Lyme disease

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

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

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Lyme disease

NICE National Institute for Health and Care Excellence

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respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[**Lyme Disease UK**]
Type	[office use only]

	Document **(full version, short version or the appendices**	**Page number** **Or 'general' for comments on the whole document**	**Line number** **Or 'general' for comments on the whole document**	**Comments** **Insert each comment in a new row.** **Do not paste other tables into this table, because your comments could get lost – type directly into this table.**
1	Short	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

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				EBV: Epstein–Barr virus ELISA: Enzyme-linked immunosorbent assay GP: General Practitioner HIV: Human immunodeficiency virus ME: Myalgic Encephalomyelitis PCR: Polymerase chain-reaction RIPL: Rare and Imported Pathogens Laboratory TB: Tuberculosis
2	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** 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 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 implicit throughout the guideline that testing is not absolutely reliable and accurate, nowhere is it explicitly 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 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 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 implicit from the instruction to repeat courses of antibiotics and/or refer to specialists, that treatment failure occurs, however this is not explicitly

				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 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 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. 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 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 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. 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 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 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 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 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", "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 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** 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/
3	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. See our further discussion on the referral to 'specialists' in the comment referring to page 7 lines 11-14.
4	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.

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5	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. e.g. Be aware that... *'There is limited research on many aspects of Lyme disease. This guideline is based on the currently available evidence.'*
6	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.'*
7	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” 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..
8	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”.
9	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”.
10	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'*.
11	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.'*
12	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…'*

13	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 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 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

14	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.'*
15	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.

16	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 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"
17	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* http://lymediseaseuk.com/2016/03/27/literature-review-of-tick-repellents-nicola-seal/

18	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.
19	Short	4	3-5	It would be helpful to tell patients how to find patient charities and other forms of support.
20	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. 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.

21	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 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_FI

				NAL.pdf https://www.cdc.gov/lyme/signs_symptoms/rashes.html http://www.medicalacademiccenter.com/presentations/ Reference: Elizabeth Maloney, Diagnosing Lyme Disease: Clinical Strategies for Disease Detection, http://www.medicalacademiccenter.com/presentations
22	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.'*
23	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.'*
24	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 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.'*
25	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
26	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”
27	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 than” or “after”. We would suggest that *‘during the 48 hours’* is less ambiguous.
28	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.
29	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 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:'*

30	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 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.
31	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. 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'*
32	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:'*
33	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. 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

34	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?
35	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.
36	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'*.
37	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 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.'* *'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”.

38	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. 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.'*
39	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
40	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 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.'*
41	Short	6	1-4	This is a spurious and confusing statement. How can a *'supportive history'* be defined when any outdoor 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 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".
42	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.
43	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.'*
44	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.
45	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. 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. 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
46	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 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 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 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 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. References: 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/ 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

47	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.
48	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 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
49	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.
50	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 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.
51	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.

52	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 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 “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: “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
53	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.
54	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?
55	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?

56	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 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.

57	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 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.
58	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 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.

59	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 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.
60	Short	8	1-3	Validated by whom?
61	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.
62	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.
63	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.
64	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 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.'*
65	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 (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 Dec 1;319(22):1441-6. https://www.ncbi.nlm.nih.gov/pubmed/3054554
66	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.
67	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 validated as some may not yet have been fully evaluated'* and provide details.

68	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.
69	4	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.
70	4	192	28-29	Why is the view of test manufacturers ignored? Where is the evidence supporting this view?
71	4	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'.*
72	4	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.

73	4	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?
74	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.
75	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 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.
76	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 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 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
77	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?
78	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. 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.
79	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.
80	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.
81	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.
82	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: - *'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. - "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, 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.

83	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.
84	Short	12	9-10	How will organ damage be distinguished from ongoing infection if there is no 'test for cure'?
85	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?
86	Short	12	13-17	The material here should appear earlier. 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* ○ *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. ·*
87	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?
88	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?
89	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.

90	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.'*
91	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?
92	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.
93	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.
94	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.'*
95	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 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.'*
96	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 would be welcome in addition to treatment, but I don't understand why it is instead of treatment"
97	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 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.* 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 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 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.
98	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.'*
99	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 clinical symptoms I was told yes it was, before even being tested”.
100	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.
101	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.'* 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/
102	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.'*
103	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 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% 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? 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'.*
104	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.
105	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 committee suggesting that any such improvement will be permanent?
106	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.

107	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?
108	Short	15	3-4	Advise people to talk to their doctor if their symptoms have not improved or if symptoms return after completing treatment.
109	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. 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.
110	Short	15	14-20	We welcome and endorse the idea of a patient focused method being used.

111	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?
112	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.
113	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 *'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?
114	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.
115	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.
116	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 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.
117	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 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.
118	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.
119	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 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".

120	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 can not 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.
121	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.
122	Short	19	19-21	Included description of rash and characteristics are inadequate.
123	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.
124	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.

125	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.
126	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 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.
127	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.
128	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 associated with B. garinii which does not specifically feature in the Virastripe test.
129	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 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.
130	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. 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).
131	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'
132	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/

133	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.
134	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.
135	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.
136	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.
137	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.

138	Short	23	5-16	Where is the evidence to support the effectiveness of a single daily dose of doxycycline?
139	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 the brackets should be the non-focal symptoms of later disease, such as chronic fatigue and dysautonomias.
140	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.
141	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.
142	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?
143	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

144	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.
145	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.
146	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 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.
147	Short	26	12-13	This presumably constitutes evidence that Lyme disease infection is not always self-resolving and may persist.
148	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.
149	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 statement? This needs to be made very clear. Where is the evidence for this?

150	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.
151	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?
152	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.
153	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.
154	Short	28	28-29	Define *'sometimes'.* What is the evidence behind the use of this word?
155	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.

156	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?
157	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?
158	Short	29	12-15	What is a *'related symptom'* in contrast to a "symptom" of Lyme disease?
159	Short	29	16-23	Why was no evidence review on these issues carried out?
160	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?
161	Short	30	4-6	What is a *'related symptom'* in contrast to a "symptom" of Lyme disease?
162	Short	30	11-15	In the *'absence of evidence'*, how can a conclusion be drawn that *'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.
163	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.

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164	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. 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.
165	Short	31	5-6	Information on the accuracy and limitations of testing has not been made clear in this guideline.
166	Short	33	20-22	The word *'overgrown'* should be removed as it creates bias away from well-tended areas which may still 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..
167	Short	33	23	'*Lyme disease can occur anywhere in the UK*'; this is not stressed enough throughout the guidelines.
168	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?
169	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?
170	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.
171	Short	34	24-25	In this 'Context' section, the committee remarks on their research recommendations to improve basic 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 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/
172	2	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 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 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.'*
173	NICE Comments form - final	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 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.
174	NICE Comments form - final	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.
175	NICE Comments form - final	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. 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. 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/
176	NICE Comments form - final	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.
177	NICE Comments form - final	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.

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

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- Include page and line number (not section number) of the text each comment is about.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 response from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Underline and highlight any confidential information or other material that you do not wish to be made public.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Spell out any abbreviations you use
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