Lyme disease

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Stakeholder	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
British Association of Dermatologists			The British Association of Dermatologists has no comments to make on this consultation. We would request that you kindly keep us updated on developments, as an interested party.	Thank you for your comment. Updates on the progress of the guideline development and the guideline documents will be published on the NICE website in due course. You can find this information by following this link: https://www.nice.org.uk/guidance/indevelopment/gid-ng10007 As a registered stakeholder for this guideline, you will be alerted to key steps in this guideline's development.
British Association of Dermatologists			The British Association of Dermatologists has no comments to make on this consultation. We would request that you kindly keep us updated on developments, as an interested party.	Thank you for your comment. Updates on the progress of the guideline development and the guideline documents will be published on the NICE website in due course. You can find this information by following this link: https://www.nice.org.uk/guidance/indevelopment/gid-ng10007 As a registered stakeholder for this guideline, you will be alerted to key steps in this guideline's development.
Caudwell LymeCo	2	50	SUGGESTED AMENDMENT Delete "Managing other tick-borne infections" from the section "Areas that will not be covered"	Thank you for your comment. The focus of this guideline is the diagnosis and management of Lyme

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			Insert "Managing other tick-borne infections" into the section "Key areas that will be covered" (page 2 below line 49) REASON Ticks carry many infections. Caudwell LymeCo has conducted a survey of UK Lyme disease patients via social media and found that a third of them had at least one other tick-borne infection in addition to Lyme disease. The necessity of assessing suspected Lyme disease patients for additional tick borne infections is mentioned in the current guidelines issued by PHE. I think it is important for this information to remain in the new NICE guidelines, and in fact be updated and explained in more detail. Based on anecdotal evidence from patients, it seems that a lot of them are not assessed for tick-borne co-infections at all. A lot of the tick-borne infections other than Lyme disease have symptoms very similar to Lyme. It may be that some patients who seem not to respond well to Lyme treatment actually have other overlooked infections as well. EVIDENCE Neglecting to tackle co-infections is the commonest cause of Lyme disease treatment failure, according to many of the doctors in the USA and Europe who focus on treating Lyme disease patients.	Disease.We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as appropriate. We will not however address the specific management of any co-infection and as such have made no change to the scope.

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Caudwell LymeCo	3	54	SUGGESTED AMENDMENT Remove "Transmission of the disease between people" from the section "Areas that will not be covered". Insert "Transmission of the disease between people" into the section "Key areas that will be covered" (page 2 below line 49) REASON Pregnant women can transmit Lyme disease to their unborn children and this is a fact which all pregnant women with Lyme disease, and their doctors, most definitely need to know. Currently the CDC in America issues an information leaflet warning pregnant women with Lyme disease that their unborn children could catch and be harmed by Lyme disease *in utero.* Similar information for patients and their practitioners should form part of the NICE guidelines to inform doctors and patients in the UK. In fact I think a case could be made for warning all pregnant women about this risk, in the same way they are made aware of the risks of varicella, rubella and toxoplasmosis during pregnancy. There is also some preliminary research suggesting that Lyme disease may be sexually transmitted, transmitted via blood transfusions and transmitted through breastfeeding.	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee.

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			Some of the evidence regarding these potential risks is recent, and the NICE guidelines committee may be the first guidelines committee to evaluate it properly. EVIDENCE More than 46 separate cases of congenital Lyme disease in human babies have been documented in peer-reviewed research, in various regions of the world and produced in a range of prestigious institutions. The CDC patient information leaflet on Lyme in pregnancy can be viewed online here: http://www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_Lyme%20disease_PregnantWoman_FACTSheet.pdf	
Caudwell LymeCo	3	55	SUGGESTED AMENDMENT Delete "preventing Lyme disease" from the section "Areas that will not be covered" and insert it into the section "Key areas that will be covered" (page 2 below line 49) REASON A lot of patients with Lyme disease in the UK realise, with hindsight, that they exposed themselves to risks which they could have avoided. We patients do our best to warn other people, and I am confident I can speak for most patients in saying we would very much like GPs to become a part of the effort to improve the level of public knowledge on this subject. The congenital transmission route seems to be overlooked by medical professionals as	Thank you for your comment. While we understand the importance of public awareness, this is a clinical guideline on the diagnosis and management of Lyme disease and it would therefore not be appropriate to review evidence on prevention. However, we hope and anticipate that the publication of this guideline will help to raise awareness among both health care professionals and the

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			well as the public. I believe it is essential to include information in the guidelines on how to prevent pregnant women from passing Lyme disease on to their babies, particularly since there are documented cases of Lyme causing miscarriages, stillbirths, and deaths in new born babies. EVIDENCE Lyme disease can be transmitted congenitally. Many papers have been published reporting evidence of this. Borrelia is also proven to remain viable under blood transfusion conditions. There is preliminary evidence that Borrelia could be transmitted from person to person via blood transfusions, congenitally, breast feeding and even sexually. Whilst there is uncertainty, I think people who are unaware of the potential risks of these kinds, need to be protected by guidelines that embrace the possibility. I think risk assessment should accept the growing knowledge base pointing to a broader range of possible routes to exposure.	public. Pregnant women, will be included in each of our evidence reviews as a special subgroup and any direct evidence for this group, if available, will be analysed and presented separately allowing the committee to make specific recommendations in this population. (This is also the case in those people who are immunocompromised). Furthermore, person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee in due course.
Caudwell LymeCo	3	69	SUGGESTED AMENDMENT Change "Diagnostic testing to confirm or rule out Lyme disease" to "Diagnostic testing to help confirm Lyme disease"	Thank you for your comment. This has now been amended to 'Diagnostic testing for Lyme disease'.

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			REASON I believe the majority of the current commercially produced, certified diagnostic tests for Lyme disease state that a negative result cannot rule out Lyme disease. On this basis, it seems Lyme disease cannot be definitively ruled out. I think this should be reflected accurately in the scoping document. EVIDENCE Test kits' instructions which I have seen typically include an explanation of the currently known causes for sero-negativity or partial sero-negativity in patients who may actually be infected with Lyme disease. The following explanation of the diagnostic significance of antibodies against Borrelia species it taken from the instructions on the interpretation of test results published by ViraMed, the manufacturer of the western blot test kit used by RIPL. "1. IgG antibodies are produced **for the first time several weeks to months after infection** and are **often not detectable in early stages** of infection (22). In suspicion of a recent infection, IgM antibodies should be checked and a second sample should be analysed later. Patients in the 2nd or 3rd stage of the disease are **usually** positive for IgG antibodies.....5. An early antibiotic therapy can **suppress the development of antibodies** (17)."	
Caudwell LymeCo	3	71-73	SUGGESTED AMENDMENT Change "What is the most clinically- and cost-effective test or combination of tests for	Thank you for your comment. The review questions will be further

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			diagnosing Lyme disease in different clinical scenarios or presentations?" to "What is the most clinically- and cost-effective test or combination of tests for diagnosing Lyme disease, **the appropriate timing for testing, and the appropriate way to interpret test results,** in different clinical scenarios or presentations?" REASON It may turn out that the same test is best for all clinical scenarios or presentations, yet that test's results may have different meanings in different clinical scenarios. The appropriate timing of the test (in relation to believed time of exposure) and whether a repeat test is necessary, also needs to be part of the guidance given to doctors. EVIDENCE Refer to the existing test kit manufacturers' instructions on interpretation of results.	developed by the Guideline Committee based on the scope of the guideline. We will bring the detail of your comment to the attention of the guideline committee to inform that development process Recommendations will then be made based on the best available evidence identified.
Caudwell LymeCo	3	74, 76	SUGGESTED AMENDMENT Delete "a tick bite" and insert "suspected time of infection" REASON Tick bites are not the only source of infection with Lyme disease. The infection can also be spread by blood transfusion and congenitally. It MAY also be spread by breast feeding, eating unpasteurised dairy products, other biting insects or sexual contact. Since these transmission routes may also be possible, patients	Thank you for your comments about the use of the phrase "tick bite". The detailed sub questions in this section have been removed from the final version of the scope. Your comments will be shared with the guideline committee for their consideration when the protocols for review questions are discussed.

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			who may have been infected in these ways should not be excluded from laboratory testing. EVIDENCE There is no proof that tick bites are the only means of spreading Lyme disease. The recently published peer-reviewed medical papers presenting new evidence for other means of transmission should be examined and reviewed.	Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee in due course.
Caudwell LymeCo	3	74-82	SUGGESTED AMENDMENT Delete all the suggested categories. New categories need to be defined AFTER examining the explanations of how to interpret the test results of each of the test kit manufacturers. Just as an example, the test currently used by RIPL **MIGHT** divide patients into the following clinical scenarios in order to interpret their test results: 1. Suspicion of a recent infection 2. Patients 2-3 weeks after onset of the disease 3. Patients given early antibiotic therapy 4. Patients infected for a longer period of time 5. Patients on certain medication or immunoglobulin therapy 6. Patients who may have Treponema, Leptospira or other bacteria with flagella, acute EBV infection, autoimmune diseases, MS, ALS, Influenza or Syphilis. REASON The categories into which patients needs to be divided to interpret the results of their tests	Thank you for your comment on the issue of the classification of Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed detail linked to the definitions of early and late

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			will be dictated by the manufacturers of those tests. They do not interpret results based on whether the patient has been infected for more or for less than 6 months, for example. An examination of the documentation provided with each test kit should form part of the work of the committee to define these categories meaningfully. EVIDENCE The above example of possible categories for interpretation of results was taken from the instructions published by ViraMed, the manufacturer of the western blot test kit used by RIPL. 1. IgG antibodies are produced for the first time several weeks to months after infection and are often not detectable in early stages of infection (22). In suspicion of a recent infection, IgM antibodies should be checked and a second sample should be analysed later. Patients in the 2nd or 3rd stage of the disease are usually positive for IgG antibodies. Antibody titers decrease gradually during convalescence (22). 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). 3. IgA antibodies are detectable at an early stage of Borreliosis in many patients, in some cases earlier than IgM antibodies. 4. The immune response and consequently the band pattern differs from patient to patient. As a general rule: The number of antibody types and therefore the number of specific bands is increasing with progression of the disease (1). 5. An early antibiotic therapy can suppress the development of antibodies (17).	Lyme disease from the final scope.

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			6. Medication and immunoglobulin therapy can cause unspecific antibody reactions (24). 7. Cross reactivities to Borrelia antigens are described for infections with Treponema, Leptospira and other bacteria with flagella (2,15,22). An acute EBV infection can cause a polyclonal stimulation of Borrelia antibodies (22). If IgM antibodies against OspC or p41 are detected without clinical symptoms for borreliosis an EBV infection needs to be tested for. Cross reactivities in cases of autoimmune diseases, MS, ALS, Influenza and Syphilis are described as well.	
Caudwell LymeCo	4	85 - 94	SUGGESTED AMENDMENT Remove all categories as listed. A new list of patient categories and clinical scenarios needs to be composed by the committee. **Firstly** patients need to be divided into specific categories. I would suggest: 1. Active Borrelia infection with symptoms. These are sometimes divided into acute cases, and disseminated or "Late Lyme" cases. The usual cut-off point for 'acute' seems to be about 6 weeks and it is widely stated that treatment outcomes are very successful in this acute or early stage of infection, but I think the committee should check if this really is based on evidence. The patient experience is that standard treatment often fails at this stage but doctors seem not to consider this at all. 2. Latent Lyme disease, i.e. bacteriologically positive but no symptoms - This category may or may not be considered the same as category 3. This is an area where there is a lack of understanding of the patient experience – where symptoms can develop many months after being infected. It is recognised that Lyme disease can be symptom free but doctors	Thank you for your comment on the issue of the classification of Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of Lyme

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			do not seem aware that symptoms may develop later. Repeat testing, monitoring of symptoms, etc is something guidelines should address. 3. Lyme disease in remission, i.e. no symptoms but bacterial infection is still present - The experience of many patients is that they may achieve this state for periods of months or even years, with or sometimes without antibiotic treatment, but any form of stress or an insult to the immune system will trigger a return of symptoms. Many patients alternate between category 1 and category 3 for the rest of their lives after being infected with Lyme disease.	disease from the final scope.
Caudwell LymeCo	4	85-94	4. Refractory Lyme disease, i.e. treated but infection persists, and symptoms continue to worsen or new ones appear - In this category, the billion dollar question is, For how long do you treat with antibiotics before deciding a patient is a refractory case? Patients who can afford it will often keep paying privately for prolonged antibiotic treatment for as long as they feel their symptoms are improving under that treatment. Taking a lot of antibiotics for months or years causes a lot of side effects, which should be telling doctors something important about how bad it really is to live with Lyme disease. The guidelines should try to find a reliable, objective way to find out if patients really have refractory Lyme disease or Lyme disease sequelae rather than simply assuming this is the case after a standard course of antibiotics. For a patient who has been very ill with Lyme disease for a long time to be told that they are not getting any more antibiotics, and that they are never going to get rid of their symptoms, is a devastating, life-changing experience, and one that should only happen on the basis of objective medical testing if at all possible.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope. We acknowledge the very specific issues related to pregnant women and

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			5. Lyme disease sequelae, post bacteriologic cure i.e. organ damage remains as a result of past infection but symptoms are no longer getting worse - This is what some researchers mean when they use the eccentric phrase "Post treatment Lyme disease syndrome" which patients universally find infuriating. The patient experience is that their doctors usually tell them they fit this category after a short course of antibiotics (without objective evidence that this is the case) and refuse to listen when they say that their symptoms are actually still progressing and getting worse. 6. Definite tick bite - patient may or may not be infected with Borrelia. **Secondly**, cutting across these categories, there will be particular treatment considerations based on the patient's symptoms. These will include thyroid, cardiac, gastrointestinal and gall bladder symptoms, for example. A full list of such examples would be far too voluminous to complete here, but should form the focus of a thorough investigation by the committee. **Thirdly**, there will be some patients with special circumstances that need to be taken into consideration when planning antibiotic treatment, which may also cut across the categories above. These would include: 7. Pregnant women: some antibiotics cannot be used in this group but adequate treatment is essential to protect the fetus. 9. Children: I would recommend making a specific review of the evidence as regards appropriate antibiotic treatment in paediatric cases, and management of symptoms in the context of full-time education. As I understand it there will be three paediatricians on the guidelines committee and I presume their presence is required for this purpose? 10. Patients with additional tick-borne infections: overlooking other infections may result in	children. We will ensure that the needs of these groups (and the immunocompromised) are addressed as part of each of our evidence reviews. The recruitment of paediatricians to this group is to ensure that the protocols that are developed are meaningful for children and that the evidence is correctly interpreted and appropriate recommendations drafted for children. Further expertise can be co-opted if necessary to inform the guideline group. We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the

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			treatment failure for Lyme disease, or a failure to resolve Lyme disease symptoms even if Lyme disease is cured. REASON Treating Lyme disease is not simply a question of finding out if the patient has been infected for more or less than 6 months and then deciding which antibiotics to prescribe and at what dosage. Six months is an arbitrarily chosen time period and has no relationship with disease progression. More importantly, the important factor to consider is symptoms. Example 1 Around 10% of patients with Lyme disease that persists for months or years develop hypothyroid or hyperthyroid conditions which require treatment with thyroid hormone replacement or thyroidectomy (SOURCE: Caudwell LymeCo survey of around 500 Lyme disease patients; our results were the same as the statistics published in some books about Lyme disease, and found by doctors who treat many Lyme patients). Some develop Hashimoto's disease whilst others have low thyroid activity without this condition. In Lyme disease patients with low T4, TSH is also typically low. This means that standard NHS screening tests of TSH will miss the Lyme patients with hypothyroidism because their TSH will normally scrape into the bottom end of the normal range. Example 2 Many Lyme disease patients develop persistent gastro-intestinal disturbances, either diarrhoea or constipation or, most often, both in alternation. According to a Caudwell	consideration of the evidence to the recommendations made as appropriate. We will not however address the specific management of any co-infection. Thank you for your comment on the

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			LymeCo patient survey, 26% of them (120 patients out of 464) were diagnosed with irritable bowel syndrome by NHS doctors. Patients who can afford private healthcare, on the other hand, are sometimes tested for small intestinal bacterial overgrowth. When these patients are treated with suitable doses of Xifaxan they can achieve dramatic improvements in their gastro-intestinal symptoms. This not only saves them from considerable pain and social embarrassment but also enables them to achieve a better level of nutrition. Example 3 Lyme carditis causes heart block (and sometimes other arrhythmias) and is the commonest cause of death from Lyme disease, according to the Centre for Disease Control in America. The CDC says this affects 1% of Lyme patients but, based on anecdotal evidence, I think in the UK it is far more common than this. Like all arrhythmias, this phenomenon is not continuous but occurs episodically. The patient experience in the UK is that patients go to A&E departments with symptoms of palpitations, chest pain and or breathlessness etc, and are sent away after an ECG, without adequate investigation, or follow up with Holter monitoring etc. Management of this life-threatening complication of Lyme disease should be overseen by a competent electrophysiologist. General observation: The medical profession already has a standard vocabulary that can describe each category of patient unambiguously. I think it would be much clearer to use this than terms like "early" or "late" coined exclusively for Lyme disease, especially as these terms lump	issue of the classification of early and late Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of early and late Lyme disease from the final scope.

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			several different scenarios into one. If we simply replace the term "Chronic Lyme disease" with "Late disease" we don't address this problem of imprecise thinking. For example, I have read some research papers talking about "chronic Lyme disease" which hadn't clarified if the researchers actually meant untreated active Lyme disease infection, refractory Lyme disease or Lyme disease sequelae. Trying out a treatment protocol on a group of patients selected at random from all these categories and then trying to draw general conclusions about the efficacy of that therapy is not going to produce meaningful results.	
Caudwell LymeCo	6	128	SUGGESTED AMENDMENT Remove proposed category definitions. Replace with the category definitions, based on conventional and unambiguous medical terminology, which I suggested in point 8. REASON As explained above, I believe this would be far more intuitive to clinicians than these arbitrarily chosen 'early' and 'late' groupings which may mislead practitioners not specialised in Lyme disease into assuming that they are based on an inherent progression of Lyme infection when in fact they are not.	Thank you for your comment. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. The Lyme disease overview is intended as a framework for how the NICE pathway might look based on

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				the scope. It will be updated to reflect the categorisation agreed by the guideline committee.
Caudwell LymeCo	6	131	SUGGESTED AMENDMENT Remove "tick-borne". REASON Lyme disease is transmitted not only by ticks but also congenitally and by blood transfusion. There is also preliminary evidence that Lyme disease may be transmitted sexually, through breastfeeding, by other biting insects and through eating unpasteurised dairy foods from infected cattle. It is no longer valid to define Lyme as a purely tick-borne disease when there is a considerable body of research casting doubt on this. EVIDENCE **Congenital transmission:** The published medical research papers documenting babies born infected with Lyme disease are far too numerous to list here. **Transmission by blood transfusion:** For example, J Infect Dis. 1990 Aug, "Borrelia Burgdorferi: survival in experimentally infected human blood processed for transfusion."	Thank you for your comment. In response to stakeholder comments we have added person-to-person transmission to the scope of this guideline.

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			Johnson SE1, Swaminathan B, Moore P, Broome CV, Parvin M.; **Sexual transmission:** A preliminary finding in humans which corresponds with previous findings in other mammals, "Culture and identification of Borrelia spirochetes in human vaginal and seminal secretions" Marianne J. Middelveen et al.	
Caudwell LymeCo	6	135	SUGGESTED AMENDMENT Delete "from a few days to one month" and replace with "of unknown length." REASON Assessing time from infection to becoming symptomatic is challenging because many people with Lyme disease have no idea when they were first infected. 90% of Lyme disease patients have no recollection of ever seeing a tick, for example, based on patient survey results and the assessment of a well known clinic in Germany. EVIDENCE There is no valid evidence that the maximum incubation period of Lyme disease is one month. In line 134 the document states that Lyme disease can be asymptomatic. This can indeed be the case for years before a patient develops symptoms.	Thank you for your comment. It is widely accepted that the incubation period ranges from a few days to about a month. However, the course of a disease is different for each individual and some people might experience a much longer incubation period. People who experience the onset of symptoms after more than one month from the time of infection will be included in the relevant reviews.
Caudwell LymeCo	6	136	SUGGESTED AMENDMENT Delete "approximately two thirds of people" and replace with "in approximately one third of	Thank you for your comment. We have changed the wording in the

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			people" or else "in some people" REASON This oft-quoted figure, based on surveys of patients in the USA, does not correspond with the observations of doctors who treat significant numbers of Lyme disease patients in Europe. EVIDENCE For example, the BCA clinic in Augsburg, which currently has 4,000 patients under its care and whose founder has treated over 10,000 patients, has on its patient records that one ONE third of patients manifest an EM at any time during the course of their illness.	scope to read: " …..in some people this is followed by ….." to reflect the uncertainty about the true proportion of people. We note the study in Germany but have not used these figures as they do not relate to the population in England and Wales.
Caudwell LymeCo	7	138-139	SUGGESTED AMENDMENT Delete "early symptoms are similar to those for flu" and replace with "doctors lack training in recognising the symptoms." REASON The claim that "early symptoms are similar to those for flu" is true only if you condense a few randomly chosen symptoms from the whole gamut of manifestations down to a brief list of keywords. Saying that Lyme symptoms are like flu does nothing to help GPs distinguish Lyme patients from the large number of flu cases they must see each year. The weirder symptoms of Lyme disease are the ones that make many a GP dismiss their	Thank you for your comment. We used the phrase "similar to flu" to reflect that the symptoms can be non-specific. We have amended the wording in the scope to read: " …early symptoms are non-specific and can be similar to those for flu." Symptoms will be addressed by a review of the evidence (see section 2.1 and 2.2) and we hope to be able to make recommendations that will

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			Lyme patient as a hypochondriac, but these are the very symptoms that could be telling them they have a case of Lyme disease on their hands, if only they were better informed. There is also a significant proportion of patients who only have the "other" symptoms and not the "flu-like" ones at all. The kind of "slam-dunk" Lyme symptoms that should be in the list given to doctors include: "The soles of my feet feel burning hot" "I keep dropping things and bumping into things but I never used to be clumsy" "I get random itchiness which moves around my body" "I get headaches that hurt all the way down my neck and the pain instantly gets much worse at the back when I lie down" "I keep forgetting words, right in the middle of a sentence" EVIDENCE Based on anecdotal evidence, I think that when Lyme disease patients recognise the symptoms of Lyme in other people and suggest they get a blood test, their prediction accuracy rate is extremely high.	enable healthcare practitioners to be aware of the symptoms that may indicate Lyme disease.
Caudwell LymeCo	7	141	SUGGESTED AMENDMENT Delete "Lyme disease is frequently self-limiting and resolves spontaneously." REASON There is absolutely no evidence that Lyme disease is a self-limiting infection.	Thank you for your comment however we do not feel any change is required to the wording currently used. We continue to present information in this section linked to the issues when Lyme Disease has not resolved

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			EVIDENCE To prove that, you would have to prove seropositivity, not treat at all, and later prove a total absence of any symptoms after a long enough period of time to be certain the disease was not just in remission, but bacteriologically cured. Based on the patterns of remission and relapse which I have observed in patient support groups over the years, I would say five years would be the bare minimum "all-clear" period, but a more meaningful and reliable criterion would be that the patient had gone through a major insult to the immune system with no Lyme relapse. Such a research project has never been done and I think it never will be, because once you have proven seropositivity for Borrelia, how can you ethically deny the patient treatment?	spontaneously to present the fullest range of experience.
Caudwell LymeCo	7	143	SUGGESTED AMENDMENT Change "Post infectious Lyme disease" to "which may be Refractory Lyme disease or may be Lyme disease sequelae." REASON Symptoms do often persist after treatment but this may be for two separate reasons: the patient may have Refractory Lyme disease, with persistent infection after the standard antibiotic treatment; or, the patient may have Lyme disease sequelae following bacteriologic cure.	Thank you for your comment. We have deleted this phrase.

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			AN ADDITIONAL QUESTION The choice of the somewhat ambiguous term "Post-infectious Lyme disease" implies that, prior to being treated, Lyme disease in humans IS infectious. But infectious to whom? To other people? To ticks? This probably requires clarification.	
Caudwell LymeCo	7	146-147	SUGGESTED AMENDMENT Delete "There is controversy over the existence of 'chronic Lyme disease' or 'post-treatment Lyme disease syndrome'." REASON There is no longer controversy over the existence of these conditions, but rather, controversy over what these terms mean. This is because a) they are eccentric terms that don't use standard medical terminology, and b) because there are, regrettably, still many doctors who have failed to keep up to date with newer research and still believe the old assumption that Borrelia is easy to cure with a short course of antibiotics. EVIDENCE There are around 700 peer-reviewed research papers documenting cases of refractory Lyme disease, which are conveniently gathered together by Dr. Richard Bransfield, author	Thank you for your comment. We have made edits to this section and removed the speech marks and changed 'controversy' to 'uncertainty'.

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			of what are currently the only operational Lyme disease treatment guidelines in America (ILADS guidelines) http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/	
Caudwell LymeCo	7	152	SUGGESTED AMENDMENT Delete "Public health England estimates that between 2000 and 3000 people develop it each year in the UK..." REASON This "estimate" by Public health England is actually a guess rather than an estimate. In a freedom of Information request, I asked their methodology and they had none. (the FOI response is online at https://www.whatdotheyknow.com/request/313568/response/773785/attach/html/2/551%20FOI%20Lyme%20testing%20reply.pdf.html please refer to item 11.) EVIDENCE On behalf of the Caudwell LymeCo charity I have conducted a survey of close to 500 UK patients, diagnosed the RIPL and in a few selected foreign labs, and extrapolated the results to formulate an estimate which comes to around 45,000 new Lyme disease cases per year in the UK. I plan to publish this research online, explaining my input data and methodology.	Thank you for your comment. The figures provided by Public Health England are an estimate only. We note that the actual number of infections might be much higher context and further acknowledge that the true incidence in England remains unknown. We would encourage you to publish your evidence to inform the debate.

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Caudwell LymeCo	7	158-159	SUGGESTED AMENDMENT It would be useful to add to this the fact that only 10% of patients actually have any idea of when a tick bit them. REASON The majority of tick bites are by nymphs, which are no larger than a poppy seed and patients are unaware of their presence and unable to say how long they have been attached. EVIDENCE I am not aware of any objective, laboratory-based research into the relationship between the duration of tick attachment and the probability of Lyme disease infection in humans, which is the only way to assess this without relying merely on the subjective accounts of patients.	Thank you for your comment. We note that not all patients are aware of having been bitten by a tick. This is captured in an earlier part of the context section. We do not feel that an exact figure should be included in the scope as we are unaware of any evidence to support this.
Caudwell LymeCo	8	167	SUGGESTED AMENDMENT Delete "People with positive tests are treated" REASON This is not true in many cases. EVIDENCE	Thank you for your comment. This sentence has now been changed to address your comment.

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			In a Caudwell LymeCo patient survey of roughly 500 UK patients, we asked patients how many weeks of antibiotics they had been given on the NHS after their positive Lyme disease blood test, and 52% of them responded 0. Very few of them were given the full duration of antibiotics currently recommended by PHE treatment guidelines.	
Caudwell LymeCo	8	167 - 168	SUGGESTED AMENDMENT "If the test is negative but symptoms persist, repeat samples are sent 3-4 weeks later." REASON In reality, this very rarely happens. EVIDENCE The typical patients' experience with their GP in Britain is that, after one negative or even equivocal test, they are told they do NOT have Lyme disease and their doctor refuses to contemplate a second test.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and aims to describe current standard practice (in this case the PHE guidance) rather than level of uptake of guidance. We acknowledge the concerns about repeat testing; however the aim of this section is to summarise the PHE guidance and not comment on its implementation. The guideline will examine available evidence and make recommendations in this area if there is evidence to support this.
Caudwell LymeCo	DQ1		PLEASE COMMENT ON 1) Is the time period of '< than 6 months since tick bite or first symptoms or signs' an	Thank you for your response and detailed comments on our questions.

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			acceptable interpretation for 'early Lyme borreliosis'? COMMENT No, and "early lyme borreliosis" is not an acceptable term either because it is not useful either for diagnosis or for treatment decisions. Please refer to my proposed category definitions in point 8.	We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	DQ2		PLEASE COMMENT ON 2) Is the time period of '> 6 months since tick bite or first symptoms or signs' or an acceptable interpretation for 'late Lyme borreliosis'? COMMENT No, and "late Lyme borreliosis" is not an acceptable term either because it is not useful either for diagnosis or for treatment decisions. Please refer to my proposed category definitions in point 8.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	DQ3		PLEASE COMMENT ON 3) The use of the British Infection Association1 position paper classification to determine the range of clinical presentations that will be considered.	Thank you for your response and detailed comments on our questions. We will bring the detail of your

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			COMMENT This list of symptoms and clinical manifestations is woefully inadequate. it neglects to mention some of the commonest symptoms and focuses instead on those which, as it states, affect around 1% of patients. A proper list of clinical manifestations and symptomatology (with prevalences of each symptom in the UK) needs to be developed by the committee on the basis of evidence gathered among UK patients. Recycled evidence from America that does not apply to UK patients will not be particularly useful.	response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	DQ4		PLEASE COMMENT ON 4) The inclusion of the following strains of Lyme Borreliosis for consideration as part of our review of the evidence: •B. burgdorferi (and the subtype B. burgdorferi sensu stricto), •B. garinii, •B. afzelii COMMENT It would obviously be ideal to test for all known strains of Borrelia Burgdorferi sensu lato which can cause Lyme disease. However, given that this may be impractical within the limitations of current western blot	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			testing, I would propose that the Borrelia Valaisiana be included as a bare minimum since it may be the Borrelia strain involved in around 7% of Lyme disease cases in Europe. EVIDENCE For example, Habálek, Z.; Halouzka, J. (1997-12-01). "Distribution of Borrelia Burgdorferi sensu lato genomic groups in Europe, a review". European Journal of Epidemiology	
Caudwell LymeCo	DQ5		PLEASE COMMENT ON 5) The appropriate diagnostic tests for consideration COMMENT At the original scoping meeting, a long list of diagnostic tests was presented. There is no logical reason or evidence at this stage that could justify excluding any of those tests from being investigated and evaluated in terms of their sensitivity and specificity. Whether or not they are chosen for use by the NHS, there may be patients who pay for those tests privately. Duly evaluated, objective data on their sensitivity and specificity should be provided to these patients' doctors in a transparent manner.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Department of Health			Thank you for the opportunity to comment on the draft scope for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.

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Department of Health			Thank you for the opportunity to comment on the draft scope for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.
Healthcare Infection Society (HIS)	General	General	The Healthcare Infection Society has received no comments on this consultation	Thank you for your comment.
Lyme Disease Action	1	5	Using a title of Lyme borreliosis, rather than Lyme disease, would bring the guidelines into line with the rest of Europe. European Lyme borreliosis is recognised to be different from Lyme disease in the USA, due to a greater variety of genospecies and strains of Borrelia endemic in Europe.	Thank you for your comment. We have decided to use the title Lyme disease as it is a widely accepted term which we feel is more accessible to non-healthcare professionals than Lyme borreliosis. In addition it directly reflects the commission received from NHS England. The guideline committee will make the final decision on whether to include evidence from outside UK and Europe.
Lyme Disease Action	2	31	We feel that individual consideration should be given to immunocompromised people and pregnant women in whom diagnosis may be more difficult and treatment may be different.	Thank you for your comment. The guideline committee will review the evidence about diagnostic test

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				accuracy and management strategies in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations for the NHS. Where no evidence is available, the committee may be able to make research recommendations. These subgroups have been included in the equality impact assessment for this guideline.
Lyme Disease Action	2	38	Consideration at assessment should be given to 'red flags' such as severe neurological, cardiac and ophthalmic complications requiring specialist referral, and also special groups such as pregnancy and immunosuppression. See also comment on line 50 of the scope.	Thank you for your comment. We will pass the detail of your comment related to severe neurological, cardiac and ophthalmic complications to the guideline committee for their consideration as they develop protocols linked to the appropriate

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				management for different presentations being considered The guideline committee will review the evidence in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations. These subgroups have been included in the equality impact assessment for this guideline.
Lyme Disease Action	2	39	In addition to clinical assessment mention should be made of the value of including assessment of risk of tick exposure and tick bite in the period prior to onset of symptoms, including assessment of travel history.	Thank you for your comment. This guideline will include assessment of risk of tick exposure and tick bite in the period prior to onset of symptoms as part of the topic area on assessment (history and

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				examination).
Lyme Disease Action	2	40	Remove "confirmatory" as it implies this leads to a diagnosis and it may not. Perhaps "first and second tier serology testing and the use of PCR" instead	Thank you for your comment. We believe that the term 'confirmatory' is a widely accepted term for second line tests after initial testing. We do not feel any change is necessary.
Lyme Disease Action	2	40	Suggest that item 2 is Testing (first and second tier tests) and that an additional point "Diagnosis" is introduced. Diagnosis is the result of assessment, investigations and tests which are building evidence to inform a diagnosis. 2nd line serology tests may yield false positives, especially in areas where seroprevalence is high, and may give false negatives, so it is important to separate diagnosis from testing.	Thank you for your comment. The guideline will look at the role of second-line tests as part of diagnosis as well as assessment and investigations. We feel that this is adequately captured in the "key areas that will be covered" section and have not made any changes. The exact review questions to cover the key area of 'diagnosis' will be developed by the Guideline Committee at a later stage. An evidence review on diagnostic test accuracy will look at the likelihood of a

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				test being false negative, for example. The Guideline Committee will take this into account and the findings from its other evidence reviews (for example, on assessment) when formulating recommendations.
Lyme Disease Action	2	41	This specifies Management to be "for example" treatment using antibiotics. It is unclear what other aspects to treatment might be covered - eg neuropathic pain relief, anti-inflammatories, treatment for unresolved facial palsy, physiotherapy for arthritis, pacemaker insertion etc. See our comment on section 3, Context.	Thank you for your comment. We have used the example of antibiotics as an illustrative example. The guideline committee will consider which other treatments of Lyme Disease are of relevance for the evidence review. This guideline will not address the management of conditions secondary to Lyme Disease although other NICE guidance is available in some of the areas that you mention such as in the management of neuropathic pain (https://www.nice.org.uk/guidance/cg173).
Lyme Disease	2	48	The information, education and support needs of healthcare professionals requires consideration.	Thank you for your comment. The information, education and support

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Action				needs of healthcare professionals will be considered by the guideline committee and acknowledged as part of the work linking evidence to recommendations rather than as a formal review question. It is anticipated that the publication of the guideline will provide helpful information for healthcare professionals which may then be further developed by relevant groups.
Lyme Disease Action	2	50	Although this guideline will not cover management of other tickborne infections, it is important to mention somewhere in the guideline that co-infections eg. Anaplasmosis, may lead to more severe symptoms, interfere with test results and possibly also response to treatment as a result of immune suppression. See comment on line 38 re Red Flags. Public Health England Porton have identified cases of Anaplasmosis, and Lyme Disease Action has had experience of some cases via the help desk.	Thank you for your comment. The focus of this guideline is the diagnosis and management of Lyme Disease. We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as appropriate. We will not however

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				address the specific management of any co-infection and as such have made no change to the scope.
Lyme Disease Action	2	51	It is not clear why CFS is specifically named as fatigue due to Lyme borreliosis does not equate to CFS/ME. Other conditions such as multiple sclerosis, rheumatoid arthritis, Sjogrens Syndrome, etc are not mentioned, so why CFS.	Thank you for your comment. The remit of this guideline is the diagnosis and management of Lyme disease.The reference to the chronic fatigue syndrome /myalgic encephalomyelitis (or encephalopathy) guideline has been included to make it clear that the guideline will not cover management of fatigue as part of the CHF/ME. It is provided as an example of another NICE guideline that is available and is not intended to be an exhaustive list.
Lyme Disease Action	3	68	This should state "What symptoms, clinical signs and history". A person's clinical history and tick exposure is an important factor in acute Lyme borreliosis when symptoms plus history might indicate immediate treatment should be started. History is also important in late Lyme borreliosis.	Thank you for your comment. The diagnosis and management of Lyme disease will be covered in this guideline. The Guideline Committee will make recommendations based on the evidence identified.

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				History taking is part of the draft question on in whom Lyme disease should be suspected and as such will inform the relevant recommendations made in the guideline.
Lyme Disease Action	3	68	Consideration should be given to adding development of a weighting table. This was one of the Top 10 James Lind Alliance Uncertainties 'What key questions (clinical and epidemiological) should be considered to help make a diagnosis of Lyme disease in children and adults in the UK and would a weighting table be useful?' This was also raised as a key area of uncertainty during the American Association for the Advancement of Science AAAS InnovationsX conference in Washington, USA 17/18 November 2015.	Thank you for your comment. After reviewing the evidence, the guideline committee will consider the most appropriate way to present the information. The committee can also make a research recommendation if this is considered appropriate.
Lyme Disease Action	3	69	Rephrase to simply "Diagnostic testing." There is no current test which can confidently rule out Lyme disease and no test which can confirm currently active disease.	Thank you for your comment. This has now been amended to 'Diagnostic testing for Lyme disease'.
Lyme Disease Action	3	7	Transmission should be included in the guideline. Clinicians need to know what evidence there is as this question will be raised in consultations.	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the

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				Guideline Committee.
Lyme Disease Action	3	72	See answers to the directly posed question 3 re clinical presentations.	Thank you for your response to this question. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Disease Action	3	77	We do not see how someone would be considered to have late disease without symptoms or signs.	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice

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				versa. This was to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only. However, we now propose to present the guideline committee with the stakeholder feedback on the issue of clinical scenarios and presentations to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of different clinical scenarios and presentations.
Lyme Disease Action	3	79	The phrase "full course" is subjective. Currently many clinicians appear to believe that a 10 day course is "full". There is no "definitive" treatment (see James Lind Alliance uncertainties) for anything other than perhaps early Lyme borreliosis with erythema migrans and given trials in progress it is unlikely that this will change in the near future. Suggest rephrase to "early or late disease where an initial course of treatment has been completed but symptoms or signs have recurred."	Thank you for your comment. The term 'definitive' has now been removed.
Lyme Disease Action	3	82	As above: there is no definitive treatment so suggest re-phrase to "…have not resolved despite an initial course of treatment."	Thank you for your comment. The term 'definitive' has been removed.
Lyme	3	83	Insert	Thank you for your comment. The

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Disease Action			• What tests for other tick-borne infections should be considered. See comments on lines 38 and 50. • What factors to consider if the pre-test probability is raised and the test results are negative or equivocal. Given the limitations of current tests, it may not be possible to make a definite diagnosis of Lyme disease, so it would be useful to give guidance on 'probable' and 'possible' Lyme disease.	remit of this guideline is Lyme disease and therefore other tick-borne infections will not be covered. Whilst we do not feel that any change to the wording of the scope is required, we will bring the detail of your second point to the committee's attention as part of their consideration of evidence and classification of any management recommendations.
Lyme Disease Action	3	83	Is antibiotics intended to be an example of treatment or the only type of treatment to be considered? Consideration should be given to management for arthritis, neurological pain, facial palsy and endocrine, auto-immune, cardiac and ophthalmic sequelae. Some of this might depend on whether this guideline is concerned with Lyme Borreliosis (ie active infection) or with Lyme disease in its potentially wider context.	Thank you for your comment. The remit of this guideline is the diagnosis and management of Lyme disease. Antibiotic treatment is the only established treatment for Lyme disease. We acknowledge that where complications of Lyme disease occur referral for specialist NHS opinion may be desirable if the evidence supports this. The Guideline Committee will consider clinical scenarios where

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				there is a need for specialist referral for management of complications. This guideline will not however, consider in detail the management of these complications.
Lyme Disease Action	3	84	See answers to the directly posed question 3 re clinical presentations.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Disease Action	4	104	Insert an additional outcome "Continuation of symptoms or signs". It may seem a question of semantics, but evidence showing a reduction of clinical symptoms may be viewed as evidence that a treatment is "successful" whereas evidence showing a continuation of symptoms should be viewed as indicating a potentially unsuccessful intervention.	Thank you for your comment. For the purpose of the scope, we believe this is covered under the outcomes 'reduction of symptoms' and 'cure'. The guideline committee will agree the key outcomes for each review and will

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				use their expertise to determine whether the results of relevant studies are significant.
Lyme Disease Action	4	90	replace the phrase "a full course of definitive treatment" with "initial treatment	Thank you for your comment. The term 'definitive' has now been removed.
Lyme Disease Action	4	93	replace the phrase "a full course of definitive treatment" with "initial treatment"	Thank you for your comment. The term 'definitive' has now been removed. No further edits have been made.
Lyme Disease Action	4	96	The information needs of other healthcare providers requires consideration. A significant barrier to diagnosis and to effective, safe care is currently the lack of experience amongst UK clinicians. Lyme borreliosis can cause many complications and a patient may be seen by a rheumatologist, endocrinologist, neurologist, gynaecologist, physiotherapist, psychiatrist, psychologist, cardiologist and immunologist. These clinicians may not recognise the possibility of Lyme disease and have no quality, experienced resource to consult. The information and education needs of infectious diseases consultants also needs consideration. Lyme Disease Action has received many comments indicating that some do not believe Lyme borreliosis can be contracted "in their area", that negative serology means that Lyme borreliosis cannot be present and that Lyme borreliosis cannot relapse. This despite Public Health England's referral pathway for GPs which counters each of those statements. Whatever other recommendations are made during the course of this	Thank you for your comment. The information, education and support needs of healthcare professionals may be considered by the guideline committee as part of its reviews of evidence in the scope areas and acknowledged when linking evidence to recommendations. It is also anticipated that the publication of the guideline will provide helpful information for healthcare professionals and this may then be subsequently taken forward by

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			guideline development, the context section of the NICE guideline must attempt to address these issues in case this is the only resource that any clinician refers to.	appropriate providers as a resource for professionals. The NICE guideline context section will be drafted in light of the recommendations made in due course.
Lyme Disease Action	4	97	A key issue with the potential to improve outcomes is the provision of a network of regional centres of expertise. These require access to specialist diagnostic facilities a multi-disciplinary approach with a variety of healthcare professionals (nurses, physiotherapists occupational therapy etc) to meet the potential complex needs of patients with Lyme disease. This was supported by the Minister, Lord Prior, in a debate in the House of Lords in October 2015.	Thank you for your comment. The point you have raised concerns service delivery, which is unfortunately outside the remit of this clinical guideline.
Lyme Disease Action	4	97	A key issue to improve knowledge and outcomes and reduce ineffective care would be research to include follow up of patients after treatment. Consideration should therefore be given to follow up as a specific key issue, rather than just including it under treatment when symptoms or signs have not resolved. This could include consideration of diverse points such as removal of temporary pacemakers, and consideration of treatment for incompletely resolved facial palsy, in addition to consideration of further antibiotic treatment in case of relapse.	Thank you for your comment. Follow up of patients after treatment is an important part of the management of a condition and this has been identified as a specific outcome. We acknowledge a specific key issue around the management of Lyme disease when symptoms or signs have not resolved. We will bring the detail of your comment to the

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				committee for their consideration when developing protocols. The committee is able to make research recommendations where evidence is lacking or inconclusive.
Lyme Disease Action	5	111	NICE guidance on treatment of neuropathic pain CG173 is relevant.	Thank you for your comment. This section only details NICE guidance whose recommendations support overarching principles of patient management rather than recommendations for specific symptom management. . As such CG173 is not included here in line with the NICE template.
Lyme Disease Action	6	130	If this context statement is to be used in the final guideline, it is imperative that it is clear and correct. This may be the only resource consulted by a busy clinician.	Thank you for your comment. The purpose of the context section in the scope is to set the scene in terms of epidemiology, nature of the condition and current practice. It is not intended to be included as part of the narrative of the published guideline. The scope

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				is usually included as an appendix to the full published guideline.
Lyme Disease Action	6	132	It is not just B burgdorferi. Not enough is known about B miyamotoi infections, but this, and infections caused by other as yet unidentified genospecies, should not be excluded. See comment on Q4.	Thank you for your comment. The context section of the scope is intended to give a short overview of what is currently known. As such, it cannot outline all areas that are potentially being researched. Lyme disease itself is currently only linked to Borrelia burgdorferi-group. The management of co-infections is outside the scope of the guideline.
Lyme Disease Action	6	134	Where is the evidence (evidence, not personal opinion quoted in a paper) that Lyme disease can be asymptomatic? This trivialises the disease and has no place in a guideline dealing with symptomatic infection.	Thank you for your comment. We have amended the text in the scope to distinguish between asymptomatic infection and Lyme disease as a symptomatic infection.
Lyme Disease Action	6	135	There is evidence of longer incubation periods tan one month (eg Logar et al 2004).	Thank you for your comment. It is widely accepted that the incubation period ranges from a few days to about a month. However, the course of a disease is different for each individual and some people might

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				experience a much longer incubation period. People who experience the onset of symptoms after more than one month from the time of infection will be included in the relevant reviews.
Lyme Disease Action	7	137	erythema migrans may not be centred on the bite and there may be multiple erythema migrans. People have been refused initial treatment because the rash was elsewhere and therefore "could not" be erythema migrans.	Thank you for your comment. We have changed the wording in the scope to read: "...in some people this is followed by a circular, target-like rash centred on the bite, known as erythema migrans…" to reflect the uncertainty about the proportion of people affected in this way.
Lyme Disease Action	7	141	Where is the evidence that Lyme disease is frequently selflimiting? It can resolve without treatment, but frequently? A statement like this is unsafe and runs the risk of encouraging a clinician to delay treatment.	Thank you for your comment. We believe our current wording is sufficient to describe the disease trajectory.
Lyme Disease	7	142	Suggest replace "risk of later symptoms" with "risk of chronic infection".	Thank you for your comment. We have chosen to maintain the wording

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Action				linked to later symptoms as this does not rely on definition of chronic infection.
Lyme Disease Action	7	143	Remove the phrase "post infectious Lyme disease" as this implies infection has been eliminated and we do not currently have the means to know this, as there is no reliable biomarker for disease activity and no test of cure.	Thank you for your comment. We have deleted this phrase.
Lyme Disease Action	7	145	Add "frank arthritis" because this is what the pathology shows in late Lyme borreliosis.	Thank you for your comment. This part of the context is intended to be very inclusive and reflect the uncertainties and difficulties around clinical presentations of Lyme disease. As such, the sentence you are referring to is intentionally very broad. We have chosen not to make the edit you suggest.
Lyme Disease Action	7	145	Suggest replace "heart problems" with "carditis". The symptoms (heart problems) may include palpitations and heart block, but the basic pathology is inflammation in cardiac tissue which is Lyme carditis.	Thank you for your comment. The term 'heart problems' has been used because we try to write the scope in plain English as far as possible. We feel that the term 'heart problems' covers carditis.
Lyme Disease	7	146/ 147	Remove quotes round chronic Lyme disease. Perhaps rephrase that sentence to "There is uncertainty about the cause of persistent symptoms, hence disagreement amongst experts	Thank you for your comment. We have removed the quote marks and

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Action			and some controversy. The cause of persistent symptoms after antibiotic treatment is poorly understood. There is scientific proof of concept for persistence of Borrelia, immune dysfunction/auto-immunity and damage to tissues and neural networks. However, current diagnostic tests are not capable of determining which factor(s) cause chronic illness and symptoms on an individual patient basis. Current research is aimed at characterising panels of biomarkers that may assist diagnosis and inform treatment choice.	changed 'controversy' to 'uncertainty' as you suggested.
Lyme Disease Action	7	152	The only evidence we can find for Public Health England's estimate of 2000-3000 is a poster at the HPA 2007 conference. Given subsequent, also unpublished, studies it might be more accurate to simply say "The true incidence of Lyme disease remains unknown and a large proportion are not diagnosed." • An audit at a Scottish GP practice (Aberfeldy) found a rate in the practice population of 370/100,000 confirmed with a Tayside reported rate of 17/100,000. • A recent Norwegian project found a rate of 449/100,000 - 22 times the reported laboratory confirmed rate. • In the USA when figures from insurance claims were included with the laboratory confirmed rate, the incidence of Lyme borreliosis increased x10 from 30,000 to 300,000/year.	Thank you for your comment. NICE guidelines are for the NHS in England only and so we look for figures that are directly relevant to this population. The figures provided by Public Health England are an estimate only. We note that the actual number of infections might be much higher, and further acknowledge that the true incidence in England remains unknown.
Lyme Disease	7	154	This should read "The distribution of laboratory confirmed cases". Erythema migrans are confirmed cases, but are not included in the reported figures.	Thank you for your comment. We have made the change as you

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Action				suggest.
Lyme Disease Action	7	155	"with over 50% diagnosed in…" should read "with 50% of these in..". We have no data on the distribution of clinically diagnosed cases.	Thank you for your comment. We have made the change as you suggest.
Lyme Disease Action	7	157/8	People with outdoor occupations tend to be more informed and thus reduce their risk of exposure (chainsaw leggings, working boots etc). Add to this sentence ".. as are those who visit these areas for recreation".	Thank you for your comment. We have amended the text in the scope as follows: "People who spend a lot of time outdoors in these areas for work or recreational purposes are at increased risk of tick exposure. Infection is more likely if the tick remains attached to the skin for more than 24 hours"
Lyme Disease Action	7	158	Insert "A significant number of people may be infected abroad and this increases the risk of mixed infection." The percentage of ticks with co-infections is greater in many countries in continental Europe and in the USA.	Thank you for your comment. The sentence 'A number of people may also have been infected abroad.' has now been added.
Lyme Disease Action	7	158/9	So that this is not taken to exclude the possibility of infection in a shorter duration of attachment, this should be re-phrased to "Some tick-borne infections can be passed immediately on tick attachment, but the risk of Lyme disease increases with duration of attachment." In Europe research seems to suggest that it takes less time for Lyme borreliosis transmission from the tick compared to American studies. Transmission has been known	Thank you for your comment. We agree that the statement 'An infection is more likely if a tick remains attached for longer periods' is not intended to imply that Lyme disease requires a tick to be attached for more

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			to occur in under 12 hours.	than 24 hours in order to develop. We do not feel a change to the scope is required.
Lyme Disease Action	7	161	Note that although Public Health England have issued the suggested referral pathway, most GPs are unaware it exists. The wording in this section says the patients are treated, are tested etc, whereas in reality this may or may not happen. Current practice is very variable and erythema migrans have been diagnosed as cellulitis, ringworm and reaction to insect bite.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and describes current standard practice. We acknowledge that not all patients are receiving the same care, a fact which has been highlighted in the following paragraphs. This is an important purpose for this work and we are keen to ensure that this guideline, once developed, improves this situation.
Lyme Disease Action	8	169	Suggest rephrase to "… serology may be repeated to shed light on relapse and other causes are considered". Serology may show evidence for relapse but it is unclear how reliable an indicator this is.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and aims to describe current standard practice (in this case the PHE guidance) rather than level of uptake of guidance. We acknowledge the concerns about repeat serological

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				testing; however the aim of this section is to summarise the PHE guidance and not comment on its implementation.
Lyme Disease Action	8	170	Suggest replace the sentence starting "Neurologists or.." with "Consultants are involved in patient care in cases of significant neurological, rheumatological, cardiac or ophthalmic complications".	Thank you for your comment. This sentence has now been amended to address your comment.
Lyme Disease Action	8	175	Lyme borreliosis is an emerging disease in the UK and so an additional factor of "a consequence of the bacteria spreading through wildlife and therefore ticks" should be added. It is important to stress that the incidence of Lyme borreliosis is actually increasing as ticks expand their geographic spread to new areas and higher altitudes. Key ecological drivers are considered to be climate change, changes in land management eg. Fragmentation of forest habitats, resulting changes in biodiversity, changes in the way humans interact with nature eg outdoor pursuits.	Thank you for your comment. The context of the scope is intended to provide a short overview of what is currently known about Lyme disease. This section mentions that the incidence of Lyme disease is increasing for various reasons. Some additional text has been added to this section.
Lyme Disease Action	8	180	This is misleading. Suggest rephrase to "In 2012 Lyme Disease Action published the top 10 research priorities reached through a process facilitated by the James Lind Alliance." http://www.lymediseaseaction.org.uk/what-we-aredoing/research/jla-process/	Thank you for your comment. We have amended the text in the scope. We have maintained the James Lind alliance hyperlink to outline the methods used in the process of this Priority Setting Partnership.
Lyme	8	181	Add "transmission" and remove "the long term consequences of the diseases" - this latter	Thank you for your comment.

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Disease Action			does not feature in the top 10 research priorities.	Interested parties can follow the URL to see the complete information about the priorities. We have included transmission for accuracy. We have amended the text about long term consequences to say 'long term outcomes' to reflect priorities 6 and 8.
Lyme Disease Action	DQ1		In principle yes, but it should be made clear that these are arbitrary stages and some people may progress to the manifestations of late-stage disease more quickly.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Disease Action	DQ2		In principle, yes, but see comment above.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The

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				information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Disease Action	DQ3		No; this is simply a "position paper" and not an appropriate resource for this use. The clinical manifestation section and Table 1 contain misleading information - eg in that erythema migrans centres on the bite; that incidence of erythema migrans is 90% (based on a selected group of highly aware practitioner and public in Germany; a low incidence (5-8%) of Lyme neuroborreliosis is quoted which is not supported by other European literature (25%). They also lack detail, for example focusing on the erythemamigrans at the apparent expense of more serious aspects of Lyme borreliosis and there is only one small paragraph to cover the whole range of late stage disseminated disease. A more appropriate resource would be Stanek et al 2011 which includes Opthalmic manifestations omitted from Table 1 of the British Infection Association statement. Stanek et al 2011 Clinical case definitions for diagnosis and management in Europe Clin Microbiol and Infect. EFNS guidelines could be used for Lyme neuroborreliosis - Mygland et al 2010 EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Disease Action	DQ4		Note that these are not strains, they are genospecies. In the review other known, though possibly rare, human pathogenic genospecies B spielmanii and B bavariensis should be included. Antigens from	Thank you for your response and detailed comments on our questions. We will bring the detail of your

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			these are included in the immunoblot used in Scotland. See also comment on Q5 re immunoblot antigens. The review should also include Borrelia miyamotoi. Although this is more nearly related to the relapsing fever group of Borrelia, it is present in UK ticks and causes a similar clinical presentation.	response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Disease Action	DQ5		The appropriate diagnostic tests for consideration: Serology, Polymerase Chain Reaction (PCR), cerebrospinal fluid studies (microscopy for cells, with assay of protein level, IgM and IgG Borrelia immunoblot, Antibody index, CXCL13, PCR), tissue biopsy (standard pathology plus PCR), magnetic resonance imaging (MRI) brain and spinal cord (possibly enhanced), single-photon emission computed tomography (SPECT) scan, cognitive neuropsychology, autonomic function tests, nerve conduction studies (which are usually normal), sural nerve biopsy (small fibre damage). Also cardiac MRI, electrocardiogram (ECG) and 24 hour ECG (Lyme carditis).Specific consideration should be given to which immunoblots are suitable for detecting infections due to the Borrelia genospecies present in UK ticks and also whether reference laboratories should use a different immunoblot if infection is likely to have occurred outside the UK. Consideration should be given to tests that are not currently used in the UK, but which are under investigation for their potential. This includes culture, tests of T cell response to	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			infection with Lyme Borreliosis, urine antigen assays and metabolomics.	
Lyme Disease UK	2	50	Co-infections in Lyme disease patients appear to be common and should always be considered as part of the clinical picture, particularly in immunocompromised patients. 'Ticks transmit more pathogens than any other arthropod, and one single species can transmit a large variety of bacteria and parasites' (Moutallier et al, 2016). This study states, 'in the past, reports of pathology due to *Babesia*, *Anaplasma*, *Ehrlichia*, and *Bartonella* species have focused on the fulminant acute forms of infection that are relatively easy to diagnose and often fatal in immunocompromised patients. More recently, these organisms have been associated with chronic persistent infection in animal models and humans. The presence of coinfecting organisms has been shown to enhance the symptoms and exacerbate the severity of Lyme disease. Thus recognition of chronic coinfections supports the concept of unresolved illness due to persistent infection with the Lyme spirochete' (Stricker and Johnson, 2011). In a patient survey conducted by the charity Caudwell LymeCo, preliminary results show that over 30% Lyme disease patients who participated also appear to have Babesia and over 15% have Bartonella henselae. According to another survey done by Lyme Research UK in 2011, co-infections were also common in patients with Lyme disease. Out of 189 people diagnosed with Lyme borreliosis, 19 were diagnosed with Bartonella henselae, 7 with Bartonella quintana, 15 with Erhlichia, 8 with Mycoplasma and 15 with Babesia (based specifically on positive tests	Thank you for your comment and the references you have provided. The focus of this guideline is the diagnosis and management of Lyme Disease. We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as appropriate. We will not however address the specific management of any co-infection and as such have made no change to the scope.

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			with clinical assessment). Over 50% of this main group were not tested for each of these co-infections and therefore the possibility of even higher infection rates, is considerable. The scope should consider the evidence relating to co-infections, as they could be a potential cause of comorbidity or complex conditions, rendering poorer treatment outcomes for Lyme disease patients. Considering and testing for other potential tick-borne infections should be included in the Lyme disease guidelines, particularly when there are indications of more varied or persistent symptoms or when standard Lyme disease treatment has failed. Even if the management of other tick-borne infections is not included in the guidelines, there should be some reference to the possible complications they may cause in Lyme disease patients so that healthcare workers and the public are at least aware of their existence. The patient experience appears to be that co-infections do not normally form part of the NHS diagnostic process, even if Lyme disease is detected, however, the ILADS guidelines state that 'the possibility of co-infections should not be casually dismissed' (Cameron et al, 2014). References: 1: Moutailler S, Valiente Moro C, Vaumourin E, Michelet L, Tran FH, Devillers E, et al. (2016) Co-infection of Ticks: The Rule Rather Than the Exception. PLoS Negl Trop Dis 10(3): e0004539. doi:10.1371/journal.pntd.0004539	

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			http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004539 2. Stricker, R.B, Johnson, L. Lyme disease: the next decade. Infect Drug Resist. 2011; 4: 1–9. doi: 10.2147/IDR.S15653 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108755/ 3. Caudwell LymeCo patient survey, 2016 http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/ 4. Lyme Research UK patient survey, 2011 (unpublished) 5. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	
Lyme Disease UK	2	51	Lyme disease can mimic many other conditions, including chronic fatigue syndrome (CFS). Why is CFS being singled out in this draft scope as a managed condition when there is no 100% accurate serological test for either Lyme disease or CFS and therefore the two cannot be easily separated? If the two are separated, this may lead to CFS patients being unable to have their diagnosis reconsidered even if they might have Lyme disease. Furthermore, the way in which CFS is managed could potentially be harmful to an undiagnosed Lyme disease patient. Even if the risk of Lyme disease is properly investigated before diagnosing CFS (which does not always appear to be happening based on shared patient experience), weaknesses of current tests mean that some might nevertheless, actually have Lyme	Thank you for your comment. The remit of this guideline is the diagnosis and management of Lyme disease. We recognise that some people may have both Lyme disease and chronic fatigue syndrome (CFS) or other diagnoses and as such any evidence found in these groups will be considered by this guideline if it relates to the specific management of their Lyme Disease.

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			disease. Additionally, CFS patients who do not have Lyme disease may be at extra risk if they do happen to catch the disease because of the similarity in symptoms and the possibility that the infection may be dismissed as an 'exacerbation of existing CFS'. Discriminating against CFS patients who, if anything, may have a greater need to be further investigated for Lyme disease, could put these patients at risk. Preliminary results from a patient survey conducted by VIRAS show that out of 44 participants, 16 people with Lyme disease have also been diagnosed with M.E. The 2011 BIA position statement acknowledges that Lyme disease symptoms can overlap with other conditions - 'late neurological sequelae of undertreated infection include a chronic encephalomyelitis, which can present with clinical features resembling multiple sclerosis.' ILADS guidelines state, 'in addition to the possible presence of co-infections, many other illnesses and conditions have clinical features which may overlap with those of Lyme disease; some examples are: infections due to Epstein–Barr virus or syphilis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and vasculitis; metabolic and endocrine disorders such as diabetes, hypo- or hyperthyroidism and adrenal dysfunction; degenerative neurologic diseases such as Parkinson's disease and amyotrophic lateral sclerosis and neurologic conditions such as peripheral neuropathy and dysautonomia; musculoskeletal diseases including fibromyalgia and osteoarthritis, psychiatric disorders, especially depression and anxiety and other conditions such as chronic fatigue syndrome	The management of CFS is covered by another NICE guideline: www.nice.org.uk/CG53.

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			and sleep apnea' (Cameron et al, 2014). Singling out CFS as an area that will not be covered may affect the literature review in terms of excluding investigations into the possibility that some CFS patients may have Lyme disease. A recent patient survey by Caudwell LymeCo involving around 500 patients revealed that over 34% of patients who have a Lyme disease diagnosis obtained privately have only been given a CFS diagnosis by the NHS. References 1. VIRAS patient survey 2016 http://counsellingme.com/VIRAS/IsabelSymptomCheckerSurvey.PDF 2. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 3. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 4. Caudwell LymeCo patient survey, 2016	

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			http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/	
Lyme Disease UK	3	54	Transmission of the disease between people should not be excluded from the scope when there are so many important issues in this area. The CDC states, in this fact sheet that, 'untreated, Lyme disease can be dangerous to your unborn child.' The scope should include points relating to the following questions: Can Lyme disease be transmitted via blood transfusions or organ donations? Can Lyme disease be transmitted sexually or via breast milk? Furthermore, is it ethical for people not to know how infectious they are, in particular women planning pregnancy? There is no definitive test that can prove that Lyme disease has been eradicated and yet there are many studies that show that Lyme disease can be a chronic, persistent infection. There is a great deal of uncertainty in the patient community in terms of how safe it is to become pregnant or to have unprotected sex. Transmission via other biting insects and vectors such as horse-flies and mosquitoes should also be explored in the interests of public health and safety. There have been a number of new research publications in these areas since the BIA position statement published in 2011 and therefore a review of the evidence would be highly beneficial both in terms of educating the medical profession and the public. References:	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope and the points you raise will be discussed by the Guideline Committee who will decide the final review question and protocol.

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			1. Centers for Disease Control and Prevention Fact Sheet http://www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_Lyme%20disease_Pregnant Woman_FACTSheet.pdf 2. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/ 3. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf	
Lyme Disease UK	3	55	Prevention should be included in the key areas that will be covered, including the issue of whether prophylactic treatment following a known tick bite is helpful in certain cases, especially as the BIA position statement, published 2011, mentions that antimicrobial prophylaxis 'may be used in immunocompromised individuals following a tick bite.' The ILADS guidelines recommend that 'clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population' (Cameron et al, 2014). It would be worth doing a literature review on the effectiveness of prophylaxis treatment and the economic costs and savings associated.	Thank you for your comment. While we understand the importance of public awareness, this is a clinical guideline on the diagnosis and management of Lyme disease and it would therefore not be appropriate to review evidence on prevention. Preventing Lyme disease as outlined in the scope refers to the prevention of tick bites and prevention of Lyme disease in the absence of a tick bite. The role of prophylactic treatment with

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			People with Lyme disease, may present without a rash (or known tick bite) and without prior basic knowledge of their risk of tick exposure. If a doctor asks them if they have been exposed to ticks and they are not even aware of their own risk (i.e. that ticks have been found in urban parks and gardens and not just geographical hotspots around the country), they may state that the chance of tick exposure is low. This could result in the patient not being tested for Lyme disease. Prevention, in terms of patient knowledge, is therefore not entirely distinct from diagnostic pathways. Education about risks and knowledge of protection should be made available to healthcare workers and the public to reduce people's chances of contracting Lyme disease. Leaflets and notices educating people about the disease should be visible in clinics and distributed widely in communities. According to this study, 'encouraging a thorough check for ticks and promptly removal of ticks are the key public health strategies to reduce the risk of LB and other tick-borne diseases' (Dehnert et al, 2012). The ILADS guidelines recommend that when patients have been diagnosed with Lyme disease, 'during the initial visit, clinicians should educate patients regarding the prevention of future tick bites' (Cameron et al, 2014). References: 1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf	antibiotics after a tick bite will be considered. We believe that the evidence considered and the recommendations made as part of this guideline could be used to develop resources by relevant groups to inform healthcare workers but this is not the remit of this committee. We will be reviewing the evidence around the information needs of people with suspected or confirmed Lyme disease.

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			2. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 3. Dehnert M, Fingerle V, Klier C, Talaska T, Schlaud M, Krause G, et al. (2012) Seropositivity of Lyme Borreliosis and Associated Risk Factors: A Population-Based Study in Children and Adolescents in Germany (KiGGS). PLoS ONE 7(8): e41321. doi:10.1371/journal.pone.0041321 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041321	
Lyme Disease UK	3	69	It is important to note that the presentation of Lyme disease can vary significantly in terms of symptoms and clinical signs. Therefore, Lyme disease testing should be routinely included as part of the differential diagnostic process for any nonspecific symptoms which could have an infectious cause and for which another cause has not been found. However, there also needs to be awareness amongst medical professionals that there is currently no 100% accurate test available for the disease and so it cannot be ruled out based purely on serology unless a more accurate test is brought to market in the UK. Doctors need to be made aware of the shortcomings of current testing methods so that they can accurately inform patients and consider making a clinical diagnosis if applicable.	Thank you for your comment. This guideline will cover the question of which symptoms or clinical signs should lead to diagnostic testing for Lyme disease. We would like to draw your attention to a NICE guideline on symptoms with unknown causes that has not yet been commissioned, which may cover differential diagnostic processes for conditions with unknown causes. While the guideline is not listed on the NICE website yet, we would advise that you

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				register as a stakeholder for this guideline development process and submit your comments as part of its scoping processes in due course.
Lyme Disease UK	3	70	The question of how doctors can make an accurate clinical diagnosis of Lyme disease should be included in the scope as well as an exploration into how often this actually occurs in reality, especially in the absence of a 100% reliable test. Are doctors really comfortable making a clinical diagnosis of Lyme disease, particularly in the absence of an EM rash? This study states 'modern medical practice expects to rely on evidence. Most physicians would not consider diagnosing Lyme disease without serological proof' (Perronne, 2014) and this appears to reflect the general patient experience. If an EM rash is present, are doctors sufficiently aware that it is diagnostic of Lyme disease without the need for serology? Patient experience would suggest that GPs often misdiagnose EM rashes. Should effects and signs of damage consistent with Lyme disease be included as part of the clinical picture? Patients who have received a clinical diagnosis of Lyme disease from qualified medical professionals either in the UK or abroad (often with accompanying positive overseas test results) are also having the diagnosis of Lyme disease frequently dismissed. As a result, they are being denied treatment in this country. Simply running the arguably flawed UK two-tiered testing should not be used as a way to override a clinical diagnosis of Lyme	Thank you for your comment. The assessment and diagnosis of Lyme disease are covered by the key areas of "assessment (history and examination)" and "diagnosis (first-line investigations and confirmatory tests)". A review of performance in clinical practice is outside of the remit of NICE guidelines. However, we would hope that this guideline will provide health care professionals with evidence based recommendations to support them in making a diagnosis of Lyme Disease in the context of practice in England. NICE guidelines provide

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			disease obtained privately from a qualified doctor or positive overseas test results. UK doctors should also be allowed to use their own clinical judgement when assessing patients with signs and symptoms of Lyme disease, especially if they have a private clinical diagnosis and/or a positive test result from an overseas laboratory. According to the ILADS panel, 'guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary' (Cameron et al, 2014). The result of the confusion surrounding diagnosis is that many Lyme disease patients are not treated at all. Preliminary results from a patient survey conducted by Caudwell LymeCo reveal that 52% of the participating Lyme disease patients were prescribed no antibiotics whatsoever on the NHS for this condition. References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 2. Caudwell LymeCo patient co-infection survey, 2016 http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/	recommendations to clinical practice but they do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient (or if appropriate their family or carer).
Lyme Disease UK	3	71-82	References:	Thank you for your comment and the references provided. The review

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			1. Stricker, R.B, Johnson, L. Lyme disease: the next decade. Infect Drug Resist. 2011; 4: 1–9. doi: 10.2147/IDR.S15653 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108755/ 2. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 3. Burrascano, Advanced Topics in Lyme Disease: Diagnostics Hints and Treatment Guidelines for Lyme and other Tick Borne Illnesses, Sixteenth Edition, October, 2008. http://www.ilads.org/lyme/B_guidelines_12_17_08.pdf 4. Horowitz, R. The Horowitz Lyme - MSIDS Questionnaire http://www.cangetbetter.com/symptom-list 5. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full 6. Caudwell LymeCo patient survey, 2016 http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/	protocols for each review question will inform the specific search strategy for that question. We will hold the references you provide for cross checking.
Lyme Disease UK	3	74-78	The 2011 BIA position statement mentions that 'some patients with previously untreated infection can develop features of late-stage disease, months or years later.' This disease cannot be easily divided into two 6 month phases as proposed in the draft scope and it isn't useful to do this, especially if people are unaware of when they were bitten or if their symptoms have a delayed onset. At present, there is no 100% accurate serological test to	Thank you for your comment on the issue of the classification of early and late Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide

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			define any of these phases of the illness. A new, more precise list of patient categories and clinical scenarios needs to be composed by the committee and used to form the basis of evidence reviews. Possible terms include; • *Acute Lyme disease* - recently infected, seronegative due to lack of antibody production (usually less than 6 weeks). • *Secondary/2nd stage Lyme disease* - seropositive unless treated in acute stage with antibiotics. Disseminated infection but no lasting damage if treated adequately. • *Tertiary/3rd stage Lyme disease* - disseminated infection with permanent damage or complications. • *Latent Lyme disease* - seropositive but no current symptoms (as demonstrated by studies showing that a percentage of forestry workers have antibodies to Borrelia whilst being asymptomatic). It is unknown whether these people will go on to become symptomatic following stress on their immune system of any kind. • *Refractory Lyme disease* - standard treatment given but symptoms persist. With clearly defined terminology which covers a wide range of scenarios, suitable evidence reviews can take place. Terms like 'chronic Lyme disease' and even 'early' and 'late' Lyme disease cannot be properly defined in medical contexts and are open to interpretation which leads to overall confusion both for physicians and patients. . <u>References:</u> 1. British Infection Association. The epidemiology, prevention, investigation and treatment	comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of early and late Lyme disease from the final scope.

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			of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf	
Lyme Disease UK	3	79	The term 'definitive treatment' should be replaced with 'standard treatment' as there is no proof that the treatment currently being offered for Lyme disease by the NHS is effective in the majority of cases. In fact this study showed that 'over 63% of the Lyme disease cases had at least one diagnosis associated with PTLDS' (post treatment Lyme disease symptoms) following early standard treatment (Adrion et al, 2015). Patients would argue that a continuation of symptoms does not mean that the treatment was 'definitive' or successful. This information is available on Lymedisease.org's website: 'The International Lyme and Associated Diseases Society (ILADS), recently published new treatment guidelines. These guidelines contained a rigorous assessment of the evidence and found treatment failure rates ranging from 16% to 39% for early treatment. Estimates for patients with chronic Lyme disease are much higher, ranging from 26% to 50%. (Johnson 2004)' Whether ongoing symptoms are due to a continuing infection or due to a past infection is uncertain, but with many studies showing Borrelia's ability to persist, ongoing infection cannot be ruled out and therefore treatment cannot be described as 'definitive'. For those who have been treated, the patient experience often seems to be that people are told categorically by GPs that they cannot possibly still have Lyme disease following a	Thank you for your comment. The term 'definitive' has been removed.

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			standard course of antibiotics from the NHS. The ILADS guidelines state that, 'there is no compelling evidence to support routinely withholding antibiotic retreatment from ill patients. While antibiotics are not always effective, the importance of providing patients with the opportunity to receive an adequate trial of antibiotic therapy is heightened by the lack of other effective treatment approaches. Palliative care may be helpful in addressing some symptoms in some cases, but it is important to bear in mind that palliative interventions also carry risks. Additionally, clinicians must not assume that palliative interventions would provide adequate treatment in the face of an underlying persistent infection. Therefore, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill' (Cameron et al, 2014). References: 1. Adrion, ER, Aucott, J, Lemke, KW and Weiner, JP. Health care costs, utilization and patterns of care following Lyme disease. PLoS One. 2015 Feb 4;10(2):e0116767. doi: 10.1371/journal.pone.0116767. eCollection 2015 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116767 2. Lymedisease.org: Chronic Lyme Disease https://www.lymedisease.org/lyme-basics/lyme-disease/chronic-lyme/ 3. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	

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			4. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/	
Lyme Disease UK	4	102-108	An extra point for 'Main Outcomes' needs to be included (point 8) and the evidence should be reviewed on issues of chronic complex sequelae and comorbidity which may relate to Lyme disease such as heart problems, gallbladder and thyroid disease, to name a few. Many Lyme disease patients appear to suffer from the conditions mentioned above and so searching for and assessing the literature on these issues and potential connections, may lead to a greater understanding and improvements in Lyme disease patient outcomes.	Thank you for your comment. For the purpose of the scope, we believe this is already covered in the outcomes and would be addressed by the outcome 'cure' The guideline committee will agree the key outcomes for each review and will use their expertise to determine whether the results of relevant studies are significant.
Lyme Disease UK	4	94-95	An extra point should be added here (point 4.6) to include groups of patients who are immunocompromised, who have co-morbidities, who are pregnant, and who have other concurrent tick-borne infections. The BIA position statement from 2011 refers to immunocompromised patients on page 334. Children may also present differently clinically and require different treatment and this should be reflected in the guidelines. This article from Lymedisease.org highlights this point: 'Children with Lyme disease have	The guideline committee will review the evidence about diagnostic test accuracy and management strategies in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that,

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			special issues. Since they can't always explain what feels wrong, they may just come across as cranky and irritable. They suffer when their bodies hurt, when their illness disrupts their sleep at night, when they struggle in school, when they don't even feel like playing. They may feel confused, lost and betrayed by parents and teachers who fail to recognize that they are sick and need help. Children with Lyme often have trouble in the classroom, because the disease can contribute to learning disabilities and behavioral problems.' References: 1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 2. Lymedisease.org. Children with Lyme disease https://www.lymedisease.org/lyme-basics/lyme-disease/children/	where evidence exists on these issues, the committee are able to make evidence-based recommendations to the NHS. These subgroups have been included in the equality impact assessment for this guideline. Children are already detailed in the scope and will form a separate group to ensure that the evidence is appropriately identified, considered and interpreted. We plan to recruit three paediatricians to the committee for this purpose. While people with co-infections will not be excluded from the evidence reviews, the focus of this guideline is the diagnosis and management of Lyme disease. However, the guideline committee will give mention to any groups who require special

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				consideration when linking evidence to recommendations.
Lyme Disease UK	7	138-139	The draft scope mentions that early symptoms of Lyme disease 'are similar to those for flu.' However, it is also important to note that Lyme disease can mimic many other conditions and present in numerous different ways, including neuropsychiatric manifestations. Fallon and Nields, in this study state that, 'up to 40% of patients with Lyme disease develop neurologic involvement of either the peripheral or central nervous system. Dissemination to the CNS can occur within the first few weeks after skin infection' and that 'early signs include meningitis, encephalitis, cranial neuritis, and radiculoneuropathies.' This quote reflects what appears to happen frequently in the patient community: 'Time and again, Fallon, an expert in hypochondria, had seen frustrated doctors dismiss medically ill patients as psychiatric cases due to their own inability to diagnose the disease. With Lyme, the mistake was especially damaging since a delay in treatment could turn a curable, acute infection into a chronic, treatment-resistant disease' (Weintraub, 2008). It is important to include in the scope and guidelines that initial symptoms of Lyme disease are not always concurrent with a dismissable flu-like illness. Doctors must be made aware of the wide variety of ways in which Lyme disease may present and not assume symptoms are restricted to those of flu in the initial stages, especially as without a known tick bite or EM rash, it is often hard to distinguish between an acute early infection and a disseminated infection. References:	Thank you for your comment. We used the phrase "similar to flu" to reflect that the symptoms can be non-specific. We have amended the wording in the scope to read: " …early symptoms are non-specific and can be similar to those for flu."

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			1. Fallon, B. A. and Nields, J. A. (1994). Lyme disease: a neuropsychiatric illness. The American Journal of Psychiatry, 151(11), 1571–83. doi:10.1176/ajp.151.11.1571 http://www.ncbi.nlm.nih.gov/pubmed/7943444 2. Weintraub, P. Lyme Disease: The Great Imitator. Psychology Today, May 1st 2008. https://www.psychologytoday.com/articles/200805/lyme-disease-the-great-imitator	
Lyme Disease UK	7	141	The sentence 'Lyme disease is frequently self-limiting and resolves spontaneously' should be removed or rephrased. It is not representative of the general patient experience and it does not take into consideration existing and emerging evidence that Lyme disease can be a persistent infection. Furthermore, in the absence of 100% reliable tests, it cannot be proven that Lyme disease has been eradicated from a patient's body. This is highlighted in this study: 'Clinicians have no diagnostic tests to check for the persistence of live borreliae. *B. burgdorferi*, having a complex genetic structure, is a highly adaptable organism capable of evading immune response through different processes' (Perronne, 2014). The ILADS guidelines state that 'ongoing symptoms at the completion of active therapy were associated with an increased risk of long-term failure in some trials and therefore clinicians should not assume that time alone will resolve symptoms' (Cameron et al, 2014). References: 1. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-	Thank you for your comment however we do not feel any change is required to the wording currently used. We continue to present information in this section linked to the issues when Lyme Disease has not resolved spontaneously to present the fullest range of experience.

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			citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/ 2. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full 3. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	
Lyme Disease UK	7	143	As there is no test that can rule out an active Lyme disease infection, the term 'post-infectious Lyme disease' should not be used, especially when there is evidence that the infection can persist. This study states, 'extensive evidence now shows that persistent symptoms of Lyme disease are due to chronic infection with the Lyme spirochete in conjunction with other tick-borne coinfections' (Stricker and Johnson, 2011). It would be more effective to review evidence and consider alternative terminology for ongoing symptoms consistent with Lyme disease. References: 1. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-	Thank you for your comment. We have deleted this phrase.

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			bransfield/ 2. Stricker, R.B, Johnson. L. Lyme disease: the next decade. Stricker, R.B, Johnson, Infect Drug Resist. 2011; 4: 1–9. doi: 10.2147/IDR.S15653 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108755/	
Lyme Disease UK	7	146	The evidence on how to define relapse should be reviewed as the ILADS guidelines state: 'given that prior *B. burgdorferi* infections do not provide durable immunoprotection, clinicians should consider the possibility that the patient was re-infected and seek information to confirm or dispel that this occurred. In the absence of clear evidence of re-infection, clinicians and patients will need to consider the relative risks and benefits of assuming that relapsing symptoms such as EM lesions or flu-like symptoms in the summer are indicative of ongoing infection and not re-infection' (Cameron et al, 2014). References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	Thank you for your comment. The definition of relapse has not been prioritised as an area for a review question; however, management of Lyme disease in people who have Lyme disease refractory to treatment will be addressed. The Guideline Committee will discuss and agree the exact protocol for this review question based on the scope.
Lyme Disease UK	7	148	The statement 'early treatment is almost always successful' requires an evidence review. This is not reflective of the overwhelming number of people in the patient community who report ongoing health problems despite standard treatment for Lyme disease. Follow ups often do not occur, especially if patients move on to seek private Lyme disease treatment after feeling let down by the NHS, as is often the case based on anecdotal evidence from	Thank you for your comment. The topic of early treatment will be addressed by an evidence review as outlined in section 1.5

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			patients. The ILADS guidelines observe that 'the optimum duration of post-treatment observation for EM has not been determined, in part, because while disease relapse is known to occur, the duration of the latent period is variable and can be prolonged' (Cameron et al, 2014). This study shows that following early treatment, 63% patients treated for Lyme disease still had symptoms which were then attributed to 'post-treatment Lyme disease symptoms (PTLDS)' (Adrion et al, 2015). In our opinion, this does not reflect 'successful' treatment. Furthermore, 'clinicians have no diagnostic tests to check for the persistence of live borreliae. *B. burgdorferi*, having a complex genetic structure, is a highly adaptable organism capable of evading immune response' (Perronne, 2014). The ILADS guidelines also state that 'the harms associated with restricting treatment of an EM rash to 20 or fewer days of oral azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin outweigh the benefits. In assessing the risk–benefit profile, the panel determined that the failure rates for antibiotic treatment of 20 or fewer days were unacceptably high and that for those who failed treatment, the magnitude of the potential harm created by delaying definitive treatment, which includes the increased risk of developing a chronic and more difficult to treat form of the disease, was too great' (Cameron et al, 2014). References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline	

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			recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 2. Adrion, ER, Aucott, J, Lemke, KW and Weiner, JP. Health care costs, utilization and patterns of care following Lyme disease. PLoS One. 2015 Feb 4;10(2):e0116767. doi: 10.1371/journal.pone.0116767. eCollection 2015 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116767 3. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full	
Lyme Disease UK	7	156	It is important to include the fact that ticks can be found in a variety of environments including urban parks (Jennett et al, 2013). Anecdotal evidence in the patient community also demonstrates that people have been bitten in urban gardens. References: 1. Jennett, AL, Smith, FD & Wall, R, 2013, 'Tick infestation risk for dogs in a peri-urban park'. *Parasites and Vectors*, vol 6. http://www.bristol.ac.uk/biology/people/richard-l-wall/pub/32548259	Thank you for your comment. We do not consider that the text in the scope needs changing because it does not specify urban or rural environments.
Lyme Disease UK	7	163-164	Anecdotal evidence from patients suggests that many doctors fail to recognise the EM rash. Many people with EM rash appear to be diagnosed with cellulitis, a bite allergy or ringworm instead and therefore the window for early treatment is frequently missed.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and

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			This study highlights this issue by stating 'this lesion may go unrecognized, or be mistaken for an "insect bite" or an "allergic rash." Mini-erythema migrans are less likely to be diagnosed' (Perronne, 2014). References: 1. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full	aims to describe current standard practice (in this case the PHE guidance) rather than level of uptake of guidance. We acknowledge the concerns about rash recognition; however the aim of this section is to summarise the PHE guidance and not comment on its implementation. We have added text about lack of recognition of rash to section 3.1
Lyme Disease UK	8	169	When there is currently no test available to distinguish past infection from ongoing infection or new infection, the evidence and tests that the term 'relapse' is based on, should be reviewed. Additionally, anecdotal evidence exists to suggest that patients who still have a positive test following 'standard' treatment for Lyme disease are told it is likely to be a false positive, even when clinical signs would suggest an ongoing infection.	Thank you for your comment. Testing will be addressed by an evidence review (as outlined in section 1.5). The review question and protocol will be developed by the guideline committee, based on the scope.
Lyme Disease UK	General	General	Lyme Disease UK is a patient support network with nearly 4000 members and bears witness daily to thousands of patients who are suffering on an inhumane scale. Many have been ridiculed by medical professionals in various disciplines, dismissed, belittled, neglected and left with increasingly frightening and painful symptoms for which no help or guidance is offered. Many people have lost their jobs, their homes, their life savings and	Thank you for your comment which supports the need for developing a NICE guideline in this topic area. We hope that this guideline will provide clarity for NHS healthcare providers

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			their relationships and are now living in isolation and poverty. Others are left with no other option but to fundraise or in order to seek private Lyme disease and co-infection treatment (often overseas) or fund it themselves in an attempt to reverse the decline in their health and save their lives. The NHS guidance currently in use is failing these patients. The general overview is that EM rashes are frequently being ignored by GPs and that people aren't being asked about potential tick exposure. Furthermore, it often appears that people are not being offered Lyme disease testing despite presenting with numerous symptoms consistent with the disease. Some people even report hostility from doctors if they request a test and many are told that Lyme disease is either very rare or that it does not exist in this country and that they should not be researching the disease online. There have been accounts of patients, who were previously told that their Lyme disease tests were negative, discovering that they were in fact positive when they requested a copy of the laboratory report, sometimes months or years later. It also appears that people are all too readily being turned away or misdiagnosed with CFS, fibromyalgia and mental health issues without tick-borne infections even being considered. As Cameron et al point out in the ILADS guidelines, a survey involving Lyme disease patients, conducted by Johnson et al, reveals that '71.6% rated their health as fair or poor. This rate is higher than that seen in other chronic diseases including congestive heart failure, fibromyalgia, post- stroke and post-myocardial infarction status, diabetes and multiple sclerosis'. It is important to note from shared patient experience that many people who have sought ongoing private treatment for Lyme disease are seeing improvements in their health after being essentially abandoned by the NHS.	and patients linked to the diagnosis and management of Lyme disease based on the best available evidence.

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			References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 2. Johnson L, Wilcox S, Mankoff J, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. Peer J 2014;2:e322 https://peerj.com/articles/322/	
Lyme Disease UK	General	General	All known pathogenic strains of Borrelia should be covered in the scope and not just Borrelia afzelii, Borrelia garinii and Borrelia burgdorferi. One in five patients is thought to be infected abroad and so could potentially be affected by different species which should also be covered by UK testing and come under the term 'Lyme disease'. Borrelia valaisiana has been found in UK ticks according to the BIA position statement on Lyme borreliosis, although it states that Borrelia valaisiana is not regarded as pathogenic. However, in this study, Borrelia valaisiana was suspected of causing infection (Saito et al, 2007). In this study, after culturing 'live Borrelia bissettii-like strain from residents of North America,' the 'results support the fact that B. bissettii is responsible for human Lyme borreliosis worldwide along with B. burgdorferi s.s. The involvement of new spirochaete species in Lyme borreliosis changes the understanding and recognition of clinical	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			manifestations of this disease' (Rudenko et al, 2016). Borrelia miyamotoi also needs to be taken into consideration and incorporated into testing as it has been found in the UK (Hansford et al) and it is known to cause disease (Molloy et al, 2015). The brief for the scope should include a review of the literature on other pathogenic strains of Borrelia, especially as there has been a number of new research papers since the BIA position statement was issued in 2011. References: 1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 2. Saito K, Ito T, Asashima N, Ohno M, Nagai R, Fujita H, Koizumi N, Takano A, Watanabe H, Kawabata H. Case report: Borrelia valaisiana infection in a Japanese man associated with traveling to foreign countries. Am J Trop Med Hyg. 2007 Dec;77(6):1124-7 http://www.ajtmh.org/content/77/6/1124.long 3. Rudenko, N et al.Isolation of live Borrelia burgdorferi sensu lato spirochaetes from patients with undefined disorders and symptoms not typical for Lyme borreliosis. Clin Microbiol Infect. 2016 Mar;22(3):267.e9-267.e15. doi: 10.1016/j.cmi.2015.11.009. http://www.ncbi.nlm.nih.gov/m/pubmed/26673735/	

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			4. Hansford, K. M., Fonville, M., Jahfari, S., Sprong, H., & Medlock, J. M. (2014). Borrelia miyamotoi in host-seeking Ixodes ricinus ticks in England. Epidemiology and Infection, 1–9. doi:10.1017/S0950268814001691 http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=9595260&fileId=S0950268814001691 5. Molloy PJ, Telford SR 3rd, Chowdri HR, Lepore TJ, Gugliotta JL, Weeks KE, Hewins ME, Goethert HK, Berardi VP (2015). Borrelia miyamotoi Disease in the Northeastern United States: A Case Series. Annals of Internal Medicine. doi:10.7326/M15-0333 http://annals.org/article.aspx?articleid=2301402	
Lyme Research UK	3	54	Transmission of Lyme borreliosis between people is not covered: This was covered in the previous version of the Guideline scope, and we think it should remain. There is published evidence for transmission between infected mothers and babies in-utero (Schlesinger et al, 1985; Weber et al, 1988; MacDonald et al, 1987). Untreated pregnant women with Lyme borreliosis have a higher incidence of adverse outcomes of pregnancy than treated women (Lakos et al, 2010). Therefore treatment of pregnant women should be included in the scope. The appropriate treatment for pregnant women should be reviewed. What constitutes appropriate antibiotic treatment in pregnant patients has yet to be determined. The U.S. Centres for Disease Control and Prevention (2016a) state "Lyme disease acquired during pregnancy may lead to infection of the placenta and possible stillbirth; however, no negative effects on the fetus	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee. Pregnant women, will be included in our evidence reviews as a special subgroup and any direct evidence for

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			have been found when the mother receives appropriate antibiotic treatment." Surviving babies born to untreated mothers may be infected and if so may need treatment, which should also be covered in the scope. There is also some evidence suggesting that sexual transmission may be possible (Middelveen et al, 2015 in review). The evidence for sexual transmission is limited and inconclusive (Stricker et al, 2015) but we suggest adopting a precautionary principle and that clinicians should inform sexually active, infected patients of the potential risks, whilst acknowledging the knowledge in this area is uncertain. Many patients are concerned about donating or receiving blood that may be contaminated with Lyme borreliosis, and we believe that this issue should be addressed. At least one study shows B. miyamotoi's ability to survive standard blood storage (Thorp et al, 2006).	this group, if available, will be analysed and presented separately allowing the committee to make specific recommendations in this population. (this is also the case in those people who are immunocompromised).
Lyme Research UK	3	55	Preventing Lyme borreliosis is not covered: Does this only refer to ways to prevent tick bites? We think that prophylactic treatment with antibiotics after a tick bite should be considered.	Thank you for your comment. While we understand the importance of public awareness, this is a clinical guideline on the diagnosis and management of Lyme disease and it would therefore not be appropriate to review evidence on prevention. Preventing Lyme disease as outlined

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				in the scope refers to the prevention of tick bites and prevention of Lyme disease in the absence of a tick bite. Prophylactic treatment with antibiotics after a tick bite will be considered.
Lyme Research UK	3	56	"Economic aspects": We hope that you will include the potential costs of misdiagnosis and inadequate antibiotic treatment leading to chronic long-term disease in your economic analysis.	Thank you for your comment. The details of the economic analyses that may be performed for this guideline will be decided in collaboration with the Guideline Committee and will depend on the availability of data. We will take your suggestion in to consideration when developing our economic analysis.
Lyme Research UK	3	70	"2.2 Starting treatment?": When Lyme borreliosis is suspected, treatment should start immediately and be based on symptoms, since rapid treatment is important to help prevent long-term problems.	Thank you for your comment. The Guideline Committee will formulate recommendations on the timing of treatment based on the evidence identified through evidence reviews.
Lyme Research UK	3-4	79, 82, 90, 93	"Definitive treatment": The term 'definitive treatment' implies that there is absolute certainty about which antibiotic treatment will be effective for which patients, but it is not always clear when patients should	Thank you for your comment. The term 'definitive' has been removed.

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			be given more powerful intravenous antibiotics. A milder term such as the "recommended antibiotic treatment" would be more suitable here.	
Lyme Research UK	4	95-96	Information needed: The NICE guideline should give guidance to the testing laboratories that in communications to clinicians and patients they should: a) Report clearly the results of the test in the manner described by test kit manufacturers. b) Inform clinicians of the test limitations and the kit manufacturers' statements that a negative result does not indicate absence of Lyme borreliosis. c) The laboratories should not reinterpret the test results in a manner not supported by the test kit manufacturers. d) The laboratories should confine themselves to reporting the test results and should not give clinical advice on specific cases without seeing the patient, and definitely not with the very basic data sent by clinicians. e) Provide clear dates for taking samples and testing samples to ensure specimens are 'fresh' as defined by the manufacturer. f) Patients should have access to their full laboratory results if they request them.	Thank you for your comment. This is a clinical guideline for the NHS. While the points you have raised are very important, we would not usually go into this level of detail from a particular evidence review for this guideline. The committee may choose to comment on reporting issues as part of the planned diagnostic test accuracy review.

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Lyme Research UK	6	135	"Incubation period": The use of the phrase "incubation period" in the context of human infection with Borrelia is not valid. The pathogen is infectious immediately. Symptoms develop as the pathogen multiplies and disseminates.	Thank you for your comment. We use the phrase 'the incubation period' to refer to the time between infection and the onset of symptoms.
Lyme Research UK	7	134-141	You write "... in approximately two thirds of people this is followed by a circular, target-like rash centred on the bite, known as erythema migrans": We have not found the source of this estimate of two thirds and think it may actually be lower. There are difficulties in getting representative patient samples which include all types of patients. We hope that that you will look into this. This estimate can of course only be based on patients diagnosed with Lyme borreliosis. Undiagnosed patients, of whom there may be many, are less likely to have had an erythema migrans aiding diagnosis.	Thank you for your comment. We have changed the wording in the scope to read: " …..in some people this is followed by ….." to reflect the uncertainty about the true proportion of people.
Lyme Research UK	7	141, 144	You write "Lyme disease is frequently self-limiting and resolves spontaneously" and "If Lyme disease does not resolve spontaneously, ...": This implies that it often resolves without any antibiotic treatment. We do not know of any evidence for this, so think that the statements should not be made.	Thank you for your comment however we do not feel any change is required to the wording currently used. We continue to present information in this section linked to the issues when Lyme Disease has not resolved spontaneously to present the fullest range of experience.

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Lyme Research UK	7	143	You call symptoms that persist after treatment "post-infectious Lyme disease": None of the Lyme borreliosis guidelines or articles in the medical literature refer to 'post-infectious Lyme disease', and we think it is not a good idea to introduce a new term that nobody else uses.	Thank you for your comment. We have deleted this phrase.
Lyme Research UK	7	146-147	You write "There is controversy over the existence of 'chronic Lyme disease' or 'post Lyme disease' syndrome": We suggest that you delete this sentence. The British Infection Association (2011), the Infectious Diseases Society of America (Wormser et al, 2006) and the Centers for Disease Control and Prevention in the United States (2016b) now all recognize that some patients have persistent symptoms lasting for many months or years after the officially recommended treatment. See also the meta-analysis on this by Cairns et al (2005). It is debated whether this is a post-infectious syndrome or ongoing infection, although it is possible that some patients have a post-infectious syndrome while others have ongoing infection. The Centers for Disease Control and Prevention in the United States (2016b) writes: "Clinical studies are ongoing to determine the cause of PTLDS [post-treatment Lyme disease syndrome] in humans." We think that a section on this should be included in the NICE Guideline, noting results from studies such as those by Bouquet et al (2016), Chandra et al (2010) and Fallon et al (2003), and any future results from the ongoing studies referred to by the Centers for Disease Control.	Thank you for your comment. We have changed 'controversy' to 'uncertainty' to reflect the ongoing discussion around this issue. The Guideline Committee will develop review questions and protocols based on the key areas as outlined in the scope. This is to ensure that the reviews follow good scientific practice and established NICE processes when identifying, synthesising and analysing the evidence. The references you provide may form part of literature to be reviewed depending on the specific content of the protocol developed by the guideline committee. Where appropriate. they may be used

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				to inform the supporting introductory text to accompany any relevant review questions.
Lyme Research UK	7	158-159	You write "Infection is more likely if the tick remains attached to the skin for more than 24 hours": This may be taken by some to mean that an infection is very unlikely if the tick is attached for a short time. However, that is not the case. Infection can occur quickly and the minimum attachment time has never been established. Risk increases with attachment time with no evidence of a safe period (Cook, 2015), and a study indicates that removal of ticks after body searches on the day of exposure to ticks does not prevent significant risk of infection (Faulde et al, 2014). We think it would be better to replace the sentence with: "Infection risk increases with attachment time but there is no safe period and infection frequently occurs in less than 8-12 hours".	Thank you for your comment. We agree that the statement 'An infection is more likely if a tick remains attached for longer periods' Is not intended to imply that Lyme disease requires a tick to be attached for more than 24 hours in order to develop. We do not feel a change to the scope is required.
Lyme Research UK	7	165-166	You write "those without a rash, but with symptoms suggestive of Lyme disease and at risk of tick exposure, have blood tests": As discussed in our general comments, test reliability is poor, with low sensitivities for the standard two-tier serological testing. Early use of antibiotics or steroids may also abrogate the immune response and produce false negative test results. Therefore we think that diagnosis should not be reliant on testing but experienced clinicians should be encouraged to make clinical diagnoses where clinical signs are strongly indicative of Lyme borreliosis.	Thank you for your comment. We acknowledge the concerns about the diagnosis and treatment of Lyme disease. The development of this guideline will see recommendations being made based on the evidence identified through evidence reviews. This will include diagnostic tests for

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			The diagnostic pathways should be amended to allow for clinical diagnoses even in the absence of a positive test result.	Lyme disease.
Lyme Research UK	8	179	You write "Experience of typical cases is limited": We suggest you delete this sentence. With a few thousand diagnosed cases per year in the UK, around 300,000 per year in the U.S. (Centers for Disease Control, 2016c), and over 200,000 per year in Germany (Mueller et al, 2012), it seems that there must be quite a bit of experience. The term 'typical case' is best avoided, as Lyme borreliosis can present with many different symptoms (making it hard to diagnose). Or do you mean "Many GPs in the UK have limited experience with Lyme disease."?	Thank you for your comment. We have deleted the sentence.
Lyme Research UK	DQ1&2		NICE questions 1 and 2 on definition of early and late Lyme borreliosis: The stages of Lyme borreliosis are defined by the British Infection Association (2011) and the Infectious Diseases Society of America (Wormser et al, 2006) according to the extent of disease, and not by time since tick bite. Patients can vary a lot in how quickly the infection spreads. The British Infection Association (2011) writes that late-stage disease can develop "months or years later". They also write that the stages are "not clear-cut phases and should be regarded as a process".	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of

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			We therefore think it is better not to connect the stage with duration of infection, and better not to give a fixed cut-point of under or over 6 months. In fact, 'early' and 'late' are not useful descriptions of the stages of Lyme borreliosis since they imply durations of infection such as you have given. Better would be to use terms like 'localised Lyme borreliosis', 'disseminated Lyme borreliosis', and 'neurological Lyme borreliosis'.	the evidence for the questions outlined in the guideline scope.
Lyme Research UK	DQ3		NICE question 3 on range of clinical presentations: We think it is very important to point out that there is a large variety in the patterns of clinical presentation at each stage of the disease, making diagnosis difficult. Lyme borreliosis should be suspected in any patient that presents with a spectrum of the symptoms listed below. Studies of symptoms reported by patients with confirmed Lyme borreliosis include the following, and the patient will usually describe a number of these or many in a relapsing/remitting pattern. Symptoms in order of frequency of occurrence compiled from Aucott et al (2012), Djukic et al (2011), Strle et al (2006) and Trevejo et al (1999): • Arthritis/arthralgia (especially back, neck, knee, ankle) • Fatigue/malaise (frequently with headache) • Neurological symptoms (peripheral neuropathy, numbness, pins and needles, neuropsychiatric symptoms)	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			• Erythema migrans rash • Cognitive dysfunction (short term memory problems, confusion, speech problems) • Myalgia • Chills • Meningeal symptoms • Radicular pain • Sweats • Tick bite • Facial palsy (more frequent in children) • Vision problems (floater, blurred/double vision) • Cardiac problems (chest pain, heart block) • Hearing problems (tinnitus, hearing loss) • Other (dizziness, vertigo, sleep disturbance, photophobia)	

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			Neuro-psychological symptoms are also part of the spectrum.	
Lyme Research UK	DQ4		NICE question 4 on inclusion of strains of Borrelia: B. valaisiana has been detected in the UK, in addition to the Borrelia species that you list. Couper et al (2010) reported that 32% of infected ticks in south-west England had B. valaisiana, similar to the 35% in the New Forest reported by Kurtenbach et al (2001), while 58% of infected ticks had B. valaisiana in a study in northern England, north Wales and the Scottish Border region (Bettridge et al, 2013). B. valaisiana is considered pathogenic for humans (Venclíková et al, 2014), and it has been isolated in patients diagnosed with Lyme borreliosis (Pancewicz et al, 2015). We think B. valaisiana should therefore be included in your list. However, since infected ticks can be transported by birds, actually any species seen in the rest of Europe could be in ticks here too. Furthermore, people travel extensively and more than 10 million people per year vacation abroad, many of them camping and hiking. A relevant proportion of Lyme borreliosis infections seen England were caught abroad. This means that any species could be the cause in a case of Lyme borreliosis seen in the England. We think therefore you should not restrict your definition of Lyme borreliosis to three species. Species that are considered pathogenic include: B. afzelii, B. bissettii, B. garinii, B. burgdorferi s.s., B. valaisiana, B. lusitaniae, and B. spielmanii. (Venclíková et al, 2014;	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			Stanek G et al, 2011). Plus there are 14 other similar Borrelia species and more than 20 Borrelia species associated with the relapsing fever group including B. miyamotoi which results in symptoms which match those of Lyme borreliosis (Wang G et al, 2014). Furthermore, although it is generally not known with which species a patient is infected, physicians need to know that patterns of presenting symptoms vary for the different species, i.e. there is no standard set of symptoms, and that the sensitivity of the laboratory tests differs for the different species, which is an area we think NICE should investigate further.	
Lyme Research UK	DQ5		NICE question 5 on appropriate diagnostic tests for consideration: There are problems with current testing. All tests used in the UK depend on detecting antibodies. All tests can generate false negatives for the following reasons: a) Poor laboratory practice and quality control. UK Lyme testing laboratories are not accredited to ISO 15189. All laboratories should (as soon as possible) be accredited to the ISO standard to meet acceptable laboratory quality management practice. b) Intrinsic insensitivity of the tests. Data from 43 independent studies selecting for commercial test kits and reporting specificity greater than 90% gives a sensitivity of 64.5% with samples that were confirmed positive using a prior serology test or culture positive (full set of references available from Lyme Research UK). Data from 78 studies shows test	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			sensitivities as low as 15% and analysis of all studies with specificity 90% or greater the mean sensitivity is 70.9% (Leeflang et al, 2016). Since most evaluation of test kits use serum panels or samples with well characterised disease state, the results do not reflect the sensitivity when used for clinically derived samples. c) The human antibody response is slow to develop making tests highly unreliable in the early stages of disease, and the response can be affected by prior use of antibiotics, immune system suppression due to use of steroids, a compromised immune system, and the normal variation of the immune system due to age, stress, diet and pregnancy, as well as effects of the Borrelia spirochaete (Elsner et al, 2015; Strle et al, 1996; Preac-Mursic et al, 1989; Tylewska-Wierzbanovska et al, 2002; Durovska et al, 2010). d) Western Blot tests used in England are based on native antigens from 2 species plus recombinant VlsE (ViraMed Laboratory Diagnostics, 2016). It requires cross reactivity with antigens from other species for them to be detected with unknown and reduced sensitivity. e) The use of a screening test followed by a confirmatory test (2-tier test) was chosen as a method to reduce false positive tests at the Second National Conference on Serologic Diagnosis of Lyme Disease 27-29 Oct 1994. It was based on poor specificity of the early ELISA tests with resulting false positives. ELISA test manufacturers now ensure that the test specificity is close to 99%. Western blot tests also have a specificity close to 99%. Combining the test in the 2-tier sequential process reduces overall sensitivity and increases false negatives.	

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			Alternative tests to aid diagnosis: • SeraSpot • Elispot • Lymphocyte Transformation Test • Any laboratory that is fully approved and validated by international laboratory certification protocols. • Culture is widely accepted for other pathogens but requires skilled microscopists. Probably not for use in mainstream laboratories but should not be excluded. • Molecular detection methods including: Polymerisation Chain Reaction • PCR and variants o PCR/Electrospray Ionisation-Mass spectrometry. o Fluorescence in situ DNA Hybridization. o Other fluorescence systems.	

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			• Other molecular detection systems. There should be funding for study of new testing technologies and evaluation, with rapid implementation of superior methods. • An example is microscopy using digital filters and pattern recognition as developed by XRAPID for detection of malaria. • Next Generation Sequencing	
Lyme Research UK	general	general	Misdiagnosis of Lyme borreliosis: In a WHO report (Lindgren et al, 2006), the authors noted that many Lyme borreliosis infections go undiagnosed. We are concerned that many undiagnosed Lyme borreliosis patients are actually misdiagnosed and so then are never tested for Lyme borreliosis. Patients with Lyme borreliosis in the later stages frequently have profound fatigue as well as notable cognitive problems. Many may thus be misdiagnosed as having chronic fatigue syndrome or Alzheimer's disease. See for example the publication by Maheshwari et al (2015) showing a 10-fold increased diagnosis of Alzheimer's disease when there is detectable evidence of spirochaetal infection. We would like to see it addressed how patients, before receiving a diagnosis of chronic fatigue syndrome or Alzheimer's disease, might be evaluated and tested for Lyme borreliosis, keeping in mind the relatively high rate of false negatives from the laboratory tests.	Thank you for your comment. This guideline will cover in whom Lyme disease should be suspected and the assessment and diagnosis of Lyme disease. The Guideline Committee will carefully consider which assessment and diagnostic strategies can be included in the evidence reviews and will make recommendations based on the identified evidence. We would like to draw your attention to a NICE guideline on symptoms with unknown causes that has not yet been

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			Many Lyme borreliosis patients believe that the Multiple Systemic Infectious Disease Syndrome (MSIDS) differential diagnosis scoring system published by Horowitz (2016) would help clinicians diagnose Lyme borreliosis and co-infections.	commissioned, which may cover differential diagnostic processes for conditions with unknown causes.
Lyme Research UK	general	general	Coinfections as far as they impact on Lyme borreliosis: Ticks can carry other infections and patients are frequently infected by other organisms at the same time as Lyme borreliosis. We think that there should be some mention of coinfections in the guideline. In addition to Borrelia, ticks can carry over 100 other human pathogens. The proportion of infected ticks co-infected by other pathogens is very high. A recent study in France indicated 45% of infected ticks were co-infected with up to 5 pathogens (Moutailler et al, 2016). This has many implications including increased difficulty in diagnosis and complications related to treatment. Whilst the guidelines relate to Lyme borreliosis they should mention the confounding implications of co-infection.	Thank you for your comment. While people with co-infections will not be excluded from the evidence reviews, the focus of this guideline is the diagnosis and management of Lyme disease and the specific management of any co-infection will not be addressed. However, the guideline committee will give mention to any groups who require special consideration when linking evidence to recommendations.
Lyme Research UK	general	general	Special patient groups: We think that the NICE guideline should include a section on special patient groups, including people who are immunocompromised, those who are more at risk of complications (e.g. the elderly and people with comorbid conditions), and pregnant women.	Thank you for your comment. As outlined in the equality impact assessment for this guideline, the guideline committee will review the evidence about diagnostic test accuracy and management strategies

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				in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations to the NHS. These subgroups have been included in the equality impact assessment for this guideline.
Lyme Research UK	general	general	Intravenous antibiotic treatment: We are very concerned that there are Lyme borreliosis patients who need but are not getting intravenous ceftriaxone or cefotaxime once the disease has progressed to later stages. They may not be getting this treatment because a diagnosis of their neuroborreliosis has not been made. Before treating Lyme borreliosis patients with intravenous antibiotics, a positive diagnosis of neuroborreliosis is necessary. The British Infection Association Position Statement (2011) says that serology testing for Lyme neuroborreliosis should include intrathecal specific antibodies and specific cerebrospinal fluid/serum antibody index. The guidelines	Thank you for your comment. The Guideline Committee will carefully consider the evidence when making recommendations on management strategies including the role of intravenous antibiotics.

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			from the European Federation of Neurological Societies guidelines (Mygland et al, 2010) state that antibody tests for cerebrospinal fluid "are useful" in the diagnosis of Lyme neuroborreliosis, but they do not state that a positive result is essential. Unfortunately, the sensitivity of the current tests of cerebrospinal fluid is relatively low. Djukic et al (2012) reported that, of 118 patients with acute neuroborreliosis, intrathecal immunoglobulin synthesis was found in the Reiber nomograms for IgM in 70.2% and for IgG in 19.5% of patients. Isoelectric focussing detected an intrathecal IgG synthesis in 70.3%. Elevation of the Borrelia burgdorferi antibody index in the cerebrospinal fluid was found in 82.2%. The sensitivity was particularly low in patients with a meningitis course (44.4% to 61.1%). Therefore many patients with Lyme neuroborreliosis who need intravenous antibiotics may not receive a positive diagnosis because the laboratory test is inadequate. We think that, until better diagnostic tools are available, the criteria for intravenous treatment should be relaxed and not require evidence of antibodies in the cerebrospinal fluid.	
Lyme Research UK	general	general	Guideline scope: We would like to see NICE address uncertainty in existing knowledge (where relevant), and recommend what kind of research is needed to improve patient outcomes (Parliamentary Office of Science and Technology, 2004).	Thank you for your comment. The Guideline Committee will make research recommendations (if appropriate) at a later stage of the guideline development once the evidence reviews have been

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				conducted and important gaps have been identified.
Lyme Research UK	general	general	Lyme borreliosis: We think the term 'Lyme borreliosis' should be used rather than 'Lyme disease' to be consistent with the rest of Europe.	Thank you for your comment. We have decided to use the term Lyme disease as it is a widely accepted term which we feel is more accessible to non-healthcare professionals than Lyme borreliosis. In addition it directly reflects the commission received from NHS England.
Lyme Research UK	general	general	REFERENCES CITED ABOVE: Aucott JN, Seifter A, Rebman AW (2012). Probable late lyme disease: a variant manifestation of untreated Borrelia burgdorferi infection. BMC Infect Dis 2012;12(1):173 Bettridge J, Renard M, Brown KJ, et al (2013). Distribution of Borrelia burgdorferi sensu lato in Ixodes ricinus populations across central Britain. Vector Borne and Zoonotic Diseases13(3):139–146 Bouquet J, Soloski MJ, Swei A et al (2016). Longitudinal transcriptome analysis reveals a sustained differential gene expression signature in patients treated for acute Lyme disease. mBio 7(1): e00100-16	Thank you for your comment and the helpful list of references provided.

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			British Infection Association (2011). The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. Journal of Infection 62:329-338 Cairns V, Godwin J (2005). Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 34:1340-1345 Centers for Disease Control and Prevention in the United States (2016a). Transmission. http://www.cdc.gov/lyme/transmission/index.html Centers for Disease Control and Prevention in the United States (2016b). Post-treatment Lyme disease syndrome. http://www.cdc.gov/lyme/postlds/ Centers for Disease Control and Prevention in the United States (2016c). How many people get Lyme disease? http://www.cdc.gov/lyme/stats/humancases.html Chandra A, Wormser GP, Klempner MS, et al (2010). Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. Brain, Behavior and Immunity 24(6):1018-1024 Cook MJ (2015) Lyme borreliosis: a review of data on transmission time after tick	

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			attachment. Int J Gen Med 2015:8 1–8 Couper D, Margos G, Kurtenbach K, et al (2010). Prevalence of Borrelia infection in ticks from wildlife in south-west England. The Veterinary Record 167:1012-4 Djukic M, Schmidt-Samoa C, Lange P et al (2012). Cerebrospinal fluid findings in adults with acute Lyme neuroborreliosis. J Neurol 259(4):630-636 Djukic M, Schmidt-Samoa C, Nau R et al (2011). The diagnostic spectrum in patients with suspected chronic Lyme neuroborreliosis--the experience from one year of a university hospital's Lyme neuroborreliosis outpatients clinic. Eur J Neurol 18(4):547-55 Durovska J, Bazovska S, Ondrisova M et al (2010). Our experience with examination of antibodies against antigens of Borrelia burgdorferi in patients with suspected Lyme disease. Bratisl Lek Listy111(3):153-5 Elsner RA, Hastey CJ, Olsen KJ et al (2015). Suppression of long-lived humoral immunity following Borrelia burgdorferi infection. PLOS Pathog 11(7):e1004976 Fallon BA, Keilp J, Prohovnik I et al (2003). Regional blood flow and cognitive deficits in chronic Lyme disease. J Neuropsychiatry Clin Neurosci 15(3):326-32	

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			Faulde MK, Rutenfranz M, Hepke J et al (2014). Human tick infestation pattern, tick-bite rate, and associated Borrelia burgdorferi s.l. infection risk during occupational tick exposure at the Seedorf military training area, northwestern Germany. Ticks Tick Borne Dis 5(5):594-9 Horowitz R (2016). Horowitz Lyme-MSIDS Questionnaire. http://lymeontario.com/wp-content/uploads/2015/03/Horowitz-Questionnaire.pdf Kurtenbach K, De Michelis S, Sewell HS, et al (2001). Distinct combinations of Borrelia burgdorferi sensu lato genospecies found in individual questing ticks from Europe. Applied and Environmental Microbiology 67(10):4926-4929 Lakos A, Solymosi N (2010). Maternal Lyme borreliosis and pregnancy outcome. Int J Infect Dis 14(6): e494 – e498 Leeflang MMG, Ang CW, Berghout J et al (2016). The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. BMC Infect Dis 16:140 Lindgren E, Jaenson TGT (2006). WHO Report. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. http://www.euro.who.int/__data/assets/pdf_file/0006/96819/E89522.pdf	

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			treatment of tick-borne diseases. Recommendations of the Polish Society of Epidemiology and Infectious Diseases. Przegl Epidemiol 69:309-316) Parliamentary Office of Science and Technology (2004). Handling uncertainty in scientific advice. Postnote June 2004, Number 220. http://www.parliament.uk/documents/post/postpn220.pdf Preac-Mursic, Weber K, Pfister HW et al (1989). Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 17(6):355-359 Schlesinger PA, Duray PH, Burke BA et al (1985). Maternal-fetal transmission of the Lyme disease spirochete, Borrelia burgdorferi. Annals of Internal Medicine 103(1):67-68 Stanek G, Reiter M (2011). The expanding Lyme Borrelia complex-clinical significance of genomic species? Clin Microbiol Infect 17:487-93 Stricker RB, Middelveen MJ (2015). Sexual transmission of Lyme disease: challenging the tickborne disease paradigm. Expert Rev Anti Infect Ther 13(11):1303-6 Strle F, Nelson JA, Ruzic-Sabljic E, et al (1996). European Lyme borreliosis: 231 culture-confirmed cases involving patients with erythema migrans. Clin Infect Dis 23(1):61 – 65	

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			Weber K, Bratzke, HJ, Neubert U et al (1988). Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatr Infect Dis J 7(4):286–289 Wormser GP, Dattwyler RJ, Shapiro EG, et al (2006). The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. Clinical Infectious Diseases 43:1089-1134	
NHS England			Thank you for the opportunity to comment on the above Clinical Guideline. I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you for your comment.
NHS England			Thank you for the opportunity to comment on the above Clinical Guideline. I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you for your comment.
NHS Highland	3	67 to 82	The key to ensuring that the NICE recommendations are clinically useful is to have clear and relevant clinical case definitions at each stage. European clinical case definitions (Stanek, G) are narrow including no category for a flu like illness, and stringent laboratory confirmation for neuroborreliosis (requiring lumber puncture). In my opinion these are too narrow. Suggest NICE guidance divides patients into clinically defined presentations, and makes testing and management recommendations for each presentation (presentation categories	Thank you for your comment on the issue of the classification of Lyme disease as described in the consultation version of the scope. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the

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			that should be included given below). I appreciate that 'Flu like' is not an ideal label and care should be taken defining the symptoms that would qualify for this presentation. 1) Tick exposure, no symptoms 2) Seropositive, no symptoms 3) Chronic tick exposure non-specific chronic symptoms (fatigue, arthralgia, parasthesia) 4) ECM, atypical rash 5) Flu like presentation without respiratory component 6) Symptoms consistent with early neuroborreliosis including radiculitis, meningitis, cranial neuropathy and mononeuritis multiplex 7) Symptoms consistent with late neuroborreliosis including encephalomyelitis, encephalopathy, cerebral vasculitis (could be called late neuroborreliosis) *IDSA includes peripheral neuropathy in late neuroborreliosis, while European guidelines state peripheral neuropathy without achrodermatitis chronicum atrophicans is vanishingly rare – this needs to be addressed as peripheral neuropathy very common in the elderly and in endemic regions many of these people will be seropositive. Geography of exposure may influence recommendation. 8) Arthritis 9) Carditis 10) Lymphocytoma 11) Achrodermatitis chronicum atrophicans 12) Ocular manifestations	guideline to take. As such, we have removed the detail linked to the definitions of Lyme disease from the final scope.

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NHS Highland	3	69	Suggest delete 'to confirm or rule out Lyme disease'.	Thank you for your comment. This has now been amended to 'Diagnostic testing for Lyme disease'.
NHS Highland	3	71	Role of CSF tests in diagnosis of lyme neuroborreliosis. When are they indicated and how interpreted (my current practice is usually not to perform LP in borrelia seropositive radiculopathy or cranial nerve palsy in absence of meningitis)	Thank you for your comment. The Guideline Committee will consider relevant diagnostic tests and procedures in the context of differing clinical presentations when defining the review questions and protocols. We will ensure that they are informed of your comment.
NHS Highland	3	77	Delete 'or without' as not disease if asymptomatic	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice versa. This was to

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				reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only. However, we now propose to present the guideline committee with the stakeholder feedback on the issue of clinical scenarios and presentations to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of different clinical scenarios and presentations.
NHS Highland	3	83	Management recommendations could be further targeted by dividing patients into possible/probable/definite Lyme disease depending on strength of clinical presentation and test results. I appreciate that this adds complexity, but until lab diagnostics improve we will be operating in an area of diagnostic uncertainty and these labels make that explicit and allow physician and patient to appreciate the balance of risks between overtreatment and under-treatment. These distinctions become most helpful when discussing pros / cons of repeat courses of antibiotics where first line therapy has failed to improve symptoms	Thank you for your comment. Whilst we do not feel that any changes to the scope are required in this area, we will bring the detail of your comment to the committee's attention when they draft their protocol for this question
NHS Highland	3	83	Management may also include referral to specialist (eg rheumatologist). Guidance on which presentations of suspected arthritis with positive Lyme serology should be referred would be useful.	Thank you for your comment. We acknowledge that where complications of Lyme disease occur

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				referral for specialist NHS opinion may be desirable if the evidence supports this. Management strategies including specialist referral in different clinical scenarios/presentations will be explored in more detail by the Guideline Committee through the evidence reviews.
NHS Highland	4	88	As for comment no. 4	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice versa. This is to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical

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				signs only.
NHS Highland	4	90 to 96	These are important questions. Suggest may be helpful to divide symptoms into objective and subjective (indicated in some papers)	Thank you for your comment. We will ensure that this information is brought to the guideline committee's attention when they are developing the review questions and protocols.
NHS Highland	4	Figure	Cannot have Lyme disease without symptoms and signs (mentioned in both boxes of figure)	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice versa. This is to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only.

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NHS Highland	6	134	You state 'Lyme disease can be asymptomatic'. I disagree. Infection with *Borrelia burgdorferi* can be asymptomatic, but I would reserve the term 'Lyme disease' for symptomatic infection.	Thank you for your comment. We have amended the text in the scope to distinguish between asymptomatic infection and Lyme disease as a symptomatic infection.
NHS Highland	7	141	Delete 'frequently' and replace with 'can be' and 'resolves' with 'may resolve'.	Thank you for your comment. The wording of the scope has been altered.
NHS Highland	8	170	Repeat testing to assess for relapse is recommended by PHE but is controversial as antibody levels persist even when patient cured and therefore ongoing positive test not helpful. May be helpful in looking for re-infection in the re-exposed with new symptoms as different blot bands may be present. Suggest unhelpful to state that blood test can diagnose relapse.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and aims to describe current standard practice (in this case the PHE guidance) rather than critiquing the guidance. We acknowledge the concerns about repeat serological testing; however the aim of this section is to summarise the PHE guidance.
NHS Highland	DQ1&2		Relating to guideline committee's Q1 and 2 above. Distinction between early and late is only of importance if different management strategies are recommended on the basis of this distinction. Many patients have ongoing exposure	Thank you for your response and detailed comments on our questions. We will bring the detail of your

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			and fluctuating symptoms making use of these timelines impractical. The time periods are arbitrary and cannot be definitive due to various factors (eg host factors, infectious dose, strain). Six month timeline is mentioned in literature and may be reasonable but the arbitrary nature of it must be stated.	response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
NHS Highland	DQ3		Relating to guideline committee's Q 3 above. (Use of BIA position paper to determine range of presentations). I would also like NICE to consider patients with ongoing tick exposure and : 1) Flu like illness as mentioned in comment no.1. 2) Fatigue and arthralgia 3) Peripheral neuropathy or mononeuritis multiplex 4) Objective memory loss but without tetraspastic syndrome, spastic-ataxic gait disorder and disturbed micturition I think these presentations should be included in the guidance as many people with these symptoms present for testing, and a proportion are seropositive. The committee may conclude that these presentations should not lead to testing, and if inadvertently tested, should not be treated for possible Lyme disease, even if seropositive. Guidance on this would be very useful.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
NHS Highland	DQ4		Relating to guideline committee's Q 4 above. *Borrelia spielmanii, Borrelia bavariensis, Borrelia bissettii, Borrelia lusitaniae, Borrelia kutchenbachii* and *Borrelia valaisiana* also	Thank you for your response and detailed comments on our questions.

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			have pathogenic potential (see Borchers A, journal autoimmunity for useful table). Review of evidence to assess relevance to diagnostics of some of these may be worthwhile.	We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
NHS Highland	DQ4		Relating to guideline committee's Q4 above. Diagnostic test should include tests and testing strategies. All tests should be included: EIA, IF, Immunoblot, western blot, CSF/serum parallel testing by EIA/Blotting, lymphocyte transformation test, PCR and culture (joint fluids, skin biopsy, CSF, urine), direct microscopy and non-specific tests such as CXCL13, CD57+, CSF biochemistry and cytology. The committee may find many of these tests lack standardisation, sensitivity and specificity but it is still useful to have them assessed.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Royal College of Genera	2	43	The RCGP hopes that the medications recommended in the guideline are those that a) Experts recommend (even if not licensed). If the guideline recommends a medication that is contrary to expert opinion then that severely will undermine the	Thank you for your comment. The Guideline Committee will consider which medications should be included

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Practitioners (RCGP)			entire guideline. b) Are (where clinically appropriate) medications that are familiar to GPs- most of these patients will present to primary care. If these are medications that generally speaking GPs won't feel confident with then it will mean more referral to secondary care with the delay and cost that that entails. (MJ) c)	in the evidence review. As stated in the scope, recommendations are generally only made within their licensed indications unless there is strong evidence for an unlicensed indication. The Guideline Committee will also consider any potential issues around prescribing (such as the lack of familiarity in prescribing that you outline) in various settings when formulating recommendations.
Royal College of Genera Practitioners (RCGP)	2	51	There is clearly a link being made between chronic fatigue syndrome and Lyme disease by the support groups for suffers of chronic fatigue. Some GPs have seen a few patients who are desperate to pursue a diagnosis of Lyme disease to explain their fatigue symptoms. The RCGP feels that it would be invaluable if this guideline helped to differentiate on clinical grounds those fatigue suffers who need further investigation and those that we can reassure without recourse to blood tests, investigations and/or referrals. (MJ)	Thank you for your comment. This guideline only covers Lyme disease. We acknowledge that the clinical presentations of Lyme disease and chronic fatigue syndrome (CFS) can be very similar and that it can be difficult to make a definitive diagnosis of one or the other. Following systematic review of the evidence available in the scope areas of assessment diagnosis and management, the Guideline

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				Committee will make recommendations in regards to Lyme disease and may wish to cross-refer to other guidelines if appropriate. The reference to the CFS / myalgic encephalomyelitis (or encephalopathy) NICE guideline (CG53) is included as an example of another available NICE guideline and will not be covered by this Lyme disease guideline.
Royal College of Genera Practitioners (RCGP)	6	147 (question 2)	What is the role of epitope mapping of antibodies to VlsE protein of Borrelia burgdorferi in post-Lyme disease syndrome. (MH)	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. Where relevant the information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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Royal College of Genera Practitioners (RCGP)	General	General	The draft scope is an excellent working document and covers the essential areas and difficulties. (PS) and points 1-5 in the first page all seem reasonable. (MJ)	Thank you for your comment.
Royal College of Genera Practitioners (RCGP)	General	General	Overall there seems to be an increasing awareness amongst the population of this condition and yet a great deal of uncertainty amongst non-specialist clinicians as to how to diagnose and treat. Therefore the RCGP feels that this guideline is much needed. The scope seems appropriate and focussed. (MJ)	Thank you for your comment.
Royal College of Nursing			This is just to inform you that the feedback I have received from nurses working in this area of health suggests that there are no comments to submit on behalf of the Royal College of Nursing to inform on the consultation of the draft scope of Lyme Disease.	Thank you for your comment.
Royal College of Nursing			This is just to inform you that the feedback I have received from nurses working in this area of health suggests that there are no comments to submit on behalf of the Royal College of Nursing to inform on the consultation of the draft scope of Lyme Disease.	Thank you for your comment.
Royal College of Paediatrics and Child Health			Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the Lyme Disease draft scope. We have not received any responses for this consultation.	Thank you for your comment.

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The British Society for Antimicrobial chemotherapy (BSAC)			Members of The British Society for Antimicrobial Chemotherapy (BSAC) have no comments for this Guideline on Lyme disease.	Thank you for your comment.
The British Society for Antimicrobial chemotherapy (BSAC)			Members of The British Society for Antimicrobial Chemotherapy (BSAC) have no comments for this Guideline on Lyme disease.	Thank you for your comment.
VIRAS Vector-borne Infection, Research – Analysis - Strategy	DQ1& 2		**VIRAS response to NICE request for comments on 6 month 'phase' (including observations on why this might have been suggested):** "1) Is the time period of '< than 6 months since tick bite or first symptoms or signs' an acceptable interpretation for 'early Lyme borreliosis'? 2) Is the time period of '> 6 months since tick bite or first symptoms or signs' or an acceptable interpretation for 'late Lyme borreliosis'?" Pertains to Draft Scope document Page 3. Lines 74 to 77 **Abbreviations** CFS, Chronic Fatigue Syndrome	Thank you for your comment on the issue of the classification of early and late Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to

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			GDG Guideline Development Group HPA, Health Protection Agency (now part of PHE) IDSA, Infectious Disease Society of America ILADS, International Lyme and Associated Diseases Society LB, Lyme Borreliosis NHS, UK National Health Service PHE, Public Health England M.E., Myalgic Encephalomyelitis NICE, National Institute for Health and Care Excellence An arbitrary time limit deemed to be a transformation point from one Lyme borreliosis phase to another has no medical or scientific logic. Miklossy (2012) states in The Open Neurology Journal: "Late Lyme neuroborreliosis is accepted by all existing guidelines in Europe, US and Canada. The terms chronic and late are synonymous and both define tertiary neurosyphilis or tertiary Lyme neuroborreliosis. The use of chronic and late Lyme neuroborreliosis as different entities is inaccurate and can be confusing. Further pathological investigations and the detection of spirochetes in infected tissues and body fluids are strongly needed." In Lyme borreliosis, the time between infection (or re-infection) and the appearance of symptoms/signs which a patient or physician might associate with LB is highly variable and could be months or years. The U.S. Library of Medicine, MedlinePlus (2015) states:	allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of early and late Lyme disease from the final scope. .

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			"Symptoms of early disseminated Lyme disease (stage 2) may occur weeks to months after the tick bite, and may include …" "Symptoms of late disseminated Lyme disease (stage 3) can occur months or years after the infection. The most common symptoms are muscle and joint pain…" Clearly the stages of LB infection do not conform to a predetermined timescale. Different stages depend upon variables impossible to compute and more rationally deduced by careful evaluation of each individual patient's symptoms and laboratory tests, if indeed a physician considers determination of a 'stage' or 'phase' to be a worthwhile exercise. What purpose is served by attempting to define the progression of a disease by a fixed time period and how would it help doctors in making their clinical decisions? It seems unlikely that re-labelling patients at 6 months is considered a useful way to suggest the best tests for a patient's infection. According to Public Health England (2014), the weaknesses they acknowledge for their tests relate to cross reactivity with other infections and "antibody tests in the first few weeks of infection may be negative". These problems would not be improved by a 6 month deadline. Once a patient has been diagnosed and treated, further standard NHS two-tier testing is rendered useless because as West (2014) states: "Both IgM and especially IgG antibodies can remain positive for years after successful therapy with antibiotics." So the	

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			determination of treatment success or failure by standard testing would not be helped by a 6 month time limit. There are no tests for LB at any stage which can reliably exclude infection or confirm that treatment or time has eradicated an infection. If such a test (or combination of tests) existed, it is certain that PHE, the CDC, the IDSA and others would have used the test in support of their opinion that persistent infection does not occur beyond what they claim is 'adequate' treatment. In contrast, the scientists and doctors of ILADS (2012) who declare that persistent LB infection does occur, provide a list of 700 peer-reviewed scientific papers indicating persistence, in 'Peer Reviewed Evidence of Persistence of Lyme Disease Spirochete Borrelia burgdorferi and Tick-Borne Diseases'. Furthermore, treatment considerations are guided by disease manifestations and sometimes supported by laboratory test results. E.g., neuroborreliosis is a diagnosis of the spread of LB spirochaetes to the central nervous system (CNS). It is suspected by symptoms, supported by examination and testing of cerebrospinal fluid (CSF) and treated by intravenous antibiotics. Neuroborreliosis can occur at any time in infected individuals because it relates to the spread of the infection. If the bacteria's 6 month 'VISA' runs out, that would not prevent it crossing the barrier into the CNS. Therefore determining the choice of tests or treatment cannot be the motive for trying to determine the phase of a patient's infection according to a calendar.	

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			A 6 month phase could not apply to an infant born infected or an infant with an immature immune system that becomes infected. How would 6 months apply to a child which is quite simply, a much smaller mammal than an adult human? Would the transformation from 'early' to 'late' infection happen at the same time in a person initially infected with a few spirochaetes compared to someone infected via multiple heavily infected tick bites which also transmitted ehrlichia and bartonella? In some regions, 10% to 20% of healthy blood donors are seropositive for Lyme antibodies. If they become ill in the future, will that be 'early' or 'late' Lyme? (Mygland, Skarpaas and Ljøstad, 2006; Hjetland et al 2014) Dr Willy Burgdorfer, who discovered the borrelia burgdorferi spirochaete in 1982, stated (Under Our Skin, 2007): "I am a believer in persistent infections because people suffering with Lyme disease, ten or fifteen or twenty years later, get sick [again]. Because it appears that this organism has the ability to be sequestered in tissues and [it] is possible that it could reappear, bringing back the clinical manifestations it caused in the first place." When asked about the similarities between *Borrelia burgdorferi* and syphilis, Dr. Burgdorfer stated: "The similarities that I know of are associated with the infection of the brain, the nervous system. The syphilis spirochete, Treponema pallidum has an affinity for nerve tissues. The Borrelia burgdorferi spirochete very likely has that too. Children are especially sensitive to Borrelia burgdorferi. The Lyme disease spirochete is far more virulent than syphilis." (Under Our Skin, 2007). Since early and late stages for Lyme borreliosis reflect similarities with syphilis, they must	

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			recognise that stages are determined by the spread and manifestation of the infection and not by a calendar. NHS Choices, (2014) remarks on Syphilis: Primary syphilis: "The initial symptoms of syphilis can appear any time from 10 days to three months after you have been exposed to the infection." Secondary syphilis: "The symptoms of secondary syphilis will begin a few weeks after the disappearance of the sore." Latent phase: "The latent stage can continue for many years (even decades) after you first become infected." Tertiary syphilis: "The symptoms of tertiary syphilis can begin years or even decades after initial infection." Specifying a 6 month or other arbitrary time-point between phases is so illogical, that one could be excused for questioning the motives behind even contemplating such a notion. Perhaps it is a coincidence that the CDC/Fukuda (1994) criteria for a diagnosis of Chronic Fatigue Syndrome requires 6 months of symptoms with fatigue criteria (which is common in LB). There is evidence which suggests that Public Health England intend that chronic LB patients should be re-diagnosed as having CFS or some other contrived 'syndrome', e.g., 'chronic arthropod neuropathy syndrome'. The HPA (now part of PHE) informed the Health and Safety Executive (2012) of their plans: "RIPL and HPA staff will discuss with Simon Wesseley's [sic] group and other interested	

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			parties the development of guidance for clinicians on dealing with the disaffected group with un-provable Lyme disease. This will cover the therapeutic approach, investigation of cases and disengagement strategies when further investigation is counter-productive." In view of their plans for 'development of guidance for clinicians', one may speculate that PHE will attempt to steer the NICE GDG process to meet their predetermined agenda. That agenda appears to include a 6 month period after which they deem it acceptable for doctors to 'disengage' from patients if the patient cannot 'prove' that they Lyme borreliosis. This agenda could deprive patients of medical care and deny them treatment and could be attractive to some who are more concerned about financial costs than patient welfare. The strategy might also be favourable to medical re-insurance companies who have saved a lot of money thanks to a few psychiatrists who compounded the neurological disease, Myalgic Encephalomyelitis with 'CFS' and then classified CFS as a Functional Somatic Disorder. This has meant that policy claims can be limited to 2 years for a notoriously chronic and severely debilitating neurological disease. Are people with chronic Lyme borreliosis destined for the same? 'Professor Sir Simon Wessely's group' are psychiatrists, and it seems that PHE would like them to take control of the fate of patients who do not recover in an allotted time. They have some history with NICE, as observed by Professor Malcolm Hooper (2007) in his written evidence to the Parliamentary Select Committee on Health regarding the NICE GDG for 'CFS/ME':	

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			"14. The advisors upon whom NICE relies have been shown to have undeclared vested interests: These psychiatrists and their adherents are heavily involved with the medical insurance industry, including UNUM Provident, Swiss Life, Canada Life, Norwich Union, Allied Dunbar, Sun Alliance, Skandia, Zurich Life and Permanent Insurance, as well as the re-insurers Swiss Re..." Dr Darrel Ho-Yen (1990), who became the head of the Lyme Reference Laboratory at Inverness, commented on the Wessely group's ideas in the Journal of the Royal College of General Practitioners: "…it has been suggested that a new approach to the treatment of patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model (Wessely S, David A, Butler S, Chalder T: Management of chronic (postviral) fatigue syndrome. JRCGP 1989:39:26-29). Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness". VIRAS rejects the concept of a 6 month period for the transformation of a patient's LB infection from one stage to another as inaccurate, negligent and unethical. We are curious to know where this idea originated and what scientific justification was provided for this notion of an infectious disease progressing according to a calendar. **References** CDC/Fukuda. 1994. *Guidelines for the Evaluation and Study of CFS*. Centres for	

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VIRAS Vector-	DQ5		**Diagnostic Testing for Lyme Disease**	Thank you for your response and detailed comments on our questions.

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borne Infection, Research – Analysis - Strategy			Diagnosis of Lyme borreliosis infections by indirect methods, i.e. looking for certain antibodies in patients' blood, has been proved to be unreliable by many studies published over the past 3 decades. The criteria necessary for providing accurate clinical decision-making and for the safe stewardship of maintaining Public Health have not been met. A recently published meta-analysis by Leeflang et al., (1), reviews all testing methods to date and shows that this problem is evident: "We found no evidence that ELISAs have a higher or lower accuracy than immunoblots; neither did we find evidence that two-tiered approaches have a better performance than single tests. "However, the data in this review do not provide sufficient evidence to make inferences about the value of the tests for clinical practice. Valid estimates of sensitivity and specificity for the tests as used in practice require well-designed cross-sectional studies, done in the relevant clinical patient populations. "Furthermore, information is needed about the prevalence of Lyme borreliosis among those tested for it and the clinical consequences of a negative or positive test result. The latter depend on the place of the test in the clinical pathway and the clinical decisions that are driven by the test results or not. Future research should primarily focus on more targeted clinical validations of these tests and research into appropriate use of these tests." It should be realised that all of the validity data sets for test kits, as published by their manufacturers, have been determined in patients with known or highly probable borreliosis	We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			infection, as seen from their symptoms, such as EM rash, or frank symptoms such as facial palsy or Bannwarth's syndrome. Rarely have any antibody tests been matched against true microbiological evidence, which would have had to have been done by checking each patient with a culture test. The test kits have not been validated in patients who have less obvious presentations of Lyme borreliosis. The only true validation would be to test each patient with manufacturer's kits and then to assess each patient by means of culture and/or DNA detection of the bacteria. It is of the utmost clinical importance that the true state of the infection in each patient should be accurately assessed, This should be done in microbiological terms by looking for evidence of the bacteria themselves, instead of looking for the immune response. There are many reasons why the immune response is variable and often suppressed in patients with Lyme borreliosis. (2) Microscopic visualization of live Borrelia spirochetes offers the strongest of all proofs that an infection is present. Borrelia burgdorferi can be visualized directly in infected vectors, reservoir hosts, laboratory animals and clinical specimens from patients with Lyme borreliosis using dark-field or phase-contrast microscopy. The spirochetes may also be microscopically visualized after Giemsa, Gram, immunological or silver staining of specimens The BIA have dismissed microscopy and culture investigations of patients. They cite the	

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			long time period necessary for the borrelia spirochetes to grow, and the cost of technical manpower. However, if we are on the brink of a public health hazard, liable to affect future generations - because of the high probability of congenital transfer of the infection, and possible contamination of the nation's blood supply - then the cost has to be met. In fact, costs will not be as high as expected, since advanced culture methods have recently been patented which enable identification of borrelia species in patient sera within 1 week, in many cases: This advanced culture method has been in operation as a successful commercial enterprise in Pennsylvania, at Advanced Laboratory Services, for the last 3 years, and has been published in the peer-reviewed literature (3, 4) and patented (5). The method is endorsed by Philip M. Tierno, Jr., PhD Frm Director of Clinical Microbiology and Immunology, New York University School of Medicine Dr Tierno refutes accusations by some CDC scientists that there might have been contamination during the method. (6). Criticism of the method by UK scientists has been quashed with research by Dr Sheila Woods and her team at Advanced labs. PHE have claimed that the spirochaetes seen in the microscope were artefacts, or pieces of collagen or fibrin. Sheila Wood used a special Rhodium-based stain which has the property of only attaching to collagen and fibrin, and it was conclusively shown that, in the very small percentage of cases where the obvious shape of Borrelia spirochaetes was not so distinct (about 2% of samples), the Rhodium	

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			stain did not attach to what were suspected to be Borrelia spirochaetes. The Rhodium stain did attach to bits of the background extra-cellular matrix, as it is designed to do, but absolutely did not stain the Borrelia. (7). The Abstract states : "In order to distinctly differentiate the organisms from the collagen of this matrix that could be observed as background in the staining process, we developed an immunostaining procedure using polyclonal and monoclonal antibodies in combination with rhodamine fibronectin. The culture samples from both control organisms and patient samples were tested using the new immunostaining protocol. Results showed clear delineation of organisms compared to the collagen pieces gathered in the harvesting process. This new immunostaining process, used with in vitro cultivation, provides for precise identification of cultured organisms." Given that the true prevalence of borreliosis in the UK has not been fully monitored, and that it will be bound to increase in the British Isles, as it has been seen to do so across the Northern hemisphere , we can expect tens of thousands of cases each year (8,9). The Health and Safety of the UK over the next 10 to 15 years will depend on how the NICE committee decides to tackle the problem of not just Lyme disease, but also other arthropod-borne infections. It is imperative that our health service chooses the best diagnostic techniques . References	

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			1)The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis Leeflang et al. BMC Infectious Diseases (2016) 16:140. DOI 10.1186/s12879-016-1468-4 2) http://www.ilads.org/ly…/primary-care-physician-brochure.pdf 3) Improved Culture Conditions for the Growth and Detection of Borrelia from Human Serum. Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Int J M.5698. ed Sci 2013; 10(4):362-376. doi:10.7150/ijms 4)Assessment of New Culture Method to Detect Borrelia species in Serum of Lyme Disease Patients". B. Johnson, Mark A. Pilgard, and Theresa M. Russell J. Clin. Microbiol. doi:10.1128/JCM.01674-13 5) http://advanced-lab.com/news/borrelia_culture_patent.pdf 6). http://www.advanced-lab.com/news/comment-lyme-tierno.pdf 7) Differentiation of Borrelia Microbes from Collagen Debris and Collagen Fibrils in Blood Cultures. J. Microbiology & Experimentation Volume 2 Issue 1. January 02, 2015 Sheila Wood, Akshita Datar, Namrata Pabbat, Divya Burugu and Amy Rattelle J. Microbiology & Experimentation Volume 2 Issue 1. January 02, 2015	

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			S http://medcraveonline.com/JMEN/JMEN-02-00033.pdf 8) http://www.nhs.uk/…/Concern-about-rise-in-UK-Lyme-disease-c… and http://www.bristol.ac.uk/n…/2015/april/big-tick-project.html 9) An estimate of Lyme borreliosis incidence in Western Europe Robert A. Sykes, Phoebe Makiello Journal of Public Health | pp. 1 –8 | doi:10.1093/pubmed/fdw017	
VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**VIRAS response to NICE request for comments on:** "4) The inclusion of the following strains of Lyme Borreliosis for consideration as part of our review of the evidence: B. burgdorferi (and the subtype B. burgdorferi sensu stricto), B. garinii, B. afzelii" **Borrelia Species causing Lyme borreliosis and Travel Risks** Key Points • Since the discovery of *borrelia burgdorferi* in 1982, more species and strains have been discovered and implicated in Lyme borreliosis (LB) • As recently as 2016, the CDC and Mayo Clinic have announced a new LB species • As recently as 2016 Rudenko et al (14) provide evidence of the involvement of *B. bissettii* in human Lyme borreliosis • Regions endemic for LB species have expanded and are expected to continue to do so • A high number of UK residents travel abroad with increased risk of exposure to a	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			greater range of LB species and strains The species of borrelia specific for 'Lyme Disease' were *b. burgdorferi s.s.*, *b. garinii* and *b. afzelii*. This artificial restriction has long been discarded by scientists and physicians to recognise additional borrelia species responsible for 'Lyme Borreliosis' (LB). All authorities recognise LB as a growing threat. The World Health Organization Europe report on Lyme Borreliosis and Global Warming states (1): "Since the 1980s, tick vectors have increased in density and spread into higher latitudes and altitudes in Europe. It can be concluded that future climate change in Europe will facilitate a spread of LB into higher latitudes and altitudes, and contribute to increased disease occurrence in endemic areas." To meet this challenge, the Guidelines must recognise that non-endemic species could spread to the UK and accept the possibility of further unknown species and strains yet to be discovered. In Scientific American's guest blog, *Lyme Time Is upon Us Again.* Pfiefer (2016)(2) remarks on *Ixodes ricinus*, (castor bean tick) which transmits LB in Europe: "In Europe, disease-ridden castor bean ticks, a relative of those in the U.S., are on the move too, spreading 300 miles north in Sweden and Norway to latitudes that were considered too cold only a generation ago. Prolific and resilient, they are even scaling mountains, climbing 1,300 feet up the Dinaric Alps of Bosnia and Herzegovina and moving to new heights in the Czech Republic and Scotland."	

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			LB species causing disease in Europe include: *burgdorferi, afzelii, garinii, spielmanii, lusitaniae, valaisiana, bisettii* (Heyman et al. 2010)(3). Rizzoli *et al* state in Eurosurviellance (4): "LB is likely to become an increasingly relevant health risk in the near future due to complex interactions between diverse environmental and socio-economic factors, which will affect various aspects of disease ecology and epidemiology". **Risk to UK Residents Travelling Abroad** Worldwide species of Lyme borreliosis spirochaetes pose a threat to UK residents travelling abroad. The CDC (2015)(5) state that LB in Europe is: "endemic from southern Scandinavia into the northern Mediterranean countries of Italy, Spain, and Greece and eastward from the British Isles into central Russia." According to the UK Government, British nationals make millions of visits abroad each year. This increases the risk of exposure to Lyme borreliosis and a greater diversity of LB species and strains. Destination — Number of visits — LB incidence per 100k pop. France — 17 million — 44 Germany — 2 million — 261 Netherlands — 1.8 million — 149 Austria — 774,000 — 300 Switzerland — 710,000 — 30 Sweden (Southern) — 664,000 — 464	

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			Czech Republic 300,000 38 Slovenia 100,000 155 UK reported incidence of LB per 100k pop: Scotland 5.9 England and Wales 1.73 (Source for travel abroad: https://www.gov.uk/foreign-travel-advice/france [change country name for other destinations in lowercase]) (Sources for incidence figures: see below) According to the Office for National Statistics (6) 62% of travel abroad by UK residents is for a holiday and 11% for visits to friends and relatives and might therefore be expected to be of at least several days. Therefore each year there are millions of visits by British nationals to other European countries where LB incidence ranges from 17 to 268 times the 'official' rate in England and Wales. Notwithstanding UK incidence figures which appear to be absurdly low, the high numbers travelling abroad are subject to a significant risk of exposure to diverse species and strains of borrelia. Pfiefer (2016)(7) observes: "In the Netherlands, rates of people diagnosed with the telltale Lyme rash ranged up to 514 per 100,000 in 2014. In areas of Germany and Sweden, studies of patient records found Lyme rates of 261 to 464 per 100,000. In Europe, the highest national rate—315 per 100,000 in 2009 – has been reported in Slovenia, one of few countries to aggressively track cases."	

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			Travel to the USA UK residents make over 3 million visits to the USA each year (6). The CDC (2013)(8) state: "Preliminary estimates released by the Centres for Disease Control and Prevention indicate that the number of Americans diagnosed with Lyme disease each year is around 300,000. ' "We know that routine surveillance only gives us part of the picture, and that the true number of illnesses is much greater," said Paul Mead, M.D., M.P.H, chief of epidemiology and surveillance for CDC's Lyme disease program. "This new preliminary estimate confirms that Lyme disease is a tremendous public health problem in the United States, and clearly highlights the urgent need for prevention." ' Kiersten et al (2015)(9) state, "Over time, the number of counties in the northeastern states identified as having high incidence of Lyme disease increased >320%: from 43 (1993–1997) to 90 (1998–2002) to 130 (2003–2007) to 182 (2008–2012)." Their map (http://wwwnc.cdc.gov/eid/article/21/8/14-1878-f1) documents the exponential spread of LB over vast areas, graphically illustrating the growing threat of LB to more regions and more people. Pfiefer (2016) (10) remarks on *Ixodes scapularis*, the 'deer tick' which transmits LB in North America: "In 1996, Ixodes scapularis, as it is known, had planted a foothold in 396 American counties. By 2015, the tick was established in 842 counties. This does not count	

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			another 578 counties—in all nearly half the continental U.S. total—in which the tick has been officially "documented." " **Borrelia species with known or suspected potential to cause LB** **Borrelia Mayonii** The Centres for Disease Control and Prevention, 2016, describe a "New Lyme-disease-causing bacteria species discovered. *Borrelia mayonii* closely related to *B. burgdorferi*. "[]. Until now, Borrelia burgdorferi was the only species believed to cause Lyme disease in North America. "Scientists at the Mayo Clinic in Rochester, Minnesota, first suspected the possibility of new bacteria after lab tests from six people with suspected Lyme disease produced unusual results, according to the findings published today in Lancet Infectious Diseases. Additional genetic testing at the Mayo Clinic and CDC found that the bacteria, provisionally named Borrelia mayonii, is closely related to B. burgdorferi. "This discovery adds another important piece of information to the complex picture of tickborne diseases in the United States," said Dr. Jeannine Petersen, microbiologist at the Centers for Disease Control and Prevention."(11) **Borrelia Bavariensis** Margos et al (2013) (12), state that *Borrelia bavariensis* is widely distributed in Europe and Asia: "Since the original description of Borrelia bavariensis sp. nov. in 2009, additional samples available from humans and ticks from Europe and Mongolia, respectively, have been used to further characterize Borrelia strains belonging to this group of spirochaetes that utilize rodents as reservoir hosts. These investigations suggested the presence of	

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			related strains in Europe and Asia and confirmed their status as representing a distinct species." **Borrelia spielmanii** Maraspin, Ruzic-Sabljic and Strle (2014)(13) conclude in their case report: "Our results corroborate previous findings that B. spielmanii is a cause of LB in Europe. Thus, in addition to the Netherlands (2), Germany (10), and Hungary (1), LB caused by B. spielmanii is also present in Slovenia." ***Borrelia Bissettii*** Rudenko et al (2016)(14) report on, "the first recovery of live B. burgdorferi sensu stricto from residents of southeastern USA and the first successful cultivation of live Borrelia bissettii-like strain from residents of North America. Our results support the fact that B. bissettii is responsible for human Lyme borreliosis worldwide along with B. burgdorferi s.s. The involvement of new spirochaete species in Lyme borreliosis changes the understanding and recognition of clinical manifestations of this disease." **Borrelia lusitaniae** While *B. lusitaniae* is distributed throughout countries in Europe and North Africa, it is believed to be the sole species of the Lyme borreliosis group in southern Portugal. Lizards of the family *Lacertidae* are thought to be important reservoir hosts of *B. lusitaniae*.(15) De Carvalho et al(2008)(16) remark: "We have described a vasculitis-like syndrome associated with the isolation of B. lusitaniae. Although the clinical presentation is not typical of Lyme borreliosis, this case	

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			had features suggestive of vasculitis, which has been described as one of the characteristic physiopathological aspects of this disease" **Borrelia Valaisiana** Diza et al (2004)(17) state: "We detected *B. valaisiana* DNA in CSF of a patient with slow progressive spastic paraparesis, which suggests that this microorganism might be the causative agent of the disease. Nucleotide sequence information of *Borrelia* strains from clinical cases and ticks from different countries will elucidate the molecular epidemiology of the disease." "The pathogenic capabilities of *B. valaisiana* are still uncertain; it has been detected by PCR and restriction fragment length polymorphism analysis in skin biopsy specimens from two erythema migrans patients and from patients with mixed infection (erythema migrans and acrodermatitis chronica atrophicans) (4). Indirect evidence suggests that B. valaisiana is involved in some chronic clinical manifestations (8)." Reference 8 above is: Ryfell, et al (1999)(18), which states: "Our results suggest an organotropism of *Borrelia* species and provide some evidence of a pathogenic potential of*B. Valaisiana* in humans." Schwab *et al*, (2013)(19) state in *Borrelia valaisiana Resist Complement-Mediated Killing Independently of the Recruitment of Immune Regulators and Inactivation of Complement Components*:	

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			"In conclusion, we demonstrated that B. valaisiana isolates differ in their susceptibility to human serum, thus providing some evidence that in particular serum-resistant isolates might cause Lyme disease. Contrary to our expectations, certain B. valaisiana isolates appear to possess different molecular mechanism(s) to inhibit complement activation, independently of the recruitment of complement regulators or by inactivation of central complement components. Even though that we are currently unable to decipher the precise molecular mechanism, it is tempting to speculate that B. valaisiana ZWU3 Ny3 expresses an outer surface protein that directly interacts with components of the complement system to inhibit complement activation. Further investigation is required to identify potential complement inhibitory protein(s) of this particular borrelial strain." Cooper *et al*, (2001)(20) tested 75 ticks taken from wild animals in SW England. 41% tested positive for the presence of *borrelia* DNA. 34% of these were also positive for *Borrelia valaisiana*, considerably more than double the prevalence of this species in the rest of Europe. **Conclusion** In view of the spreading areas endemic for Lyme borreliosis and the diversity of borrelia species which pose a threat to humans; restricting Lyme borreliosis to just 3 of those species would inevitably fail to protect UK residents. **Sources for Lyme Borreliosis Incidence in Europe:** Austria, 2005, Elisabet Lindgren, Thomas G.T. Jaenson. 2006. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation	

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VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**VIRAS response to: Who is the Focus?** **And excluded groups placed at risk by the Draft Scope** 30 1.1 Who is the focus? 49 Areas that will not be covered 51 Managing chronic fatigue syndrome. This is covered by the NICE 51 guideline: Chronic fatigue syndrome/myalgic encephalomyelitis (or 52 encephalopathy) (CG53) **Abbreviations** AIDS, Acquired Immune Deficiency Syndrome BIA, British Infection Association CDC, Centres for Disease Control and Prevention, (USA) CFS, Chronic Fatigue Syndrome	Thank you for your comment. This guideline will cover all people with Lyme disease regardless of their symptoms presentation or treatment history. The key areas were drafted in a way to ensure that those who clearly have Lyme, as well as those who may have Lyme but have never been investigated for Lyme receive the best possible assessment and diagnostic tests, and subsequently the best possible treatment.

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			CRD, Centre for Reviews and Dissemination DoH, Department of Health (UK) FDA, Food and Drug Administration, (USA) IDSA, Infectious Disease Society of America LB, Lyme borreliosis M.E., Myalgic Encephalomyelitis HPA, Health Protection Agency NATO, North Atlantic Treaty Organization PCR, Polymerase Chain Reaction PHE, Public Health England WHO, World Health Organization **The following groups are at risk of being neglected by the NICE Guideline:** Infected in the past and presently ill due to: • never investigated for LB • not investigated properly for LB • misdiagnosed with something other than LB Since the Lyme disease spirochaete *Borrelia burgdorferi* was discovered in 1982 by Dr Willy Burgdorfer, multiple species of Lyme Borreliosis-causing spirochaetes have been found in Europe. In the decades following these discoveries, UK doctors have probably encountered many thousands of patients with symptoms highly suggestive of LB, just as doctors have in all the other countries of north-western Europe.	Thank you for your comment concerning chronic Lyme disease and post-Lyme disease syndrome. This clarification has been very helpful.

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			Yet many of those doctors never considered Lyme borreliosis (LB) as a cause of their patient's illness - let alone conducted a careful evaluation or ordered tests, because: • they had no experience of LB and little, if any, knowledge about the infection • UK reported incidence figures made LB appear rare (and therefore unlikely) • the doctor believed Lyme is only present in certain areas of the country • if they did order tests and the results were negative they wrongly believed this excluded LB (and may even have been told by the test laboratory staff that this was so) In England and Wales, in the 15 years from 1997 to 2011 there were a total of 7,903 cases of LB reported at an average of 527 cases per annum giving an average annual incidence of ~0.93 per 100k population. (Public Health England. 2013.) This apparent rarity has meant that in past decades, many doctors were not alert to the risk of the disease, except perhaps for some of those practising in LB 'hot-spots'. Yet significant risk to UK residents has been present and known to some, for decades. In 1993, Nuttall et al (1993) submitted data to NATO's Second European Symposium on Lyme Borreliosis on the Ecology of Lyme borreliosis in the United Kingdom: showing that *Ixodes ricinus* (principal vector of LB in Europe) could be found throughout "Most of the UK" and that around 40% of unfed nymph and adult ticks "collected in Lyme disease foci" carried *Borrelia burgdorferi*, as shown by PCR. In 2007, the late Professor Klaus Kurtenbach of Bath University told the BBC, "In France	

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			they have diagnosed 10 times as many cases as here; yet we've found the same number of ticks here carrying the disease." (BBC. 2007) Dr Darrel Ho-Yen, who was head of the Scottish Lyme Reference Laboratory at Inverness, was quoted in The Field (2005) magazine: "He believes that the known number of proven cases should be multiplied by ten "to take account of wrongly-diagnosed cases, tests giving false results, sufferers who weren't tested, people who are infected but not showing symptoms, failures to notify and infected individuals who don't consult a doctor"." Bruce Alexander (2012) wrote in the Scotsman, "A recent audit of patients at a Perthshire Medical Practice found a ratio of confirmed cases equivalent to 125 per 100,000 people. Applying this ratio across Scotland, there could be around 6,500 people contracting Lyme disease each year, the vast majority going undiagnosed and untreated." This computes to 30 times the reported incidence for Scotland, a country which has 3 times more recorded LB than England and Wales; and where more doctors are aware of the risks and symptoms of LB. Some of the tens of thousands of 'the vast majority going undiagnosed and untreated' who had symptoms, have probably recovered. But without doubt, some of those who became chronically ill, were misdiagnosed with Myalgic Encephalomyelitis (M.E.) or Chronic Fatigue Syndrome (CFS); illnesses with very poor recovery rates and symptoms highly suggestive of chronic Lyme borreliosis.	

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			VIRAS will argue that those patients, some of whom by now have been infected for decades, deserve proper investigation and a correct diagnosis. Even if some believe that patients with chronic LB infections may suffer the same fate as Tertiary Syphilis patients, who can have intractable infection and symptoms, it would be unethical to leave these patients misdiagnosed with CFS. Excluding these patients would be negligence reminiscent of the Tuskegee Syphilis Experiment (Wikipedia 2016). The symptoms of some patients diagnosed with long-term M.E. or CFS should lead a well-informed doctor to suspect LB and duly investigate. We are not aware of a single case where this has happened. Instead, it has been left to patients to find out about Lyme borreliosis by sheer chance. Then, when they do consider their symptoms, risk factors and the course of their illness and consult their doctor; they are all too often dismissed or misled by an unreliable blood test which they are told definitively excludes LB. With UK 'CFS' prevalence estimated at 256,000 (NICE 2007), and full recovery occurring in only ~10% (CRD 2002), if just 10% of M.E. or CFS patients were actually misdiagnosed cases of chronic LB, that could be 25,000 cases in the UK whose illness might respond to treatment. That will not happen while they are misdiagnosed. Far from leading the way in recognising and addressing the silent epidemic of LB, PHE (and the former HPA) have been effective in suppressing the problem, in the worst traditions of national medical authorities who made a complete mess of dealing with the early years of AIDS. Patients who remain ill with every indication of chronic LB, frequently	

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			with laboratory confirmation, and who do not accept PHE's simplistic notions about a complex disease, have been branded "disaffected" and described as coming from a "parallel universe". It is an old political strategy to denigrate those whose views you wish to suppress and is a resort of those who have power and influence but no scientific evidence to back-up their arguments. M.E. and CFS patients and campaigners have been subject to years of the same, with orchestrated efforts in the media to portray them as neurotic, hypochondriac and anti-science. And for whose benefit have chronically sick people been made the target of denigrating propaganda? Not the patients. Not their doctors. The winners are the medical insurance companies that avoid paying for the sustained treatment and management that chronically ill patients require; and those that have been negligent in protecting the Nation's health. Schwarzwalder et al (2010) found that 14% of Lyme disease infection was misdiagnosed by patients and 20% misdiagnosed by physicians. This review was in Maryland, a USA state where many counties were classed by the CDC as 'high incidence' by the early 2000's (Kiersten et al. 2015). If that is what happens where LB is common and well-known to doctors, what chance do UK patients have? Quite simply, the UK has a low incidence rate because PHE produce low incidence rates, making the disease appear rare, obscuring the risk, and misleading doctors and the public. In the UK, Lyme is not rare, but it is rarely diagnosed.	

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			Dr Hugh Derham (2014) in Australia tested 300 of his ME, CFS and FM patients and found that 95% were positive for Lyme. Dr Samuel Shor (2011) in the USA reviewed 210 patients and found that a "potentially substantial proportion of patients with what would otherwise be consistent with internationally case defined CFS [...] actually have a perpetuation of their symptoms driven by a persistent infection by *Borrelia burgdorferi*." Dr. Kenny De Meirleir (2014) in a presentation to the Belgium Senate, observed that 95% of Chronic Fatigue Syndrome and ME (Fukuda & Canadian criteria) were cases of Late Stage Lyme Disease. 95% having had positive *Borrelia burgdorferi* LTT tests. **Chronic LB and Post Treatment Lyme Disease Syndrome** VIRAS consider the term 'chronic Lyme' legitimate. The infection can be persistent just as Syphilis, Leptospirosis and other bacterial infections such as TB can be persistent. There is no medical or scientific basis for rejecting the term 'chronic Lyme'. Whilst this invidious reservation may serve the purposes of those that have motives to portray Lyme as a simple, acute illness – it denies the complexity of the infection and flies in the face of common sense and a wealth of published evidence. Dr Willy Burgdorfer, who discovered the Lyme spirochaete, *Borrelia burgdorferi*, in 1982, told investigators for *Under Our Skin* (2007): "I am a believer in persistent	

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			infections because people suffering with Lyme disease, ten or fifteen or twenty years later, get sick [again]. Because it appears that this organism has the ability to be sequestered in tissues and [it] is possible that it could reappear, bringing back the clinical manifestations it caused in the first place." (Square brackets as published) VIRAS consider the term 'post treatment Lyme disease syndrome' (PTLDS) misleading, though this depends to an extent on what is meant by 'post treatment'. The term is loaded and intentionally or not, implies that the 'treatment' aspect must have been sufficient and effective. The term suggests that if a patient remains ill after treatment it is not because their treatment was ineffective and the infection remained and relapsed. If this was not the intention of those who use the term, we might also have the term 'Failed Treatment Lyme Disease Syndrome', which would accurately indicate failure to cure a patient who had received some treatment. Unfortunately, in some people's minds the responsibility for the latter might fall on physicians rather than the bacteria or patient. So it may lack a certain appeal to those who coin these terms and foist them on unsuspecting patients. We are not aware of any scientific evidence that 'post treatment Lyme disease syndrome' even exists; or that anyone deemed to have the syndrome has ever been repeatedly tested to the full extent of available methods. An experiment like that could provide convincing evidence that the infection really had been eliminated and make PTLDS a plausible explanation for their ongoing symptoms. Whereas the contrary is true. When chronically ill UK patients are thoroughly investigated the infection is often found to remain present long after they received 'adequate treatment'.	

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			It is widely recognised that LB infection even in the quite short-term, can cause serious damage to almost any parts and systems of the body. It seems reasonable to believe that the injury could be long lasting or permanent. But that does not mean that it is the only cause in patients whose symptoms persist. The fact that patients continue to experience exacerbations and relapses, sometimes decline and are afflicted with new, debilitating and distressing symptoms, suggests an ongoing disease process for which persistent infection is a strong candidate supported by scientific evidence. (See: ILADS. 2012. Peer Reviewed Evidence of Persistence of Lyme Disease Spirochete *Borrelia burgdorferi* and Tick-Borne diseases. And Moyer. 2015. Scientific American. Lyme Disease May Linger for 1 in 5 Because of "Persisters") Without evidence meeting scientific standards of thoroughness, reliability and reproducibility, 'post treatment Lyme disease syndrome' is simply an opinion based upon a one-size-fits-all notion of 'treatment' and is in our experience, used by those with biased opinions and conflicting interests. When patients with chronic LB research the field to try and find out how science could help them, what they find is that 'science' has been usurped by 'opinions'. It is not the patients and campaigners that are anti-science; our views are almost invariably supported by scientific research. But examine the IDSA or BIA or PHE Guidelines for LB and where there is controversy, those guidelines are based on mere opinion with no scientific evidence to support them. These opinions might look good, thanks to 'paper-pile'	

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			publishing and 'circular-referencing' and quoting (and misquoting!) of each others opinions creating an appearance of authority. Challenges to anything that threatens their views are slipped under the door of peer review as "a quibble, couched in the language of an exposé" (Earp. 2015). Critical examination reveals nothing more substantial than repetition of opinions lacking objective evidence. Ioannidis, (2005) stated in Plos Medicine, "Empirical evidence on expert opinion shows that it is extremely unreliable". Yet much of the information about LB supplied by the DoH, NHS, PHE and BIA is nothing more than 'expert opinion' imported from the American IDSA and parroted to patients and physicians as though it is scientific fact. These opinions (which happen to serve the interests of medical insurance and re-insurance companies) portray Lyme borreliosis as a simple, self-limiting, acute infection, easily detected and diagnosed and eradicated with a few weeks of antibiotics. Professor Charlton (2008) remarks: "And when a branch of science based on phoney theories serves a useful but non-scientific purpose, it may be kept-going indefinitely by continuous transfusions of cash from those whose interests it serves. If this happens, real science expires and a 'zombie science' evolves." The converse is true. When the research needed to identify, understand and treat UK borreliosis is not being undertaken (because according to those charged with the protection of the nation's health, it is so rare in the UK), it is little wonder that many LB patients have been misdiagnosed with M.E. or CFS. Yet UK authorities continue to rely on	

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			either non-UK sources, or UK sources which are simply repeating opinions which actually originate from the IDSA. We hope that NICE Guidelines for LB will recognise a duty to the thousands of LB patients who have never been properly evaluated or diagnosed and treated. These patients have been failed by the authorities appointed to protect them and too often have been misdiagnosed with 'CFS'. Notwithstanding NICE guidelines for that illness, these patients have been subject to prejudice and abuse by all and sundry; portrayed as neurotic, blamed for their illness and marginalised, whilst their lives have been ruined by a chronic infectious disease. **REFERENCES** Alexander, Bruce. 2012. More must be done to combat Lyme disease. The Scotsman. http://www.scotsman.com/news/bruce-alexander-more-must-be-done-to-combat-lyme-disease-1-2498193 BBC. 2007. Lyme Disease. Inside Out West. http://www.bbc.co.uk/insideout/west/series11/week6_lyme_disease.shtml Charlton BG. 2008. Zombie science: a sinister consequence of evaluating scientific theories purely on the basis of enlightened self-interest. Med Hypotheses. ep;71(3):327-9. doi: 10.1016/j.mehy.2008.05.018. http://www.ncbi.nlm.nih.gov/pubmed/18603380	

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VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**Lyme-Like Illnesses** In view of the increasing public health risk from tick bites, and indeed from other arthropod bites, the committee should consider broadening the scope for intervention and management of Lyme disease to include "Lyme-like" borreliosis infections, as well as all possible infections from the many other pathogenic microbes being identified in ticks;(1) even if only for the purposes of accurate differential diagnosis. There is growing evidence from support groups in the UK that patients have multiple tick-borne infections: please see Lyme Disease UK web site and Veronica Hughes CEO Caudwell Lyme Co., where the data shows that the NHS is failing to detect and treat these infections. Daniel Cameron MD, (http://danielcameronmd.com/coinfections/) observes: Co-infections can be challenging to diagnose, as clinical features often overlap with many of the other tick-borne diseases, including Lyme disease. However, the importance of identifying and treating polymicrobial infections is critical in getting a patient well. Practitioners should consider co-infections in the diagnosis when a patients symptoms are severe, persistent, and resistant to antibiotic therapy. Physicians have found that co-	Thank you for your comment. This guideline covers Lyme disease only. While people with co-infections will not be excluded from the evidence reviews in this guideline, the management of other tick-borne related infections or illnesses are outside the remit of this guideline. However, the guideline committee can give mention to any groups who require special consideration when linking evidence to recommendations.

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			infections typically exacerbate Lyme disease symptoms. The most "Lyme-like" symptom presentations from tick-borne infections are due to infections with members of the large family of borrelia spirochetes. In Brazil during the last 10 years, a Lyme-like disease has been identified which is indistinguishable from Lyme, termed *Baggio-Yoshinari syndrome* (2), and similarly, in the southern states of the USA, there is *Master's disease* or *Southern Tick-Associated Rash Illness* (3) Willy Burgdorfer wrote in 1998 that Relapsing Fever is far more widely distributed than was realised, and hardly anyone was looking for it. He found that most patients who had antibodies to the relapsing fever, caused by *B. hermsii*, were serologically positive for *B. burgdorferi*, and Western Blotting consequently demonstrated false positivity of testing for *Borrleia burgdorferi* (4) In Britain, we know that at least 13 million birds, carrying over 1 million ticks, arrive in Britain from Africa every Spring (5). Africa has the highest prevalence of relapsing fever borrelia strains, and of human illnesses and deaths due to the infection. It is reasonable to conjecture that relapsing fever strains of borrelia have been introduced into the British Isles by bird ticks, and consequently into the ecosystem. It has recently been shown by Public Health England that B. miyamotoi is present in Britain	

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			in *Ixodes* ticks. *B. miyamotoi* is genetically related to tick-borne relapsing fever (TBRF) strains. However, in clinical presentation, it can appear more like Lyme borreliosis. In North America, researchers have shown that, in 182 cases of febrile illness from ticks, presenting as very similar to Lyme disease, most patients who were eventually found to have antibodies to *B. hermsii* were serologically positive for *B. burgdorferi*, and it was only the second tier testing (Western blot) that demonstrated false positivity of testing for *B. burgdorferi*. "This study demonstrates that TBRF is underrecognized and underreported and may be falsely identified as Lyme disease" (4). Similarly, Scoles et al in 2001 found that yet another TBRF strain in the US was transmitted by *Ixodes* ticks (6) Of greatest relevance to Britain, European scientists Richter et al have found a third strain of the relapsing fever borrelia in Europe and state "We now know that a third member of this group infects I. ricinus ticks in central Europe. We conclude that each of the various kinds of ticks that serve as vectors for Lyme disease spirochetes, I. ricinus, I. persulcatus, I. scapularis [= dammini], may be infected by relapsing fever–like spirochetes" and they state "Exposure risk for relapsing fever–like spirochetes is similar to that of certain Lyme disease genospecies." (7) Many patients report to us that they have had positive results on the initial ELISA tests for Lyme disease, but that subsequent Western blot tests have proved negative. It seems possible that they might have been in fact infected with a TBRF strain, even one that is as	

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			yet unrecognised, which would have produced such test results. Thus it is necessary to include the TBRF illnesses into the scope of this committee, as they may be indistinguishable from Lyme disease. **References** 1) Co-infection of Ticks: The Rule Rather Than the Exception Sara Moutailler, Claire Valiente Moro, Elise Vaumourin, Lorraine Michelet, Florence Hélène Tran, Elodie Devillers, Jean-François Cosson,, Patrick Gasqui, Van Tran Van, Patrick Mavingui, Gwenaël Vourc'h, Muriel Vayssier-Taussat. PLOS Neglected Tropical Diseases | DOI:10.1371/journal.pntd.0004539 March 17, 2016 2) [Brazilian lyme-like disease or Baggio-Yoshinari syndrome: exotic and emerging Brazilian tick-borne zoonosis]. Yoshinari NH1, Mantovani E, Bonoldi VL, Marangoni RG, Gauditano G. Rev Assoc Med Bras. 2010 May-Jun;56(3):363-9. http://www.ncbi.nlm.nih.gov/pubmed/20676548 3) http://www.columbia-lyme.org/patients/tbd_stari.html 4) Tick-Borne Relapsing Fever in the Northwestern United States and Southwestern	

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VIRAS Vector-borne Infection, Research –	General	General	**Co infections must be considered in tick-bite patients.** The Anaplasmataceae are already being diagnosed as tick-bite infections, and co-infections, by PHE microbiologists: it is hoped that infectious disease consultants in England and Wales are aware of the possibility.	Thank you for your comment. While people with co-infections will not be excluded from the evidence reviews, the focus of this guideline is the diagnosis and management of Lyme

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Analysis - Strategy			However, it is patient experience that testing for the infection is not routine, despite patients presenting with signs and symptoms of a febrile illness - even in those with a known tick bite. This must change, especially because climate warming means that all vector-borne diseases will increase in incidence in the next decade. It has been well known for 40 years at least, that ticks carry and may transmit to humans, a wide variety of pathogens, including nematodes, trypanosomes, and Rickettsiae, as well as a number of viruses(1). A recent review of the relevance to public health by Professor Christian Peronne deserves careful perusal (2). Bartonellosis is one of the most frequently diagnosed infections found as a co-infection in UK Lyme disease patients. Yet we know that diagnosis, especially after the acute phase, can be a difficult task. It is our experience that chronically infected patients are not offered tests. Even when tested, most are negative by UK methods, yet they have been found to be positive for Bartonella species by non-UK laboratories. Ticks play a role in the natural cycles of some of the bartonellae including those pathogenic for humans. Consequently, bartonelloses should be included in the differential diagnosis for patients exposed to tick bites(3). Health authorities must take into account the possibility of bartonellosis in persons exposed to tick bites, and the Bartonella species recognised as tick-borne pathogens (4).	disease. The specific management of co-infections will not be addressed by this guideline. However, the guideline committee will give mention to any groups who require special consideration when linking evidence to recommendations.

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			Bartonella infection causes symptoms which are similar to LB, in many ways including neurological signs, but the therapeutic treatment is different from that used for borreliosis(5, 6). Thus an accurate diagnosis is crucial for successful treatment, and patient survival and quality of life. Babesiosis German scientists A. Hildebrandt, J. S. Gray and K.-P. Hunfeld, in their report "Human Babesiosis in Europe: what clinicians need to know" (7) state: " Although best known as an animal disease, human babesiosis is attracting increasing attention as a worldwide emerging zoonosis. Humans are commonly infected by the bite of ixodid ticks. Rare ways of transmission are transplacental, perinatal and transfusion-associated. Infection of the human host can cause a very severe host-mediated pathology including fever, and hemolysis leading to anemia, hyperbilirubinuria, hemoglobinuria and possible organ failure. In recent years, apparently owing to increased medical awareness and better diagnostic methods, the number of reported cases in humans is rising steadily worldwide. Hitherto unknown zoonotic Babesia spp. are now being reported from geographic areas where babesiosis was not previously known to occur, and the growing numbers of travelers and immunocompromised individuals suggest that the frequency of cases in Europe will also continue to rise." Babesia, though relatively rarely diagnosed in the UK other than in cattle, has caused canine deaths in Leeds and Nottingham this year (2016) and there are many cases of	

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			debilitating human illness. A one-hour discussion on the UK's largest Lyme forum revealed 5 fully-diagnosed patients responding, within that short time on Wednesday 16th March, 9 am - 10 am, to state that they had acquired Babesiosis in the UK. No one knows how many human deaths may have been attributable to Babesiosis, because there has been no surveillance in potential clinical cases which could have been due to the infection. For example, stroke patients are not screened for this piroplasm, yet blood dyscrasias from the infection are bound to have effects on blood clotting etc. Within the last three decades a dramatic rise in numbers of reported transfusion-associated cases in the US has been documented, with at least 12 fatalities and 160 cases [8, 9]. Outside America only two other cases of transfusion-transmitted babesiosis had been reported by 2013, one from Japan that involved a B. microti-like parasite [10] and one from Germany caused by B. microti (11). VIRAS urges the NICE guideline committee, and all health protection agencies, to include Babesia from tick bites into the scope of the Lyme guidelines. It is a a clear threat to the health and safety of British citizens, not just through transmission through tick bites, but as a potential blood supply contaminant. **REFERENCES** 1) Aspects nouveaux du rôle de vecteur joué par Ixodes ricinus L. en Suisse Note préliminaire. Aeschlimann A, Burgdorfer W, Matile H, Peter O, Wyler R. Acta Tropica 36. 181-191 (1979)	

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			2) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. Peronne C. Front Cell Infect Microbiol. 2014; 4: 74. 3) Vector Competence of the Tick Ixodes ricinus for Transmission of Bartonella birtlesii. Caroline Reis, Martine Cote, Danielle Le Rhun, Benoit Lecuelle, Michael L. Levin, Muriel Vayssier-Taussat, and Sarah I. Bonnet, David H. Walker, Editor. PLoS Negl Trop Dis. 2011 May; 5(5): e1186. (4)Transmission of Bartonella henselae by Ixodes ricinus Violaine Cotté, Sarah Bonnet, Danielle Le Rhun, Evelyne Le Naour, Alain Chauvin, Henri-Jean Boulouis, Benoit Lecuelle, Thomas Lilin, and Muriel Vayssier-Taussat. Emerg Infect Dis. 2008 Jul; 14(7): 1074–1080. 5) Bartonella vinsonii subsp. berkhoffii and Bartonella henselae bacteremia in a father and daughter with neurological disease. Breitschwerdt EB, Maggi RG, Lantos PM, Woods CW, Hegarty BC, Bradley JM. Parasit Vectors. 2010 Apr 8;3(1):29. 05-3-29. 6) Maggi RG, Ericson M, Mascarelli PE, Bradley JM, Breitschwerdt EB. Parasit Vectors. 2013 Apr 15;6:101. 7) Hildebrandt, A, Gray J S, Hunfeld, K-P "Human Babesiosis in Europe: what clinicians need to know" Infection DOI 10.1007/s15010-013-0526-8 8) Herwaldt BL, Linden JV, Bosserman E, Young C, Olkowska D, Wilson M. Transfusion-	

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			associated babesiosis in the United States: a description of cases. Ann Intern Med. 2011;155: 509–19. 9) Leiby DA. Transfusion-transmitted Babesia spp.: bull's-eye on Babesia microti. Clin Microbiol Rev. 2011;24:14–28. 10) Matsui T, Inoue R, Kajimoto K, Tamekane A, Okamura A, Katayama Y, Shimoyama M, Chihara K, Saito-Ito A, Tsuji M. First documentation of transfusion-associated babesiosis in Japan. Rinsho Ketsueki. 2000;41:628–34 11) Hildebrandt A, Hunfeld KP, Baier M, Krumbholz A, Sachse S, Lorenzen T, Kiehntopf M, Fricke HJ, Straube E. First confirmed autochthonous case of human Babesia microti infection in Europe. Eur J Clin Microbiol Infect Dis. 2007;26:595–601.	
VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**VIRAS - Introduction** Vector-borne Infection - Research, Analysis, Strategy VIRAS is a non-profit group comprised of patients and carers with knowledge and experience in Lyme borreliosis and co-infections, Myalgic Encephalomyelitis (M.E.) and Chronic Fatigue Syndrome (CFS). Our members are qualified in science and research, ethics, biology, psychology, psychotherapy, teaching, business and media.	Thank you for your comment.

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			We are glad to have the opportunity to provide comments and feedback on the NICE Draft Scope for Lyme borreliosis	
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British Association of Dermatologists			The British Association of Dermatologists has no comments to make on this consultation. We would request that you kindly keep us updated on developments, as an interested party.	Thank you for your comment. Updates on the progress of the guideline development and the guideline documents will be published on the NICE website in due course. You can find this information by following this link: https://www.nice.org.uk/guidance/indevelopment/gid-ng10007 As a registered stakeholder for this guideline, you will be alerted to key steps in this guideline's development.
Department of Health			Thank you for the opportunity to comment on the draft scope for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment.

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The British Society for Antimicrobial chemotherapy (BSAC)			Members of The British Society for Antimicrobial Chemotherapy (BSAC) have no comments for this Guideline on Lyme disease.	Thank you for your comment.
Royal College of Nursing			This is just to inform you that the feedback I have received from nurses working in this area of health suggests that there are no comments to submit on behalf of the Royal College of Nursing to inform on the consultation of the draft scope of Lyme Disease.	Thank you for your comment.
NHS England			Thank you for the opportunity to comment on the above Clinical Guideline. I wish to confirm that NHS England has no substantive comments to make regarding this consultation.	Thank you for your comment.
Royal College of Paediatrics and Chil Health			Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the Lyme Disease draft scope. We have not received any responses for this consultation.	Thank you for your comment.
Lyme Disease Action	1	5	Using a title of Lyme borreliosis, rather than Lyme disease, would bring the guidelines into line with the rest of Europe. European Lyme borreliosis is recognised to be different from Lyme disease in the USA, due to a greater variety of genospecies and strains of Borrelia endemic in Europe.	Thank you for your comment. We have decided to use the title Lyme disease as it is a widely accepted term which we feel is more accessible to non-healthcare professionals than Lyme borreliosis. In addition it directly

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				reflects the commission received from NHS England. The guideline committee will make the final decision on whether to include evidence from outside UK and Europe.
Lyme Disease Action	2	31	We feel that individual consideration should be given to immunocompromised people and pregnant women in whom diagnosis may be more difficult and treatment may be different.	Thank you for your comment. The guideline committee will review the evidence about diagnostic test accuracy and management strategies in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations for the NHS. Where no evidence is available, the committee may be able to make research recommendations. These subgroups have been included in the equality impact assessment for this

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				guideline.
Lyme Disease Action	2	38	Consideration at assessment should be given to 'red flags' such as severe neurological, cardiac and ophthalmic complications requiring specialist referral, and also special groups such as pregnancy and immunosuppression. See also comment on line 50 of the scope.	Thank you for your comment. We will pass the detail of your comment related to severe neurological, cardiac and ophthalmic complications to the guideline committee for their consideration as they develop protocols linked to the appropriate management for different presentations being considered The guideline committee will review the evidence in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations. These subgroups have been included in the equality impact assessment for this guideline.

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Lyme Disease Action	2	39	In addition to clinical assessment mention should be made of the value of including assessment of risk of tick exposure and tick bite in the period prior to onset of symptoms, including assessment of travel history.	Thank you for your comment. This guideline will include assessment of risk of tick exposure and tick bite in the period prior to onset of symptoms as part of the topic area on assessment (history and examination).
Lyme Disease Action	2	40	Remove "confirmatory" as it implies this leads to a diagnosis and it may not. Perhaps "first and second tier serology testing and the use of PCR" instead	Thank you for your comment. We believe that the term 'confirmatory' is a widely accepted term for second line tests after initial testing. We do not feel any change is necessary.
Lyme Disease Action	2	40	Suggest that item 2 is Testing (first and second tier tests) and that an additional point "Diagnosis" is introduced. Diagnosis is the result of assessment, investigations and tests which are building evidence to inform a diagnosis. 2nd line serology tests may yield false positives, especially in areas where seroprevalence is high, and may give false negatives, so it is important to separate diagnosis from testing.	Thank you for your comment. The guideline will look at the role of second-line tests as part of diagnosis as well as assessment and investigations. We feel that this is adequately captured in the "key areas that will be covered" section and have not made

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				any changes. The exact review questions to cover the key area of 'diagnosis' will be developed by the Guideline Committee at a later stage. An evidence review on diagnostic test accuracy will look at the likelihood of a test being false negative, for example. The Guideline Committee will take this into account and the findings from its other evidence reviews (for example, on assessment) when formulating recommendations.
Lyme Disease Action	2	41	This specifies Management to be "for example" treatment using antibiotics. It is unclear what other aspects to treatment might be covered - eg neuropathic pain relief, anti-inflammatories, treatment for unresolved facial palsy, physiotherapy for arthritis, pacemaker insertion etc. See our comment on section 3, Context.	Thank you for your comment. We have used the example of antibiotics as an illustrative example. The guideline committee will consider which other treatments of Lyme Disease are of relevance for the evidence review. This guideline will not address the management of conditions secondary to Lyme

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				Disease although other NICE guidance is available in some of the areas that you mention such as in the management of neuropathic pain (https://www.nice.org.uk/guidance/cg173).
Royal College of Genera Practitioners (RCGP)	2	43	The RCGP hopes that the medications recommended in the guideline are those that a) Experts recommend (even if not licensed). If the guideline recommends a medication that is contrary to expert opinion then that severely will undermine the entire guideline. b) Are (where clinically appropriate) medications that are familiar to GPs- most of these patients will present to primary care. If these are medications that generally speaking GPs won't feel confident with then it will mean more referral to secondary care with the delay and cost that that entails. (MJ) c)	Thank you for your comment. The Guideline Committee will consider which medications should be included in the evidence review. As stated in the scope, recommendations are generally only made within their licensed indications unless there is strong evidence for an unlicensed indication. The Guideline Committee will also consider any potential issues around prescribing (such as the lack of familiarity in prescribing that you outline) in various settings when formulating recommendations.
Lyme Disease Action	2	48	The information, education and support needs of healthcare professionals requires consideration.	Thank you for your comment. The information, education and support needs of healthcare professionals will

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				be considered by the guideline committee and acknowledged as part of the work linking evidence to recommendations rather than as a formal review question. It is anticipated that the publication of the guideline will provide helpful information for healthcare professionals which may then be further developed by relevant groups.
Lyme Disease UK	2	50	Co-infections in Lyme disease patients appear to be common and should always be considered as part of the clinical picture, particularly in immunocompromised patients. 'Ticks transmit more pathogens than any other arthropod, and one single species can transmit a large variety of bacteria and parasites' (Moutallier et al, 2016). This study states, 'in the past, reports of pathology due to *Babesia*, *Anaplasma*, *Ehrlichia*, and *Bartonella* species have focused on the fulminant acute forms of infection that are relatively easy to diagnose and often fatal in immunocompromised patients. More recently, these organisms have been associated with chronic persistent infection in animal models and humans. The presence of coinfecting organisms has been shown to enhance the symptoms and exacerbate the severity of Lyme disease. Thus recognition of chronic coinfections supports the concept of unresolved illness due to persistent infection with the Lyme spirochete' (Stricker and Johnson, 2011).	Thank you for your comment and the references you have provided. The focus of this guideline is the diagnosis and management of Lyme Disease. We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as appropriate. We will not however

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			In a patient survey conducted by the charity Caudwell LymeCo, preliminary results show that over 30% Lyme disease patients who participated also appear to have Babesia and over 15% have Bartonella henselae. According to another survey done by Lyme Research UK in 2011, co-infections were also common in patients with Lyme disease. Out of 189 people diagnosed with Lyme borreliosis, 19 were diagnosed with Bartonella henselae, 7 with Bartonella quintana, 15 with Erhlichia, 8 with Mycoplasma and 15 with Babesia (based specifically on positive tests with clinical assessment). Over 50% of this main group were not tested for each of these co-infections and therefore the possibility of even higher infection rates, is considerable. The scope should consider the evidence relating to co-infections, as they could be a potential cause of comorbidity or complex conditions, rendering poorer treatment outcomes for Lyme disease patients. Considering and testing for other potential tick-borne infections should be included in the Lyme disease guidelines, particularly when there are indications of more varied or persistent symptoms or when standard Lyme disease treatment has failed. Even if the management of other tick-borne infections is not included in the guidelines, there should be some reference to the possible complications they may cause in Lyme disease patients so that healthcare workers and the public are at least aware of their existence. The patient experience appears to be that co-infections do not normally form part of the	address the specific management of any co-infection and as such have made no change to the scope.

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			NHS diagnostic process, even if Lyme disease is detected, however, the ILADS guidelines state that 'the possibility of co-infections should not be casually dismissed' (Cameron et al, 2014). References: 1: Moutailler S, Valiente Moro C, Vaumourin E, Michelet L, Tran FH, Devillers E, et al. (2016) Co-infection of Ticks: The Rule Rather Than the Exception. PLoS Negl Trop Dis 10(3): e0004539. doi:10.1371/journal.pntd.0004539 http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004539 2. Stricker, R.B, Johnson, L. Lyme disease: the next decade. Infect Drug Resist. 2011; 4: 1–9. doi: 10.2147/IDR.S15653 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108755/ 3. Caudwell LymeCo patient survey, 2016 http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/ 4. Lyme Research UK patient survey, 2011 (unpublished) 5. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	
Lyme Disease Action	2	50	Although this guideline will not cover management of other tickborne infections, it is important to mention somewhere in the guideline that co-infections eg. Anaplasmosis, may lead to more severe symptoms, interfere with test results and possibly also response to	Thank you for your comment. The focus of this guideline is the diagnosis and management of Lyme Disease.

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			treatment as a result of immune suppression. See comment on line 38 re Red Flags. Public Health England Porton have identified cases of Anaplasmosis, and Lyme Disease Action has had experience of some cases via the help desk.	We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as appropriate. We will not however address the specific management of any co-infection and as such have made no change to the scope.
Caudwell LymeCo	2	50	SUGGESTED AMENDMENT Delete "Managing other tick-borne infections" from the section "Areas that will not be covered" Insert "Managing other tick-borne infections" into the section "Key areas that will be covered" (page 2 below line 49) REASON Ticks carry many infections. Caudwell LymeCo has conducted a survey of UK Lyme disease patients via social media and found that a third of them had at least one other tick-borne infection in addition to Lyme disease. The necessity of assessing suspected Lyme disease patients for additional tick borne infections is mentioned in the current guidelines	Thank you for your comment. The focus of this guideline is the diagnosis and management of Lyme Disease.We will bring your comments on the issue of co-infection to the guideline committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as

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			issued by PHE. I think it is important for this information to remain in the new NICE guidelines, and in fact be updated and explained in more detail. Based on anecdotal evidence from patients, it seems that a lot of them are not assessed for tick-borne co-infections at all. A lot of the tick-borne infections other than Lyme disease have symptoms very similar to Lyme. It may be that some patients who seem not to respond well to Lyme treatment actually have other overlooked infections as well. EVIDENCE Neglecting to tackle co-infections is the commonest cause of Lyme disease treatment failure, according to many of the doctors in the USA and Europe who focus on treating Lyme disease patients.	appropriate. We will not however address the specific management of any co-infection and as such have made no change to the scope.
Lyme Disease UK	2	51	Lyme disease can mimic many other conditions, including chronic fatigue syndrome (CFS). Why is CFS being singled out in this draft scope as a managed condition when there is no 100% accurate serological test for either Lyme disease or CFS and therefore the two cannot be easily separated? If the two are separated, this may lead to CFS patients being unable to have their diagnosis reconsidered even if they might have Lyme disease. Furthermore, the way in which CFS is managed could potentially be harmful to an undiagnosed Lyme disease patient.	Thank you for your comment. The remit of this guideline is the diagnosis and management of Lyme disease. We recognise that some people may have both Lyme disease and chronic fatigue syndrome (CFS) or other diagnoses and as such any evidence

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			Even if the risk of Lyme disease is properly investigated before diagnosing CFS (which does not always appear to be happening based on shared patient experience), weaknesses of current tests mean that some might nevertheless, actually have Lyme disease. Additionally, CFS patients who do not have Lyme disease may be at extra risk if they do happen to catch the disease because of the similarity in symptoms and the possibility that the infection may be dismissed as an 'exacerbation of existing CFS'. Discriminating against CFS patients who, if anything, may have a greater need to be further investigated for Lyme disease, could put these patients at risk. Preliminary results from a patient survey conducted by VIRAS show that out of 44 participants, 16 people with Lyme disease have also been diagnosed with M.E. The 2011 BIA position statement acknowledges that Lyme disease symptoms can overlap with other conditions - 'late neurological sequelae of undertreated infection include a chronic encephalomyelitis, which can present with clinical features resembling multiple sclerosis.' ILADS guidelines state, 'in addition to the possible presence of co-infections, many other illnesses and conditions have clinical features which may overlap with those of Lyme disease; some examples are: infections due to Epstein–Barr virus or syphilis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and vasculitis; metabolic and endocrine disorders such as diabetes, hypo- or hyperthyroidism and adrenal dysfunction;	found in these groups will be considered by this guideline if it relates to the specific management of their Lyme Disease. The management of CFS is covered by another NICE guideline: www.nice.org.uk/CG53.

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			degenerative neurologic diseases such as Parkinson's disease and amyotrophic lateral sclerosis and neurologic conditions such as peripheral neuropathy and dysautonomia; musculoskeletal diseases including fibromyalgia and osteoarthritis, psychiatric disorders, especially depression and anxiety and other conditions such as chronic fatigue syndrome and sleep apnea' (Cameron et al, 2014). Singling out CFS as an area that will not be covered may affect the literature review in terms of excluding investigations into the possibility that some CFS patients may have Lyme disease. A recent patient survey by Caudwell LymeCo involving around 500 patients revealed that over 34% of patients who have a Lyme disease diagnosis obtained privately have only been given a CFS diagnosis by the NHS. References 1. VIRAS patient survey 2016 http://counsellingme.com/VIRAS/IsabelSymptomCheckerSurvey.PDF 2. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 3. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema	

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Lyme Disease Action	2	51	It is not clear why CFS is specifically named as fatigue due to Lyme borreliosis does not equate to CFS/ME. Other conditions such as multiple sclerosis, rheumatoid arthritis, Sjogrens Syndrome, etc are not mentioned, so why CFS.	Thank you for your comment. The remit of this guideline is the diagnosis and management of Lyme disease.The reference to the chronic fatigue syndrome /myalgic encephalomyelitis (or encephalopathy) guideline has been included to make it clear that the guideline will not cover management of fatigue as part of the CHF/ME. It is provided as an example of another NICE guideline that is available and is not intended to be an exhaustive list.
Royal College of Genera Practitioners (RCGP)	2	51	There is clearly a link being made between chronic fatigue syndrome and Lyme disease by the support groups for suffers of chronic fatigue. Some GPs have seen a few patients who are desperate to pursue a diagnosis of Lyme disease to explain their fatigue symptoms. The RCGP feels that it would be invaluable if this guideline helped to differentiate on clinical grounds those fatigue suffers who need further investigation and those that we can	Thank you for your comment. This guideline only covers Lyme disease. We acknowledge that the clinical presentations of Lyme disease and chronic fatigue syndrome (CFS) can

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			reassure without recourse to blood tests, investigations and/or referrals. (MJ)	be very similar and that it can be difficult to make a definitive diagnosis of one or the other. Following systematic review of the evidence available in the scope areas of assessment diagnosis and management, the Guideline Committee will make recommendations in regards to Lyme disease and may wish to cross-refer to other guidelines if appropriate. The reference to the CFS / myalgic encephalomyelitis (or encephalopathy) NICE guideline (CG53) is included as an example of another available NICE guideline and will not be covered by this Lyme disease guideline.
Lyme Research UK	3	54	Transmission of Lyme borreliosis between people is not covered: This was covered in the previous version of the Guideline scope, and we think it should remain. There is published evidence for transmission between infected mothers and babies in-utero (Schlesinger et al, 1985; Weber et al, 1988; MacDonald et al, 1987).	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now

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			Untreated pregnant women with Lyme borreliosis have a higher incidence of adverse outcomes of pregnancy than treated women (Lakos et al, 2010). Therefore treatment of pregnant women should be included in the scope. The appropriate treatment for pregnant women should be reviewed. What constitutes appropriate antibiotic treatment in pregnant patients has yet to be determined. The U.S. Centres for Disease Control and Prevention (2016a) state "Lyme disease acquired during pregnancy may lead to infection of the placenta and possible stillbirth; however, no negative effects on the fetus have been found when the mother receives appropriate antibiotic treatment." Surviving babies born to untreated mothers may be infected and if so may need treatment, which should also be covered in the scope. There is also some evidence suggesting that sexual transmission may be possible (Middelveen et al, 2015 in review). The evidence for sexual transmission is limited and inconclusive (Stricker et al, 2015) but we suggest adopting a precautionary principle and that clinicians should inform sexually active, infected patients of the potential risks, whilst acknowledging the knowledge in this area is uncertain. Many patients are concerned about donating or receiving blood that may be contaminated with Lyme borreliosis, and we believe that this issue should be addressed. At least one study shows B. miyamotoi's ability to survive standard blood storage (Thorp et al, 2006).	included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee. Pregnant women, will be included in our evidence reviews as a special subgroup and any direct evidence for this group, if available, will be analysed and presented separately allowing the committee to make specific recommendations in this population. (this is also the case in those people who are immunocompromised).

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Lyme Disease UK	3	54	Transmission of the disease between people should not be excluded from the scope when there are so many important issues in this area. The CDC states, in this fact sheet that, 'untreated, Lyme disease can be dangerous to your unborn child.' The scope should include points relating to the following questions: Can Lyme disease be transmitted via blood transfusions or organ donations? Can Lyme disease be transmitted sexually or via breast milk? Furthermore, is it ethical for people not to know how infectious they are, in particular women planning pregnancy? There is no definitive test that can prove that Lyme disease has been eradicated and yet there are many studies that show that Lyme disease can be a chronic, persistent infection. There is a great deal of uncertainty in the patient community in terms of how safe it is to become pregnant or to have unprotected sex. Transmission via other biting insects and vectors such as horse-flies and mosquitoes should also be explored in the interests of public health and safety. There have been a number of new research publications in these areas since the BIA position statement published in 2011 and therefore a review of the evidence would be highly beneficial both in terms of educating the medical profession and the public. References: 1. Centers for Disease Control and Prevention Fact Sheet	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope and the points you raise will be discussed by the Guideline Committee who will decide the final review question and protocol.

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			http://www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_Lyme%20disease_Pregnant Woman_FACTSheet.pdf 2. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/ 3. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf	
Caudwell LymeCo	3	54	SUGGESTED AMENDMENT Remove "Transmission of the disease between people" from the section "Areas that will not be covered". Insert "Transmission of the disease between people" into the section "Key areas that will be covered" (page 2 below line 49) REASON Pregnant women can transmit Lyme disease to their unborn children and this is a fact which all pregnant women with Lyme disease, and their doctors, most definitely need to know. Currently the CDC in America issues an information leaflet warning pregnant women with Lyme disease that their unborn children could catch and be harmed by Lyme disease *in*	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee.

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			utero. Similar information for patients and their practitioners should form part of the NICE guidelines to inform doctors and patients in the UK. In fact I think a case could be made for warning all pregnant women about this risk, in the same way they are made aware of the risks of varicella, rubella and toxoplasmosis during pregnancy. There is also some preliminary research suggesting that Lyme disease may be sexually transmitted, transmitted via blood transfusions and transmitted through breastfeeding. Some of the evidence regarding these potential risks is recent, and the NICE guidelines committee may be the first guidelines committee to evaluate it properly. EVIDENCE More than 46 separate cases of congenital Lyme disease in human babies have been documented in peer-reviewed research, in various regions of the world and produced in a range of prestigious institutions. The CDC patient information leaflet on Lyme in pregnancy can be viewed online here: http://www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_Lyme%20disease_PregnantWoman_FACTSheet.pdf	
Lyme Research	3	55	Preventing Lyme borreliosis is not covered:	Thank you for your comment. While we understand the importance of

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UK			Does this only refer to ways to prevent tick bites? We think that prophylactic treatment with antibiotics after a tick bite should be considered.	public awareness, this is a clinical guideline on the diagnosis and management of Lyme disease and it would therefore not be appropriate to review evidence on prevention. Preventing Lyme disease as outlined in the scope refers to the prevention of tick bites and prevention of Lyme disease in the absence of a tick bite. Prophylactic treatment with antibiotics after a tick bite will be considered.
Lyme Disease UK	3	55	Prevention should be included in the key areas that will be covered, including the issue of whether prophylactic treatment following a known tick bite is helpful in certain cases, especially as the BIA position statement, published 2011, mentions that antimicrobial prophylaxis 'may be used in immunocompromised individuals following a tick bite.' The ILADS guidelines recommend that 'clinicians should promptly offer antibiotic prophylaxis for known *Ixodes* tick bites in which there is evidence of tick feeding, regardless of the degree of tick engorgement or the infection rate in the local tick population' (Cameron et al, 2014). It would be worth doing a literature review on the effectiveness of prophylaxis treatment and the economic costs and savings associated.	Thank you for your comment. While we understand the importance of public awareness, this is a clinical guideline on the diagnosis and management of Lyme disease and it would therefore not be appropriate to review evidence on prevention. Preventing Lyme disease as outlined in the scope refers to the prevention of tick bites and prevention of Lyme disease in the absence of a tick bite. The role of prophylactic treatment with

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			People with Lyme disease, may present without a rash (or known tick bite) and without prior basic knowledge of their risk of tick exposure. If a doctor asks them if they have been exposed to ticks and they are not even aware of their own risk (i.e. that ticks have been found in urban parks and gardens and not just geographical hotspots around the country), they may state that the chance of tick exposure is low. This could result in the patient not being tested for Lyme disease. Prevention, in terms of patient knowledge, is therefore not entirely distinct from diagnostic pathways. Education about risks and knowledge of protection should be made available to healthcare workers and the public to reduce people's chances of contracting Lyme disease. Leaflets and notices educating people about the disease should be visible in clinics and distributed widely in communities. According to this study, 'encouraging a thorough check for ticks and promptly removal of ticks are the key public health strategies to reduce the risk of LB and other tick-borne diseases' (Dehnert et al, 2012). The ILADS guidelines recommend that when patients have been diagnosed with Lyme disease, 'during the initial visit, clinicians should educate patients regarding the prevention of future tick bites' (Cameron et al, 2014). References: 1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf	antibiotics after a tick bite will be considered. We believe that the evidence considered and the recommendations made as part of this guideline could be used to develop resources by relevant groups to inform healthcare workers but this is not the remit of this committee. We will be reviewing the evidence around the information needs of people with suspected or confirmed Lyme disease.

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			2. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 3. Dehnert M, Fingerle V, Klier C, Talaska T, Schlaud M, Krause G, et al. (2012) Seropositivity of Lyme Borreliosis and Associated Risk Factors: A Population-Based Study in Children and Adolescents in Germany (KiGGS). PLoS ONE 7(8): e41321. doi:10.1371/journal.pone.0041321 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041321	
Caudwell LymeCo	3	55	SUGGESTED AMENDMENT Delete "preventing Lyme disease" from the section "Areas that will not be covered" and insert it into the section "Key areas that will be covered" (page 2 below line 49) REASON A lot of patients with Lyme disease in the UK realise, with hindsight, that they exposed themselves to risks which they could have avoided. We patients do our best to warn other people, and I am confident I can speak for most patients in saying we would very much like GPs to become a part of the effort to improve the level of public knowledge on this subject. The congenital transmission route seems to be overlooked by medical professionals as well as the public. I believe it is essential to include information in the guidelines on how to prevent pregnant women from passing Lyme disease on to their babies, particularly since	Thank you for your comment. While we understand the importance of public awareness, this is a clinical guideline on the diagnosis and management of Lyme disease and it would therefore not be appropriate to review evidence on prevention. However, we hope and anticipate that the publication of this guideline will help to raise awareness among both health care professionals and the public.

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			there are documented cases of Lyme causing miscarriages, stillbirths, and deaths in new born babies. EVIDENCE Lyme disease can be transmitted congenitally. Many papers have been published reporting evidence of this. Borrelia is also proven to remain viable under blood transfusion conditions. There is preliminary evidence that Borrelia could be transmitted from person to person via blood transfusions, congenitally, breast feeding and even sexually. Whilst there is uncertainty, I think people who are unaware of the potential risks of these kinds, need to be protected by guidelines that embrace the possibility. I think risk assessment should accept the growing knowledge base pointing to a broader range of possible routes to exposure.	Pregnant women, will be included in each of our evidence reviews as a special subgroup and any direct evidence for this group, if available, will be analysed and presented separately allowing the committee to make specific recommendations in this population. (This is also the case in those people who are immunocompromised). Furthermore, person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee in due course.
Lyme Research UK	3	56	"Economic aspects": We hope that you will include the potential costs of misdiagnosis and inadequate antibiotic treatment leading to chronic long-term disease in your economic analysis.	Thank you for your comment. The details of the economic analyses that may be performed for this guideline will be decided in collaboration with the Guideline Committee and will depend on the availability of data. We

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				will take your suggestion in to consideration when developing our economic analysis.
NHS Highland	3	67 to 82	The key to ensuring that the NICE recommendations are clinically useful is to have clear and relevant clinical case definitions at each stage. European clinical case definitions (Stanek, G) are narrow including no category for a flu like illness, and stringent laboratory confirmation for neuroborreliosis (requiring lumber puncture). In my opinion these are too narrow. Suggest NICE guidance divides patients into clinically defined presentations, and makes testing and management recommendations for each presentation (presentation categories that should be included given below). I appreciate that 'Flu like' is not an ideal label and care should be taken defining the symptoms that would qualify for this presentation. 1) Tick exposure, no symptoms 2) Seropositive, no symptoms 3) Chronic tick exposure non-specific chronic symptoms (fatigue, arthralgia, parasthesia) 4) ECM, atypical rash 5) Flu like presentation without respiratory component 6) Symptoms consistent with early neuroborreliosis including radiculitis, meningitis, cranial neuropathy and mononeuritis multiplex 7) Symptoms consistent with late neuroborreliosis including encephalomyelitis, encephalopathy, cerebral vasculitis (could be called late neuroborreliosis)	Thank you for your comment on the issue of the classification of Lyme disease as described in the consultation version of the scope. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of Lyme disease from the final scope.

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			*IDSA includes peripheral neuropathy in late neuroborreliosis, while European guidelines state peripheral neuropathy without achrodermatitis chronicum atrophicans is vanishingly rare – this needs to be addressed as peripheral neuropathy very common in the elderly and in endemic regions many of these people will be seropositive. Geography of exposure may influence recommendation. 8) Arthritis 9) Carditis 10) Lymphocytoma 11) Achrodermatitis chronicum atrophicans 12) Ocular manifestations	
Lyme Disease Action	3	68	This should state "What symptoms, clinical signs and history". A person's clinical history and tick exposure is an important factor in acute Lyme borreliosis when symptoms plus history might indicate immediate treatment should be started. History is also important in late Lyme borreliosis.	Thank you for your comment. The diagnosis and management of Lyme disease will be covered in this guideline. The Guideline Committee will make recommendations based on the evidence identified. History taking is part of the draft question on in whom Lyme disease should be suspected and as such will inform the relevant recommendations made in the guideline.

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Lyme Disease Action	3	68	Consideration should be given to adding development of a weighting table. This was one of the Top 10 James Lind Alliance Uncertainties 'What key questions (clinical and epidemiological) should be considered to help make a diagnosis of Lyme disease in children and adults in the UK and would a weighting table be useful?' This was also raised as a key area of uncertainty during the American Association for the Advancement of Science AAAS InnovationsX conference in Washington, USA 17/18 November 2015.	Thank you for your comment. After reviewing the evidence, the guideline committee will consider the most appropriate way to present the information. The committee can also make a research recommendation if this is considered appropriate.
NHS Highland	3	69	Suggest delete 'to confirm or rule out Lyme disease'.	Thank you for your comment. This has now been amended to 'Diagnostic testing for Lyme disease'.
Lyme Disease UK	3	69	It is important to note that the presentation of Lyme disease can vary significantly in terms of symptoms and clinical signs. Therefore, Lyme disease testing should be routinely included as part of the differential diagnostic process for any nonspecific symptoms which could have an infectious cause and for which another cause has not been found. However, there also needs to be awareness amongst medical professionals that there is currently no 100% accurate test available for the disease and so it cannot be ruled out based purely on serology unless a more accurate test is brought to market in the UK. Doctors need to be made aware of the shortcomings of current testing methods so that they can accurately inform patients and consider making a clinical diagnosis if applicable.	Thank you for your comment. This guideline will cover the question of which symptoms or clinical signs should lead to diagnostic testing for Lyme disease. We would like to draw your attention to a NICE guideline on symptoms with unknown causes that has not yet been commissioned, which may cover differential diagnostic processes for conditions with unknown causes. While the guideline is not listed on the NICE website yet, we would advise that you

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				register as a stakeholder for this guideline development process and submit your comments as part of its scoping processes in due course.
Lyme Disease Action	3	69	Rephrase to simply "Diagnostic testing." There is no current test which can confidently rule out Lyme disease and no test which can confirm currently active disease.	Thank you for your comment. This has now been amended to 'Diagnostic testing for Lyme disease'.
Caudwell LymeCo	3	69	SUGGESTED AMENDMENT Change "Diagnostic testing to confirm or rule out Lyme disease" to "Diagnostic testing to help confirm Lyme disease" REASON I believe the majority of the current commercially produced, certified diagnostic tests for Lyme disease state that a negative result cannot rule out Lyme disease. On this basis, it seems Lyme disease cannot be definitively ruled out. I think this should be reflected accurately in the scoping document. EVIDENCE Test kits' instructions which I have seen typically include an explanation of the currently known causes for sero-negativity or partial sero-negativity in patients who may actually be infected with Lyme disease. The following explanation of the diagnostic significance of antibodies against Borrelia species it taken from the instructions on the interpretation of test results published by	Thank you for your comment. This has now been amended to 'Diagnostic testing for Lyme disease'.

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			ViraMed, the manufacturer of the western blot test kit used by RIPL. "1. IgG antibodies are produced **for the first time several weeks to months after infection** and are **often not detectable in early stages** of infection (22). In suspicion of a recent infection, IgM antibodies should be checked and a second sample should be analysed later. Patients in the 2nd or 3rd stage of the disease are **usually** positive for IgG antibodies.....5. An early antibiotic therapy can **suppress the development of antibodies** (17)."	
Lyme Disease Action	3	7	Transmission should be included in the guideline. Clinicians need to know what evidence there is as this question will be raised in consultations.	Thank you for your comment. We have discussed your comment in detail and reviewed the decision to exclude other ways of transmission. Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee.
Lyme Research UK	3	70	"2.2 Starting treatment?": When Lyme borreliosis is suspected, treatment should start immediately and be based on symptoms, since rapid treatment is important to help prevent long-term problems.	Thank you for your comment. The Guideline Committee will formulate recommendations on the timing of treatment based on the evidence identified through evidence reviews.

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Lyme Disease UK	3	70	The question of how doctors can make an accurate clinical diagnosis of Lyme disease should be included in the scope as well as an exploration into how often this actually occurs in reality, especially in the absence of a 100% reliable test. Are doctors really comfortable making a clinical diagnosis of Lyme disease, particularly in the absence of an EM rash? This study states 'modern medical practice expects to rely on evidence. Most physicians would not consider diagnosing Lyme disease without serological proof' (Perronne, 2014) and this appears to reflect the general patient experience. If an EM rash is present, are doctors sufficiently aware that it is diagnostic of Lyme disease without the need for serology? Patient experience would suggest that GPs often misdiagnose EM rashes. Should effects and signs of damage consistent with Lyme disease be included as part of the clinical picture? Patients who have received a clinical diagnosis of Lyme disease from qualified medical professionals either in the UK or abroad (often with accompanying positive overseas test results) are also having the diagnosis of Lyme disease frequently dismissed. As a result, they are being denied treatment in this country. Simply running the arguably flawed UK two-tiered testing should not be used as a way to override a clinical diagnosis of Lyme disease obtained privately from a qualified doctor or positive overseas test results. UK doctors should also be allowed to use their own clinical judgement when assessing patients with signs and symptoms of Lyme disease, especially if they have a private clinical diagnosis and/or a positive test result from an overseas laboratory. According to the ILADS	Thank you for your comment. The assessment and diagnosis of Lyme disease are covered by the key areas of "assessment (history and examination)" and "diagnosis (first-line investigations and confirmatory tests)". A review of performance in clinical practice is outside of the remit of NICE guidelines. However, we would hope that this guideline will provide health care professionals with evidence based recommendations to support them in making a diagnosis of Lyme Disease in the context of practice in England. NICE guidelines provide recommendations to clinical practice but they do not override the responsibility of healthcare professionals to make decisions

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			panel, 'guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary' (Cameron et al, 2014). The result of the confusion surrounding diagnosis is that many Lyme disease patients are not treated at all. Preliminary results from a patient survey conducted by Caudwell LymeCo reveal that 52% of the participating Lyme disease patients were prescribed no antibiotics whatsoever on the NHS for this condition. References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 2. Caudwell LymeCo patient co-infection survey, 2016 http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/	appropriate to the circumstances of each patient, in consultation with the patient (or if appropriate their family or carer).
NHS Highland	3	71	Role of CSF tests in diagnosis of lyme neuroborreliosis. When are they indicated and how interpreted (my current practice is usually not to perform LP in borrelia seropositive radiculopathy or cranial nerve palsy in absence of meningitis)	Thank you for your comment. The Guideline Committee will consider relevant diagnostic tests and procedures in the context of differing clinical presentations when defining the review questions and protocols.

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				We will ensure that they are informed of your comment.
Caudwell LymeCo	3	71-73	SUGGESTED AMENDMENT Change "What is the most clinically- and cost-effective test or combination of tests for diagnosing Lyme disease in different clinical scenarios or presentations?" to "What is the most clinically- and cost-effective test or combination of tests for diagnosing Lyme disease, **the appropriate timing for testing, and the appropriate way to interpret test results,** in different clinical scenarios or presentations?" REASON It may turn out that the same test is best for all clinical scenarios or presentations, yet that test's results may have different meanings in different clinical scenarios. The appropriate timing of the test (in relation to believed time of exposure) and whether a repeat test is necessary, also needs to be part of the guidance given to doctors. EVIDENCE Refer to the existing test kit manufacturers' instructions on interpretation of results.	Thank you for your comment. The review questions will be further developed by the Guideline Committee based on the scope of the guideline. We will bring the detail of your comment to the attention of the guideline committee to inform that development process Recommendations will then be made based on the best available evidence identified.
Lyme Disease UK	3	71-82	<u>References:</u> 1. Stricker, R.B, Johnson, L. Lyme disease: the next decade. Infect Drug Resist. 2011; 4: 1–9. doi: 10.2147/IDR.S15653 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108755/	Thank you for your comment and the references provided. The review protocols for each review question will inform the specific search strategy for that question. We will hold the

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			2. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 3. Burrascano, Advanced Topics in Lyme Disease: Diagnostics Hints and Treatment Guidelines for Lyme and other Tick Borne Illnesses, Sixteenth Edition, October, 2008. http://www.ilads.org/lyme/B_guidelines_12_17_08.pdf 4. Horowitz, R. The Horowitz Lyme - MSIDS Questionnaire http://www.cangetbetter.com/symptom-list 5. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full 6. Caudwell LymeCo patient survey, 2016 http://lymediseaseuk.com/2016/03/21/caudwell-lymeco-surveys-results-sneak-peek/	references you provide for cross checking.
Lyme Disease Action	3	72	See answers to the directly posed question 3 re clinical presentations.	Thank you for your response to this question. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of

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				the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	3	74, 76	SUGGESTED AMENDMENT Delete "a tick bite" and insert "suspected time of infection" REASON Tick bites are not the only source of infection with Lyme disease. The infection can also be spread by blood transfusion and congenitally. It MAY also be spread by breast feeding, eating unpasteurised dairy products, other biting insects or sexual contact. Since these transmission routes may also be possible, patients who may have been infected in these ways should not be excluded from laboratory testing. EVIDENCE There is no proof that tick bites are the only means of spreading Lyme disease. The recently published peer-reviewed medical papers presenting new evidence for other means of transmission should be examined and reviewed.	Thank you for your comments about the use of the phrase "tick bite". The detailed sub questions in this section have been removed from the final version of the scope. Your comments will be shared with the guideline committee for their consideration when the protocols for review questions are discussed. Person-to-person transmission is now included as a key question in the scope. The review question and protocol will be developed by the Guideline Committee in due course.
Lyme Disease UK	3	74-78	The 2011 BIA position statement mentions that 'some patients with previously untreated infection can develop features of late-stage disease, months or years later.' This disease cannot be easily divided into two 6 month phases as proposed in the draft scope and it isn't useful to do this, especially if people are unaware of when they were bitten or if their	Thank you for your comment on the issue of the classification of early and late Lyme disease as described in the consultation version of the scope. We

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			symptoms have a delayed onset. At present, there is no 100% accurate serological test to define any of these phases of the illness. A new, more precise list of patient categories and clinical scenarios needs to be composed by the committee and used to form the basis of evidence reviews. Possible terms include; • *Acute Lyme disease* - recently infected, seronegative due to lack of antibody production (usually less than 6 weeks). • *Secondary/2nd stage Lyme disease* - seropositive unless treated in acute stage with antibiotics. Disseminated infection but no lasting damage if treated adequately. • *Tertiary/3rd stage Lyme disease* - disseminated infection with permanent damage or complications. • *Latent Lyme disease* - seropositive but no current symptoms (as demonstrated by studies showing that a percentage of forestry workers have antibodies to Borrelia whilst being asymptomatic). It is unknown whether these people will go on to become symptomatic following stress on their immune system of any kind. • *Refractory Lyme disease* - standard treatment given but symptoms persist. With clearly defined terminology which covers a wide range of scenarios, suitable evidence reviews can take place. Terms like 'chronic Lyme disease' and even 'early' and 'late' Lyme disease cannot be properly defined in medical contexts and are open to interpretation which leads to overall confusion both for physicians and patients. . <u>References:</u>	have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of early and late Lyme disease from the final scope.

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			1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf	
Caudwell LymeCo	3	74-82	SUGGESTED AMENDMENT Delete all the suggested categories. New categories need to be defined AFTER examining the explanations of how to interpret the test results of each of the test kit manufacturers. Just as an example, the test currently used by RIPL **MIGHT** divide patients into the following clinical scenarios in order to interpret their test results: 1. Suspicion of a recent infection 2. Patients 2-3 weeks after onset of the disease 3. Patients given early antibiotic therapy 4. Patients infected for a longer period of time 5. Patients on certain medication or immunoglobulin therapy 6. Patients who may have Treponema, Leptospira or other bacteria with flagella, acute EBV infection, autoimmune diseases, MS, ALS, Influenza or Syphilis. REASON The categories into which patients needs to be divided to interpret the results of their tests will be dictated by the manufacturers of those tests. They do not interpret results based on whether the patient has been infected for more or for less than 6 months, for example. An examination of the documentation provided with each test kit should form part of the work of the committee to define these categories meaningfully.	Thank you for your comment on the issue of the classification of Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed detail linked to the definitions of early and late Lyme disease from the final scope.

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			EVIDENCE The above example of possible categories for interpretation of results was taken from the instructions published by ViraMed, the manufacturer of the western blot test kit used by RIPL. 1. IgG antibodies are produced for the first time several weeks to months after infection and are often not detectable in early stages of infection (22). In suspicion of a recent infection, IgM antibodies should be checked and a second sample should be analysed later. Patients in the 2nd or 3rd stage of the disease are usually positive for IgG antibodies. Antibody titers decrease gradually during convalescence (22). 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). 3. IgA antibodies are detectable at an early stage of Borreliosis in many patients, in some cases earlier than IgM antibodies. 4. The immune response and consequently the band pattern differs from patient to patient. As a general rule: The number of antibody types and therefore the number of specific bands is increasing with progression of the disease (1). 5. An early antibiotic therapy can suppress the development of antibodies (17). 6. Medication and immunoglobulin therapy can cause unspecific antibody reactions (24). 7. Cross reactivities to Borrelia antigens are described for infections with Treponema, Leptospira and other bacteria with flagella (2,15,22). An acute EBV infection can cause a polyclonal stimulation of Borrelia antibodies (22). If IgM antibodies against OspC or p41	

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			are detected without clinical symptoms for borreliosis an EBV infection needs to be tested for. Cross reactivities in cases of autoimmune diseases, MS, ALS, Influenza and Syphilis are described as well.	
NHS Highland	3	77	Delete 'or without' as not disease if asymptomatic	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice versa. This was to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only. However, we now propose to present the guideline committee with the stakeholder feedback on the issue of clinical scenarios and presentations to allow

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				them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of different clinical scenarios and presentations.
Lyme Disease Action	3	77	We do not see how someone would be considered to have late disease without symptoms or signs.	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice versa. This was to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only. However, we now propose to present the guideline committee with the stakeholder feedback on the

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				issue of clinical scenarios and presentations to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of different clinical scenarios and presentations.
Lyme Disease UK	3	79	The term 'definitive treatment' should be replaced with 'standard treatment' as there is no proof that the treatment currently being offered for Lyme disease by the NHS is effective in the majority of cases. In fact this study showed that 'over 63% of the Lyme disease cases had at least one diagnosis associated with PTLDS' (post treatment Lyme disease symptoms) following early standard treatment (Adrion et al, 2015). Patients would argue that a continuation of symptoms does not mean that the treatment was 'definitive' or successful. This information is available on Lymedisease.org's website: 'The International Lyme and Associated Diseases Society (ILADS), recently published new treatment guidelines. These guidelines contained a rigorous assessment of the evidence and found treatment failure rates ranging from 16% to 39% for early treatment. Estimates for patients with chronic Lyme disease are much higher, ranging from 26% to 50%. (Johnson 2004)' Whether ongoing symptoms are due to a continuing infection or due to a past infection is uncertain, but with many studies showing Borrelia's ability to persist, ongoing infection	Thank you for your comment. The term 'definitive' has been removed.

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			cannot be ruled out and therefore treatment cannot be described as 'definitive'. For those who have been treated, the patient experience often seems to be that people are told categorically by GPs that they cannot possibly still have Lyme disease following a standard course of antibiotics from the NHS. The ILADS guidelines state that, 'there is no compelling evidence to support routinely withholding antibiotic retreatment from ill patients. While antibiotics are not always effective, the importance of providing patients with the opportunity to receive an adequate trial of antibiotic therapy is heightened by the lack of other effective treatment approaches. Palliative care may be helpful in addressing some symptoms in some cases, but it is important to bear in mind that palliative interventions also carry risks. Additionally, clinicians must not assume that palliative interventions would provide adequate treatment in the face of an underlying persistent infection. Therefore, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill' (Cameron et al, 2014). References: 1. Adrion, ER, Aucott, J, Lemke, KW and Weiner, JP. Health care costs, utilization and patterns of care following Lyme disease. PLoS One. 2015 Feb 4;10(2):e0116767. doi: 10.1371/journal.pone.0116767. eCollection 2015 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116767 2. Lymedisease.org: Chronic Lyme Disease https://www.lymedisease.org/lyme-basics/lyme-disease/chronic-lyme/ 3. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline	

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			recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 4. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/	
Lyme Disease Action	3	79	The phrase "full course" is subjective. Currently many clinicians appear to believe that a 10 day course is "full". There is no "definitive" treatment (see James Lind Alliance uncertainties) for anything other than perhaps early Lyme borreliosis with erythema migrans and given trials in progress it is unlikely that this will change in the near future. Suggest rephrase to "early or late disease where an initial course of treatment has been completed but symptoms or signs have recurred."	Thank you for your comment. The term 'definitive' has now been removed.
Lyme Disease Action	3	82	As above: there is no definitive treatment so suggest re-phrase to "…have not resolved despite an initial course of treatment."	Thank you for your comment. The term 'definitive' has been removed.
NHS Highland	3	83	Management recommendations could be further targeted by dividing patients into possible/probable/definite Lyme disease depending on strength of clinical presentation and test results. I appreciate that this adds complexity, but until lab diagnostics improve we will be operating in an area of diagnostic uncertainty and these labels make that explicit and allow physician and patient to appreciate the balance of risks between overtreatment and under-	Thank you for your comment. Whilst we do not feel that any changes to the scope are required in this area, we will bring the detail of your comment to the committee's attention when they draft their protocol for this question

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			treatment. These distinctions become most helpful when discussing pros / cons of repeat courses of antibiotics where first line therapy has failed to improve symptoms	
NHS Highland	3	83	Management may also include referral to specialist (eg rheumatologist). Guidance on which presentations of suspected arthritis with positive Lyme serology should be referred would be useful.	Thank you for your comment. We acknowledge that where complications of Lyme disease occur referral for specialist NHS opinion may be desirable if the evidence supports this. Management strategies including specialist referral in different clinical scenarios/presentations will be explored in more detail by the Guideline Committee through the evidence reviews.
Lyme Disease Action	3	83	Insert • What tests for other tick-borne infections should be considered. See comments on lines 38 and 50. • What factors to consider if the pre-test probability is raised and the test results are negative or equivocal. Given the limitations of current tests, it may not be possible to make a definite diagnosis of Lyme disease, so it would be useful to give guidance on 'probable' and 'possible' Lyme disease.	Thank you for your comment. The remit of this guideline is Lyme disease and therefore other tick-borne infections will not be covered. Whilst we do not feel that any change to the wording of the scope is required, we will bring the detail of your second point to the committee's attention as part of their consideration

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				of evidence and classification of any management recommendations.
Lyme Disease Action	3	83	Is antibiotics intended to be an example of treatment or the only type of treatment to be considered? Consideration should be given to management for arthritis, neurological pain, facial palsy and endocrine, auto-immune, cardiac and ophthalmic sequelae. Some of this might depend on whether this guideline is concerned with Lyme Borreliosis (ie active infection) or with Lyme disease in its potentially wider context.	Thank you for your comment. The remit of this guideline is the diagnosis and management of Lyme disease. Antibiotic treatment is the only established treatment for Lyme disease. We acknowledge that where complications of Lyme disease occur referral for specialist NHS opinion may be desirable if the evidence supports this. The Guideline Committee will consider clinical scenarios where there is a need for specialist referral for management of complications. This guideline will not however, consider in detail the management of these complications.
Lyme Disease Action	3	84	See answers to the directly posed question 3 re clinical presentations.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline

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				Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Research UK	3-4	79, 82, 90, 93	"Definitive treatment": The term 'definitive treatment' implies that there is absolute certainty about which antibiotic treatment will be effective for which patients, but it is not always clear when patients should be given more powerful intravenous antibiotics. A milder term such as the "recommended antibiotic treatment" would be more suitable here.	Thank you for your comment. The term 'definitive' has been removed.
Lyme Disease UK	4	102-108	An extra point for 'Main Outcomes' needs to be included (point 8) and the evidence should be reviewed on issues of chronic complex sequelae and comorbidity which may relate to Lyme disease such as heart problems, gallbladder and thyroid disease, to name a few. Many Lyme disease patients appear to suffer from the conditions mentioned above and so searching for and assessing the literature on these issues and potential connections, may lead to a greater understanding and improvements in Lyme disease patient outcomes.	Thank you for your comment. For the purpose of the scope, we believe this is already covered in the outcomes and would be addressed by the outcome 'cure' The guideline committee will agree the key outcomes for each review and will use their expertise to determine

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				whether the results of relevant studies are significant.
Lyme Disease Action	4	104	Insert an additional outcome "Continuation of symptoms or signs". It may seem a question of semantics, but evidence showing a reduction of clinical symptoms may be viewed as evidence that a treatment is "successful" whereas evidence showing a continuation of symptoms should be viewed as indicating a potentially unsuccessful intervention.	Thank you for your comment. For the purpose of the scope, we believe this is covered under the outcomes 'reduction of symptoms' and 'cure'. The guideline committee will agree the key outcomes for each review and will use their expertise to determine whether the results of relevant studies are significant.
Caudwell LymeCo	4	85 - 94	SUGGESTED AMENDMENT Remove all categories as listed. A new list of patient categories and clinical scenarios needs to be composed by the committee. **Firstly** patients need to be divided into specific categories. I would suggest: 1. Active Borrelia infection with symptoms. These are sometimes divided into acute cases, and disseminated or "Late Lyme" cases. The usual cut-off point for 'acute' seems to be about 6 weeks and it is widely stated that treatment outcomes are very successful in this acute or early stage of infection, but I think the committee should check if this really is based on evidence. The patient experience is that standard treatment often fails at this stage but doctors seem not to consider this at all.	Thank you for your comment on the issue of the classification of Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to

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			2. Latent Lyme disease, i.e. bacteriologically positive but no symptoms - This category may or may not be considered the same as category 3. This is an area where there is a lack of understanding of the patient experience – where symptoms can develop many months after being infected. It is recognised that Lyme disease can be symptom free but doctors do not seem aware that symptoms may develop later. Repeat testing, monitoring of symptoms, etc is something guidelines should address. 3. Lyme disease in remission, i.e. no symptoms but bacterial infection is still present - The experience of many patients is that they may achieve this state for periods of months or even years, with or sometimes without antibiotic treatment, but any form of stress or an insult to the immune system will trigger a return of symptoms. Many patients alternate between category 1 and category 3 for the rest of their lives after being infected with Lyme disease.	allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of Lyme disease from the final scope.
Caudwell LymeCo	4	85-94	4. Refractory Lyme disease, i.e. treated but infection persists, and symptoms continue to worsen or new ones appear - In this category, the billion dollar question is, For how long do you treat with antibiotics before deciding a patient is a refractory case? Patients who can afford it will often keep paying privately for prolonged antibiotic treatment for as long as they feel their symptoms are improving under that treatment. Taking a lot of antibiotics for months or years causes a lot of side effects, which should be telling doctors something important about how bad it really is to live with Lyme disease. The guidelines should try to find a reliable, objective way to find out if patients really have refractory Lyme disease or Lyme disease sequelae rather than simply assuming this is the case after a standard course of antibiotics. For a patient who has been very ill with Lyme	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions

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			disease for a long time to be told that they are not getting any more antibiotics, and that they are never going to get rid of their symptoms, is a devastating, life-changing experience, and one that should only happen on the basis of objective medical testing if at all possible. 5. Lyme disease sequelae, post bacteriologic cure i.e. organ damage remains as a result of past infection but symptoms are no longer getting worse - This is what some researchers mean when they use the eccentric phrase "Post treatment Lyme disease syndrome" which patients universally find infuriating. The patient experience is that their doctors usually tell them they fit this category after a short course of antibiotics (without objective evidence that this is the case) and refuse to listen when they say that their symptoms are actually still progressing and getting worse. 6. Definite tick bite - patient may or may not be infected with Borrelia. **Secondly**, cutting across these categories, there will be particular treatment considerations based on the patient's symptoms. These will include thyroid, cardiac, gastrointestinal and gall bladder symptoms, for example. A full list of such examples would be far too voluminous to complete here, but should form the focus of a thorough investigation by the committee. **Thirdly**, there will be some patients with special circumstances that need to be taken into consideration when planning antibiotic treatment, which may also cut across the categories above. These would include: 7. Pregnant women: some antibiotics cannot be used in this group but adequate treatment is essential to protect the fetus. 9. Children: I would recommend making a specific review of the evidence as regards	outlined in the guideline scope. We acknowledge the very specific issues related to pregnant women and children. We will ensure that the needs of these groups (and the immunocompromised) are addressed as part of each of our evidence reviews. The recruitment of paediatricians to this group is to ensure that the protocols that are developed are meaningful for children and that the evidence is correctly interpreted and appropriate recommendations drafted for children. Further expertise can be co-opted if necessary to inform the guideline group. We will bring your comments on the issue of co-infection to the guideline

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			appropriate antibiotic treatment in paediatric cases, and management of symptoms in the context of full-time education. As I understand it there will be three paediatricians on the guidelines committee and I presume their presence is required for this purpose? 10. Patients with additional tick-borne infections: overlooking other infections may result in treatment failure for Lyme disease, or a failure to resolve Lyme disease symptoms even if Lyme disease is cured. REASON Treating Lyme disease is not simply a question of finding out if the patient has been infected for more or less than 6 months and then deciding which antibiotics to prescribe and at what dosage. Six months is an arbitrarily chosen time period and has no relationship with disease progression. More importantly, the important factor to consider is symptoms. Example 1 Around 10% of patients with Lyme disease that persists for months or years develop hypothyroid or hyperthyroid conditions which require treatment with thyroid hormone replacement or thyroidectomy (SOURCE: Caudwell LymeCo survey of around 500 Lyme disease patients; our results were the same as the statistics published in some books about Lyme disease, and found by doctors who treat many Lyme patients). Some develop Hashimoto's disease whilst others have low thyroid activity without this condition. In Lyme disease patients with low T4, TSH is also typically low. This means that standard NHS screening tests of TSH will miss the Lyme patients with hypothyroidism because their	committee's attention to ensure that this issue is appropriately addressed as part of our evidence reviews or in our sections where we link the consideration of the evidence to the recommendations made as appropriate. We will not however address the specific management of any co-infection.

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			TSH will normally scrape into the bottom end of the normal range. Example 2 Many Lyme disease patients develop persistent gastro-intestinal disturbances, either diarrhoea or constipation or, most often, both in alternation. According to a Caudwell LymeCo patient survey, 26% of them (120 patients out of 464) were diagnosed with irritable bowel syndrome by NHS doctors. Patients who can afford private healthcare, on the other hand, are sometimes tested for small intestinal bacterial overgrowth. When these patients are treated with suitable doses of Xifaxan they can achieve dramatic improvements in their gastro-intestinal symptoms. This not only saves them from considerable pain and social embarrassment but also enables them to achieve a better level of nutrition. Example 3 Lyme carditis causes heart block (and sometimes other arrhythmias) and is the commonest cause of death from Lyme disease, according to the Centre for Disease Control in America. The CDC says this affects 1% of Lyme patients but, based on anecdotal evidence, I think in the UK it is far more common than this. Like all arrhythmias, this phenomenon is not continuous but occurs episodically. The patient experience in the UK is that patients go to A&E departments with symptoms of palpitations, chest pain and or breathlessness etc, and are sent away after an ECG, without adequate investigation, or follow up with Holter monitoring etc. Management of this life-threatening complication of Lyme disease should be overseen by a competent electrophysiologist.	Thank you for your comment on the issue of the classification of early and late Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of early and late Lyme disease from the final scope.

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			General observation: The medical profession already has a standard vocabulary that can describe each category of patient unambiguously. I think it would be much clearer to use this than terms like "early" or "late" coined exclusively for Lyme disease, especially as these terms lump several different scenarios into one. If we simply replace the term "Chronic Lyme disease" with "Late disease" we don't address this problem of imprecise thinking. For example, I have read some research papers talking about "chronic Lyme disease" which hadn't clarified if the researchers actually meant untreated active Lyme disease infection, refractory Lyme disease or Lyme disease sequelae. Trying out a treatment protocol on a group of patients selected at random from all these categories and then trying to draw general conclusions about the efficacy of that therapy is not going to produce meaningful results.	
NHS Highland	4	88	As for comment no. 4	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily

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				measured by someone else, e.g. feeling unwell or a headache) or vice versa. This is to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only.
Lyme Disease Action	4	90	replace the phrase "a full course of definitive treatment" with "initial treatment	Thank you for your comment. The term 'definitive' has now been removed.
NHS Highland	4	90 to 96	These are important questions. Suggest may be helpful to divide symptoms into objective and subjective (indicated in some papers)	Thank you for your comment. We will ensure that this information is brought to the guideline committee's attention when they are developing the review questions and protocols.
Lyme Disease Action	4	93	replace the phrase "a full course of definitive treatment" with "initial treatment"	Thank you for your comment. The term 'definitive' has now been removed. No further edits have been made.
Lyme Disease UK	4	94-95	An extra point should be added here (point 4.6) to include groups of patients who are immunocompromised, who have co-morbidities, who are pregnant, and who have other concurrent tick-borne infections. The BIA position statement from 2011 refers to immunocompromised patients on page 334.	The guideline committee will review the evidence about diagnostic test accuracy and management strategies in pregnant women and

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			Children may also present differently clinically and require different treatment and this should be reflected in the guidelines. This article from Lymedisease.org highlights this point: 'Children with Lyme disease have special issues. Since they can't always explain what feels wrong, they may just come across as cranky and irritable. They suffer when their bodies hurt, when their illness disrupts their sleep at night, when they struggle in school, when they don't even feel like playing. They may feel confused, lost and betrayed by parents and teachers who fail to recognize that they are sick and need help. Children with Lyme often have trouble in the classroom, because the disease can contribute to learning disabilities and behavioral problems.' References: 1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 2. Lymedisease.org. Children with Lyme disease https://www.lymedisease.org/lyme-basics/lyme-disease/children/	immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations to the NHS. These subgroups have been included in the equality impact assessment for this guideline. Children are already detailed in the scope and will form a separate group to ensure that the evidence is appropriately identified, considered and interpreted. We plan to recruit three paediatricians to the committee for this purpose. While people with co-infections will not be excluded from the evidence reviews, the focus of this guideline is

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				the diagnosis and management of Lyme disease. However, the guideline committee will give mention to any groups who require special consideration when linking evidence to recommendations.
Lyme Research UK	4	95-96	Information needed: The NICE guideline should give guidance to the testing laboratories that in communications to clinicians and patients they should: a) Report clearly the results of the test in the manner described by test kit manufacturers. b) Inform clinicians of the test limitations and the kit manufacturers' statements that a negative result does not indicate absence of Lyme borreliosis. c) The laboratories should not reinterpret the test results in a manner not supported by the test kit manufacturers. d) The laboratories should confine themselves to reporting the test results and should not give clinical advice on specific cases without seeing the patient, and definitely not with the very basic data sent by clinicians. e) Provide clear dates for taking samples and testing samples to ensure specimens are	Thank you for your comment. This is a clinical guideline for the NHS. While the points you have raised are very important, we would not usually go into this level of detail from a particular evidence review for this guideline. The committee may choose to comment on reporting issues as part of the planned diagnostic test accuracy review.

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			'fresh' as defined by the manufacturer. f) Patients should have access to their full laboratory results if they request them.	
Lyme Disease Action	4	96	The information needs of other healthcare providers requires consideration. A significant barrier to diagnosis and to effective, safe care is currently the lack of experience amongst UK clinicians. Lyme borreliosis can cause many complications and a patient may be seen by a rheumatologist, endocrinologist, neurologist, gynaecologist, physiotherapist, psychiatrist, psychologist, cardiologist and immunologist. These clinicians may not recognise the possibility of Lyme disease and have no quality, experienced resource to consult. The information and education needs of infectious diseases consultants also needs consideration. Lyme Disease Action has received many comments indicating that some do not believe Lyme borreliosis can be contracted "in their area", that negative serology means that Lyme borreliosis cannot be present and that Lyme borreliosis cannot relapse. This despite Public Health England's referral pathway for GPs which counters each of those statements. Whatever other recommendations are made during the course of this guideline development, the context section of the NICE guideline must attempt to address these issues in case this is the only resource that any clinician refers to.	Thank you for your comment. The information, education and support needs of healthcare professionals may be considered by the guideline committee as part of its reviews of evidence in the scope areas and acknowledged when linking evidence to recommendations. It is also anticipated that the publication of the guideline will provide helpful information for healthcare professionals and this may then be subsequently taken forward by appropriate providers as a resource for professionals. The NICE guideline context section will be drafted in light of the recommendations made in due

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				course.
Lyme Disease Action	4	97	A key issue with the potential to improve outcomes is the provision of a network of regional centres of expertise. These require access to specialist diagnostic facilities a multi-disciplinary approach with a variety of healthcare professionals (nurses, physiotherapists occupational therapy etc) to meet the potential complex needs of patients with Lyme disease. This was supported by the Minister, Lord Prior, in a debate in the House of Lords in October 2015.	Thank you for your comment. The point you have raised concerns service delivery, which is unfortunately outside the remit of this clinical guideline.
Lyme Disease Action	4	97	A key issue to improve knowledge and outcomes and reduce ineffective care would be research to include follow up of patients after treatment. Consideration should therefore be given to follow up as a specific key issue, rather than just including it under treatment when symptoms or signs have not resolved. This could include consideration of diverse points such as removal of temporary pacemakers, and consideration of treatment for incompletely resolved facial palsy, in addition to consideration of further antibiotic treatment in case of relapse.	Thank you for your comment. Follow up of patients after treatment is an important part of the management of a condition and this has been identified as a specific outcome. We acknowledge a specific key issue around the management of Lyme disease when symptoms or signs have not resolved. We will bring the detail of your comment to the committee for their consideration when developing protocols. The committee is able to make research recommendations where evidence is lacking or inconclusive.

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NHS Highland	4	Figure	Cannot have Lyme disease without symptoms and signs (mentioned in both boxes of figure)	Thank you for your comment. We had intended for 'without symptoms or signs' to refer to the absence of either clinical signs or symptoms, and not the absence of both. For example a person could have a clinical sign (something than can be easily measured by someone else, e.g. a rash) but no symptoms (something that cannot be easily measured by someone else, e.g. feeling unwell or a headache) or vice versa. This is to reflect the issue around the difficulty of diagnosing or ruling out Lyme disease using clinical signs only.
Lyme Disease Action	5	111	NICE guidance on treatment of neuropathic pain CG173 is relevant.	Thank you for your comment. This section only details NICE guidance whose recommendations support overarching principles of patient management rather than

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				recommendations for specific symptom management. . As such CG173 is not included here in line with the NICE template.
Caudwell LymeCo	6	128	SUGGESTED AMENDMENT Remove proposed category definitions. Replace with the category definitions, based on conventional and unambiguous medical terminology, which I suggested in point 8. REASON As explained above, I believe this would be far more intuitive to clinicians than these arbitrarily chosen 'early' and 'late' groupings which may mislead practitioners not specialised in Lyme disease into assuming that they are based on an inherent progression of Lyme infection when in fact they are not.	Thank you for your comment. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. The Lyme disease overview is intended as a framework for how the NICE pathway might look based on the scope. It will be updated to reflect the categorisation agreed by the guideline committee.
Lyme Disease	6	130	If this context statement is to be used in the final guideline, it is imperative that it is clear and correct. This may be the only resource consulted by a busy clinician.	Thank you for your comment. The purpose of the context section in the

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Action				scope is to set the scene in terms of epidemiology, nature of the condition and current practice. It is not intended to be included as part of the narrative of the published guideline. The scope is usually included as an appendix to the full published guideline.
Caudwell LymeCo	6	131	SUGGESTED AMENDMENT Remove "tick-borne". REASON Lyme disease is transmitted not only by ticks but also congenitally and by blood transfusion. There is also preliminary evidence that Lyme disease may be transmitted sexually, through breastfeeding, by other biting insects and through eating unpasteurised dairy foods from infected cattle. It is no longer valid to define Lyme as a purely tick-borne disease when there is a considerable body of research casting doubt on this. EVIDENCE **Congenital transmission:** The published medical research papers documenting babies born infected with Lyme disease are far too numerous to list here.	Thank you for your comment. In response to stakeholder comments we have added person-to-person transmission to the scope of this guideline.

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			Transmission by blood transfusion: For example, J Infect Dis. 1990 Aug, "Borrelia Burgdorferi: survival in experimentally infected human blood processed for transfusion." Johnson SE1, Swaminathan B, Moore P, Broome CV, Parvin M.; **Sexual transmission:** A preliminary finding in humans which corresponds with previous findings in other mammals, "Culture and identification of Borrelia spirochetes in human vaginal and seminal secretions" Marianne J. Middelveen et al.	
Lyme Disease Action	6	132	It is not just B burgdorferi. Not enough is known about B miyamotoi infections, but this, and infections caused by other as yet unidentified genospecies, should not be excluded. See comment on Q4.	Thank you for your comment. The context section of the scope is intended to give a short overview of what is currently known. As such, it cannot outline all areas that are potentially being researched. Lyme disease itself is currently only linked to Borrelia burgdorferi-group. The management of co-infections is outside the scope of the guideline.
NHS Highland	6	134	You state 'Lyme disease can be asymptomatic'. I disagree. Infection with *Borrelia burgdorferi* can be asymptomatic, but I would reserve the term 'Lyme disease' for symptomatic infection.	Thank you for your comment. We have amended the text in the scope to distinguish between asymptomatic

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				infection and Lyme disease as a symptomatic infection.
Lyme Disease Action	6	134	Where is the evidence (evidence, not personal opinion quoted in a paper) that Lyme disease can be asymptomatic? This trivialises the disease and has no place in a guideline dealing with symptomatic infection.	Thank you for your comment. We have amended the text in the scope to distinguish between asymptomatic infection and Lyme disease as a symptomatic infection.
Lyme Research UK	6	135	"Incubation period": The use of the phrase "incubation period" in the context of human infection with Borrelia is not valid. The pathogen is infectious immediately. Symptoms develop as the pathogen multiplies and disseminates.	Thank you for your comment. We use the phrase 'the incubation period' to refer to the time between infection and the onset of symptoms.
Lyme Disease Action	6	135	There is evidence of longer incubation periods tan one month (eg Logar et al 2004).	Thank you for your comment. It is widely accepted that the incubation period ranges from a few days to about a month. However, the course of a disease is different for each individual and some people might experience a much longer incubation period. People who experience the onset of symptoms after more than one month from the time of infection

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				will be included in the relevant reviews.
Caudwell LymeCo	6	135	SUGGESTED AMENDMENT Delete "from a few days to one month" and replace with "of unknown length." REASON Assessing time from infection to becoming symptomatic is challenging because many people with Lyme disease have no idea when they were first infected. 90% of Lyme disease patients have no recollection of ever seeing a tick, for example, based on patient survey results and the assessment of a well known clinic in Germany. EVIDENCE There is no valid evidence that the maximum incubation period of Lyme disease is one month. In line 134 the document states that Lyme disease can be asymptomatic. This can indeed be the case for years before a patient develops symptoms.	Thank you for your comment. It is widely accepted that the incubation period ranges from a few days to about a month. However, the course of a disease is different for each individual and some people might experience a much longer incubation period. People who experience the onset of symptoms after more than one month from the time of infection will be included in the relevant reviews.
Caudwell LymeCo	6	136	SUGGESTED AMENDMENT Delete "approximately two thirds of people" and replace with "in approximately one third of people" or else "in some people" REASON This oft-quoted figure, based on surveys of patients in the USA, does not correspond with	Thank you for your comment. We have changed the wording in the scope to read: " …..in some people this is followed by ….." to reflect the uncertainty about the true proportion of people. We note the study in

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			the observations of doctors who treat significant numbers of Lyme disease patients in Europe. EVIDENCE For example, the BCA clinic in Augsburg, which currently has 4,000 patients under its care and whose founder has treated over 10,000 patients, has on its patient records that one ONE third of patients manifest an EM at any time during the course of their illness.	Germany but have not used these figures as they do not relate to the population in England and Wales.
Royal College of Genera Practitioners (RCGP)	6	147 (question 2)	What is the role of epitope mapping of antibodies to VlsE protein of Borrelia burgdorferi in post-Lyme disease syndrome. (MH)	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. Where relevant the information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Research UK	7	134-141	You write "... in approximately two thirds of people this is followed by a circular, target-like rash centred on the bite, known as erythema migrans":	Thank you for your comment. We have changed the wording in the scope to read: " …..in some people

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			We have not found the source of this estimate of two thirds and think it may actually be lower. There are difficulties in getting representative patient samples which include all types of patients. We hope that that you will look into this. This estimate can of course only be based on patients diagnosed with Lyme borreliosis. Undiagnosed patients, of whom there may be many, are less likely to have had an erythema migrans aiding diagnosis.	this is followed by ….." to reflect the uncertainty about the true proportion of people.
Lyme Disease Action	7	137	erythema migrans may not be centred on the bite and there may be multiple erythema migrans. People have been refused initial treatment because the rash was elsewhere and therefore "could not" be erythema migrans.	Thank you for your comment. We have changed the wording in the scope to read: "...in some people this is followed by a circular, target-like rash centred on the bite, known as erythema migrans…" to reflect the uncertainty about the proportion of people affected in this way.
Lyme Disease UK	7	138-139	The draft scope mentions that early symptoms of Lyme disease 'are similar to those for flu.' However, it is also important to note that Lyme disease can mimic many other conditions and present in numerous different ways, including neuropsychiatric manifestations. Fallon and Nields, in this study state that, 'up to 40% of patients with Lyme disease develop neurologic involvement of either the peripheral or central nervous system. Dissemination to the CNS can occur within the first few weeks after skin infection' and that 'early signs include meningitis, encephalitis, cranial neuritis, and radiculoneuropathies.'	Thank you for your comment. We used the phrase "similar to flu" to reflect that the symptoms can be non-specific. We have amended the wording in the scope to read: " …early symptoms are non-specific and can be similar to those for flu."

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			This quote reflects what appears to happen frequently in the patient community: 'Time and again, Fallon, an expert in hypochondria, had seen frustrated doctors dismiss medically ill patients as psychiatric cases due to their own inability to diagnose the disease. With Lyme, the mistake was especially damaging since a delay in treatment could turn a curable, acute infection into a chronic, treatment-resistant disease' (Weintraub, 2008). It is important to include in the scope and guidelines that initial symptoms of Lyme disease are not always concurrent with a dismissable flu-like illness. Doctors must be made aware of the wide variety of ways in which Lyme disease may present and not assume symptoms are restricted to those of flu in the initial stages, especially as without a known tick bite or EM rash, it is often hard to distinguish between an acute early infection and a disseminated infection. References: 1. Fallon, B. A. and Nields, J. A. (1994). Lyme disease: a neuropsychiatric illness. The American Journal of Psychiatry, 151(11), 1571–83. doi:10.1176/ajp.151.11.1571 http://www.ncbi.nlm.nih.gov/pubmed/7943444 2. Weintraub, P. Lyme Disease: The Great Imitator. Psychology Today, May 1st 2008. https://www.psychologytoday.com/articles/200805/lyme-disease-the-great-imitator	
Caudwell LymeCo	7	138-139	SUGGESTED AMENDMENT Delete "early symptoms are similar to those for flu" and replace with "doctors lack training in recognising the symptoms."	Thank you for your comment. We used the phrase "similar to flu" to reflect that the symptoms can be non-specific. We have amended the

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			REASON The claim that "early symptoms are similar to those for flu" is true only if you condense a few randomly chosen symptoms from the whole gamut of manifestations down to a brief list of keywords. Saying that Lyme symptoms are like flu does nothing to help GPs distinguish Lyme patients from the large number of flu cases they must see each year. The weirder symptoms of Lyme disease are the ones that make many a GP dismiss their Lyme patient as a hypochondriac, but these are the very symptoms that could be telling them they have a case of Lyme disease on their hands, if only they were better informed. There is also a significant proportion of patients who only have the "other" symptoms and not the "flu-like" ones at all. The kind of "slam-dunk" Lyme symptoms that should be in the list given to doctors include: "The soles of my feet feel burning hot" "I keep dropping things and bumping into things but I never used to be clumsy" "I get random itchiness which moves around my body" "I get headaches that hurt all the way down my neck and the pain instantly gets much worse at the back when I lie down" "I keep forgetting words, right in the middle of a sentence" EVIDENCE Based on anecdotal evidence, I think that when Lyme disease patients recognise the symptoms of Lyme in other people and suggest they get a blood test, their prediction accuracy rate is extremely high.	wording in the scope to read: " …early symptoms are non-specific and can be similar to those for flu." Symptoms will be addressed by a review of the evidence (see section 2.1 and 2.2) and we hope to be able to make recommendations that will enable healthcare practitioners to be aware of the symptoms that may indicate Lyme disease.

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NHS Highland	7	141	Delete 'frequently' and replace with 'can be' and 'resolves' with 'may resolve'.	Thank you for your comment. The wording of the scope has been altered.
Lyme Disease UK	7	141	The sentence 'Lyme disease is frequently self-limiting and resolves spontaneously' should be removed or rephrased. It is not representative of the general patient experience and it does not take into consideration existing and emerging evidence that Lyme disease can be a persistent infection. Furthermore, in the absence of 100% reliable tests, it cannot be proven that Lyme disease has been eradicated from a patient's body. This is highlighted in this study: 'Clinicians have no diagnostic tests to check for the persistence of live borreliae. *B. burgdorferi*, having a complex genetic structure, is a highly adaptable organism capable of evading immune response through different processes' (Perronne, 2014). The ILADS guidelines state that 'ongoing symptoms at the completion of active therapy were associated with an increased risk of long-term failure in some trials and therefore clinicians should not assume that time alone will resolve symptoms' (Cameron et al, 2014). References: 1. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-	Thank you for your comment however we do not feel any change is required to the wording currently used. We continue to present information in this section linked to the issues when Lyme Disease has not resolved spontaneously to present the fullest range of experience.

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			bransfield/ 2. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full 3. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	
Lyme Disease Action	7	141	Where is the evidence that Lyme disease is frequently selflimiting? It can resolve without treatment, but frequently? A statement like this is unsafe and runs the risk of encouraging a clinician to delay treatment.	Thank you for your comment. We believe our current wording is sufficient to describe the disease trajectory.
Caudwell LymeCo	7	141	SUGGESTED AMENDMENT Delete "Lyme disease is frequently self-limiting and resolves spontaneously." REASON There is absolutely no evidence that Lyme disease is a self-limiting infection. EVIDENCE To prove that, you would have to prove seropositivity, not treat at all, and later prove a total	Thank you for your comment however we do not feel any change is required to the wording currently used. We continue to present information in this section linked to the issues when Lyme Disease has not resolved spontaneously to present the fullest range of experience.

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			absence of any symptoms after a long enough period of time to be certain the disease was not just in remission, but bacteriologically cured. Based on the patterns of remission and relapse which I have observed in patient support groups over the years, I would say five years would be the bare minimum "all-clear" period, but a more meaningful and reliable criterion would be that the patient had gone through a major insult to the immune system with no Lyme relapse. Such a research project has never been done and I think it never will be, because once you have proven seropositivity for Borrelia, how can you ethically deny the patient treatment?	
Lyme Research UK	7	141, 144	You write "Lyme disease is frequently self-limiting and resolves spontaneously" and "If Lyme disease does not resolve spontaneously, ...": This implies that it often resolves without any antibiotic treatment. We do not know of any evidence for this, so think that the statements should not be made.	Thank you for your comment however we do not feel any change is required to the wording currently used. We continue to present information in this section linked to the issues when Lyme Disease has not resolved spontaneously to present the fullest range of experience.
Lyme Disease Action	7	142	Suggest replace "risk of later symptoms" with "risk of chronic infection".	Thank you for your comment. We have chosen to maintain the wording linked to later symptoms as this does

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				not rely on definition of chronic infection.
Lyme Research UK	7	143	You call symptoms that persist after treatment "post-infectious Lyme disease": None of the Lyme borreliosis guidelines or articles in the medical literature refer to 'post-infectious Lyme disease', and we think it is not a good idea to introduce a new term that nobody else uses.	Thank you for your comment. We have deleted this phrase.
Lyme Disease UK	7	143	As there is no test that can rule out an active Lyme disease infection, the term 'post-infectious Lyme disease' should not be used, especially when there is evidence that the infection can persist. This study states, 'extensive evidence now shows that persistent symptoms of Lyme disease are due to chronic infection with the Lyme spirochete in conjunction with other tick-borne coinfections' (Stricker and Johnson, 2011). It would be more effective to review evidence and consider alternative terminology for ongoing symptoms consistent with Lyme disease. References: 1. List of 700 Articles Citing Chronic Infection Associated with Tick-Borne Disease Compiled By Dr Robert Bransfield http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/ 2. Stricker, R.B, Johnson. L. Lyme disease: the next decade. Stricker, R.B, Johnson, Infect Drug Resist. 2011; 4: 1–9. doi: 10.2147/IDR.S15653	Thank you for your comment. We have deleted this phrase.

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			http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3108755/	
Lyme Disease Action	7	143	Remove the phrase "post infectious Lyme disease" as this implies infection has been eliminated and we do not currently have the means to know this, as there is no reliable biomarker for disease activity and no test of cure.	Thank you for your comment. We have deleted this phrase.
Caudwell LymeCo	7	143	SUGGESTED AMENDMENT Change "Post infectious Lyme disease" to "which may be Refractory Lyme disease or may be Lyme disease sequelae." REASON Symptoms do often persist after treatment but this may be for two separate reasons: the patient may have Refractory Lyme disease, with persistent infection after the standard antibiotic treatment; or, the patient may have Lyme disease sequelae following bacteriologic cure. AN ADDITIONAL QUESTION The choice of the somewhat ambiguous term "Post-infectious Lyme disease" implies that, prior to being treated, Lyme disease in humans IS infectious. But infectious to whom? To other people? To ticks? This probably requires clarification.	Thank you for your comment. We have deleted this phrase.
Lyme Disease Action	7	145	Add "frank arthritis" because this is what the pathology shows in late Lyme borreliosis.	Thank you for your comment. This part of the context is intended to be very inclusive and reflect the

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				uncertainties and difficulties around clinical presentations of Lyme disease. As such, the sentence you are referring to is intentionally very broad. We have chosen not to make the edit you suggest.
Lyme Disease Action	7	145	Suggest replace "heart problems" with "carditis". The symptoms (heart problems) may include palpitations and heart block, but the basic pathology is inflammation in cardiac tissue which is Lyme carditis.	Thank you for your comment. The term 'heart problems' has been used because we try to write the scope in plain English as far as possible. We feel that the term 'heart problems' covers carditis.
Lyme Disease UK	7	146	The evidence on how to define relapse should be reviewed as the ILADS guidelines state: 'given that prior *B. burgdorferi* infections do not provide durable immunoprotection, clinicians should consider the possibility that the patient was re-infected and seek information to confirm or dispel that this occurred. In the absence of clear evidence of re-infection, clinicians and patients will need to consider the relative risks and benefits of assuming that relapsing symptoms such as EM lesions or flu-like symptoms in the summer are indicative of ongoing infection and not re-infection' (Cameron et al, 2014). References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema	Thank you for your comment. The definition of relapse has not been prioritised as an area for a review question; however, management of Lyme disease in people who have Lyme disease refractory to treatment will be addressed. The Guideline Committee will discuss and agree the exact protocol for this review question based on the scope.

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			migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900	
Lyme Disease Action	7	146/147	Remove quotes round chronic Lyme disease. Perhaps rephrase that sentence to "There is uncertainty about the cause of persistent symptoms, hence disagreement amongst experts and some controversy. The cause of persistent symptoms after antibiotic treatment is poorly understood. There is scientific proof of concept for persistence of Borrelia, immune dysfunction/auto-immunity and damage to tissues and neural networks. However, current diagnostic tests are not capable of determining which factor(s) cause chronic illness and symptoms on an individual patient basis. Current research is aimed at characterising panels of biomarkers that may assist diagnosis and inform treatment choice.	Thank you for your comment. We have removed the quote marks and changed 'controversy' to 'uncertainty' as you suggested.
Lyme Research UK	7	146-147	You write "There is controversy over the existence of 'chronic Lyme disease' or 'post Lyme disease' syndrome": We suggest that you delete this sentence. The British Infection Association (2011), the Infectious Diseases Society of America (Wormser et al, 2006) and the Centers for Disease Control and Prevention in the United States (2016b) now all recognize that some patients have persistent symptoms lasting for many months or years after the officially recommended treatment. See also the meta-analysis on this by Cairns et al (2005). It is debated whether this is a post-infectious syndrome or ongoing infection, although it is possible that some patients have a post-infectious syndrome while others have ongoing	Thank you for your comment. We have changed 'controversy' to 'uncertainty' to reflect the ongoing discussion around this issue. The Guideline Committee will develop review questions and protocols based on the key areas as outlined in the scope. This is to ensure that the reviews follow good scientific practice and established NICE processes

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			infection. The Centers for Disease Control and Prevention in the United States (2016b) writes: "Clinical studies are ongoing to determine the cause of PTLDS [post-treatment Lyme disease syndrome] in humans." We think that a section on this should be included in the NICE Guideline, noting results from studies such as those by Bouquet et al (2016), Chandra et al (2010) and Fallon et al (2003), and any future results from the ongoing studies referred to by the Centers for Disease Control.	when identifying, synthesising and analysing the evidence. The references you provide may form part of literature to be reviewed depending on the specific content of the protocol developed by the guideline committee. Where appropriate. they may be used to inform the supporting introductory text to accompany any relevant review questions.
Caudwell LymeCo	7	146-147	SUGGESTED AMENDMENT Delete "There is controversy over the existence of 'chronic Lyme disease' or 'post-treatment Lyme disease syndrome'." REASON There is no longer controversy over the existence of these conditions, but rather, controversy over what these terms mean. This is because a) they are eccentric terms that don't use standard medical terminology, and b) because there are, regrettably, still many doctors who have failed to keep up to date with newer research and still believe the old assumption that Borrelia is easy to cure with a short course of antibiotics.	Thank you for your comment. We have made edits to this section and removed the speech marks and changed 'controversy' to 'uncertainty'.

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			EVIDENCE There are around 700 peer-reviewed research papers documenting cases of refractory Lyme disease, which are conveniently gathered together by Dr. Richard Bransfield, author of what are currently the only operational Lyme disease treatment guidelines in America (ILADS guidelines) http://www.ilads.org/ilads_news/2015/list-of-700-articles-citing-chronic-infection-associated-with-tick-borne-disease-compiled-by-dr-robert-bransfield/	
Lyme Disease UK	7	148	The statement 'early treatment is almost always successful' requires an evidence review. This is not reflective of the overwhelming number of people in the patient community who report ongoing health problems despite standard treatment for Lyme disease. Follow ups often do not occur, especially if patients move on to seek private Lyme disease treatment after feeling let down by the NHS, as is often the case based on anecdotal evidence from patients. The ILADS guidelines observe that 'the optimum duration of post-treatment observation for EM has not been determined, in part, because while disease relapse is known to occur, the duration of the latent period is variable and can be prolonged' (Cameron et al, 2014). This study shows that following early treatment, 63% patients treated for Lyme disease still had symptoms which were then attributed to 'post-treatment Lyme disease symptoms (PTLDS)' (Adrion et al, 2015). In our opinion, this does not reflect 'successful' treatment. Furthermore, 'clinicians have no diagnostic tests to check for the persistence of live borreliae. *B. burgdorferi*, having a complex genetic structure, is a highly adaptable	Thank you for your comment. The topic of early treatment will be addressed by an evidence review as outlined in section 1.5

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			organism capable of evading immune response' (Perronne, 2014). The ILADS guidelines also state that 'the harms associated with restricting treatment of an EM rash to 20 or fewer days of oral azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin outweigh the benefits. In assessing the risk–benefit profile, the panel determined that the failure rates for antibiotic treatment of 20 or fewer days were unacceptably high and that for those who failed treatment, the magnitude of the potential harm created by delaying definitive treatment, which includes the increased risk of developing a chronic and more difficult to treat form of the disease, was too great' (Cameron et al, 2014). References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900 http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 2. Adrion, ER, Aucott, J, Lemke, KW and Weiner, JP. Health care costs, utilization and patterns of care following Lyme disease. PLoS One. 2015 Feb 4;10(2):e0116767. doi: 10.1371/journal.pone.0116767. eCollection 2015 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0116767 3. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi:	

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			10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full	
Lyme Disease Action	7	152	The only evidence we can find for Public Health England's estimate of 2000-3000 is a poster at the HPA 2007 conference. Given subsequent, also unpublished, studies it might be more accurate to simply say "The true incidence of Lyme disease remains unknown and a large proportion are not diagnosed." • An audit at a Scottish GP practice (Aberfeldy) found a rate in the practice population of 370/100,000 confirmed with a Tayside reported rate of 17/100,000. • A recent Norwegian project found a rate of 449/100,000 - 22 times the reported laboratory confirmed rate. • In the USA when figures from insurance claims were included with the laboratory confirmed rate, the incidence of Lyme borreliosis increased x10 from 30,000 to 300,000/year.	Thank you for your comment. NICE guidelines are for the NHS in England only and so we look for figures that are directly relevant to this population. The figures provided by Public Health England are an estimate only. We note that the actual number of infections might be much higher, and further acknowledge that the true incidence in England remains unknown.
Caudwell LymeCo	7	152	SUGGESTED AMENDMENT Delete "Public health England estimates that between 2000 and 3000 people develop it each year in the UK..." REASON This "estimate" by Public health England is actually a guess rather than an estimate. In a freedom of Information request, I asked their methodology and they had none. (the FOI response is online at	Thank you for your comment. The figures provided by Public Health England are an estimate only. We note that the actual number of infections might be much higher context and further acknowledge that the true incidence in England remains unknown. We would encourage you to

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			https://www.whatdotheyknow.com/request/313568/response/773785/attach/html/2/551%20FOI%20Lyme%20testing%20reply.pdf.html please refer to item 11.) EVIDENCE On behalf of the Caudwell LymeCo charity I have conducted a survey of close to 500 UK patients, diagnosed the RIPL and in a few selected foreign labs, and extrapolated the results to formulate an estimate which comes to around 45,000 new Lyme disease cases per year in the UK. I plan to publish this research online, explaining my input data and methodology.	publish your evidence to inform the debate.
Lyme Disease Action	7	154	This should read "The distribution of laboratory confirmed cases". Erythema migrans are confirmed cases, but are not included in the reported figures.	Thank you for your comment. We have made the change as you suggest.
Lyme Disease Action	7	155	"with over 50% diagnosed in…" should read "with 50% of these in..". We have no data on the distribution of clinically diagnosed cases.	Thank you for your comment. We have made the change as you suggest.
Lyme Disease UK	7	156	It is important to include the fact that ticks can be found in a variety of environments including urban parks (Jennett et al, 2013). Anecdotal evidence in the patient community also demonstrates that people have been bitten in urban gardens. References: 1. Jennett, AL, Smith, FD & Wall, R, 2013, 'Tick infestation risk for dogs in a peri-urban	Thank you for your comment. We do not consider that the text in the scope needs changing because it does not specify urban or rural environments.

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			park'. *Parasites and Vectors*, vol 6. http://www.bristol.ac.uk/biology/people/richard-l-wall/pub/32548259	
Lyme Disease Action	7	157/8	People with outdoor occupations tend to be more informed and thus reduce their risk of exposure (chainsaw leggings, working boots etc). Add to this sentence ".. as are those who visit these areas for recreation".	Thank you for your comment. We have amended the text in the scope as follows: "People who spend a lot of time outdoors in these areas for work or recreational purposes are at increased risk of tick exposure. Infection is more likely if the tick remains attached to the skin for more than 24 hours"
Lyme Disease Action	7	158	Insert "A significant number of people may be infected abroad and this increases the risk of mixed infection." The percentage of ticks with co-infections is greater in many countries in continental Europe and in the USA.	Thank you for your comment. The sentence 'A number of people may also have been infected abroad.' has now been added.
Lyme Disease Action	7	158/9	So that this is not taken to exclude the possibility of infection in a shorter duration of attachment, this should be re-phrased to "Some tick-borne infections can be passed immediately on tick attachment, but the risk of Lyme disease increases with duration of attachment." In Europe research seems to suggest that it takes less time for Lyme borreliosis transmission from the tick compared to American studies. Transmission has been known to occur in under 12 hours.	Thank you for your comment. We agree that the statement 'An infection is more likely if a tick remains attached for longer periods' is not intended to imply that Lyme disease requires a tick to be attached for more than 24 hours in order to develop. We do not feel a change to the scope is

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				required.
Lyme Research UK	7	158-159	You write "Infection is more likely if the tick remains attached to the skin for more than 24 hours": This may be taken by some to mean that an infection is very unlikely if the tick is attached for a short time. However, that is not the case. Infection can occur quickly and the minimum attachment time has never been established. Risk increases with attachment time with no evidence of a safe period (Cook, 2015), and a study indicates that removal of ticks after body searches on the day of exposure to ticks does not prevent significant risk of infection (Faulde et al, 2014). We think it would be better to replace the sentence with: "Infection risk increases with attachment time but there is no safe period and infection frequently occurs in less than 8-12 hours".	Thank you for your comment. We agree that the statement 'An infection is more likely if a tick remains attached for longer periods' Is not intended to imply that Lyme disease requires a tick to be attached for more than 24 hours in order to develop. We do not feel a change to the scope is required.
Caudwell LymeCo	7	158-159	SUGGESTED AMENDMENT It would be useful to add to this the fact that only 10% of patients actually have any idea of when a tick bit them. REASON The majority of tick bites are by nymphs, which are no larger than a poppy seed and patients are unaware of their presence and unable to say how long they have been attached. EVIDENCE	Thank you for your comment. We note that not all patients are aware of having been bitten by a tick. This is captured in an earlier part of the context section. We do not feel that an exact figure should be included in the scope as we are unaware of any evidence to support this.

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			I am not aware of any objective, laboratory-based research into the relationship between the duration of tick attachment and the probability of Lyme disease infection in humans, which is the only way to assess this without relying merely on the subjective accounts of patients.	
Lyme Disease Action	7	161	Note that although Public Health England have issued the suggested referral pathway, most GPs are unaware it exists. The wording in this section says the patients are treated, are tested etc, whereas in reality this may or may not happen. Current practice is very variable and erythema migrans have been diagnosed as cellulitis, ringworm and reaction to insect bite.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and describes current standard practice. We acknowledge that not all patients are receiving the same care, a fact which has been highlighted in the following paragraphs. This is an important purpose for this work and we are keen to ensure that this guideline, once developed, improves this situation.
Lyme Disease UK	7	163-164	Anecdotal evidence from patients suggests that many doctors fail to recognise the EM rash. Many people with EM rash appear to be diagnosed with cellulitis, a bite allergy or ringworm instead and therefore the window for early treatment is frequently missed. This study highlights this issue by stating 'this lesion may go unrecognized, or be mistaken for an "insect bite" or an "allergic rash." Mini-erythema migrans are less likely to be	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and aims to describe current standard practice (in this case the PHE guidance) rather than level of uptake

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			diagnosed' (Perronne, 2014). References: 1. Perronne C (2014) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. *Front. Cell. Infect. Microbiol*. 4:74. doi: 10.3389/fcimb.2014.00074 http://journal.frontiersin.org/article/10.3389/fcimb.2014.00074/full	of guidance. We acknowledge the concerns about rash recognition; however the aim of this section is to summarise the PHE guidance and not comment on its implementation. We have added text about lack of recognition of rash to section 3.1
Lyme Research UK	7	165-166	You write "those without a rash, but with symptoms suggestive of Lyme disease and at risk of tick exposure, have blood tests": As discussed in our general comments, test reliability is poor, with low sensitivities for the standard two-tier serological testing. Early use of antibiotics or steroids may also abrogate the immune response and produce false negative test results. Therefore we think that diagnosis should not be reliant on testing but experienced clinicians should be encouraged to make clinical diagnoses where clinical signs are strongly indicative of Lyme borreliosis. The diagnostic pathways should be amended to allow for clinical diagnoses even in the absence of a positive test result.	Thank you for your comment. We acknowledge the concerns about the diagnosis and treatment of Lyme disease. The development of this guideline will see recommendations being made based on the evidence identified through evidence reviews. This will include diagnostic tests for Lyme disease.
Caudwell LymeCo	8	167	SUGGESTED AMENDMENT Delete "People with positive tests are treated" REASON This is not true in many cases.	Thank you for your comment. This sentence has now been changed to address your comment.

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			EVIDENCE In a Caudwell LymeCo patient survey of roughly 500 UK patients, we asked patients how many weeks of antibiotics they had been given on the NHS after their positive Lyme disease blood test, and 52% of them responded 0. Very few of them were given the full duration of antibiotics currently recommended by PHE treatment guidelines.	
Caudwell LymeCo	8	167 - 168	SUGGESTED AMENDMENT "If the test is negative but symptoms persist, repeat samples are sent 3-4 weeks later." REASON In reality, this very rarely happens. EVIDENCE The typical patients' experience with their GP in Britain is that, after one negative or even equivocal test, they are told they do NOT have Lyme disease and their doctor refuses to contemplate a second test.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and aims to describe current standard practice (in this case the PHE guidance) rather than level of uptake of guidance. We acknowledge the concerns about repeat testing; however the aim of this section is to summarise the PHE guidance and not comment on its implementation. The guideline will examine available evidence and make recommendations in this area if there is evidence to support this.

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Lyme Disease UK	8	169	When there is currently no test available to distinguish past infection from ongoing infection or new infection, the evidence and tests that the term 'relapse' is based on, should be reviewed. Additionally, anecdotal evidence exists to suggest that patients who still have a positive test following 'standard' treatment for Lyme disease are told it is likely to be a false positive, even when clinical signs would suggest an ongoing infection.	Thank you for your comment. Testing will be addressed by an evidence review (as outlined in section 1.5). The review question and protocol will be developed by the guideline committee, based on the scope.
Lyme Disease Action	8	169	Suggest rephrase to "… serology may be repeated to shed light on relapse and other causes are considered". Serology may show evidence for relapse but it is unclear how reliable an indicator this is.	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and aims to describe current standard practice (in this case the PHE guidance) rather than level of uptake of guidance. We acknowledge the concerns about repeat serological testing; however the aim of this section is to summarise the PHE guidance and not comment on its implementation.
NHS Highland	8	170	Repeat testing to assess for relapse is recommended by PHE but is controversial as antibody levels persist even when patient cured and therefore ongoing positive test not helpful. May be helpful in looking for re-infection in the re-exposed with new symptoms as	Thank you for your comment. The 'current practice' section is a standard section in NICE guideline scopes and

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			different blot bands may be present. Suggest unhelpful to state that blood test can diagnose relapse.	aims to describe current standard practice (in this case the PHE guidance) rather than critiquing the guidance. We acknowledge the concerns about repeat serological testing; however the aim of this section is to summarise the PHE guidance.
Lyme Disease Action	8	170	Suggest replace the sentence starting "Neurologists or.." with "Consultants are involved in patient care in cases of significant neurological, rheumatological, cardiac or ophthalmic complications".	Thank you for your comment. This sentence has now been amended to address your comment.
Lyme Disease Action	8	175	Lyme borreliosis is an emerging disease in the UK and so an additional factor of "a consequence of the bacteria spreading through wildlife and therefore ticks" should be added. It is important to stress that the incidence of Lyme borreliosis is actually increasing as ticks expand their geographic spread to new areas and higher altitudes. Key ecological drivers are considered to be climate change, changes in land management eg. Fragmentation of forest habitats, resulting changes in biodiversity, changes in the way humans interact with nature eg outdoor pursuits.	Thank you for your comment. The context of the scope is intended to provide a short overview of what is currently known about Lyme disease. This section mentions that the incidence of Lyme disease is increasing for various reasons. Some additional text has been added to this section.
Lyme Research UK	8	179	You write "Experience of typical cases is limited": We suggest you delete this sentence. With a few thousand diagnosed cases per year in	Thank you for your comment. We have deleted the sentence.

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			the UK, around 300,000 per year in the U.S. (Centers for Disease Control, 2016c), and over 200,000 per year in Germany (Mueller et al, 2012), it seems that there must be quite a bit of experience. The term 'typical case' is best avoided, as Lyme borreliosis can present with many different symptoms (making it hard to diagnose). Or do you mean "Many GPs in the UK have limited experience with Lyme disease."?	
Lyme Disease Action	8	180	This is misleading. Suggest rephrase to "In 2012 Lyme Disease Action published the top 10 research priorities reached through a process facilitated by the James Lind Alliance." http://www.lymediseaseaction.org.uk/what-we-aredoing/research/jla-process/	Thank you for your comment. We have amended the text in the scope. We have maintained the James Lind alliance hyperlink to outline the methods used in the process of this Priority Setting Partnership.
Lyme Disease Action	8	181	Add "transmission" and remove "the long term consequences of the diseases" - this latter does not feature in the top 10 research priorities.	Thank you for your comment. Interested parties can follow the URL to see the complete information about the priorities. We have included transmission for accuracy. We have amended the text about long term consequences to say 'long term outcomes' to reflect priorities 6 and 8.

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Lyme Disease Action	DQ1		In principle yes, but it should be made clear that these are arbitrary stages and some people may progress to the manifestations of late-stage disease more quickly.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	DQ1		PLEASE COMMENT ON 1) Is the time period of '< than 6 months since tick bite or first symptoms or signs' an acceptable interpretation for 'early Lyme borreliosis'? COMMENT No, and "early lyme borreliosis" is not an acceptable term either because it is not useful either for diagnosis or for treatment decisions. Please refer to my proposed category definitions in point 8.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
NHS	DQ1&		Relating to guideline committee's Q1 and 2 above.	Thank you for your response and

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Highland	2		Distinction between early and late is only of importance if different management strategies are recommended on the basis of this distinction. Many patients have ongoing exposure and fluctuating symptoms making use of these timelines impractical. The time periods are arbitrary and cannot be definitive due to various factors (eg host factors, infectious dose, strain). Six month timeline is mentioned in literature and may be reasonable but the arbitrary nature of it must be stated.	detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Research UK	DQ1& 2		NICE questions 1 and 2 on definition of early and late Lyme borreliosis: The stages of Lyme borreliosis are defined by the British Infection Association (2011) and the Infectious Diseases Society of America (Wormser et al, 2006) according to the extent of disease, and not by time since tick bite. Patients can vary a lot in how quickly the infection spreads. The British Infection Association (2011) writes that late-stage disease can develop "months or years later". They also write that the stages are "not clear-cut phases and should be regarded as a process". We therefore think it is better not to connect the stage with duration of infection, and better not to give a fixed cut-point of under or over 6 months. In fact, 'early' and 'late' are not useful descriptions of the stages of Lyme borreliosis since they imply durations of infection such as you have given. Better would be to use terms like 'localised Lyme borreliosis',	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			'disseminated Lyme borreliosis', and 'neurological Lyme borreliosis'.	
VIRAS Vector-borne Infection, Research – Analysis - Strategy	DQ1& 2		**VIRAS response to NICE request for comments on 6 month 'phase' (including observations on why this might have been suggested):** "1) Is the time period of '< than 6 months since tick bite or first symptoms or signs' an acceptable interpretation for 'early Lyme borreliosis'? 2) Is the time period of '> 6 months since tick bite or first symptoms or signs' or an acceptable interpretation for 'late Lyme borreliosis'?" Pertains to Draft Scope document Page 3. Lines 74 to 77 **Abbreviations** CFS, Chronic Fatigue Syndrome GDG Guideline Development Group HPA, Health Protection Agency (now part of PHE) IDSA, Infectious Disease Society of America ILADS, International Lyme and Associated Diseases Society LB, Lyme Borreliosis NHS, UK National Health Service PHE, Public Health England M.E., Myalgic Encephalomyelitis NICE, National Institute for Health and Care Excellence	Thank you for your comment on the issue of the classification of early and late Lyme disease as described in the consultation version of the scope. We have invited stakeholders to provide comment on this in a specific question at consultation to ensure that we collected the widest views on this issue. We now propose to present the guideline committee with the stakeholder feedback on this issue to allow them to determine the best approach for the guideline to take. As such, we have removed the detail linked to the definitions of early and late Lyme disease from the final scope. .

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			An arbitrary time limit deemed to be a transformation point from one Lyme borreliosis phase to another has no medical or scientific logic. Miklossy (2012) states in The Open Neurology Journal: "Late Lyme neuroborreliosis is accepted by all existing guidelines in Europe, US and Canada. The terms chronic and late are synonymous and both define tertiary neurosyphilis or tertiary Lyme neuroborreliosis. The use of chronic and late Lyme neuroborreliosis as different entities is inaccurate and can be confusing. Further pathological investigations and the detection of spirochetes in infected tissues and body fluids are strongly needed." In Lyme borreliosis, the time between infection (or re-infection) and the appearance of symptoms/signs which a patient or physician might associate with LB is highly variable and could be months or years. The U.S. Library of Medicine, MedlinePlus (2015) states: "Symptoms of early disseminated Lyme disease (stage 2) may occur weeks to months after the tick bite, and may include …" "Symptoms of late disseminated Lyme disease (stage 3) can occur months or years after the infection. The most common symptoms are muscle and joint pain…" Clearly the stages of LB infection do not conform to a predetermined timescale. Different stages depend upon variables impossible to compute and more rationally deduced by careful evaluation of each individual patient's symptoms and laboratory tests, if indeed a physician considers determination of a 'stage' or 'phase' to be a worthwhile exercise.	

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			What purpose is served by attempting to define the progression of a disease by a fixed time period and how would it help doctors in making their clinical decisions? It seems unlikely that re-labelling patients at 6 months is considered a useful way to suggest the best tests for a patient's infection. According to Public Health England (2014), the weaknesses they acknowledge for their tests relate to cross reactivity with other infections and "antibody tests in the first few weeks of infection may be negative". These problems would not be improved by a 6 month deadline. Once a patient has been diagnosed and treated, further standard NHS two-tier testing is rendered useless because as West (2014) states: "Both IgM and especially IgG antibodies can remain positive for years after successful therapy with antibiotics." So the determination of treatment success or failure by standard testing would not be helped by a 6 month time limit. There are no tests for LB at any stage which can reliably exclude infection or confirm that treatment or time has eradicated an infection. If such a test (or combination of tests) existed, it is certain that PHE, the CDC, the IDSA and others would have used the test in support of their opinion that persistent infection does not occur beyond what they claim is 'adequate' treatment. In contrast, the scientists and doctors of ILADS (2012) who declare that persistent LB infection does occur, provide a list of 700 peer-reviewed scientific papers indicating persistence, in 'Peer Reviewed Evidence of Persistence of Lyme Disease	

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			Spirochete Borrelia burgdorferi and Tick-Borne Diseases'. Furthermore, treatment considerations are guided by disease manifestations and sometimes supported by laboratory test results. E.g., neuroborreliosis is a diagnosis of the spread of LB spirochaetes to the central nervous system (CNS). It is suspected by symptoms, supported by examination and testing of cerebrospinal fluid (CSF) and treated by intravenous antibiotics. Neuroborreliosis can occur at any time in infected individuals because it relates to the spread of the infection. If the bacteria's 6 month 'VISA' runs out, that would not prevent it crossing the barrier into the CNS. Therefore determining the choice of tests or treatment cannot be the motive for trying to determine the phase of a patient's infection according to a calendar. A 6 month phase could not apply to an infant born infected or an infant with an immature immune system that becomes infected. How would 6 months apply to a child which is quite simply, a much smaller mammal than an adult human? Would the transformation from 'early' to 'late' infection happen at the same time in a person initially infected with a few spirochaetes compared to someone infected via multiple heavily infected tick bites which also transmitted ehrlichia and bartonella? In some regions, 10% to 20% of healthy blood donors are seropositive for Lyme antibodies. If they become ill in the future, will that be 'early' or 'late' Lyme? (Mygland, Skarpaas and Ljøstad, 2006; Hjetland et al 2014) Dr Willy Burgdorfer, who discovered the borrelia burgdorferi spirochaete in 1982, stated	

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			(Under Our Skin, 2007): "I am a believer in persistent infections because people suffering with Lyme disease, ten or fifteen or twenty years later, get sick [again]. Because it appears that this organism has the ability to be sequestered in tissues and [it] is possible that it could reappear, bringing back the clinical manifestations it caused in the first place." When asked about the similarities between *Borrelia burgdorferi* and syphilis, Dr. Burgdorfer stated: "The similarities that I know of are associated with the infection of the brain, the nervous system. The syphilis spirochete, Treponema pallidum has an affinity for nerve tissues. The Borrelia burgdorferi spirochete very likely has that too. Children are especially sensitive to Borrelia burgdorferi. The Lyme disease spirochete is far more virulent than syphilis." (Under Our Skin, 2007). Since early and late stages for Lyme borreliosis reflect similarities with syphilis, they must recognise that stages are determined by the spread and manifestation of the infection and not by a calendar. NHS Choices, (2014) remarks on Syphilis: Primary syphilis: "The initial symptoms of syphilis can appear any time from 10 days to three months after you have been exposed to the infection." Secondary syphilis: "The symptoms of secondary syphilis will begin a few weeks after the disappearance of the sore." Latent phase: "The latent stage can continue for many years (even decades) after you first become infected." Tertiary syphilis: "The symptoms of tertiary syphilis can begin years or even decades after	

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			initial infection." Specifying a 6 month or other arbitrary time-point between phases is so illogical, that one could be excused for questioning the motives behind even contemplating such a notion. Perhaps it is a coincidence that the CDC/Fukuda (1994) criteria for a diagnosis of Chronic Fatigue Syndrome requires 6 months of symptoms with fatigue criteria (which is common in LB). There is evidence which suggests that Public Health England intend that chronic LB patients should be re-diagnosed as having CFS or some other contrived 'syndrome', e.g., 'chronic arthropod neuropathy syndrome'. The HPA (now part of PHE) informed the Health and Safety Executive (2012) of their plans: "RIPL and HPA staff will discuss with Simon Wesseley's [sic] group and other interested parties the development of guidance for clinicians on dealing with the disaffected group with un-provable Lyme disease. This will cover the therapeutic approach, investigation of cases and disengagement strategies when further investigation is counter-productive." In view of their plans for 'development of guidance for clinicians', one may speculate that PHE will attempt to steer the NICE GDG process to meet their predetermined agenda. That agenda appears to include a 6 month period after which they deem it acceptable for doctors to 'disengage' from patients if the patient cannot 'prove' that they Lyme borreliosis. This agenda could deprive patients of medical care and deny them treatment and could be attractive to some who are more concerned about financial costs than patient welfare.	

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			The strategy might also be favourable to medical re-insurance companies who have saved a lot of money thanks to a few psychiatrists who compounded the neurological disease, Myalgic Encephalomyelitis with 'CFS' and then classified CFS as a Functional Somatic Disorder. This has meant that policy claims can be limited to 2 years for a notoriously chronic and severely debilitating neurological disease. Are people with chronic Lyme borreliosis destined for the same? 'Professor Sir Simon Wessely's group' are psychiatrists, and it seems that PHE would like them to take control of the fate of patients who do not recover in an allotted time. They have some history with NICE, as observed by Professor Malcolm Hooper (2007) in his written evidence to the Parliamentary Select Committee on Health regarding the NICE GDG for 'CFS/ME': "14. The advisors upon whom NICE relies have been shown to have undeclared vested interests: These psychiatrists and their adherents are heavily involved with the medical insurance industry, including UNUM Provident, Swiss Life, Canada Life, Norwich Union, Allied Dunbar, Sun Alliance, Skandia, Zurich Life and Permanent Insurance, as well as the re-insurers Swiss Re..." Dr Darrel Ho-Yen (1990), who became the head of the Lyme Reference Laboratory at Inverness, commented on the Wessely group's ideas in the Journal of the Royal College of General Practitioners: "…it has been suggested that a new approach to the treatment of	

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			patients with postviral fatigue syndrome would be the adoption of a cognitive behavioural model (Wessely S, David A, Butler S, Chalder T: Management of chronic (postviral) fatigue syndrome. JRCGP 1989:39:26-29). Those who are chronically ill have recognised the folly of the approach and, far from being maladaptive, their behaviour shows that they have insight into their illness". VIRAS rejects the concept of a 6 month period for the transformation of a patient's LB infection from one stage to another as inaccurate, negligent and unethical. We are curious to know where this idea originated and what scientific justification was provided for this notion of an infectious disease progressing according to a calendar. **References** CDC/Fukuda. 1994. *Guidelines for the Evaluation and Study of CFS*. Centres for Disease Control and Prevention. http://www.cdc.gov/cfs/case-definition/1994.html Health and Safety Executive (2012). *Lyme disease and services in the HPA*. Advisory Committee on Dangerous Pathogens (ACDP) - ACDP/99/P62. http://www.hse.gov.uk/aboutus/meetings/committees/acdp/161012/acdp_99_p62.pdf Hjetland R1, Nilsen RM, Grude N, Ulvestad E. 2014. *Seroprevalence of antibodies to Borrelia burgdorferi sensu lato in healthy adults from western Norway: risk factors and methodological aspects*. APMIS. 2014 Nov;122(11):1114-24. doi: 10.1111/apm.12267. http://www.ncbi.nlm.nih.gov/pubmed/24730472	

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			Hooper, Malcolm. 2007. *Evidence submitted by Professor Malcolm Hooper (NICE 07).* Select Committee on Health. http://www.publications.parliament.uk/pa/cm200607/cmselect/cmhealth/503/503we79.htm ILADS (International Lyme and Associated Diseases Society). 2012. Peer Reviewed Evidence of Persistence of Lyme Disease Spirochete Borrelia burgdorferi and Tick-Borne Diseases. http://www.ilads.org/ilads_news/wp-content/uploads/2015/09/EvidenceofPersistence-V2.pdf Miklossy J. 2012. *Chronic or late lyme neuroborreliosis: analysis of evidence compared to chronic or late neurosyphilis*. *The Open Neurology Journal*. 2012;6:146–157. doi: 10.2174/1874205X01206010146. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3551238/ Mygland A, Skarpaas T, Ljøstad U. (2006). *Chronic polyneuropathy and Lyme disease*. Eur J Neurol. 2006 Nov;13(11):1213-5. http://www.ncbi.nlm.nih.gov/pubmed/17038034 NHS Choices. 2014. *Syphilis*. http://www.nhs.uk/Conditions/Syphilis/Pages/Symptomspg.aspx Public Health England. 2015. Lyme disease: diagnosis and treatment. https://www.gov.uk/government/publications/lyme-disease-diagnosis-and-treatment/lyme-disease-diagnosis-and-treatment	

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			Under Our Skin. 2007. *LYME DISCOVERER WILLY BURGDORFER BREAKS SILENCE ON HEATED CONTROVERSY 2007*. Online: http://underourskin.com/news/lyme-discoverer-willy-burgdorfer-breaks-silence-heated-controversy U.S. Library of Medicine, MedlinePlus. 2015. *Lyme Disease*. https://www.nlm.nih.gov/medlineplus/ency/article/001319.htm West, Stirling. 2014. *Rheumatology Secrets*. Elsevier Health Sciences. Mosbey. 3rd edition. ISBN-13: 978-0323037006.	
Lyme Disease Action	DQ2		In principle, yes, but see comment above.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell	DQ2		PLEASE COMMENT ON	Thank you for your response and

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LymeCo			2) Is the time period of '> 6 months since tick bite or first symptoms or signs' or an acceptable interpretation for 'late Lyme borreliosis'? COMMENT No, and "late Lyme borreliosis" is not an acceptable term either because it is not useful either for diagnosis or for treatment decisions. Please refer to my proposed category definitions in point 8.	detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
NHS Highland	DQ3		Relating to guideline committee's Q 3 above. (Use of BIA position paper to determine range of presentations). I would also like NICE to consider patients with ongoing tick exposure and : 1) Flu like illness as mentioned in comment no.1. 2) Fatigue and arthralgia 3) Peripheral neuropathy or mononeuritis multiplex 4) Objective memory loss but without tetraspastic syndrome, spastic-ataxic gait disorder and disturbed micturition I think these presentations should be included in the guidance as many people with these symptoms present for testing, and a proportion are seropositive. The committee may conclude that these presentations should not lead to testing, and if inadvertently tested, should not be treated for possible Lyme disease, even if seropositive. Guidance on this would be very useful.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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Lyme Research UK	DQ3		NICE question 3 on range of clinical presentations: We think it is very important to point out that there is a large variety in the patterns of clinical presentation at each stage of the disease, making diagnosis difficult. Lyme borreliosis should be suspected in any patient that presents with a spectrum of the symptoms listed below. Studies of symptoms reported by patients with confirmed Lyme borreliosis include the following, and the patient will usually describe a number of these or many in a relapsing/remitting pattern. Symptoms in order of frequency of occurrence compiled from Aucott et al (2012), Djukic et al (2011), Strle et al (2006) and Trevejo et al (1999): • Arthritis/arthralgia (especially back, neck, knee, ankle) • Fatigue/malaise (frequently with headache) • Neurological symptoms (peripheral neuropathy, numbness, pins and needles, neuropsychiatric symptoms) • Erythema migrans rash • Cognitive dysfunction (short term memory problems, confusion, speech problems) • Myalgia	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			• Chills • Meningeal symptoms • Radicular pain • Sweats • Tick bite • Facial palsy (more frequent in children) • Vision problems (floater, blurred/double vision) • Cardiac problems (chest pain, heart block) • Hearing problems (tinnitus, hearing loss) • Other (dizziness, vertigo, sleep disturbance, photophobia) Neuro-psychological symptoms are also part of the spectrum.	
Lyme Disease Action	DQ3		No; this is simply a "position paper" and not an appropriate resource for this use. The clinical manifestation section and Table 1 contain misleading information - eg in that erythema migrans centres on the bite; that incidence of erythema migrans is 90% (based on a selected group of highly aware practitioner and public in Germany; a low incidence (5-	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline

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			8%) of Lyme neuroborreliosis is quoted which is not supported by other European literature (25%). They also lack detail, for example focusing on the erythemamigrans at the apparent expense of more serious aspects of Lyme borreliosis and there is only one small paragraph to cover the whole range of late stage disseminated disease. A more appropriate resource would be Stanek et al 2011 which includes Opthalmic manifestations omitted from Table 1 of the British Infection Association statement. Stanek et al 2011 Clinical case definitions for diagnosis and management in Europe Clin Microbiol and Infect. EFNS guidelines could be used for Lyme neuroborreliosis - Mygland et al 2010 EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis. Eur J Neurol.	Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	DQ3		PLEASE COMMENT ON 3) The use of the British Infection Association1 position paper classification to determine the range of clinical presentations that will be considered. COMMENT This list of symptoms and clinical manifestations is woefully inadequate. it neglects to mention some of the commonest symptoms and focuses instead on those which, as it states, affect around 1% of patients. A proper list of clinical manifestations and symptomatology (with prevalences of each symptom in the UK) needs to be developed by the committee on the basis of evidence gathered among UK patients. Recycled evidence from America that does not apply to UK patients will not be particularly	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			useful.	
NHS Highland	DQ4		Relating to guideline committee's Q 4 above. *Borrelia spielmanii, Borrelia bavariensis, Borrelia bissettii, Borrelia lusitaniae, Borrelia kutchenbachii* and *Borrelia valaisiana* also have pathogenic potential (see Borchers A, journal autoimmunity for useful table). Review of evidence to assess relevance to diagnostics of some of these may be worthwhile.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
NHS Highland	DQ4		Relating to guideline committee's Q4 above. Diagnostic test should include tests and testing strategies. All tests should be included: EIA, IF, Immunoblot, western blot, CSF/serum parallel testing by EIA/Blotting, lymphocyte transformation test, PCR and culture (joint fluids, skin biopsy, CSF, urine), direct microscopy and non-specific tests such as CXCL13, CD57+, CSF biochemistry and cytology. The committee may find many of these tests lack standardisation, sensitivity and specificity but it is still useful to have them assessed.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions

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				outlined in the guideline scope.
Lyme Research UK	DQ4		NICE question 4 on inclusion of strains of Borrelia: B. valaisiana has been detected in the UK, in addition to the Borrelia species that you list. Couper et al (2010) reported that 32% of infected ticks in south-west England had B. valaisiana, similar to the 35% in the New Forest reported by Kurtenbach et al (2001), while 58% of infected ticks had B. valaisiana in a study in northern England, north Wales and the Scottish Border region (Bettridge et al, 2013). B. valaisiana is considered pathogenic for humans (Venclíková et al, 2014), and it has been isolated in patients diagnosed with Lyme borreliosis (Pancewicz et al, 2015). We think B. valaisiana should therefore be included in your list. However, since infected ticks can be transported by birds, actually any species seen in the rest of Europe could be in ticks here too. Furthermore, people travel extensively and more than 10 million people per year vacation abroad, many of them camping and hiking. A relevant proportion of Lyme borreliosis infections seen England were caught abroad. This means that any species could be the cause in a case of Lyme borreliosis seen in the England. We think therefore you should not restrict your definition of Lyme borreliosis to three species. Species that are considered pathogenic include: B. afzelii, B. bissettii, B. garinii, B. burgdorferi s.s., B. valaisiana, B. lusitaniae, and B. spielmanii. (Venclíková et al, 2014; Stanek G et al, 2011). Plus there are 14 other similar Borrelia species and more than 20	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			Borrelia species associated with the relapsing fever group including B. miyamotoi which results in symptoms which match those of Lyme borreliosis (Wang G et al, 2014). Furthermore, although it is generally not known with which species a patient is infected, physicians need to know that patterns of presenting symptoms vary for the different species, i.e. there is no standard set of symptoms, and that the sensitivity of the laboratory tests differs for the different species, which is an area we think NICE should investigate further.	
Lyme Disease Action	DQ4		Note that these are not strains, they are genospecies. In the review other known, though possibly rare, human pathogenic genospecies B spielmanii and B bavariensis should be included. Antigens from these are included in the immunoblot used in Scotland. See also comment on Q5 re immunoblot antigens. The review should also include Borrelia miyamotoi. Although this is more nearly related to the relapsing fever group of Borrelia, it is present in UK ticks and causes a similar clinical presentation.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Caudwell LymeCo	DQ4		PLEASE COMMENT ON 4) The inclusion of the following strains of Lyme Borreliosis for consideration as part of our review of the evidence:	Thank you for your response and detailed comments on our questions. We will bring the detail of your

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			•B. burgdorferi (and the subtype B. burgdorferi sensu stricto), •B. garinii, •B. afzelii COMMENT It would obviously be ideal to test for all known strains of Borrelia Burgdorferi sensu lato which can cause Lyme disease. However, given that this may be impractical within the limitations of current western blot testing, I would propose that the Borrelia Valaisiana be included as a bare minimum since it may be the Borrelia strain involved in around 7% of Lyme disease cases in Europe. EVIDENCE For example, Habálek, Z.; Halouzka, J. (1997-12-01). "Distribution of Borrelia Burgdorferi sensu lato genomic groups in Europe, a review". European Journal of Epidemiology	response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Research UK	DQ5		NICE question 5 on appropriate diagnostic tests for consideration: There are problems with current testing. All tests used in the UK depend on detecting antibodies. All tests can generate false negatives for the following reasons: a) Poor laboratory practice and quality control. UK Lyme testing laboratories are not accredited to ISO 15189. All laboratories should (as soon as possible) be accredited to the ISO standard to meet acceptable laboratory quality management practice. b) Intrinsic insensitivity of the tests. Data from 43 independent studies selecting for	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of

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			commercial test kits and reporting specificity greater than 90% gives a sensitivity of 64.5% with samples that were confirmed positive using a prior serology test or culture positive (full set of references available from Lyme Research UK). Data from 78 studies shows test sensitivities as low as 15% and analysis of all studies with specificity 90% or greater the mean sensitivity is 70.9% (Leeflang et al, 2016). Since most evaluation of test kits use serum panels or samples with well characterised disease state, the results do not reflect the sensitivity when used for clinically derived samples. c) The human antibody response is slow to develop making tests highly unreliable in the early stages of disease, and the response can be affected by prior use of antibiotics, immune system suppression due to use of steroids, a compromised immune system, and the normal variation of the immune system due to age, stress, diet and pregnancy, as well as effects of the Borrelia spirochaete (Elsner et al, 2015; Strle et al, 1996; Preac-Mursic et al, 1989; Tylewska-Wierzbanovska et al, 2002; Durovska et al, 2010). d) Western Blot tests used in England are based on native antigens from 2 species plus recombinant VlsE (ViraMed Laboratory Diagnostics, 2016). It requires cross reactivity with antigens from other species for them to be detected with unknown and reduced sensitivity. e) The use of a screening test followed by a confirmatory test (2-tier test) was chosen as a method to reduce false positive tests at the Second National Conference on Serologic Diagnosis of Lyme Disease 27-29 Oct 1994. It was based on poor specificity of the early ELISA tests with resulting false positives. ELISA test manufacturers now ensure that the	the evidence for the questions outlined in the guideline scope.

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			test specificity is close to 99%. Western blot tests also have a specificity close to 99%. Combining the test in the 2-tier sequential process reduces overall sensitivity and increases false negatives. Alternative tests to aid diagnosis: • SeraSpot • Elispot • Lymphocyte Transformation Test • Any laboratory that is fully approved and validated by international laboratory certification protocols. • Culture is widely accepted for other pathogens but requires skilled microscopists. Probably not for use in mainstream laboratories but should not be excluded. • Molecular detection methods including: Polymerisation Chain Reaction • PCR and variants o PCR/Electrospray Ionisation-Mass spectrometry.	

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			○ Fluorescence in situ DNA Hybridization. ○ Other fluorescence systems. • Other molecular detection systems. There should be funding for study of new testing technologies and evaluation, with rapid implementation of superior methods. • An example is microscopy using digital filters and pattern recognition as developed by XRAPID for detection of malaria. • Next Generation Sequencing	
VIRAS Vector-borne Infection, Research – Analysis - Strategy	DQ5		**Diagnostic Testing for Lyme Disease** Diagnosis of Lyme borreliosis infections by indirect methods, i.e. looking for certain antibodies in patients' blood, has been proved to be unreliable by many studies published over the past 3 decades. The criteria necessary for providing accurate clinical decision-making and for the safe stewardship of maintaining Public Health have not been met. A recently published meta-analysis by Leeflang et al., (1), reviews all testing methods to date and shows that this problem is evident: "We found no evidence that ELISAs have a higher or lower accuracy than immunoblots;	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions

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			neither did we find evidence that two-tiered approaches have a better performance than single tests. "However, the data in this review do not provide sufficient evidence to make inferences about the value of the tests for clinical practice. Valid estimates of sensitivity and specificity for the tests as used in practice require well-designed cross-sectional studies, done in the relevant clinical patient populations. "Furthermore, information is needed about the prevalence of Lyme borreliosis among those tested for it and the clinical consequences of a negative or positive test result. The latter depend on the place of the test in the clinical pathway and the clinical decisions that are driven by the test results or not. Future research should primarily focus on more targeted clinical validations of these tests and research into appropriate use of these tests." It should be realised that all of the validity data sets for test kits, as published by their manufacturers, have been determined in patients with known or highly probable borreliosis infection, as seen from their symptoms, such as EM rash, or frank symptoms such as facial palsy or Bannwarth's syndrome. Rarely have any antibody tests been matched against true microbiological evidence, which would have had to have been done by checking each patient with a culture test. The test kits have not been validated in patients who have less obvious presentations of Lyme borreliosis. The only true validation would be to test each patient with manufacturer's kits and then to assess each patient by means of culture and/or DNA detection of the	outlined in the guideline scope.

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			bacteria. It is of the utmost clinical importance that the true state of the infection in each patient should be accurately assessed, This should be done in microbiological terms by looking for evidence of the bacteria themselves, instead of looking for the immune response. There are many reasons why the immune response is variable and often suppressed in patients with Lyme borreliosis. (2) Microscopic visualization of live Borrelia spirochetes offers the strongest of all proofs that an infection is present. Borrelia burgdorferi can be visualized directly in infected vectors, reservoir hosts, laboratory animals and clinical specimens from patients with Lyme borreliosis using dark-field or phase-contrast microscopy. The spirochetes may also be microscopically visualized after Giemsa, Gram, immunological or silver staining of specimens The BIA have dismissed microscopy and culture investigations of patients. They cite the long time period necessary for the borrelia spirochetes to grow, and the cost of technical manpower. However, if we are on the brink of a public health hazard, liable to affect future generations - because of the high probability of congenital transfer of the infection, and possible contamination of the nation's blood supply - then the cost has to be met. In fact, costs will not be as high as expected, since advanced culture methods have recently been patented which enable identification of borrelia species in patient sera within 1 week, in many cases:	

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			This advanced culture method has been in operation as a successful commercial enterprise in Pennsylvania, at Advanced Laboratory Services, for the last 3 years, and has been published in the peer-reviewed literature (3, 4) and patented (5). The method is endorsed by Philip M. Tierno, Jr., PhD Frm Director of Clinical Microbiology and Immunology, New York University School of Medicine Dr Tierno refutes accusations by some CDC scientists that there might have been contamination during the method. (6). Criticism of the method by UK scientists has been quashed with research by Dr Sheila Woods and her team at Advanced labs. PHE have claimed that the spirochaetes seen in the microscope were artefacts, or pieces of collagen or fibrin. Sheila Wood used a special Rhodium-based stain which has the property of only attaching to collagen and fibrin, and it was conclusively shown that, in the very small percentage of cases where the obvious shape of Borrelia spirochaetes was not so distinct (about 2% of samples), the Rhodium stain did not attach to what were suspected to be Borrelia spirochaetes. The Rhodium stain did attach to bits of the background extra-cellular matrix, as it is designed to do, but absolutely did not stain the Borrelia. (7). The Abstract states : "In order to distinctly differentiate the organisms from the collagen of this matrix that could be observed as background in the staining process, we developed an immunostaining procedure using polyclonal and monoclonal antibodies in combination with rhodamine fibronectin. The culture samples from both control organisms and patient	

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			samples were tested using the new immunostaining protocol. Results showed clear delineation of organisms compared to the collagen pieces gathered in the harvesting process. This new immunostaining process, used with in vitro cultivation, provides for precise identification of cultured organisms." Given that the true prevalence of borreliosis in the UK has not been fully monitored, and that it will be bound to increase in the British Isles, as it has been seen to do so across the Northern hemisphere , we can expect tens of thousands of cases each year (8,9). The Health and Safety of the UK over the next 10 to 15 years will depend on how the NICE committee decides to tackle the problem of not just Lyme disease, but also other arthropod-borne infections. It is imperative that our health service chooses the best diagnostic techniques . References 1)The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis Leeflang et al. BMC Infectious Diseases (2016) 16:140. DOI 10.1186/s12879-016-1468-4 2) http://www.ilads.org/ly…/primary-care-physician-brochure.pdf 3) Improved Culture Conditions for the Growth and Detection of Borrelia from Human	

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Stakeholder	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			Serum. Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Int J M.5698. ed Sci 2013; 10(4):362-376. doi:10.7150/ijms 4)Assessment of New Culture Method to Detect Borrelia species in Serum of Lyme Disease Patients". B. Johnson, Mark A. Pilgard, and Theresa M. Russell J. Clin. Microbiol. doi:10.1128/JCM.01674-13 5) http://advanced-lab.com/news/borrelia_culture_patent.pdf 6). http://www.advanced-lab.com/news/comment-lyme-tierno.pdf 7) Differentiation of Borrelia Microbes from Collagen Debris and Collagen Fibrils in Blood Cultures. J. Microbiology & Experimentation Volume 2 Issue 1. January 02, 2015 Sheila Wood, Akshita Datar, Namrata Pabbat, Divya Burugu and Amy Rattelle J. Microbiology & Experimentation Volume 2 Issue 1. January 02, 2015 S http://medcraveonline.com/JMEN/JMEN-02-00033.pdf 8) http://www.nhs.uk/…/Concern-about-rise-in-UK-Lyme-disease-c… and http://www.bristol.ac.uk/n…/2015/april/big-tick-project.html 9) An estimate of Lyme borreliosis incidence in Western Europe Robert A. Sykes, Phoebe Makiello Journal of Public Health | pp. 1 –8 | doi:10.1093/pubmed/fdw017	

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Lyme Disease Action	DQ5		The appropriate diagnostic tests for consideration: Serology, Polymerase Chain Reaction (PCR), cerebrospinal fluid studies (microscopy for cells, with assay of protein level, IgM and IgG Borrelia immunoblot, Antibody index, CXCL13, PCR), tissue biopsy (standard pathology plus PCR), magnetic resonance imaging (MRI) brain and spinal cord (possibly enhanced), single-photon emission computed tomography (SPECT) scan, cognitive neuropsychology, autonomic function tests, nerve conduction studies (which are usually normal), sural nerve biopsy (small fibre damage). Also cardiac MRI, electrocardiogram (ECG) and 24 hour ECG (Lyme carditis).Specific consideration should be given to which immunoblots are suitable for detecting infections due to the Borrelia genospecies present in UK ticks and also whether reference laboratories should use a different immunoblot if infection is likely to have occurred outside the UK. Consideration should be given to tests that are not currently used in the UK, but which are under investigation for their potential. This includes culture, tests of T cell response to infection with Lyme Borreliosis, urine antigen assays and metabolomics.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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Caudwell LymeCo	DQ5		PLEASE COMMENT ON 5) The appropriate diagnostic tests for consideration COMMENT At the original scoping meeting, a long list of diagnostic tests was presented. There is no logical reason or evidence at this stage that could justify excluding any of those tests from being investigated and evaluated in terms of their sensitivity and specificity. Whether or not they are chosen for use by the NHS, there may be patients who pay for those tests privately. Duly evaluated, objective data on their sensitivity and specificity should be provided to these patients' doctors in a transparent manner.	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.
Lyme Research UK	general	general	Misdiagnosis of Lyme borreliosis: In a WHO report (Lindgren et al, 2006), the authors noted that many Lyme borreliosis infections go undiagnosed. We are concerned that many undiagnosed Lyme borreliosis patients are actually misdiagnosed and so then are never tested for Lyme borreliosis. Patients with Lyme borreliosis in the later stages frequently have profound fatigue as well as notable cognitive problems. Many may thus be misdiagnosed as having chronic fatigue syndrome or Alzheimer's disease. See for example the publication by Maheshwari et al (2015) showing a 10-fold increased diagnosis of Alzheimer's disease when there is detectable evidence of spirochaetal infection. We would like to see it addressed how patients, before receiving a diagnosis of chronic fatigue syndrome or Alzheimer's disease,	Thank you for your comment. This guideline will cover in whom Lyme disease should be suspected and the assessment and diagnosis of Lyme disease. The Guideline Committee will carefully consider which assessment and diagnostic strategies can be included in the evidence reviews and will make recommendations based on the identified evidence.

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			might be evaluated and tested for Lyme borreliosis, keeping in mind the relatively high rate of false negatives from the laboratory tests. Many Lyme borreliosis patients believe that the Multiple Systemic Infectious Disease Syndrome (MSIDS) differential diagnosis scoring system published by Horowitz (2016) would help clinicians diagnose Lyme borreliosis and co-infections.	We would like to draw your attention to a NICE guideline on symptoms with unknown causes that has not yet been commissioned, which may cover differential diagnostic processes for conditions with unknown causes.
Lyme Research UK	general	general	Coinfections as far as they impact on Lyme borreliosis: Ticks can carry other infections and patients are frequently infected by other organisms at the same time as Lyme borreliosis. We think that there should be some mention of coinfections in the guideline. In addition to Borrelia, ticks can carry over 100 other human pathogens. The proportion of infected ticks co-infected by other pathogens is very high. A recent study in France indicated 45% of infected ticks were co-infected with up to 5 pathogens (Moutailler et al, 2016). This has many implications including increased difficulty in diagnosis and complications related to treatment. Whilst the guidelines relate to Lyme borreliosis they should mention the confounding implications of co-infection.	Thank you for your comment. While people with co-infections will not be excluded from the evidence reviews, the focus of this guideline is the diagnosis and management of Lyme disease and the specific management of any co-infection will not be addressed. However, the guideline committee will give mention to any groups who require special consideration when linking evidence to recommendations.
Lyme Research UK	general	general	Special patient groups: We think that the NICE guideline should include a section on special patient groups, including people who are immunocompromised, those who are more at risk of	Thank you for your comment. As outlined in the equality impact assessment for this guideline, the

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			complications (e.g. the elderly and people with comorbid conditions), and pregnant women.	guideline committee will review the evidence about diagnostic test accuracy and management strategies in pregnant women and immunocompromised people. It is anticipated that these populations will form sub-groups in each of our evidence reviews to ensure that, where evidence exists on these issues, the committee are able to make evidence-based recommendations to the NHS. These subgroups have been included in the equality impact assessment for this guideline.
Lyme Research UK	general	general	Intravenous antibiotic treatment: We are very concerned that there are Lyme borreliosis patients who need but are not getting intravenous ceftriaxone or cefotaxime once the disease has progressed to later stages. They may not be getting this treatment because a diagnosis of their neuroborreliosis has not been made. Before treating Lyme borreliosis patients with intravenous antibiotics, a positive diagnosis	Thank you for your comment. The Guideline Committee will carefully consider the evidence when making recommendations on management strategies including the role of intravenous antibiotics.

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			of neuroborreliosis is necessary. The British Infection Association Position Statement (2011) says that serology testing for Lyme neuroborreliosis should include intrathecal specific antibodies and specific cerebrospinal fluid/serum antibody index. The guidelines from the European Federation of Neurological Societies guidelines (Mygland et al, 2010) state that antibody tests for cerebrospinal fluid "are useful" in the diagnosis of Lyme neuroborreliosis, but they do not state that a positive result is essential. Unfortunately, the sensitivity of the current tests of cerebrospinal fluid is relatively low. Djukic et al (2012) reported that, of 118 patients with acute neuroborreliosis, intrathecal immunoglobulin synthesis was found in the Reiber nomograms for IgM in 70.2% and for IgG in 19.5% of patients. Isoelectric focussing detected an intrathecal IgG synthesis in 70.3%. Elevation of the Borrelia burgdorferi antibody index in the cerebrospinal fluid was found in 82.2%. The sensitivity was particularly low in patients with a meningitis course (44.4% to 61.1%). Therefore many patients with Lyme neuroborreliosis who need intravenous antibiotics may not receive a positive diagnosis because the laboratory test is inadequate. We think that, until better diagnostic tools are available, the criteria for intravenous treatment should be relaxed and not require evidence of antibodies in the cerebrospinal fluid.	
Lyme Research UK	general	general	Guideline scope: We would like to see NICE address uncertainty in existing knowledge (where relevant),	Thank you for your comment. The Guideline Committee will make research recommendations (if

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			and recommend what kind of research is needed to improve patient outcomes (Parliamentary Office of Science and Technology, 2004).	appropriate) at a later stage of the guideline development once the evidence reviews have been conducted and important gaps have been identified.
Lyme Research UK	general	general	Lyme borreliosis: We think the term 'Lyme borreliosis' should be used rather than 'Lyme disease' to be consistent with the rest of Europe.	Thank you for your comment. We have decided to use the term Lyme disease as it is a widely accepted term which we feel is more accessible to non-healthcare professionals than Lyme borreliosis. In addition it directly reflects the commission received from NHS England.
Lyme Research UK	general	general	REFERENCES CITED ABOVE: Aucott JN, Seifter A, Rebman AW (2012). Probable late lyme disease: a variant manifestation of untreated Borrelia burgdorferi infection. BMC Infect Dis 2012;12(1):173 Bettridge J, Renard M, Brown KJ, et al (2013). Distribution of Borrelia burgdorferi sensu lato in Ixodes ricinus populations across central Britain. Vector Borne and Zoonotic Diseases13(3):139–146 Bouquet J, Soloski MJ, Swei A et al (2016). Longitudinal transcriptome analysis reveals a	Thank you for your comment and the helpful list of references provided.

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			sustained differential gene expression signature in patients treated for acute Lyme disease. mBio 7(1): e00100-16 British Infection Association (2011). The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. Journal of Infection 62:329-338 Cairns V, Godwin J (2005). Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. Int J Epidemiol 34:1340-1345 Centers for Disease Control and Prevention in the United States (2016a). Transmission. http://www.cdc.gov/lyme/transmission/index.html Centers for Disease Control and Prevention in the United States (2016b). Post-treatment Lyme disease syndrome. http://www.cdc.gov/lyme/postlds/ Centers for Disease Control and Prevention in the United States (2016c). How many people get Lyme disease? http://www.cdc.gov/lyme/stats/humancases.html Chandra A, Wormser GP, Klempner MS, et al (2010). Anti-neural antibody reactivity in patients with a history of Lyme borreliosis and persistent symptoms. Brain, Behavior and	

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			Immunity 24(6):1018-1024 Cook MJ (2015) Lyme borreliosis: a review of data on transmission time after tick attachment. Int J Gen Med 2015:8 1–8 Couper D, Margos G, Kurtenbach K, et al (2010). Prevalence of Borrelia infection in ticks from wildlife in south-west England. The Veterinary Record 167:1012-4 Djukic M, Schmidt-Samoa C, Lange P et al (2012). Cerebrospinal fluid findings in adults with acute Lyme neuroborreliosis. J Neurol 259(4):630-636 Djukic M, Schmidt-Samoa C, Nau R et al (2011). The diagnostic spectrum in patients with suspected chronic Lyme neuroborreliosis--the experience from one year of a university hospital's Lyme neuroborreliosis outpatients clinic. Eur J Neurol 18(4):547-55 Durovska J, Bazovska S, Ondrisova M et al (2010). Our experience with examination of antibodies against antigens of Borrelia burgdorferi in patients with suspected Lyme disease. Bratisl Lek Listy111(3):153-5 Elsner RA, Hastey CJ, Olsen KJ et al (2015). Suppression of long-lived humoral immunity following Borrelia burgdorferi infection. PLOS Pathog 11(7):e1004976	

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			Fallon BA, Keilp J, Prohovnik I et al (2003). Regional blood flow and cognitive deficits in chronic Lyme disease. J Neuropsychiatry Clin Neurosci 15(3):326-32 Faulde MK, Rutenfranz M, Hepke J et al (2014). Human tick infestation pattern, tick-bite rate, and associated Borrelia burgdorferi s.l. infection risk during occupational tick exposure at the Seedorf military training area, northwestern Germany. Ticks Tick Borne Dis 5(5):594-9 Horowitz R (2016). Horowitz Lyme-MSIDS Questionnaire. http://lymeontario.com/wp-content/uploads/2015/03/Horowitz-Questionnaire.pdf Kurtenbach K, De Michelis S, Sewell HS, et al (2001). Distinct combinations of Borrelia burgdorferi sensu lato genospecies found in individual questing ticks from Europe. Applied and Environmental Microbiology 67(10):4926-4929 Lakos A, Solymosi N (2010). Maternal Lyme borreliosis and pregnancy outcome. Int J Infect Dis 14(6): e494 – e498 Leeflang MMG, Ang CW, Berghout J et al (2016). The diagnostic accuracy of serological tests for Lyme borreliosis in Europe: a systematic review and meta-analysis. BMC Infect Dis 16:140	

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			Lindgren E, Jaenson TGT (2006). WHO Report. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. http://www.euro.who.int/__data/assets/pdf_file/0006/96819/E89522.pdf MacDonald AB, Benach JL, Burgdorfer W. (1987). Stillbirth following maternal Lyme disease, N Y State J Med 87(11):615-6 Maheshwari P, Eslick GD (2015). Bacterial infection and Alzheimer's disease: a meta-analysis. J Alzheimers Dis 43(3):957-66 Middelveen MJ, Burke J, Sapi E et al (2015). Culture and identification of Borrelia spirochetes in human vaginal and seminal secretions [version 3; referees: 1 approved, 2 not approved]. F1000Research 2015, 3:309 Moutailler S, Valiente Moro C, Vaumourin E et al (2016). Co-infection of ticks: the rule rather than the exception. PLoS Negl Trop Dis10(3):e0004539 Mueller I, Freitag MH, Poggensee G, et al (2012). Evaluating Frequency, Diagnostic Quality, and Cost of Lyme Borreliosis Testing in Germany: A Retrospective Model Analysis. Clinical and Developmental Immunology 2012, Article ID 595427, Epub. Mygland A, Ljostad U, Fingerle V, et al (2010). EFNS on the diagnosis and management of	

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			European Lyme neuroborreliosis. Eur J Neurology 17:8-16 Pancewicz SA, Garlicki AM, Moniuszko-Malinowska A et al (2015). Diagnosis and treatment of tick-borne diseases. Recommendations of the Polish Society of Epidemiology and Infectious Diseases. Przegl Epidemiol 69:309-316) Parliamentary Office of Science and Technology (2004). Handling uncertainty in scientific advice. Postnote June 2004, Number 220. http://www.parliament.uk/documents/post/postpn220.pdf Preac-Mursic, Weber K, Pfister HW et al (1989). Survival of Borrelia burgdorferi in antibiotically treated patients with Lyme borreliosis. Infection 17(6):355-359 Schlesinger PA, Duray PH, Burke BA et al (1985). Maternal-fetal transmission of the Lyme disease spirochete, Borrelia burgdorferi. Annals of Internal Medicine 103(1):67-68 Stanek G, Reiter M (2011). The expanding Lyme Borrelia complex-clinical significance of genomic species? Clin Microbiol Infect 17:487-93 Stricker RB, Middelveen MJ (2015). Sexual transmission of Lyme disease: challenging the tickborne disease paradigm. Expert Rev Anti Infect Ther 13(11):1303-6	

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			Strle F, Nelson JA, Ruzic-Sabljic E, et al (1996). European Lyme borreliosis: 231 culture-confirmed cases involving patients with erythema migrans. Clin Infect Dis 23(1):61 – 65 Strle F, Ruzić-Sabljić E, Cimperman J (2006). Comparison of findings for patients with Borrelia garinii and Borrelia afzelii isolated from cerebrospinal fluid. Clin Infect Dis 43(6):704-10 Thorp AM, Tonnetti L (2006). Distribution and survival of Borrelia miyamotoi in human blood components. Transfusion 56(3):705-11 Trevejo RT1, Krause PJ, Sikand VK et al (1999). Evaluation of two-test serodiagnostic method for early Lyme disease in clinical practice. J Infect Dis 179(4):931-8 Tylewska-Wierzbanovska S, Chmielewski T (2002). Limitation of serological testing for Lyme borreliosis: evaluation of ELISA and western blot in comparison with PCR and culture methods. Wien Klin Wochenschr 114(113-14):601-5 Venclíková K, Betasova L, Sikutova S et al (2014). Human pathogenic borreliae in Ixodes ricinus ticks in natural and urban ecosystem (Czech Republic). Acta Parasitol 59(4):717-20 ViraMed Laboratory Diagnostics (2016). Borrelia ViraStripe® IgG, IgM Test Kit. http://www.viramed.de/en/bacteria/borrelia-species/borrelia-virastripe	

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			Wang G, Liverus D, Mukherjee P et al (2014). Molecular Typing of Borrelia burgdorferi. Curr Protoc Microbiol. 2014;34:12C.5.1-31 Weber K, Bratzke, HJ, Neubert U et al (1988). Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy. Pediatr Infect Dis J 7(4):286–289 Wormser GP, Dattwyler RJ, Shapiro EG, et al (2006). The clinical assessment, treatment and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: Clinical practice guidelines by the Infectious Diseases Society of America. Clinical Infectious Diseases 43:1089-1134	
Lyme Disease UK	General	General	Lyme Disease UK is a patient support network with nearly 4000 members and bears witness daily to thousands of patients who are suffering on an inhumane scale. Many have been ridiculed by medical professionals in various disciplines, dismissed, belittled, neglected and left with increasingly frightening and painful symptoms for which no help or guidance is offered. Many people have lost their jobs, their homes, their life savings and their relationships and are now living in isolation and poverty. Others are left with no other option but to fundraise or in order to seek private Lyme disease and co-infection treatment (often overseas) or fund it themselves in an attempt to reverse the decline in their health and save their lives. The NHS guidance currently in use is failing these patients. The general overview is that EM rashes are frequently being ignored by GPs and that	Thank you for your comment which supports the need for developing a NICE guideline in this topic area. We hope that this guideline will provide clarity for NHS healthcare providers and patients linked to the diagnosis and management of Lyme disease based on the best available evidence.

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			people aren't being asked about potential tick exposure. Furthermore, it often appears that people are not being offered Lyme disease testing despite presenting with numerous symptoms consistent with the disease. Some people even report hostility from doctors if they request a test and many are told that Lyme disease is either very rare or that it does not exist in this country and that they should not be researching the disease online. There have been accounts of patients, who were previously told that their Lyme disease tests were negative, discovering that they were in fact positive when they requested a copy of the laboratory report, sometimes months or years later. It also appears that people are all too readily being turned away or misdiagnosed with CFS, fibromyalgia and mental health issues without tick-borne infections even being considered. As Cameron et al point out in the ILADS guidelines, a survey involving Lyme disease patients, conducted by Johnson et al, reveals that '71.6% rated their health as fair or poor. This rate is higher than that seen in other chronic diseases including congestive heart failure, fibromyalgia, post- stroke and post-myocardial infarction status, diabetes and multiple sclerosis'. It is important to note from shared patient experience that many people who have sought ongoing private treatment for Lyme disease are seeing improvements in their health after being essentially abandoned by the NHS. References: 1. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. 2014 Sep;12(9):1103-35. doi: 10.1586/14787210.2014.940900	

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			http://www.tandfonline.com/doi/full/10.1586/14787210.2014.940900 2. Johnson L, Wilcox S, Mankoff J, Stricker RB. Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. Peer J 2014;2:e322 https://peerj.com/articles/322/	
Lyme Disease UK	General	General	All known pathogenic strains of Borrelia should be covered in the scope and not just Borrelia afzelii, Borrelia garinii and Borrelia burgdorferi. One in five patients is thought to be infected abroad and so could potentially be affected by different species which should also be covered by UK testing and come under the term 'Lyme disease'. Borrelia valaisiana has been found in UK ticks according to the BIA position statement on Lyme borreliosis, although it states that Borrelia valaisiana is not regarded as pathogenic. However, in this study, Borrelia valaisiana was suspected of causing infection (Saito et al, 2007). In this study, after culturing 'live Borrelia bissettii-like strain from residents of North America,' the 'results support the fact that B. bissettii is responsible for human Lyme borreliosis worldwide along with B. burgdorferi s.s. The involvement of new spirochaete species in Lyme borreliosis changes the understanding and recognition of clinical manifestations of this disease' (Rudenko et al, 2016). Borrelia miyamotoi also needs to be taken into consideration and incorporated into testing as it has been found in the UK (Hansford et al) and it is known to cause disease (Molloy et al, 2015).	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			The brief for the scope should include a review of the literature on other pathogenic strains of Borrelia, especially as there has been a number of new research papers since the BIA position statement was issued in 2011. References: 1. British Infection Association. The epidemiology, prevention, investigation and treatment of Lyme borreliosis in United Kingdom patients: A position statement by the British Infection Association. J Infect. 2011 May;62(5):329-38. doi: 10.1016/j.jinf.2011.03.006. http://www.aldf.com/pdf/BIA%202011statement%20on%20Lyme%20disease.pdf 2. Saito K, Ito T, Asashima N, Ohno M, Nagai R, Fujita H, Koizumi N, Takano A, Watanabe H, Kawabata H. Case report: Borrelia valaisiana infection in a Japanese man associated with traveling to foreign countries. Am J Trop Med Hyg. 2007 Dec;77(6):1124-7 http://www.ajtmh.org/content/77/6/1124.long 3. Rudenko, N et al.Isolation of live Borrelia burgdorferi sensu lato spirochaetes from patients with undefined disorders and symptoms not typical for Lyme borreliosis. Clin Microbiol Infect. 2016 Mar;22(3):267.e9-267.e15. doi: 10.1016/j.cmi.2015.11.009. http://www.ncbi.nlm.nih.gov/m/pubmed/26673735/ 4. Hansford, K. M., Fonville, M., Jahfari, S., Sprong, H., & Medlock, J. M. (2014). Borrelia miyamotoi in host-seeking Ixodes ricinus ticks in England. Epidemiology and Infection, 1–9. doi:10.1017/S0950268814001691 http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=9595260&fileId=S0950268814001691 5. Molloy PJ, Telford SR 3rd, Chowdri HR, Lepore TJ, Gugliotta JL, Weeks KE, Hewins	

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			ME, Goethert HK, Berardi VP (2015). Borrelia miyamotoi Disease in the Northeastern United States: A Case Series. Annals of Internal Medicine. doi:10.7326/M15-0333 http://annals.org/article.aspx?articleid=2301402	
VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**VIRAS - Introduction** Vector-borne Infection - Research, Analysis, Strategy VIRAS is a non-profit group comprised of patients and carers with knowledge and experience in Lyme borreliosis and co-infections, Myalgic Encephalomyelitis (M.E.) and Chronic Fatigue Syndrome (CFS). Our members are qualified in science and research, ethics, biology, psychology, psychotherapy, teaching, business and media. We are glad to have the opportunity to provide comments and feedback on the NICE Draft Scope for Lyme borreliosis	Thank you for your comment.
VIRAS Vector-borne Infection, Research – Analysis -	General	General	**VIRAS response to NICE request for comments on:** "4) The inclusion of the following strains of Lyme Borreliosis for consideration as part of our review of the evidence: B. burgdorferi (and the subtype B. burgdorferi sensu stricto), B. garinii, B. afzelii"	Thank you for your response and detailed comments on our questions. We will bring the detail of your response to the Guideline Committee's attention. The information will be used to inform the

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Strategy			**Borrelia Species causing Lyme borreliosis and Travel Risks** Key Points • Since the discovery of *borrelia burgdorferi* in 1982, more species and strains have been discovered and implicated in Lyme borreliosis (LB) • As recently as 2016, the CDC and Mayo Clinic have announced a new LB species • As recently as 2016 Rudenko et al (14) provide evidence of the involvement of *B. bissettii* in human Lyme borreliosis • Regions endemic for LB species have expanded and are expected to continue to do so • A high number of UK residents travel abroad with increased risk of exposure to a greater range of LB species and strains The species of borrelia specific for 'Lyme Disease' were *b. burgdorferi s.s.*, *b. garinii* and *b. afzelii*. This artificial restriction has long been discarded by scientists and physicians to recognise additional borrelia species responsible for 'Lyme Borreliosis' (LB). All authorities recognise LB as a growing threat. The World Health Organization Europe report on Lyme Borreliosis and Global Warming states (1): "Since the 1980s, tick vectors have increased in density and spread into higher latitudes and altitudes in Europe. It can be concluded that future climate change in Europe will facilitate a spread of LB into higher latitudes and altitudes, and contribute to increased disease occurrence in endemic areas." To meet this challenge, the Guidelines must recognise that non-endemic species could spread to the UK and accept the possibility of further unknown species and strains yet to be discovered.	Committee's decision making as they develop the review protocols that guide the searches for and review of the evidence for the questions outlined in the guideline scope.

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			In Scientific American's guest blog, *Lyme Time Is upon Us Again.* Pfiefer (2016)(2) remarks on *Ixodes ricinus*, (castor bean tick) which transmits LB in Europe: "In Europe, disease-ridden castor bean ticks, a relative of those in the U.S., are on the move too, spreading 300 miles north in Sweden and Norway to latitudes that were considered too cold only a generation ago. Prolific and resilient, they are even scaling mountains, climbing 1,300 feet up the Dinaric Alps of Bosnia and Herzegovina and moving to new heights in the Czech Republic and Scotland." LB species causing disease in Europe include: *burgdorferi, afzelii, garinii, spielmanii, lusitaniae, valaisiana, bisettii* (Heyman et al. 2010)(3). Rizzoli *et al* state in Eurosurviellance (4): "LB is likely to become an increasingly relevant health risk in the near future due to complex interactions between diverse environmental and socio-economic factors, which will affect various aspects of disease ecology and epidemiology". **Risk to UK Residents Travelling Abroad** Worldwide species of Lyme borreliosis spirochaetes pose a threat to UK residents travelling abroad. The CDC (2015)(5) state that LB in Europe is: "endemic from southern Scandinavia into the northern Mediterranean countries of Italy, Spain, and Greece and eastward from the British Isles into central Russia." According to the UK Government, British nationals make millions of visits abroad each year. This increases the risk of exposure to Lyme borreliosis and a greater diversity of LB	

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			species and strains. Destination — Number of visits — LB incidence per 100k pop. France — 17 million — 44 Germany — 2 million — 261 Netherlands — 1.8 million — 149 Austria — 774,000 — 300 Switzerland — 710,000 — 30 Sweden (Southern) — 664,000 — 464 Czech Republic — 300,000 — 38 Slovenia — 100,000 — 155 UK reported incidence of LB per 100k pop: Scotland — 5.9 England and Wales — 1.73 (Source for travel abroad: https://www.gov.uk/foreign-travel-advice/france [change country name for other destinations in lowercase]) (Sources for incidence figures: see below) According to the Office for National Statistics (6) 62% of travel abroad by UK residents is for a holiday and 11% for visits to friends and relatives and might therefore be expected to be of at least several days. Therefore each year there are millions of visits by British nationals to other European countries where LB incidence ranges from 17 to 268 times the	

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			'official' rate in England and Wales. Notwithstanding UK incidence figures which appear to be absurdly low, the high numbers travelling abroad are subject to a significant risk of exposure to diverse species and strains of borrelia. Pfiefer (2016)(7) observes: "In the Netherlands, rates of people diagnosed with the telltale Lyme rash ranged up to 514 per 100,000 in 2014. In areas of Germany and Sweden, studies of patient records found Lyme rates of 261 to 464 per 100,000. In Europe, the highest national rate—315 per 100,000 in 2009 – has been reported in Slovenia, one of few countries to aggressively track cases." **Travel to the USA** UK residents make over 3 million visits to the USA each year (6). The CDC (2013)(8) state: "Preliminary estimates released by the Centres for Disease Control and Prevention indicate that the number of Americans diagnosed with Lyme disease each year is around 300,000. ' "We know that routine surveillance only gives us part of the picture, and that the true number of illnesses is much greater," said Paul Mead, M.D., M.P.H, chief of epidemiology and surveillance for CDC's Lyme disease program. "This new preliminary estimate confirms that Lyme disease is a tremendous public health problem in the United States, and clearly highlights the urgent need for prevention." ' Kiersten et al (2015)(9) state, "Over time, the number of counties in the northeastern states	

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			identified as having high incidence of Lyme disease increased >320%: from 43 (1993–1997) to 90 (1998–2002) to 130 (2003–2007) to 182 (2008–2012)." Their map (http://wwwnc.cdc.gov/eid/article/21/8/14-1878-f1) documents the exponential spread of LB over vast areas, graphically illustrating the growing threat of LB to more regions and more people. Pfiefer (2016) (10) remarks on *Ixodes scapularis*, the 'deer tick' which transmits LB in North America: "In 1996, Ixodes scapularis, as it is known, had planted a foothold in 396 American counties. By 2015, the tick was established in 842 counties. This does not count another 578 counties—in all nearly half the continental U.S. total—in which the tick has been officially "documented." " **Borrelia species with known or suspected potential to cause LB** **Borrelia Mayonii** The Centres for Disease Control and Prevention, 2016, describe a "New Lyme-disease-causing bacteria species discovered. *Borrelia mayonii* closely related to *B. burgdorferi*. "[]. Until now, Borrelia burgdorferi was the only species believed to cause Lyme disease in North America. "Scientists at the Mayo Clinic in Rochester, Minnesota, first suspected the possibility of new bacteria after lab tests from six people with suspected Lyme disease produced unusual results, according to the findings published today in Lancet Infectious Diseases. Additional genetic testing at the Mayo Clinic and CDC found that the bacteria, provisionally named Borrelia mayonii, is closely related to B. burgdorferi.	

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			"This discovery adds another important piece of information to the complex picture of tickborne diseases in the United States," said Dr. Jeannine Petersen, microbiologist at the Centers for Disease Control and Prevention."(11) **Borrelia Bavariensis** Margos et al (2013) (12), state that *Borrelia bavariensis* is widely distributed in Europe and Asia: "Since the original description of Borrelia bavariensis sp. nov. in 2009, additional samples available from humans and ticks from Europe and Mongolia, respectively, have been used to further characterize Borrelia strains belonging to this group of spirochaetes that utilize rodents as reservoir hosts. These investigations suggested the presence of related strains in Europe and Asia and confirmed their status as representing a distinct species." **Borrelia spielmanii** Maraspin, Ruzic-Sabljic and Strle (2014)(13) conclude in their case report: "Our results corroborate previous findings that B. spielmanii is a cause of LB in Europe. Thus, in addition to the Netherlands (2), Germany (10), and Hungary (1), LB caused by B. spielmanii is also present in Slovenia." ***Borrelia Bissettii*** Rudenko et al (2016)(14) report on, "the first recovery of live B. burgdorferi sensu stricto from residents of southeastern USA and the first successful cultivation of live Borrelia bissettii-like strain from residents of North America. Our results support the fact that B. bissettii is responsible for human Lyme borreliosis worldwide along with B. burgdorferi s.s. The involvement of new spirochaete species in Lyme borreliosis changes the	

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			understanding and recognition of clinical manifestations of this disease." **Borrelia lusitaniae** While *B. lusitaniae* is distributed throughout countries in Europe and North Africa, it is believed to be the sole species of the Lyme borreliosis group in southern Portugal. Lizards of the family *Lacertidae* are thought to be important reservoir hosts of *B. lusitaniae*.(15) De Carvalho et al(2008)(16) remark: "We have described a vasculitis-like syndrome associated with the isolation of B. lusitaniae. Although the clinical presentation is not typical of Lyme borreliosis, this case had features suggestive of vasculitis, which has been described as one of the characteristic physiopathological aspects of this disease" **Borrelia Valaisiana** Diza et al (2004)(17) state: "We detected *B. valaisiana* DNA in CSF of a patient with slow progressive spastic paraparesis, which suggests that this microorganism might be the causative agent of the disease. Nucleotide sequence information of *Borrelia* strains from clinical cases and ticks from different countries will elucidate the molecular epidemiology of the disease." "The pathogenic capabilities of *B. valaisiana* are still uncertain; it has been detected by PCR and restriction fragment length polymorphism analysis in skin biopsy specimens from two erythema migrans patients and from patients with mixed infection (erythema migrans and acrodermatitis chronica atrophicans) (4). Indirect evidence suggests that B. valaisiana is involved in some chronic clinical manifestations (8)."	

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			Reference 8 above is: Ryfell, et al (1999)(18), which states: "Our results suggest an organotropism of *Borrelia* species and provide some evidence of a pathogenic potential of*B. Valaisiana* in humans." Schwab *et al*, (2013)(19) state in *Borrelia valaisiana Resist Complement-Mediated Killing Independently of the Recruitment of Immune Regulators and Inactivation of Complement Components*: "In conclusion, we demonstrated that B. valaisiana isolates differ in their susceptibility to human serum, thus providing some evidence that in particular serum-resistant isolates might cause Lyme disease. Contrary to our expectations, certain B. valaisiana isolates appear to possess different molecular mechanism(s) to inhibit complement activation, independently of the recruitment of complement regulators or by inactivation of central complement components. Even though that we are currently unable to decipher the precise molecular mechanism, it is tempting to speculate that B. valaisiana ZWU3 Ny3 expresses an outer surface protein that directly interacts with components of the complement system to inhibit complement activation. Further investigation is required to identify potential complement inhibitory protein(s) of this particular borrelial strain." Cooper *et al*, (2001)(20) tested 75 ticks taken from wild animals in SW England. 41% tested positive for the presence of *borrelia* DNA. 34% of these were also positive for *Borrelia valaisiana*, considerably more than double the prevalence of this species in the	

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			rest of Europe. **Conclusion** In view of the spreading areas endemic for Lyme borreliosis and the diversity of borrelia species which pose a threat to humans; restricting Lyme borreliosis to just 3 of those species would inevitably fail to protect UK residents. **Sources for Lyme Borreliosis Incidence in Europe:** Austria, 2005, Elisabet Lindgren, Thomas G.T. Jaenson. 2006. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. World Health Organization Europe. http://www.euro.who.int/__data/assets/pdf_file/0006/96819/E89522.pdf Belgium , 2009, K. Vanthomme & N. Bossuyt & N. Boffin & V. Van Casteren. 2012. Incidence and management of presumption of Lyme borreliosis in Belgium: recent data from the sentinel network of general practitioners. Eur J Clin Microbiol Infect Dis (2012) 31:2385–2390. DOI 10.1007/s10096-012-1580-3 [figures referenced relate to confirmed EM rash] Czech Republic, 2005-14, Czech Republic 38/100k (Avg 2005-14). Ministry of Health. State Health Institute. Selected Infectious Diseases in the Czech Republic in the years 2005-2014. http://www.szu.cz/modules/makepdf/make.php?id=1346 England and Wales, 2011, Public Health England. https://www.gov.uk/government/publications/lyme-borreliosis-epidemiology/lyme-borreliosis-epidemiology-and-surveillance France , 2012, A Vandenesch, C Turbelin, E Couturier, C Arena, B Jaulhac, E Ferquel, V	

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			Choumet, C Saugeon, E Coffinieres, T Blanchon, V Vaillant, T Hanslik. 2015., RIVM (2015). INCIDENCE AND HOSPITALISATION RATES OF LYME BORRELIOSIS, FRANCE, 2004 TO 2012. Eurosurveillance, Volume 19, Issue 34, 28 August 2014. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20883 Germany, 2008, I. Müller, M. H. Freitag, G. Poggensee, E. Scharnetzky, E. Straube, Ch. Schoerner, 1H. Hlobil, H.-J. Hagedorn, G. Stanek, A. Schubert-Unkmeir, D. E. Norris, J. Gensichen, and K.-P. Hunfeld. Evaluating Frequency, Diagnostic Quality, and Cost of Lyme Borreliosis Testing in Germany: A Retrospective Model Analysis. Clin Dev Immunol. 2012; 2012: 595427. PMCID: PMC3254124. Published online 2011 Dec 27. doi: 10.1155/2012/595427 Netherlands, 2011, Coumou J1, van der Poll T, Speelman P, Hovius JW. Tired of Lyme borreliosis. Lyme borreliosis in the Netherlands. Neth J Med. 2011 Mar;69(3):101-11. http://www.ncbi.nlm.nih.gov/pubmed/21444934 Scotland, 2013, NHS Scotland http://www.documents.hps.scot.nhs.uk/giz/10-year-tables/lyme.pdf Slovenia, 2006, See 2. Switzerland, 2005, See 2. **References** 1. Elisabet Lindgren Thomas G.T. Jaenson. 2006. Lyme borreliosis in Europe: influences of climate and climate change, epidemiology, ecology and adaptation measures. World Health Organization Europe.	

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VIRAS Vector-borne	General	General	**VIRAS response to: Who is the Focus?** **And excluded groups placed at risk by the Draft Scope** 30 1.1 Who is the focus?	Thank you for your comment. This guideline will cover all people with Lyme disease regardless of their

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Infection, Research – Analysis - Strategy			49 Areas that will not be covered 51 Managing chronic fatigue syndrome. This is covered by the NICE 51 guideline: Chronic fatigue syndrome/myalgic encephalomyelitis (or 52 encephalopathy) (CG53) **Abbreviations** AIDS, Acquired Immune Deficiency Syndrome BIA, British Infection Association CDC, Centres for Disease Control and Prevention, (USA) CFS, Chronic Fatigue Syndrome CRD, Centre for Reviews and Dissemination DoH, Department of Health (UK) FDA, Food and Drug Administration, (USA) IDSA, Infectious Disease Society of America LB, Lyme borreliosis M.E., Myalgic Encephalomyelitis HPA, Health Protection Agency NATO, North Atlantic Treaty Organization PCR, Polymerase Chain Reaction PHE, Public Health England WHO, World Health Organization **The following groups are at risk of being neglected by the NICE Guideline:** Infected in the past and presently ill due to:	symptoms presentation or treatment history. The key areas were drafted in a way to ensure that those who clearly have Lyme, as well as those who may have Lyme but have never been investigated for Lyme receive the best possible assessment and diagnostic tests, and subsequently the best possible treatment. Thank you for your comment concerning chronic Lyme disease and post-Lyme disease syndrome. This clarification has been very helpful.

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			• never investigated for LB • not investigated properly for LB • misdiagnosed with something other than LB Since the Lyme disease spirochaete *Borrelia burgdorferi* was discovered in 1982 by Dr Willy Burgdorfer, multiple species of Lyme Borreliosis-causing spirochaetes have been found in Europe. In the decades following these discoveries, UK doctors have probably encountered many thousands of patients with symptoms highly suggestive of LB, just as doctors have in all the other countries of north-western Europe. Yet many of those doctors never considered Lyme borreliosis (LB) as a cause of their patient's illness - let alone conducted a careful evaluation or ordered tests, because: • they had no experience of LB and little, if any, knowledge about the infection • UK reported incidence figures made LB appear rare (and therefore unlikely) • the doctor believed Lyme is only present in certain areas of the country • if they did order tests and the results were negative they wrongly believed this excluded LB (and may even have been told by the test laboratory staff that this was so) In England and Wales, in the 15 years from 1997 to 2011 there were a total of 7,903 cases of LB reported at an average of 527 cases per annum giving an average annual incidence of ~0.93 per 100k population. (Public Health England. 2013.) This apparent rarity has meant that in past decades, many doctors were not alert to the risk of the disease, except perhaps for some of those practising in LB 'hot-spots'. Yet significant risk to UK residents	

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			has been present and known to some, for decades. In 1993, Nuttall et al (1993) submitted data to NATO's Second European Symposium on Lyme Borreliosis on the Ecology of Lyme borreliosis in the United Kingdom: showing that *Ixodes ricinus* (principal vector of LB in Europe) could be found throughout "Most of the UK" and that around 40% of unfed nymph and adult ticks "collected in Lyme disease foci" carried *Borrelia burgdorferi*, as shown by PCR. In 2007, the late Professor Klaus Kurtenbach of Bath University told the BBC, "In France they have diagnosed 10 times as many cases as here; yet we've found the same number of ticks here carrying the disease." (BBC. 2007) Dr Darrel Ho-Yen, who was head of the Scottish Lyme Reference Laboratory at Inverness, was quoted in The Field (2005) magazine: "He believes that the known number of proven cases should be multiplied by ten "to take account of wrongly-diagnosed cases, tests giving false results, sufferers who weren't tested, people who are infected but not showing symptoms, failures to notify and infected individuals who don't consult a doctor"." Bruce Alexander (2012) wrote in the Scotsman, "A recent audit of patients at a Perthshire Medical Practice found a ratio of confirmed cases equivalent to 125 per 100,000 people. Applying this ratio across Scotland, there could be around 6,500 people contracting Lyme disease each year, the vast majority going undiagnosed and untreated." This computes to 30 times the reported incidence for Scotland, a country which has 3 times more recorded	

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			LB than England and Wales; and where more doctors are aware of the risks and symptoms of LB. Some of the tens of thousands of 'the vast majority going undiagnosed and untreated' who had symptoms, have probably recovered. But without doubt, some of those who became chronically ill, were misdiagnosed with Myalgic Encephalomyelitis (M.E.) or Chronic Fatigue Syndrome (CFS); illnesses with very poor recovery rates and symptoms highly suggestive of chronic Lyme borreliosis. VIRAS will argue that those patients, some of whom by now have been infected for decades, deserve proper investigation and a correct diagnosis. Even if some believe that patients with chronic LB infections may suffer the same fate as Tertiary Syphilis patients, who can have intractable infection and symptoms, it would be unethical to leave these patients misdiagnosed with CFS. Excluding these patients would be negligence reminiscent of the Tuskegee Syphilis Experiment (Wikipedia 2016). The symptoms of some patients diagnosed with long-term M.E. or CFS should lead a well-informed doctor to suspect LB and duly investigate. We are not aware of a single case where this has happened. Instead, it has been left to patients to find out about Lyme borreliosis by sheer chance. Then, when they do consider their symptoms, risk factors and the course of their illness and consult their doctor; they are all too often dismissed or misled by an unreliable blood test which they are told definitively excludes LB.	

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			With UK 'CFS' prevalence estimated at 256,000 (NICE 2007), and full recovery occurring in only ~10% (CRD 2002), if just 10% of M.E. or CFS patients were actually misdiagnosed cases of chronic LB, that could be 25,000 cases in the UK whose illness might respond to treatment. That will not happen while they are misdiagnosed. Far from leading the way in recognising and addressing the silent epidemic of LB, PHE (and the former HPA) have been effective in suppressing the problem, in the worst traditions of national medical authorities who made a complete mess of dealing with the early years of AIDS. Patients who remain ill with every indication of chronic LB, frequently with laboratory confirmation, and who do not accept PHE's simplistic notions about a complex disease, have been branded "disaffected" and described as coming from a "parallel universe". It is an old political strategy to denigrate those whose views you wish to suppress and is a resort of those who have power and influence but no scientific evidence to back-up their arguments. M.E. and CFS patients and campaigners have been subject to years of the same, with orchestrated efforts in the media to portray them as neurotic, hypochondriac and anti-science. And for whose benefit have chronically sick people been made the target of denigrating propaganda? Not the patients. Not their doctors. The winners are the medical insurance companies that avoid paying for the sustained treatment and management that chronically ill patients require; and those that have been negligent in protecting the Nation's health.	

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			Schwarzwalder et al (2010) found that 14% of Lyme disease infection was misdiagnosed by patients and 20% misdiagnosed by physicians. This review was in Maryland, a USA state where many counties were classed by the CDC as 'high incidence' by the early 2000's (Kiersten et al. 2015). If that is what happens where LB is common and well-known to doctors, what chance do UK patients have? Quite simply, the UK has a low incidence rate because PHE produce low incidence rates, making the disease appear rare, obscuring the risk, and misleading doctors and the public. In the UK, Lyme is not rare, but it is rarely diagnosed. Dr Hugh Derham (2014) in Australia tested 300 of his ME, CFS and FM patients and found that 95% were positive for Lyme. Dr Samuel Shor (2011) in the USA reviewed 210 patients and found that a "potentially substantial proportion of patients with what would otherwise be consistent with internationally case defined CFS [...] actually have a perpetuation of their symptoms driven by a persistent infection by *Borrelia burgdorferi*." Dr. Kenny De Meirleir (2014) in a presentation to the Belgium Senate, observed that 95% of Chronic Fatigue Syndrome and ME (Fukuda & Canadian criteria) were cases of Late Stage Lyme Disease. 95% having had positive *Borrelia burgdorferi* LTT tests. **Chronic LB and Post Treatment Lyme Disease Syndrome**	

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			VIRAS consider the term 'chronic Lyme' legitimate. The infection can be persistent just as Syphilis, Leptospirosis and other bacterial infections such as TB can be persistent. There is no medical or scientific basis for rejecting the term 'chronic Lyme'. Whilst this invidious reservation may serve the purposes of those that have motives to portray Lyme as a simple, acute illness – it denies the complexity of the infection and flies in the face of common sense and a wealth of published evidence. Dr Willy Burgdorfer, who discovered the Lyme spirochaete, *Borrelia burgdorferi*, in 1982, told investigators for *Under Our Skin* (2007): "I am a believer in persistent infections because people suffering with Lyme disease, ten or fifteen or twenty years later, get sick [again]. Because it appears that this organism has the ability to be sequestered in tissues and [it] is possible that it could reappear, bringing back the clinical manifestations it caused in the first place." (Square brackets as published) VIRAS consider the term 'post treatment Lyme disease syndrome' (PTLDS) misleading, though this depends to an extent on what is meant by 'post treatment'. The term is loaded and intentionally or not, implies that the 'treatment' aspect must have been sufficient and effective. The term suggests that if a patient remains ill after treatment it is not because their treatment was ineffective and the infection remained and relapsed. If this was not the intention of those who use the term, we might also have the term 'Failed Treatment Lyme Disease Syndrome', which would accurately indicate failure to cure a patient who had received some treatment. Unfortunately, in some people's minds the responsibility for the latter might fall on physicians rather than the bacteria or patient. So it may lack a certain	

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			appeal to those who coin these terms and foist them on unsuspecting patients. We are not aware of any scientific evidence that 'post treatment Lyme disease syndrome' even exists; or that anyone deemed to have the syndrome has ever been repeatedly tested to the full extent of available methods. An experiment like that could provide convincing evidence that the infection really had been eliminated and make PTLDS a plausible explanation for their ongoing symptoms. Whereas the contrary is true. When chronically ill UK patients are thoroughly investigated the infection is often found to remain present long after they received 'adequate treatment'. It is widely recognised that LB infection even in the quite short-term, can cause serious damage to almost any parts and systems of the body. It seems reasonable to believe that the injury could be long lasting or permanent. But that does not mean that it is the only cause in patients whose symptoms persist. The fact that patients continue to experience exacerbations and relapses, sometimes decline and are afflicted with new, debilitating and distressing symptoms, suggests an ongoing disease process for which persistent infection is a strong candidate supported by scientific evidence. (See: ILADS. 2012. Peer Reviewed Evidence of Persistence of Lyme Disease Spirochete *Borrelia burgdorferi* and Tick-Borne diseases. And Moyer. 2015. Scientific American. Lyme Disease May Linger for 1 in 5 Because of "Persisters") Without evidence meeting scientific standards of thoroughness, reliability and reproducibility, 'post treatment Lyme disease syndrome' is simply an opinion based upon a	

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			one-size-fits-all notion of 'treatment' and is in our experience, used by those with biased opinions and conflicting interests. When patients with chronic LB research the field to try and find out how science could help them, what they find is that 'science' has been usurped by 'opinions'. It is not the patients and campaigners that are anti-science; our views are almost invariably supported by scientific research. But examine the IDSA or BIA or PHE Guidelines for LB and where there is controversy, those guidelines are based on mere opinion with no scientific evidence to support them. These opinions might look good, thanks to 'paper-pile' publishing and 'circular-referencing' and quoting (and misquoting!) of each others opinions creating an appearance of authority. Challenges to anything that threatens their views are slipped under the door of peer review as "a quibble, couched in the language of an exposé" (Earp. 2015). Critical examination reveals nothing more substantial than repetition of opinions lacking objective evidence. Ioannidis, (2005) stated in Plos Medicine, "Empirical evidence on expert opinion shows that it is extremely unreliable". Yet much of the information about LB supplied by the DoH, NHS, PHE and BIA is nothing more than 'expert opinion' imported from the American IDSA and parroted to patients and physicians as though it is scientific fact. These opinions (which happen to serve the interests of medical insurance and re-insurance companies) portray Lyme borreliosis as a simple, self-limiting, acute infection, easily detected and diagnosed and eradicated with a few weeks of antibiotics.	

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			Professor Charlton (2008) remarks: "And when a branch of science based on phoney theories serves a useful but non-scientific purpose, it may be kept-going indefinitely by continuous transfusions of cash from those whose interests it serves. If this happens, real science expires and a 'zombie science' evolves." The converse is true. When the research needed to identify, understand and treat UK borreliosis is not being undertaken (because according to those charged with the protection of the nation's health, it is so rare in the UK), it is little wonder that many LB patients have been misdiagnosed with M.E. or CFS. Yet UK authorities continue to rely on either non-UK sources, or UK sources which are simply repeating opinions which actually originate from the IDSA. We hope that NICE Guidelines for LB will recognise a duty to the thousands of LB patients who have never been properly evaluated or diagnosed and treated. These patients have been failed by the authorities appointed to protect them and too often have been misdiagnosed with 'CFS'. Notwithstanding NICE guidelines for that illness, these patients have been subject to prejudice and abuse by all and sundry; portrayed as neurotic, blamed for their illness and marginalised, whilst their lives have been ruined by a chronic infectious disease. **REFERENCES** Alexander, Bruce. 2012. More must be done to combat Lyme disease. The Scotsman.	

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VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**Lyme-Like Illnesses** In view of the increasing public health risk from tick bites, and indeed from other arthropod bites, the committee should consider broadening the scope for intervention and management of Lyme disease to include "Lyme-like" borreliosis infections, as well as all possible infections from the many other pathogenic microbes being identified in ticks;(1) even if only for the purposes of accurate differential diagnosis. There is growing evidence from support groups in the UK that patients have multiple tick-borne infections: please see Lyme Disease UK web site and Veronica Hughes CEO Caudwell Lyme Co., where the data shows that the NHS is failing to detect and treat these infections.	Thank you for your comment. This guideline covers Lyme disease only. While people with co-infections will not be excluded from the evidence reviews in this guideline, the management of other tick-borne related infections or illnesses are outside the remit of this guideline. However, the guideline committee can give mention to any groups who require special consideration when linking evidence to recommendations.

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			Daniel Cameron MD, (http://danielcameronmd.com/coinfections/) observes: Co-infections can be challenging to diagnose, as clinical features often overlap with many of the other tick-borne diseases, including Lyme disease. However, the importance of identifying and treating polymicrobial infections is critical in getting a patient well. Practitioners should consider co-infections in the diagnosis when a patients symptoms are severe, persistent, and resistant to antibiotic therapy. Physicians have found that co-infections typically exacerbate Lyme disease symptoms. The most "Lyme-like" symptom presentations from tick-borne infections are due to infections with members of the large family of borrelia spirochetes. In Brazil during the last 10 years, a Lyme-like disease has been identified which is indistinguishable from Lyme, termed *Baggio-Yoshinari syndrome* (2), and similarly, in the southern states of the USA, there is *Master's disease* or *Southern Tick-Associated Rash Illness* (3) Willy Burgdorfer wrote in 1998 that Relapsing Fever is far more widely distributed than was realised, and hardly anyone was looking for it. He found that most patients who had antibodies to the relapsing fever, caused by *B. hermsii*, were serologically positive for *B. burgdorferi*, and Western Blotting consequently demonstrated false positivity of testing for *Borrleia burgdorferi* (4)	

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			In Britain, we know that at least 13 million birds, carrying over 1 million ticks, arrive in Britain from Africa every Spring (5). Africa has the highest prevalence of relapsing fever borrelia strains, and of human illnesses and deaths due to the infection. It is reasonable to conjecture that relapsing fever strains of borrelia have been introduced into the British Isles by bird ticks, and consequently into the ecosystem. It has recently been shown by Public Health England that B. miyamotoi is present in Britain in *Ixodes* ticks. *B. miyamotoi* is genetically related to tick-borne relapsing fever (TBRF) strains. However, in clinical presentation, it can appear more like Lyme borreliosis. In North America, researchers have shown that, in 182 cases of febrile illness from ticks, presenting as very similar to Lyme disease, most patients who were eventually found to have antibodies to *B. hermsii* were serologically positive for *B. burgdorferi*, and it was only the second tier testing (Western blot) that demonstrated false positivity of testing for *B. burgdorferi*. "This study demonstrates that TBRF is underrecognized and underreported and may be falsely identified as Lyme disease" (4). Similarly, Scoles et al in 2001 found that yet another TBRF strain in the US was transmitted by *Ixodes* ticks (6) Of greatest relevance to Britain, European scientists Richter et al have found a third strain of the relapsing fever borrelia in Europe and state "We now know that a third member of this group infects I. ricinus ticks in central Europe. We conclude that each of the various	

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			kinds of ticks that serve as vectors for Lyme disease spirochetes, I. ricinus, I. persulcatus, I. scapularis [= dammini], may be infected by relapsing fever–like spirochetes" and they state "Exposure risk for relapsing fever–like spirochetes is similar to that of certain Lyme disease genospecies." (7) Many patients report to us that they have had positive results on the initial ELISA tests for Lyme disease, but that subsequent Western blot tests have proved negative. It seems possible that they might have been in fact infected with a TBRF strain, even one that is as yet unrecognised, which would have produced such test results. Thus it is necessary to include the TBRF illnesses into the scope of this committee, as they may be indistinguishable from Lyme disease. **References** 1) Co-infection of Ticks: The Rule Rather Than the Exception Sara Moutailler, Claire Valiente Moro, Elise Vaumourin, Lorraine Michelet, Florence Hélène Tran, Elodie Devillers, Jean-François Cosson,, Patrick Gasqui, Van Tran Van, Patrick Mavingui, Gwenaël Vourc'h, Muriel Vayssier-Taussat. PLOS Neglected Tropical Diseases | DOI:10.1371/journal.pntd.0004539 March 17, 2016 2) [Brazilian lyme-like disease or Baggio-Yoshinari syndrome: exotic and emerging	

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			Agent. Dania Richter, Daniela B. Schlee,and Franz-Rainer Matuschka. Emerging Infectious Diseases • Vol. 9, No. 6, June 2003	
VIRAS Vector-borne Infection, Research – Analysis - Strategy	General	General	**Co infections must be considered in tick-bite patients.** The Anaplasmataceae are already being diagnosed as tick-bite infections, and co-infections, by PHE microbiologists: it is hoped that infectious disease consultants in England and Wales are aware of the possibility. However, it is patient experience that testing for the infection is not routine, despite patients presenting with signs and symptoms of a febrile illness - even in those with a known tick bite. This must change, especially because climate warming means that all vector-borne diseases will increase in incidence in the next decade. It has been well known for 40 years at least, that ticks carry and may transmit to humans, a wide variety of pathogens, including nematodes, trypanosomes, and Rickettsiae, as well as a number of viruses(1). A recent review of the relevance to public health by Professor Christian Peronne deserves careful perusal (2). Bartonellosis is one of the most frequently diagnosed infections found as a co-infection in UK Lyme disease patients. Yet we know that diagnosis, especially after the acute phase, can be a difficult task. It is our experience that chronically infected patients are not offered	Thank you for your comment. While people with co-infections will not be excluded from the evidence reviews, the focus of this guideline is the diagnosis and management of Lyme disease. The specific management of co-infections will not be addressed by this guideline. However, the guideline committee will give mention to any groups who require special consideration when linking evidence to recommendations.

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			tests. Even when tested, most are negative by UK methods, yet they have been found to be positive for Bartonella species by non-UK laboratories. Ticks play a role in the natural cycles of some of the bartonellae including those pathogenic for humans. Consequently, bartonelloses should be included in the differential diagnosis for patients exposed to tick bites(3). Health authorities must take into account the possibility of bartonellosis in persons exposed to tick bites, and the Bartonella species recognised as tick-borne pathogens (4). Bartonella infection causes symptoms which are similar to LB, in many ways including neurological signs, but the therapeutic treatment is different from that used for borreliosis(5, 6). Thus an accurate diagnosis is crucial for successful treatment, and patient survival and quality of life. Babesiosis German scientists A. Hildebrandt, J. S. Gray and K.-P. Hunfeld, in their report "Human Babesiosis in Europe: what clinicians need to know" (7) state: " Although best known as an animal disease, human babesiosis is attracting increasing attention as a worldwide emerging zoonosis. Humans are commonly infected by the bite of ixodid ticks. Rare ways of transmission are transplacental, perinatal and transfusion-associated. Infection of the human host can cause a very severe host-mediated pathology including fever, and hemolysis leading to anemia, hyperbilirubinuria, hemoglobinuria and possible organ failure. In recent years, apparently owing to increased medical awareness and better diagnostic	

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			methods, the number of reported cases in humans is rising steadily worldwide. Hitherto unknown zoonotic Babesia spp. are now being reported from geographic areas where babesiosis was not previously known to occur, and the growing numbers of travelers and immunocompromised individuals suggest that the frequency of cases in Europe will also continue to rise." Babesia, though relatively rarely diagnosed in the UK other than in cattle, has caused canine deaths in Leeds and Nottingham this year (2016) and there are many cases of debilitating human illness. A one-hour discussion on the UK's largest Lyme forum revealed 5 fully-diagnosed patients responding, within that short time on Wednesday 16th March, 9 am - 10 am, to state that they had acquired Babesiosis in the UK. No one knows how many human deaths may have been attributable to Babesiosis, because there has been no surveillance in potential clinical cases which could have been due to the infection. For example, stroke patients are not screened for this piroplasm, yet blood dyscrasias from the infection are bound to have effects on blood clotting etc. Within the last three decades a dramatic rise in numbers of reported transfusion-associated cases in the US has been documented, with at least 12 fatalities and 160 cases [8, 9]. Outside America only two other cases of transfusion-transmitted babesiosis had been reported by 2013, one from Japan that involved a B. microti-like parasite [10] and one from Germany caused by B. microti (11). VIRAS urges the NICE guideline committee, and all health protection agencies, to include Babesia from tick bites into the scope of the Lyme guidelines. It is a a clear threat to the	

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			health and safety of British citizens, not just through transmission through tick bites, but as a potential blood supply contaminant. **REFERENCES** 1) Aspects nouveaux du rôle de vecteur joué par Ixodes ricinus L. en Suisse Note préliminaire. Aeschlimann A, Burgdorfer W, Matile H, Peter O, Wyler R. Acta Tropica 36. 181-191 (1979) 2) Lyme and associated tick-borne diseases: global challenges in the context of a public health threat. Peronne C. Front Cell Infect Microbiol. 2014; 4: 74. 3) Vector Competence of the Tick Ixodes ricinus for Transmission of Bartonella birtlesii. Caroline Reis, Martine Cote, Danielle Le Rhun, Benoit Lecuelle, Michael L. Levin, Muriel Vayssier-Taussat, and Sarah I. Bonnet, David H. Walker, Editor. PLoS Negl Trop Dis. 2011 May; 5(5): e1186. (4)Transmission of Bartonella henselae by Ixodes ricinus Violaine Cotté, Sarah Bonnet, Danielle Le Rhun, Evelyne Le Naour, Alain Chauvin, Henri-Jean Boulouis, Benoit Lecuelle, Thomas Lilin, and Muriel Vayssier-Taussat. Emerg Infect Dis. 2008 Jul; 14(7): 1074–1080. 5) Bartonella vinsonii subsp. berkhoffii and Bartonella henselae bacteremia in a father and daughter with neurological disease. Breitschwerdt EB, Maggi RG, Lantos PM, Woods CW, Hegarty BC, Bradley JM. Parasit Vectors. 2010 Apr 8;3(1):29. 05-3-29.	

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			6) Maggi RG, Ericson M, Mascarelli PE, Bradley JM, Breitschwerdt EB. Parasit Vectors. 2013 Apr 15;6:101. 7) Hildebrandt, A, Gray J S, Hunfeld, K-P "Human Babesiosis in Europe: what clinicians need to know" Infection DOI 10.1007/s15010-013-0526-8 8) Herwaldt BL, Linden JV, Bosserman E, Young C, Olkowska D, Wilson M. Transfusion-associated babesiosis in the United States: a description of cases. Ann Intern Med. 2011;155: 509–19. 9) Leiby DA. Transfusion-transmitted Babesia spp.: bull's-eye on Babesia microti. Clin Microbiol Rev. 2011;24:14–28. 10) Matsui T, Inoue R, Kajimoto K, Tamekane A, Okamura A, Katayama Y, Shimoyama M, Chihara K, Saito-Ito A, Tsuji M. First documentation of transfusion-associated babesiosis in Japan. Rinsho Ketsueki. 2000;41:628–34 11) Hildebrandt A, Hunfeld KP, Baier M, Krumbholz A, Sachse S, Lorenzen T, Kiehntopf M, Fricke HJ, Straube E. First confirmed autochthonous case of human Babesia microti infection in Europe. Eur J Clin Microbiol Infect Dis. 2007;26:595–601.	
Healthcare	Gener	Gen	The Healthcare Infection Society has received no comments on this consultation	Thank you for your comment.

Lyme disease

Consultation on draft scope
Stakeholder comments table

17 March – 14 April 2016

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Stakeholder	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Infection Society (HIS)	al	eral		
Royal College of Genera Practitioners (RCGP)	General	General	The draft scope is an excellent working document and covers the essential areas and difficulties. (PS) and points 1-5 in the first page all seem reasonable. (MJ)	Thank you for your comment.
Royal College of Genera Practitioners (RCGP)	General	General	Overall there seems to be an increasing awareness amongst the population of this condition and yet a great deal of uncertainty amongst non-specialist clinicians as to how to diagnose and treat. Therefore the RCGP feels that this guideline is much needed. The scope seems appropriate and focussed. (MJ)	Thank you for your comment.

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