comment. The committee were aware of uncertainty as to the cause of ongoing symptoms and whether these are related to infection. In the absence of evidence of effect of prolonged courses of antibiotics, it would not be appropriate to recommend these.
SH	Lyme Disease UK	Short	26	17-20	The study was for 30 days and yet the recommendation has been reduced because antibiotics are available in weekly packs. Pharmacists can, and frequently do, split drugs packs. Recommendations should depend on evidence, not packaging. If recommendations must be for whole weeks then over-caution would be the sensible route with 35 days being prescribed.	Thank you for your comment. The committee discussed this and while accepting your point considered that courses in weeks were more easily understood. The committee considered that 28 days is a more standard dosing and that this is already the recommendation e.g. in the BNF for Lyme arthritis. The committee considered that both arthritis and ACA were conditions where antibiotic penetration is more difficult and consistency was appropriate between these.
SH	Lyme Disease UK	Short	26	2-3	The study was for 30 days and yet the recommendation has been reduced because antibiotics are available in weekly packs. Pharmacists	Thank you for your comment. The committee discussed this and while accepting your point considered that courses in weeks were more

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					can, and frequently do, split drugs packs. Recommendations should depend on evidence, not packaging. If recommendations must be for whole weeks then over-caution would be the sensible route with 35 days being prescribed.	easily understood. The committee considered that 28 days is already the recommendation e.g. in the BNF for Lyme arthritis and that continuing with this dosage would help implementation.
SH	Lyme Disease UK	Short	26	12-13	This presumably constitutes evidence that Lyme disease infection is not always self-resolving and may persist.	Thank you for your comment.
SH	Lyme Disease UK	Short	27	6-9	Given that it is unknown which treatments are effective for other symptoms of Lyme disease, it is misleading to imply that recommendations for treatment for heart problems caused by the disease have been extrapolated from knowledge to uncertainty rather than from one area of uncertainty to another. Why not apply what is known from clinical experience rather than from an area in which there is no evidence? In the absence of evidence for how to treat heart problems, the committee should consider looking to experience drawn from elsewhere in the world rather than looking at evidence-light protocols for other symptoms.	Thank you for your comment. The committee used the evidence available for treating other symptoms of Lyme disease, their experience of current practice and their knowledge of care for people with heart problems to develop the recommendations. We agree that this was not clear and have now amended this section for clarity.
SH	Lyme Disease UK	Short	27	9-11	We are surprised that the overriding consideration is not to cure patients and have them returning to fully functioning, meaningful lives with the ability to contribute to society. Is this really what the committee meant?	Thank you for your comment. The statement you refer to was about antibiotic treatment but this has now been removed.
SH	Lyme Disease UK	Short	27	18-20	The size of antibiotic packs is of no scientific importance. Furthermore, given the studies used to form this guideline focused on a 30 day course, surely this should be the minimum prescription.	Thank you for your comment. This comment appears to relate to page 26 and response is as for comment 353.
SH	Lyme Disease UK	Short	27	4-5	Is it rare that it affects the heart or rare that it causes damage to the heart? Where is the evidence for this? What is meant by *'other heart problems'* in this	Thank you for your comment. The wording has been changed to 'sometimes' affects the heart. Other heart problems is purposely left undefined

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					statement? This needs to be made very clear. Where is the evidence for this?	here as a number of problems are possible and any list would indicate a defined group.
SH	Lyme Disease UK	Short	28	12-14	What are NHS specialists supposed to do when faced with patients with non-neurological ocular manifestations of Lyme disease if there is 'no evidence for the management' of these manifestations? Is the specialist meant to treat or not treat, especially if this is the only manifestation? This needs to be made much clearer.	Thank you for your comment. It would be expected that the specialist would discuss with other colleagues to agree on treatment. If ocular manifestations were combined with other manifestations where there is some evidence, that would likely influence the decision about treatment.
SH	Lyme Disease UK	Short	28	28-29	Define *'sometimes'.* What is the evidence behind the use of this word?	Thank you for your comment. The wording was considered to best capture what is known about Lyme disease,
SH	Lyme Disease UK	Short	29	16-23	Why was no evidence review on these issues carried out?	Thank you for your comment. There are guidelines available for the management of symptoms such as chronic pain, fatigue and depression. The aim of this guideline was to identify the best way to treat the bacterial infection, as this is an area in which there is little guidance. However, the committee agreed the importance of consideration of management and support for these symptoms and therefore made a recommendation that physicians consider the possibility of such needs.
SH	Lyme Disease UK	Short	29	25-31	Where is the evidence to suggest that Lyme disease can persist between two courses of antibiotics but not beyond? How can the committee be sure that there is *'a small number of people with recurrent symptoms' ?* Where is the evidence for this?	Thank you for your comment. The evidence examined in the guideline can be found in the evidence reports. The decision on treatment is based on the lack of evidence of benefit of further or prolonged treatment.
SH	Lyme Disease UK	Short	29	8-11	What is the NHS specialist meant to do with this information? By *'not routinely offered',* does this mean they can be offered in certain circumstances? If so, which circumstances?	Thank you for your comment. This does mean that further antibiotics are not recommended but recognised that an individual specialist can make a clinical judgement on the best approach for a patient based on their assessment.

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SH	Lyme Disease UK	Short	29	12-15	What is a *'related symptom'* in contrast to a "symptom" of Lyme disease?	Thank you for your comment. The exact cause of symptoms is not always clear for example, depression may occur as a result of having a long-term illness or be specifically associated with a disease. The term 'related' is used to cover a number of such possibilities.
SH	Lyme Disease UK	Short	29	3-5	The absence of evidence needs to be made much clearer throughout the guideline. Where is the evidence that Lyme disease cannot persist beyond a second course of antibiotics? Some degree of persistence is acknowledged here with the term *'treatment failure'* and the offer of a second course of antibiotics but in the absence or a test for cure, how can persistence be limited to the time period between a first and second course of treatment and not beyond?	Thank you for your comment. The lack of evidence and the quality of the evidence is referred to repeatedly in the rationale, the short version and the evidence reports.
SH	Lyme Disease UK	Short	14, 15	23,24 and 1,2	Is this referring to a Herxheimer reaction? Further up, it states that a Herxheimer reaction can occur on day 1, whereas here it says *'early in treatment'* which suggests it can happen after day 1. The timeframe needs to be consistent and clarified, particularly as drug allergies are also possible and doctors need advice on distinguishing between a Herxheimer reaction and a drug allergy. What are the recommendations for dealing with a Herxheimer reaction?	Thank you for your comment. The time period included in the recommendation on Jarisch-Herxheimer reaction has been amended. Specific recommendations on dealing with the reaction are not included in the guideline.
SH	Lyme Disease UK	Short	30	21-26	This conflicts with statement on Line 18 above; *'symptoms of Lyme disease in babies are not known'*. Guidance would be useful. Are there any paediatric infectious disease NHS specialists in the UK with experience or knowledge of paediatric Lyme disease? Please see our general concerns about NHS specialists above.	Thank you for your comment. We do not think the statements conflict. The recommendations were made on a precautionary principle to reassure parents. The recommendation suggests consideration of treatment if IgM is found or if there is clinical suspicion.

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					Why is IgM going to be used in isolation? Looking for IgM antibodies in the baby, as evidence of infection, assumes that introduction of the pathogen happened after the development of self-nonself discrimination in the foetus. This paper, Conceptual aspects of self and nonself discrimination, Segundo Gonzalez, Ana Pilar González-Rodríguez, Beatriz Suárez-Álvarez, Alejandro López-Soto, Leticia Huergo-Zapico, and Carlos Lopez-Larrea : Self Nonself: 2011 Jan-Mar; 2(1): 19–25 states; *'For instance, foreign antigens presented during foetal life are considered self because adaptative immunity learns to discriminate self from nonself during their maturation in primary lymphoid organs and any antigen present during this selection process is consider as self.'* Has the committee considered this problem in recommending use of IgM to identify infected babies? What is the evidence that IgM testing is able to overcome this problem in babies potentially infected at the very start of gestation? We know of women who have had the cord blood tested for Lyme disease in the US using PCR. Perhaps this could be explored.	
SH	Lyme Disease UK	Short	30	11-15	In the *'absence of evidence'*, how can a conclusion be drawn tha*t 'the risk appears to be very low'?* How can women be *'reassured that pregnancy and their baby are unlikely to be affected'* when there is no evidence to back this up? This "reassurance" is based on nothing, especially when *'the symptoms of Lyme disease in babies are not known'* and babies are unable to communicate symptoms.	The evidence review searched for evidence of an effect on pregnancy and fetus and did not find any convincing evidence. The committee was reassured by the lack of evidence of a specific effect on pregnancy and fetus by Lyme disease from areas of the world where the prevalence is much higher than in the UK. The committee, however, agreed to err on the side of caution and recommend a pathway for review of infants at risk.

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SH	Lyme Disease UK	Short	30	17-20	Surely that is what these guidelines are intended to provide, but there does not appear to be sufficient guidance for the care of pregnant women and babies.	Thank you for your comment. The guideline recommendations are based on a precautionary principle given the lack of evidence of harm.
SH	Lyme Disease UK	Short	30	4-6	What is a *'related symptom'* in contrast to a "symptom" of Lyme disease?	Thank you for your comment. The exact cause of symptoms is not always clear for example, depression may occur as a result of having a long-term illness or be specifically associated with a disease. The term 'related' is used to cover a number of such possibilities.
SH	Lyme Disease UK	Short	31	5-6	Information on the accuracy and limitations of testing has not been made clear in this guideline.	Thank you for your comment. We have added recommendations on accuracy of testing and on need for clinical judgement following stakeholder comments.
SH	Lyme Disease UK	Short	33	24-28	This is poor logic. It may be that years of being told that Lyme disease is more common in certain areas predisposes doctors to look for it more carefully in these areas, leading to more testing. There is no mention of Asia here whereas Asia is mentioned further up (without listing which areas of Asia). *'Specific areas of Europe'* is not helpful unless countries are listed. Why pick out these regions without being more specific? Wouldn't it be better to simply mention the northern hemisphere in general, as suggested above?	Thank you for your comment. The committee considered that in this section they wished to highlight that Lyme disease appears more common in certain geographical locations. It is recognised that looking for a disease more carefully is likely to result in more cases being found but this alone is unlikely to account for the differences in reported cases. The committee recognise that the areas indicated are not precise but considered a more general statement was more helpful in raising awareness.
SH	Lyme Disease UK	Short	33	20-22	The word *'overgrown'* should be removed as it creates bias away from well-tended areas which may still	Thank you for your comment. We have removed the term 'overgrown'.

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					harbour ticks such as urban parks and gardens (as shown in this 2016 study). Many of our 8000+ members have reported being infected in such areas including back gardens and whilst sitting on mown lawns. Reference: Hansford et al *Ticks and Borrelia in urban and peri-urban green space habitats in a city in southern England.* Ticks Tick Borne Dis. 2017 Mar;8(3):353-361. doi: 10.1016/j.ttbdis.2016.12.009. Epub 2016 Dec 21 https://www.ncbi.nlm.nih.gov/pubmed/?term=Hansford%2C+K.M.%2C+et+al.%2C+Ticks+and+Borrelia+in+urban+and+peri-urban+green+space+habitats+in+a+city+in+southern+England.+Ticks+Tick+Borne+Dis%2C+2016..	
SH	Lyme Disease UK	Short	33	23	'*Lyme disease can occur anywhere in the UK*'; this is not stressed enough throughout the guidelines.	Thank you for your comment. This is included in the recommendations.
SH	Lyme Disease UK	Short	34	2-8	If *'many diagnoses will also be made clinically without laboratory testing'*, why does this guideline not encourage clinical diagnosis and instead places a strong emphasis on relying on serology?	Thank you for your comment. Following stakeholder comments recommendations have been added to emphasise the place of clinical judgement in diagnosis.
SH	Lyme Disease UK	Short	34	15-20	In this guideline, no distinction is made between acute cases and people who have had long term, untreated Lyme disease. Practitioners familiar with Lyme disease do make a distinction, especially concerning treatment protocols. The guideline should challenge the commonly held belief amongst doctors that Lyme is "self-limiting", especially in cases with untreated erythema migrans and systemic, debilitating symptoms.	Thank you for your comment. The recommendations were based on the evidence available and the studies available did not provide clear distinctions as you describe.
SH	Lyme Disease UK	Short	34	24-25	In this 'Context' section, the committee remarks on their research recommendations to improve basic	Thank you for your comment. The context section is designed to give a brief overview of the

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					epidemiology and understanding of the natural history of Lyme disease. This is welcome. This section should be much more obvious and the state of knowledge about the natural history of Lyme disease should be much more clearly remarked on. The average GP reading this guideline will not have any idea how much is NOT known about Lyme disease and this will give him a confidence that the committee, who have seen the evidence base, will not share. An example of this is the complete absence of any mention of gut symptoms in the guideline. It is common among Lyme disease patients that they show a number of gut-related issues. There is an undoubted dearth of material about this group of symptoms in the literature and so it is not surprising that it does not appear in the guideline. But the committee should note with concern this type of discrepancy. In an informal survey by Caudwell LymeCo charity, 22% of late Lyme patients had had either a colonoscopy or gastroscopy in the previous year, indicating gut symptoms severe enough for that NHS spend, 7% had had their gallbladder removed during the previous year and 25% had a diagnosis of Irritable Bowel Syndrome. This, it is stressed, is only an informal survey, but the committee should note the contrast of an apparently common group of symptoms and their complete absence in the evidence base. The exclusion of seronegative, late sufferers from the literature should also be noted as a hurdle standing in the way of a better understanding of the natural history of the disease. Independent Lyme disease experts	guideline. The limitations of the evidence are discussed fully in the evidence reviews. We have added an additional sentence to the context section on the poor quality evidence available. As you indicate, there is a dearth of material about gut symptoms in the literature and this issue was not highlighted in scoping of the guideline or by the committee. A clinical epidemiological study as suggested in the research recommendations would provide more evidence on these associations. We have made it clear in the detailed research recommendation that people who are seronegative and people who are diagnosed at different times must be included in the research. .

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					note that many of their most ill patients are seronegative and their exclusion from most studies prevents any exploration of the possibility that, if there is a subset of patients who do not, for some reason, produce antibodies, this may be a contributor to succumbing to intractable disease. The guideline should communicate clearly how much is NOT known about the natural history of Lyme disease. The James Lind Alliance has summarised the state of understanding of disease and this should be made very clear to anyone who reads the guideline. References: Caudwell LymeCo Charity, *Lyme Disease on the NHS*, Patient Survey 2016 https://caudwelllymedotnet.files.wordpress.com/2016/07/lyme-disease-on-the-nhs-ppt-v1.pdf James Lind Alliance, *Lyme Disease Top 10* http://www.jla.nihr.ac.uk/priority-setting-partnerships/lyme-disease/top-10-priorities/	
SH	Lyme Disease UK	Short	17,18	26-30, 1-3	We understand the need for cost-effectiveness generally, but surely in terms of diagnosis which is KEY to understanding this disease, cost-effectiveness should be low on the priorities. In practice where is the *'in part'*? When a patient has lots of signs and symptoms but negative serology, does this mean that the committee accepts that diagnosis may not include positive tests? It is worrying that many symptoms which appear to be common in our support group over 8000 people, are downplayed and labelled as "uncommon" in Lyme disease. If the underlying message is that presentation of the disease is very	Thank you for your comment. Cost-effectiveness always forms part of decision making in NICE guidance. Following stakeholder consultation, we have added recommendations to clarify the importance of clinical judgement in diagnosis and of diagnosis and treatment in the presence of negative serology.

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					variable, why is this not emphasised further up in the guidelines? The guideline not allow for diagnosis of Lyme disease without positive serology. The only option for a person with all signs, symptoms and supportive history of Lyme disease but with negative UK serology, is referral to a specialist. We have already expressed our concern about what constitutes a Lyme disease NHS specialist and this is why people explore private treatment options.	
SH	Lyme Disease UK	Short	28, 29	29, 1-2	In the absence of evidence, there is no way of knowing what "sufficient" initial treatment involves as there is no 'test for cure'. The possibility of persistence beyond a first course of antibiotics is not emphasised enough here. It should come at the beginning of the list of reasons for persistent symptoms.	Thank you for your comment. This section has been re-written following stakeholder consultation.
SH	Lyme Research UK	Evidence review B	7	26	As indicated earlier in the discussion about EM, rashes, secondary multiple rashes similar to these and are very common, and this therefore need to be made clear to physicians and patients. This review included a study by Aucott (2009) - who makes it very clear that rashes can be different from the bulls eye form, but in NICE's review this finding is not taken into consideration. The review is weighted in a way which means that it is overly focused on 'exclusive' rather than 'inclusive' symptomology. This is not useful in the real world of patients where rashes can appear in less typical ways. These people should not be disadvantaged in the guidelines for their implementation, simply because there seem or have been traditionally been defined as being less specific to Lyme disease.	Thank you for your comment. The wording of the recommendation about EM was chosen to describe the general characteristics of EM rash but other rashes are also recognised in rec 1.2.4 The committee have worked with NICE to provide images of typical and less typical rashes and these are linked from the guideline in the tools and resources section on the NICE website.
SH	Lyme Research UK	Evidence review C	144	8	Three of these studies were unrelated to the commercial test kits used by the NHS and PHE and so	Thank you for your comment. The limitations of the evidence for confirmatory tests were reflected

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					irrelevant to UK Lyme testing. The Christova 2003 study demonstrated a sensitivity of 49% for IgM antibodies and 17% for IgG antibodies. This indicates that the NICE guideline that a positive test is required will miss many cases of Lyme disease. The Trevejo 2001 study related to vaccinated and non-vaccinated subjects and asymptomatic people. The Coyle 1993 study used cerebrospinal fluid and this is not used in the UK for diagnosing Lyme disease. It is suggested for use to diagnose neuroborreliosis but without proof of accuracy. The Blaauw 1999 study showed that 79% of patients with Lyme disease were negative (missed) by the test.	in the very low quality rating and the committee considered the entirety of the evidence (initial, combination and confirmatory) when making recommendations. Following stakeholder comments the recommendations now make clear the place of testing in diagnosis.
SH	Lyme Research UK	Evidence review C	300	2	Excluded studies Appendix I. More than 360 studies were excluded, representing the work of more than 150 independent researchers. No details or justifications were given for the exclusions. (Incorrect analysis, incorrect study design,	Thank you for your comment. Studies are assessed for eligibility against the review protocols (appendix A of the evidence reviews). For example, if the review protocol specified randomised controlled trials, then any study design other than an RCT would be 'excluded due to an incorrect study design'.
SH	Lyme Research UK	Evidence review M	General		The search failed to find an important paper that demonstrated adverse outcomes with pregnancies of infected mothers. 66 cases with adverse events including miscarriage, stillbirth, perinatal death, congenital anomalies, early onset fulminant sepsis and later onset chronic progressive infection from 263 cases where the outcome of gestational Lyme borreliosis where recorded See: Page 571 Gardner, Tessa. 2001. "Lyme Disease." in *Infectious diseases of the Fetus and New Borne*, edited by J. S. Remington and J. O. Klein. Phildelphia: W.B. Saunders Co.	Thank you for your comment. We have been unable to find this study using the reference provided, only reference to a book that cites the study. Published full text studies are preferred to ensure there is adequate information to carry out full critical appraisal of the study and outcomes.
SH	Lyme Research UK	Evidence review M	7	24-27	The requirement for positive serology for mother and child would be ideal however other methodologies	Thank you for your comment. The main limitation of correlation studies relating maternal infection

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					such as correlation studies relating maternal infection to pregnancy outcome are valid.	to pregnancy outcome is that there is no evidence of a causal link, particularly as symptoms of Lyme disease in babies are not known.
SH	Lyme Research UK	Evidence review M	8	Table 2	Lakos 2010 demonstrated that all mothers IgG positive delivered IgG positive new-borns. This meets condition required on page 7 lines 24-28 however the result is ignored and defined as "No direct evidence cause and effect. If these cases were rejected due to negative IgM results that would not be valid since test kit manufacturers consider either IgM or IgG indicative of infection. Also 21.1% of pregnancies had adverse outcome and apart from cavernous haemangioma the outcome was comparable to the average for Hungary (21.1% adverse outcome of pregnancies in Hungary????)	Thank you for your comment. If a mother who has had Lyme disease is IgG positive, IgG antibodies in the infant may be an indication of placental transmission of antibody only. This study reported individual adverse pregnancy outcomes, compared with the average incidence in Hungary, for example, the frequency of spontaneous abortion in the study group was 6.3%, whereas the average incidence in Hungary was 14.8%. For several of the outcomes, national incidence data was not available. The 21.1% figure represents the overall adverse outcome rate in the study population, not the national average.
SH	Lyme Research UK	Evidence review M	9	Table 2	MacDonald 1986. This study demonstrated borrelia spirochaetes in fetal tissue. Despite this gold standard method and the impossibility of tick transmission to the fetus the committee incorrectly concluded there was no proof of transmission from mother because the mothers were not diagnosed during pregnancy.	Thank you for your comment. The guideline committee considered that evidence from this study was limited by inherent selection bias associated with case series, small sample size, potential for culture contamination and lack of a diagnosis or any evidence of Lyme disease reported in any of the mothers. The evidence was therefore not strong enough upon which to conclude that Lyme disease can be transmitted vertically. These limitations have now been clarified in the discussion of benefits and harms section in the evidence report. Despite the quality of the evidence, the committee acknowledged that this type of

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						transmission is possible in theory and made recommendations to emphasise the importance of completing the full course of antibiotic treatment in pregnant women with Lyme disease, to advise women to tell their healthcare professional that they had Lyme disease during pregnancy if they have concerns about their baby, to discuss management of babies born to mothers who had Lyme disease during pregnancy with a paediatric infectious disease specialist and to treat babies on clinical suspicion or positive serology.
SH	Lyme Research UK	Evidence review M	9	Table 2	MacDonald 1989: Of 24 perinatal autopsies 17% were positive for Lyme disease. There is no comment on this evidence.	Thank you for your comment. This was included in discussion of benefits and harms section of the evidence report, in the paragraph on laboratory evidence of vertical transmission. The main finding of the study, as well as the limitations of the techniques used has now been added to this paragraph for clarity.
SH	Lyme Research UK	Evidence review M	14	Table 2	Williams 1995: The NICE analysis in table 2 says that only endemic area data was published. This statement is false, data for endemic and control area is shown and demonstrates a significantly higher rate of Cardiac malformation.	Thank you for your comment. The information in Table 2 does not state that only endemic area data were published. Malformation rates as a percentage of Lyme disease pregnancies are only reported for the endemic area. Malformation rates of the endemic and control areas are also reported but do not account for presence of maternal Lyme disease.
SH	Lyme Research UK	Evidence review M	20	21-25	The C6 test has the lowest sensitivity of any test. The phrase "relatively high degree of sensitivity" does not accurately represent the facts. This is demonstrated in two references that were excluded by the NICE committee. One is by the European Center for Disease Prevention and	Thank you for your comment. Both of these studies were systematic reviews, which included meta-analyses. The reviews were excluded because the methodology differed from NICE methodology, but the reference lists were

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					Control an EU organisation Ref: Zeller, Herve and Wim Van Bortel. 2016. *A Systematic Literature Review on the Diagnosis Accuracy of Serological Tests for Lyme Borreliosis*. (http://ecdc.europa.eu/en/publications/Publications/Lyme-borreliosis-diagnostic-accuracy-serological-tests-systematic-review.pdf). And the second, incorrectly excluded as a systematic review when it is a meta analysis: Cook, Michael J. and Basant K. Puri. 2016. "Commercial Test Kits for the Detection of Lyme Borreliosis: A Meta-Analysis of Test Accuracy." *International journal of general medicine* 9:427–40. Retrieved December 7, 2016 (https://www.ncbi.nlm.nih.gov/pubmed/27920571).	screened to ensure that we included any relevant papers in our review.
SH	Lyme Research UK	short	general	general	The NHS is not an accreditation body. NHS and PHE laboratories are accredited by UCAS to two different standards ISO 15189 and the lower standard granted to RIPL of the Clinical Accreditation Pathology Ltd standard. The NHS should accept any overseas laboratory that meets ISO 15189 accreditation or similar.	Thank you for your comment. The recommendations to which you refer have now been amended from 'NHS-accredited' to 'UKAS-accredited'.
SH	Lyme Research UK	short	15-18	15 line 8 – 18 line 17	It appears there are whole raft of issues and perspectives on Lyme disease that are begging for investigation through research. There is a distinct lack of emphasis here on basic science, and research, much of which points in a 'different direction' to clinical research. Therefore some	Thank you for your comment. The NICE process is that research recommendations are developed from the evidence reviews in the guideline where a search for evidence has been made and a clear research recommendation can be outlined. The list therefore is limited in terms of possible areas

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					distinct work reviewing some of this literature, particularly that persistence of infection and failed treatment and its reasons would be helpful . Perhaps these two areas of basic science research and clinical search research need to be brought closer together. There is also no emphasis on social and health services perspectives, but also need to be understood more clearly beyond anecdotal patient reports et cetera. Social epidemiology is a growing disciple that it proving itself to tackle questions of prevention, diagnosis and effective outcomes from that, in a more 'holistic' manner that has real potential for improvement in these areas. For example; How are cases distributed geographically in the UK and where might there be more problems with misdiagnosis or lack of care? Some other areas that are potentially very useful include research that; • Also allows monitoring of long term trends and outcomes such as patterns of diagnosis and related morbidity. What is the lived experience of people with Lyme disease including those who were not acute cases? • Assesses physician knowledge, or health services research e.g. access to care etc. or experience of care; health improvement i.e. assessment of health care outcomes rather	of research that would increase understanding, including as you point out in the area of basic research among others.

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					than more limited clinical outcomes (not the same). • These issues are commonly address in healthcare design, planning and service delivery and 'improvement science' research - which would have considerable relevance here since there are a multiplicity of reasons as to why treatment regime's and programmes of services delivery fail etc. It's not just the epidemiology of the disease where there is a lack of knowledge - but the aetiology of different types of cases, scenarios, and symptoms sets - as well as response to treatment at different stages taking these factors into consideration etc.	
SH	Lyme Research UK	short	3	18-21	This is good advice about prevention, in terms of tick protection behaviour. There is a clear need for better knowledge amongst doctors - 61.7% of patients in the survey above felt their GP was 'not informed about the risks from ticks'. Only 27.9% felt that their GP was informed. Therefore there should be a focus on Lyme 'prevention' as well as 'tick protection'. An overemphasis of 'risk factors' tends to discourage doctors from testing or consideration of symptoms for Lyme disease and delays treatment. Add a line that states: give people advice about: the range of symptoms and long timescales within which symptoms related to Lyme disease can develop, and advise patients to take swift action and consult with medical advisers appropriately	Thank you. The guideline scope did not cover prevention but the committee considered it important to make some reference to this with a direction to other sources such as PHE. .

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SH	Lyme Research UK	Short	3	5-6	Of 152 people surveyed in 2011 who had a diagnosis of Lyme disease from a professional 62.4% were exposed to ticks deemed likely to cause their illness outside of 'wild spaces' (including 42.5% in a garden allotment or park, campsite/picnic area/outdoor or leisure site). There is ample published evidence that tick removal and protection techniques, is poor even in the well informed. So advice needs to be precautionary - and not just focus on those who (traditionally) are considered at high risk. Change to : ticks can be found in a variety of urban, semi urban or rural environments such as grassy or wooded areas, gardens and parks etc.	Thank you for your comment. The wording of this recommendation has been revised in line with your suggestion following stakeholder consultation.
SH	Lyme Research UK	Short	3	16-17	Time to transmission is not relevant - it is more important to emphasize prompt and correct removal whilst also educating people on indicative symptoms and signs etc. change to: 'whilst not all ticks carry Lyme disease any one of them can, and correct removal of them can be preventative but not always enable prevention of infection'	Thank you for your comment. The recommendation now includes the need for correct removal.
SH	Lyme Research UK	Short	3	7	Of 152 people surveyed in 2011 who had a diagnosis of Lyme disease from a professional 38.8% did not recall a tick bite, one third of whom had positive test results on the NHS. This needs changing to: 'tick bites and therefore the symptoms of Lyme disease may not be understood by the pubic therefore doctors need to be proactive in assessing the potential for Lyme disease (without this information being available)	Thank you for your comment. Recommendation wording is based around actions rather than explanations. It is hoped that the guideline and recommendations will result in healthcare professionals being more pro-active in assessing the potential for Lyme disease.

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SH	Lyme Research UK	Short	3	13	This statement is not supported by line 10 which states that UK prevalence data is incomplete so cannot be compared - and so it should be removed as it is misleading	Thank you for your comment. The recommendation is based on best available evidence while including information of the incompleteness of data.
SH	Lyme Research UK	short	4	8-21	There needs to be mention of the possibility of primary atypical rashes as well as secondary multiple or disseminated rashes (not at the site of the bite) in the guide here or elsewhere. As Aucott, J et al. (2009). (Diagnostic challenges of early Lyme disease: lessons from a community case series. BMC Infectious Diseases, 79(9), 1–8. http://doi.org/1471-2334-9-79 [pii] 10.1186/1471-2334-9-79); *Borchers, A. T. et al. (2014). (Lyme disease: A rigorous review of diagnostic criteria and treatment. Journal of Autoimmunity, 57C, 82–115. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/25451629) ;* Steere AC.,et al . (1983). (The Early Clinical Manifestations of Lyme Disease. Ann Intern Med, 99(1), 76–82. http://doi.org/10.1059/0003-4819-99-1-76Of) These articles make a number of points worthy of consideration; 1. Physicians are often unaware the morphology or significance of EM rashes (and therefore they need much better, clearer advice). 2. Only 19% of Lyme cases had the stereotypical bull's eye appearance. 3. Rashes can be triangular, rectangular, or distorted from the bull eye shape.	Thank you for your comment. The committee have agreed a number of images of typical and atypical EM to accompany the guideline, as providing images was considered clearer than attempting descriptions of these.

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					4. Atypical features mimic other common skin problems, e.g. spider's bites. 5. Secondary rashes can look like, primarily rashes - and this can happen in disseminated disease early on 6. Secondary rashes are extremely common in people with primary rashes (which of course may have been missed in the first instance which is sadly the norm in undiagnosed cases). All of these points need to be made clear to doctors so they do not dismiss rashes as common skin complaints. NICE needs to make the diagnostic process more relevant to the clinical situations patients and doctors experience. We advise that these points are made clear as per above.	
SH	Lyme Research UK	short	4	22-24; 1-8	The words "but uncommon" should be removed. The committee have stated that incidence and prevalence data is inadequate. And the number of people misdiagnose is unknown.	Thank you for your comment. This statement is not intended to suggest that Lyme disease is uncommon, but that it is an uncommon cause of the symptoms outlined in the bullet points. For example, Lyme disease is unlikely to be the cause of the majority of cases of headache.
SH	Lyme Research UK	short	4	1-2	These actions reduce but do not eliminate the risk of infection – and so this needs to be clear in the guidelines. See: Faulde, Michael K. et al. 2014. "Human Tick Infestation Pattern, Tick-Bite Rate, and Associated Borrelia Burgdorferi S.l. Infection Risk during Occupational Tick Exposure at the Seedorf Military Training Area, Northwestern Germany." *Ticks and tick-borne diseases* 5(5):594–99. Retrieved September 7, 2014 (http://www.ncbi.nlm.nih.gov/pubmed/24993582).	Thank you for this information. We have reviewed the reference to check if it was relevant to any of the review questions. We did not do a review of evidence for preventative measures but refer to other NHS sources.

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SH	Lyme Research UK	short	4	9	The requirement that the size must increase not valid. All rashes reach a maximum size before resolving. A clinician cannot determine expansion at the first visit and the patient may not know. It is critical that early treatment is started quickly and the instruction results in doctors asking the patients to return and demonstrate and increased size, which may not happen, they may not return to the same doctor and it introduces critical delays in treatment. The rash should be diagnosed on appearance and not that it must be seen to be expanding.	Thank you for your comment. It is usual clinical practice to ascertain the history of a rash and the detail of the recommendation is relevant to this.
SH	Lyme Research UK	Short	5	21-29	This guide section suggests looking at longevity of symptoms and history of possible exposure in people with symptoms suggestive of Lyme disease. These symptoms can take time to develop completely so a precautionary note should be issued. Doctors may take line 28-29 to mean that patients who are concerned and seek advice should be dismissed even if they have had a tick bite. There needs to be follow up later on - this is a classic scenario. We suggest the guide encourages doctors here to: 'tell patients at risk of Lyme disease to make a diary of symptoms, monitor their own health, and to consult immediately when there's any kind of change, and they do experience symptoms later on'.	Thank you for your comment. It is unclear which people at risk should do this so the recommendations have not been altered; we have however added more detail to the evidence review.
SH	Lyme Research UK	short	5	1-8	The kind of symptoms that may be associated with chronic or more complex forms of illness that could be untreated cases of Lyme disease - such as 'chronic fatigue' are not mentioned. Our concern would be how doctors in reality, make judgements about chronic cases versus acute - since the guidelines seem to be	Thank you for your comment. The committee acknowledge the difficulty for health care professionals in making these judgements until more evidence is available. The recommendations include the symptoms you suggest.

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					more orientated towards 'easily described' acute cases. E.g. neuro-psychiatric symptoms such as anxiety, panic attacks, fear, depression etc. are common (and not always, but can be, in acute stages). Many diseases have 'shared symptoms' with other conditions and that is not used to exclude those conditions from consideration - so it is not clear why these symptoms sets should be for Lyme disease - simply because they are also seen in other diagnostic categories. We think it is very important to point out that there is a large variety in the patterns of clinical presentation. Lyme borreliosis should be suspected in any patient that presents with a spectrum of the symptoms listed below. Studies of symptoms reported by patients with confirmed Lyme borreliosis include the following, and the patient will usually describe a number of these or many in a relapsing/remitting pattern. Symptoms in order of frequency of occurrence compiled from Aucott et al (2012), Djukic et al (2011), Strle et al (2006) and Trevejo et al (1999): Arthritis/arthralgia (especially back, neck, knee, ankle) Fatigue/malaise (frequently with headache) Neurological symptoms (peripheral neuropathy, numbness, pins and needles, neuropsychiatric symptoms) Erythema migrans and other types of rash; and secondary rashes Cognitive dysfunction (short term memory problems, confusion, speech problems)	

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					Myalgia Chills Meningeal symptoms Radicular pain Sweats Tick bite Facial palsy (more frequent in children) Vision problems (floater, blurred/double vision) Cardiac problems (chest pain, heart block) Hearing problems (tinnitus, hearing loss) Other (dizziness, vertigo, sleep disturbance, photophobia) Headache Neuro-psychological symptoms are also part of the spectrum	
SH	Lyme Research UK	short	5	4	Add : Stabbing, aching, burning, prickly pains in joints or tissue, limbs or skin	Thank you for your comment. The committee has reviewed the recommendation and considered this detail was not helpful to add.
SH	Lyme Research UK	short	5	11	Remove the words "but uncommon". Lyme disease is the most common vector borne disease in the UK and EU.	Thank you for your comment. The phrase is referring to the underlying cause of symptoms.
SH	Lyme Research UK	short	5	24	List them: camping, country walks, dog walking, fishing, agricultural work, forestry, gardening, hiking, survival exercises, army training, nature excursions, school playing fields and trips, outdoor pursuits, mountain climbing and biking, allotment digging, veterinary practice, dog grooming, agricultural working, conservation work, farming any kind including handling livestock outside the farm, etc. People have even been bitten by ticks just via contact with clothes and other	Thank you for your comment. We try to make the recommendations as concise as possible without losing any information; therefore, we did not elaborate on the types of activities. In addition, we aim to be inclusive and did not want to miss any activity where there is a possibility for a tick bite.

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					equipment (from other people exposed to these environments) in their own home - and from pets.	
SH	Lyme Research UK	short	6	12-24	Comment: there is no clear mention of neuroborreliosis in this draft guide - other than with regard to very specific and limited set of symptomatology. We are very concerned that there are Lyme borreliosis patients who need but are not getting intravenous ceftriaxone or cefotaxime once the disease has progressed to later stages. They may not be getting this treatment because a diagnosis of their neuroborreliosis has not been made sometimes because testing is inadequate for diagnosis. The guidelines from the European Federation of Neurological Societies guidelines (Mygland et al, 2010) state that antibody tests for cerebrospinal fluid "are useful" in the diagnosis of Lyme neuroborreliosis, but they do not state that a positive result is essential. Unfortunately, the sensitivity of the current tests of cerebrospinal fluid is relatively low. Djukic et al (2012) reported that, of 118 patients with acute neuroborreliosis, intrathecal immunoglobulin synthesis was found in the Reiber nomograms for IgM in 70.2% and for IgG in 19.5% of patients. Isoelectric focussing detected an intrathecal IgG synthesis in 70.3%. Elevation of the Borrelia burgdorferi antibody index in the cerebrospinal fluid was found in 82.2%. The sensitivity was particularly low in patients with a meningitis course. We think that, until better diagnostic tools are available, the criteria and interpretation of test results	Thank you for your comment. Following stakeholder consultation, recommendations have been added to emphasise the importance of clinical assessment and to recognise the limitations of tests.

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					for intravenous treatment should be relaxed - and not require evidence of antibodies in the cerebrospinal fluid. Neuroborreliosis diagnosed should be based on neurological symptoms, which could be supported by positive serology (ie tests are sufficient but not necessary)	
SH	Lyme Research UK	short	6	1-4	We need to be careful not to encourage doctors to avoid considering Lyme disease in situations where antibodies or symptoms have yet to develop. Other possible diagnosable conditions should not be ignored - but at the same time, not be considered 'exclusive alternatives' to Lyme disease - as this could be comorbidity or overlapping conditions (with shared or linked pathology). Change this section to; • Be cautious about dismissing patients whose symptoms or antibody response may have yet to develop. • Simultaneously consider other diagnoses that may be either alternative or overlapping with Lyme disease. • Consider the possibility of comorbidity where diagnosis for another condition has already been made	Thank you for your comment. The committee reviewed the recommendation following stakeholder consultation and made changes to emphasise the importance of clinical judgement. Clinicians are expected to use clinical judgement when multiple possible diagnoses could be considered.
SH	Lyme Research UK	short	6	16-19	Comment: These are indirect antibody tests with poor sensitivity.	Thank you for your comment. The recommendations have been changed following stakeholder comments to emphasise the importance of clinical assessment and to recognise the limitations of tests.
SH	Lyme Research UK	short	6	20-21	Comment: This is the two-tier test recommended by BIA. It generates high levels of false negatives.	Thank you for your comment. The Cook 2017 paper was excluded from the diagnostic tests

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					Ref: Cook, Michael J. and Basant K. Puri. 2017. "Application of Bayesian Decision-Making to Laboratory Testing for Lyme Disease and Comparison with Testing for HIV." *International journal of general medicine* 10:113–23. Retrieved (https://www.dovepress.com/articles.php?article_id=32303).	review because it is not a clinical diagnostic study. The committee decided to make this recommendation having reviewed all the available evidence.
SH	Lyme Research UK	short	6	1,2	This should be. "Bear in mind that the test kit manufacturers state that a negative test result does not exclude the possibility of Lyme disease". Ref: A negative result does not exclude a contact with the pathogen or the presence of a disease. Viramed. 2012. *Borrelia ViraStripe IgM Testkit*.	Thank you for your comment. The recommendations have been altered following stakeholder consultation to indicate the limitations of tests.
SH	Lyme Research UK	short	6	3	What alternatives, they should not include diseases without known cause. Alternative diagnoses must be supported by objective measures.	Thank you for your comment. Alternative diagnoses will vary by clinical presentation and context. This is therefore up to the clinician to investigate.
SH	Lyme Research UK	short	6	14	Comment: This is tacit understanding that the tests have poor sensitivity in the early stage. The tests don't suddenly become sensitive when there is no EM rash present.	Thank you for your comment. The committee agreed that laboratory testing is unnecessary for people presenting with erythema migrans, because the rash is very specific to Lyme disease and the benefits of prompt treatment outweigh the potential harms of waiting for a positive test.
SH	Lyme Research UK	short	7	16-23	The term 'unexplained symptoms' is an oxymoron. They are only unexplained until better diagnosis or tools to do so are available. Assessment by other specialties can be useful since that can highlight	Thank you for your comment. The word 'unexplained' has now been removed.

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					alternative, comorbid or overlapping conditions. This would include autoimmune or hormonal silique. Further tests on CSF or fluids from joints, biopsy etc. can be useful if uncertainties related to these tests are taken into account. However, there is no data that indicates that synovial fluid aspirate, or biopsy or cerebrospinal fluid analysis is accurate and useful.	
SH	Lyme Research UK	short	7	11-15	Since all criteria are met for diagnosis, why discuss, or refer to an ID specialist. Allowing GPs and other key specialists to diagnose or treat will mean less delays, quicker treatment and prevention of chronic and possibly untreated or untreatable disease. This must be the aim of this guide.	Thank you for your comment. The recommendation specifies that treatment should not be delayed and is relevant to people with focal symptoms. However, the committee considered that many general practitioners might not have experience of Lyme disease causing focal symptoms and discussion with a specialist would aid care and follow up.
SH	Lyme Research UK	short	7	16-19	Comment: This can result in the specialist making a recommendation to stop treatment, even without seeing the patient.	Thank you for your comment. The recommendation has been amended to put more emphasis on clinical judgement and the limitations of tests and consideration of treatment despite negative results.
SH	Lyme Research UK	short	7	1-3	Retesting will not guarantee high probability of a positive result. As stated before the tests so not suddenly become sensitive: See Leeflang et al (Mmg, L., Cw, A., Berkhout, J., Ha, B., & W, V. B. (2016). The diagnostic accuracy of serological tests for Lyme borreliosis : a systematic review and meta-analysis . BMC Infectious Diseases. http://doi.org/10.1186/s12879-016-1468-4? Date). Retesting is only useful if the unreliability of tests is considered in the diagnostic process for later stages of the disease. This should be reflected in the wording in the guide.	Thank you for your comment. The committee decided to recommend that a negative ELISA test be repeated if it was taken within 4 weeks of symptom onset, because of the possibility that antibodies have not yet developed.

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SH	Lyme Research UK	short	7	24-26	Delete. This is unnecessary. An asymptomatic person would be likely not be presenting to a doctor unless they thought that they were at risk of Lyme disease through exposure to ticks - in which case they need to be monitored for future illness or disease	Thank you for your comment. The committee considered that this scenario can occur and therefore included the recommendation.
SH	Lyme Research UK	short	7	6-7	What actions should be taken based on the results of these tests?	Thank you for your comment. The actions are outlined in the subsequent recommendations.
SH	Lyme Research UK	short	7	25-26	It currently difficult to distinguish between reinfection and someone who's had a past infection - if they have symptoms, and known recent exposure to ticks, especially. There are no diagnostic tools or indicators that can clearly do that. It's not helpful to treat differently people who happen to live in an area known to have a high risk profession. People are more at risk of Lyme disease are less likely to be treated if symptoms are dismissed. This happens on a regular basis from experience of patients. We feel this should be revised or deleted as it's not helpful to doctors.	Thank you for your comment. Following stakeholder comments, the recommendation was deleted.
SH	Lyme Research UK	short	7	27	Comment. Does this mean the NHS will not treat based on a foreign x-ray, MRI scan, or TB test in the UK? It's not entirely clear why NHS or other doctors cannot utilise laboratories outside of the NHS system – particularly for innovative laboratories of tests that have been of use to NHS doctors. This policy appears to exclude private testing in principle, and other types of tests in principle. We are particularly concerned where newer tests are emerging that will have known efficacy - and have been through normal lab or manufacturers regulatory, monitoring and production processes.	Thank you for your comment. The guideline is directed to people receiving NHS care and rec.1.2.23 and 1.2.24 indicate criteria for performing NHS and non-NHS tests. It is not uncommon for tests done outside the UK to be repeated depending on the source and interpretation of test. Innovative tests require validation and the recommendations are pointing to the need to use validated tests.

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SH	Lyme Research UK	short	8	11-16	Comment. Excellent, and indicates that page 8 lines 11-16 are misleading/ incorrect. However (11-13) the NICE guideline should also give guidance to the testing laboratories (and any clinicians using them) that in communications to clinicians and patients they should: a) Report clearly the results of the test in the manner described by test kit manufacturers. b) Inform clinicians of the test limitations and the kit manufacturers' statements that a negative result does not indicate absence of Lyme borreliosis. c) The laboratories should not reinterpret the test results in a manner not supported by the test kit manufacturers. D)The laboratories should confine themselves to reporting the test results and should not give clinical advice on specific cases without seeing the patient, and definitely not with the very basic data sent by clinicians. e) Provide clear dates for taking samples and testing samples to ensure specimens are 'fresh' as defined by the manufacturer. f) Patients should have access to their full laboratory results if they request them.	Thank you for your comment and these suggestions. The detail you suggest is however not appropriate in a NICE guideline where the emphasis is on the main actions required.
SH	Lyme Research UK	short	8	20-24	If so called 'non-specific' symptoms are used to exclude Lyme disease - this runs the risk of missing treatable cases. We must avoid constructing a simplistic a view on a complex disease. It's the clinical context (i.e. potential for infection) that define if a symptom is specific or not – it's relative not absolute. If patients have previously been diagnosed with another condition are then diagnosed with Lyme disease,	Thank you for your comment. The recommendation does not indicate that these symptoms are used to rule out Lyme disease.

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					treatment should be enabled. This section needs reconsideration and rewriting to recognise that symptoms indicative of Lyme disease do and can be shared with those seen in other conditions.	
SH	Lyme Research UK	short	8	5-7	Diagnosis of Lyme disease should be a clinical one with test evidence considered. This should not state explicitly that LD should not be diagnosed without a positive test. Page 8 lines 11-16 gives reasons for low test sensitivity	Thank you for your comment. The recommendations have been amended to put more emphasis on clinical judgement and consideration of treatment based on clinical suspicion.
SH	Lyme Research UK	short	8	17-19	Tests used in Germany are fully validated according to ISO15289 standards and CE registered. Also tests used in the United States are either FDA approved or the laboratory testing accuracy validated by the CLIA organization.	Thank you for your comment. It is not the intention to suggest all private and foreign laboratories are using tests that have not been validated. The recommendations are for people treated in the NHS and the recommendation emphasises the need for tests to be validated as well as for laboratories to be accredited.
SH	Lyme Research UK	short	8	1	Comment. What is the definition of "validated? All tests used in the UK and Europe are CE marked.	Thank you for your comment. Validation is outlined in the recommendation as requiring published evidence on test methodology, its relation to Lyme disease and independent reports of performance.
SH	Lyme Research UK	short	8	4	Comment: Not all quality assurance programmes are equal the World standard for microbiology labs is ISO15189 and this is superior to CPA accreditation. NICE should advocate for rapid implantation of the HNS programs for IOS 1519 for all Lyme laboratories.	Thank you for this information. The recommendation has been re-worded to indicate UK accredited laboratories. The previous wording was an error.
SH	Lyme Research UK	short	8	9	This should state: Discuss with the patient that a negative test does not indicate absence of Lyme disease. Ref: Viramed. 2012. "Borrelia ViraStripe IgG Testkit (2012)." Retrieved (http://www.viramed.de/images/stories/pdf/Arbeits	Thank you for your comment. The recommendations have been amended to clarify the limitations of tests.

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					anleitungen_EN/2550_Borrelia_ViraStripe_IgG_AL_en.pdf).	
SH	Lyme Research UK	short	12	11-17	this is a very good addition to the policy	Thank you for your comment.
SH	Lyme Research UK	short	12	21-26	See above - it's not clear what evidence there is to support this idea that all cases (irrespective of clinical history) have resolved regarding active infection. Closing the door on more complex treatments regimes for people with complex manifestations is a lost opportunity and could undermines clinical judgement	Thank you for your comment. The guideline examined what interventions would be of benefit to people with symptoms following treatment and not the underlying pathophysiology of ongoing symptoms. No evidence was found for longer courses of antibiotics, which is why they are not recommended although referral to specialist for review should be considered.
SH	Lyme Research UK	short	12	18-20	Doctors need to be able to use their discretion since patients have benefitted from longer term antibiotics - and whilst these are difficult clinical decisions to make, this should not be ruled out for all cases (as their history and clinical issues vary so much)	Thank you for your comment. There was insufficient evidence to suggest that further treatment is beneficial, therefore the committee decided that further antibiotic treatment should not routinely be offered. The recommendation to consider discussion with or referral to a specialist allows the possibility for a specialist to offer further antibiotic treatment.
SH	Lyme Research UK	short	13	1-9	This is good because as a long term or chronic condition, Lyme disease is not recognised - and impacts in various ways as a result - patients need as much additional support they can get. This could apply to either those who remain undiagnosed or those for whom treatment did not resolve symptoms	Thank you for your comment.
SH	Lyme Research UK	short	13	11-19	Need to consider vitamin deficiencies, hormonal imbalance and neurological damage specifically	Thank you for these suggestions. Healthcare professionals need to make assessments of the needs of individual patients in continuing care.

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SH	Lyme Research UK	short	14	5-7	This does not reflect the risk and severity of congenital and gestational Lyme disease. 66 cases with adverse events including miscarriage, stillbirth, perinatal death, congenital anomalies, early-onset fulminant sepsis and later onset chronic progressive infection from 263 cases where the outcome of gestational Lyme borreliosis where recorded. See Remington, Klein Infectious Disease of the Fetus and Newborn Infant Fifth Edition WB Saunders Co.Page 571 That is a 25% risk of a serious outcome. MC	Thank you for your comment. Having reviewed the evidence available, the committee concluded that vertical transmission is unlikely. We have been unable to find this study using the reference provided.
SH	Lyme Research UK	short	14	14	This section misrepresents the disease. Lyme is a relapsing remitting infection that is tolerant to antibiotics and has cell wall deficient forms that are not affected by antibiotics. Barthold, Stephen W. et al. 2010. "Ineffectiveness of Tigecycline against Persistent Borrelia Burgdorferi." *Antimicrobial Agents and Chemotherapy* 54(2):643–51. Hodzic, Emir, Denise Imai, Sunlian Feng, and Stephen W. Barthold. 2014. "Resurgence of Persisting Non-Cultivable Borrelia Burgdorferi Following Antibiotic Treatment in Mice" edited by R. M. Wooten. *PLoS ONE* 9(1):e86907. Caskey, John R. and Monica E. Embers. 2015. "Persister Development by Borrelia Burgdorferi Populations In Vitro." *Antimicrobial agents and chemotherapy* 59(10):6288–95. Hodzic, Emir, Sunlian Feng, Kevin Holden, Kimberly J. Freet, and Stephen W. Barthold. 2008. "Persistence of Borrelia Burgdorferi Following Antibiotic Treatment in Mice." *Antimicrobial agents and chemotherapy* 52(5):1728–36. Hunfeld KP et al 2005 In Vitro Susceptibility Testing of Borrelia burgdorferi Sensu Lato Isolates Cultured from	Thank you for these references. We have reviewed the references to ensure that those that are relevant to the review questions were considered for inclusion. As per NICE process, we do not consider animal or in vitro studies.

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					Patients with Erythema Migrans before and after Antimicrobial Chemotherapy. Miklossy, Judith et al. 2008. "Persisting Atypical and Cystic Forms of Borrelia Burgdorferi and Local Inflammation in Lyme Neuroborreliosis." *Journal of Neuroinflammation* 5:40. Retrieved (http://www.jneuroinflammation.com/content/5/1/40).	
SH	Lyme Research UK	short	14	17	This should be deleted or modified to 'some people recover completely'.	Thank you for your comment. The recommendation is covering the wide range of presentations of Lyme disease and the committee considered that from that perspective most people do recover completely.
SH	Lyme Research UK	Short	15	10-20	Should be reworded as follows: A core outcome set should be developed for clinical trials of management of Lyme disease. Can a core outcome set be developed for clinical trials of management of Lyme disease?" Outcomes must include areas important to patients such as quality of life, psychiatric indicators, mobility, mortality (i.e. beyond 'cure') and not just focussed on acute cases. E.g. what is the full range of symptoms experienced by people with different disease etiological pathways?	Thank you for your comment. The committee reviewed the research recommendations wording following stakeholder comments and agreed on the existing wording.
SH	Lyme Research UK	short	16	16-32	Seroprevalence of Lyme disease-specific antibodies etc.:	Thank you for your comment and this information. The research recommendations are not prescriptive in how they can be conducted

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					The focus on seroprevalence does not cover some issues related to environmental risk and needs to be considered alongside research that addresses patterns of illness related to that in the community. Different research projects need to be linked and part of a broader knowledge creation strategy based on gaps in understanding. Restricting this kind of work to just those diagnosed with a restricted range of tests, misses a lot of clinically diagnosed cases so other approaches to this type of work need to be considered. A member of this response ream has written a paper with colleagues on the incidence of Lyme disease in the UK based on data from the Clinical Practice Research Datalink (CPRD) covering about 8% of the UK population. This epidemiological study will be submitted to the British Journal of General Practice and we will let you know if it is accepted for publication.	and we agree that a variety of research projects are often required to answer each research question.
SH	Lyme Research UK	short	17	3-18	Antimicrobial management of Lyme disease: What are the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease in the UK? From patients experiences clinical outcomes are poor even in those with acute cases treated early. This would be useful work as it would confirm that treatment protocols for various reasons are not working to prevent chronic ill-health. This work needs to link to work on outcomes (which must	Thank you for your comment. The current research recommendation does not specify treatment in acute cases only nor decide on which antibiotic regime should be studied

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					come first) to enable better ways of measuring those outcomes. This area of research is important but mono therapy needs reviewing vs multiple antimicrobial regimes - as well as the impact of other types of treatment (i.e. non antibiotic) that are known to help with chronic symptoms - especially for those who are untreated or suffer delayed treatment. The focus should not be just on the treatment of acute cases as the number of people outside of this scenario is potentially far greater.	
SH	Lyme Research UK	short	17	19-30	What are the best laboratory tests to diagnose initial and ongoing 19 infection and determine re-infection in the different presentations 20 of Lyme disease in the UK: • In time more research will come available in relation to other types of testing - and so these should be included in this programme - to see what stages these tests work best i.e. to explore; What type of physiological process or disease state they identify; and how they may compare with other testing regimes? If new and substantial research is done on other types of testing innovation will not be supressed and patients will be likely get access to adequate treatment early enough. This is a win win situation if handled with prior	Thank you for your comment. NICE research recommendations are developed from the specific evidence reviews which were carried out in guideline development which is why some tests that looked promising were included. We have however amended the recommendation to indicate the assessment of novel tests as appropriate.

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					understanding and a more inclusive research agenda and strategy	
SH	Lyme Research UK	short	20	21-25	The C6 test has the lowest sensitivity of any test. The phrase "relatively high degree of sensitivity" does not accurately represent the facts. This is demonstrated in two references that were excluded by the NICE committee. One is by the European Centre for Disease Prevention and Control an EU organisation Ref: Zeller, Herve and Wim Van Bortel. 2016. *A Systematic Literature Review on the Diagnosis Accuracy of Serological Tests for Lyme Borreliosis*. (http://ecdc.europa.eu/en/publications/Publications/Lyme-borreliosis-diagnostic-accuracy-serological-tests-systematic-review.pdf). And the second, incorrectly excluded as a systematic review when it is a meta analysis: Cook, Michael J. and Basant K. Puri. 2016. "Commercial Test Kits for the Detection of Lyme Borreliosis: A Meta-Analysis of Test Accuracy." *International journal of general medicine* 9:427–40. Retrieved December 7, 2016 (https://www.ncbi.nlm.nih.gov/pubmed/27920571).	Thank you for your comment. Both of these references were systematic reviews, which included meta-analyses. The systematic reviews were excluded because the methodology differed from NICE methodology, but the reference lists were screened to ensure that we included any relevant papers in our review.
SH	Lyme Research UK	short	20	26-30	The confirmatory immunoblot test makes the test even less sensitive than single tests. Specificity in increased slightly.	Thank you for your comment. This section has been changed following stakeholder comment and the addition of recommendations highlighting the importance of treatment if there is high

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						clinical suspicion both while waiting for test results and if results are negative.
SH	Lyme Research UK	short	21	2-5	There is no evidence to suggest that even with delayed testing that antibodies will be generated at a level that exceeds the cut-off threshold for the test.	Thank you for your comment. The recommendations and this section have been amended following consultation. Repeat testing in this scenario is still suggested because of what is generally accepted about how antibody response develops. The recommendations do include the possibility that tests may remain negative.
SH	Lyme Research UK	short	21	5-7	This defines a two-tier test method which is proven to generate more than 500 times more false negative results (people with the disease who test negative). This is shown in a reference excluded without justification by the NICE committee. Cook, Michael J. and Basant K. Puri. 2017. "Application of Bayesian Decision-Making to Laboratory Testing for Lyme Disease and Comparison with Testing for HIV." *International journal of general medicine* 10:113–23. Retrieved (https://www.dovepress.com/articles.php?article_id=32303).	Thank you for your comment. The Cook 2017 paper was excluded from the diagnostic tests review because it is not a clinical diagnostic study. It is a modelling study and the 500 times more false negatives are in a comparison with 2-stage HIV testing, which is an inappropriate comparison for answering the guideline review question.
SH	Neonatal and Paediatric Pharmacists Group (NPPG)	Short	General	General	We would suggest that the guidelines highlight that the recommended doses and durations may differ from those recommended in the BNF and BNF for Children. The rationale for the doses and durations presented in the guidelines looks sound. However, it would be prudent to alert prescribers and other healthcare professionals to differences between these	Thank you for your comment. In the management evidence chapters, in 'the committee's discussion of the evidence' and sub section: 'Cost effectiveness and resource use' we have highlighted where the recommendations differ from BNF and BNF for children.

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					recommendations and those found in the national first line prescribing resource.	
SH	Neonatal and Paediatric Pharmacists Group (NPPG)	Short	11	3	Question 5: All the recommended dosing for doxycycline in children in the American DrugDex database refers to doses in children over 8 years of age. Therefore it would seem reasonable to use under specialist advice in children ≥9 years. REF: Doxycycline. In: DRUGDEX® System (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/ [cited: 02 November 2017].	Thank you for this information.
SH	NHS Highland	Evidence Review A	6	24	Statistical measures (any clinical presentation related to Lyme disease). This seems a loose term to define incidence and prevalence. There are some clinical presentations which are obvious and others are more non-specific but still related to Lyme disease yet may not be if patient is seronegative. A more specific definition is required.	Thank you for your comment. The committee decided to use a broad definition in order to ensure that all types of clinical presentations of Lyme disease would be captured, including non-specific presentations. The majority of the studies included in the evidence review reported national or regional incidence estimates of Lyme disease in the UK according to positive two-tier testing.
SH	NHS Highland	Evidence Review A	7	6	The following study was not included in the review or even in the list of excluded studies. 'Seroprevalence of Lyme borreliosis in Scottish blood donors.' Munro H, Mavin S, Duffy K, Evans R, Jarvis LM. Transfusion Medicine 2015. Letter to the Editor pp1-3. doi 10.1111/tmc/2197 I believe it meets the inclusion criteria but if not it should be assessed.	Thank you for your comment. The reference cited was not assessed because it is a letter rather than a published study. Published full text studies are preferred to ensure there is adequate information to carry out full critical appraisal of the study and outcomes.
SH	NHS Highland	Evidence Review A	20	18	'*Borrelia'* should be replaced with '*B. burgdorferi* sensu lato' (or appropriate abbreviation after first use in document).	Thank you for your comment. We have corrected terminology in line with your suggestion.
SH	NHS Highland	Evidence Review C	7	16-17	Serology tests cannot indicate Lyme disease. They indicate infection and a positive result can support a	Thank you for your comment. The review questions were structured in this way to allow us

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					clinical diagnosis of Lyme disease. A symptomatic patient can be seropositive for *Borrelia burgdorferi* antibodies but not have Lyme disease.	to identify evidence for the diagnostic accuracy of different tests. The committee were aware that in clinical practice, serology tests are used to support a diagnosis rather than diagnose Lyme disease. This is discussed in greater detail in section 4.4. Following stakeholder comments, the recommendations have been altered to explain this more clearly and we have clarified terminology in the short guideline.
SH	NHS Highland	Evidence Review C	7	10	Include 'DNA' in sentence 'can identify fragments of bacteria DNA'.	Thank you for your comment. This has now been added.
SH	NHS Highland	Evidence Review C	7	18	As for comment 33.	Thank you for your comment. The review questions were structured in this way to allow us to identify evidence for the diagnostic accuracy of different tests. The committee were aware that in clinical practice, serology tests are used to support a diagnosis rather than diagnose Lyme disease.
SH	NHS Highland	Evidence Review C	7	21	As for comment 33. Change 'to identify whether Lyme disease is present' to 'to aid in the clinical diagnosis of Lyme disease'.	Thank you for your comment. The review questions were structured in this way to allow us to identify evidence for the diagnostic accuracy of different tests. The committee were aware that in clinical practice, serology tests are used to support a diagnosis rather than diagnose Lyme disease. This is discussed in greater detail in section 4.4. Following stakeholder comments, the recommendations have been altered to explain this more clearly and we have clarified terminology in the short guideline.
SH	NHS Highland	Evidence Review C	8	7	There was no search carried out for CSF/serum antibody index, which is a major omission as it is an important test that should be carried out for patients with suspected neuroborreliosis	Thank you for your comment. CSF/serum antibody index was included in the evidence review. Index tests were listed in the review protocol by name of the test to allow us to

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						capture all relevant evidence for their diagnostic accuracy, including different markers and sample types. The clinical evidence summary (tables 7-10), forest plots (appendix E) and clinical evidence tables (appendix D) provide more detail on the specific markers and sample types used in each study.
SH	NHS Highland	Evidence Review C	190	14-18	The use of paired CSF/serum serology to calculate antibody index, together with consideration of CSF parameters (cell counts, protein and glucose) is essential for the diagnosis of neuroborreliosis (see comment 2). See EFNS guidelines, European Journal of Neurology 2010;17: 8-16, Stanek *et al* Lyme borreliosis. Lancet 2012; 379:461-473. Dessau RB *et al* To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis. Clinical Microbiology and Infection (2017) doi: 10.1016/j.cmi.2017.08.025We suggest that the reason the evidence was not strong enough to inform a recommendation for CSF testing is because a search was not carried out for CSF/serum antibody index.	Thank you for your comment. CSF/serum antibody index was included in the evidence review. Index tests were listed in the review protocol by name of the test to allow us to capture all relevant evidence for their diagnostic accuracy, including different markers and sample types. The clinical evidence summary (tables 7-10), forest plots (appendix E) and clinical evidence tables (appendix D) provide more detail on the specific markers and sample types used in each study.
SH	NHS Highland	Evidence Review C	190	28	Disagree with the statement that Borrelia culture and PCR have low specificity. Although they have low sensitivity the specificity of these tests is very high.	Thank you for your comment. This statement was incorrect and has now been amended.
SH	NHS Highland	Evidence Review C	191	30-38	As stated in our comments 15 in the short draft version, we do not agree with the recommendation that those who test negative and continue to be symptomatic for greater than 12 weeks should have a repeat ELISA along with an immunoblot as there is no evidence-based rationale for this. As also previously stated (comment 15), we do not agree that the proportion of people to whom this new recommendation would apply would be relatively small	Thank you for your comment. Following stakeholder comments, the recommendations have been changed to remove the second ELISA. This paragraph relates to a significant resource impact as defined by NICE, which is a recommendation that leads to an additional

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					and would not have a significant resource impact. As stated in detail in our comment 15 on the short draft, this would affect approximately 30% of the patients that we test, increasing the number of immunoblot tests by 373% and the monthly cost from £5,749.02 to £21,453.66 and put considerable strain on the reference facility that does the confirmatory testing.	£1million pounds in NHS spending in a year in England. The committee did not anticipate that additional testing would exceed this annual cost. The committee reviewed the recommendations and added more detail about treating based on clinical suspicion without testing and of considering alternate diagnoses. This should reduce the number of people included.
SH	NHS Highland	Evidence Review C	191	50-51	As stated in our comments 17 of the short draft version, we disagree that further tests may be needed for suspected Lyme disease. If the patient is still seronegative there is no evidence to suggest that *B. burgdorferi* may be detected in a CSF, synovial fluid aspirate or biopsy.	Thank you for your comment. We have added to the text to indicate that the reason for referral is to consider alternate diagnoses as well as consider whether other tests are appropriate. The committee agreed that seronegativity makes Lyme disease less likely but that the sensitivity and specificity of the tests are such that false negatives can be ruled out.
SH	NHS Highland	Evidence Review C	193	37-42	This paragraph is confusing. We agree that the bacteria may not exist in the sample but the negative antibody test is indicating that there is no infection. We agree that these patients should be referred to an appropriate specialist but further testing for *B.burgdorferi* is not indicated.	We have added to the text to indicate that the reason for referral is to consider alternate diagnoses as well as consider whether other tests are appropriate. The committee agreed that seronegativity makes Lyme disease less likely but that the sensitivity and specificity of the tests are such that false negatives cannot be ruled out.
SH	NHS Highland	Evidence Review C	193	10-14	We do not agree with this recommendation as there is no evidence-based rationale. See comment 15	Thank you for your comment. Please see responses to your detailed comments 467 and 515.
SH	NHS Highland	Evidence Review C	193	23-25	We agree that for patients with focal symptoms of Lyme disease referral to the appropriate specialist should be considered. However, additional testing, such as CSF, synovial fluid or biopsy should be	Thank you for your comment. The recommendations do suggest referral to specialists to conduct additional testing.

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					considered so that Lyme disease can be confirmed. As we stated in our general comments on the short draft version (comment 2), there is no mention about the use of other sample types to diagnose Lyme disease in patients with focal symptoms of Lyme disease.	
SH	NHS Highland	Evidence Review C	193	21	Suggest line 21 should be changed to 'If the presence of *B. burgdorferi* antibodies is confirmed and that the clinical picture fits with that of Lyme disease, treatment should be started immediately'. As highlighted in our comment 12 on the short draft version, a positive ELISA and confirmatory immunoblot cannot confirm Lyme disease, only the presence of *B. burgdorferi* antibodies, signifying infection.	Thank you for your comment. The wording in the recommendations and the text was reviewed following stakeholder comment to clarify the importance of clinical presentation in diagnosis. The committee recognised that antibodies can only confirm infection but agreed that usual clinical usage is to use terminology of 'diagnosis' of a disease in this way. An explanation to this effect has been added to the glossary and to the short guideline in the 'terms used in this guideline' section.
SH	NHS Highland	Evidence Review C	193	36	Replace 'Borrelia' with '*B.burgdorferi* sensu lato'.	Thank you for your comment. We have corrected terminology as you suggest.
SH	NHS Highland	Evidence Review C	298	7	Table 35 Scenario 1. The FP and FN figures stated in this scenario do not add up to the totals stated of 267 and 9. The totals should be 266 and 10. Need to check original data.	Thank you for your comment. This is due to rounding of numbers. The table has been updated so all numbers are to one decimal place to avoid confusion.
SH	NHS Highland	Evidence Review D	24	Table 10	Table of data from Wormser 2003. 'Reduction of symptoms' data in your table taken from 'partial response' data in original paper, without inclusion of the 'complete response' population whose symptoms also resolved. This has lead to reversal of the conclusions from the paper. That is, the committee concludes that 20 days is better than 10 days for 'symptom reduction', whereas the full data shows that for example at 1 year, 42/61 (69%) of patients taking 10 days have either complete or partial response; compared with 40/59 (68%) of those on 20 days. The	Thank you for your comment. We agree that there was an error in interpretation of the evidence for this outcome and have now amended this in the evidence report. Data for 'complete response' was extracted for cure and data for 'partial response' was extracted for reduction of symptoms in order to avoid double-counting data. The reduction of symptoms outcome should have been further downgraded for indirect outcome and this has now been amended. The committee reviewed the evidence

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					only reason that your data appears to favour 20 days is that paradoxically, more people are 'complete responders' in the 10 day group, leaving less available for a 'partial response' which you appear to have transposed into 'symptom reduction'.	again following stakeholder comments and considered that this outcome was based on very low quality evidence and there was no difference in any other outcome under this comparison. The limitations of the evidence and committee interpretations detailed in sections 2.9 and 2.10 have also now been amended to acknowledge the issue.
SH	NHS Highland	Evidence Review D	42	31	See comment 47. The statement *'Very Low quality evidence from 1 RCT, however, showed that a 20-day course was more effective in reduction of symptoms at 1 year than a 10-day course of oral doxycycline',* does not follow from the evidence due to mis-interpretation of the Wormser 2003 paper – see comment 1. The evidence shows no difference in the two durations in symptom reduction. We consider this very important and urge the committee to review this in full as this mis-interpretation of this paper appears to be the basis on which the 21 day course of doxycycline is recommended, while all the evidence suggests 15, or even 10 days is just as good.	Thank you for your comment. We agree that there was an error in interpretation of the evidence for this outcome and have now amended this in the evidence report. The evidence statements are intended to give a narrative summary of the evidence. The limitations of the evidence and committee interpretations are detailed in sections 2.9 and 2.10 of the chapter, which have now been amended to acknowledge the issue you describe. The committee reviewed the evidence again following stakeholder comments and decided that the justification for recommending 21 days was still valid. The evidence for length of treatment is weak and the committee decided to err on the side of caution and recommend longer courses of 21 days of treatment as standard because of their concern at low cure rates in some studies, the lack of clear evidence for shorter courses and concern that people being treated for Lyme may be concerned that they are undertreated if they continue to have symptoms and have received a shorter course. They were reassured that

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						adverse rates were not increased for longer courses.
SH	NHS Highland	Evidence Review D	44	Table 30	We agree with the increase in dose of amoxicillin on basis of use of probenecid previously.	Thank you for your comment.
SH	NHS Highland	Evidence Review D	44	Table 30	The long course of azithromycin recommended is longer than that used in all the evidence quoted.	Thank you for your comment. The committee decided that the longer course was in keeping with the overall strategy of treating Lyme disease with higher doses. The committee considered that the evidence presented did not in itself provide an adequate basis for deciding on length of treatment. From a pharmacological perspective, azithromycin (like all macrolides and doxycycline, a tetracycline) is bacteriostatic, so there is no microbiological sense in using treatment courses less than the equivalent dose beta lactam antibiotics (which are bactericidal). The evidence for length of treatment is weak and the committee decided to err on the side of caution and recommend longer courses of treatment as standard because of their concern at low cure rates in some studies, the lack of clear evidence for shorter courses and concern that people being treated for Lyme may be concerned that they are undertreated if they continue to have symptoms and have received a shorter course. Due to the pharmacology of azithromycin specifically (long half-life), treatment courses are 4 days less than doxycycline or beta lactam equivalents. So the treatment regimen for azithromycin is 17 days, which provides 21 days of effective drug levels in vivo. Also, daily dosing

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						has been used (not 3 consecutive days per week) in similar fashion as for routine use in other slow-growing bacterial conditions such as atypical mycobacterial infection. In these conditions, azithromycin is used daily for the treatment course, reaching higher steady state than if 3 consecutive days/used. The committee decided on this regime for the same reason as the higher dose regimens for doxycycline and amoxicillin have been recommended.
SH	NHS Highland	Evidence Review D	44	Table 30	We agree that doxycycline should be first line, but disagree with the recommendation for 21 days doxycycline for erythema migrans as there is evidence that 10 or 15 days is adequate. 14 days is our practice, and I believe standard practice across Europe. Recommending 21 days will send a message to all the previously treated patients that they have been inadequately treated, and will expose all future patients to an extra week of antibiotic against the available evidence. You state elsewhere that you are trying to achieve consistency across presentations. EM is the commonest presentation and doxycycline is the most commonly prescribed antibiotic, so we do not think that it is warranted to increase the recommended duration of doxycycline to keep it in line with alternatives where	Thank you for your comment. The committee reviewed the recommendations for antibiotic management following stakeholder comment. This included discussion of interpretation of the evidence, which we have adjusted following your comments. The previous wording about consistency was not accurate and we have altered this. Rather the committee wished to aim for clarity and reduction of ambiguity. Most current guidelines suggest treatments over a range of time periods; for example, the BNF suggests doxycycline for 10 to 14 days and amoxicillin for 14 to 21 days. The committee considered that providing a range of times was not useful for generalists, as it is unclear when to use the shorter or longer course. The evidence for length of treatment is weak and the committee decided to err on the side of caution and recommend longer courses of 21 days of treatment as standard because of their concern at low cure rates in some studies, the

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					evidence that 14 days is non-inferior to longer courses may not be as strong. It is mentioned elsewhere that there is evidence that longer courses are better for symptom reduction, but as highlighted in comment 1 this appears to be a mis-reading of the evidence.	lack of clear evidence for shorter courses and concern that people being treated for Lyme may be concerned that they are undertreated if they continue to have symptoms and have received a shorter course. They were reassured that adverse rates were not increased for longer courses.
SH	NHS Highland	Evidence Review D	46	2-6	We agree with these research objectives and would be keen to participate in this research.	Thank you for your comment and your support for our research recommendations.
SH	NHS Highland	Evidence Review D	46	9-11	We do not think standardising treatment across presentations should be a goal. Providing the best treatment, supported by evidence is the goal. There can be consistency and clarity without making the durations of antibiotic courses the same for the many different presentations of Lyme Disease. We can explain to patients that evidence indicates two weeks is sufficient for erythema migrans regardless of duration required for other presentations. While longer durations may not significantly increase the number of patients reporting side effects in the comparative studies, they do increase the duration of the side effects, and clearly increase overall antibiotic exposure which is against antibiotic stewardship principles.	Thank you for your comment. The committee reviewed the evidence and recommendations following stakeholder comment. The evidence for length of treatment is weak but with a lack of clear evidence for shorter courses. The committee did not consider that the evidence for shorter courses for EM was good enough to be definitive about this.
SH	NHS Highland	Evidence Review D	47	3-4	Please retract the statement that "*There was some evidence of a greater reduction in symptoms using a longer course of doxycycline"* assuming you accept error in data interpretation highlighted in comment 47 and that there were no additional adverse events when compared with a shorter course.	Thank you for your comment. This statement has now been removed and this section has been rewritten following stakeholder consultation.
SH	NHS Highland	Evidence Review D	47	5-6	Only three studies are included to investigating duration of antibiotic (Steer 1983, Weber 2003 and Stupica 2012), none of which "*showed more treatment*	Thank you for your comment. This statement has now been removed and this section has been rewritten following stakeholder consultation.

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					failure and ongoing symptoms with shorter courses" according to your tables. So we recommend that this statement is removed. If the statement refers to comparisons of outcomes across studies then we also suggest it is removed as outcomes across studies should not be compared (for many well known reasons). If committee wish to retain this statement then please qualify by stating that it is based only on cross study comparison (if this is the case).	
SH	NHS Highland	Evidence Review D	48	23-25	It is stated '*The committee noted that neither treatment arm reflected current prescribing practice. People in the doxycycline group received 100 milligrams doxycycline twice daily for 10 days in 1 study and 14 days in the other'.* Doxycycline 100mg bd for 14 days is our standard practice and is recommended in current IDSA guideline and BIA position paper. We feel it is disingenuous to suggest that this is not current prescribing practice, and suggest this sentence is removed or modified.	Thank you for your comment. This sentence has now been amended.
SH	NHS Highland	Evidence Review D	48	8,9,10	Recommend remove statement "*Evidence from 1 study showed that a 20-day course of doxycycline 100 milligrams twice daily resulted in a better long-term reduction of symptoms compared to a 10-day course of doxycycline.'.* assuming you accept error in data interpretation highlighted in comment 47.	Thank you for your comment. This statement has now been amended to explain the problem with the evidence and why it could not be considered a benefit.
SH	NHS Highland	Evidence Review D	48	20,21	It is stated "*Oral doxycycline was less effective than oral azithromycin for cure with a high absolute rate for cure for both interventions".* Your assessment of Barsic and Massorotti's studies assesses them as very low grade, the numbers studied are small, and your combined forrest plot (page 123 figure 2) shows the 95% confidence intervals including 1, suggesting the difference does not reach statistical significance. We	Thank you for your comment. We consider clinical rather than statistical significance. The absolute effect of doxycycline for this outcome was 146 more people cured per 1000, which the committee considered to be a clinical benefit, whilst acknowledging the limitations of the evidence.

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					think this data is interesting and warrants further study, but that the unqualified statement made may lead to misunderstanding of the evidence. We suggest the statement be changed to "studies did not show a statistically significant difference between doxycycline and azithromycin, though there was a trend towards greater cure in the azithromycin arm.	
SH	NHS Highland	Evidence Review D	48	22,23	It is stated '*The absolute chance of preventing symptom relapse was very low in both groups'.* We wondered if this should read 'The absolute chance of symptom relapse was very low in both groups', though we have not read either paper in full your forest plots do not indicate a high rate of relapse.	Thank you for your comment. This has now been amended.
SH	NHS Highland	Evidence Review D	50	42-44	It is stated '*The committee recommended a longer duration of doxycycline than current practice based on clinical evidence of a reduction of symptoms and no additional adverse events (20 versus 10 days)'.* We suggest the committee remove this sentence if you agree that it is based on mis-interpretation of the study data (see comment 47); and consider decreasing the preferred duration to 14 (or 15) days in line with the evidence.	Thank you for your comment. 'Clinical evidence of a reduction of symptoms' has now been removed from this sentence.
SH	NHS Highland	Evidence Review D	51	5-8	Cefuroxime-axetil is a useful alternative, (albeit not first or second line) and we would be grateful if committee could clarify this statement. Do they believe there is clinical evidence of inferiority, or not enough evidence of efficacy compared to other choices?	Thank you for your comment. There were no clinically important differences between cefuroxime-axetil and doxycycline (3 RCTs in adults). In children, the evidence was inconsistent. The committee did not recommend cefuroxime-axetil as there was no evidence of clinical superiority compared to other treatments and due to the higher cost of this drug. The wording has been amended in this section to clarify this.

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SH	NHS Highland	Evidence Review D	51	10-11	It is stated *'the evidence did not show any difference in effect between azithromycin and doxycycline or amoxicillin'.* We agree with this statement which is in contrast to the statement highlighted in comment 14 above.	Thank you for your comment. The guideline committee decided that overall, considering all of the outcomes as a whole for this comparison and evidence quality, there was no difference in effect.
SH	NHS Highland	Evidence Review D	51	32 - 33	It is stated '*The committee considered it important to standardise dose and duration of treatments for people with Lyme disease to ensure consistency and clarity for treatment'.* See comment 56 above.	Thank you for your comment. We have removed this phrase and provided further detail on committee decision.
SH	NHS Highland	Evidence Review D	128	Fig 35	See comment 47, data is for 'partial response' not 'reduction in symptoms as labelled'	Thank you for your comment. The figure titles have now been amended to reflect the data extracted.
SH	NHS Highland	Evidence Review D	128	Fig 36	See comment 47, data is for 'partial response' not 'reduction in symptoms as labelled'	Thank you for your comment. The figure titles have now been amended to reflect the data extracted.
SH	NHS Highland	Evidence Review D	129	Fig 37	See comment 47, data is for 'partial response' not 'reduction in symptoms as labelled'	Thank you for your comment. The figure titles have now been amended to reflect the data extracted.
SH	NHS Highland	Evidence Review D	129	Fig 38	See comment 47, data is for 'partial response' not 'reduction in symptoms as labelled'	Thank you for your comment. The figure titles have now been amended to reflect the data extracted.
SH	NHS Highland	Evidence Review F	6	18 (table 1)	Cranial nerve lesions (excluding optic nerve), and the autonomic nervous system should be in the peripheral nervous system section not central nervous system. This is important given different treatment approaches recommended.	Thank you for your comment. Cranial nerve lesions and autonomic nerve dysfunction have now been relisted under the peripheral nervous system heading.
SH	NHS Highland	Evidence Review F	12	Table 4	Unclear why this double blind RCT was considered at risk of bias at 4 month outcome but not at 1 year. The Cochrane systematic review found this study to be "at low risk of bias". Why does the committee consider it to be at risk of bias?	Thank you for your comment. This study was reported across 2 papers. Measurement of the outcomes you refer to was based on clinical assessment with some objective and subjective components. The paper reporting outcomes at 1 year conducted a sensitivity analysis of

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						objective/subjective components, but the paper reporting outcomes at 4 months did not, which is why evidence for the outcome at 4 months was judged to be at high risk of bias. In the Cochrane review to which you refer, risk of bias was assessed on a per study basis, while we assessed risk of bias according to outcome.
SH	NHS Highland	Evidence Review F	21	1-2	It is stated: '*The committee noted that the study used a short, 14-day course of antibiotics and felt that a longer course could be beneficial'.* This sort of statement is unhelpful, please qualify – on what basis?	Thank you for your comment. This section has been changed to clarify that the study used a 14-day course of antibiotics, which is below the maximum treatment durations recommended by some current guidelines.
SH	NHS Highland	Evidence Review F	24	3-4	It is stated '*The evidence showed a clinical benefit of high-dose cefotaxime (2 g every 8 hours for 10 days) over low-dose ceftriaxone (2 g every 24 hours for 10 days).* It does not show this - see original paper - low numbers (n=27), no difference, see Cochrane review 2016, page 39, comparison 6. We are concerned that a dose of 4g daily will have increased adverse effects (particularly neutropenia) but also probably *C. difficile*. 4g a day is usually tolerated fine for the 7-10 days usual for a bacterial meningitis patient, 21 days is significantly longer. The change will also result in many previously treated patients with persistent symptoms believing that they have been undertreated. If the committee wishes to increase the dose as a precaution, then clearly stating that there is no evidence to suggest that 2g daily is inferior to 4g daily would be helpful in allaying the fears of patients previously treated with the lower dose.	Thank you for your comment. This was an error and has now been removed. The committee reviewed the evidence again following stakeholder consultation and decided that the recommendation for 4g ceftriaxone is still justified, as this is the recommended dose for bacterial meningitis. We have added that there is no evidence to suggest 2g is inferior to the evidence report. The committee reviewed the evidence again following stakeholder comments and decided that the justification for recommending 21 days was still valid. The evidence for length of treatment is weak and the committee decided to err on the side of caution and recommend longer courses of 21 days of treatment as standard because of their concern at low cure rates in some studies, the lack of clear evidence for shorter courses and

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						concern that people being treated for Lyme may be concerned that they are undertreated if they continue to have symptoms and have received a shorter course. The limitations of the evidence are discussed in the evidence review. The guideline does make reference to the option to change to oral treatment if the person is well.
SH	NHS Highland	Evidence Review F	26	31-36	We agree that the PK/PD paper cited provides some basis for a higher dose of doxycycline, as do some animal studies. MIC of strains as above to doxycycline 0.125mg/L – 1mg/L. While the change will not have major impact on future diagnoses of Lyme Disease, it will result in many previously treated patients with persistent symptoms believing that they have been undertreated. If the committee has reviewed all the evidence available in making this decision then we would support it. If the committee feels there is still equipoise then a trial would be preferred.	Thank you for your comment. The committee considered there was adequate rationale to make the recommendation for higher dose for people with central nervous system borreliosis. The committee considered that, although the evidence was limited, central nervous system symptoms in Lyme disease should be treated with a similar antibiotic dose to that recommended for neurosyphilis. The text does discuss the limitations of the evidence.
SH	NHS Highland	Short	General	General	Thank you for the opportunity to comment on this draft document. It is an extensive report and the work done to produce it is very much appreciated. I am submitting this report on behalf of my colleagues at NHS Highland and we have collectively commented on the draft document. However, I would raise the same concerns as stated in these comments in my role as co-chair of the Lyme disease sub-group, Scottish Health Protection Network. In this role my main concern is conclusions do not appear to be based on	Thank you for your comment.

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					the scientific evidence provided as stated specifically in some of the comments below. The language used on many occasions is not scientific and, at times, is incorrect throughout the document. For example, comment made in short version page 3, line 4. We understand that the document is to be read and understood by the lay public but it is important that the language is factually correct. Changes are being made to treatment guidelines which may have major repercussions to clinician and patient without a strong evidence base as stated by the guidelines. Unfortunately, due to time constraints we have not been able to consider some documents (namely documents 8,9,10,11,12,13). It may be useful to have an extension on the consultation process to address these documents.	The wording is intended to ensure clarity of understanding and reflects NICE style. The wording in the line you quote has now been amended to 'the bacteria that cause Lyme disease are transmitted by the bite of an infected tick' for accuracy.
SH	NHS Highland	Short	General	General	There is no mention about the use of other sample types to diagnose Lyme disease in patients with focal symptoms, such as CSF, synovial fluid or biopsy (apart from in section 1.2.19, where their investigations in seronegative patients with persistent unexplained symptoms is not warranted). In particular, the use of paired CSF/serum serology to calculate antibody index, together with consideration of CSF parameters (cell counts, protein and glucose) is essential for the diagnosis of neuroborreliosis but has not been	Thank you for your comment. The committee reviewed the evidence for the use of different sample types, including CSF, synovial fluid and biopsy (evidence review C). The committee decided that there was insufficient evidence to recommend routine testing of these sample types, however the recommendation to discuss with or refer to a specialist for those with negative tests and persisting symptoms allows for further tests such as synovial fluid aspirate or biopsy, or

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					considered in these guidelines (ref. EFNS guidelines). Likewise, PCR of synovial fluid can be useful to confirm Lyme arthritis and PCR of skin biopsies can confirm cutaneous Lyme disease. CSF testing is briefly mentioned in evidence review 4 (page 190) but it was stated 'the evidence was not strong enough to inform a recommendation'. If a specific review was carried out on the diagnosis of neuroborreliosis the need for CSF testing would become evident. See Dessau RB *et al* To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis. *Clinical Microbiology and Infection* (2017) doi: 10.1016/j.cmi.2017.08.025	lumbar puncture for cerebrospinal fluid analysis to be carried out. It is presumed that in many cases people will be under the care of a specialist who will direct investigations as part of making a diagnosis. The Dessau 2017 paper was published after the date cut-off for evidence searches, therefore it was not considered. However, it would not have met the criteria for inclusion as narrative reviews are not considered as per NICE process.
SH	NHS Highland	Short	General	General	We are concerned about the emphasis on the use of the C6 ELISA throughout the guidelines. There is only one manufacturer of the C6 ELISA, therefore it is not appropriate to advocate the use of just one kit from one manufacturer. The NICE guidelines could be seen to have commercial conflict of interest. There are several other kits on the market that are just as sensitive and specific.	Thank you for your comment. We understand that the C6 term is used more widely than a specific test but we have altered the wording of the recommendation to IR6 to clarify that we are not recommending a specific test from a specific manufacturer.
SH	NHS Highland	Short	General	General	It needs to be made clear that IgM testing is not helpful (or indeed recommended) in patients with a longer onset of symptoms, such as those with Lyme arthritis and ACA. IgM can persist for several months/years, therefore does not necessarily indicate recent infection.	Thank you for your comment. It is current practice to use IgM and IgG blots for acute cases and many labs use IgG alone for cases with a long history (months) of symptoms. It would be difficult to specify the type of immunoblot in the recommendation without defining 'a longer onset of symptoms'. In addition, some labs use both IgM and IgG because they do not receive enough information on the patient to say when they developed symptoms. We have added some text regarding IgM and IgG testing and duration of symptoms to section 4.4.3 of evidence report C.

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SH	NHS Highland	Short	3	4	Replace this sentence with 'The bacterium that causes Lyme disease, *Borrelia burgdorferi* sensu lato (referred to hereafter as *B. burgdorferi*) is transmitted by the bite of an infected tick.'	Thank you for your comment. The wording of this recommendation has been revised following stakeholder consultation to clarify that it is the bacteria that are transmitted.
SH	NHS Highland	Short	3	16	Replace 'Lyme disease' with '*B.burgdorferi*'.	Thank you for your comment. It was decided to use the term Lyme disease, as it is a widely accepted term that was felt to be more accessible to non-healthcare professionals.
SH	NHS Highland	Short	4	8	Footnote. The picture of the bull's eye rash is excellent but we suggest a second picture of a spreading rash as EM can present in different ways.	Thank you for your comment. The committee have worked with NICE to provide images of typical and atypical EM to support health care professionals.
SH	NHS Highland	Short	4	9	A rash ≥5cm in diameter is indicated as descriptive of EM. If smaller then there should be a history of tick bite, a delay of two days since tick bite and it should be an expanding rash. This should be mentioned in this subsection. (See Stanek G et al. Lyme borreliosis. *Lancet* 2012; 379: 461-473, Table 1 and Stanek G, Fingerle V, Hunfeld KP, et al. Lyme borreliosis: Clinical case definitions for diagnosis and management in Europe. *Clin Microbiol Infect* 2011; 17: 69–79).	Thank you for your comment. The committee recognised that the size of the rash could be considered descriptive but wanted to ensure that a likely EM rash was treated promptly and that the size of the rash might distract from this.
SH	NHS Highland	Short	6	2	Replace 'positive testing' with 'positive serological testing'.	Thank you for your comment. The recommendation has been amended accordingly.
SH	NHS Highland	Short	6	13	The algorithm has to be completely changed in view of our comment numbers 11,12,14,15.	Thank you for your comment. The algorithm has been revised to reflect the final guideline following stakeholder comments.
SH	NHS Highland	Short	6	16	Suggest replacing 'using an enzyme-linked immunosorbent assay (ELISA) for Lyme disease that tests both IgM and IgG antibodies and is based on the C6 peptide or an equivalent purified or synthetic VlsE antigen' with 'using an enzyme-linked immunosorbent assay (ELISA) for *B. burgdorferi* that includes the C6 peptide or an equivalent purified or synthetic VlsE	Thank you for your comment. The wording of the recommendations has been revised following stakeholder consultation. A 'terms used' section has also been included, which explains that for the purposes of this guideline, the term Lyme disease is used when referring to both the disease and to tests for an antibody response as

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					antigen and that tests for both IgM and IgG or IgG to VlsE antigen. The reasons are the ELISA detects antibodies to *B. burgdorferi*, which indicates evidence of infection and not Lyme disease, and that the VlsE antigen based ELISAs that detect IgG alone are as sensitive and specific as those that detect IgG and IgM. See Dessau RB *et al* To test or not to test? Laboratory support for the diagnosis of Lyme borreliosis. *Clinical Microbiology and Infection* (2017) doi: 10.1016/j.cmi.2017.08.025, Lawrenz et al Human antibody responses to VlsE antigenic variation protein of *Borrelia burgdorferi*. *Journal of Clinical Microbiology* 1999; 37:3997-4004.	this reflects the terminology used in clinical practice. The recommendation is not specifying that the test needs to test for both IgG and IgM, rather that both tests are required.
SH	NHS Highland	Short	6	20	Replace 'an immunoblot test to confirm diagnosis of Lyme disease' with ' an immunoblot test should be used to confirm the detection of antibodies to *B.burgdorferi*'. The reasons for the change are that an immunoblot must be used to confirm the presence of *B. burgdorferi* specific antibodies after ELISA testing and so should not be offered. Serology cannot confirm the diagnosis of Lyme disease rather it only detects antibodies to *B. burgdorferi* which indicates evidence of infection, rather than disease. See also comment number 11.	Thank you for your comment. The committee recognised that antibodies can only confirm infection but agreed that usual clinical usage is to use terminology of 'diagnosis' of a disease in this way. An explanation to this effect has been added to the glossary and to the short guideline in the 'terms used in this guideline' section.
SH	NHS Highland	Short	6	22	Either delete 'for Lyme disease' or replace with 'antibodies to *B. burgdorferi*'. See comment 11.	Thank you for your suggestion. The committee recognised that antibodies can only confirm infection but agreed that usual clinical usage is to use terminology of 'diagnosis' of a disease in this way. An explanation to this effect has been added to the glossary and to the short guideline in the 'terms used in this guideline' section.
SH	NHS Highland	Short	7	1	Suggest it should read 'consider repeating the ELISA 8 weeks after the onset of symptoms' instead of	Thank you for your comment. The committee reviewed the wording and considered it important

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					'consider repeating the ELISA 4 to 6 weeks after the first ELISA test'. There is no evidence base for the time taken for a detectable antibody response to be produced in a patient. There are a number of variables: inoculum dose, host response, strain of *B.burgdorferi*, which EIA used, etc. However, it is generally accepted that it should be detectable about 8 weeks after onset of symptoms (although on little hard evidence). This is preferred rather than 4-6 weeks after first sample as the first sample may be within 1-2 weeks of onset and so a third sample may have to be taken.	to include timing after a test since timing of symptom onset may be vaguer.
SH	NHS Highland	Short	7	4	We understand the rationale for this statement, which is based on reducing overall NHS costs and presumably reassuring the patient. However we strongly disagree and recommend that it is not included in the guideline because there is no scientific evidence to justify the use of immunoblot in patients that are negative by ELISA. The immunoblot kits specify that their purpose is to confirm samples that are reactive in screening assays and that they should not be used as a screening test. It is questionable that deviating from kit specifications will be acceptable for UKAS laboratory accreditation without sufficient evidence to do so. What is the evidence base for the 12 week cut-off? Question 1 This recommendation will be a challenging change in practice because it will increase the workload of the reference laboratories greatly. At the National Lyme borreliosis testing laboratory, Inverness during September 2017, 769 patients were tested in our laboratory: 82 patients were reactive in the screening ELISA and were tested by immunoblot, 224 (29%) were	Thank you for your comment. This consensus recommendation was made based on clinical experience of the committee and was done in part to provide reassurance to individuals. These people are unlikely to have Lyme disease but this further testing will enable them to seek other diagnoses such as rheumatoid arthritis. In addition, it may identify Lyme disease in those who had not yet developed an immune response or had a false negative result the first time. The 12 week cut off was selected by the committee in this recommendation as it should give sufficient time to detect IgG immune response. A significant resource impact is defined by NICE as a recommendation that leads to an additional £1million pounds in NHS spending in a year in

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					negative in the screening ELISA but had chronic conditions/ documented onset of symptoms >8weeks. Using the guidelines suggested in this section, these would all have to be tested by immunoblot. Therefore, for one month alone this would have meant an extra 306 patients would have had an immunoblot (an increase of 373%). Question 2. This would have a significant cost implication for the National Lyme borreliosis testing laboratory in Inverness. Implementation of this guideline would increase the monthly cost from £5,749.02 to £21,453.66 with an annual increase of over £150 000 - £180 000. I have taken account of possible monthly variations to give a range of figures. The figures are calculated on the costs from the NICE guidelines. This figure is the amount RIPL charges for Lyme disease testing. It does not include staffing costs with the associated increase in workload. Although this figure may be less compared to the costs of further referrals to hospitals etc. it would be difficult to continue this service without guaranteed further funding.	England. The committee did not anticipate that additional testing would exceed this annual cost. Based on your calculations, again this is unlikely to be considered a significant resource impact.
SH	NHS Highland	Short	7	11	Suggest it should read 'If the presence of *B. burgdorferi* antibodies is confirmed' instead of 'If Lyme disease is confirmed'. See comment 11.	Thank you for your suggestion. The committee recognised that antibodies can only confirm infection but agreed that usual clinical usage is to use terminology of 'diagnosis' of a disease in this way. An explanation to this effect has been added to the glossary and to the short guideline in the 'terms used in this guideline' section.
SH	NHS Highland	Short	7	16	What is the evidence base for suggesting further testing, such as PCR, when the patient has long term symptoms and is seronegative? There is no indication	Thank you for your comment. This recommendation does not imply that further testing should be carried out on all seronegative

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					for testing if the patient is seronegative. If the patient was seropositive there may be an indication for testing as seropositivity is only indicating infection and not disease and the detection of the organism, say by PCR, may be useful to the clinician for the diagnosis. In the absence of convincing evidence to the contrary I would delete the first bullet point but keep the second one. Question 1. If included in the guideline this would impact the testing laboratories with an increase in testing that is not useful. Question 2. Due to the increase in workload this may have a significant increase in costs. Question 3. Looking for alternative diagnoses would be good practice and help users overcome these challenges.	symptomatic patients, but in the absence of a test with 100% sensitivity, allows specialists to make a clinical judgement on whether further testing may be appropriate.
SH	NHS Highland	Short	7	27	NHS-accredited laboratories are accredited to ISO 15189 standards. I would suggest that this is included in this sub section. 'Carry out tests for Lyme disease only at NHS-accredited or ISO15189 accredited laboratories that: ...'	Thank you for your comment. The committee has amended the laboratories to be inclusive of UKAS-accredited laboratories.
SH	NHS Highland	Short	10	Table 1	Disagree with duration of antibiotics for erythema migrans – prefer 14 days for doxycycline in line with current practice and evidence. We would question 2g bd for ceftriaxone in CNS neuroborreliosis – an increase in side effects would be expected. If the higher dose is included suggest research objective to determine if it is superior than 1g bd.	Thank you for your comment. The committee wished to aim for clarity and reduction of ambiguity. Most current guidelines suggest treatments over a range of time periods; for example, the BNF suggests doxycycline for 10 to 14 days and amoxicillin for 14 to 21 days. The committee considered that providing a range of

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						times was not useful for generalists, as it is unclear when to use the shorter or longer course. The evidence for length of treatment is weak, and the committee decided to err on the side of caution and recommend longer courses of 21 days of treatment as standard because of its concern at low cure rates in some studies, the lack of clear evidence for shorter courses, and the concern that people being treated for Lyme may be concerned that they are undertreated if they continue to have symptoms and have received a shorter course. The committee was reassured that adverse rates were not increased for longer courses. The SPC for ceftriaxone recommends up to 4g for bacterial meningitis with the higher end of recommended dose range suggested in documented bacteraemia. The committee considered that the potentially catastrophic effects of neuroborreliosis made it difficult to recommend more limited treatment, despite the lack of good evidence. The committee made a research recommendation to determine the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease, which we hope will answer this question.
SH	NHS Highland	Short	12	13	We agree that the option of further antibiotics should be open, but believe this section is not balanced, but is written to suggest that a second course would effectively be indicated in all patients with persistent symptoms. This is against available evidence and we	Thank you for your comment. The committee discussed your comment but agreed that adding the detail you describe would not be helpful. The recommendations were reviewed and further detail added about symptom patterns that might

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					believe will affect a lot of patients. In our experience the majority of patients treated for possible Lyme Disease in Highland do have persistent symptoms both because these are common in Lyme disease, and because many people are treated on the basis of long duration of non-specific symptoms plus positive serology. Suggest include a sentence to highlight that symptoms such as fatigue, myalgia, arthralgia, 'brain fog' do not usually resolve completely during the antibiotic course, and that studies suggest that further courses of antibiotics are not helpful. Similarly, cranial nerve palsies are often slow to resolve. Suggest include sentences such as: 'Health professional should consider the potential benefits and harms of further antibiotics. Harms may outweigh benefits, particularly in patients where the likelihood of Lyme Disease is low, or where symptoms are following natural course of disease progression post treatment.' This is in keeping with standard antibiotic stewardship and patient care but should be highlighted to help avoid overtreatment. We note some of these issues are discussed in page 29 but feel strongly this balance should be brought into the main recommendation section as many health professionals will not have time to delve into the latter sections when making treatment decisions.	be of concern such as persistence of symptoms, symptom worsening, or not continuing to improve. The committee considered that many people do not have ongoing symptoms and only return if unwell. As you suggest, information about potential harms and benefits is usual clinical practice and so has not been added to the recommendations.

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SH	NHS Highland	Short	12	16	We would question the use of amoxicillin for Lyme arthritis if doxycycline has failed. Our current practice is to use ceftriaxone.	Thank you for this information. IV ceftriaxone is included as an option for treatment.
SH	NHS Highland	Short	12	16	Is there evidence that alternative antibiotic is more likely to be beneficial? Did the committee make this comment due to concerns about emerging antibiotic resistance?	Thank you for our comment. This was a consensus decision based on common practice if a person has not responded to antibiotic treatment
SH	NHS Highland	Short	14	13	This advice essentially means that we should test all babies born to mothers with Lyme Disease for IgM and treat those who are positive. IgM is known to be non-specific. We strongly believe that given no evidence of mother to child transmission leading to child harm, the institution of this policy would lead to much greater harm than good. Antibiotics in children can affect microbiota with possible detriment to development and should not be instituted lightly. This advice, which implies mother to child transmission and child harm will also understandably lead to high levels of anxiety in pregnant women areas of high tick exposure, without basis in evidence. If the committee does include this controversial advice then a clear testing and treatment strategy should be given, that is, when to test the neonate, and when to treat.	Thank you for your comment. The recommendation only applies if there is concern about the baby and the committee did not agree that this means all babies require testing and treating.
SH	NHS Highland	Short	14	15	Please include – most people recover completely through their own immune response, but antibiotics are indicated to reduce the chance of late complications. I find that this is not widely appreciated, and is very reassuring for people who find that they are seropositive and think they have had this 'untreated infection for years'.	Thank you for your comment. The guideline is clear that people who are not unwell do not have Lyme disease. The wording of the recommendations was reviewed but additional wording was considered unhelpful as this is true for many infections and not unique to Lyme.

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SH	NHS Highland	Short	15	8	Agree with all the research recommendations but also believe should include: 1) There should be planned program of surveillance of antibiotic susceptibility of human pathogenic *Borrelia* sp. in the UK. In the population of patients who have non-specific symptoms a placebo controlled trial would be indicated to ascertain if antibiotic treatment has any benefit.	Thank you for your support for the research recommendations. The guideline is a clinical guideline and would not usually make recommendations on areas like antibiotic susceptibility surveillance. It is unclear how this could be carried out since organism is not usually available in humans unless you are suggesting tick surveillance.
SH	NHS Highland	Short	16	18	Is there any reliable evidence that Q fever is transmitted to humans by ticks?? Similarly with Bartonella?? If not, we suggest the sentence is re-phrased.	Thank you for your comment. The wording of the recommendation has been changed. We understand it can be tick borne, but this is not the usual mode of transmission.
SH	NHS Highland	Short	23	21	It is stated: *"There is some evidence of a greater reduction in symptoms...."* We believe this statement is based on erroneous interpretation of the Wormser study. See detailed comment 47.	Thank you for your comment. This statement has now been removed.
SH	NHS Highland	Short	29	35	While only a small number of people with erythema migrans have recurrent symptoms, a large proportion of the total number of people treated for 'possible Lyme disease' are treated because of persistent, non-organ, specific symptoms (fatigue etc.) with positive serology. In areas such as Highland, Scotland where >5% of the population is seropositive, this is a large patient cohort. Most of these patients do not improve (as most do not have *B. burgdorferi* sensu lato infection), and therefore clinicians following your recommendations will need to 'consider' a further course of antibiotics. When you are considering the impact of increased treatment please consider all those who will be treated (and potentially harmed).	Thank you for your comment. The committee did discuss this scenario. Following stakeholder comments the recommendations were amended to add further guidance to the pattern of symptoms that might be considered to come under this category. The committee considered that the potential benefit outweighed potential risk.
SH	NHS Highland	Short	33	24	South East England includes a huge population; do you include London in this? I know there are ticks in London parks but saying that 50% of cases are	Thank you for your comment. South East England is a defined region in England and does not include Greater London. It is densely

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					diagnosed in South East and South West is not particularly helpful. Likelihood of infection in populations can easily be determined by seroprevalence. Suggest include seroprevalence in the populations where data exists.	populated which is likely to contribute to the reason why there are a large number of diagnoses.
SH	North of Scotland Faculty, RCGP	SHORT	3	3	*Be aware that:* We are concerned that awareness of Lyme disease is not targeted at high risk groups by location, occupation or recreation. Extra bullet points would help e.g. • Occupational groups in high risk areas are at particularly high risk with regular exposure to ticks. Forestry workers, Outdoor education leaders, Surveyors, Environmentalists and Gardeners. • Employers have a duty of care under COSHH regulations to provide information on tick removal and tick removal devices. They have a duty of care under RIDDOR regulations to report occupational episodes of Lyme disease. • Lyme disease can affect all ages including children and the fit elderly who may be walkers or gardeners. People may travel from a rural area with infected ticks after sport or recreation and present their symptoms to city based NHS services.	Thank you for your comment. The committee sought to strike a balance between raising awareness that people anywhere may have Lyme disease either because of a tick bite sustained locally or when travelling; and that there are areas of higher risk and people at higher risk because of occupational or recreation. The committee considered that raising awareness that Lyme may occur anywhere was the more important part of the message and listing more detail about people/areas of high risk could detract from that message.
SH	North of Scotland Faculty, RCGP	SHORT	3	18	*Give people advice about:* An extra bullet point suggesting the use of mobile phones to capture evolving rashes e.g. Use mobile phones to capture pictures of rashes to discuss with health professionals.	Thank you for this suggestion. The committee discussed this, but decided not to make this recommendation, as it is not specific to Lyme disease.
SH	North of Scotland Faculty, RCGP	SHORT	4	2	The bullet point *'How to check themselves and their children for ticks on the skin'* . There is a major weakness in the NICE Guidelines in that the weak	Thank you for your comment. Prevention was outside the scope of the guideline. The committee however wished to highlight important

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					evidence for tick removal is not documented, considered or interpreted. This is a fundamental question in public health policy and I believe there is current harm being done by continuing to recommend fine tipped insect tweezers in NHS policy. The WHO insect tweezers are designed for insects and not ticks. Ticks are not insects. Insects include mosquitoes which may transmit malaria or zika and are clearly supported by evidence in that context. They have been adopted into current NHS information on tick removal with no evidence. However, they are very likely to crush a questing nymph tick, increase borrelial transmission in a similar manner to fingernails. The public remain confused by any recommendation to use 'tweezers' and actually use domestic eyebrow style tweezers thinking they are doing the correct thing because of this erroneous recommendation. I believe on the basis of extensive clinical experience that the plastic purpose designed tick removal tools such as the twister or card should be the only public health recommendation in the UK on tick removal. The absence of evidence on this topic needs to be acknowledged and recommendations made on first principles and UK clinical experience.	areas for public health and refer to other sources of information.
SH	North of Scotland Faculty, RCGP	SHORT	4	3	*'sources of information on Lyme disease, such as NHS Choices and Public Health England and organisations providing information and support such as patient charities'.* This information needs to be expanded to include public health authorities in all 4 nations. There needs to be a recommendation somewhere after reviewing their available policy that targeted information needs to be provided for children and young adults in particular on tick removal using plastic	Thank you for your comment. NICE guidelines are developed for England, which is why Public Health England is included in the recommendation.

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					tools as a method of gaining a generational shift in the public understanding of tick removal and reduction of late Lyme morbidity.	
SH	North of Scotland Faculty, RCGP	SHORT	4	8	*Diagnose Lyme disease in people with erythema migrans that is:* the list of bullet points is clumsy. '*The rash is usually slightly itchy around the tick bite but not hot or painful. The third bullet point 'usually becomes visible from 1 – 4 weeks (but can appear from 3 days – 3 months) after exposure and lasts for several weeks*' is clumsy and unhelpful. It does not reflect clinical experience of erythema migrans in Scotland. The rash usually becomes visible within 7 days of a tick bite which the patient can easily see. Delayed presentations of the rash may occur in body areas the patient may not easily see including the back, behind the knee, in the groin, perineum or in the armpits. In babies and toddlers the tick may attach in neck creases or nappy area. In older children the ticks may attach in the hairline. The rash usually appears at the site of the recognised tick bite but another area of the body may have picked up a tiny questing nymph tick which has gone unrecognised. There needs to be an extra bullet point under erythema migrans which requires all primary care providers including GPs, Out of Hours and A+E departments to code erythema migrans correctly with SNOMED or REED or ICD 10 codes. This is crucial if we are ever to understand the epidemiology of Lyme in the UK.	Thank you for your comment. The current wording covers the situation you describe. The issues of surveillance and coding were outside the scope of the guideline. We are aware that the Department of Health have commissioned work in this area and the reviews were recently published at http://eppi.ioe.ac.uk/cms/.
SH	North of Scotland Faculty, RCGP	SHORT	4	15	*Be aware that a rash can develop as a reaction to a tick bite, which is not erythema migrans, that:* More clarity is needed here. I suggest:	Thank you for your comment. The wording of the recommendation has been changed following stakeholder comments.

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					• 'usually develops and receeds over 48 hours from the time of the tick bite and is smaller than a 5 pence coin. • It may be slightly itchy but is not hot or painful. May be caused by an inflammatory reaction secondary to the tick's injection of anti-coagulant for a blood meal.	
SH	North of Scotland Faculty, RCGP	SHORT	5	9	There needs to be a clear bullet point to code disseminated Lyme correctly in secondary care clinics or hospital discharge letters. An appropriate formulary of ICD 10 codes and equivalent SNOMED or REED codes needs to be included in discharge letters to primary care which can then be summarised in the patient record and be available for future epidemiological searches.	Thank you for these suggestions. Coding is beyond the scope of the guideline. We are aware that the department of health commissioned systematic reviews which included surveillance processes and these are available at http://eppi.ioe.ac.uk/cms/
SH	North of Scotland Faculty, RCGP	SHORT	5	21	*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:* An extra bullet point suggested includes: • Their occupational and recreational exposure to ticks. Their understanding of tick removal and whether they have used a tick removal tool within the estimated time limits (12-24 hours of tick attachment to transmit infection).	Thank you for your comment. The recommendations were reviewed following stakeholder comment and the committee considered additional detail potentially unhelpful. Occupational and recreational exposure would be included in history of possible tick exposure and are covered by the recommendation.
SH	North of Scotland Faculty, RCGP	SHORT	6	1	*Be cautious about diagnosing Lyme disease in people without a supportive history of positive testing because of the risk of:* I would suggest an extra bullet point: Consider further management under 'medically unexplained symptoms' pathways.	Thank you for your comment. . The committee did not think 'medically unexplained symptoms'' pathways are readily available.

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SH	North of Scotland Faculty, RCGP	SHORT	14	14	*Information for People with Lyme disease.* The British Association of Infection Guidelines 2011 introduced the concept of Lyme borreliosis for disease classification in contrast to 'Lyme disease'. While this remains a point of debate on disease clarification and comparison with other countries. Within the UK a move to Lyme borreliosis would fundamentally improve medical and patient understanding and adjustment to different stages of the disease. It is a major deficiency in these guidelines that this debate has been not acknowledged and indeed set aside to the detriment of future patient care. The term disease has a huge amount of psychological baggage. It probably accounts for why some patients believe they have 'Lyme disease' with no biological proof and the varied human immune response to infective disease is better reflected with the term Lyme borreliosis. People with persisting antibodies and immunity can therefore be described as having Lyme borreliosis. The semantics of language does have an impact in the clinical care of patients and return of well-being after effective treatment. There are clearly analogies with cancer and HIV which prove this point.	Thank you for your comment. It was decided to use Lyme disease, as it is a widely accepted term, which we feel is more accessible to non-healthcare professionals than Lyme borreliosis. We have added an explanation as to how the term is used in the short guideline and in the glossary in the Methods chapter. In the guideline, people who are not unwell will not be diagnosed with Lyme disease.
SH	North of Scotland Faculty, RCGP	SHORT	15	21	*Clinical epidemiology of Lyme disease in the UK.* There needs to be a clear and explicit expectation of an improvement in disease coding and a recommendation from the current formulary codes within SNOMED, REED and ICD 10 by the NICE Guidelines.	Thank you for your comment. The committee recognise the importance of coding. The committee were aware that department of health have commissioned research into surveillance systems for Lyme disease to evaluate further improved collection of information. These are available here http://eppi.ioe.ac.uk/cms/
SH	North of Scotland Faculty, RCGP	SHORT	32	17	*Putting this guideline into practice. Identify a lead.* The specialities which require a clinical champion on Lyme disease need to be specified as follows: General	Thank you for your response. These suggestions will be considered by NICE where relevant support activity is being planned

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					Practice, Out of Hours, A+E, Infectious Diseases, Neurology, Psychiatry, Care of the Elderly, Old Age Psychiatry, Acute Psychiatry, Paediatrics, Rheumatology, Cardiology, Laboratory Medicine, Public Health, Dermatology, ENT.	
SH	Royal College of General Practitioners	appendices	19	13	Lyme Disease is uncommon' - there is a repeated reference to LD being uncommon despite the lack of a reporting system for anything other than laboratory diagnosed cases, and the fact that the scope document states that the incidence is unknown. Scope document also acknowledges that many cases are undiagnosed thus the total number of chronic cases needs to be added to the annual incidence figures to give a true reflection of numbers. It would be helpful use the RCGP Research and Surveillance Centre (RSC) to monitor the condition. Established in 1957, the RSC is an active research and surveillance unit which collects and monitors data since 1967, in particular influenza and other respiratory diseases, from over 230 practices across England. The RSC is a representative network, having only small differences with the national population, which have now been quantified and can be assessed for clinical relevance for specific studies. With twice weekly data extractions, the dataset is one of the most up to date in the UK	Thank you for your comment and this suggestion. The use of surveillance centre as you describe would be one useful way to collect epidemiological data as suggested in the research recommendations.
SH	Royal College of General Practitioners	General	General	General	Q1 - These guidelines fail to acknowledge the limited evidence upon which they are based. They fail to make doctors aware of the limitations of testing and the uncertainties identified by the James Lind Alliance (alluded to in the Scope). General Practitioners are highly experienced 'generalists' who are required to	Thank you for your comment. The detail of the evidence is included in each evidence review where the limited evidence is discussed. The committee also made recommendations for

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					apply their clinical acumen to complex cases on a daily basis. These guidelines fail to acknowledge the very real gap between positively diagnosing and reliably excluding Lyme Disease. They place an over-reliance on serological results, which serves to disempower the doctor and undermine the doctor-patient relationship.	further research, which acknowledged that there were gaps in the evidence base. Following stakeholder comments recommendations have been added to make clear that diagnosis needs to be based on clinical judgement and assessment and to indicate that false positives and false negatives occur with serological testing.
SH	Royal College of General Practitioners	General	General	General	Q2 - The Scope document acknowledges that Lyme Disease is under diagnosed in the UK. (The reason for the under diagnosis has not been established.) These guidelines are unlikely to alter this situation. Many patients with Lyme disease report that they have undergone numerous NHS referrals and investigations prior to diagnosis. The NHS and social costs of managing the chronic symptoms of Lyme Disease is likely to continue to rise as the incidence of Lyme Disease increases. There needs to be a significant educational follow-up with a quality improvement program with these guidelines to ensure a change in clinical practice, a monitoring system and investment in primary care research in this area.	Thank you for your comment. The aim of this guideline is to highlight Lyme disease and provide all primary and secondary care physicians with guidelines of how to address whether or not Lyme is the cause of symptoms, how to test, treat and provide reassurance if not Lyme disease. The committee recognises the need for educational follow up of the guideline and hope the RCGP can be part of that process.
SH	Royal College of General Practitioners	General	General	General	Q3 - General Practitioners face the challenges of diagnosing and managing cases of acute and late Lyme Disease. The provision of specialist Lyme disease clinics within the UK would provide early support and advice for GPs and their patients. The development of local guidelines in areas of high incidence of tick-borne infections would be helpful. In these areas it would be appropriate for GPs to be aware of the risks and to diagnose and treat early,	Thank you for your comment and these suggestions for management of people with Lyme disease. The guideline did not examine service delivery. Secondary and Tertiary secondary specialists in infectious diseases and in paediatric infectious disease already see and treat Lyme disease.

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					based on clinical suspicion - without waiting for test results.	
SH	Royal College of General Practitioners	General	General	General	Q4 - Standardisation of initial treatment is logical. Patients who fail to respond within a couple of weeks should be considered for alternative antibiotic regimes. There is international research supporting individualised treatment regimes. Standardising treatment regimes for the benefit of providing clarity for physicians, must be balanced with ensuring adequate treatment of patients	Thank you for your comment. The evidence review for the guideline did not find evidence for prolonged or individualised treatment regimes.
SH	Royal College of General Practitioners	General	General	General	Q5 - This is a specialist question for ID and paediatric consultants. Not relevant to General Practice	Thank you.
SH	Royal College of General Practitioners	Short	General	General	Clear and useful It does not cover the group of 'self-diagnosed' who are cynical of NHS testing who have had several courses already of high dose long term antibiotics and how to help them.	Thank you for your comment. Recommendations 1.3.11 to 1.3.16 refer to management in people with ongoing symptoms following 2 completed courses of antibiotics.
SH	Royal College of General Practitioners	short	3	1	"People have the right to be involved in decisions about their care" - These guidelines will help patients reporting tick exposure and symptoms consistent with Lyme Disease to receive early treatment Diagnosing Lyme disease is often difficult as many of the symptoms are similar to other conditions.	Thank you.

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SH	Royal College of General Practitioners	short	4	9	This description of an Erythema Migrans rash is vague and nonspecific. no indication of size. no reference to that fact that up to 50% of cases of Lyme Disease may not develop an Erythema Migrans rash	Thank you for your comment. The guideline is not intended to replicate clinical textbooks. The committee have agreed a number of images of typical and atypical EM to accompany the guideline, as providing images was considered clearer than attempting descriptions of these.
SH	Royal College of General Practitioners	short	4	24	Repeated use of 'an uncommon cause of' - what is the evidence it is an uncommon cause	Thank you for your comment. This statement is not intended to suggest that Lyme disease is uncommon, but that it is an uncommon cause of the symptoms outlined in the bullet points. For example, Lyme disease is unlikely to be the cause of the majority of cases of headache.
SH	Royal College of General Practitioners	short	5	1-8	There is no mention of seasonal variation in incidence tick bites and exposure to Lyme disease. pain is often migratory - which is uncommon in other diseases.	Thank you for your comment. The committee considered that raising awareness that Lyme may occur anywhere and at any time was the more important part of the message and listing more detail about people/areas/periods of high risk could detract from that message. The wording has been amended to 'migratory joint or muscle pain' in accordance with your suggestion.
SH	Royal College of General Practitioners	short	6	1	The guideline suggests that a supportive history or +ve testing is required but subsequently repeatedly advises against treating based on symptoms alone. No acknowledgement is made of the limitations of testing. No reference is made to the 2016 European Centre for Disease Prevention and Control Review of Serology study - which report an overall sensitivity of 80% and a specificity of 95%. The review advised that there was insufficient evidence to make inferences about the value of the tests for clinical practice.	Thank you for your comment. The intention was not to suggest that treatment could not be based on symptoms alone and the recommendations have been altered to reflect this. The 2016 European Centre for Disease Prevention and Control review was excluded because the methodology differed from NICE methodology, but the reference list was screened to ensure that we included any relevant papers in our review.

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					https://ecdc.europa.eu/en/publications-data/systematic-literature-review-diagnostic-accuracy-serological-tests-lyme	
SH	Royal College of General Practitioners	short	7	8	"consider treatment with antibiotics before tests results become available if there is a high probability of LD." Lyme Disease is a potentially life altering disease. Why are practitioners not advised to treat if there is a high probability? Delay in treatment is known to affect long term outcome and testing can take a minimum of two weeks. Prostatitis (usually a clinical diagnosis) and acne are both regularly treated with extended courses of tetracyclines.	Thank you for your comment. The wording of the recommendation is line with NICE policy where strong evidence is not available.
SH	Royal College of General Practitioners	short	8	5	Limitations of testing at NHS laboratories need to be acknowledged	Thank you for your comment. The recommendation has been re-worded to indicate UK accredited laboratories. The previous wording was an error.
SH	Royal College of General Practitioners	short	12	13	Doxycycline covers several potential tick borne infections. If a short course of doxycycline has failed then it seems unlikely that amoxycillin will be more effective. azithromycin may be more effective	Thank you for your comment. The committee considered that the evidence for penicillin as an option was convincing.
SH	Royal College of General Practitioners	short	12	23	There are significant amounts of peer reviewed research suggesting that extended courses of treatment may be beneficial. The uncertainties should be acknowledged in the guidelines so that doctors are in a position to discuss these issues with their patients. A dogmatic approach from the doctor serves to undermine the doctor-patient relationship.	Thank you for your comment. The evidence review did not find evidence to support extended courses of treatment as discussed in evidence report L.
SH	Royal College of Nursing	General	General	General	The RCN has no comments to submit to inform on this consultation at this present time	Thank you.
SH	Royal College of Paediatrics and Child Health	General	General	General	We are happy with this draft guideline.	Thank you

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SH	Royal College of Pathologists	General			The two main controversies (although there are many) which concern the patient advocacy groups are : 1. Diagnostic tests. Can someone have established, not early, Lyme disease with entirely negative serology? It would be worth commenting on the evidence for or against this. 2. Does chronic Lyme exist, ie persistence of viable bacteria after apparently appropriate treatment? Comment on the evidence of or against this. I think it is important to make a statement on these issues, otherwise the guidance is just sitting on the fence and is unhelpful to patients or clinicians. Helpful statements would be 1. Current evidence does not support a diagnosis of established borreliosis if serology is negative (this does not apply to early infection) 2. Current evidence does not support the persistence of borrelia in appropriately treated Lyme disease 3. Chronic non-specific symptoms in patients who are serologically negative for borrelia, do not have Lyme disease and may need referral to an appropriate specialist team for further management.	Thank you for your comment. NICE clinical guideline development uses evidence reviews built around clinical questions to develop recommendations. Recommendations are directed to action in clinical care and not underlying pathophysiology. In this guideline, the committee preferred to avoid contested definitions and to use symptoms and history as basis for recommendations. Rather than consider whether chronic Lyme exists for example, the guideline searched for evidence for repeated or prolonged treatment with antibiotics, but the evidence identified was insufficient.
SH	Royal College of Pathologists	General			It might be worth suggesting an LP when central neuroborreliosis is suspected.	Thank you for your comment. The recommendations are to discuss with a specialist if focal disease is present. The committee presumed that people with suspected central neuroborreliosis would be under the care of a

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						neurologist who would direct appropriate investigations.
SH	Royal College of Pathologists	Short	General	General	The committee should be congratulated on the scope and presentation of these guidelines. They provide independent UK based guidance to support management of patients in the UK and they mirror previous professional society recommendations such as the IDSA guidelines on Lyme and the BIA position statement. The guidance is carefully and considerately worded and the recommendations are based on the best evidence that exists. However they may not satisfy certain groups of patients and may not help physicians who are trying to help such patients. They do not directly address the main controversy in Lyme which generates the greatest political backlash. The main controversy in Lyme is not how to diagnose it, or how to manage it, but how to manage patients with non-specific chronic symptoms who test negative for borreliosis by conventional diagnostic methods. It is this group of patients who deny the efficacy of conventional diagnostic methods for borreliosis and complain about the inadequacy of NHS treatment for Lyme. It is this group of patients who turn to unvalidated diagnostic methods and non-evidence based treatments. The Australian government commission on Lyme (which does not exist in Australia) recommended that patients with chronic illness be investigated for this and that Lyme be removed from the description of this condition. These NICE guidelines have been very diplomatic and guarded in their approach to this controversial area and it would be worth considering whether slightly stronger statements should be made. For example: 1.	Thank you for your comment and for information regarding the Australian approach.

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					the following tests – LTT, ELISPOT, CD 57 etc. are not sufficiently specific to diagnose active borreliosis. 2. Patients with chronic symptoms and who test negative by conventional serology are unlikely to have active borreliosis and should be investigated for a full differential diagnosis of chronic illness. This is stated somewhat obliquely in 1.2.28 and 1.2. 29	
SH	Royal College of Pathologists	Short	General	General	Alternative diagnostic tests are widely used by patients who believe they have Lyme. I have found it quite difficult to pull out the strength of evidence (or not) for alternative diagnostic methods e.g. LTT, PCR, direct microscopy, CD 57. Could the guidance be more specific about what tests should NOT be used?	Thank you for your comment. The clinical evidence summary tables in evidence review C contain the associated evidence quality rating for all of the tests identified. The majority of the evidence was for ELISA and Immunoblot tests and there was insufficient evidence on the other tests for the committee to make any recommendation for or against their use.
SH	Royal College of Pathologists	Short	General	General	Could the guidance be more specific about alternative treatment regimens i.e. prolonged courses of antibiotics, nutritional supplements, herbal treatments, bioelectronics? If there is no evidence to support these, could there be a specific statement to that effect? Perhaps after section 1.3.13	Thank you for your comment. The guideline scope did not include treatments such as nutritional supplements, herbal treatments or bioelectronics. The protocols would have allowed the reporting of prolonged courses of antibiotics but no such evidence was found.
SH	Royal College of Pathologists	Short	General	General	I may have missed it but it would be helpful if there was a statement on the evidence for and a recommendation for or against antibiotic prophylaxis following tick bite.	Thank you for your comment. The guideline does not make a specific recommendation about prophylaxis but does say that Lyme disease should not be diagnosed and therefore treatment not given unless a person has symptoms.
SH	Royal College of Pathologists	Short	General	General	Should there be a specific statement somewhere that Lyme disease is NOT transmitted from person to person (except in very rare cases of vertical transmission)?	Thank you for your comment. No evidence was identified for transmission through blood products or sexual transmission and no specific action is therefore required to mitigate any risk. The committee decided it would not be helpful to

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						make any statement regarding the possibility of these types of person-to-person transmission.
SH	Royal College of Pathologists	Short	6	5	1.2.29. This would be a good section to be specific about the investigation of patients with chronic symptoms who are seronegative for borrelia.	Thank you for your comment. The recommendation referred to appears to be 1.2.9, which concerns management of symptoms only and not testing.
SH	Royal College of Pathologists	Short	17	19	Has LTT, ELISPOT, PCR been deliberately left out of this section for research on newer diagnostic methods? As these are the main tests used by some private labs, it would be helpful to have some comment on future research required.	Thank you for your comment. The tests were listed as examples from the evidence review but the research recommendation has now been re-worded to clarify the intended wider scope of the research recommendation.
SH	Royal College of Psychiatrists	General	Sections 5 -14	Appendix C	Out of 212 papers on management that were assessed for eligibility, only 34 were included in the Lyme disease guideline (The majority of references listed in the various sections refer to excluded papers): • 20 papers relate to management of the erythema migrans rash stage of very early Lyme infection. • Only 7 papers which are low and very low quality are eligible for inclusion in Section 7 (Neurological Lyme disease). Included studies show marked differences in inclusion/exclusion criteria, 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. Outcome measures show that response rates vary with low rates of cure, and are particularly poor in those who are diagnosed late. It is hard to draw firm, general conclusions about the most	Thank you for your comment and observations of the available literature. The committee have made a number of broad research recommendations. Research could be carried out in a specialist clinic but this would only involve those referred to a clinic and other models such as via a GP network would also be possible with different advantages and disadvantages of each. Service delivery was not included in the scope of the guideline and given the lack of general evidence it is unlikely there is clinical or cost effectiveness evidence for different models of care.

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					clinically effective treatment when there are so many gaps in this section of the evidence base. Further research on the effective clinical treatment of Lyme disease, including that affecting the nervous system is needed, as stated in the short guideline page 17, lines 3-5. • Only 3 papers, 2 of which are of low and very low quality inform the recommendations for persistent symptoms. The remaining paper by Krupp 2003 suggests that retreatment with intravenous ceftriaxone is effective for persisting symptoms of pain and fatigue. • Only 3 papers meet quality standards for Lyme arthritis, with 1 for acrodermatitis. • For some less common aspects such as carditis, lymphocytoma, and ocular non-neurological presentations there is no available evidence. • The NICE process has helped highlight the gaps in the evidence base for Lyme disease and areas in need of further research, particularly within a UK setting. There is an opportunity for development of a specialist service, which could address some of these research needs in a clinical context. This would be a benefit to patients and doctors. • In terms of implementing the guidelines and addressing the challenges, it would help if NICE were able to recommend, or make some comment about the need for development of	

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					specialist services in order to raise the profile of Lyme disease.	
SH	Royal College of Psychiatrists	Short	1	"Who is it for?"	Re: The first bullet point: • "specialists and microbiologists" might be misinterpreted as "infectious diseases specialists and microbiologists". It may be better stated as "clinicians from a range of specialities and laboratory-based microbiologists." This would help raise awareness that Lyme disease may present in a variety of clinical settings.	Thank you for this suggestion. We have changed the wording to make the range of specialists clear depending on clinical presentation.
SH	Royal College of Psychiatrists	Short	6	14/15	• This recommendation would be challenging for psychiatrists to put into practice, because they may not recognise the significance of an erythema migrans rash, or feel confident in diagnosing it, despite the description on page 4 of the short guideline (lines 9-14). • Psychiatrists do not routinely prescribe antibiotics. They would probably seek specialist advice, or refer the patient to their general practitioner depending on the circumstances and clinical presentation at this point.	Thank you for your comment. We agree that if a psychiatrist or other healthcare professional is unsure of a rash they should seek advice. The guideline committee have identified images of rashes that may be of help and these can be found on the NICE website.
SH	Royal College of Psychiatrists	Short	6	18	Re: Table 1 PICO characteristics of review question: Population, 3rd bullet point "Psychiatric". Psychiatrists using this guideline would probably prefer it to be consistent with International Classification of Diseases 10 (ICD10) Mental, Behavioral and Neurodevelopmental disorders F01-F99 and to list the bullets as:	Thank you for your comment. We are unable to change the protocol at this stage. The information specialists use the wording as a guide. This search was run using the overall Lyme population only so no specific terms for psychiatric disorders were included.

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					• Disturbed cognitive function eg delirium and dementia[1] • Organic psychosis[2] • Mood disorders eg depression [1] It is important for healthcare practitioners to recognise that "cognitive decline" due to neurological Lyme disease is a potentially treatable cause of dementia, and that it responds to treatment with antibiotics. "Disturbed" or "impaired cognitive function" would be a better word to use as it alerts the treating clinician to the potentially reversible nature of Lyme-related dementia. It allows the inclusion of delirium. Both dementia and delirium are conditions covered by other NICE guidelines. It is important to flag up delirium, as this is often under-recognised, especially if the patient is under-active and apathetic. It may be associated with significant morbidity and mortality if untreated. [2] This avoids confusion by specifying the organic nature of any psychotic symptoms and would prompt clinicians to look for other symptoms of organic brain disease eg confusional states, or perceptual disturbances such as visual hallucinations or illusions, which might assist in diagnosis and providing appropriate clinical treatment. Historically psychiatrists and mental health practitioners have been familiar with the neuropsychiatric and systemic complications of syphilis which was commonly be included as a differential diagnosis. However, they may not know very much about Lyme disease if they have not yet come across	

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					it. There will be a need for education and training in this area, as the incidence of Lyme disease is gradually increasing. Though Lyme disease is not yet common, it is becoming an important organic condition to be considered in the psychiatric differential diagnosis of a range of mental health disorders that may affect any age group.	
SH	Royal College of Psychiatrists	Short	7	18	Re: "Referral to a specialist appropriate for the person's symptoms". This will have implications for mental health services which are likely to receive referrals for patients presenting at various stages of their illness with a range of neuropsychiatric symptom or unexplained medical symptoms, which may or may not be related to Lyme disease. • There will need to be an awareness-raising campaign, and education and training for mental health professionals generally, with resource and cost implications as stated on page 32 of the short guideline. • The Royal College of Psychiatrists has an online elearning website for members' continuous professional development which could be a useful resource for developing an elearning module for Lyme disease, addressing the particular needs of psychiatrists. A free access 30 minute elearning module with basic information on Lyme disease is already hosted on the Royal College of General Practitioners elearning website and this would be a useful general resource, accessible to all mental health practitioners from all disciplines. There is a plan for this to be updated once	Thank you for this information.

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					NICE guidelines on Lyme disease are published, to ensure consistency.	
SH	Royal College of Psychiatrists	Short	8	9-10	Re: "Discuss with the person the accuracy and limitations of the different tests for diagnosing Lyme disease" • Psychiatrists would need access to further information and support in order to discuss the accuracy and limitations of Lyme serology tests, and would probably seek further specialist advice. Some mental health practitioners ie neuropsychiatrists, or those involved in assessing possible functional disorders, or who assess patients with cognitive dysfunction for any treatable causes of dementia may require enhanced education and training in this area in order to develop expertise within psychiatry.	Thank you for your comment. We agree that further education for psychiatrists may be required.
SH	Royal College of Psychiatrists	Short	9	9-19	As per comment 2	Please see our response to your previous comment.
SH	Royal College of Psychiatrists	Short	12		Re: "continuing symptoms does not necessarily mean they still have an active infection". • There is currently no test of cure or disease activity and psychiatrists are extremely cautious about foreclosing on any physical underlying conditions, especially those that are a potentially treatable cause of psychiatric symptoms. Instead, suggest rewording of this sentence, "continuing symptoms may not necessarily mean they still have an active infection", as this allows scope for further consideration of persisting infection as a possible cause of otherwise unexplained symptoms.	Thank you for your comment. The wording of the recommendation has been altered to clarify the meaning.

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SH	Royal College of Psychiatrists	Short	13	3-9	Re: 1.3.12 • Recovery following treatment, for late-diagnosed Lyme disease patients as stated can slow or incomplete, and patients may experience a range of debilitating symptoms, including fatigue and chronic pain which are often challenging to treat effectively. • They may experience secondary psychosocial problems such as an inability to work through ill-health and resulting financial hardship which may make them vulnerable to developing mental health problems. • Children may be affected in terms of their education and social development. It is this group of patients with complex issues who are very likely to be referred to mental health services and there will be a need to raise awareness of Lyme disease as discussed on page 22 of the short guideline.	Thank you for your comment.
SH	Royal College of Psychiatrists	Short	13	10	Re: Non-antibiotic management of symptoms: • The prevalence/rate of psychiatric symptoms and disorders in patients with Lyme disease has not been studied in the UK and there are only limited studies from elsewhere in Europe and the USA. This would be a useful research recommendation. • The NICE Clinical Guideline "Depression in adults with a chronic physical health problem: recognition and management" CG91 has particular relevance for patients with persistent	Thank you for your comment and providing this information. It is hoped that the research recommendation for a clinical epidemiological studies of Lyme disease in the UK will answer the prevalence/rate of psychiatric symptoms and disorders in patients with Lyme disease. It is acknowledged in the section 1.12.2 of evidence report L that some people with Lyme disease may present with related symptoms, such as chronic pain, depression or fatigue and guidance for managing these symptoms already exists.

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					symptoms related to Lyme disease, including attending to any associated suicide risk. • The cause of psychiatric symptoms related to Lyme disease is not fully understood and the best approach to treatment is uncertain. Lyme disease is known to cause inflammation in nervous tissue and this may be an appropriate target for treatment, along with assessment of the effectiveness of more conventional approaches. Psychoneuroimmunology is a key frontier in neuropsychiatry and experts and researchers in this field could be a useful group to approach regarding future research, especially regarding biomarkers and potential novel treatments.	
SH	Royal College of Psychiatrists	Short	14	18-22	Re: The list of bullet points: • It is important to add another bullet point to fully acknowledge those patients who have chronic illness following on from Lyme disease, and who do not fully recover. The medical literature on Lyme disease consistently suggests that this may be between 10-20% of patients treated, especially at a later stage. • Line 20: "Should continue to improve" may not apply to patients who do not continue to do so. Such patients may face difficulties as a result of the unrealistic expectations of others that they should be better, possibly creating significant strain in relationships, both socially and in the healthcare setting. At worst, this may result in relationship strain and generate	Thank you for your comment. We have reviewed the recommendations and recognise the issue you raise about this recommendation. This however is balanced with information for people with ongoing symptoms which recognises the ongoing nature of some symptoms and delayed recovery.

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					stigma, so it is important to reduce the risk of this. It is important for healthcare practitioners to be able to validate this particular group of vulnerable patients, who may have a range of unmet needs as a result of continuing disability.	
SH	Royal College of Psychiatrists	Short	17	Lines 7-9	Regarding the evidence: • There have been no randomised controlled trials of late-stage Lyme disease (duration longer than 6 months) in Europe. This is a major gap in the evidence base and it may not be possible to extrapolate from treatment of early Lyme disease, to late-stage disease with any confidence. It would be worth making this gap in the evidence base more explicit in the short guideline, linked to an appropriate research recommendation. The prognosis even following treatment, for late-diagnosed and Lyme disease patients as stated can be poor and patients may experience a range of debilitating symptoms, including fatigue and chronic pain which are often challenging to treat effectively. They may experience secondary psychosocial problems such as an inability to work through ill-health and resulting financial hardship which may make them vulnerable to further mental health problems.	Thank you for your comment and this information. Information on evidence identified and gaps in the evidence is detailed in the evidence reports
SH	Royal Pharmaceutical Society	General	General	General	The Royal Pharmaceutical Society welcomes the NICE guideline on Lyme disease. People commonly present to community pharmacies following bites and symptoms of rash or other symptoms of Lyme Disease. Pharmacists would be able to advise patients	Thank you.

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					and refer to a prescriber where appropriate. Pharmacists play an important role in ensuring that appropriate antibiotic prescribing occurs and support patients with adherence to antibiotic therapies.	
SH	Tick Talk Ireland	Short	General	General	Overall Tick Talk Ireland are concerned that the draft guidelines are too restrictive in the diagnosis and treatment of Lyme Disease, particularly late stage and progressive Lyme. Question 1. Why have the ILA DS guidelines for the clinical management of known tick bites, erythema migrans rashes and persistent disease not been referred to? While the draft NICE guidelines do refer to the the sparsity of evidence and research on the whole area they do not take from a wide enough range of existing research and would appear to complete ignore the research that underpins the ILADS guidelines. We believe this approach is detrimental to patient care and will lead to cases of Lyme Disease being missed, misdiagnosed, left untreated and inadequately treated.	Thank you for your comment. The NICE process is outlined in the NICE guideline development manual. Evidence reviews are conducted to answer the questions identified in the scope and informed by the guideline committee. Other guidelines are not usually used as a source of evidence.
SH	Tick Talk Ireland	Short	General	General	Question 2. In the absence of definitive research and evidence, why have you produced such definitive guidelines? Excerpt from the ILADS guidelines: 'Although Lyme disease is not rare, the treatment of Lyme disease has not attracted pharmaceutical interest and the evidence base for treating Lyme disease is best described as sparse, conflicting and	Thank you for your comment. The recommendations are worded in line with NICE methods and are not 'strong' recommendations because of the low quality of the evidence.

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					emerging. For example, Hayes and Mead of the CDC performed a systematic review of the evidence regarding the treatment of late neurologic Lyme disease and their GRADE-based evaluation rated the quality of the evidence as very low. The low quality of evidence seen in Lyme disease is consistent with the evidence base for the field as a whole. When the evidence base is of low or very low quality, guideline panels should be circumspect about making strong recommendations to avoid encouraging uniform practices that are not in the patient's best interest and to ensure that research regarding benefits and risks is not suppressed (Scott IA, Guyatt GH. Suggestions for improving guideline utility and trustworthiness. We believe that the draft NICE guidelines as presented here, are too definitive in terms of stating what the testing, diagnosis and treatment should be despite the fact that there is little research or evidence to support that approach.	
SH	Tick Talk Ireland	Short	General	General	Tick Talk Ireland is also very concerned at the overall tone of the drat NICE guidelines and language used to refer to patients with late stage and progressive lyme disease. Question 3. Why are the draft NICE guidelines so value laded and dismissive of the reality of late stage and progressive Lyme Disease?	Thank you for your comment. We disagree that the guidelines are value laden. The guideline is built around a series of systematic evidence reviews.

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					Chest 2006;129(1):174-81) when evidence is weak, the values of those on the panel, including differing specialty perspectives, may carry more weight. Evid Based Med 2013;19:41-6). One of the goals of the GRADE scheme is to make the value judgments underlying recommendations transparent Evid Based Med 2013;19:41-6). Guidelines panels should also make the role of their values and those of patients in recommendations explicit and should promote informing and empowering patients to engage in shared decision-making'. 'All national health services have an obligation not to knowingly implement policies that obstruct access to medical care for any patient group who might have a serious need for it. Given that there is a significant possibility that chronic Lyme patients are in need of medical care, clarity on this point makes it clear that organisations have an obligation not to implement any policy that would obstruct patients' access to medical care for chronic Lyme disease.' Taken from Dr.Diane O'Leary's paper presented in June 7, 2017 to the Special Rapporteur regarding Lyme disease. We believe this approach of using value judgements to underpin the draft NICE guidelines is detrimental to patient care and will lead to cases of Lyme Disease being missed, misdiagnosed, left untreated and inadequately treated. We further believe it is deeply unethical.	
SH	Tick Talk Ireland	Short	General	General	Question 4. Was the human rights dimension of withholding medical care considered when developing the draft NICE guidelines?	Thank you for your comment. Evidence was sought for antibiotic treatment of specific and non-specific symptoms associated with Lyme

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					As it is currently written it looks like people with Persistent Lyme Disease manifestations are going to be denied adequate treatment, and this is an abuse of the human rights of people with Lyme Disease given that there are international guidelines which accept the idea of persistent Lyme disease and the need for prolonged antimicrobial treatment. Taken from a report by Jenna Luche-Thayer report on issues related to Lyme Disease and Human Rights abuses of people with Lyme Disease. We believe that it is a significant human rights issue to deprive people of enough treatment when there is no real evidence to support this approach and a wealth of evidence to show that the inadequacy of treatment at an early stage leads to very significant problems in health and quality of life for people with Lyme Disease and Coinfections. See (Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology 2003;60(12):1923-30; Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001;345(2):85-92; Shadick NA, Phillips CB, Logigian EL, et al. The long-term clinical outcomes of Lyme disease. A population-based retrospective cohort study. Ann Intern Med 1994;121(8):560-7; Eikeland R, Mygland A, Herlofson K, Ljostad U. European neuroborreliosis: quality of life 30 months after treatment. Acta Neurol Scand	disease without time limit. We have not used terminology such as 'late' or 'progressive' Lyme as these terms are contested and not clearly defined. No evidence was found for prolonged courses of antibiotics. Recommendations are made for ongoing supportive care. The recommendation of prolonged courses of antibiotics without evidence would not be appropriate considering the potential harms of inappropriately treating people. We have reviewed the references to ensure that those that are relevant to the review questions were considered for inclusion.

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					2011;124(5):349-54; Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 2005;34(6):1340-5; Oksi J, Nikoskelainen J, Hiekkanen H, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. Eur J Clin Microbiol Infect Dis 2007;26(8):571-81)	
SH	Tick Talk Ireland	Short	General	General	Question 5. Where is the patient voice in the draft NICE guidelines? The draft NICE guidelines state (page 3, under Recommendations) that 'people have the right to be involved in discussion and make informed decisions about their care, as described in your care.' However there is very little evidence that patient concerns, experiences and views were taken into account when developing the draft NICE guidelines. Effective patient and public engagement leads to improvement in health service delivery and is an underpinning strategy of the NHS. Yet we see no evidence of it in the guidelines. Instead we see value laden language that undermines and side lines patient input. We would ask that patient concerns, experiences and knowledge be given greater weight in the guidelines.	Thank you for your comment. Patient groups are represented at a workshop when the scope is discussed, the written consultation on scope and consultation on draft guidelines. The guideline included an evidence review of the information needs of people with suspected, confirmed or treated Lyme disease, which formed part of the basis for the recommendations for information for patients. Lay members are also part of the guideline committee. NICE has developed guidelines on patient experience of care where recommendations are made on information, communication and decision-making.
SH	Tick Talk Ireland	Short	General	General	Question 6. Why is there no information on the treatment of confections in the draft NICE guidelines?	Thank you for your comment. The management of other tick borne infections was not in the scope of this guideline.

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					There is no mention of any coinfections in the draft NICE guidelines. It is widely recognised that the infected ticks do not just host borrelia, but also quite a number of other infections. Often the problem for the person who has Lyme Disease is the coinfections that cause treatment not to work. Some research that deals with this issue include: (Institute of Medicine (US) Committee on Lyme Disease and Other Tick-Borne Diseases: The State of the Science. In: Critical needs and gaps in understanding prevention, amelioration, and resolution of lyme and other tick-borne diseases: the short-term and long-term outcomes: workshop report. National Academies Press; Washington, DC, USA: 2011) (Costello CM, Steere AC, Pinkerton RE, Feder HM Jr. A prospective study of tick bites in an endemic area for Lyme disease. J Infect Dis 1989;159(1):136-9). We believe that the NICE guidelines must contain information on the diagnosis, treatment and management of coinfections so that patients receive the best possible care.	
SH	Tick Talk Ireland	Short	General	General	We are concerned that the draft NICE guidelines are not expansive or detailed enough. • This draft guideline appears to exclude the rich international body of peer-reviewed publications that show the Lyme Borreliosis — spirochetes similar to syphilis— are known to form biofilms and persist despite antibiotic treatment.	Thank you for your comment. NICE guidelines are not intended to provide comprehensive information about a condition. The evidence reviews are intended to answer specific questions on diagnosis and management and look for important patient outcomes. Pathophysiology and surrogate outcomes are therefore not usually included although the committee may use this background knowledge to inform the recommendations.

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					• It appears to ignore the hundreds of peer reviewed publications describe serious physical conditions caused by the infection including Lyme nephritis, hepatitis, aortic aneurysms, persistent infection, Lyme Parkinsonism, dementia, and strokes • It seems to downplay the risk of congenital Lyme borreliosis —portraying it as virtually impossible • Little recognition of the bacteria's evasion of immune response and is only superficially described without any scientific references If you do not take the full impact of Lyme Disease into account the treatment guidelines will lead to patients being misdiagnosed, going undiagnosed, being left untreated and/or treated inadequately.	
SH	Tick Talk Ireland	Short	General	General	There is no reference to blood and organ donation in the guidelines. We would like to see a recommendation that people at risk of and those diagnosed with Lyme Disease do not donate blood or organs.	Thank you for your comment. No evidence for transmission of Lyme disease through blood products was identified for the evidence review of person-to-person transmission. The UK blood and transplant service advise that in case of Lyme disease people should be healed/recovered from any infection for at least 14 days before you give blood and if taking antibiotics to wait for 7 days after last tablet.
SH	Tick Talk Ireland	Short	Page 3	Line 16, 17	We would like more information provided to put this recommendation in context and to ensure it is not misleading	Thank you for your comment. The recommendation is not phrased as absolute and not related to whether Lyme disease should or should not be suspected. The recommendation

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					"Be aware that most tick bites do not transmit Lyme Disease and that prompt removal of the tick reduces the rate of transmission" This is not absolute and should not be relied on. The guideline as written could cause GPs to underestimate the risk of lyme disease infection and to delay treatment. In addition, further information should be provided concerning the proper removal of ticks. GPs and other medical progressional should know best practice in tick removal.	has been altered following stakeholder consultation to include reference to correct removal.
SH	Tick Talk Ireland	Short	Page 4	Line 8	We would like more information provided to put this recommendation in context and to ensure it is not misleading "Diagnosis Lyme disease in people with erthema migrans……." Not every case of Lyme Disease produces a rash.There is a wealth of research to show that the rash is not present in all or even the majority of cases: Of the 51 patients studied in the outbreak of Lyme disease in the town of Old Lyme, Connecticut, "One quarter of the patients had an unusual skin lesion before the onset of joint symptoms". (http://www.ct.gov/dph/lib/dph/infectious_diseases/lyme/1976_circular_letter.pdf). Closer to home, Smith et al, (2000) state in: 'Lyme disease surveillance in England and Wales, 1986 –	Thank you for your comment. The recommendation is to diagnose Lyme disease if erythema migrans is identified but not that erythema migrans must be present to diagnose Lyme disease.

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					1998',"Erythema migrans was reported in 41% of patients". (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640888 Knudtzen et al (March 2017) analysed 431 confirmed cases of Lyme neuroborreliosis of which 37% reported a tick bite and only 20% had an Erythema Migrans rash. (https://doi.org/10.1093/cid/cix568). It is important that GPs and other medical professionals do not wait to see a rash before diagnosis and do not over associate Lyme Disease with erthema migrans creating a situation where cases of Lyme disease are missed or misdiagnosed.	
SH	Tick Talk Ireland	Short	Page 5	Line 28,29	We are very concerned about the following guideline/statement: 'Do not diagnose Lyme disease in people without symptoms, even if they have had a tick bite' What is the research basis for this statement? . Given that there is a significant amount of research about the need for very speedy treatment to avoid some of the devastating longer term consequences of disseminated persistent Lyme Disease, then we, as patients, would feel in the absence of research to show otherwise, that the preference should be to safeguard the patient by providing a treatment with antibiotics to prevent the possibility of developing Lyme Disease.	Thank you for your comment. It would not be appropriate to recommend antibiotic treatment for people who have no symptoms for prophylactic reasons unless there is good evidence of risk and the benefit of antibiotics to the individual.
SH	Tick Talk Ireland	Short	Page 6	Line 1,2	We re very concerned about the following statement/guideline:	Thank you for your comment. The guideline is not advocating a hands-off approach but including

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					'Be cautious about diagnosing Lyme disease in people without a supportive history or positive testing because of the risk of: missing an alternative diagnosis; providing inappropriate treatment." We feel that this is a misleading statement, and may prevent medical staff from beginning treatment for people with potential of Lyme Disease. As per previous point, it is better from the patients' perspective to err on the side of being aggressive in treating Lyme Disease instead of the hands off approach, especially considering the devastation that Lyme Disease causes in a person's quality of life.	the need for consideration of other possible diagnoses.
SH	Tick Talk Ireland	Short	Page 6	Line 5,6,7	We re very concerned about the following statement/guideline: 'Follow usual clinical practice to manage symptoms, for example pain relief for headaches or muscle pain, in people being assessed for Lyme disease. This statement should read, additional to treating the person for Lyme, follow usual clinical practice to …… It is essential that a two prong approach is taken to the treatment of lyme disease and its symptoms including pain.	Thank you for your comment. This section is before treatment for Lyme disease and is intended as a reminder to clinicians to provide symptoms management during the patient's assessment and diagnosis.
SH	Tick Talk Ireland	short	page 6	line 22, 23, 24	We are very concerned about this statement/guideline 'If the ELISA for Lyme disease is negative and the person still has symptoms, review their history and	Thank you for your comment. We disagree with your interpretation. The recommendations need to be interpreted together and they clearly state

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					symptoms again, and consider whether an alternative diagnosis is likely.' The assumption in this statement is that there is 100% accuracy in the testing, therefore if the test result is negative, it is more likely not to be Lyme Disease. The evidence would totally disagree with this stance. Much of the research would show that there is a very low level of accuracy in the ELISA. Some say as low as 20%, and the very best was 50%, so at best, the test is missing half of the people who actually have Lyme Disease. (Schmidt C, et al. A prospective study on the role of CXCL13 in Lyme neuroborreliosis. Neurology. 2011;76:1051–1058. doi: 10.1212/WNL.0b013e318211c39a. ; 32. Xu G, et al. Detection of heterogeneity of Borrelia burgdorferi in ixodes ticks by culture-dependent and culture-independent methods. J Clin Microbiol. 2013;51:615–617. doi: 10.1128/JCM.03009-12.; Coulter P, et al. Two-year evaluation of Borrelia burgdorferi culture and supplemental tests for definitive diagnosis of Lyme disease. J Clin Microbiol. 2005;43:5080–5084. doi: 10.1128/JCM.43.10.5080; Cerar T, et al. Validation of cultivation and PCR methods for diagnosis of Lyme neuroborreliosis. J Clin Microbiol. 2008;46:3375–3379. doi: 10.1128/JCM.00410-08) Aucott J, Morrison C, Munoz B, et al. Diagnostic challenges of early Lyme disease: lessons from a community case series. BMC Infect Dis 2009;9:79	that referral for other testing or review should be considered if Lyme is still suspected. We have reviewed the references to ensure that those that are relevant to the review questions were considered for inclusion.

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					The CDC themselves have come out recently and said that it may be necessary to retest the person four or five times to ensure that they do not have Lyme Disease. There is a lot of evidence to say that people who have Lyme are immune suppressed and as a result may not produce the antibodies expected but do have Lyme Disease. Therefore we believe this statement should say that even if a negative result occurs, that it is possible the person could have Lyme disease if all the clinical symptoms support the diagnosis.	
SH	Tick Talk Ireland	short	page 7	line 8	We are very concerned about the following statement/guideline: 'Consider treatment with antibiotics (see section 1.3) before test results become available if there is a high probability that the person has Lyme disease.' We feel that the word Consider should be removed from this sentence. It is imperative that treatment should begin straight away, and the fact that this sentence is dealing with the 'High probability that the person has Lyme Disease' then the sooner the treatment starts, the better for the patient and the increased likelihood that the person may be saved from developing persistent late stage Lyme disease.	Thank you for your comment. The wording of the recommendation is line with NICE policy where strong evidence is not available.
SH	Tick Talk Ireland	Short	page 7	line 5,6,7	We are concerned about the following statement/guideline: For people with a negative ELISA who have had symptoms for 12 weeks or more and Lyme disease is still suspected:	Thank you for your comment. This recommendation has been revised following stakeholder consultation. The repeat ELISA has been removed and the recommendation is for the immunoblot test only.

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					• repeat the ELISA and • perform an immunoblot test. • We do not see the point of repeating the ELISA – if you are going to do the Immunoblot anyway. Why not just complete an Immunoblot rather than waste valuable time?	
SH	Tick Talk Ireland	short	page 8	line 5, 6, 7	We are very concerned about the following statement/guideline: 'When tests have been done in laboratories that do not fulfil the criteria in recommendation 1.2.21, do not diagnose Lyme disease, but carry out testing again using an NHS-accredited laboratory.' There is a totally dismissive approach taken to any test which is carried out outside of the NHS. The reality is that all labs that people are having their tests completed in are all fully accredited labs, and are more likely to have even higher standards than those in the UK. Also the accuracy of the testing carried out in NHS labs is very questionable, and so this should also be stated in this statement. There is significant evidence supporting the position on the inaccuracies of testing. Furthermore, even if the test result is being ignored, the clinical symptoms should not be ignored which is what GPs tend to do when they see tests that were undertaken abroad. It is likely that the patient is experiencing many clinical symptoms which is why they are opting for the tests abroad.	Thank you for your comment. The recommendations have been amended following stakeholder consultation to emphasise the importance of clinical presentation and treatment does not need to wait for test results if there is high clinical suspicion of Lyme disease. We have also indicated that judgement about non-validated tests should take place within the context of clinical presentation.

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					The statement should say to focus on the clinical symptoms, as the test process used in the UK is so inaccurate that a safer diagnosis would be by using clinical symptoms.	
SH	Tick Talk Ireland	Short	Page 8	Line 21,22, 23, 24	We are very concerned about the following statement/guideline: 'Discuss with people who may have Lyme disease that: • the symptoms and signs associated with Lyme disease are similar to those for other conditions • symptoms such as tiredness, headache and muscle pain are common and a specific medical cause is often not found We have great concerns about this statement. Not alone would it be worrying for patients to read this, but it is also confusing for GPs. There is enough evidence about the difficulty in diagnosing LB using the standard testing, so if there is a history that supports the possibility of the person having Lyme Disease, the focus should be the clinical symptoms rather than the results of tests. This statement should say more about the idea that the person's clinical symptoms should guide the next steps in the treatment of the disease. The impact of a misdiagnosis of Lyme Disease needs to be treated with more urgency. Lyme and relapsing fever borreliosis bacteria —spirochetes similar to	Thank you for your comment. We have reviewed the wording and changed it to emphasise overlap with other conditions. The committee considered it usual clinical practice to explore symptoms with patients and consider their cause as part of differential diagnosis.

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					syphilis— are known to evade immune response and form biofilms that are difficult to eradicate. Hundreds of peer reviewed publications describe serious physical conditions caused by the Lyme borreliosis (LB) infection. They include Lyme nephritis, hepatitis, aortic aneurysms, persistent infection, strokes, dementia, and congenital Lyme disease. This statement should say more about the idea that the person's clinical symptoms should guide the next steps in the treatment of the disease.	
SH	Tick Talk Ireland	Short	Page 9	Line 13, 14	We are very concerned about this statement/guideline "For children (under 12) diagnosed with Lyme disease, offer antibiotic treatment according to their symptoms as described in table 2" . The treatment length seems to be more in line with the IDSA guidelines, which themselves have been discredited and delisted from the National Guidelines Clearing House. There is much research that would support a longer treatment of Lyme Disease, especially the persistent/stage 3 of Lyme disease. Limiting people's treatment based on very weak evidence we believe is a human rights abuse; limiting the possibility and accessibility of treatment for people who are suffering from a very debilitating disease. It also risks that people will go on to develop some of the terrible complications that can occur if the treatment of Lyme Borreliosis is inadequate at the early stage of the disease. There are two issues within this statement. The first is a recognition of 'persistent late stage Lyme' and the second is the decision that it is correct to treat	Thank you for your comment. The recommendations have been developed using NICE processes which are described in the NICE manual. Other guidelines are not used in the development of NICE guidelines unless explicitly stated. The guidelines are based on the available evidence, which does not currently provide support for long-term antibiotics.

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					persistent late stage disease with longer term antimicrobials. The treatment length seems to be more in line with the IDSA guidelines, which themselves have been discredited and delisted from the National Guidelines Clearing House. We would question why the guidelines are being used when they have been delisted.	
SH	Tick Talk Ireland	Short	Page 9	Line 18, 19	We are very concerned about this statement/guideline "If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction." A 'herx' or significant 'die-off' of the bacteria can occur at any time during treatment before the infection burden is substantially reduced. Patients receiving antibiotic treatment should be routinely provided with information about 'herxes' as they occur and manifest in Lyme, including what to do if they experience a severe worsening of symptoms.	Thank you for your comment. The wording of the recommendation has been altered to remove the emphasis on first day.
SH	Tick Talk Ireland	Short	Page 9	Line 9, 10, 11, 12	We are very concerned about this statement/guideline "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." The treatment length seems to be more in line with the IDSA guidelines, which themselves have been	Thank you for your comment. The recommendations have been developed using NICE processes which are described in the NICE manual. Other guidelines are not used in the

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					discredited and delisted from the National Guidelines Clearing House. We would question why the guidelines are being used when they have been delisted. There is much research that would support a longer treatment of Lyme Disease, especially the persistent/stage 3 of Lyme disease. Limiting people's treatment based on very weak evidence we believe is a human rights abuse; limiting the possibility and accessibility of treatment for people who are suffering from a very debilitating disease. It also risks that people will go on to develop some of the terrible complications that can occur if the treatment of Lyme Borreliosis is inadequate at the early stage of the disease. There are two issues within this statement. The first is a lack of recognition of 'persistent late stage Lyme' and the second is the decision that it is correct to treat persistent late stage disease with longer term antimicrobials. See Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology 2008;70(13): 992-1003 : Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. N Engl J Med 2001;345(2):85-92 19.: Corapi KM, White MI, Phillips CB, et al. Strategies for primary and secondary prevention of Lyme disease. Nat Clin Pract Rheumatol 2007;3(1):20-5 : Cameron	development of NICE guidelines unless explicitly stated. The guidelines are based on the available evidence, which does not currently provide support for long-term antibiotics. The guideline examined original studies to look for evidence and in terms of the studies you cite: The Fallon (2008) study has now been included in evidence review L, but the committee did not consider that the additional evidence changed the conclusions or recommendations. Klempner (2001) was already included in evidence review L. Corapi (2007) was not assessed for inclusion because it is a review rather than an original study. Cameron (2007) was not assessed for inclusion because it was not relevant to any of the review questions.

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					DJ. Consequences of treatment delay in Lyme disease. J Eval Clin Pract 2007;13(3):470-2 5: The treatment length seems to be more in line with the IDSA guidelines, which themselves have been discredited and delisted from the National Guidelines Clearing House. We would question why the guidelines are being used when they have been delisted.	
SH	Tick Talk Ireland	Short	Page 9	Line 15, 16, 17	We are very concerned about this statement/guideline "Ask women whether they might be pregnant before offering antibiotic treatment for Lyme disease (see recommendation 1.3.15 on treatment in pregnancy)." We are unsure what the purpose of this guideline is and what the impact will be on patient care. CDC factsheets state that if left untreated, Lyme disease can be dangerous to the fetes. It is essential that pregnant women obtain treatment. If there are concerns about the use of certain antibiotics, such as doxycycline, that can affect fetal development, then more information should be provided here about safe and appropriate antibiotic treatment for women at risk of and with Lyme disease who are pregnant. Furthermore, even in the absence of symptoms where it is known that a tick bite occurred both woman and baby should be monitored for an extended period as the manifestation of Lyme disease can take several months or even years.	Thank you for your comment. This recommendation is intended to ensure that pregnant women receive appropriate antibiotics for the stage of pregnancy. The recommendations specific to management of Lyme disease during and after pregnancy state that suspected Lyme disease should be managed during pregnancy in the same way as for people who are not pregnant, meaning that Lyme disease should not be diagnosed or treated in those without symptoms.

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					The treatment of pregnant women at risk of Lyme disease and with symptoms of Lyme disease requires a more tailored and detailed guideline.	
SH	Tick Talk Ireland	Short	Page 12	Line 18, 19, 20	We are very concerned about this statement/guideline "Do not routinely offer further antibiotics if a person has persisting symptoms following 2 courses of antibiotics. Consider discussion with or referral to a specialist as outlined in recommendation 1.2.19." We would like to see the research base that is used to support this stance on the management of Lyme Disease.	Thank you for your comment. The evidence used to inform this recommendation as well as the committee discussion is reported in evidence report L.
SH	Tick Talk Ireland	Short	Page 12	Line 21, 22, 23, 24, 25, 26	We are very concerned about this statement/guideline "Explain to people with persisting symptoms following antibiotic treatment that: • symptoms of Lyme disease may take months to resolve even after treatment • continuing symptoms does not necessarily mean they still have an active infection" This is one of the most worrying statements in the guideline as it gives medical professionals the right to ignore clinical symptoms that are persisting. It is ignoring the evidence around the persistent late stage LB, and there is a significant amount of evidence on this issue. It is risking that people become worse, as their medical profession advices them that ongoing	Thank you for your comment. The recommendation does not give professionals the right to ignore clinical symptoms but explains the context in which these symptoms need to be managed. The recommendation is a consensus recommendation informed by experience of the committee and their knowledge of Lyme disease.

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					symptoms are normal and will wear themselves out, as many of us have been told to our total detriment. We would like to see the research base that is used to support this stance on the management of Lyme Disease.	
SH	Tick Talk Ireland	Short	Page 13	13, 14, 15, 16, 17, 18, 19	We are deeply concerned about the following statement/guideline: "Be alert to the possibility of symptoms related to Lyme disease that may need assessment and management, including: * depression and anxiety * chronic pain * sleep disturbances * fatigue" We would question why the guidelines lead with depression and anxiety rather than the more common symptoms of chronic pain and fatigue. We would also question why other common symptoms such as cognitive decline and neurological difficulties are not included. There is a value laden and dismissive tone to much of the guidelines, including this section which could impact negatively on patient care and create difficulties for patient and GP alike. We would like to see the guidelines "proofed" for value judegement.	Thank you for your comment. The symptoms are not listed in order of prevalence, nor is the list intended to be exhaustive. This recommendation is intended to encourage clinicians to consider assessment and management of the symptoms as well as the infection.
SH	Tick Talk Ireland	Short	Page 14	Line 5, 6, 7	We are very concerned about this statement/guideline	Thank you for your comment. The evidence used to inform this recommendation as well as the

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					"Inform 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." There is significant evidence that would disagree with this position. We would like to see the evidence that supports the position stated here. Can they definitely state this? How do they explain the fact that there can be seroprevalance in bloods, so how does this prevent being transferred to the foetus? It would be very interesting to see more evidence for this and to have the full range of available research taken into account.	committee discussion is reported in evidence report M.
SH	Tick Talk Ireland	Short	Page 15	Line 8	Recommendations for Research We would like to see this section expanded. The guidelines acknowledge that there is an absence of research on the prevalence of Lyme Disease in the UK and we would like to see more weight given to this section of the guidelines. The guidelines use vague language in significant parts of the guidelines. For example saying 'most people recover' where there is no evidence to support this statement. Where there is no clear research and evidence we would like to see research recommendations for same. We would also like to see recommendations for research into the patient experience of living with Lyme	Thank you for your comment. The guideline is unable to make research recommendations in areas that were not systematically examined in the guideline. The committee is aware that the department of health have commissioned work in the areas you outline. These are available here http://eppi.ioe.ac.uk/cms/

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					disease, of their experience interacting with medical professionals, and research to track recovery of patients with Lyme Disease particularly persistent Lyme disease.	
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short			As doxycycline is not recommended and yet HGA may be a differential diagnosis then should not HGA be tested for (incuding haematology and cytology of blood cells for morulae). If a validated PCR test is not available and it's too early for an antibody test then shouldn't risks be discussed with the patient. This scenario also applies to children aged under 12	Thank you for your comment. The committee considered that risks should be discussed with the patient and parent or carer when doxycycline is considered or any other drug outside its licence.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	1	text box – end of paragraph one	*'It does not cover preventing Lyme disease'* - Addressing prevention is as important as treatment. Every prevented case not only avoids illness but avoids an awkward and potentially distracting diagnosis? What advice does NICE suggest that healthcare professionals provide on prevention when requested by concerned families?	Thank you for your comment. Prevention is outside the scope of this guideline. Cross – reference has been made to sources of information such as NHS choices where this is covered.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	3	1 text box – first sentence	*'People have the right to be involved in discussions and make informed decisions about their care, as described in your care.'* – this must be viewed and maintained as core principle.	Thank you.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	3	5	Replace the word '*ticks'* with: In areas where ticks occur, they . . .	Thank you for your comment. The wording was reviewed and changing as you suggest was judged to make the recommendation more complicated than necessary.

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SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	3	17	Define what is meant by '*prompt'* and does it apply universally to all active tick stages and sources?	Thank you for your comment. The wording of the recommendation was changed and the term 'correct' has been added. The committee considered the wording self-evident and in line with the advice in the next recommendation on how on when tick exposure may occur and checking for ticks.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	3	18	No mention is made of attached or unattached ticks found on pets, livestock and wild animals	Thank you for your comment. This was outside the scope of the guideline.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	4	6	Diagnosis should always involve consideration of differentials. Consideration of Lyme disease suggests a history of an actual or possible tick bite and so other tick-borne diseases should be considered, especially those that can mimic signs and symptoms of Lyme disease such as Rickettsias and Anaplasma. Unavailability of specific tests for such agents or that such differentials have been described in the UK yet should not stop all clinicians considering them as differentials and using general, clinical pathology tests (such as checking for a thrombocytopenia in HGA) Awareness of other zoonotic tick-borne diseases enzootic to an area can be sourced from local veterinary practices	Thank you for your comment. Whilst the committee agreed that other tick-borne diseases should be considered as differential diagnoses, specific information on tests and management is outside the scope of the guideline.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	5	17	(usually marked swelling but relatively unpainful, and non-erosive)	Thank you for your comment. We try to make the recommendations as concise as possible without losing any information. This detail such as whether the arthritis is erosive would only be apparent following investigation and is not appropriate to this recommendation.

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SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	5	17	(usually large joint(s) and in particularly the stifle)	Thank you for your comment. We try to make the recommendations as concise as possible without losing any information; therefore, we did not elaborate on the current description of inflammatory arthritis.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	5	24	'*uncommon*' is too vague an adjective; can this be more usefully correlated with the incidence of erythema migrans being seen within a practice area thereby creating an expected incidence of non-EM syndromes for each practice?	Thank you for your comment. Your suggestion warrants further study but to our knowledge the current epidemiological evidence would not allow more precise predictions of numbers at this time.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	5	24	and in particular, those people handling dead animals (eg abattoir workers, deer stalkers, pest controllers and vets and their staff) that are subject to detaching 'unreplete' ticks (including larvae) capable of immediate (and high level) inoculation of Borrelia	Thank you for your comment. We try to make the recommendations as concise as possible without losing any information; therefore, we did not elaborate on the types of activities. In addition, we aim to be inclusive and did not want to miss any activity where there is a possibility for a tick bite.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	5	12 – 20	these syndromes do not show equal 'uncommonness'. and may vary geographically because of different species of Borrelia Clinicians should be made aware of different trophisms resulting from different Borrelia species that can, in turn, emanate from bites from different species of ticks especially sheep (rural) versus hedgehog (peri-urban) ticks.	Thank you for your comment and this information. The committee felt that a 'consider' recommendation was appropriate given the varying degrees of these symptoms.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	6	14 & 15	il the clinician is confident to do so. Otherwise laboratory tests could include skin scrapes, woods lamp to rule out other differentials and biopsy to rule in/out Borrelia on culture or PCR.	Thank you for your comment and these suggestions.

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SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	7	21	Detection of Borrelia in synovial fluid is insensitive compared to joint capsule - this should be pointed out.	Thank you for your comment. This is included in evidence review C.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	7	22	. . . or PCR on the removed tick(s) that the patient had the presence of mind to store.	Thank you for this suggestion.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	7	24 to 26	. . . but positive serology without Lyme disease nevertheless confirms that tick-borne infection took place so be aware of disease from other tick-borne infections.	Thank you for your comment. Following stakeholder comments, this recommendation has been removed from the guidance.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	8	13	This line should read '*and that the* INTERPRETATION OF THE *accuracy* of blood tests may be reduced if: . . .'	Thank you for your comment. The wording of the recommendations was reviewed and we have added further detail. However, we do mean the accuracy and limitations of the tests.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	8	22	List these conditions.	Thank you for your comment. The wording has been changed to indicate the issue is overlap with other conditions. The committee considered the specific examples would depend on clinical presentation and any list would not be meaningful.
SH	Uist deer management Lyme and other	Short	9	19	Is the incidence or severity of Jarisch-Herxheimer different between cidal (amoxicillin) and static (doxycycline) antibiotics?	Thank you for your comment. This was not examined in the guideline but is an interesting question.

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	tick-borne disease subgroup					
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	10	Table 1	Give dose rates per Kg bodyweight (e.g.Doxycycline at 2-5mg/kg for 50kg bodyweight, dose = 100-250mg and for 150kg bodyweight, dose = 300-600mg).	Thank you for your comment. The information has been changed to include weight cut offs.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	12	10	or Lyme disease immune-mediated disease	Thank you for your comment. Autoimmunity related to Lyme is a possible mechanism of action and it is unclear how including it here would help
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	14	4	and breast feeding?	Thank you for your comment. Healthcare professionals are expected to prescribe taking into account the individual patient and adding further circumstances was not considered helpful by the committee.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	15	1 & 2	*'and not to stop their antibiotic treatment'* - Are you not assuming this is definitely a Jarisch Herxheimer reaction? It would be more prudent to contact their doctor prior to taking their next due dose	Thank you for your comment. The recommendation does say they should contact their doctor.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	15	5	replace '*does not'* with - may not	Thank you for your comment. The committee reviewed the recommendation following consultation and decided not to make this change.

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SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	15	8	Priority should be given to assessing the role of Anaplasmosis' well recognised immuno-suppression and, therefore, its potential for worsening the course and severity of Lyme disease. In particuar to investigate the disparity between the serological prevalence of infection and disease incidence in Europe. The geographically heterogenous strains of Anaplasma of different pathogenicity would make any UK-wide standard advice unsafe.	Thank you for your comment and this suggestion. Anaplasmosis was in the guideline scope. The committee understand it is relatively rare in the UK. A research recommendation in this area is therefore not appropriate in this guideline.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	16	17	Should not population seroprevalence studies be carried out in sentinel animals?	Thank you for your comment. This area is outside the scope of a clinical guideline.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	16	31	Many patients are also concerned about other tick-borne infections occurring alone without concomitant Borrelia infection Why are other tick-borne infections only viewed as co-infections? This is especially so with Anaplasma which is usually at a higher prevalence in ticks than Borrelia and may involve an earlier innoculation after tick attachment.	Thank you for your comment. The guideline is a Lyme disease guideline hence the term co-infection.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	16	18 & 19	This list mixes tick-borne diseases such as babesiosis and anaplasmosis and perhaps bartonellosis with tick-related diseases such as Q fever while not mentioning agents such as louping ill virus and chlamydia. In addition, surveillance for continental tick-borne agents such as tick-borne encephlitis or tuleraemia should be prioritised along with potential disease agents present in the UK but not tested for such as Rickettsia helvetica, R raoulti, R. massiliae and Borrelia miyamotoi.	Thank you for your comment. The research recommendation has been re-worded removing the examples which were misleading.

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					All ticks submitted from pet animals that must have been attached at the time of their entrance into the UK should be checked as a routine by Public health England for all potential tick-borne agents Is Ehrlichiosis endemic or enzootic anywhere in the UK?	
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	17	1	Until studies determine this, should you not be following the precautionary principle and discuss with the patient?	Thank you for your comment. The need to discuss with the patient would depend on clinical circumstances.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	17	7 to 9	And so on what are you basing the recommended drug protocols that are listed in tables 1 & 2 above on?	Thank you for your comment. The current recommendations are based on best evidence currently available and guideline committee consensus.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	17	14 to 18	This paragraph confirms our previous comment (29).	Thank you.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	19	22 - 25	The general public should be encouraged to store (in their deep freeze) any attached ticks they remove along with written details such as time and place. This would allow subsequent testing of the tick(s) in the event of any subsequent suspect symptoms. This is standard practice in many parts of America	Thank you for this information.

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SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	19	13	Insert 'in some regions of the UK' after '*uncommon'.*	Thank you for your comment. We have removed this phrase as it was unhelpful.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	19	20	PCR on biopsy of EM may be appropriate for some clinicians and PCR on fine needle aspirates of EM should be trialed.	Thank you for this information. This section is about clinical diagnosis so reference to PCR is not appropriate.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	19	6, 7 & 8	Insert. 'or any of the other tick-borne diseases' between lines 6 and 7 and 'or any of the other tick-borne diseases after '*disease,*' on line 8.	Thank you for your comment. The guideline topic is Lyme disease and it is not appropriate to mention other tick borne diseases here.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	20	2	and EM should be viewed as a robust, highly specific diagnosis and be recorded as such in the patient's medical record	Thank you for your comment. This section is explaining the rationale for the recommendations.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	23	5	This comment also applies to notes on use in other syndromes below: Doxycycline is advised as first line treatment in non pregnant people aged over 12 for its apparent clinical effectiveness. However doxycycline's immunomodulatory action, that occurs at a lower dose rate than its antimicrobial action, may 'cure' symptoms of Lyme disease while not producing a bacterial cure. In addition if doxycycline is indeed being used sub-optimally in some individuals then resistant strains of	Thank you for your comment. The rationale for use of doxycycline is described in the rationale and the evidence reports. The effect on other tick borne infections was not considered.

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					Borrelia may develop in those individuals. Although such resistance will not be passed on to other humans, it is not inconceivable that latent, resistant strains could recrudesce with subsequent ineffective treatment endangering that particular individual. If use of doxycycline is preferred because penicillins are ineffective against tick-borne pathogens such as Anaplasma phagocytophila and Rickettsia helvetica then this 'pragmatic' use should be stated in these guidelines. This would then raise the need to the clincian to consider and discuss an informed testing and treatment protocol with those patients where doxycycline is contraindicated.	
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	24	17	see previous comment (36) on doxycycline.	Thank you for your comment. We have answered in comment 642.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	28	29	and by another genospecies or even a different strain of the same genospecies.	Thank you for your comment and suggestion. This section is intended as an overview of the evidence and discussion in the evidence report. This addition did not seem to add helpful information and was an area discussed by the committee.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	33	20	Ticks can survive in short (not overgrown) vegetation mats that are able to supply (and on the Uists can) the 85% relative humidity that the sheep ticks require.	Thank you for your comment. We have removed the term 'overgrown'.

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SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	33	19 & 20	unless from a detaching, unreplete infected tick, including larvae, when infection can begin immediately.	Thank you for this information.
SH	Uist deer management Lyme and other tick-borne disease subgroup	Short	33	21 & 22	As are family members who may not frequent tick areas but nevertheless are likely to handle the clothes of those that do.	Thank you for this information.
SH	VIRAS	Short	General	General	Abbreviations used in the comments: A&E: Accident and Emergency hospital department BIA: British Infection Association CBT: Cognitive Behavioural Therapy CDC: Centres for Disease Control and Prevention (USA) CFS: Chronic Fatigue Syndrome ELISA: Enzyme-linked immunosorbent assay EM (rash): Erythema Migrans GDC: Guideline Development Committee GDG: Guideline Development Group GP: General Practitioner (physician) HPA: Health Protection Agency – now part of PHE HSE: Health and Safety Executive IDSA: Infectious Disease Society of America M.E.: Myalgic Encephalomyelitis MTBC: Mycobacterium tuberculosis NIH: National Institute for Health PCR: polymerase chain-reaction PHE: Public Health England REC: Research Ethics Committee	Thank you.

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					RIPL: Rare and Imported Pathogens Laboratory (Lyme reference laboratory for England) TB: Tuberculosis	
SH	VIRAS	Short	General	General	MAJOR OMISSIONS OF THE NICE DRAFT GUIDELINE 1/ Blood Donation The Short Draft omits to inform doctors that patients should not donate blood or organs. M.E. and CFS are the most probable and common missed and misdiagnoses of Lyme disease – especially chronic Lyme. Patients with M.E. and CFS diagnoses are banned for life from being blood donors in the UK since 1st November 2010 (http://www.bbc.co.uk/news/health-11465723). The Department of Health Advisory Committee on the Microbiological Safety of Blood and Tissues for Transplantation MSBT (http://webarchive.natonalarchives.gov.uk/20031201101311/http://www.doh.gov.uk:80/msbt/msbt.pdf) Defines the Lyme bacterium as: "Unusual bacterial / fungal / and protozoal infections" "Infections which lie dormant or are difficult to eradicate (e.g. Brucellosis, Lyme disease, Typhoid)" And in section: "Did the donor have a past history of an infection which might transmit to and reactivate in the recipient?" Question: "Has the donor had Lyme disease (Borrelia), brucellosis, or tuberculosis?" The CDC state:	Thank you for your comment. (1) The UK blood and transplant service advise that in case of Lyme disease people should be healed/recovered from any infection for at least 14 days before giving blood and if taking antibiotics to wait for 7 days after last tablet. No evidence was identified for transmission through blood products or sexual transmission.

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					"Although no cases of Lyme disease have been linked to blood transfusion, scientists have found that the Lyme disease bacteria can live in blood from a person with an active infection that is stored for donation. Individuals being treated for Lyme disease with an antibiotic should not donate blood." The World Health Organisation. Guidelines on Assessing Donor Suitability for Blood Donation. 2012. Recommend that blood donors who have had Lyme disease: "Defer for 28 days following full recovery and completion of treatment, whichever is longer". VIRAS await with interest to learn how NICE will define 'full recovery' from Lyme disease, especially as the tests it recommends do not detect the infection, but only antibodies which are known to decline over time regardless of infection status. If a recipient gets a lot of antibodies from donor blood, that might not do them any harm, but if they also get a dose of dormant borrelia cells, it might not be good for them. NICE have had ample warnings about borrelia persisting beyond so-called 'adequate treatment' by dormant and other resistant forms of borrelia. If they fail to provide adequate information about the risk of transmission by tissue donation, the blood will – so to speak, be on their hands. 2/ Exclusion of cases that the UK health authorities have failed to detect over decades of mismanagement of Lyme disease	(2) The guideline acknowledges that the true incidence of Lyme disease is not known and includes an evidence review to collect available published data. Research recommendations are also made to improve both clinical epidemiology and knowledge of sero-prevalence. Surveillance programmes may also be required to improve reporting but this is outside the remit of a clinical guideline.

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					In the USA since the turn of the century around 17 to 30 thousand cases per year of Lyme disease have been officially recorded, with many of these 'official' cases concentrated in a small number of states. The CDC have admitted that the true USA incidence is probably 10 to 12 times higher than these figures, in a country where doctors and the public are much more aware of Lyme than in the UK. It is ridiculous for the HPA and PHE to claim that the true UK incidence is only 2 to 3 times higher than reported cases (see http://counsellingme.com/VIRAS/UKLymeIncidence2.pdf). Therefore it is logical to conclude that for decades the UK has been accumulating many thousands of undiagnosed and untreated patients per year who are infected with Lyme disease. An unknown proportion of these patients will have gone on to become chronically and severely ill and many of these will have been misdiagnosed with M.E or CFS which have very similar complex and varied symptom profiles (see (http://counsellingme.com/VIRAS/IsabelSymptomCheckerSurvey.PDF). Substantial evidence for this was provided in the VIRAS comments on the draft Scope for these guidelines (see http://counsellingme.com/VIRAS/NICE/consultationcommentsandresponses.pdf) Omitting to address this major health problem of overlooked and untreated Lyme disease in the UK is inexcusable. Excluding consideration of the most likely misdiagnoses of unrecognised Lyme disease is at best, negligent and constitutes discrimination against Lyme patients injured due to PHE policies. These patients are not only marginalised by these guidelines, but have been actively discriminated against, which	(3) Thank you for this information.

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					might reasonably be interpreted as evasion of accountability. 3/ Common Lyme disease co-infections, opportunistic infection Ozcaglar et al (2012) state: *"Co-infection:* Co-infection is the infection of a host by at least two different types of pathogens. TB and HIV dynamics have a correlation, as HIV weakens the immune system of the host, which creates a proper medium for MTBC to infect the host. Therefore, in areas with high HIV prevalence, TB is one of the main causes of death." (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3330831/ doi: 10.1016/j.mbs.2012.02.003) A tick bite carries the risk of transmitting at least 10 serious infections to humans. Some doctors in the USA are finding that treatment of Lyme disease is hampered by coinfections and recommend that these must also be addressed in Lyme disease patients (see (https://www.nytimes.com/roomfordebate/2013/08/11/deconstructing-lyme-disease/to-treat-lyme-disease-focus-on-the-co-infections). Nicolson remarks "Lyme Disease patients are at risk for a variety of opportunistic infections, including other bacterial infections, viral and fungal infections. These can complicate diagnosis and treatment, but they may be principally a problem in the late persistent phase of the disease. Late stage patients with neurological manifestations, meningitis, encephalitis, peripheral neuropathy and other signs and symptoms may have	(4) Clinical guidelines are primarily concerned with diagnosis and management and not on underlying pathophysiology. The guideline therefore looked for evidence of effectiveness of interventions for patient symptoms and not at underlying mechanism.

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					complicated co-infections that are neither recognized nor treated by their physicians." (see http://www.prohealth.com/library/showarticle.cfm?libid=8026) 4/ Immune Suppression Singh and Girschick (2004) state: "Long-term exposure of the host immune system to spirochaetes and/or borrelial compounds may induce chronic autoimmune disease. The study of bacterium-host interactions has revealed a variety of proinflammatory and also immunomodulatory-immunosuppressive features caused by the pathogen." (see http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(14)62887-1/fulltext DOI: 10.1111/j.1469-0691.2004.00895.x) The compounding and confounding factors in 3 and 4 above are routinely anticipated by experienced Lyme treating doctors, and should as a bare minimum be described within a credible guideline for Lyme disease. Their omission appears to be a non-medical and non-scientific attempt at simplifying a complex disease and will result in foreseeable harms to patients, and sustained harm to the patients that PHE havalready failed.	
SH	VIRAS	Short	General		It is notable that in the past 16 years the Medical Research Council has not allocated funding for a single study into Lyme disease. In the past 16 years, of the 7 billion pounds allocated to around 20,000 research projects of medically related research by the Wellcome Trust, only 2 projects were vaguely relevant	Thank you for this information. The research recommendations arise from the evidence reviews. There is a process for research recommendations from NICE guidance to be highlighted to national funding bodies.

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					to Lyme disease patients and doctors. One was a study of pathogens found in ticks in Europe led by the late Professor Klaus Kurtenbach which included investigation of borrelia species in ticks in the UK. The second was a study of borrelia spirochaetes in ticks in the Baltic region of Europe, led by Dr Sarah Randolph. The Cochrane library list one systematic review of Lyme disease treatment, relating to treatment of neurological complications but not focussed on the UK. The National Institute for Health Research (NIHR) list no projects for Lyme disease. However, the University of Liverpool is getting some funding from NIHR for Health Protection Research and indicate that zoonoses including Lyme: "will explore new ways of detecting and characterising pathogens". This is a drop in the ocean and cannot be expected to translate into benefit for patients or doctors in the foreseeable future. Where do NICE imagine that the millions of pounds needed to make their research recommendations a reality, are going to come from?	
SH	VIRAS	Short	General	General	At first glance the Research Recommendations appear encouraging. Further evaluation suggests that they are disingenuous. NICE do not conduct or fund research and neither they nor anyone else will never have to deliver on their recommendations. The gaping holes in Lyme research for UK patients have remained exactly the same for 30 years and in all that time the need for research has gone unanswered. PHE have been telling doctors and patients for years that the UK is different from the USA and the rest of Europe. That Lyme is different here and that is why France and Holland record >10 times as many cases. Yet they are	Thank you for this information. The research recommendations arise from the evidence reviews. There is a process for research recommendations from NICE guidance to be highlighted to national funding bodies.

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					prepared to import tests, diagnostic criteria and treatment protocols from all and sundry without a shred of UK research to show whether these are applicable – even after telling us that they are not. The repeated calls for "Priority" research are empty in the context of the whole draft guideline. The contents of the draft contradict the stated objectives of these 'priorities'.	
SH	VIRAS	Short	General	General	CONCLUSION TO THE VIRAS STAKEHOLDER COMMENTS In view of the extraordinary number of opportunities that these NICE guidelines provide for putting doctors and patients at serious risk, it is essential for all interested parties to be aware that NICE take no responsibility for any misleading information or dangerous advice included in their guidelines. Here is a typical NICE Guidance disclaimer: "Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidances. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources. The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guidance and the literature used in support of this guidance."	Thank you for your comment. Advice to healthcare professionals is included in all guidance on the NICE website, which indicates that healthcare professionals need to consider their individual patient when using a guideline. The recommendations in the guideline are based on the best available evidence and provide a framework for current care. The committee agree that further research is required and hope that updates of the guideline will be informed by a stronger evidence base. Following stakeholder consultation, further recommendations have been added to clarify the need for clinical assessment and judgement and of the limitations of testing. Full details of the NICE methods for developing guidelines can be accessed via the NICE website

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					(https://www.nice.org.uk/guidance/cg138/evidence/full-guideline-pdf-185142637) Whilst NICE have discarded a wealth of research and evidence as unsuitable in preparing their guidance, that same evidence may nevertheless stand-up in court. Examples of foreseeable harms to patients are: if and when the restrictive treatment recommendations fail to eradicate a Lyme infection and a patient suffers injury as a result, or, if and when laboratory testing deprives a patient of a necessary diagnosis and treatment, and they suffer injury as a result. Then the evidence that has been ignored may receive a fair hearing in legal proceedings, especially as much of this information comes from very experienced scientists and physicians. Harms to patients and complaints against doctors are not just predictable, they are inevitable if doctors with Lyme disease patients follow the advice as presented in the draft form. However, none of this is any consolation to doctors who do not want to spend their time dealing with GMC complaints and law suits, but who simply want to help their patients based on a balanced presentation of the available pool of knowledge. VIRAS and others have provided ample evidence of foreseeable harms resulting from misleading advice about Lyme disease. NICE may wash their hands of any responsibility by claiming that individual doctors are responsible for their clinical decisions, but they can and will be held to account for negligently misleading the public and government agencies, discriminating against sick and disabled patients, and permitting their	https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-guidelines

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					procedures to be exploited by groups and individuals with competing interests. Doctors do not have to follow NICE guidelines but they must be able to justify their clinical decisions. The USA Centers for Disease Control and Prevention (CDC) now estimate that they have over 300,000 cases of Lyme disease per year. Some of the most experienced and knowledgeable Lyme disease doctors and scientists in the USA have produced reliable and trustworthy advice on the management of diverse aspects of Lyme disease. For doctors who want a thorough understanding of Lyme disease medicine, including the limitations of current knowledge, VIRAS recommends the authoritative resources listed here: http://www.ilads.org/lyme/treatment-guideline.php. VIRAS reject the NICE draft guideline as unfit for purpose. It contains some downright dangerous advice and too many contradictions to even form the basis of a semi-reasonable guideline. It is biased, discriminatory and appears to be designed to serve undeclared agendas. It implies certainty where there is none. Where it admits uncertainty it omits to provide balanced views to allow doctor's and patients to make informed choices or permit informed consent. This makes the draft unethical. It evades awkward and potentially embarrassing issues such as the inaccuracy of testing provided by the NHS, which it misrepresents with false assurances. The guideline is neither quantitative or qualitative or a rational amalgam of both. It is bereft of scientific discipline or basic humanistic and medical values.	

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					NICE should have halted the process and rejected the task of producing a guideline when it became apparent that the vast majority of research did not meet the threshold for inclusion. Instead, it has produced a draft based on just a tiny and biased proportion of decades of research. The draft guideline is irrelevant to 99% of UK Lyme patients who would be harmed by its publication. The number and nature of the Research Recommendations clearly shows that not enough is known to produce a guideline that could remotely approach the required standards for a NICE Guidance. These Research Recommendations relate to absolutely basic medical science concerned with the diagnosis, treatment and management of Lyme disease. Without good data to work with, or a balanced presentation of the evidence available, the end product could only ever be a self-contradictory and impractical mess. Thousands of UK Lyme disease patients have been obliged to take matters into their own hands due to the ignorance and incompetence of Public Health England. PHE (incorporating the HPA) have actively obstructed the diagnosis and treatment of Lyme disease patients for decades. The victims of this discrimination have been forced to either accept terrible illness which for many, represents a life-sentence of loss and suffering, or to seek medical help elsewhere. Patients spend their often meagre income and all their savings to get accurate tests and treatment that have been denied to them by the NHS. The outcome of the treatment that they are forced to pay for, may not always be the cure	

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					that they sought. This is partly due to the incompetence that has delayed their diagnosis and treatment for months, years or even decades. Yet for many, their treatment brings great relief. Some of the appalling chronic symptoms improve or resolve completely. Physical and mental functioning which could have been reduced to just a tiny percentage of their pre-Lyme infection levels, are substantially improved and can be maintained with treatment. These patients KNOW what PHE policies have done to them and are doing to others. They will recognise the PHE official position on Lyme disease permeating the NICE draft guideline. They are not paranoid or conspiracy-theorists, they know from their own lived experience that Lyme disease is a national health threat that is being controlled by vested interests that disregard their Human Rights and the most basic tenets for the practice of medicine. It is in spite of PHE that many of these patients have improved health, and such is the suffering that many have endured, they do not want others to have a similar experience. With the finest motives that grace humanity, even though their health and fitness may still be just a sad remnant of the energy they once enjoyed, they give of that time and energy to help others who will otherwise be doomed by PHE to the living hell of chronic Lyme disease. The draft guideline shames UK medicine and will bring the good names of the NHS and NICE into disrepute. The danger to patients is obvious. This confused and confusing guide will predictably harm patients and threaten the reputation and values of doctors who place their trust in it.	

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SH	VIRAS	Short	3	4	"Lyme disease is transmitted by the bite of an infected tick" Should read 'Lyme disease can be caught by the bite of an infected tick' since the infection has been identified in biting flies and mosquitoes. The bacteria has been detected in human semen and vaginal secretions and therefore could be transmitted through sexual intercourse. Trans-placental transmission is documented. Furthermore, it is not known if 'an infected tick' will definitely transmit the infection. We are not aware of any research into what percentage of infected ticks transmit infection with a bite. The latter might seem overly pernickety, but the question is, do NICE want to make accurate statements or not?	Thank you for this suggestion. The wording of the recommendation has been changed to 'the bacteria that causes Lyme are transmitted by the bite of an infected tick'.
SH	VIRAS	Short	3	8	"infected ticks are found throughout the UK and Ireland" is quite sufficient. The remainder of the sentence is just likely to confuse. More ticks probably means more infected ticks, but it might not. Do NICE really want to burden doctor's memories with this when there is so much they need to remember?	Thank you for your comment. The committee sought to strike a balance between raising awareness that people anywhere may have Lyme disease either because of a tick bite sustained locally or when travelling; and that there are areas of higher risk.
SH	VIRAS	Short	3	12	"but infection can occur in many areas" unnecessary after stating that infected ticks are found 'throughout the UK and Ireland'.	Thank you for your comment. The committee wished to emphasise this point in the recommendation.
SH	VIRAS	Short	3	13	This statement about prevalence seems superfluous especially as there is no proof that Lyme disease is any more prevalent in these places than in the UK which has no accurate prevalence data	Thank you for your comment. The committee considered it unhelpful not to acknowledge both that there are areas of apparent higher prevalence and the incompleteness of the data.

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SH	VIRAS	Short	3	18	"Give people advice about:" There is some good advice here, but it hardly seems that it would be the role of a doctor to know and give advice about some of these. It seems rather like a doctor telling their patients who are cyclists to wear a helmet and test their brakes before setting off. Weird.	Thank you for your comment. The committee wished to include information about preventative measures for people who have consulted healthcare professionals about Lyme and to indicate sources of information such as NHS choices.
SH	VIRAS	Short	4	1	"insect repellents" It has not been demonstrated that insect repellents provide protection (we believe it has been shown that they do not guarantee protection) – if advice like this is going to be given it needs qualification if it is to be reliable. A false sense of security could increase the risk to the public.	Thank you for your comment. The recommendation now says to use a repellent that repels ticks.
SH	VIRAS	Short	4	8	"Diagnose Lyme disease in people with erythema migrans, that is:" Add to this list or make it absolutely clear elsewhere, that an Erythema Migrans rash is an uncommon presenting symptom. E.g., occurring in only one fifth to one quarter of patients. Doctors must be informed that the majority of Lyme disease cases will have to be diagnosed without any visible signs. Smith et al, (2000) state in: 'Lyme disease surveillance in England and Wales, 1986 – 1998', "Erythema migrans was reported in 41% of patients". (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2640888/ doi: 10.3201/eid0604.000416) Knudtzen et al (March 2017) analysed 431 confirmed cases of Lyme neuroborreliosis of which 37% reported	Thank you for your comment. The recommendation is to diagnose Lyme disease if erythema migrans is identified but not that erythema migrans must be present to diagnose Lyme disease. The rationale for the recommendation does state that EM is not always present.

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					a tick bite and only 20% had an Erythema Migrans rash. (https://doi.org/10.1093/cid/cix568) Of the 51 patients studied in the outbreak of Lyme disease in the town of Old Lyme, Connecticut, "One quarter of the patients had an unusual skin lesion before the onset of joint symptoms". (http://www.ct.gov/dph/lib/dph/infectious_diseases/lyme/1976_circular_letter.pdf). As a discrete event representing an 'outbreak' which was studied by the CDC, the latter was completely objective. This is very important statistical evidence and represents data from a real-world 'experiment' that is unlikely to be replicated. Virtually all epidemiological data following this event has been skewed by the recognition of an EM rash as not only indicative of Lyme, but often the only sign. Knudtzen et al (March 2017) analysed 431 confirmed cases of Lyme neuroborreliosis of which 37% reported a tick bite and only 20% had an Erythema Migrans rash. (https://doi.org/10.1093/cid/cix568) Of the 51 patients studied in the outbreak of Lyme disease in the town of Old Lyme, Connecticut, "One quarter of the patients had an unusual skin lesion before the onset of joint symptoms". (http://www.ct.gov/dph/lib/dph/infectious_diseases/lyme/1976_circular_letter.pdf). Failure to make it explicit that most cases will not report an EM rash will predictably put patients at risk of	

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					not being diagnosed and treated.	
SH	VIRAS	Short	4	15	Add to this section: An EM rash may be atypical, almost unnoticeable (faint) and may be less noticeable on dark coloured skin.	Thank you for your comment. The committee have agreed a number of images of typical and atypical EM to accompany the guideline, as providing images was considered clearer than attempting descriptions of these.
SH	VIRAS	Short	4	22	This list is rather limited and is probably not much help to doctors without more information to trigger a suspicion of Lyme. Suspecting Lyme in the absence of an EM rash and/or absence of a reported tick bite – especially in 'non-hotspot' areas (where both patient and doctor could be unfamiliar with Lyme), could rely upon a doctor's intuition if patients are going to be investigated and treated promptly. Therefore symptoms that the patient has no previous experience of, which might be noted by the doctor or patient, as odd or unexpected could be very informative. VIRAS recommend that doctors working in the USA and Germany should be consulted on how to question a patient if suspicions of Lyme are aroused. Doctors in those countries are far more experienced than any UK doctors. E.g. the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire (HMQ) when tested it was found: "The results consistently demonstrated that the HMQ accurately differentiated those with Lyme disease from healthy individuals. Three migratory pain survey items (persistent muscular pain, arthritic pain, and nerve pain/paresthesias) robustly identified individuals with verified Lyme disease. The results support the use of	Thank you for your comment and this information. The recommendations are intended to be taken together such that the clinical presentations and possible exposure to ticks are reviewed together. The study you cite is interesting but would require validation in a larger UK population and needs to differentiate people with other disease from people with Lyme disease before it could be considered useful. The committee hope that the guideline will increase awareness of Lyme disease.

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					the HMQ as a valid, efficient, and low-cost screening tool for medical practitioners to decide if additional testing is warranted to distinguish between Lyme disease and other illnesses." (https://www.dovepress.com/empirical-validation-of-the-horowitz-multiple-systemic-infectious-dise-peer-reviewed-fulltext-article-IJGM DOI https://doi.org/10.2147/IJGM.S140224)	
SH	VIRAS	Short	5	9 - 20	"Consider the possibility of Lyme disease in people presenting with". Add to this list: Cerebral vasculitis (https://www.ncbi.nlm.nih.gov/pubmed/?term=cerebral+vasculitis+borreliosis) Ischaemic strokes (https://www.ncbi.nlm.nih.gov/pubmed/?term=ischaemic+borreliosis) Demyelinating disease (https://www.ncbi.nlm.nih.gov/pubmed/?term=demyelinating+borreliosis) Parkinsonian presentations (https://www.ncbi.nlm.nih.gov/pubmed/12946221) Dementias (www.ncbi.nlm.nih.gov/pmc/articles/PMC2831066/) (https://www.ncbi.nlm.nih.gov/pubmed/15894409/) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171359/) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981904/)	Thank you for your comment and references. The list of symptoms we have provided is not intended to be exhaustive. As the references indicate some of these presentations are rare.
SH	VIRAS	Short	5	21	This is section is not appropriately laid out. The bulleted points in lines 24 and 25 makes it appear that	Thank you for your comment. We have included urban gardens and parks in the

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					these are priorities rather than just factors. These points are actually inferior in significance to the presenting symptoms and any further symptoms revealed by careful questioning. The danger is that cases could be overlooked because the patient has not been hunting in the Scottish highlands nor spent a week in a hide in the New Forest. NICE have got to get over the notion and stop giving the impression that people get Lyme disease from going camping or hunting etc in hot-spots. People get Lyme disease in their garden and local parks. These might be less common, but partly due to the overemphasis on risk-factors, cases with low risk-factors are more likely to be overlooked and result in serious and injurious disease. The draft makes some concession to this, but not enough – these 'bullet points' make this evident.	recommendations regarding awareness of Lyme disease and indicated that infected ticks are found throughout the UK and Ireland.
SH	VIRAS	Short	5	28	"Do not diagnose Lyme disease in people without symptoms, even if they have had a tick bite." Which symptoms does this refer to? Lyme Disease Action list 130 symptoms on their page: http://www.lymediseaseaction.org.uk/about-lyme/symptoms/ and doctors experienced in diagnosing and treating Lyme disease have also produced lists (i.e.>60) of symptoms that can occur with the infection. This is why Lyme is sometimes referred to as the 'new great imitator' after syphilis, which was the original 'great imitator', and is why Sir William Osler stated: "He who knows syphilis knows medicine". Therefore we suggest rephrase to 'Do not diagnose Lyme disease in people ONLY based on a tick bite	Thank you for your comment. The committee considered that people do know when they feel well and do not have any symptoms. The committee agreed on the more common symptoms as indeed does Lyme Disease Action (LDA) on their website. Clinical judgement is required when assessing people with less common symptoms, which may have other causes.

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					when careful examination does not reveal indicative symptoms'. As remarked above, people bitten by a tick should received appropriate information. Professor Klaus Kurtenbach told the BBC: "Lyme disease is wicked - the onset of the disease might be up to a year later, so it is difficult to diagnose - many cases are misdiagnosed and we have no real figures for the incidence in the UK" (http://news.bbc.co.uk/1/hi/health/466809.stm)	
SH	VIRAS	Short	6	16	"Offer testing if there is a clinical suspicion of Lyme disease". The first tier (ELISA) of the two tier tests provided by the NHS are an aid to confirming diagnosis in around 50% of POSITIVE cases according to independent research, which generally used well characterised samples already determined by similar methodology. When these tests are used in the real-world and followed-up by a test that is supposed to be even less sensitive, their performance can be expected to drop significantly. What this means to patients and doctors sending samples to RIPL, is that of the ~12,000 tests per year sent for testing, and ~1,000 positive results, at least 1,000 more have been dismissed as negative when they are positive. Of the remaining 10,000 tests deemed 'negative', an unknown number are actually positive because the test was badly timed, or the species of borrelia is not detected by RIPL tests (e.g., myamotoi), the initial level of infection was low or the infection results from low immunogenic round-bodies of borrelia and the slow reproducing borrelia have not evoked a significant immune response (see above quote from	Thank you for your comment. The recommendation has been amended to clarify the limitations of tests.

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					Kurtenbach: "the onset of the disease might be up to a year later"). All these add-up to possibly thousands of false-negative tests, and exclude those who were not tested because their doctor was ill-informed, they did not go to the doctor or they were misdiagnosed with something else. It is a disservice to doctors not to warn them of these facts at every appropriate opportunity. Failure to do so puts them at risk of wrongly dismissing infected patients without treatment. When doctors order a laboratory test, they often do so with some knowledge of the test's reliability and this informs them of how much weight they should give to the results. Lyme serology as used by the NHS produces around 500 times more false-negatives than testing for HIV (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5391870/). Doctors must be made aware of the serious limitations of Lyme testing or patients will be harmed and doctors may be held to account for making bad decisions. Not only does the draft fail to make this degree of error clear to doctors, it appears to be designed to actively conceal it.	
SH	VIRAS	Short	6	20	"If the ELISA is positive or equivocal, offer an immunoblot test to confirm diagnosis of Lyme disease". Add: 'the second test increases specificity but further reduces the sensitivity of the overall result.' Doctors are entitled to know if NICE guidance risks exposing them to a Fitness to Practice complaint or law suit for negligence, e.g., should they misdiagnose an absence of Lyme and withhold treatment based on a unreliable laboratory tests.	Thank you for your comment. Following stakeholder consultation recommendations have been added to indicate the importance of clinical judgement and the limitations of tests.

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SH	VIRAS	Short	7	24	If antibodies can remain for 3 years, then standard NHS tests are useless for people that get re-infected, or for those who relapse due to so-called 'adequate treatment' proving to be inadequate. Kindly address this.	Thank you for your comment. This recommendation has been removed. The point you make however is valid and the committee agree that there are currently no tests for active infection.
SH	VIRAS	Short	7	27	"1.2.21 Carry out tests for Lyme disease only at NHS-accredited laboratories" The Rare and Imported Pathogens Laboratory (RIPL), Porton Down, is not listed as a UKAS accredited laboratory meeting ISO 15189. (https://www.ukas.com/search-accredited-organisations/). Where will the NHS source testing for UK patients? What steps will be taken to retest patients whose Lyme serology was provided by this unaccredited laboratory in order to meet the requirement at Page 8 Line 5?: "When tests have been done in laboratories that do not fulfil the criteria in recommendation 1.2.21, do not diagnose Lyme disease, but carry out testing again using an NHS-accredited laboratory"	Thank you for your comment. NHS and PHE laboratories are accredited by UKAS to two different standards ISO 15189 and the Clinical Accreditation Pathology (CPA) standard. We understand that RIPL has been assessed for ISO 15189 and is awaiting sign off as part of the UKAS accreditation cycle.
SH	VIRAS	Short	7	11 to 23	This advice (as with much of the earlier advice) could fail patients who present long after they became infected. There is no human spirochaete infection which does not have a chronic presentation.	Thank you for your comment. The recommendations have been reviewed following consultation and amended where necessary to put more emphasis on clinical judgement. The intention of the recommendations is to improve care informed by best available evidence.
SH	VIRAS	Short	8	20 - 24	More 'Discussions'? Do NICE seriously believe that patients need to be told that, "symptoms such as tiredness, headache and muscle pain are common and	Thank you for your comment. The committee discussed your comment but agreed that it is an

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					a specific medical cause is often not found"? These puerile statements have no medical or clinical value except that they might be useful to make patients feel like idiots and persuade them that they are wasting the doctor's time. Achieving this would be a good step towards setting-up the patient for a 'disengagement' strategy planned by PHE to get rid of nuisance patients. (http://www.hse.gov.uk/aboutus/meetings/committees/acdp/161012/acdp_99_p62.pdf) Lyme patients (at any stage) may suffer exhaustion, anxiety and confusion and be unable to assert themselves in the face of a doctor who has been coached by NICE Guidelines to patronise, condescend and dismiss them and their illness as neurotic and hypochondriac because all they have is, 'common symptoms' which are subjective. It is notable that doctors are hardly encouraged to probe for more symptoms before deciding that the patient is just neurotic and must now, somehow be got out of the surgery and kept out. For NICE to coach doctors to condescend in this way is disturbing in its disregard for patient welfare. Patient autonomy means that doctors do not 'fob-off' patients with strategic but meaningless 'discussions' about 'common symptoms'.	important part of clinical practice to inform and educate people about their symptoms.
SH	VIRAS	Short	8	1	These requirements appear to be contrived on the basis of: 'what statements can we make about the VIRAMED tests as employed at the RIPL testing laboratory?' We then recommend these as the requirements for testing. This would give RIPL automatic 'validation' by NICE, so that they can keep their virtual monopoly on testing in England. These recommendations appear to be contrived to suppress	Thank you for your comment. The requirements for validation of a test are not intended to endorse any particular laboratory. The recommendations have been amended to clarify the limitations of tests and research recommendations have been developed to

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					competition. The Health Protection Agency (HPA, now part of Public Health England) 'validated' the VIRAMED tests themselves by comparing them with the test kits they formerly used. If one poor test is compared with another poor test which employs the same or similar methodology, the outcome might 'validate' that the new is similar to the old, but it does not show that either are accurate or useful. The ELISA/Western Blot combination has consistently been shown to have low sensitivity. The sensitivity is so poor that it would be unacceptable in many other serious infections demanding urgent diagnosis and treatment. Furthermore, these tests have not been validated for the UK population and UK strains of borrelia which could only be done by employing a full gamut of comparison tests such as culture, microscopy, PCR, immuno-fluorescent antibody, with multiple tissue types and repeat testing over a period of time. It may be cheap and convenient to pick a testing product off the shelf, but if it leaves thousands of patients undiagnosed, that is not convenient for them.	improve testing and knowledge of serology in the UK. .
SH	VIRAS	Short	8	9	"Discuss with the person the accuracy and limitations of the different tests for diagnosing Lyme disease." This is NOT a 'discussion'. Patients are entitled to expect accurate and balanced INFORMATION from their doctors as required by GMC guidelines for Consent and Good Medical Practice. Replace with: "Inform patients about the limited accuracy of the tests currently used by the NHS. Explain that false-negative results are common and that false-positive results can also occur."	Thank you for your comment. The wording of this recommendation has been revised following stakeholder consultation to include reference to false positive and false negative tests. The wording is according to NICE style.

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					The draft guideline persistently seeks to downplay or even evade the fact that Lyme serology as used by the NHS is insensitive. This evasion is dangerous and will predictably lead to patients not being diagnosed and treated. Why are NICE so bent on producing 'advice' that will allow this foreseeable harm to occur?	
SH	VIRAS	Short	8	11	Good, but omits important codicils – see below	Thank you for your comment.
SH	VIRAS	Short	8	14	"Explain […] that the accuracy of blood tests may be reduced if:" "testing is carried out too early (before antibodies have developed)" "the person has reduced immunity, which might affect the development of antibodies, for example people on immunosuppressant treatments." Add these equally important and relevant qualifiers: 1/ "the infecting species of borrelia might not be detected by NHS tests" 2/ "testing is carried out too late and the infection is now hidden from the immune system" E.g., Berndtson, (2013): (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3636972/) "This review describes known and suspected mechanisms by which spirochetes of the *Borrelia* genus evade host immune defenses and survive antibiotic challenge." And Citera et al (2017):	Thank you for your comment and this information. The committee reviewed the wording and considered it would not be appropriate to add further detail. The occurrence of false negatives has been added to the recommendations.

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					"Identifying Borrelia has proven challenging because it has the ability to evade the immune system[2] and "the bacteria is able to traverse the blood brain barrier, endothelial tissue, and imbed itself in joints, entering certain cells intercellularly and invaginating itself in a manner that reduces the potential exposure of antigens, enabling it to avoid immune recognition".[1]" (https://www.dovepress.com/empirical-validation-of-the-horowitz-multiple-systemic-infectious-dise-peer-reviewed-fulltext-article-IJGM DOI https://doi.org/10.2147/IJGM.S140224) 3/ "testing is carried out too late and the infection has itself become immunosuppressant" E.g., Jarfores et al, 2007 state (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810439/): "Furthermore, we showed that chronic LB had higher amounts of *Borrelia*-specific FoxP3 mRNA than healthy controls, which might imply that chronic LB patients have an immunosuppression caused by the increased T_{reg} population."	
SH	VIRAS	short	8	14	"testing is carried out too early (before antibodies have developed)" Define "too early". See 6, 16 above. When a person has an infection in which successful treatment could be time-dependent, and when the prevention of severe symptoms and injury occurring could be time-dependent, it is nonsensical to use a test which could delay treatment by weeks.	Thank you for your comment. The recommendations have been amended to clarify that treatment should be considered where there is high clinical suspicion of Lyme disease without waiting for test results.

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					LabTestsOnline state: "If the ELISA test is carried out within a few weeks of a tick bite or possible exposure it may fail to detect antibodies to *B. burgdorferi*, and will usually be repeated a few weeks later. About 30% of tests are positive by two weeks and about 80% by six weeks." (http://labtestsonline.org.uk/understanding/analytes/lyme/tab/test/) Explain to doctors and patients, by what logic NICE have decided to put patients at risk of having delayed treatment. Include in the guideline, the mean, standard deviation and min/max of days between patients attending a physician with a tick bite (or sequelae) and getting a positive test result and commencing treatment. Heroldová et al state in "Growth parameters of Borrelia burgdorferi sensu stricto at various temperatures": that the "Growth of Borrelia burgdorferi sensu stricto (prototype strain B-31) was studied in Barbour-Stoenner-Kelly BSK-H liquid medium, supplemented with 4.5% rabbit serum and antibiotics (phosphomycin, rifampicin)"[…] "generation time was between 8.26 and 12.36 h" (https://www.ncbi.nlm.nih.gov/pubmed/9987182) Doubling the Heroldová et al maximum replication time to 24 hours to allow for in-vivo conditions could result in the following levels of infection in a 60Kg (132 lbs) person infected with 10 borrelia organisms, which reproduce @ x 2 per day and assuming that these reside only in extra-cellular body fluids:	

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					Days from tick bite # borrelia cells Mean cells per microlitre 1 20 0 7 1,280 0 14 163,840 0 21 20,971,520 2 28 2,684,354,560 268 Withholding treatment for any duration so that "antibodies have developed" represents a significant risk to the patient's health.	
SH	VIRAS	Short	8	17	"Advise people that tests available privately (including from overseas) may not have been fully evaluated or meet the standards needed to diagnose Lyme disease" If this statement is included then it is essential to also state that NHS/RIPL tests have absolutely NOT "been fully evaluated or meet the standards needed to diagnose Lyme disease". Otherwise this statement is prejudicial against non-NHS laboratories which it lumps together. The purpose of this appears to be in order deprive patients of choice and to maintain RIPL's monopoly on testing for England. The tests used by RIPL have not been 'fully evaluated' – ever, and RIPL and its tests do not "meet the required standards needed to diagnose Lyme disease". No test ever marketed has met all the requirements to "diagnose Lyme disease". Implying that RIPL are capable of this feat using a methodology that is hardly better than flipping a coin is dangerously misleading. If you omit to make this fundamental element of serology testing	Thank you for your comment. The intention of the recommendation is to inform people that they need to be cautious about testing and ensure tests are validated and laboratories accredited. The wording of the accreditation recommendation has been changed to UKAS accreditation, as the previous wording was an error. The committee considered that tests at RIPL or elsewhere should meet or be working to meet these points. If they do not then this should be transparent and available publicly.

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					absolutely explicit in the guidelines, and cease the ploy of 'implying', 'suggesting', 'hinting' or prompting readers to 'draw conclusions' from muddy and misleading information, it is going to cause serious harm to patients and threaten their doctor's values and careers.	
SH	VIRAS	Short	8	14 to 16	Infection with borrelia Lyme spp is itself an 'immunosuppressant'. The infection can suppress the immune response by various means, making detection of the infection by immune response non-viable. Failure to warn doctors and patients of this basic clinical fact would be negligent. E.g.: Immune evasion- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3636972/ B. burgdorferi actively attaches to, invades, and kills human B and T Lymphocytes https://www.ncbi.nlm.nih.gov/pubmed/9233657 In mice - http://journals.plos.org/plospathogens/article?id=10.1371%2Fjournal.ppat.1004976 This AIDS-like capability of borrelia may not manifest as dramatically as in HIV, but it can lead to serious consequences, especially in long-infected patients. These consequences might be avoided by the conscientious application of good medical practice.	Thank you for this information.
SH	VIRAS	Short	9	6	This is bogus and frankly, quite shocking. Children are an especially 'at risk' group for Lyme disease, but thanks to the HPA and PHE, paediatricians – as with most other doctors, have probably absorbed a fair amount of misinformation. If doctors need advice on	Thank you for your comment and your suggestion about sharing of experience. The intention of the recommendation is to ensure that the child or young person has appropriate care and follow up. The committee considered that

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					managing complicated Lyme disease, they should get it from someone with experience of the illness and its management. If the UK has paediatricians with experience of more than a handful of cases, then start a register so that doctors needing paediatric advice can consult someone who at least has first-hand experience. Alternatively, ask for advice from specialist USA or European doctors working in countries where they have got experience. NICE have got to wake-up to the fact that the UK is 30 years behind the rest of the world in Lyme disease management. Not only do we not have the expertise and skills, we have a home-grown knowledge base that is in many respects, worse than useless and potentially dangerous. The phenomenon known as the 'Teacher's dilemma', describes how teaching students with preconceptions is more difficult than educating those who start with a 'blank slate'. False premises must be eliminated before learning can take place. Due to the misinformation that UK doctors have been exposed to, this is not going to be a straightforward task. The immediate need of doctors and patients is to have access to the skills of the world's most experienced doctors who recognise the complexities of Lyme disease and have risen to the challenge in getting properly educated.	children with for example focal neurological symptoms would benefit from having their management discussed with a specialist as focal neurological symptoms are uncommon in children.
SH	VIRAS	Short	9	18	"If symptoms worsen within the first day of antibiotic treatment, assess the person for Jarisch-Herxheimer reaction."	Thank you for your comment. The recommendation has been altered to clarify the reaction can occur during treatment.

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					In the treatment of Lyme disease, a 'herx' or significant die-off of the bacteria can occur at any time during treatment before the infection burden is substantially reduced. Giving doctors and patients a false sense of security once the 'first day of antibiotic treatment' is passed, is dangerously misleading. Some doctors experienced in treating Lyme patients recommend pausing treatment if a severe worsening of symptoms occurs at any time. Patients receiving antibiotic treatment should be routinely provided with information about 'herxes' as they occur and manifest in Lyme, including what to do if they experience a severe worsening of symptoms or new symptoms.	
SH	VIRAS	Short	9	10 to 12	"offer antibiotic treatment according to their symptoms as described in table 1" These guidelines stick patients in boxes and doctors in other boxes. It is convenient, neat and unethical. Straightforward treatment of a complex illness is a lovely dream, but for those patients that end-up in a living nightmare because their skilled physician felt constrained by what was 'described in table 1' is not by any stretch, the practice of medicine. The consequences to the patient are potentially catastrophic. Halting treatment before the infection is eradicated could allow the remaining infection to re-establish. The infection could become worse than it was before treatment and result in serious injury – especially if necessary treatment is withheld because	Thank you for your comment. The intention of guideline is to guide treatment according to available evidence. NICE guidelines recognise the need for individual healthcare professionals to use their clinical judgement and do not override individual clinician's responsibility to their patients. These recommendations are intended to ensure people treated with Lyme disease are given

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					the patient's continued and/or relapsing symptoms are explained away as normal. E.g.: "1.3.11 Explain to people with persisting symptoms following antibiotic treatment that: "symptoms of Lyme disease may take months to resolve even after treatment " continuing symptoms does not necessarily mean they still have an active infection" "1.3.12 Support people who have a slow recovery from Lyme disease by: "encouraging and helping them to access additional services, including "referring to adult social care for a care and support needs assessment, if they would benefit from these "communicating with social services, educational services and employers about the person's need for "gradual return to activities, if relevant" In the context of these draft guidelines and its contrived and illogical restrictions for treatment, the meaning of these statements is obvious – 'patients should not get any more treatment even if they remain ill (infected), or relapse or deteriorate.' This would be unacceptable in any other disease and is a disgraceful abandonment of basic medical ethics. There is NO evidence to support depriving a patient of treatment when their symptoms indicate a progressive Lyme infection. If treatment fails to eradicate the infection, this may also increase the risk of antimicrobial resistance, not only of the Lyme spirochaetes, but of other infections	information about time taken to recover from Lyme disease and that they receive the support they require. The recommendations suggest that people with ongoing symptoms be referred and specialists can make individual decisions on appropriate treatment according to a person's response. There is no evidence for prolonged antibiotic treatment for people with Lyme which is why we are unable to make a recommendation for this use.

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					transmitted by the tick bite, as well as opportunistic infections that take advantage of the immune suppression caused by the Lyme bacteria. All Infectious disease doctors treat chronic infections with individualised care. Bone infections need 6 weeks of intravenous antibiotics, but if the patient is a diabetic this can sometimes increase to 12 weeks followed by oral doxycycline plus co-trimoxazole for months, based on the patient's clinical response. These guidelines should state that treating Lyme disease needs a similar approach. This could start with a three month trial of doxycycline or co-trimoxazole, extended as necessary according to the patient's clinical response. Clinical guidance for dermatology is to treat for a 3 to 6 month period for 'bad acne' with doxycycline or sometimes co trimoxazole, as precedent to considering the more toxic and more expensive acne drugs like roaccutane. Recommended treatment for Tuberculosis is for 6 or 9 months with high dose combination antibiotics. If a 14 day or longer break in treatment occurs, the whole treatment regime must start again from scratch. Patients that are re-infected can repeat this treatment and patients that relapse or do not respond can have alternative combinations and repeated and/or extended phases of treatment. Chronic Q fever is difficult to treat and can require up to four years of treatment with doxycycline and quinolones or doxycycline with hydroxychloroquine. This NICE guidance is dangerous and will result in entirely foreseeable iatrogenic harm to patients. It will	

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					result in large numbers of patients suffering avoidable illness and injury and justifiably seeking compensation.	
SH	VIRAS	Short	10	1	"Antibiotic treatment for Lyme disease in adults and young people". As already described, this table should only be a suggestion for initial treatment to be followed with careful reassessment. E.g.: "Suggestions for initial antibiotic treatment for Lyme disease in adults and young people" It is the view of VIRAS that in a significant number of cases these fixed treatments will prove inadequate and result in continued infection and serious consequences to patients.	Thank you for your comment. As with all NICE guidelines, when exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. The guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.
SH	VIRAS	Short	12	18	"Do not routinely offer further antibiotics if a person has persisting symptoms following 2 courses of antibiotics. Consider discussion with or referral to a specialist as outlined in recommendation 1.2.19." This advice is dangerous and has no clinical basis. Where and who are these 'specialists' that the draft refers to? Virtually all of the consultant physicians claiming Lyme expertise that VIRAS are aware of, are Chronic Lyme deniers, indoctrinated by IDSA and BIA propaganda to serve the interests of medical re-insurance companies by promulgating the belief that Lyme is rare, easy to detect and straightforward to treat with a short course of antibiotics. Complicated and chronic Lyme is far outside their experience or expertise. It is entirely predictable that this advice will result in harm to patients, and represents nothing more than non-medical 'disengagement' strategies to dismiss patients who remain symptomatic due to	Thank you for your comment. There was insufficient evidence to suggest that further treatment after 2 courses of antibiotics or prolonged courses of antibiotics is beneficial. The recommendation to consider discussion with or referral to a specialist appropriate for the person's history or symptoms (for example, an adult or paediatric infection specialist, rheumatologist or neurologist) allows the possibility for a specialist to offer further antibiotic treatment or investigation as appropriate.

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					continuing infection following 6 weeks of antimicrobial treatment. These patients do, and will continue to exist, and in their current form these draft NICE guidelines will perpetuate and compound this entirely foreseeable threat to patient safety. Doctors that follow this NICE guidance in good faith will inevitably face Fitness to Practice complaints. No wonder NICE include such a comprehensive Disclaimer with their guidelines if this is an example of their cavalier approach to patient care.	
SH	VIRAS	Short	12	26	The guideline refers to "persistent symptoms" however they do not recognised the existence of persistent infection. Borrelia can evade the human immune system and the bacteria can tolerate antibiotics and there are numerous articles that demonstrate this. The possibility that persistent infection may require more than 6 weeks of antibiotics is not considered, but should be communicated to clinicians. TB, leprosy and acne patients can all benefit from long courses of antibiotics. Citations of works by recognised Lyme experts that demonstrate persistent infection after antibiotics: * Sleeper cells: the stringent response and persistence in the Borreliella (Borrelia) burgdorferi enzootic cycle. 2017. Cabello FC, Godfrey HP, Bugrysheva JV, Newman SA. The metabolic and morphologic changes resulting from activation of the stringent response in B. burgdorferi may also be involved in the recently described non-genetic phenotypic phenomenon of tolerance to	Thank you for your comment. Persistent/ongoing symptoms rather than infection are referred to in the guideline because it is not known whether these symptoms are due to persisting infection, tissue damage, autoimmune reaction or some other process and there is currently no test that helps determine this. The guideline looked for evidence for prolonged courses of antibiotic treatment and did not find this for Lyme disease. Evidence of benefit to patients is sought in NICE clinical guidelines and in vitro and animal studies are not considered in evidence reviews.

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					otherwise lethal doses of antimicrobials and to other antimicrobial activities. It may thus constitute a linchpin in multiple aspects of infections with Lyme disease borrelia, providing a link between the micro-ecological challenges of its enzootic life-cycle and long-term residence in the tissues of its animal reservoirs, with the evolutionary side effect of potential persistence in incidental human hosts. (https://www.ncbi.nlm.nih.gov/pubmed/28836724 doi: 10.1111/1462-2920.13897) * These results extended previous studies with ceftriaxone, indicating that antibiotic treatment is unable to clear persisting spirochetes, which remain viable and infectious, but are nondividing or slowly dividing From <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2812145/?tool=pmcentrez> Barthold, Stephen W. et al. 2010. "Ineffectiveness of Tigecycline against Persistent Borrelia Burgdorferi." Antimicrobial Agents and Chemotherapy 54(2):643-51. Retrieved (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2812145&tool=pmcentrez&rendertype=abstract). * The agent of Lyme borreliosis, Borrelia burgdorferi, evades host immunity and establishes persistent infections in its varied mammalian hosts. Hodzic, Emir, Denise Imai, Sunlian Feng, and Stephen W. Barthold. 2014. "Resurgence of Persisting Non-Cultivable Borrelia Burgdorferi Following Antibiotic Treatment in Mice" edited by R. M. Wooten. PLoS	

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					ONE 9(1):e86907. Retrieved January 24, 2014 (http://dx.plos.org/10.1371/journal.pone.0086907). * We demonstrated that B. burgdorferi treated in the stationary phase has a higher probability of regrowth following removal of antibiotic. Caskey, John R. and Monica E. Embers. 2015. "Persister Development by Borrelia Burgdorferi Populations In Vitro." Antimicrobial agents and chemotherapy 59(10):6288-95. Retrieved January 18, 2016 (http://aac.asm.org/content/early/2015/07/21/AAC.00883-15). * Results indicated that following antibiotic treatment, mice remained infected with nondividing but infectious spirochetes, particularly when antibiotic treatment was commenced during the chronic stage of infection. Hodzic, Emir, Sunlian Feng, Kevin Holden, Kimberly J. Freet, and Stephen W. Barthold. 2008. "Persistence of Borrelia Burgdorferi Following Antibiotic Treatment in Mice." Antimicrobial agents and chemotherapy 52(5):1728-36. Retrieved November 7, 2010 (http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2346637&tool=pmcentrez&rendertype=abstract). * Our study substantiates borrelial persistence in some EM patients at the site of the infectious lesion despite antibiotic treatment over a reasonable time period. Hunfeld KP et al 2005 In Vitro Susceptibility Testing of Borrelia burgdorferi Sensu Lato Isolates Cultured from Patients with Erythema Migrans before and after Antimicrobial Chemotherapy.	

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SH	VIRAS	Short	14	8	"Advise women to tell their healthcare professional that they had Lyme disease during pregnancy" Suggest this should read: 'Advise women to tell all of their healthcare professionals that they had Lyme disease during pregnancy.'	Thank you for your comment. The recommendation was reviewed following stakeholder consultation. The committee was happy with the existing wording and thus did not make this change.
SH	VIRAS	Short	14	10	The manifestation of Lyme disease symptoms can be delayed for months or years. It is essential that both mother and baby are monitored for an extended period. Given the time that it takes most patients to get a diagnosis and treatment after the initial infection, the unreliability of tests and failure of treatment, it can be expected that a significant number of women give birth whilst infected with Lyme bacteria. Some of these will be identified cases, some will not. Where the infection has been identified and treated, an absence of symptoms should not lead to the assumption that the infection has been eradicated. Of all Lyme disease patients, babies and children probably have the greatest number of years to suffer the consequences of bad clinical judgement. Mother and child must be monitored long-term specifically for Lyme disease relapse.	Thank you for your comment. The committee considered that monitoring over a long time was not practical or necessary. It is usual clinical practice to take a history of infections or other circumstances in pregnancy if there is concern about a child. Moreover, women should be empowered to report infections in pregnancy if there is concern at any time point.
SH	VIRAS	Short	14	17	The draft states: "most people recover completely". This claim is meaningless without data or an evidence based estimate. If you claim to have a number or range, then state it: e.g., "90% to 95% recover completely". If you do not have an authoritative figure or range then this statement is an outright lie. It is unsubstantiated and dangerously creates a false sense of security. The epidemiology of Lyme in the	Thank you for your comment. The recommendation is covering the wide range of presentations of Lyme disease and the committee considered that from that perspective most people do recover completely. The recommendation was informed by knowledge and experience of the committee and is consistent with statements made for example by

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					UK is wholly inadequate to make this insupportable claim. The authorities responsible for public health in the UK have no idea how many people in the UK get Lyme, nor what happens to them, because the vast majority never even get diagnosed let alone treated for the infection. Define 'recover completely', are you claiming that this means that the infection is eradicated? Also explain how you know that this occurs in 'most people'. Also explain why, if 'most people recover completely', the draft also claims: "The development of a core outcome set was identified as a high priority"? If most patients recover completely, then the development of a 'core outcome set' would be a ridiculous waste of resources. The Centres for Disease Control and Prevention in the USA admit that the true incidence of Lyme is 10 to 12 times higher than the number of reported cases. That is in a country where 14 states have an officially recorded average incidence of 43 per 100k compared to England and Wales measly 1.7 per 100k. Public Health England are deluded if they believe that UK surveillance for Lyme is 4 times more efficient than that of the USA. Therefore it is a logical deduction that as an absolute minimum, 9,000 cases of Lyme disease in the UK go unrecorded every year. That could be ~160,000	the Centres for Disease Control and Prevention (CDC) in the US and European trials.. The guideline also acknowledges that some people have ongoing symptoms. The development of a core outcome set is required to establish best treatments which might involve different regimens than are recommended in this guideline and would also include treatments for people with ongoing symptoms.

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					missed cases since the turn of the century. How can the NICE guidelines imply that they or anyone else, knows what has happened to these tens of thousands of undiagnosed and untreated patients? Stop making ludicrous claims based on nothing more concrete than wishful thinking and wilful ignorance. These attempts at diverting patients are propaganda and they have no scientific validity. If NICE are so bent on manipulating doctor's into accepting false information, then one must assume that the pretence of having a public consultation and gathering different viewpoints – is primarily for the purpose of producing more effective and acceptable propaganda. There appears to be an underlying agenda in the guideline's constant use of insupportable statements. As these mostly seem intended to create a false sense of security, and thereby justification for dismissing patient's concerns, it can be concluded that these deceptions reveal an underlying contempt for patients and patient rights.	
SH	VIRAS	Short	14	23	"Explain to people who are starting antibiotic treatment for Lyme disease that some people may experience a worsening of symptoms early in treatment." […] "Tell them to contact their doctor if this happens and not to stop their antibiotic treatment". NO! It is evident that for years PHE have portrayed Lyme disease as rare and not very serious and patients, especially those who do not respond to treatment as PHE dictate, as hypochondriacs and neurotics. This contemptuous attitude also appears to have pervaded NICE and its GDC so thoroughly, that they seem to forget that a lot of people are actually,	Thank you for your comment. The recommendation has been altered and further information on Jarish–Herxheimer reaction added to the short guideline in the 'terms used' section.

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					stoical. As patients, these people don't like making a fuss, and even if they are able to 'contact their doctor' may not give adequate information to receive appropriate advice. If you tell people that they might feel worse on treatment but not to stop their treatment, then you are going to have some very seriously ill patients. This is foreseeable due to the wrong advice the guideline gives on Jarisch-Herxheimer reactions. If the NICE GDC possessed a basic knowledge of Lyme, or had taken advantage of the wealth of published information about Lyme disease then they would recognise how stupid and dangerous this advice is. If a person is experiencing a herx but they put it down to, 'the doctor told me I might feel worse', and they continue treatment they could have a crisis that will land them in A&E. Some experienced doctors are concerned that a severe herx can result in permanent injury. NICE have to break this down and give better advice. A good first step towards achieving this would be to show some respect for patients. The second step would be to have some knowledge of the borrelia pathogen that causes Lyme disease and the antigens and bio-toxins exposed when it is killed. It is basic vaccine science and it is astounding that NICE lack understanding of this simple biology.	
SH	VIRAS	Short	15	8	The following comments relate to the sections in: Recommendations for research	Thank you for your comment. Please see our responses to your individual comments.
SH	VIRAS	Short	15	11	"Can a core outcome set be developed for clinical trials of management of Lyme disease?"	Thank you for your comment. The guideline committee sought to strike a balance using the best evidence available for the questions covered

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					"The development of a core outcome set was identified as a high priority because it would allow comparison across trials and allow appropriate meta-analysis to strengthen results." NICE affect to recognise the weakness of the available evidence and acknowledge that better is required. But notwithstanding this lack of evidence meeting their requirements, the draft guideline makes treatment recommendations with such authority and confidence that they consider it appropriate to set definite limits on treatment and make the unsubstantiated claim that 'most people recover completely'. If this were true, then there would be little point in spending hundreds of thousands of pounds developing a 'core outcome set'. That NICE appear to have been selective in the opinions that they chose to upgrade to 'evidence' shows that bias is involved. That bias is in favour of those who hold the opinion that a Lyme infection at any stage is easily eradicated with a few weeks treatment, and that despite all evidence to the contrary, the infection is self-limiting. The opinion of those who hold that a Lyme infection could take longer to eradicate is ignored. No balance, no evidence and no science, just opinions prejudiced against patients who need longer treatment for a disseminated and persisting infection. Producing a Core Outcome Set and calling for multiple Clinical Trials adopting those criteria, is a contradiction in the context of the draft guideline. The draft treatment recommendations have predetermined that most patients will be cured with 3 weeks of antibiotics	by the guideline while acknowledging the quality of the evidence. The committee consider that the development of a core outcome set would help improve the evidence base. The development of such a set should involve professionals and patients and include assessment of areas important to patients. The search for evidence and the evidence examined in the guideline and the committee discussions are reported in the evidence reports. The approach used is to search for evidence of benefit of interventions and not opinion. The guideline recognises that symptoms persist but no evidence of benefit for prolonged courses of antibiotics was found. The evidence reviews make clear the uncertainty around the current recommendations and why research is required. The guideline committee would value robust research on treatment regimens to inform updates to the guideline and improve care for patients. Research on clinical epidemiology as outlined in the research recommendations would provide information to support or refute this view with an understanding of how many people are affected.

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					and all of the remainder will be cured with a further 3 weeks treatment with a single antibiotic. Therefore, a "core outcome set" would be superfluous and the call to establish a set is contradictory and suspect. VIRAS and many others are well aware that the draft treatment regimen would leave substantial numbers of patients infected. Following treatment some patients will continue to have symptoms due to an ongoing infection, others will relapse later. This is exactly what happens with inadequately treated tuberculosis and other difficult infections. The contradiction makes sense when one understands that a 'core outcome set' will provide 'evidence' to facilitate the re-diagnosis of patients with persisting or relapsing symptoms, which in any other resistant infection would be interpreted as 'treatment failure'. Once a 'core outcome set' has determined that 'adequately treated' patients can have persisting, relapsing or even deteriorating symptoms, the patient can nevertheless be classed as 'adequately treated'. Patient's ongoing disease and symptoms can be attributed to tissue damage or acquired autoimmune disease, and they can be re-diagnosed as having post-treatment Lyme disease syndrome (PTLDS). This will mean that they require no further investigations or treatment beyond symptom management. Alternatively, some could be re-diagnosed with CFS or any other convenient label that gets rid of them with less expense to the NHS. Informed patients have	A core outcome set should include clinical and patient reported outcomes as well as tests. The aim is to have clearly defined terms and measurements for all items including subjective items such as fatigue. While current tests may not be adequate, other aspects of a core outcome set would be of benefit in studies.

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					been aware of PHE's plans to realise this outcome for chronic Lyme patients for some years (see below). EVIDENCE THAT A 'CORE OUTCOME SET' IS IMPRACTICAL WITHOUT RELIABLE TESTS AND THAT ANTIBODY TESTS ARE INAPPLICABLE IN CHRONIC LYME DISEASE J Infect Dis. 1992 Aug;166(2):440-4. Fibroblasts protect the Lyme disease spirochete, Borrelia burgdorferi, from ceftriaxone in vitro. Georgilis K1, Peacocke M, Klempner MS. Abstract The Lyme disease spirochete, Borrelia burgdorferi, can be recovered long after initial infection, even from antibiotic-treated patients, indicating that it resists eradication by host defense mechanisms and antibiotics. Since B. burgdorferi first infects skin, the possible protective effect of skin fibroblasts from an antibiotic commonly used to treat Lyme disease, ceftriaxone, was examined. Human foreskin fibroblasts protected B. burgdorferi from the lethal action of a 2-day exposure to ceftriaxone at 1 microgram/mL, 10-20 x MBC. In the absence of fibroblasts, organisms did not survive. Spirochetes were not protected from ceftriaxone by glutaraldehyde-fixed fibroblasts or fibroblast lysate, suggesting that a living cell was required. The ability of the organism to survive in the presence of fibroblasts was not related to its infectivity. Fibroblasts protected B. burgdorferi for at least 14 days of exposure to ceftriaxone. Mouse keratinocytes, HEp-	

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					2 cells, and Vero cells but not Caco-2 cells showed the same protective effect. Thus, several eukaryotic cell types provide the Lyme disease spirochete with a protective environment contributing to its long-term survival. (https://www.ncbi.nlm.nih.gov/pubmed/1634816) N Engl J Med. 1988 Dec 1;319(22):1441-6. Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to Borrelia burgdorferi. Dattwyler RJ1, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Abstract The diagnosis of Lyme disease often depends on the measurement of serum antibodies to Borrelia burgdorferi, the spirochete that causes this disorder. Although prompt treatment with antibiotics may abrogate the antibody response to the infection, symptoms persist in some patients. We studied 17 patients who had presented with acute Lyme disease and received prompt treatment with oral antibiotics, but in whom chronic Lyme disease subsequently developed. Although these patients had clinically active disease, none had diagnostic levels of antibodies to B. burgdorferi on either a standard enzyme-linked immunosorbent assay or immunofluorescence assay. On Western blot analysis, the level of immunoglobulin reactivity against B. burgdorferi in serum from these patients was no greater than that in serum from normal controls. The patients had a vigorous T-cell proliferative response to whole B. burgdorferi, with a mean (+/- SEM)	As stated above, the aim in an intervention study is to evaluate patient outcomes and not whether infection is present or not.

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					stimulation index of 17.8 +/- 3.3, similar to that (15.8 +/- 3.2) in 18 patients with chronic Lyme disease who had detectable antibodies. The T-cell response of both groups was greater than that of a control group of healthy subjects (3.1 +/- 0.5; P less than 0.001). We conclude that the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against B. burgdorferi and that a specific T-cell blastogenic response to B. burgdorferi is evidence of infection in seronegative patients with clinical indications of chronic Lyme disease. HOW ARE NICE GOING TO PROVE THAT PATIENTS ARE NO LONGER INFECTED? Without a validated method to show this, the whole 'research recommendation' section is nonsense as far as patient care is concerned. Ignoring this requirement means that a 'core outcome set' would simply be a means of establishing arbitrary thresholds beyond which patients can be denied further treatment. Many of the patients formerly misdiagnosed with M.E., but who later discovered that they have borreliosis are aware of this stratagem, because it has already been used to marginalise those patients. PHE intend to use the same strategy on Lyme patients. E.g., in the PACE Trial (2011) of treatments for M.E. and CFS, the treatments failed to reach the reach the Primary Outcome Thresholds for 'recovery' and 'improved'. But after all the data had been collected, the Primary Outcome Measures were discarded, and	

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					new ones were designed with much lower thresholds, which created the appearance of a Treatment Effect. In November 2016 the Journal of Health Psychology published: 'PACE-Gate': When clinical trial evidence meets open data access,by Keith J Geraghty of the University of Manchester. Geraghty observes: "The data were only released after a protracted freedom of information case brought by a patient with CFS. A tribunal ordered the lead author's institution to release their data. Upon release, re-analysis showed that the levels of improvement and recovery observed in the released data were much lower than the levels reported in the published report (White et al., 2011a) and other related publications. The released data showed that the effectiveness of cognitive behavioural therapy (CBT) and graded exercise therapy (GET), in comparison to standard medical care (SMC) and adaptive pacing therapy (APT), fell by almost two-thirds." (Volume: 22 issue: 9, page(s): 1106-1112. http://journals.sagepub.com/doi/10.1177/1359105316675213 https://doi.org/10.1177/1359105316675213) Therefore the call for research to establish a 'core outcome set' has no validity but is a stratagem which would allow chronically ill and chronically infected Lyme patients to be deemed 'successfully treated'.	
SH	VIRAS	Short	15	14	"Antibiotic treatment is the mainstay of management for Lyme disease."	Thank you for your comment. This paragraph is specifically about the research recommendation.

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					This statement is false and without understanding why, it is impossible to recognise that what follows the statement is meaningless. The actual 'mainstay of management for Lyme disease' in the UK, which has been applied to the vast majority of Lyme disease patients (>90%) is: 1/ do not recognise the disease 2/ diagnose the patient with something else, probably M.E. or CFS. 3/ try to get rid of them. Therefore the 'mainstay' of Lyme disease management in the UK is to misdiagnose the patient and thereby deprive them of the treatment that they need. This is the 'management' that has been given to tens of thousands of patients, who were often previously fit and successful, but were then left to rot in their homes among the shattered remnants of their former life. Thanks to PHE (and the HPA), the NHS has been providing this mainstay service for at least 30 years. The outcome of this 'mainstay' of Lyme disease management in the UK is fairly well established for patients who became and remained symptomatic for longer than 6 months. Few patients recover (<10%). The majority improve somewhat over a course of years and decades with a fluctuating course of remission and relapse, around 25% remain very severely ill and a proportion of these have progressively worsening disease. A substantial proportion of patients with M.E. remain more chronically ill and disabled and with a lower quality of life, than patients with almost all other	It is hoped that the research recommendations can inform future research and improve care and outcomes for patients.

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					diseases*. A patient's risk of being among the 25% of severely ill is increased if in the course of their illness they had a period of extreme illness and incapacity, especially if this was prolonged. However, even some of the 25% can improve substantially with long-term treatment targeting Lyme disease and co-infections. *QUALITY OF LIFE AND FUNCTIONAL STATUS IN M.E. AND CFS The following papers show greater incapacity and worse quality of life in ME/CFS than virtually all other diseases http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0132421 https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-11-402 http://www.amjmed.com/article/S0002-9343(96)00174-X/pdf The draft NICE guideline shows no concern and does not even acknowledge the existence of the tens of thousands of Lyme disease patients that are chronically ill because they were never diagnosed or treated. For those who were misdiagnosed with 'CFS', their plight was specifically excluded from the NICE guideline Scope, and their situation is permanently compounded by getting a 'waste-basket' diagnosis that obstructs further investigation or treatment. That is all the evidence that VIRAS or any reasonable person needs in order to recognise that from the outset, the NICE guideline was never about helping patients with Lyme disease. It was only ever about protecting PHE	

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					and covering-up a shameful medical scandal representing decades of incompetence.	
SH	VIRAS	Short	16	2	"There is a lack of robust epidemiological data on Lyme disease in the UK". Replace with: 'The epidemiology of Lyme disease in the UK is wholly inadequate to deduce risk or inform healthcare planning.' The true incidence is likely to be at least 10 times higher than reported cases and due to many years of inadequate identification of cases, the prevalence is probably tens or hundreds of thousands of chronic cases. That is what the situation actually is. The fact that this draft guideline continuously implies that Lyme in the UK is under control and simply filling-in a few gaps in knowledge will sort it all out is ludicrous. This overconfidence suggests either a lack of understanding of the gravity of the situation and the consequences to patients of this cavalier approach, or a callous attempt to manipulate opinion with propaganda and spin. Neither of these can help doctors and patients. See the VIRAS stakeholder comment on the Scope https://www.nice.org.uk/guidance/gid-ng10007/documents/consultation-comments-and-responses page 148, and the VIRAS article: http://counsellingme.com/VIRAS/UKLymeIncidence2.pdf "Estimating the Incidence of Lyme Borreliosis in England and Wales."	Thank you for your comment. The committee considered the current wording is appropriate.
SH	VIRAS	Short	16	3 to 6	"A large clinico-epidemiological study to collect data on incidence […] would generate population-based statistics".	Thank you for your comment. While there are clear challenges in conducting this type of study the collection of improved clinical epidemiological

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					This claim is misleading. An epidemiological study is not possible without an accurate method for identifying cases and one does not exist. The exercise as it is described would predictably maintain the current gross underestimation of incidence and ignore prevalence altogether. It may be acceptable to PHE who appear to enjoy ridiculous Lyme disease statistics but will do nothing for patients, doctors or the population at risk.	data is essential to improve understandings and services.
SH	VIRAS	Short	16	17	"What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections" For the reasons outlined above (16,2. 16,3 to 6) this exercise would produce predictably misleading information, especially in view of the proviso for using the PHE approved test method of serology which has been shown to be inaccurate. This statement appears to show a willingness to make concessions to the concerns of patients. However, when read in the context of the remainder of this draft guideline and the historical claims of PHE and the HPA, it can be recognised as just another ruse to protect those responsible for the incompetent management of Lyme disease. Furthermore, it facilitates those who wish to enforce antimicrobial stewardship on doctors and an unsuspecting patient population, and maintain the illusion that regarding Lyme in the UK – everything is under control.	Thank you for your comment. The intention of the research recommendation is to improve understanding of Lyme disease and care of patients.
SH	VIRAS	Short	16	17	"What is the current seroprevalence of Lyme disease-specific antibodies and other tick-borne infections (such as babesiosis, ehrlichiosis, anaplasmosis, bartonellosis or Q fever) in people in the UK when	Thank you for your comment. The intention of the research recommendation is to improve understanding of Lyme disease and care of patients.

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					performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?" And on line 22: "This information is not currently available and is of high priority". It is of higher priority to recognise the deceptive nature of these grandiose calls for research and the specific meaning and consequences of this particular recommendation, i.e., for somebody else to spend hundreds of thousands, if not millions of pounds on projects that will not help doctors or patients. All that anyone needs to recognise at the present time, is the patent fact that Lyme disease in the UK has not been, and is not being monitored or handled effectively. Acquiring evidence about seroprevalence in the population is of LOW priority and in fact, has no practical application to protect the nation's health from the threat of Lyme disease. Claiming that this is 'high priority' appears to be in order to create an impression that Lyme disease is being taken seriously. Whereas the predictable result of this stratagem would be to show that healthy people are seropositive in substantial numbers – just as has been found in other countries. This would aid RIPL and the former Reference Laboratory at Southampton to defend their disgraceful record of obstructing the diagnosis of patients requiring treatment, but do nothing for doctors or their patients who suffer serious and chronic illness due to infection with Lyme bacteria. E.g.: "Screening of IgG antibodies against *B.*	

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					burgdorferi in blood donors as a proxy for the presence in the healthy population showed seroprevalences of 2.7% both in Hamburg and Bavaria [16], [17]. In France (3.2%) [18], Italy (4.9%) [19] and Romania (4.3%) [20], similar proportions of seropositive individuals among blood donors were assessed. In population-based surveys, higher seroprevalences were seen in Germany (Berlin: 8%, n = 3,736 [21]; Bavaria: 15%, n = 4,896 [22]; Baden-Württemberg: 16.9%, n = 1,228 [5]) and Finland (19.3%, n = 3,248 [23]). In individuals with higher risk of exposure to ticks such as forestry and agricultural workers seroprevalences between 8% and 52% have been described [15], [18], [19], [24]–[26].", etc., etc. (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041321 https://doi.org/10.1371/journal.pone.0041321) A really callous move.	
SH	VIRAS	Short	16	19	"What is the current seroprevalence of Lyme disease-specific antibodies […] in people in the UK when performed using UK-accredited assays (ELISA based on C6 antigen and immunoblot)?" There is no such thing as a "UK-accredited assay" for Lyme disease. This Research Recommendation is nonsense.	Thank you for your comment. This was an error and has been removed.
SH	VIRAS	Short	16	22	VIRAS consider these recommendations for 'Priority' research, to be nothing more than a subterfuge intended to placate patients and patient groups. They are structured in such a way that even if they were	Thank you for your comment. The intention of the research recommendation is to improve understanding of Lyme disease and care of patients.

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					actually carried out, they will not change UK Lyme statistics, will not improve patient care and will protect PHE and RIPL from claims for compensation. The recommendations are based on the same research exploited by USA Lyme deniers of the IDSA, which has been used to deny patients diagnosis and treatment, deny chronic Lyme disease exists and to protect those with vested interests in those denials.	
SH	VIRAS	Short	16	31	"Many patients are concerned about the possible presence of co-infections transmitted by ticks". As this concern was specifically excluded from the Scope and has not been properly addressed in the draft guideline and is represented only as a concern of 'many patients', it is safe to assume that this is not a concern of PHE or of NICE. This statement is just another stratagem to try and mollify patients. It in no way addresses the evidence, including that provided in the stakeholder responses to the Scope. E.g., Lyme Disease UK: page 53, 54, 72. Lyme Research UK: page 95, 176, 285. VIRAS: page 159, 327. Caudwell LymeCo: page 2, Lyme Disease Action: page 33 and many other references to Lyme coinfections which can cause serious complications in the effective treatment of Lyme disease and some of which represent serious diseases in their own right.	Thank you for your comment. The management of other tick borne infections is outside the scope but it seems reasonable to include serological assessment of other possible infections as part of a study.
SH	VIRAS	Short	17	7	"The evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme diseases is of poor quality, out-dated and often based on small studies. Most studies are not UK based."	Thank you for pointing out that this comment is inaccurate. It has been removed.

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					We are unaware of and cannot locate ANY Trials of antimicrobial treatment conducted in the UK, on PubMed or the Health Research Agency (HRA, providing the Ethical approval service). Please provide VIRAS with references for all of the UK studies this statement refers to. Please also provide the REC reference code and date. VIRAS are concerned that the UK trials that the statement refers to could include covert and unethical experiments conducted without Informed Consent or Ethical Approval. Please supply the requested information as a matter of urgency.	
SH	VIRAS	Short	17	10	"A series of prospective multicentre studies is needed to compare the clinical and cost-effectiveness of different dosages and length of treatment". The draft NICE guideline provides restrictive treatment recommendations, which VIRAS believe are unfounded, unethical and dangerous. This proposal for 'multicentre studies' appears to support our view. NICE admit that the clinical effect of "different dosages and length of treatment" are unknown, yet they nevertheless make insupportable and restrictive treatment recommendations which cannot be 'Evidence Based'. The only rationale for an expensive 'multicentre' study would be if various borrelia species produce different responses to treatment and these are expected to vary according to different regions of England and Wales. 'Multicentre' studies are not generally required for 'prospective' studies, they are only required for such	Thank you for your comment. Multi-centre studies are recommended to ensure adequate numbers of people can be included in a properly powered trial. The current recommendations are based on available evidence and informed by the committee.

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					time as a full-scale Clinical Trial is designed. That is, unless wide variations are actually anticipated – in which case explain why they are expected. This research proposition seems wildly excessive and as such, it does not appear to be authentic.	
SH	VIRAS	Short	17	22	"What is the most clinically and cost effective serological antibody-based test, biomarker (such as CXCL13), lymphocyte transformation and ELISPOT for diagnosing Lyme disease in the UK at all stages, including reinfection?" and Line 26: "Determining the most clinically and cost effective diagnostic tests for Lyme disease will improve patient care and is of high priority. The clinical presentation of Lyme disease is very variable, with diagnosis of all presentations except erythema migrans relying in part on laboratory testing" VIRAS appreciate the acknowledgement that NHS testing is inadequate and that improving it is 'high priority', but this statement reveals some disturbing assumptions. Direct detection tests are not mentioned: culture, immuno-flourescent antibody staining, including molecular beacons (the latter being 100% specific) and PCR (highly specific) which detect the presence of the actual infective organism – not only an immune response which NICE have already indicated can last for 3 years after treatment, making the tests they	Thank you for your comment. The tests were listed as examples from the evidence review but the research recommendation has now been re-worded to clarify the intended wider scope of the research recommendation.

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					specify irrelevant to a substantial number of patients at risk and useless for determining prevalence. Line 6 states: "However, we know little about the evolution of antibody titres over time in those who have been treated successfully and in those who have persisting symptoms." [emphasis added] This loaded statement implies that there are only two possible outcomes to treatment: 1/ success or 2/ "persisting symptoms", and as already noted, the latter are explained as NOT treatment failure (p12 lines 1 – 10). Even though "treatment failure" is mentioned in the draft, it is not addressed. There are no good medical or scientific justifications for this omission. The draft guideline evasion of treatment failure is a prejudice and discrimination against patients. 'Reinfection' is mentioned but failed-treatment and delayed-relapse due to failed-treatment are not. Perhaps NICE do not want these patients to have a valid test, which could be interpreted as a strategy to discriminate against and marginalise those patients, deny them treatment and permit their ongoing infection to progress. This stratagem would permit PHE to claim that all cases of proven 'post-treatment' Lyme must represent 'reinfection'. That would give PHE and individual doctors a useful get-out for their years of individual and collaborative failures. They can evade blame for harms due to inadequate treatment because the patient must have got 'reinfected'. Therefore this serves the interests of PHE whilst discriminating against patients and their medical needs.	The guideline does not ignore treatment failure and specifically refers to it in recommendation 1.3.8. The guideline has chosen not to specify the cause of ongoing symptoms but does search for evidence of effect of prolonged antibiotic treatment and did not find this. The recommendations have been amended following stakeholder comments to clarify the importance of clinical diagnosis and judgement and to indicate the limitations of tests.

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					How will 'cost effectiveness' be calculated? What price will NICE put on a formerly healthy person spending years or decades confined to their home by untreated or under-treated Lyme disease? The claim that "diagnosis of all presentations except erythema migrans relying in part on laboratory testing", is badly misleading and reconfirms our objection that this draft guideline assumes that NHS testing for Lyme can reliably diagnose the disease and must therefore also be able to rule it out. No diagnosis of Lyme disease can 'rely' in part or whole on NHS laboratory tests. These tests can only provide support for a clinical diagnosis in-line with the test kit manufacturer's instructions. VIRAS recommend replacing, "diagnosis of all presentations except erythema migrans relying in part on laboratory testing" with: "diagnosis of all presentations are always a clinical decision based on assessment of the evidence and are not required to agree with any laboratory test results obtained." The gold-standard test for any infection is direct detection of the infective organism, which for some reason best known to themselves, NICE have omitted. The draft guideline specifies a "serological antibody-based test". This suggests bias which might allow PHE/RIPL tests to be judged only against tests with related methodologies, rather than against the best that can be achieved. This bias, which would predictably help to preserve the PHE/RIPL monopoly	Full details of NICE's preferred methods for cost-effectiveness analysis are detailed in the NICE guidelines manual and associated methodological reports. In summary, we would expect assessment of cost effectiveness to consider how patient outcomes would be differentially affected with different diagnostic strategies taking into account both any impact on length of life or quality of life. The preferred outcome metric is quality-adjusted life years. As such, the impact of being confined at home would be incorporated via quality of life measures. Differences in cost to the NHS between strategies would then also be considered incorporating not only differences due to initial testing cost but also downstream costs. So for example if a diagnostic strategy improved accuracy of diagnosis you may well expect downstream cost savings. The time horizon for a cost effectiveness analysis should be long

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					on UK testing has anti-trust implications and must be eliminated. The draft is supposed to represent a clinical guideline, not an illegal business venture. Even though these are research recommendations, their inclusion requires that they meet the standard for a Clinical Guideline. The 'customer' for NHS Lyme tests is not PHE or RIPL or doctors, it is the patients that get tested. It is the interests of patients and what they want and need that must come first. Patients may understandably place a high value on their health. They may appreciate being able to go to work, have holidays and play an active role in their social circles. They may enjoy being able to walk, talk, read and watch TV. Those that understand that a severe case of Lyme disease could deprive them of all of those things, might well consider that a £200 test with 60% sensitivity would be a far better purchase than a £50 test with 50% sensitivity. Society at large might also agree, if it understands that inaccurate testing could deprive it of thousands of formerly productive citizens who have become disabled because of a false-saving on testing. The question posed in the draft is a compound question when it should have represented two completely different issues. This indicates a disturbing lack of understanding of the complexities, consequences and costs of Lyme disease diagnosis and misdiagnosis, and an even more disturbing lack of caring.	enough to capture any differences in costs and outcomes. This is often a lifetime. NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that committees should consider when judging whether an intervention offers good value for money. In general, an intervention would be considered to be cost effective if either of the following criteria applied: 1) The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or 2) The intervention costs less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

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						We recognise the question is a compound question but wished to emphasise both aspect of the question in the title. The format of the question does not dictate the detail of the research.
SH	VIRAS	Short	20	13	"Many symptoms associated with Lyme disease have more common causes, so testing is helpful to ensure accurate diagnosis and appropriate treatment" This bizarre sentence appears to be contrived to mislead with assumptions. A test with ~50% accuracy cannot possibly be "helpful to ensure accurate diagnosis" – it is impossible. In all cases, diagnosis is based on a physician's evaluation of the evidence. Laboratory testing as used by the NHS is already known to be unreliable. Just HOW unreliable remains to be seen and will only ever become clear when those tests can be compared with better tests, which have been demonstrated to have sufficient accuracy to actually provide an acceptably reliable diagnosis, e.g., with sensitivity and specificity equivalent to tests for HIV. Numerous aspects of these draft guidelines are not only bereft of scientific exactitude, they appear to be innocent of the most basic powers of logic. Thank goodness this is only a draft.	Thank you for your comment. This section has been changed following stakeholder comment and the addition of recommendations highlighting the importance of treatment if there is high clinical suspicion both while waiting for test results and if results are negative.

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SH	VIRAS	Short	21	8	"Because of the limitations of tests for Lyme disease the committee also agreed that people with negative test results who continue to have symptoms might be discussed with or referred to an infectious disease specialist or a specialist appropriate for the person's symptoms to review whether further tests are needed or to consider alternative diagnoses." This statement appears innocent enough even though it actually makes no sense. But for those who are aware that PHE have formulated cynical plans to marginalise chronically ill Lyme patients, it appears that this statement is part of that agenda. EVERY patient with ongoing symptoms gets further investigation when initial investigations do not find the cause of their symptoms. This is routine practice, which makes the draft guideline statement bizarre. The claim that the referral of patients to a specialist is: "Because of the limitations of tests for Lyme disease", appears disingenuous and evidence is provided below to support this view. The NICE draft guideline statement appears to be just one stage of a planned DISENGAGEMENT STRATEGY to get rid of problem patients, who have negative Lyme serology but remain ill with symptoms correlating to Lyme. This criteria will predictably apply to the vast majority of UK patients with chronic Lyme disease. The procedure for this particular 'stage' of disengagement is that a 'Consultant physician' will	Thank you for your comment. The recommendations in this section and the rationale have been re-worded. The intention of the committee is that the guideline will improve awareness and knowledge of Lyme disease and improve patient care. The research recommendations were developed to provide information on clinical course including response to treatment and long-term follow up.

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					have examined the case or discussed it with a GP, and when they cannot find anything wrong and based-on-all-the-evidence, declare that they are certain that it is not Lyme disease. This is to be followed by the Penultimate Stage when the 'Specialist' says, "I am sorry that you have these (subjective) symptoms, but we cannot find any cause for them, perhaps you should see a psychiatrist". The Final Stage is for the GP to provide a diagnosis of Chronic Fatigue Syndrome (CFS) and offer a course of CBT or Graded Exercise. Whatever the patient does or says, their symptoms have been investigated to the fullest extent necessary to prevent a successful complaint and they are now officially, on a medical rubbish-heap where they can be refused any further investigations or treatment. If they don't like it, they can take themselves and their illness elsewhere. If they do not get a label of 'CFS', alternatives might include Post-Treatment Lyme Disease Syndrome (if they had any treatment for Lyme) Somatic Symptom Disorder, Bodily Distress Disorder, Malingering or Being a Nuisance, or any other convenient waste-basket label which all amount to the same thing. This is PHE's plan for the 'disengagement' of chronically ill Lyme patients from their healthcare provider. PHE must be delighted with the contribution that the draft guidelines makes towards realising this goal. EVIDENCE OF PLANS TO MARGINALISE AND DISENFRANCHISE PATIENTS WITH CHRONIC LYME DISEASE	

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					In a document prepared by PHE and submitted to the Health and Safety Executive (HSE) (http://www.hse.gov.uk/aboutus/meetings/committees/acdp/161012/acdp_99_p62.pdf) are the following remarks: "As a significant proportion of self-acclaimed Lyme sufferers are self diagnosed, with no objective evidence of infection, it is essential to develop protocols that identify true cases, and refer those with other conditions sympathetically but firmly to appropriate practitioners for their problems." (p.3) "RIPL and HPA staff will discuss with Simon Wesseley's (sic) group and other interested parties the development of guidance for clinicians on dealing with the disaffected group with unprovable Lyme disease. This will cover the therapeutic approach, investigation of cases and "disengagement" strategies when further investigation is counter-productive." (p.24) According to these draft NICE Guidelines, and in fact, most other guidelines for Lyme disease, the only objective sign of the infection is an EM rash which occurs in around 25% of cases. If PHE took the trouble to actually communicate with patients, they would find that many of these so-called "self diagnosed" patients, have in fact had EM rashes. Aside from an EM rash, the only practical currently available 'objective evidence' is direct detection of the infective organism, or as a second best - indirect detection by the presence of immune markers. Contrary to the assertions of PHE, many of the	

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					patients that they have denigrated and intend to marginalise, do actually have 'objective evidence' of infection with Lyme bacteria, identified by top-class laboratories, some of which have accreditation superior to that of RIPL. Furthermore, in those patients that did not have or do not recall having a rash and whose only serology was provided by the inaccurate tests supplied at RIPL, it is often found that they have (or had) high risk occupations and/or leisure and sporting activities. It is also often found that they live in or have visited highly endemic areas called 'hot spots'. Also, investigation of the so-called "self diagnosed" patients would frequently show that prior to becoming ill, many of these patients were very fit and active with no history of significant physical or mental illness, and that they have an illness which has devastated their health and deprived them of their social roles and careers. They also have symptoms which strongly correlate to Lyme disease. These observations about common features of patients are based on VIRAS member's years of participation in support groups. We now witness almost daily occurrences of patients joining groups because they have illness following a tick bite, some with EM rashes, and too many of these have been dismissed by their doctor without even a test for Lyme disease. Some are told that 'there is no Lyme disease in this area', or incredibly that, 'there is no Lyme disease in the UK'. People with symptom profiles highly indicative of Lyme who do get tested are told by their doctor that 'your test results were negative so you do not have Lyme',	

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					without informing the patient that negative serology cannot exclude Lyme (rather suggesting that the doctor may be unaware of this basic fact). Many patients who had been misdiagnosed with 'Chronic Fatigue Syndrome' and M.E. and who learn about Lyme disease, share a history which strongly suggests that Lyme disease has been the cause of their illness, yet they have never been investigated. We now frequently witness patients who had been diagnosed with an EM rash or NHS positive serology, who were treated with 2 or 3 weeks of antibiotics, but weeks, months or even years later their symptoms are not just relapsing, but are worse than they were before they were originally treated. The mismanagement of Lyme disease has caused untold suffering. But instead of admitting its failings, PHE are arranging matters so that the very patients that it has so egregiously failed, will take the blame for their illness and suffer even more. The denigrating remarks in the document sent to the HSE are an insult to these patients who would be entirely justified in laying the blame for the chronic and devastating nature of their illness squarely at the door of PHE. But instead of honesty and an apology, these often terribly ill patients, they get more insults and stratagems to 'disengage' them from their healthcare providers. No ELISA, Western blot or combination of these two has ever been independently validated for UK patients or the UK strains of borrelia causing disease. In addition to its disturbing misrepresentation of sensitivity figures, the HPA then shockingly state that	

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					"A negative ELISA does not require a confirmatory western blot and is recorded as negative (Centre for Disease Control 1995)." Whilst the HPA imply that this practice will result in a tiny percentage of false negatives, the reality is that it has, and will continue to result in a substantial and foreseeable percentage of false negatives: In a study of 90 patients, Tylewska-Wierzbanowska and Chmielewski concluded that (https://www.ncbi.nlm.nih.gov/pubmed/12422608): "There is no correlation between the level of antibodies (ELISA), the number of protein bands (Western blot) and the presence of spirochetes in body fluids (culture and PCR), indicating that in addition to serological testing the use of PCR and cultivation in the diagnosis of Lyme borreliosis should be recommended." The implications of this are important. This study was a rare example of the type of study needed to quantify the comparative efficiency of different testing methods. This type of investigation is almost completely absent from Lyme disease literature and with good reason. It must cause serious consternation to test kit manufacturers and anyone who has made exaggerated claims for these tests and whose credibility could depend on those same kits being reliable. Yet the research showed unequivocally that whenever a single testing methodology is used, its sensitivity is unacceptable. Please remember, that even with 2 tier testing, diagnosis is by two SINGLE tests. This DOUBLES the chances for low sensitivity to exclude patients from a diagnosis and treatment.	

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					RIPL omitted to apply this basic scientific discipline when they chose the VIRAMED tests for UK patients. They 'validated' the new test against the two-tier test they had previously been using, and which relied on virtually identical methodology. What Tylewska-Wierzbanowska and Chmielewski showed, is that the presence of borrelia antibodies has no reliable correlation to the presence of Lyme spirochaetes infecting a patient. The implications of this finding has been continuously evaded by test kit manufacturers and testing laboratories such as RIPL. There can be only one interpretation of this anti-evidence, anti-science conduct, and that is that the intention is to NOT diagnose and not treat Lyme disease. So, whilst we do not know exactly how many false negative ELISA's RIPL produce, according to the literature it will be a bare minimum of 30% and would probably be shown to be double that amount if alternative methods were used and increase again if UK isolates were included. In two-tier testing (as required by PHE for Lyme serology) the number of false negatives would render the method entirely useless except perhaps in helping to confirm a small percentage of TRUE POSITIVES, whilst at the same time producing numbers of FALSE NEGATIVES that would be unacceptable in any other serious infectious disease.	

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					We do not know whether RIPL's current virtual monopoly on Lyme disease testing for patients in England represents a conflict of interests for members of the GDC, but the recommendations in the draft guideline would obviously ensure that the monopoly continues. Whilst that monopoly cannot do RIPL's reputation any harm, it is reasonable to speculate that it serves their purposes, whether those purposes include costs, or control over diagnosis and treatment of Lyme disease in the UK, and control over antibiotic prescriptions for infected patients. In the production of this draft guideline, it appears that NICE have permitted the GDC to be controlled by those who are in collusion with highly questionable conduct, have interests which would predictably compete with the most effective diagnostic methods and treatment of patients, anti-trust issues preventing open competition for laboratories to market their tests on a level-playing-field, preconceived opinions about patients and outright abuse of those patient's, their rights and needs. The whole thing reeks of a predefined agenda that has been facilitated and promoted by NICE, and which from all appearances will be endorsed and 'validated' by the auspices of NICE.	
SH	Wiltshire Council	Evidence Review M	6	7	Person to person transmission: Really important question to address and helpful for the public	Thank you for your comment.
SH	Wiltshire Council	Evidence Review N	8	7	Good to acknowledge this uncertainty	Thank you.
SH	Wiltshire Council	Evidence Review N	14	22	Do new need to be specific about insect repellents containing DEET to be effective and also that insect	Thank you for your comment. Recommendations related to repellents are discussed in evidence

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					repellents for dogs, for example may be different from those used for humans – this should be clearer	review A. We have altered the recommendation in the 'awareness' section to include need to use repellents that repel ticks.
SH	Wiltshire Council	Short	21	27	Need to ensure this change might affect practice is highlighted (and possibly where this is stated elsewhere – Would it be helpful for this to be at the front of this document, so that busy clinicians are aware of this? Tabulated?	Thank you for your comment. It is currently not usual NICE practice to highlight changes in practice as you suggest; however, an algorithm has been produced.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*