SUBMISSION BY AUSTRALIAN CHRONIC INFECTIOUS AND INFLAMMATORY DISEASE SOCIETY (ACIIDS) IN RELATION TO CONSULTATION ON COMPLEMENTARY AND UNCONVENTIONAL MEDICINE AND EMERGING TREATMENTS

June 3 2019

1. INTRODUCTION AND SUMMARY

ACIIDS is an organisation of Australian doctors, primarily general practitioners, with an interest in chronic infectious and inflammatory diseases. Most ACIIDS members work in the field of integrative medicine.

Members of ACIIDS were invited to give expert evidence at the Senate inquiry into Lyme-like illness in Australia and the parliamentary inquiry into mould-induced illness.

This submission provides responses to the questions asked by the Medical Board of Australia ("the Board"), and comments on other specific issues relevant to the discussion paper.

The opinions of ACIIDS members in regard to the proposed new guidelines can be summarised as follows:

- No additional regulation of doctors practising complementary medicine is required. ACIIDS prefers Option 1.

- There is no justification for the proposed new guidelines, as there is no evidence that patients of integrative GPs are more likely to suffer harm as a result of their medical treatment than the patients of other GPs.

- All GPs should be subject to the same guidelines.

- The proposed new guidelines constitute discrimination against GPs who practice integrative medicine.

- Increased regulation of integrative medicine will deter GPs from entering the field of integrative medicine. This would be to the detriment of the Australian public.

- ACIIDS is concerned that the proposed new guidelines might represent the commencement of a campaign to prevent doctors from practising integrative medicine. This would restrict the right of the public to have access to the health care of their choice.

This submission is accompanied by six attachments.

2. THE VALUABLE ROLE OF INTEGRATIVE MEDICINE

Integrative GPs fulfil a valuable role in the Australian medical landscape; Australian patients are increasingly seeking out integrative GPs for a variety of reasons.

Many patients have a philosophical interest in alternatives to pharmaceutical management of illness. Integrative doctors, due to their extensive training, are able to determine when complementary therapies are safe and appropriate and when pharmaceutical management is necessary. This role ensures safety for patients who do not trust orthodox doctors and where less qualified naturopaths may not recognise real risk and cannot access pharmaceutical treatments.

Another common reason many patients consult integrative GPs is because they suffer from chronic illness and have not received a diagnosis or have had treatment which has been ineffective or caused excessive side effects. These patients deserve the right of freedom of choice to consult with doctors with experience in integrative medicine who can offer a wider range of evidence-based treatment options, often with significantly superior clinical outcomes.

Integrative GPs are amongst the most highly educated of GPs, and work from a broader knowledge base than most GPs. They are constantly improving their skills and enhancing their knowledge base. It is not uncommon for integrative GPs to attend three or four medical conferences in a year, as well as to maintain a regular schedule of reading and online webinars. This is a stark contrast to most other GPs, who only do the bare minimum of activities necessary to receive their CME points. Integrative doctors are involved in a high level of peer interaction and review.

Integrative medicine should be encouraged, fostered and supported, as a new speciality which brings a high level of expertise to bear in improving patient management and outcomes.

3. RESPONSE TO QUESTION 1.

We do not agree with the proposed term “complementary and unconventional medicine and emerging treatments”.

Complementary medicine, unconventional medicine and emerging treatments are disparate issues and should not be grouped together or covered under the one definition as proposed by the Board.

As the Board has noted, there is no widely accepted definition of complementary medicine; various definitions have been proposed and the Board has mentioned some of these.

ACIIDS considers that the term “complementary medicine” should be reserved to describe treatment modalities primarily used by non-medical health practitioners; examples include acupuncture, herbal medicine and the use of nutritional supplements.

ACIIDS prefers the AIMA definition of integrative medicine proposed by the Australian Integrative Medicine Association (AIMA):

Integrative medicine is a philosophy of health care with a focus on individual patient care. It combines the best of conventional Western medicine with evidence-based complementary medicine and therapies.

Integrative medicine reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals and disciplines to achieve optimal health and healing.

Integrative medicine takes into account the physical, psychological, social and spiritual wellbeing of the person with aim of using the most appropriate, safe and evidence-based treatments available.

Integrative medicine is practiced by doctors who have augmented their training in conventional Western medicine with further training in complementary therapies and more extensive training in conventional Western medicine as relating to chronic disease. Integrative GPs thus work from a wider knowledge base than most GPs.

The Board has noted in the discussion paper that NSW Medical Council of NSW has equated complementary with non-evidence-based care. ACIIDS does not agree with the assertion that complementary medicine is not evidence-based (see 5.3). Furthermore, it is noted by ACIIDS that such a statement is denoting a prejudged bias which is a cause for concern.

Doctors practising integrative medicine may use unconventional treatments if they are known to be safe; unconventional treatments are used from time to time in most medical specialties.

ACIIDS is puzzled by the Board's focus on emerging treatments. Emerging treatments are a feature of every medical speciality and should be embraced. There can be no advances in medicine, and innovation will be stifled, if the use of emerging treatments is discouraged.

4. RESPONSE TO QUESTION 2

It is unreasonable to propose a global definition of complementary medicine, unconventional medicine and emerging treatments. As noted above, these issues are disparate and should not be grouped together.

5. RESPONSE TO QUESTION 3

ACIIDS wishes to comment on the following issues identified in the discussion paper:

5.1 HARM

There is no evidence that patients of integrative GPs are more likely to suffer harm as a result of their medical treatment than the patients of other GPs. On the contrary, integrative medical practice is generally much safer than pharmaceutical medical treatment.

ACIIDS is aware that the Board is concerned that the use of integrative medicine might result in harm due to missed opportunities for other forms of potentially more effective treatments. Integrative GPs are, however, because of their training in both conventional and unconventional therapies, ideally placed to ensure that such harm does not occur.

5.2 COMPLEX CASES

In the discussion paper the Board has commented that "There are reports of medical practitioners who are not specialists providing treatment for complex conditions…"

ACIIDS rejects the implication that complex cases should only be managed by specialists.

GPs are better placed than specialists to manage patients with multisystem illness, as most specialists have little expertise outside their own specialty.

Integrative doctors have a broad skill base and extensive experience in seeing patients suffering from complex health problems, are highly skilled at managing these patients, and are willing to provide the long consultations that are often required for the management of complex illness.

5.3 "UNPROVEN" AND "NON-EVIDENCE-BASED" TREATMENTS

The board has used the terms "unproven therapies" and "non-evidenced-based-treatments" in the discussion paper. ACIIDS wishes to comment on these terms.

All therapeutic modalities used by integrative GPs have an evidence base; this evidence base may be high- level, mid-level or low-level. The term "non-evidence-based treatments" thus should not be used in any discussion relating to integrative medicine.

"Unproven therapies" is a nebulous term. ACIIDS rejects any assertion that doctors should only use treatment that have a level 1 evidence base; any such expectation is not based on historical or contemporary precedent.

Many treatments used in mainstream Western medicine do not have a level 1 evidence base.

Doctors should be free to use treatments that are considered unproven as long as the treatments are known to safe and the patients are informed that the treatments are unproven.

Personal clinical experience is a significant and traditional evidence base, important to the advancement of medical practice, and should not be dismissed.

The use of some medicines for "off-label" indications is not uncommon in many medical specialties.

5.4 FINANCIAL REWARDS

Doctors do not work in the field of integrative medicine for financial reward, and generally earn no more than GPs who work in orthodox general practice.

Out-of-pocket expenses for patients seeking help from integrative doctors can be substantial, but this is because of low Medicare rebates. The Medicare Benefits Schedule is weighted in favour of short consultations, with rebates for long consultations being unrealistically low. This translates to greater out of pocket costs for patients attending longer consultations, but little increase in income for doctors providing longer consultations.

ACIIDS favours the introduction of specific item numbers for integrative medicine that reflect the extra training undertaken by integrative GPs as well as the longer consultations generally needed.

5.5 UNACCREDITED LABORATORIES

Integrative GPs sometimes use unaccredited and overseas laboratories for pathology, but this is because many of the investigations required in integrative medicine are not provided by accredited laboratories in Australia.

Some doctors dismiss results from all overseas laboratories, even when those laboratories are accredited in their home countries. This is unreasonable.

Integrative doctors will only use unaccredited and overseas laboratories if those laboratories are known to have good quality control.

5.6 LYME-LIKE ILLNESS IN AUSTRALIA

There is strong evidence that a chronic debilitating illness, similar to Lyme disease, can be acquired from a tick bite in Australia; this evidence is summarised in Attachment 1. The attachment also includes a discussion of important issues relating to the diagnosis and treatment of Lyme disease and Lyme-like illness.

A new species of Borrelia has been identified in Australian ticks. This new species of Borrelia may be the cause of the Lyme-like illness seen in Australia (Attachment 1).

In Australia the doctors with the greatest expertise in the management of tick-borne diseases are GPs.

ACIIDS doctors were invited to give expert evidence to the Senate inquiry into Lyme-like illness in Australia and to contribute to the development of a Clinical Pathway, as commissioned by the Department of Health, to assist patients suffering from debilitating symptom complexes attributed to ticks.

The final report of the Senate inquiry is attached (Attachment 2).

Lyme-like illness in Australia constitutes a public health crisis that needs to be addressed by state and federal authorities. Many of these patients are severely unwell with multisystem disease and are a major drain on medical resources. The economic burden to the community is considerable due to the expense of medical treatment and the fact that many patients are unable to work because of their illness.

GPs and specialists need to be taught how to recognise the illness and refer patients appropriately to doctors experienced in treating the illness. ACIIDS doctors would be pleased to contribute to medical education in this field.

Many patients suffering from this illness have been emotionally traumatised as a result of their contacts with the medical profession and have been incorrectly diagnosed as conversion disorder or somatoform disorder

It is unfortunate that many Australian doctors continue to refuse to consider the possibility of Lyme disease or Lyme-like illness in patients with chronic illness when the patients have travelled to countries where Lyme disease is endemic.

It is also unfortunate, and a disservice to patients, that many doctors are unwilling to treat this illness because of a well-founded fear of punitive action by regulatory authorities.

ACIIDS believes that doctors with expertise and experience in managing patients with Lyme-like illness are required to optimally differentiate those patients suffering from this condition from those patients suffering from other illnesses.

Attachments 3,4,5 and 6 relate to the issues of Lyme disease and Lyme-like illness and are referred to in Attachment 1.

6. RESPONSE TO QUESTION 4

ACIIDS does not have concerns with the practice of integrative medicine.

7. RESPONSE TO QUESTION 5

Safeguards are necessary for every patient who sees a doctor. ACIIDS believes the current guidelines are sufficient to ensure the safety of the public. No additional safeguards are necessary for patients who seek help from integrative GPs.

8. RESPONSE TO QUESTION 6

The current regulation is adequate.

9. RESPONSE TO QUESTION 7

ACIIDS considers that additional guidelines for integrative GPs are unnecessary.

Option 2 would unfairly create an administrative burden for integrative GPs not shared by other GPs. This would increase costs to the patient and limit the patient's choice of doctor.

10. RESPONSE TO QUESTION 8

ACIIDS considers that additional guidelines for integrative GPs are unnecessary.

11. RESPONSE TO QUESTION 9

ACIIDS considers that the proposed new guidelines should be discarded.

12. RESPONSE TO QUESTION 10

ACIIDS considers that this question is poorly drafted and that the meaning of the question is unclear.

13. RESPONSE TO QUESTION 11

ACIIDS prefers Option 1.

14. COAG PRINCIPLES FOR BEST PRACTICE REGULATION

ACIIDS wishes to comment on the Board's assessment specific to each of the COAG principles expressed in the AHPRA procedures.

A. Whether the proposal is the best option for achieving the proposal's stated purpose and protection of the public.

ACIIDS consider no additional guidelines are required for protection of the public.

ACIIDS contends that the additional guidelines would have the effect of reducing access by the public to integrative doctors with high levels of experience and expertise, and result in

- patients seeking guidance from naturopaths
- internet searches for self-diagnosis and treatments
- travel to overseas countries for potentially dangerous treatments.

These various unintended consequences would combine to significantly lessen protection of the public.

B. Whether the proposal results in an unnecessary restriction of competition among health practitioners.

ACIIDS considers the new guidelines would result in unnecessary restriction of competition.

The proposed new guidelines create a two-tiered system of regulation in which integrative doctors are required to provide patients with a more detailed explanation and discussion of management strategies than is the case with non-integrative doctors. This unequal regulatory system is intrinsically discriminatory and will result in restriction of fair competition among health practitioners.

C. Whether the proposal results in an unnecessary restriction of consumer choice.

It is likely that that the number of doctors practising integrative medicine will be reduced if the proposed new guidelines are instituted. This will result in restriction of consumer choice as it will be more difficult for consumers to see an integrative GP. The right of members of the public to have access to the health care of their choice is paramount.

There are several reasons why it is likely that the number of doctors practising integrative medicine will be reduced if the proposed new guidelines are instituted:

- Some doctors currently practising integrative medicine might depart the field because of the increased regulation, administrative burden and fear of disciplinary action.

- Fewer doctors will enter the field of integrative medicine because of the increased regulation, administrative burden and fear of disciplinary action.

- Some integrative doctors may be prevented from practicing due to disciplinary action.

D. Whether the overall costs of the proposal to members of the public and/or registrants and/or governments are reasonable in relation to the benefits achieved.

The proposed new guidelines would significantly increase the overall direct financial costs to members of the public.

Integrative doctors will be forced to increase their fees due to

- time spent in developing protocols, information brochures and consent forms

- the need for longer consultations in order to communicate the complex requirements of the new guidelines.

Furthermore, we note that if patients with chronic disorders, not resolving with other treatment modalities, remain untreated, the costs to government will increase due to

- ongoing social security payments

- ongoing health care costs

- loss of income-associated taxation revenue.

Non-financial costs to patients may also increase as a result of patients not being able to have access to their health care of choice.

E. Whether the proposal's requirements are clearly stated using "plain language" to reduce uncertainty, enable the public to understand the requirements, and enable understanding and compliance by registrants.

The proposals are clearly stated.

F. Whether the board has procedures in place to ensure that the proposed registration standard, code or guideline remains relevant and effective over time.

The draft guidelines should be discarded.

15. CONCLUSIONS

The Medical Board of Australia discussion paper concerning proposed new guidelines in relation to “complementary and unconventional medicine and emerging treatments” is a deeply flawed document and the appropriate action is to discard the option 2 and continue with the current guidelines, as per option 1.

The rationale for the proposed new guidelines refers to a small number of anecdotal cases. There is no reference to any systematic studies showing any overall increase risk to the public from the areas of concern, nor comparison with the risks of other modalities of practice. Integrative medicine is very safe when compared with pharmaceutical treatments. There is no argument as to why the current guidelines do not adequately deal with the areas of concern.

The areas of concern, “complementary and unconventional medicine and emerging treatments” are too diverse in nature to be considered together and too ill-defined to be practically meaningful. The lack of a clear definition of “complementary and unconventional medicine and emerging treatments” creates the risk of arbitrary interpretation on an ad hoc case by case basis that is a denial of natural justice and open for abuse.

The proposed new guidelines would reduce the ability of patients to have access to the medical treatment of their choice, increase costs, and of significant concern, potentially result in patients seeking treatment from unqualified practitioners or overseas clinics. This will reduce patient safety and increase risk to the public.

16. ATTACHMENTS

Attachment 1	Lyme-like illness in Australia	20 pages
Attachment 2	The Senate Community Affairs References Committee Final Report – Senate Inquiry into Lyme-Like Illness in Aust. Nov 2016	123 pages
Attachment 3	International Lyme and Associated Diseases Society Evidence-based guidelines for the management of Lyme disease	13 pages
Attachment 4	Expert Review of Anti-infective Therapy 2014 Evidence assessments and guideline recommendations in Lyme disease	34 pages
Attachment 5	Counterpoint: Long-term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease Raphael Stricker	9 pages
Attachment 6	Human Tick Borne Diseases in Australia Dehhagi,M;Panahi,H;Holmes,E;Hudson,B;Schloeffel,R;Guillemin,G. Frontiers in Cellular and Infection Microbiology. 2019.	7 pages

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AUSTRALIAN CHRONIC INFECTIOUS AND INFLAMMATORY DISEASE SOCIETY

ATTACHMENT 1 June 3 2019

LYME-LIKE ILNESS IN AUSTRALIA

Terminology

1. Lyme disease is caused by a bacterium known as Borrelia, a spirochaete. There are several strains of Borrelia; in North America Lyme disease is primarily caused by Borrelia burgdorferi (B.burgdorferi).

2. Borreliosis is a term which means infection with Borrelia bacteria.

3. When Borrelia infection is acquired overseas, the illness is generally described as Lyme disease. When Borrelia infection is acquired in Australia, it is more appropriate to describe the illness as borreliosis.

4. Persistent borreliosis is defined as a case of borreliosis in which symptoms have persisted for more than six months.

Lyme-like Illness in Australia – The Evidence

5. There is strong evidence that a Lyme-like illness can be acquired from a tick bite in Australia.

6. This issue was the subject of a recent Senate inquiry.

7. The preponderance of evidence suggests that Borrelia is the primary causative organism responsible for this illness.

8. The evidence for a Lyme-like illness in Australia is as follows:

   a) Many people are developing a chronic debilitating illness after a tick bite in Australia.

   b) The clinical features of this illness are similar to the clinical features of borreliosis (Lyme disease).

9. Many of these patients have positive blood tests for tick-borne infections such as Borrelia, Rickettsia, babesiosis, bartonellosis, ehrlichisosis and anaplasmosis.

10. Most of these patients respond to treatment with the same antibiotics that are used to treat borreliosis. This suggests that the illness is a bacterial infection. The antibiotic treatment often needs to be continued for an extended period.

11. The members of ACIIDS have treated over 5000 patients suffering from this illness. Most of these patients have positive blood tests for Borrelia at Australian and/or overseas laboratories. The overseas laboratories are fully accredited in their respective countries.

12. The members of ACIIDS have treated approximately 300 patients with positive blood tests for Borrelia who have never left Australia.

13. The first cases of Lyme disease being acquired in Australia were reported in the Medical Journal of Australia in 1982 (27) and 1986 (28).

14. A study that found the bacteria that cause Lyme disease had been found in Australian ticks was reported in the Medical Journal of Australia in 1991 (29).

15. Russell and Dogget in 1994 studied Australian ticks; although they did not find B. burgdorferi they found “spirochetal objects” which may have been fragments of a different species of Borrelia (30).

16. Hudson in 1998 reported in the Medical Journal of Australia a case in which he had cultured (found definite evidence of) Borrelia in the skin biopsy of a patient. The patient had travelled to Europe, but the clinical details indicated that the infection may have been acquired in Australia (31).

17. Borrelia burgdorferi, the bacterium that causes Lyme disease, was found in skin biopsies of two patients bitten by ticks in Australia in 2014 (32).

18. Irwin in 2015 and 2016 has identified two new species of Borrelia in Australian ticks (33,34,35).

19. Irwin in 2015 identified new species of Anaplasma and Ehrlichia in Australian ticks; bacteria of these classes commonly cause co-infections seen in Lyme disease patients in the USA. He also identified the new species Ca. Neoehrlichia. It is unclear if these new species are responsible for illness in humans (36).

20. Mayne in 2014 described a series of 500 confirmed cases of borreliosis, 89 of whom had never left Australia (37).

21. There have been numerous cases in Australia of patients who have developed an erythema migrans rash, as seen in Lyme disease in the United States, after a tick bite, and then developed a Lyme-like illness.

22. ACIIDS acknowledges that Borrelia burgdorferi, the species of Borrelia that causes Lyme disease in North America, has not been identified in Australian ticks, with the exception of the skin biopsy study in 2014 (32).

23. It appears likely that the Lyme-like illness sometimes seen after a tick bite in Australia is caused by a species of Borrelia unique to Australia, possibly one of the new species identified by Irwin.

24. This issue of pathogens harboured by Australian ticks is the subject of ongoing research by Dr Irwin at Murdoch University, the Tick Borne Diseases Unit at Sydney University and the Karl McManus Foundation.

25. It is possible that there are many as yet undiscovered pathogens in Australian ticks that are contributing to illness in humans.

26. In 2018 year a scientific advisory committee (SAC) was established to further investigate the issue of Lyme-like illness in Australia. The committee is comprised of esteemed researchers and clinicians. The members are as follows:

Chairman - Gilles Guillemin, Professor of Neurosciences, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Head of the Motor Neurone Disease laboratory; Dr Julian A. Barden, Director of Research, Biosceptre International Ltd, Australia; Dr John Duley, expert in diseases of metabolism, and individual responses to drugs (pharmacogenetics); Dr Bernie Hudson, Head of Infectious Diseases, Royal North Shore Hospital;Dr Micheline Kergoat, Head of Biology at Metabrain Research, France; Dr Lance Sanders, BSc, Hons, PhD, MASM; Dr Richard Schloeffel, OAM, Pymble Grove Health Centre, co-author on Australian recommendation of protocols for Lyme disease; Dr Neil Spector, is the Sandra Coates Associate Professor of Medicine, an Associate Professor of Cancer Biology and Pharmacology and the Associate Director of Developmental Therapeutics for the Duke Cancer Institute, Duke University.

27. Dr Richard Schloeffel et al have published an excellent overview of human tick-borne diseases in Australia (Attachment 6).

Seronegativity

28. Laboratory testing for borreliosis is complex and controversial, and can be unreliable, because of the high incidence of false negative results. False positive results can be seen, but false negative results are much more common than false positive results.

29. The main reason for false negative results is seronegativity; this means that some patients with borreliosis do not have detectable antibodies to Borrelia on a blood test. Negative serology does not exclude a diagnosis of borreliosis.

30. Immune suppression and dysregulation by Borrelia is an important issue, and one of which many clinicians are unaware.

31. There are many references in the scientific literature relating to seronegativity and immune evasion in borreliosis, and the fact the Borrelia is an immunosuppressive organism

32. One particularly pertinent article published in the New England Journal of Medicine concludes that:

33. “…the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against B. burgdorferi...” (23)

34. There are several reasons why seronegativity might occur in borreliosis:

    - Serologic tests may be performed too early (before antibodies are formed); B.burgdorferi may not be present in the blood (it may be in tissues) or may have eluded the immune system by adopting a cell wall-deficient L–form.

    - Antibodies in the patient's blood may be bound into immune complexes.

    - Antibodies may not be present in the patient's blood for other reasons (e.g., the use of antibiotics early in the course of the disease or systemic steroid therapy may abrogate the immune response to B. burgdorferi, and late in the disease, antibody levels may fall to very low levels) (24).

    Recent studies have shown that tick saliva carries immunosuppressive substances that enable tick-borne agents to invade tissues while paralysing the local immune response.

35. It has been the observation of ILADS and ACIIDS doctors that patients suffering from borreliosis sometimes do not become seropositive (ie develop antibodies) until after they have been commenced on treatment, and that IgM antibodies may persist for months or years.

36. In 2013, Virginia (USA) Governor Bob McDonnell signed the Lyme Disease Testing Disclosure Act, which mandates that all physicians who suspect and test patients for Lyme disease must disclose that a negative test result does not necessarily mean that the patient does not have Lyme disease.

The Two-Tier Protocol

37. Internationally there are two schools of thought regarding diagnosis and treatment of Lyme disease/borreliosis - the opinions promulgated by the Infectious Disease Society of America (IDSA) and Centres for Disease Control (CDC), and the opinions promulgated by ILADS.

38. The views of ACIIDS members are in line with those of ILADS; the views of Australian infectious disease specialists are largely aligned with IDSA.

39. With regard to diagnosis of Lyme disease/ borreliosis, the main difference of opinion between IDSA and ILADS is in relation to the so-called "two-tier" test.

40. IDSA and CDC maintain that the so-called “two-tier” protocol should be used for the laboratory diagnosis of borreliosis. This protocol involves firstly performing the ELISA serology test; if the ELISA test is positive then the Western Blot or Immunoblot serology test is performed. According to this protocol, the diagnosis of borreliosis can only be made if both the ELISA and Western Blot/Immunoblot are positive.

41. The two-tier protocol for testing for Borrelia is not universally accepted. This protocol was established for disease surveillance, but pathologists and infectious disease specialists have misused the surveillance criteria for diagnosis.

42. The CDC has cautioned that the surveillance case definition was developed for reporting of Lyme disease, and that it is not appropriate for clinical diagnosis (25).

43. The CDC further notes that it is inappropriate to use surveillance case definitions “for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement” (25).

44. ILADS and ACIIDS consider that the two-tier protocol should be abandoned because of the high incidence of seronegativity and the poor sensitivity of the ELISA test. The ELISA is not sensitive enough to detect most cases of borreliosis.

45. The following is from the 2004 ILADS guidelines (Attachment 3):

46. “Treatment decisions should not be based routinely or exclusively on laboratory findings. The two-tier diagnostic criteria, requiring both a positive ELISA and Western Blot, lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated. These diagnostic criteria were intended to improve the specificity of tests to aid in identifying well-defined Lyme disease cases for research studies. Though arbitrarily chosen, these criteria have been used as rigid diagnostic benchmarks that have prevented individuals with Lyme disease from obtaining treatment. Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or unresolved infection”.

47. There is a large body of scientific opinion that the first-line laboratory test for borreliosis should be the Western Blot or Immunoblot. This is the position held by ILADS and ACIIDS.

48. Recent studies by the group responsible for the Lyme disease proficiency testing for the College of American Pathologists came to the conclusion that the currently available ELISA tests do not have adequate sensitivity to meet the two-tiered approach recommended by the CDC for surveillance (26)

Treatment of Acute Lyme Disease

49. IDSA and ILADS are in agreement that the treatment for acute Lyme disease in adults is a four week course of doxycycline. Other antibiotics are available for children under the age of eight.

Persistent Borreliosis

50. Some patients who acquire borreliosis but do not receive an initial course of treatment, or who fail to respond to an initial course of treatment, develop a persistent form of the illness, known as persistent borreliosis.

51. Persistent borreliosis is defined as a case of borreliosis in which symptoms have persisted more than six months.

52. Persistent borreliosis is a major public health issue, causing widespread illness in the community - in some cases profound disability – and a drain on medical, family and public resources.

53. There is considerable scientific evidence that persistence of symptoms in this illness is due to ongoing active infection.

54. Several studies have identified bacteria that have been labelled “persisters”; these are Borrelia bacteria that have persisted after an initial course of treatment (38,39,40,41,42,43,44,45,46,47,48,49,50,51,52).

55. Some infectious disease specialists deny the existence of chronic Lyme disease or persistent borreliosis, and often ascribe a psychiatric aetiology to patients who have persistent symptoms after an episode of acute Lyme disease.

56. Conspicuously, IDSA fail to address the issue of the patient with Lyme disease who has inadequate initial treatment, or no treatment at all. It would be unsurprising if such patients developed an ongoing or persistent infection.

Treatment of Persistent Borreliosis

57. The treatments used by ACIIDS members for persistent borreliosis base are based on the peer-reviewed literature and recommendations of internationally respected authorities including ILADS (Attachments 3,4), the German Borreliosis Society and infectious disease specialist Dr Richard Horowitz.

58. Dr Horowitz is the world's leading authority on Lyme disease; he has advised many governments on the management of Lyme disease epidemics. His treatment protocols are outlined in appendix A of his book "Why Can't I Get Better?" (St Martins Press 2017).

59. The members of ILADS and ACIIDS have found from clinical experience that patients suffering from persistent borreliosis often require extended courses of antibiotics to recover from their illness.

60. In persistent borreliosis antibiotic treatment is continued until symptoms have resolved, as there is no reliable laboratory test that can be used to determine when treatment should be ceased.

61. Duration of treatment depends in part on the length of time the patient has suffered from the illness.

62. In most cases treatment is with oral antibiotics, but IV antibiotics are sometimes required.

Pleomorphism and Combination Treatment

63. It is generally necessary to use a combination of antibiotics to ensure that all three forms of Borrelia, and any associated co-infections, are treated.

64. Borrelia is a pleomorphic organism, with three different morphological forms. There are many studies supporting the use of a combination of antibiotics to treat the three different morphological forms of Borrelia

65. Combination antibiotic therapy is explored in depth by Dr Richard Horowitz and is also explained in the guidelines the German Borreliosis Society.

66. The following antibiotics are used for the three forms of Borrelia:

    a) For the cell-wall form of Borrelia (the spirochaete): Penicillins and cephalosporins

    b) For the cell-wall deficient ("L") form of Borrelia: Doxycycline, minocycline, macrolides

    c) For the "cystic" or "round-bodied" form of Borrelia: Tinidazole, metronidazole.

67. Plaquenil is also frequently used. As well as being a treatment for babesiosis, one of the common co-infections, Plaquenil increases the efficacy of macrolides and tetracyclines.

Long – Term Antibiotics

68. There is considerable evidence that a four-week course of antibiotics is inadequate for many cases of Lyme disease/borreliosis.

69. Persistent symptoms have been noted in 25%-80% of pts with Lyme disease after 2-4 weeks of antibiotic treatment (Attachment 5). Infection that was determined to be persistent on the basis of either culture or PCR evidence has been documented in up to 40% of patients following receipt of the "adequate" antibiotic treatment recommended by the IDSA (Attachment 5). 34% of a population-based, retrospective cohort were ill an average of 6.2 years after antibiotic Rx (Attachment 4). 62% of a retrospective evaluation of 215 Lyme disease pts from Westchester County, NY, remained ill an average of 3.2 years after antibiotic treatment (attachment 4).

70. A number of studies attest to the need for, safety of, and efficacy of, long-term antibiotics (including IV antibiotics) in the treatment of persistent borreliosis. These studies are summarized in Stricker's paper (Attachment 5).

71. There is a need for further research to determine the optimal duration of antibiotic treatment in persistent borreliosis.

72. Patients receiving long-term antibiotic treatment are closely monitored and any side-effects of antibiotic treatment are dealt with in the early stages before they become problematic.

73. It is considered that the risk of not treating this illness is greater than the risk of potential adverse reactions to treatment.

74. Persistent borreliosis is not the only condition that requires treatment with long-term antibiotics. Other conditions include
    - osteomyelitis
    - leprosy (24 months antibiotics)
    - drug-susceptible tuberculosis (6-9 months antibiotics)
    - multidrug-resistant tuberculosis (18-24 months antibiotics)
    - acne (6-18 months antibiotics)
    - prophylaxis for recurrent urinary tract infections
    - Q fever endocarditis (36 months antibiotics)
    - Reiter's syndrome
    - Chronic Q fever
    - prophylaxis of at-risk populations such as asplenic children and young children with sickle cell disease

Parenteral Antibiotics

75. Parenteral antibiotics are used
    - in patients who have not responded to twelve months of oral antibiotics.
    - in patients who cannot tolerate oral antibiotics.
    - in cases where there is severe neurological involvement.

76. The most commonly used intravenous antibiotic for persistent borreliosis is ceftriaxone. Intravenous azithromycin and metronidazole can also be useful.

77. Intramuscular benzathine penicillin (Bicillin) can be used in patients who require parenteral antibiotics but in whom the administration of intravenous antibiotics is logistically difficult.

Biofilm

78. Biofilm is another factor that needs to be taken into consideration in the treatment of persistent borreliosis (58,59,60,61,62,63,64,65,66,67).

79. A biofilm is a structured community of micro-organisms within a self-developed polymeric matrix and adherent to a living or inert surface; biofilm provides a physical barrier that protects bacteria from antibiotics and the immune system.

80. Biofilm reduces the efficacy of antibiotics and is one of the reasons that extended course of antibiotics are required to treat persistent borreliosis.

81. Doctors treating persistent borreliosis uses a variety of protocols to reduce biofilm.

82. Biofilm is discussed in Appendix A of Dr Horowitz’s book.

Treatment of Borreliosis in Australia

83. In Australia most cases of borreliosis and co-infections in Australia are treated, and treated well, by general practitioners.

The Senate Inquiry

84. Members of ACIIDS were invited to give expert evidence to the recent Australian Senate inquiry into “Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness in many Australian patients”.

85. The final report of the Senate inquiry is attached (Attachment 2).

Sexual Transmission of Borreliosis

86. There is evidence that borreliosis can be transmitted by sexual contact (68, 69).

87. Many cases of sexual transmission have been documented by ILADS and ACIIDS doctors.

Transplacental Transmission of Borreliosis

88. Transplacental transmission is well documented, and confirmed by CDC. A pregnant woman suffering from Borrelia infection can pass on the infection to the foetus (70, 71, 72, 73).

Asymptomatic Borrelia Infection

89. Asymptomatic Borrelia infection is well documented (74, 75).

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The International Lyme and Associated Diseases Society

Evidence-based guidelines for the management of Lyme disease

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Summary & disclaimer

These guidelines represent an evidence-based review of Lyme and associated tickborne diseases by the International Lyme and Associated Diseases Society (ILADS). Although the guidelines present evidence-based approaches to the diagnosis and treatment of Lyme and associated tickborne diseases, they were not intended to be a standard of medical care. Physicians must use their own judgment based on a thorough review of all available clinical information and the Lyme disease literature to decide on the best course of treatment for an individual patient.

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Table of contents

Section I: Introduction to guidelines

This report, completed in November 2003, is intended to serve as a resource for physicians, public health officials and organizations involved in the evaluation and treatment of Lyme disease.

1. International Lyme and Associated Diseases Society (ILADS)

ILADS is an interdisciplinary organization of health science professionals established in 1999 to accomplish the following objectives:

- Analyze the medical literature, position statements and practice parameters related to Lyme and associated diseases
- Improve the management of these diseases through evaluation of established and innovative therapies
- Educate a broad range of healthcare providers and serve as an effective advocate for clinicians seeking cost-effective state-of-the-art treatment regimens

ILADS identified the need for new and expanded guidelines for the diagnosis and treatment of Lyme and associated diseases. In 2001, a working party was formed to evaluate current practices and to encourage new standards of care. This report, completed in November 2003, is intended to serve as a resource for physicians, public health officials and organizations involved in the evaluation and treatment of Lyme disease.

2. Chronic Lyme disease: a growing epidemic

The Centers for Disease Control and Prevention (CDC) consider Lyme disease the fastest growing vector-borne disease in the USA. By conservative estimate, the number of new Lyme disease infections per year may be ten times higher than the 17,730 cases reported to the CDC during 2000 [1,2].

The prevalence of chronic Lyme disease ranges from 34% in a population-based, retrospective cohort study [3] to 62% in a specialty clinic located in an area endemic for Lyme disease [4]. Clinic patients presented with arthralgia, arthritis, cardiac and neurologic symptoms [4].

A widening array of chronic presentations is associated with the Lyme spirochete, *Borrelia burgdorferi*. There are great challenges in determining optimal cost-effective means for appropriate diagnosis, clinical management and public health control of Lyme disease throughout the world. Additional problems include the identification and management of tickborne coinfections including *Ehrlichia*, *Babesia* and *Bartonella* species [5].

3. The need for new guidelines

Guidelines of the Infectious Disease Society of America (IDSA) fall short of meeting the needs for diagnosis and treatment of individuals with chronic Lyme disease [6]. The latest IDSA Guidelines (2000) fail to take into account the compelling, peer-reviewed, published evidence confirming persistent, recurrent and refractory Lyme disease and, in fact, deny its existence [6].

The IDSA's symptomatic approaches to Lyme disease are limited and exclude many individuals with persisting clinical and laboratory evidence of active *B. burgdorferi* infection. In addition, physicians treating individuals with Lyme and other tick-borne infections recognize the need for new guidelines to better serve the patient population [6].

Previous guidelines for management of Lyme disease have been published in the *New England Journal of Medicine* in 1990 by Rahn [7]; in *Conn's Current Therapy* in 1997 by Burrascano and in 1998 by Steere [8,9]; in Burrascano's Guidelines on the ILADS website (www.ilads.org); and in the *Journal of Infectious Diseases* by Wormser and colleagues in 2000 [6]. The ILADS Guidelines expand on these protocols using the evidence-based approach and Cochrane methodology employed by the IDSA [6,10].

Our goal is to present practitioners with practical and defensible guidelines for treating all individuals with Lyme disease including those with persistent, recurrent and relapsing symptoms of *B. burgdorferi* infection.

The ILADS Guidelines focus on which patients to evaluate, what tests to order, what antibiotics to use and what steps to take to ensure that concerns over antibiotic use are addressed.

The ILADS Working Group that formulated these guidelines included primary care clinicians, researchers, community healthcare providers and patient advocates. In developing these treatment guidelines, the group considered factors such as incidence of Lyme disease; severity of disease in terms of morbidity; comorbidities and determinants of when Lyme disease is most likely to become chronic; feasibility, efficacy and cost of antibiotic treatment; impact of antibiotic therapy on quality of life, including adverse drug events; and the potential for drug resistance to develop.

Because of the complexity and variability of Lyme disease symptoms, the guidelines are flexible. Treatment depends on the severity of each case, the patient's response to therapy and the physician's own clinical judgment.

4. A problem of definitions

Lyme disease was initially investigated by CDC epidemiologists focusing on erythema migrans, heart block, meningitis and arthritis. The ELISA test and later, the western blot, were introduced for seroepidemiologic studies. Chronic, persistent, recurrent and refractory Lyme disease were not included in these studies; consequently cases of chronic Lyme disease still go unrecognized.

For the purpose of the ILADS guidelines, 'chronic Lyme disease' is inclusive of persistent symptomatologies including fatigue, cognitive dysfunction, headaches, sleep disturbance and other neurologic features, such as demyelinating disease, peripheral neuropathy and sometimes motor neuron disease; neuropsychiatric presentations; cardiac presentations including electrical conduction delays and dilated cardiomyopathy; and musculoskeletal problems. Symptoms may continue despite 30 days of treatment (persistent Lyme disease). The patient may relapse in the absence of another tickbite or erythema migrans rash (recurrent Lyme disease), or be poorly responsive to antibiotic treatment (refractory Lyme disease).

By these definitions, almost two-thirds of 215 Lyme disease patients in a recent retrospective cohort from an endemic region had chronic Lyme disease [4]. Case definitions for Lyme disease have evolved and will continue to develop as a better understanding of chronic Lyme disease emerges to shape a common lexicon.

5. Competency and training

The appropriateness of treatment hinges on the clinician's experience in treating Lyme disease. Competence requires diagnostic and treatment skills heretofore not offered in medical school or postresidency training.

Clinicians more practiced in treating Lyme disease achieve better outcomes and encounter fewer complications because of an enhanced ability to interpret clinical data, the prompt prescription of antibiotics and the use of measures to reduce adverse events, e.g., employing acidophilus to replace normal intestinal flora that is depleted by antibiotics.

6. The increasing role of primary care

The primary care physician has an important role as the first and at times, the principal medical contact for the person with Lyme disease.

Primary care physicians focus on the resolution of symptoms, monitoring for side effects, maintenance or improvement of functional status and prevention of recurrent symptoms.

These guidelines incorporate the evidence used by primary care physicians for the care of patients with Lyme disease.

7. Highlights of guidelines

- Since there is currently no definitive test for Lyme disease, laboratory results should not be used to exclude an individual from treatment
- Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physician's judgment
- The early use of antibiotics can prevent persistent, recurrent and refractory Lyme disease
- The duration of therapy should be guided by clinical response, rather than by an arbitrary (i.e., 30 day) treatment course
- The practice of stopping antibiotics to allow for delayed recovery is not recommended for persistent Lyme disease. In these cases, it is reasonable to continue treatment for several months after clinical and laboratory abnormalities have begun to resolve and symptoms have disappeared

Section II: New presentatons

Lyme disease was first described in 1977 as 'Lyme arthritis' among patients initially thought to have arthritis or juvenile rheumatoid arthritis [11]. It was later renamed 'Lyme disease' following recognition of a combination of cardiac, neurologic and rheumatologic presentations, including heart block, meningitis and Bell's palsy. For more than 10 years, variable symptomatic conditions have been recognized including encephalopathy and neuropsychiatric presentations.

8. Symptomatic presentation

Variable symptomatic presentations have been increasingly documented in Lyme disease, with the best example being encephalopathy [12]. Encephalopathic presentations were described in an initial cohort of 27 patients as a symptom complex including memory loss (81%), fatigue (74%), headache (48%), depression (37%), sleep disturbance (30%) and irritability (26%), often without objective markers [12]. Only two of the 27 patients presented with objective findings on lumbar puncture: one had pleocytosis (seven cells) and a second had an antibody index of greater than one [12].

Neuropsychiatric presentations in acute and chronic Lyme disease have been increasingly recognized and can include depression, anxiety and rage [13]. These are presumably related to persistent infection and are potentially reversible with antibiotics. Neuropsychiatric symptoms may reflect additional psychosocial processes including the stress of coping with a chronic illness.

Asch and colleagues found that more than half of 215 patients in a Lyme-endemic region had symptomatic presentations of chronic Lyme disease [4]. The patients presented with chronic fatigue, headaches and joint pain (but not headaches alone) in this retrospective cohort study.

9. Symptoms of Lyme disease

- Fatigue
- Low grade fevers, 'hot flashes' or chills
- Night sweats
- Sore throat
- Swollen glands
- Stiff neck
- Migrating arthralgias, stiffness and, less commonly, frank arthritis
- Myalgia
- Chest pain and palpitations
- Abdominal pain, nausea
- Diarrhea
- Sleep disturbance
- Poor concentration and memory loss
- Irritability and mood swings
- Depression
- Back pain
- Blurred vision and eye pain
- Jaw pain
- Testicular/pelvic pain
- Tinnitus
- Vertigo
- Cranial nerve disturbance (facial numbness, pain, tingling, palsy or optic neuritis)
- Headaches
- 'Lightheadedness'
- Dizziness

10. Increasing evidence of persistent infection

Persistent, recurrent and refractory presentations from ongoing infection are the most feared of the long-term complications of Lyme disease.

Laboratory culture of *B. burgdorferi* has documented persistent infection in chronic Lyme disease patients, but the yields are quite low by current methods [14]. In fact, there is no reliable, commercially available culture assay that can confirm the eradication of the organism. Using experimental techniques, however, *B. burgdorferi* has been detected in virtually every organ in the body, and the spirochete has a strong predilection for the central nervous system. Oral antibiotic levels in the central nervous system are low, and this fact may necessitate the addition of drugs with good penetration across the blood–brain barrier [15], such as intravenous ceftriaxone or cefotaxime.

Most studies demonstrate a beneficial effect of antibiotics in the management of chronic Lyme disease, but the extent of optimal treatment is still uncertain [4,12,13,16–22]. Recent clinical trials questioning the benefits of antibiotics have been criticized for enrolling patients with refractory Lyme disease who were sick for a mean of 4.7 years despite an average of three courses of antibiotics, and for relying only on one treatment protocol (1 month of i.v. ceftriaxone followed by 2 months of low-dose oral doxycycline) [23]. In view of these methodological problems, persistent infection remains a continued concern for physicians.

11. Disappointing results of symptomatic treatment

A theoretical immune mechanism has been proposed to explain persistent symptoms in chronic Lyme disease, but no clinical or laboratory test can confirm this theory. The immune mechanism theory is based on physiological events (often in the form of cascades) that are not reversed by simply killing the infecting organism.

The presentation of chronic Lyme disease can be identical to that of other multisystem disorders, including systemic lupus erythematosus, rheumatoid arthritis and fibromyalgia. In the seminal article describing fibromyalgia in a Lyme disease population, antibiotic treatment failure and relapse of symptoms were considered to be proof of the absence of *B. burgdorferi* infection, and persistent symptoms were assumed to be due to postinfectious sequelae [24]. However, the failure of short-course (2–4 week) antibiotic treatment in 14 (94%) of 15 fibromyalgia patients is consistent with a persistent, inadequately treated infection with *B. burgdorferi* [24].

The increasing successes of repeated and prolonged antibiotic treatment in chronic Lyme disease are more consistent with a persistent infection mechanism.

12. Severity of chronic Lyme disease

For patients with chronic Lyme disease, the quality of life has been evaluated in a clinical trial sponsored by the National Institutes of Health (NIH) using a standardized questionnaire [23]. The quality of life of the 107 individuals with chronic Lyme disease was worse than that of patients with Type 2 diabetes or a recent heart attack, and equivalent to that of patients with congestive heart failure or osteoarthritis. Moreover, the average Lyme disease duration of 4.7 years in subjects enrolling in the study emphasized the chronic nature of the condition. Finally, the failure of 1 month of i.v. ceftriaxone followed by 2 months of oral doxycycline delineated the potential for a poor outcome in chronic Lyme disease [25].

Section III: Diagnostic concerns

The most important method for preventing chronic Lyme disease is recognition of the early manifestations of the disease.

13. Atypical early presentations

Early Lyme disease classically presents with a single erythema migrans (EM or 'bullseye') rash. The EM rash may be absent in over 50% of Lyme disease cases, however [25]. Patients should be made aware of the significance of a range of rashes beyond the classic EM, including multiple, flat, raised or blistering rashes. Central clearing was absent in over half of a series of EM rashes [26]. Rashes can also mimic other common presentations including a spider bite, ringworm, or cellulitis. One series of eleven EM rashes was misdiagnosed and treated as cellulitis, with all eleven patients showing clinical evidence of Lyme disease progression [27].

Physicians should be aware that fewer than 50% of all Lyme disease patients recall a tickbite [28]. Early Lyme disease should also be considered in an evaluation of 'off-season' onset when flu-like symptoms, fever and chills occur in the summer and fall. Early recognition of atypical early Lyme disease presentation is most likely to occur when the patient has been educated on this topic.

14. New chronic Lyme disease presentations

A detailed history may be helpful for suggesting a diagnosis of chronic Lyme disease. Headache, stiff neck, sleep disturbance and problems with memory and concentration are findings frequently associated with neurologic Lyme disease. Other clues to Lyme disease have been identified, although these have not been consistently present in each patient: numbness and tingling, muscle twitching, photosensitivity, hyperacusis, tinnitus, lightheadedness and depression.

Most patients diagnosed with chronic Lyme disease have an indolent onset and variable course. Neurologic and rheumatologic symptoms are characteristic, and increased severity of symptoms on wakening is common. Neuropsychiatric symptoms alone are more often seen in chronic than acute Lyme disease. Although many studies have found that such clinical features are often not unique to Lyme disease, the striking association of musculoskeletal and neuropsychiatric symptoms, the variability of these symptoms and their recurrent nature may support a diagnosis of the disease.

15. The limitations of physical findings

A comprehensive physical examination should be performed, with special attention to neurologic, rheumatologic and cardiac symptoms associated with Lyme disease.

Physical findings are nonspecific and often normal, but arthritis, meningitis and Bell's palsy may sometimes be noted. Available data suggest that objective evidence alone is inadequate to make treatment decisions, because a significant number of chronic Lyme disease cases may occur in symptomatic patients without objective features on examination or confirmatory laboratory testing.

Factors other than physical findings, such as a history of potential exposure, known tickbites, rashes or symptoms consistent with the typical multisystem presentation of Lyme disease, must also be considered in determining whether an individual patient is a candidate for antibiotic therapy.

16. Sensitivity limitations of testing

Treatment decisions should not be based routinely or exclusively on laboratory findings [2,25]. The two-tier diagnostic criteria, requiring both a positive ELISA and western blot, lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated [29,30]. These diagnostic criteria were intended to improve the specificity of tests to aid in identifying well-defined Lyme disease cases for research studies [31]. Though arbitrarily chosen, these criteria have been used as rigid diagnostic benchmarks that have prevented individuals with Lyme disease from obtaining treatment. Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection [21].

The CDC considers a western blot positive if at least 5 of 10 IgG bands or 2 of 3 IgM bands are positive [31]. However, other definitions for western blot confirmation have been proposed to improve the test sensitivity [30,32–36]. In fact, several studies showed that sensitivity and specificity for both the IgM and IgG western blot range from 92 to 96% when only two specific bands are positive [34–36].

Lumbar puncture has also been disappointing as a diagnostic test to rule out concomitant central nervous system infection. In Lyme disease, evaluation of cerebrospinal fluid is unreliable for a diagnosis of encephalopathy and neuropathy because of poor sensitivity (see Section II.8). For example, pleocytosis was present in only one of 27 patients (sensitivity 3%) and with only seven cells [12]. The antibody index was positive (>1) in only one of 27 patients (sensitivity 3%) [12]. An index is the ratio between Lyme ELISA antibodies in the spinal fluid and Lyme ELISA antibodies in the serum. The proposed index of 1.3 would be expected to have even worse sensitivity.

Several additional tests for Lyme disease have been evaluated. These include antigen capture, urine antigen and polymerase chain reaction. Each has advantages and disadvantages in terms of convenience, cost, assay standardization, availability and reliability. These tests remain an option to identify people at high risk for persistent, recurrent and refractory Lyme disease but have not been standardized.

17. Seronegative Lyme disease

A patient who has tested seronegative may have a clinical presentation consistent with Lyme disease, especially if there is no evidence to indicate another illness.

Although many individuals do not have confirmatory serologic tests, surveillance studies show that these patients may have a similar risk of developing persistent, recurrent and refractory Lyme disease compared with the seropositive population. A prospective observational study of 1094 patients [21] and the Klempner clinical trials [23] found no difference in measured outcomes (e.g., success of retreatment) among seropositive or seronegative Lyme disease patients.

18. Continued importance of differential diagnosis

The differential diagnosis of Lyme disease requires consideration of both infectious and noninfectious etiologies. Among noninfectious causes are thyroid disease, degenerative arthritis, metabolic disorders (vitamin B12 deficiency, diabetes), heavy metal toxicity, vasculitis and primary psychiatric disorders.

Infectious causes can mimic certain aspects of the typical multisystem illness seen in chronic Lyme disease. These include viral syndromes such as parvovirus B19 or West Nile virus infection, and bacterial mimics such as relapsing fever, syphilis, leptospirosis and mycoplasma.

The clinical features of chronic Lyme disease can be indistinguishable from fibromyalgia and chronic fatigue syndrome. These illnesses must be closely scrutinized for the possibility of etiological *B. burgdorferi* infection.

19. Clinical judgment

Clinical judgment remains necessary in the diagnosis of late Lyme disease. A problem in some studies that relied on objective evidence was that treatment occurred too late, leaving the patient at risk for persistent and refractory Lyme disease.

As noted, time-honored beliefs in objective findings and two-tier serologic testing have not withstood close scrutiny [21,30,34,37]. Lyme disease should be suspected in patients with newly acquired or chronic symptoms (headaches, memory and concentration problems and joint pain). Management of patients diagnosed on the basis of clinical judgment needs to be tested further in prospective trials, and diagnostic reproducibility must be verified.

20. Testing for coinfection

Polymicrobial infection is a new concern for individuals with Lyme disease, and coinfection is increasingly reported in critically ill individuals [25,38]. Although *B. burgdorferi* remains the most common pathogen in tickborne illnesses, coinfections including *Ehrlichia* and *Babesia* strains are increasingly noted in patients with Lyme disease, particularly in those with chronic illness. *Bartonella* is another organism that is carried by the same ticks that are infected with *B. burgdorferi,* and evidence suggests that it is a potential coinfecting agent in Lyme disease [25].

Recent animal and human studies suggest that Lyme disease may be more severe and resistant to therapy in coinfected patients [25,38]. Thus, concurrent testing and treatment for coinfection is mandatory in Lyme disease patients.

Section IV: Treatment considerations

Since Lyme disease can become persistent, recurrent and refractory even in the face of antibiotic therapy, evaluation and treatment must be prompt and aggressive.

21. Prompt use of antibiotics

Although no well designed studies have been carried out, the available data support the prompt use of antibiotics to prevent chronic Lyme disease. Antibiotic therapy may need to be initiated upon suspicion of the diagnosis, even without definitive proof. Neither the optimal antibiotic dose nor the duration of therapy has been standardized, but limited data suggest a benefit from increased dosages and longer treatment, comparable to the data on tuberculosis and leprosy which are caused by similarly slow-growing pathogens [25].

22. Choosing an antibiotic

In acute Lyme disease, the choice of antibiotics should be tailored to the individual and take into account the severity of the disease as well as the patient's age, ability to tolerate side effects, clinical features, allergy profile, comorbidities, prior exposure, epidemiologic setting and cost.

Conversely, persistent and refractory Lyme disease treatment is more likely to include intravenous and/or intramuscular antibiotics. The choices depend in part on the patient's response to antibiotic therapy and on the success of antibiotics in treating other Lyme disease patients (see below).

Therapy usually starts with oral antibiotics, and some experts recommend high dosages. The choice of antibiotic therapy is guided by weighing the greater activity of intravenous antibiotics in the central nervous system against the lower cost and easy administration of oral antibiotics for *B. burgdorferi*.

23. Oral antibiotic options

For many Lyme disease patients, there is no clear advantage of parenteral therapy. Along with cost considerations and pressure to treat patients with Lyme disease with the least intervention, there is growing interest in the use of oral therapy.

First-line drug therapies for Lyme disease may include (in alphabetical order): oral amoxicillin, azithromycin [39–41], cefuroxime [42], clarithromycin [43], doxycycline and tetracycline. These antibiotics have similar favorable results in comparative trials of early Lyme disease. In one study, azithromycin performed slightly less well when compared to amoxicillin and doxycycline. However, the efficacy of azithromycin was underestimated because the antibiotic was only given for 10 days [39].

One study has suggested that oral doxycycline (100 mg twice daily for 30 days) is as effective as intravenous ceftriaxone (2 g daily for 30 days) in early disseminated Lyme disease [40]. Two European studies have demonstrated similar efficacy of oral doxycycline and parenteral penicillin and ceftriaxone in early Lyme disease [44,45].

There are no studies comparing oral with intravenous antibiotics for persistent, recurrent and refractory Lyme disease.

24. Intravenous antibiotic options

It is common practice to consider intravenous antibiotics upon failure of oral medications in patients with persistent, recurrent or refractory Lyme disease, and as the first line of therapy for certain conditions, (i.e., encephalitis, meningitis, optic neuritis, joint effusions and heart block).

Ideally, the intravenous antibiotic should be selected on the basis of *in vitro* sensitivity testing or clinical experience [101]. Intravenous antibiotics are also justified by concern for penetration into the central nervous system [15].

Until recently, ceftriaxone, cefotaxime and penicillin were the only intravenous antibiotics routinely studied for use in Lyme disease. Intravenous imipenem, azithromycin and doxycycline have an adequate antispirochetal spectrum of activity and may represent suitable alternative therapies. However, the latter two drugs are often considered for intravenous use only if they are not tolerated orally.

There is a paucity of data on alternative intravenous antibiotics, and their success is less predictable in chronic Lyme disease.

25. Intramuscular antibiotic options

Intramuscular benzathine penicillin (1.2 to 2.4 million units per week) is sometimes effective in patients who do not respond to oral and intravenous antibiotics. If intramuscular benzathine penicillin is used, long-term therapy may be necessary due to the low serum concentration of this form of penicillin [46]. Luft and colleagues report, "It was demonstrated that while *B. burgdorferi* may be sensitive to relatively small concentrations of penicillin and ceftriaxone, the organism is killed slowly. This implies that, as in syphilis, prolonged blood levels of these drugs may be necessary in order to ensure cure" [46].

One-third of a chronic Lyme disease population responded to intramuscular benzathine penicillin (1.2 to 2.4 million units per week) [16–18]. Benzathine penicillin has mainly been used in patients who have had multiple relapses while receiving oral or intravenous antibiotic therapy or who are intolerant of oral or intravenous antibiotics.

26. Combination antibiotic treatment

Combination therapy with two or more antibiotics is now increasingly used for refractory Lyme disease [11,41,45,46–49] and has also been given as initial therapy for some chronic presentations.

This approach is already used for another tickborne illness, babesiosis [50]. Oral amoxicillin, cefuroxime or (more recently) cefdinir combined with a macrolide (azithromycin or clarithromycin) are examples of combination regimens that have proven successful in clinical practice, although controlled clinical trials are lacking in persistent, recurrent and refractory Lyme disease.

Combination therapy in patients with Lyme disease raises the risk of adverse events. This risk must be weighed against the improved response to combination therapy in Lyme disease patients failing single agents [47–49].

27. Sequential treatment

Clinicians increasingly use the sequence of an intravenous antibiotic followed by an oral or intramuscular antibiotic [19,37,101,47,48]. In two recent case series that employed combination therapy and sequential therapy, most patients were successfully treated [19,47]. A logical and attractive sequence would be to use intravenous therapy first (e.g., intravenous ceftriaxone), at least until disease progression is arrested and then follow with oral therapy for persistent and recurrent Lyme disease.

28. Dosage

Increasingly, clinicians recommend that certain drugs used for Lyme disease be given at higher daily doses: for example, 3000–6000 mg of amoxicillin, 300–400 mg doxycycline and 500–600 mg of azithromycin. Some clinicians prescribe antibiotics using blood levels to guide higher doses. Close monitoring of complete blood counts and chemistries are also required with this approach.

With higher doses, there may be an increase in adverse events in general and gastrointestinal problems in particular. Acidophilus has reportedly reduced the incidence of *C. difficile* colitis and non-*C. difficile* antibiotic-related diarrhea.

Serious adverse effects of antibiotics, however, were less common than previous estimates. In a recent clinical trial of chronic Lyme disease, the overall serious adverse event rate was 3% after three months of antibiotics, including 1 month of intravenous antibiotics [23]. Clinicians who have experience with higher-dose antibiotic therapy must balance the benefit of higher drug levels achieved with this therapy against the modest risk of gastrointestinal and other side effects.

Research is needed to determine the added benefits of higher doses of antibiotics in chronic Lyme disease.

29. Duration of therapy

Because of the disappointing long-term outcome with shorter courses of antibiotics, the practice of stopping antibiotics to allow for a delayed recovery is no longer recommended for patients with persistent, recurrent and refractory Lyme disease. Reports show failure rates of 30–62% within 3 years of short-course treatment using antibiotics thought to be effective for Lyme disease [3,4,12]. Conversely for neurologic complications of Lyme disease, doubling the length of intravenous ceftriaxone treatment from 2 to 4 weeks improved the success rate from 66 to 80% [12,51].

The management of chronic Lyme disease must be individualized, since patients will vary according to severity of presentation and response to previous treatment.

Concurrent risk factors (i.e., coinfections, previous treatment failures, frequent relapses, neurologic involvement, or previous use of corticosteroids) or evidence of unusually severe Lyme disease should lead to the initiation of prolonged and/or intravenous antibiotic treatment. Physicians should always assess the patient's response to treatment before deciding on appropriate duration of therapy (i.e., weeks versus months).

30. Empiric treatment

The importance of establishing the diagnosis of Lyme disease is heightened in light of increasing concern about antibiotic overuse. After an appropriate history, physical examination and laboratory testing are completed, empiric antimicrobial therapy should be initiated on the basis of clinical clues, the severity of the patient's acute illness, underlying disease and the likelihood of *B. burgdorferi* infection. The ILADS working group recommends that empiric treatment be considered routine for patients with a likely diagnosis of Lyme disease.

31. Persistent Lyme disease

Persistent Lyme disease is more resistant to treatment and more likely to produce a relapse. Although persistent Lyme disease may resolve without additional therapy, many experts believe that this condition should be treated with repeated and prolonged antibiotics. Physicians should extend the duration of antibiotics to prevent or delay recurrent and refractory Lyme disease.

32. Recurrent Lyme disease

Despite previous antibiotic treatment, Lyme disease has a propensity for relapse and requires careful follow-up for years. The data suggest that failure to eradicate the organism may be the reason for a recurrence of symptoms [12]. Early and aggressive treatment with antibiotics is indicated for recurrent Lyme disease. The ultimate impact from retreating each episode of recurrent Lyme disease is currently unclear.

33. Refractory Lyme disease

Refractory Lyme disease is a devastating condition that usually affects patients with persistent symptomatology and long-term disability. Prompt and aggressive institution of antibiotic therapy may be essential to prevent refractory disease. Increasing evidence shows that antibiotics have a beneficial effect on the course of refractory Lyme disease even in cases where the patient is intolerant of antibiotics or when a previous regimen has failed. Several months of therapy are often required to produce clear evidence of improvement. During this time, symptomatic treatment may be combined with antibiotic treatment.

34. Treatment failure

When patients fail to respond or their conditions deteriorate after initiation of empiric therapy, a number of possibilities should be considered other than Jarisch-Herxheimer reaction. These include adverse events that limit treatment, allergic history to medication, inappropriate or inadequate dosing regimen, compliance problems, incorrect medication, immune sequelae and sequestering of the organism (e.g., in the central nervous system). An alternative diagnosis or coinfection should also be considered.

35. Symptomatic treatment

Although there may be a potential role for symptomatic treatment in chronic Lyme disease, this approach has little support due to the strong possibility of persistent infection. Owing to the potential hazard of immunosuppression and the poor outcome in

one study, steroid therapy is not recommended [52]. Surgical synovectomy is associated with significant morbidity and does not address neurologic presentations; it should be reserved for knee pain failing antibiotic treatment [53]. Intra-articular steroid injection may be useful as a temporizing procedure in patients with persistent knee pain but this runs the risk of masking persistent infection.

Symptomatic therapy (particularly anti-inflammatory medications, tricyclic antidepressants, selective serotonin re-uptake inhibitors and hydroxychloroquine) may be useful in concert with antibiotics and in individuals failing antibiotics.

Hyperbaric oxygen therapy (HBOT) is under study but is not recommended for routine therapeutic use [25,54]. Other treatments, including cholestyramine (CSM), antifungal therapy and antiviral agents require further study.

Since patients are becoming more interested in alternative therapies (e.g., traditional Chinese medicine, anti-oxidants, hyperthermia, bee venom, naturopathy and homeopathy), physicians should be prepared to address questions regarding these topics.

36. Fibromyalgia

The outcome of treating fibromyalgia secondary to Lyme disease with nonantibiotic regimens has been poor. The most encouraging clinical trial showed success in only one of 15 patients and only modest improvement in 6 of 15 individuals with fibromyalgia despite 2 years of treatment [24].

Antibiotic therapy has been much more effective than supportive therapy in symptomatic patients with fibromyalgia secondary to Lyme disease.

Fibromyalgia treatment alone without antibiotics raises the risk of conversion to refractory chronic Lyme disease and/or exacerbation of an undiagnosed persistent infection and is not recommended. Increasingly, clinicians do not feel comfortable treating fibromyalgia in Lyme disease without antibiotics.

37. Decision to stop antibiotics

Several studies of patients with Lyme disease have recommended that antibiotics be discontinued after 30 days of treatment. Complicating the decision to stop antibiotics is the fact that some patients present with disease recurrence after the resolution of their initial Lyme disease symptoms. This is consistent with incomplete antibiotic therapy. Although the optimal time to discontinue antibiotics is unknown, it appears to be dependent on the extent of symptomatology, the patient's previous response to antibiotics and the overall response to therapy (see below).

Rather than an arbitrary 30-day treatment course, the patient's clinical response should guide duration of therapy. Patients must therefore be carefully evaluated for persistent infection before a decision is made to withhold therapy.

The decision to discontinue antibiotics should be made in consultation with the patient and should take into account such factors as the frequency and duration of persistent infection, frequency of recurrence, probability of refractory Lyme disease, gains with antibiotics, the importance to the patient of discontinuing antibiotics and potential for careful follow-up.

The ideal approach would be to continue therapy for Lyme disease until the Lyme spirochete is eradicated. Unfortunately there is currently no test available to determine this point [25]. Therefore, the clinician must rely on the factors outlined above to decide on the length of antibiotic therapy for chronic Lyme disease.

38. Alternative antibiotics

There is compelling evidence that Lyme disease can result in serious and potentially refractory illness. Use of alternative antibiotics to treat early Lyme disease with erythema migrans is generally not indicated unless coinfection is suspected.

The ILADS Working Group believes that the risk of alternative antibiotics is acceptable in selected Lyme disease patients presenting with chronic Lyme disease. Alternative antibiotics include less commonly used oral antibiotics (cefixime, cefdinir, metronidazole) and intravenous antibiotics (imipenem, azithromycin). The role of alternative antibiotics in low-risk patients is less certain and there is less consensus within the Working Group as to whether the potential benefits outweigh the risks.

39. Therapy for coinfection

Therapy for polymicrobial infection in Lyme disease is a rapidly changing area of clinical practice [25]. Uncomplicated Lyme disease may be managed without addressing coinfection by means of standard oral or parenteral antibiotic therapy. Some but not all experts recommend therapy for subclinical or chronic coinfection with *Ehrlichia*, *Babesia* or *Bartonella* on the basis of their belief that responses are more prompt with this approach.

The dose, duration and type of treatment for coinfections have not been defined. Published reports of coinfection are limited to a small number of patients treated in open-label, nonrandomized studies. Doxycycline has been indicated for *Ehrlichia*. A recently published randomized trial determined that treatment of severe *Babesia microti* with the combination of atovaquone and azithromycin was as effective as the use of standard oral therapy with clindamycin and quinine [55].

The decision to use alternative antibiotics should be based on the individual case, including a careful assessment of the patient's risk factors and personal preferences. Patients managed in this way must be carefully selected and considered reliable for follow-up. Further controlled studies are needed to address the optimal antimicrobial agents for coinfections and the optimal duration of therapy.

Additional research is needed to determine which antibiotics work best for *Bartonella,* but fluoroquinolones, azithromycin, doxycycline and rifampin have good *in vitro* activity.

Section V: Research needs

The ILADS Working Group encourages centers that treat large numbers of Lyme disease patients symptomatically using IDSA treatment guidelines to perform a formal evaluation of their own programs. This will allow researchers to compare the results of treatment guidelines that use more antibiotics with those that do not.

40. Ongoing development of treatment guidelines

The IDSA guidelines recommending one-time short-term antibiotic therapy have not been successful. Physician demands for better outcomes have led to the development of the ILADS guidelines, and the continued evolution of an evidence-based approach is critical for the treatment of persistent, recurrent and refractory Lyme disease.

41. Validation of guidelines

Most studies of Lyme disease were retrospective, unblinded and uncontrolled. Furthermore, the antibiotic dose and duration of therapy were not standardized.

The first double-blind clinical trial found that weekly benzathine penicillin for 3 weeks was more effective than placebo for Lyme arthritis [56]. At the other end of the spectrum, a recently completed randomized clinical trial failed to demonstrate any efficacy of 90 days of antibiotic therapy in previously treated patients with neurologic Lyme disease [23].

Two additional randomized trials are examining the practice of retreating chronic Lyme disease patients with antibiotics, and these results should be available shortly [57,58]. The retreatment approach is being validated using a single-center, prospective surveillance database.

42. Comparative studies

The IDSA and ILADS Guidelines differ substantially, revealing the wide variation in diagnosis and treatment (TABLE 1) [59,60]. This variation suggests that physicians do not use a uniform strategy to diagnose and treat Lyme disease. Physicians often treat for Lyme disease longer than 4 weeks and also retreat [8,19,47,48,57–62]. These decisions are made despite warnings against overdiagnosis and overtreatment [63–65].

Community-based clinicians and academic centers often have different criteria for diagnosis and divergent goals of care [8]. The guidelines and standards of practice used for diagnosis of Lyme disease in academic research settings may not be applicable or appropriate for community-based settings. Moreover, the clinical manifestations of Lyme disease are often subtle or atypical in the community.

Because important data concerning the treatment of chronic Lyme disease was not considered by the IDSA expert panel, ILADS introduced an evidence-based review to determine which recommendations warranted revision. This evidence-based review gave rise to the current guidelines.

Section VI: Periodic review of guidelines

New data on treatment of Lyme disease is emerging, and randomized controlled trials that address various unresolved issues in Lyme disease are ongoing. The ILADS Working Group has therefore developed a mechanism for routinely and periodically reviewing this information and for updating the guidelines on a regular basis. The most recent information will be available from the ILADS website at www.ILADS.org.

43. Grading system for evidence-based guidelines

The ILADS system for grading recommendations is similar to that used by the expert panel of the IDSA. However, the ILADS panel includes primary care clinicians, researchers and international leaders in the treatment of Lyme disease. Thus, the ILADS group is more inclusive and clinically oriented than the IDSA panel, and the ILADS guidelines reflect this diversity.

44. Table 1. Comparison of key IDSA and ILADS guidelines.

Condition	IDSA	ILADS
Lyme arthritis	B - II	A - II
Encephalopathy	A - II	A - II
Retreatment	None	A - II
Prolonged antibiotics	None	A - II
Benzathine penicillin	D - III	B - III
Intra-articular steroid	B - III	D - III
Arthroscopic Synovectomy	B - II	D - II
Coinfection	B - III	B - III
Seronegative Lyme disease	None	A - III
Combination treatment	None	B - III
Empiric treatment	None	B - III

45. Criteria for evidence-based guidelines

The ILADS recommendations are based on two criteria [10]:

- The strength of the evidence (denoted by categories A–E)
- The quality of the data (denoted by Roman numerals I–III)

Recommendations rated 'A' are considered good evidence to support the recommendation. Those rated 'B' have moderate evidence to support the recommendation. Those rated 'C' are considered optional. Measures designated 'D' generally should not be offered; those designated 'E' are contraindicated.

A rating of I indicates that at least one randomized controlled trial supports the recommendation; II, evidence from at least one well-designed clinical trial without randomization supports the recommendation; and III, 'expert opinion'.

Sources

Our data sources are English-language articles published from 1975 to 2003. The selection panel synthesized the recommendations from published and expert opinion. Human studies of Lyme disease were identified from MEDLINE (1975 to 2003) and from references in pertinent articles and reviews. Also included are abstracts and material presented at professional meetings and the collective experience of the ILADS Working Group treating tens of thousands of Lyme disease patients.

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Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease

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EXPERT REVIEWS

Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease

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Evidence-based guidelines for the management of patients with Lyme disease were developed by the International Lyme and Associated Diseases Society (ILADS). The guidelines address three clinical questions – the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans treatment and the role of antibiotic retreatment in patients with persistent manifestations of Lyme disease. Healthcare providers who evaluate and manage patients with Lyme disease are the intended users of the new ILADS guidelines, which replace those issued in 2004 (Exp Rev Anti-infect Ther 2004;2:S1–13). These clinical practice guidelines are intended to assist clinicians by presenting evidence-based treatment recommendations, which follow the Grading of Recommendations Assessment, Development and Evaluation system. ILADS guidelines are not intended to be the sole source of guidance in managing Lyme disease and they should not be viewed as a substitute for clinical judgment nor used to establish treatment protocols.

KEYWORDS: antibiotic prophylaxis • antibiotics • erythema migrans • GRADE • Lyme disease • persistent disease • treatment

Evidence-based medicine is the integration of best research evidence with clinical expertise and patient values [1]. The International Lyme and Associated Diseases Society (ILADS) has adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as its basis for evidence assessment and the development of recommendations to ensure a transparent and trustworthy guideline process [2–5].

These guidelines address three fundamental treatment questions: the usefulness of antibiotic prophylaxis for known tick bites, the effectiveness of erythema migrans (EM) treatment and the role of antibiotic retreatment in patients with persistent manifestations of Lyme disease. ILADS anticipates performing GRADE assessments on additional topics related to the diagnosis and treatment of tick-borne diseases in the future.

The GRADE scheme classifies the quality of the evidence as high, moderate, low or very low. The quality of evidence from randomized controlled trials (RCTs) is initially rated as high, but may be downgraded based on five limitations: study bias, publication bias, indirectness (generalizability), imprecision and inconsistency. Evidence quality from observational studies is generally low, but may be upgraded based on a large effect or

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dose–response gradient [6]. Rather than labeling recommendations as strong or weak, these guidelines use the terms 'recommendation' or 'strong recommendation' for or against a medical intervention. The GRADE scheme itself is a continually evolving system. These guidelines attempt to incorporate the current state of GRADE.

Although Lyme disease is not rare, the treatment of Lyme disease has not attracted pharmaceutical interest and the evidence base for treating Lyme disease is best described as sparse, conflicting and emerging. For example, Hayes and Mead of the CDC performed a systematic review of the evidence regarding the treatment of late neurologic Lyme disease and their GRADE-based evaluation rated the quality of the evidence as very low [7]. The ILADS guidelines working group reached a similar conclusion after assessing the research evidence pertaining to its three clinical questions, rating the evidence quality as very low. The low quality of evidence seen in Lyme disease is consistent with the evidence base for the field as a whole. Indeed, the majority of recommendations in infectious disease medicine generally are based on low-quality evidence [8].

When high-quality evidence is not available, guideline panels are faced with making recommendations based on low- or very low-quality evidence. Although evidence alone is never sufficient to determine guideline recommendations [2], when evidence is weak, the values of those on the panel, including differing specialty perspectives, may carry more weight [8]. One of the goals of the GRADE scheme is to make the value judgments underlying recommendations transparent.

When the evidence base is of low or very low quality, guideline panels should be circumspect about making strong recommendations to avoid encouraging uniform practices that are not in the patient's best interest and to ensure that research regarding benefits and risks is not suppressed [8]. Guidelines panels should also make the role of their values and those of patients in recommendations explicit and should promote informing and empowering patients to engage in shared decision-making [8].

This panel has placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary [9].

In addition, this panel believes the goals of medical care in Lyme disease are to prevent the illness whenever possible and to cure the illness when it occurs. When this is not possible, the panel believes the emphasis for treatment should be on reducing patient morbidity. Therefore, the panel placed a high value on reducing patient risks for developing the chronic form of the disease and on reducing the serious morbidity associated with these disease forms. Thus, the panel's values align with the Institute of Medicine (IOM) goal of reducing the impact of chronic illness at the individual and national levels by, among other things, treating the treatable [10]. To this end, the panel valued primary prevention (by effectively treating a tick bite), secondary prevention (by treating an EM rash sufficiently so as to restore health and prevent disease progression) and tertiary prevention (by treating patients whose illness may be responsive to additional therapy, thereby reducing the morbidity associated with the chronic forms of the disease).

ILADS is mindful of the role of patient preferences and values in GRADE as well as the IOM's call for patient-centered care that is responsive to the needs, values and expressed preferences of individual patients [11]. Patient-centered care focuses on achieving treatment outcomes that patients value [11], including the restoration of health, prevention of health deterioration and the provision of treatments that have the potential to improve quality of life (QoL). To facilitate the development of treatment plans addressing the unique circumstances and values of individual patients, patient-centered care encourages shared medical decision-making.

Shared decision-making takes into account the best scientific evidence available, clinical expertise and the role of patient's values and preferences in deciding among available treatment options [12,13]. Despite the terminology, decision-making is not truly shared between clinician and patient; the responsibility for choosing between options remains with the clinician.

To effectively engage in shared decision-making, patients need to understand the implications of their choices. Physicians should not assume that patients share their values in making risk/benefit determinations. Studies have demonstrated that patients and physicians may have very different assessments of preferences and risk tolerance [8]. In addition, there is considerable variation among individual patients in their tolerance for risk and in what they regard as a valuable benefit. Patients may also tolerate more risk when they have severe presentations of disease or when there are no other treatment options available [14].

In the GRADE system, recommendations take into account not only the quality of the evidence, but also the balance between benefits and harms and patient values and preferences [5]. In instances where a GRADE evaluation concludes that the evidence quality is low or very low or that there are trade-offs between risks and benefits that depend on the values of the individual, the GRADE system recommends that recommendations should identify a range of therapeutic options and acknowledge that different choices may be appropriate for different patients.

In assessing the balance between the risks and benefits of antibiotic treatments for Lyme disease, the panel weighed the burden of disease, the magnitude and relative importance of patient-centered outcomes as well as treatment-associated risks and the risks attendant on not treating. The panel acknowledged that the health-related and economic consequences of chronic disease are enormous for individuals, families, communities, healthcare systems and the nation, impacting the wellbeing of individuals, family functioning and economic productivity [15–18]. Therefore, the panel recommends that patients be informed of the risks and benefits of treating and not treating, including the risks of continuing to suffer significant morbidity or permitting a serious systemic infection to progress.

The panel assessed risks and benefits of treatment on a generalized basis. In addition, the panel recognizes that there is a need for clinicians, in the context of shared medical decision-

making, to engage in a risk–benefit assessment that reflects the individual values of the particular patient.

Guidelines for the diagnosis and treatment of Lyme disease are conflicting (Supplementary Appendix I [Supplementary material can be found online at www.informahealthcare.com/suppl/10.1586/14787210.2014.940900]) The IOM recently highlighted the conflicting Lyme guidelines of ILADS and the Infectious Diseases Society of America (IDSA) and noted that the National Guidelines Clearinghouse has identified at least 25 different conditions in which conflicting guidelines exist [19]. According to the IOM, conflicting guidelines most often arise when evidence is weak, organizations use different assessment schemes or when guideline developers place different values on the benefits and harms of interventions [20].

The adoption of GRADE by ILADS is, in part, an effort to use the same assessment scheme as the IDSA, although it should be noted that the IDSA's Lyme disease guidelines listed on the National Guidelines Clearinghouse were originally published in 2006 and do not reflect the organization's adoption of GRADE for guideline revisions after 2008. Additionally, the use of GRADE is one element of ILADS' compliance with the eight standards identified by the IOM as being integral to creating trustworthy treatment guidelines (Supplementary Appendix II).

The guidelines were developed in phases. A working group identified three questions to address, conducted a literature search and subsequent assessment of the evidence quality and evaluated the role of patient preferences and values for each question. A preliminary draft of the guidelines was sent to the full guidelines panel and, subsequently, outside reviewers for review and comment, with the document being further refined. The panel and working group members were required to disclose potential financial conflicts of interest. The full panel, which consisted of the board of directors of ILADS, determined that fee for service payments are inherent in the provision of healthcare and did not disqualify experienced clinicians from serving on the guideline panel nor did serving on the boards of nonprofit organizations related to Lyme disease. Financial relationships exceeding US$10,000 per year that were not intrinsic to medical practice were viewed as potential conflicts; no panel or working group members held such financial conflicts of interest.

Scope of problem

The burden of Lyme disease for individuals and society remains high. Despite the availability of numerous preventative measures [21,22], the incidence of acute Lyme disease is significant. The CDC currently estimates that the annual number of new cases of Lyme disease in the USA exceeds 300,000 [23]; how these individual patients fare is an important consideration and ILADS is primarily interested in preventing and reducing the morbidity associated with chronic disease. Although some prospective studies found long-term outcomes were good, many had significant limitations [24–26]. There is substantial evidence of varying quality demonstrating that the severity [16–18,27–29], duration [16,18,27,29,30] and cost [15,31] of persistent manifestations of Lyme disease can be profound. While the etiology of these manifestations is uncertain, their impact is clear. Two retrospective cohorts [27,30], two case series [32,33], a meta-analysis [34], two prospective European studies and four NIH-sponsored clinical trials [16–18] describe significant long-term consequences of Lyme disease. Findings include:

- Thirty-four percent of a population-based, retrospective cohort were ill an average of 6.2 years after antibiotic treatment [27];
- Sixty-two percent of a retrospective evaluation of 215 Lyme disease patients from Westchester County, NY, remained ill an average of 3.2 years after antibiotic treatment [30];
- A meta-analysis of 504 patients treated for Lyme disease found this group had more fatigue, musculoskeletal pain and neurocognitive difficulties than 530 controls [34]. Additionally, it demonstrated that persistent Lyme disease symptoms were a distinct set of symptoms, which differed from those of fibromyalgia, chronic fatigue syndrome and depression [34];
- Among 23 European pediatric patients with objective findings of Lyme neuroborreliosis sequelae, daily activities or school performance were negatively impacted in 10 (43%) [28];
- A European study of adults treated for neuroborreliosis found that at 30 months post-treatment, 16% were cognitively impaired [29];
- On entrance, patients enrolling in the four NIH-sponsored clinical trials on antibiotic retreatment had experienced poor long-term outcomes from their prior therapy. Participants in the two trials by Klempner *et al*. had persistent symptoms, which were sufficiently severe as to interfere with daily functioning [18];
- Using a combined total of 22 standardized measures of QoL, fatigue, pain and cognition [16–18], the investigators of the four NIH-sponsored retreatment trials documented that the patients' QoL was consistently worse than that of control populations [16–18] and equivalent to that of patients with congestive heart failure [18]; pain levels were similar to those of post-surgical patients and fatigue was on par with that seen in multiple sclerosis [16,18]. Table 1 compares the QoL scores of the NIH Lyme disease participants at the time of their study enrollment to those of patients with other chronic diseases, including diabetes, heart disease, depression, osteoarthritis, rheumatoid arthritis, lupus, fibromyalgia and epilepsy [35–40].

Executive summary of treatment recommendations

With the goal of fostering evidence-based, patient-centered care for patients with Lyme disease, the panel performed a deliberate GRADE assessment of the pertinent trial evidence regarding three fundamental treatment questions and reviewed the risks and benefits of antibiotic therapies used in the treatment of Lyme disease. The panel also considered the ramifications of withholding antibiotic treatments or using non-curative regimens and acknowledged that either may result in a significant disease burden. Following the completion of these activities, the panel drew several conclusions regarding the treatment of Lyme disease.

Table 1. Long-term consequences (or impairments) of Lyme disease.

	Clinical trials	Lyme disease cases mean (SD)	Healthy controls mean (SD)	Impairments in other illnesses – (mean)	Ref.
QoL PCS – range 1–100 (the lower the score, the worse the QoL)†					
PCS	Klempner *et al.*, seropositive	33.1 (9.9)	50 (10)	Diabetes (42), heart disease (39), depression (45), osteoarthritis (39) and rheumatoid arthritis (42)	[18,202]
PCS	Klempner *et al.*, seropositive	35.8 (8.8)	50 (10)		[18]
PCS	Cameron recurrent	39.6 (9.7)	50 (10)		[87]
PCS	Fallon *et al.*	37.1 (8.6)	55.9 (3.6)		[16,38]
QoL MCS – range 1–100 (the lower the score, the worse the QoL)‡					
MCS	Klempner *et al.*, seropositive	43.4 (11.6)	50 (10)	Diabetes (48), heart disease (49), depression (37), osteoarthritis (49) and rheumatoid arthritis (48)	[18]
MCS	Klempner *et al.*, seropositive	46.7 (9.7)	50 (10)		[18]
MCS	Cameron recurrent	35.9 (14.6)	50 (10)		[87]
MCS	Fallon *et al.*	39.2 (11.6)	56.2 (2.9)‡		[16,38]
Fatigue – FSS – range 0–7, severe fatigue (>4.0)§					
FSS	Krupp *et al.*, post-treatment	5.7 (1.4)	2.1 (0.5)	ALS (4.35), multiple sclerosis (5.1)	[16,17]
FSS	Fallon *et al.*	5.2 (1.5)	2.1 (0.5)		[16,203,204]
FIQ – range 0–100 [205] (the higher the score, the greater the impairment)¶					
FIQ	Klempner *et al.*, seropositive	58.4 (19.7)	14 and 21.9	Fibromyalgia (58–78)	[18,35,36,39,206]
FIQ	Klempner *et al.*, seropositive	47.9 (15.2)	14 and 21.9		[18,206]
Pain – MPQ range 0–78 [207] and VAS range 0–10 (the higher the scores, the greater the pain) [208]#					
MPQ	Fallon *et al.*	11.6 (1.5)	1.1 (2.5)	Widespread pain after breast cancer surgery (7.0)	[16,40]
VAS	Fallon *et al.*	5.2 (3.1)	0.1 (0.2)	Fibromyalgia (6.48)	[16,35]
Neurocognitive dysfunction index††					
Index	Fallon *et al.*	–0.49 (0.63)	0.55 (0.40)		[16]

†The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].
‡The MCS on the SF-36 measure of QoL is a measure of mental health, emotional role functioning, social functioning and vitality [209].
§The FSS assesses the impact of fatigue on everyday functioning [210].
¶The FIQ is a measure of 'functional disability, ability to have a job, pain intensity, sleep function, stiffness, anxiety, depression and the overall sense of wellbeing' adopted by Burckhardt *et al.* for fibromyalgia [211] and subsequently used in Lyme disease [16,212].
#The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively [213].
††An index based on motor, psychomotor, attention, total memory, Buschke, Benton, working memory, fluency, IQ by Barona, IQ by NAART-R, immediate memory and delayed memory; higher values indicate better cognitive functioning. Additional outcomes described in the NIH-sponsored retreatment trials include cognitive, role functioning and pain on MOS abnormalities [18], psychopathology [16] and a OspA measure of spinal fluid [17].
ALS: Amyotrophic lateral sclerosis; FIQ: Fibromyalgia impact questionnaire; FSS: Fatigue severity scale; MCS: Mental component score; MPQ: McGill Pain Questionnaire; MOS: Medical outcome scale; PCS: Physical component score; SD: Standard deviation; VAS: Visual analog scale; QoL: Quality of life.

Based on these conclusions, the panel formulated treatment recommendations reflecting ILADS values and patient preferences. Recommendations for the individual clinical questions are summarized here. A detailed discussion of each question, including the complete GRADE analysis, the risk–benefit evaluation, ILADS statement of values and the subsequent individual treatment recommendations, in full, follows this summary.

Q1. Does a single 200 mg dose of doxycycline following a tick bite provide effective prophylaxis for Lyme disease?

Organizational values

The panel placed a high value on preventing disease, thereby avoiding both the unnecessary progression from a potentially preventable infection to one that is chronic and associated with significant morbidity and costs. The panel placed a high value on not causing the abrogation of the immune response. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 1a

Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The relative trade-offs between risks and benefits are clear enough that most patients will place a high value on avoiding a seronegative state and its attendant delays in diagnosis and treatment.

Recommendation 1b

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. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Most patients will place a high value on preventing chronic illness. However, some patients will value avoiding unnecessary antibiotics and prefer to not treat a tick bite prophylactically. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 1c

During the initial visit, clinicians should educate patients regarding the prevention of future tick bites, the potential manifestations of both early and late Lyme disease and the manifestations of the other tick-borne diseases that may have been contracted as a result of the recent bite. Patients receiving antibiotic prophylaxis should also be given information describing the symptoms and signs of a *Clostridium difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any and all tick-borne disease manifestations and manifestations suggestive of a *C. difficile* infection (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Q2. Should the treatment of an EM rash be restricted to 20 or fewer days of oral azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin?

Organizational values

The panel placed a high value on avoiding both the unnecessary progression from a potentially curable infection to one that is chronic and the morbidity and costs associated with chronic disease. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 2a

Treatment regimens of 20 or fewer days of phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline and 10 or fewer days of azithromycin are not recommended for patients with EM rashes because failure rates in the clinical trials were unacceptably high. Failure to fully eradicate the infection may result in the development of a chronic form of Lyme disease, exposing patients to its attendant morbidity and costs, which can be quite significant. (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Although many patients will value avoiding the risk of treatment failure over a potentially modest increase in the risk of significant adverse events that may be associated with longer treatment durations, others may prefer to avoid the additional risks of longer treatment. Clinicians should inform patients that: the combined failure rate for the individual agents investigated in the previously discussed EM trials were judged by this panel to be unacceptably high when antibiotic treatment was restricted to 20 or fewer days (provide the appropriate value for each); the evidence supporting the use of longer treatment durations is limited and of low quality [41–43] and increases in antibiotic duration may increase the risk of antibiotic-associated adverse events, although the risks associated with oral antibiotics are low and some of this risk can be mitigated by the concomitant use of probiotics [44,45]. Treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2b

Clinicians should prescribe amoxicillin, cefuroxime or doxycycline as first-line agents for the treatment of EM. Azithromycin is also an acceptable agent, particularly in Europe, where trials demonstrated it either outperformed or was as effective as the other first-line agents [46–49]. Initial antibiotic therapy should employ 4–6 weeks of amoxicillin 1500–2000 mg daily in divided doses, cefuroxime 500 mg twice daily or doxycycline 100 mg twice daily or a minimum of 21 days of azithromycin 250–500 mg daily. Pediatric dosing for the individual agents is as follows: amoxicillin 50 mg/kg/day in three divided doses, with a maximal daily dose of 1500 mg; cefuroxime 20–30 mg/kg/day in two divided doses, with a maximal daily dose of 1000 mg and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily, with a maximal daily dose of 500 mg. For children 8 years and older, doxycycline is an additional option. Doxycycline is dosed at 4 mg/kg/day in two divided doses, with a maximal daily dose of 200 mg. Higher daily doses of the individual agents may be appropriate in adolescents.

Selection of the antibiotic agent and dose for an individual patient should take several factors into account. In the absence of contraindications, doxycycline is preferred when concomitant Anaplasma or Ehrlichia infections are possibilities. Other considerations include the duration [27,32,50] and severity [50–53] of symptoms, medication tolerability, patient age, pregnancy status, co-morbidities, recent or current corticosteroid use [54,55] cost, the need for lifestyle adjustments to accommodate certain antibiotics and patient preferences. Variations in patient-specific

details and the limitations of the evidence imply that clinicians may, in a variety of circumstances, need to select therapeutic regimens utilizing higher doses, longer durations or combinations of first-line agents (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: See recommendation 2a.

Recommendation 2c

Clinicians should provide ongoing assessments to detect evidence of disease persistence, progression or relapse or the presence of other tick-borne diseases. Lacking a test of cure, ongoing assessments are crucial for determining if treatment has been clinically effective. The first assessment should immediately follow the completion of therapy and subsequent evaluations should occur on an as-needed basis (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of monitoring the response to treatment clearly outweigh any attendant risks associated with monitoring.

Recommendation 2d

Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. 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. There is a wide range of options and choices must be individualized, based on the strength of the patient's initial response.

Strong-to-moderate responses favor extending the duration of therapy of the initial agent; modest responses may prompt an increase in the dose of the original antibiotic or a switch to a different first-line agent or tetracycline. Minimal or absent responses suggest a need for a combination of first-line agents, which includes at least one that is able to effectively reach intracellular compartments; injectable penicillin G benzathine (Bicillin LA) or intravenous (iv.) ceftriaxone are other options. Disease progression or recurrence suggests that the iv. antibiotics or injectable penicillin G benzathine, as discussed previously, may be required. For patients requiring antibiotic therapy beyond the initial treatment period, subsequent decisions regarding the modification or discontinuation of treatment should be based on the therapeutic response and treatment goals. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (see remarks following Recommendation 2f). (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: While most patients will place a high value on the potential of regaining their pre-morbid health status and preventing chronic illness by continuing treatment, a substantial portion may also value avoiding unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2e

Clinicians should retreat patients who were successfully treated initially but subsequently relapse or have evidence of disease progression. Therapeutic options include repeating the initial agent, changing to another oral agent or instituting injectable penicillin G benzathine or iv. ceftriaxone therapy. Choices must be individualized and based on several factors, including: the initial response to treatment; the time to relapse or progression; the current disease severity and the level of QoL impairments.

Prior to instituting additional antibiotic therapy, the original diagnosis should be reassessed and clinicians should evaluate patients for other potential causes that would result in the apparent relapse or progression of symptoms and/or findings (see remarks following Recommendation 2f). The presence of other tick-borne diseases, in particular, should be investigated if that had not already been done.

Following a long period of disease latency, minimal manifestations causing little deterioration in the patient's QoL favor continued observation or repeating therapy with the initial agent; mild manifestations or QoL impairments may prompt a switch to a different first-line agent, tetracycline or the use of a combination of first-line agents. Disease relapse or progression with mild manifestations or QoL impairments occurring within a few months of treatment suggests a need for longer regimens using either tetracycline, a combination of oral first-line agents, injectable penicillin G benzathine or iv. ceftriaxone. Regardless of the duration of disease latency, when disease manifestations or QoL impairments are significant or rapidly progressive, injectable penicillin G benzathine or iv. ceftriaxone may be required. Subsequent decisions regarding the modification or discontinuation of a patient's treatment should be based on individual therapeutic response and preferences (Recommendation, very low-quality evidence).

Role of patient preferences

High: While most patients will place a high value on the potential of regaining their pre-morbid health status and improving their QoL and preventing chronic disease through continued antibiotic treatment, a substantial portion will also value avoiding potentially unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2f

Clinicians should educate patients regarding the potential manifestations of Lyme disease, carefully explaining that disease latency can be prolonged. Education should also include information on preventing future bites, the manifestations of the other tick-borne diseases that they may have contracted as well

as the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any recurrent or newly developing manifestation of Lyme disease as well as those suggestive of other tick-borne diseases or a *C. difficile* infection. Clinicians should emphasize that the need to report manifestations of tick-borne diseases never expires (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Q3. Should patients with persistent manifestations of Lyme disease be retreated with antibiotics?

Organizational values

The panel placed a high value on reducing the morbidity associated with chronic Lyme disease and improving the patient's QoL as well as on the need for individualized risk/benefit assessment and informed shared decision-making. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong compelling evidence to the contrary.

Recommendation 3a

Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk–benefit assessments for each treatment option and include information regarding *C. difficile* infection and the preventative effect of probiotics (although none of the subjects in the retreatment trials developed *C. difficile* infection). (Strong recommendation, very low-quality evidence. *Note*: In GRADE, a strong recommendation may be made in the face of very low-quality evidence when the risk–benefit analysis favors a particular intervention such that most patients would make the same choice).

Role of patient preferences

Low: The benefits of educating patients about the potential benefits of retreatment and the risks associated with various treatment options, including not treating, clearly outweigh any attendant risks associated with education.

Recommendation 3b

While continued observation alone is an option for patients with few manifestations, minimal QoL impairments and no evidence of disease progression, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill. Prior to instituting antibiotic retreatment, the original Lyme disease diagnosis should be reassessed and clinicians should evaluate the patient for other potential causes of persistent disease manifestations. The presence of other tick-borne illnesses should be investigated if that had not already been done. Additionally, clinicians and their patients should jointly define what constitutes an adequate therapeutic trial for this particular set of circumstances.

When antibiotic retreatment is undertaken, clinicians should initiate treatment with 4–6 weeks of the selected antibiotic; this time span is well within the treatment duration parameters of the retreatment trials. Variations in patient-specific details and the limitations of the evidence imply that the proposed duration is a starting point and clinicians may, in a variety of circumstances, need to select therapeutic regimens of longer duration.

Treatment options are extensive and choices must be individualized. Each of these options would benefit from further study followed by a GRADE assessment of the evidence and consideration of associated risks and benefits, but until this information is available, clinicians may act on the currently available evidence.

In choosing between regimens, clinicians should consider the patient's responsiveness to previous treatment for Lyme disease, whether the illness is progressing and the rate of this progression; whether untreated co-infections are present; whether the patient has impaired immune system functioning or has received immunosuppressant corticosteroids and whether other co-morbidities or conditions would impact antibiotic selection or efficacy. Clinicians should also weigh the extent to which the illness interferes with the patient's QoL, including their ability to fully participate in work, school, social and family-related activities and the strength of their initial response against the risks associated with the various therapeutic options. Antibiotic selection should also consider medication tolerability, cost, the need for lifestyle adjustments to accommodate the medication and patient preferences.

For patients with mild impairments who had a strong-to-moderate response to the initial antibiotic, repeat use of that agent is favored. Patients with moderate impairments or only a modest response to the initial antibiotic may benefit from switching to a different agent or combination of agents. For patients with significant impairments and/or a minimal or absent therapeutic response, a combination of oral antibiotics, injectable penicillin G benzathine or iv. ceftriaxone (with the latter two used alone or in combination with other agents) is preferred. For patients who experienced disease progression despite earlier therapy, treatment with injectable penicillin G benzathine or iv. ceftriaxone, alone or in combination with other antibiotics, is advisable. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (Recommendation, very low-quality evidence).

Role of patient preferences

High: The heterogeneous nature of the patient population seen in clinical practice, particularly with regard to variations in disease severity, QoL impairments and aversion to treatment-related risk is likely to affect the risk–benefit assessment. Although many patients will value the opportunity to improve their individual QoL through antibiotic treatment over the risk

of adverse events, others may prefer to avoid the risks associated with treatment. Hence, treatment options, including their associated risks and benefits, should be discussed with the patient in the context of shared medical decision-making.

Recommendation 3c

Clinicians should re-assess patients immediately following the completion of the initial course of retreatment to evaluate the effectiveness of retreatment and the need for therapeutic adjustments. Reassessment may need to be done much earlier and with greater scrutiny in patients with severe disease or when the therapeutic intervention carries substantial risk.

For patients who improve yet continue to have persistent manifestations and continuing QoL impairments following 4–6 weeks of antibiotic retreatment, decisions regarding the continuation, modification or discontinuation of treatment should be based on several factors. In addition to those listed in Recommendation 3b, the decision to continue treatment may depend on the length of time between the initial and subsequent retreatment, the strength of the patient's response to retreatment, the severity of the patient's current impairments, whether diagnostic tests, symptoms or treatment response suggest ongoing infection and whether the patient relapses when treatment is withdrawn.

In cases where the patient does not improve after 4–6 weeks of antibiotic retreatment, clinicians should reassess the clinical diagnosis as well as the anticipated benefit. They should also confirm that other potential causes of persistent manifestations have been adequately investigated prior to continuing antibiotic retreatment. Decisions regarding the continuation, modification or discontinuation of treatment should consider the factors noted above as well as the definition of an adequate therapeutic trial.

Whenever retreatment is continued, the timing of subsequent follow-up visits should be based on the level of the therapeutic response, the severity of ongoing disease, the duration of current therapy and the need to monitor for adverse events. (Recommendation, very low-quality evidence).

Role of patient preferences

High: See Recommendation 3b.

The complete discussion of the individual clinical questions

Q1. Does a single 200 mg dose of doxycycline following a tick bite provide effective prophylaxis for Lyme disease?

Evidence

The panel conducted a Medline search on 5 March 2013 for RCTs and meta-analyses, which investigated using a single dose of doxycycline for antibiotic prophylaxis of *Ixodes scapularis* bites. The search used this strategy: *Ixodes scapularis* bites OR erythema migrans/prevention OR erythema chronicum migrans/prevention OR Lyme disease/prevention and these filters: comparative study, clinical trial, meta-analysis, humans. The search identified 99 papers. Four trials of antibiotic prophylaxis following an *I. scapularis* bite that were conducted in the USA and two meta-analyses involving some or all of those trials were identified and reviewed [56–61]. Three trials were excluded because they investigated the efficacy of various 10-day antibiotic regimens rather than the efficacy of a single 200 mg dose of doxycycline [56–58]. Given that the two meta-analyses drew substantially from these trials, both were excluded. The fourth trial evaluated the effectiveness of a single 200 mg dose of doxycycline following a tick bite for the prevention of an EM rash at the bite site [59].

Bias

The single-dose doxycycline trial was designed using prevention of an EM rash at the bite site as a surrogate for the prevention of Lyme disease [62]. This surrogate has not been validated. Although 15 years of CDC surveillance data documented that 31% of reported surveillance cases lacked an EM rash [63], the single-dose doxycycline trial was not designed to detect cases of Lyme disease in which the rash was absent. Instead, the trial design regarded all subjects lacking an EM as disease negative, thus biasing the trial in favor of finding treatment effective.

It should be noted that the single-dose doxycycline trial identified three subjects with clinical and laboratory evidence (seroconversion) of early Lyme disease who lacked an EM at the bite site, thus demonstrating that the prevention of an EM rash at the bite site is not an appropriate surrogate for prevention of Lyme disease [62].

Later manifestations of Lyme disease may take months or years to develop [64–68]. The trial's 6-week observation period was therefore insufficient to detect treatment failure and thus biased the trial toward finding treatment to be effective [62].

Investigators neglected to state that failed treatment resulted in seronegative disease as exhibited by one subject in the study [62]. This unfavorable outcome was not included in the risk–benefit assessment, biasing the study in favor of treatment.

Precision

The single-dose doxycycline trial was incapable of measuring the effectiveness of a single 200 mg dose of doxycycline for Lyme disease prevention because outcome measurements were limited to documenting the occurrence of an EM rash at the bite site as opposed to all disease manifestations [62]. However, the trial did demonstrate that treatment with doxycycline resulted in fewer EM rashes than placebo, 1 of 235 (0.4%) and 8 of 247 (3.2%), respectively ($p < 0.04$) [59]. Yet the data here are sparse, coming from a single study with few events, and, thus, imprecise.

The corresponding relative treatment effectiveness was reported to be 87%, with a 95% CI of 25–98% [59]. The wide CI indicates that the finding was imprecise. This value, however, appears to be incorrect. Although the authors reported using the Fisher exact test to calculate the odds ratio, by our calculations, the correct CI is 0.003–0.968, corresponding to a 95% CI on the scaled risk difference from 3.2 to 99.7%. This wider 95% CI suggests the study findings are consistent with a

Table 2. Quality of the evidence, in aggregate, supporting single-dose doxycycline for Lyme disease prophylaxis.

No. of studies	Limitations	Imprecision	Inconsistency	Indirectness	Quality
1	Inappropriate surrogate (EM) Insufficient duration of observation Insufficient reporting of negative treatment-associated outcomes	Few events Wide CI Unsupported assumption regarding outcomes in dropouts	Non-replicated in humans Inconsistent with animal model	Not applicable to patients bitten by species other than *Ixodes scapularis* Not applicable to patients exposed to multiple tick-borne diseases Efficacy not applicable to other antibiotics Effectiveness findings applicable to prevention of EM only and not other, non-EM presentations	Very low

EM: Erythema migrans.

much smaller minimum treatment effect, with the lower limit of the CI reflecting the possibility of only a 3.2% reduction in the risk of EM in the antibiotic arm compared with placebo. Thus, the trial was not well powered to precisely measure the treatment effect despite being adequately powered to detect statistical significance.

Although the dropout rate was low (11%), the assumption that none of the participants who dropped out developed an EM is unsupported and biased the estimated incidence in each arm downward. Furthermore, had a single EM in the antibiotic arm been missed due to patient dropout, then the statistical significance of the primary outcome would have been lost ($p = 0.11$). It is unsettling when changing one participant's outcome can dramatically affect a study's conclusion.

Consistency

No other clinical trials have evaluated the effectiveness of a single 200 mg dose of doxycycline for the prevention of an EM rash at the bite site; therefore, the consistency of this finding in humans cannot be judged.

However, the effectiveness of doxycycline prophylaxis has been studied in a murine model [69,70] and the findings were inconsistent with that of the single-dose doxycycline trial [62]. In contrast to the human trial, which used a surrogate marker, the murine study used tissue cultures and post-treatment necropsy findings to provide direct evidence of treatment effectiveness. In the murine model, single-dose oral doxycycline was 43% effective for preventing Lyme disease [69]. A second murine study using ticks dually infected with *Borrelia burgdorferi* and *Anaplasma phagocytophilum* demonstrated that single-dose oral doxycycline was 20 and 30% effective for preventing *B. burgdorferi* and *A. phagocytophilum* infections, respectively [70].

While it has been suggested that the lower efficacy of doxycycline in the murine studies was related to differences between mice and humans with regard to the duration of time that doxycycline levels exceeded the minimal inhibitory concentration for *B. burgdorferi* following a single oral dose of doxycycline (T > minimal inhibitory concentration) [71], subsequent pharmacodynamic modeling found that other pharmacodynamic parameters correlated better with efficacy [72]. However, these findings were based on flawed assumptions. Thus, the reason for the apparently lower efficacy of single-dose oral doxycycline in mice is unclear. It is worth noting that the 95% CI in the study by Nadelman *et al.* was quite large, 3.2–99.7% (see precision discussion above), suggesting that true treatment effectiveness was approximately 50% [69], a value comparable to that of the murine study [69].

Directness (generalizability)

The directness of the trial is limited to patients bitten by *I. scapularis* ticks treated with a single-dose doxycycline. The effectiveness of single-dose regimens using other antibiotics and the effectiveness of single-dose doxycycline in other *Ixodes* species have not been evaluated. Further, animal models suggest single-dose oral doxycycline prophylaxis is less effective when multiple pathogens are simultaneously transmitted to a host [70]; therefore, the findings are not applicable to patients exposed to *B. burgdorferi* and *A. phagocytophilum* and the applicability to patients exposed to *B. burgdorferi* and other co-infecting pathogens cannot be assumed.

Evidence quality, in aggregate

Overall, the quality of the evidence supporting the use of a single 200 mg dose doxycycline following a tick bite is very low (Table 2), implying that the true effectiveness of a single 200 mg dose of doxycycline is likely to be substantially different from the trial's reported effectiveness rate [6].

Benefits

The single 200 mg dose doxycycline trial design employed an unvalidated and inappropriate surrogate and the duration of the observation period was inadequate. The reported 87% efficacy of single-dose doxycycline therapy was with regard to the observed reduction in the incidence of an EM rash at the bite site in the doxycycline subjects compared with the placebo subjects (Table 3) [59], but the reliability of this finding is diminished by its imprecision and its clinical significance is questionable (see quality of evidence discussion above). Therefore, the trial's significant design deficiencies prohibit conclusions regarding the efficacy and, thus, the benefits of single-dose doxycycline therapy for the prevention of Lyme disease.

Table 3. Summary of findings regarding the effectiveness of single-dose doxycycline for prevention of erythema migrans rashes.

	Incidence placebo	Incidence single-dose doxy	Treatment efficacy	N (trials)	Evidence quality
EM prevention	8/247	1/235	87%; 95% CI: 3.2–99.7%	482 (1)	Very low

Safety of single-dose doxycycline.
N = 235; Adverse events: 1 patient who failed therapy was persistently seronegative; no other serious adverse events.
EM: Erythema migrans.

Harms

Treatment failure may result in seronegative Lyme disease. Although the single-dose doxycycline trial was not designed to determine whether this regimen could result in seronegative Lyme disease, the subject in the doxycycline arm who failed treatment remained negative on follow-up serologic testing, suggesting that this occurred [62,73]. Clinical trials, case reports and studies in non-human primates have also documented instances of seronegative disease [33,74–76]. While the mechanisms allowing for seronegative disease have yet to be fully investigated, antibiotic treatment has been shown to abrogate the immune response in *Coccidioides* spp. [77], primary syphilis [78], rheumatic fever [79] as well as Lyme disease [80,81]. It is postulated that antibiotic therapy reduces the antigenemia needed for the immune system to establish an immunologic response [77]. Inducing a seronegative disease state may lead to diagnostic and treatment delays, which are associated with poorer outcomes, and the development of a chronic form of the illness [16,27,32,82,83].

Risk–benefit assessment

The potential harms of the single-dose oral doxycycline prophylactic regimen and the magnitude of those harms significantly outweigh its benefits. In assessing the risk–benefit profile, the panel considered the unknown efficacy of single dose prophylaxis in preventing the development of Lyme disease and the magnitude of the potential harm created by inducing a seronegative state, including its concomitant diagnostic and treatment delays and the resultant increased risk of developing a chronic form of the disease, which is more difficult to treat successfully. The panel also considered findings from a murine model, which demonstrated that the effectiveness of single-dose doxycycline is further reduced in dual infections involving *B. burgdorferi* and *A. phagocytophilum*, an important consideration in many regions of the USA. Additionally, the panel noted that the effects of this regimen on the clinical presentation, detection and prevention of other common *Ixodes*-borne co-infections are unknown.

Values

The panel placed a high value on preventing disease, thereby avoiding both the unnecessary progression from a potentially preventable infection to one that is chronic and associated with significant morbidity and costs. The panel placed a high value on not causing the abrogation of the immune response. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 1a

Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis. (Recommendation, very low-quality evidence)

Role of patient preferences

Low: The relative trade-offs between risks and benefits are clear enough that most patients will place a high value on avoiding a seronegative state and its attendant delays in diagnosis and treatment.

Recommendation 1b

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. The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis (see remarks below). (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Most patients will place a high value on preventing chronic illness. However, some patients will value avoiding unnecessary antibiotics and prefer to not treat a tick bite prophylactically. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 1c

During the initial visit, clinicians should educate patients regarding the prevention of future tick bites, the potential manifestations of both early and late Lyme disease and the manifestations of the other tick-borne diseases that may have been contracted as a result of the recent bite. Patients receiving antibiotic prophylaxis should also be given information describing the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any and all tick-borne disease manifestations and manifestations suggestive of a *C. difficile* infection (Recommendation, very low-quality evidence).

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Remarks

Lyme disease often results from unrecognized tick bites [32,84], which do not provide an opportunity for administering antibiotic prophylaxis. When antibiotic prophylaxis is employed for known bites, it is imperative that treatment begin without delay. A recent murine study demonstrated that prophylaxis was most effective when given immediately after a bite and that effectiveness diminished with treatment delays [85]. Although no studies to date have specifically investigated the efficacy of antibiotic prophylaxis for bites from other *Ixodes* species, it is reasonable to provide prophylaxis for such bites pending future research.

The evidence supporting use of 20 days of antibiotics is limited to the previously mentioned murine trials [69,70]. In the first trial, investigators demonstrated that a long-acting form of doxycycline, with measurable levels for 19 days, was 100% effective for preventing Lyme disease [69]. In the dual-exposure model, the long-acting form of doxycycline was 100% effective for preventing *B. burgdorferi* and *A. phagocytophilum* infections [70]. No long-acting, injectable doxycycline preparation is available for use in humans [62], which is why the panel recommends using 100–200 mg of doxycycline twice daily for a minimum of 20 days. One advantage to this regimen is that it would also address situations where patients are exposed to both *B. burgdorferi* and *A. phagocytophilum*.

Analysis of the single-dose doxycycline trial highlights the problems inherent in formulating treatment recommendations on the basis of a single study and demonstrates that a randomized, placebo-controlled study design, in and of itself is not a guarantee that the study will produce high-quality evidence. The panel recognizes that recommendations based solely on animal models are also problematic. Therefore, the panel encourages the NIH to fund appropriately designed trials in order to investigate the optimum duration of treatment for a known *Ixodes* bite.

Given that doxycycline dosages of 100 mg twice daily may not provide adequate levels in all tissues or in all patients [86], some clinicians may prefer to prescribe higher daily doses [52,86–89]. Regardless of the selected dose, clinicians should advise patients to take probiotics daily while on antibiotic therapy. Probiotics reduce the risk of *C. difficile* colitis and antibiotic-associated diarrhea [44,45].

'Watchful waiting' does not satisfy a strict definition of prophylaxis. Rather than acting to prevent disease, this option seeks the early identification and treatment of Lyme disease infections resulting from a known bite. The hallmark of early disease is the EM rash; and as previously noted, almost a third of reported surveillance cases of Lyme disease lack this finding [16,18,63]. Given the possible absence of an EM rash in a patient with a known bite, this option not only withholds primary preventative therapy, it potentially loses an opportunity to provide secondary prevention as well, should the early, non-EM manifestations of the infection be missed. However, patients wishing to avoid antibiotics may prefer this option, in which case clinicians should emphasize that patients must immediately report the occurrence of Lyme-related symptoms so that appropriate antibiotic therapy can be instituted.

In cases where doxycycline is contraindicated, clinicians may consider using other antibiotics known to be effective in Lyme disease, such as amoxicillin, cefuroxime or azithromycin, although there is no evidence to guide decisions with regard to the dose and duration of use for these agents. The excluded trials of antibiotic prophylaxis investigated the therapeutic efficacy of 10 days of amoxicillin, three-times daily [58]; penicillin, four-times daily [56,57] and tetracycline, four-times daily [57]. None of the trials was able to demonstrate efficacy, primarily due to the low incidence of disease in the placebo groups [56,57].

Some guidelines recommend that clinicians learn to estimate attachment times for recovered ticks based on their scutal index, but expertise is required to do this and it is unrealistic to assume that all clinicians can or will acquire such skills. In the single-dose doxycycline study, 9.9% of the bites from nymphal ticks that exhibited any degree of engorgement resulted in the development of an EM at the bite site [59]. Therefore, the panel determined that it was prudent to routinely offer prophylaxis under such circumstances and that withholding therapy from patients who failed to meet an arbitrary minimum tick attachment time was inappropriate. Similarly, the panel recognizes that clinicians frequently lack information regarding current infection rates for a given tick population (often because the research to establish local infectivity rates has not been done) and that tick infection rates in the same locale vary significantly on an annual basis [90]. Therefore, the panel concluded that meeting a specific tick infection rate should not be a prerequisite for antibiotic prophylaxis.

Q2. Should the treatment of an EM rash be restricted to 20 or fewer days of the first-line oral agents (azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin)?

Evidence

The panel conducted a Medline search on 5 March 2013 for prospective randomized clinical trials investigating the effectiveness of 5–20 days of oral azithromycin, cefuroxime, doxycycline, phenoxymethylpenicillin or amoxicillin for the treatment of EM. The search used the following strategy: (erythema migrans OR erythema chronicum migrans OR lyme OR lyme borreliosis) AND (amoxicillin/therapeutic use OR azithromycin/therapeutic use OR penicillin/therapeutic use OR cefuroxime/therapeutic use OR doxycycline/therapeutic use) AND (Clinical trial OR comparative study OR meta-analysis). The search identified 76 papers; 51 reported trial outcomes.

A preliminary assessment found that 27 papers described studies that either investigated antibiotic treatment of non-EM presentations (23); were primarily interested in disseminated disease (3) or did not involve any of the antibiotics of interest

Table 4. Quality of the evidence, in aggregate, that supports restricting the antibiotic treatment of erythema migrans to 20 or fewer days.

No. of studies	Limitations	Precision	Consistency	Indirectness	Evidence quality
9 [46–49,53,74,88,91,92]	No single trial design investigated all agents Trials differed by agents, duration of therapy, length of observation Insufficient observation in most Overly broad definitions of success Lack of a standard outcome definition Use of non-ITT longitudinal data methods	Limited number of trials Small sample sizes Only 3 of 9 reported CI	No trial investigated all 4 classes of antibiotics. As originally reported: - Efficacies of individual agents were inconsistent - Relative efficacies among trials investigating the same agents were inconsistent When uniform design elements applied and outcomes assessed by treatment duration: - Inconsistent intra-agent success rates - Inconsistent relative outcomes in inter-agent comparisons	Not applicable to non-EM early Lyme; EM with CNS dissemination, co-infected or immunocompromised patients European trials may not be applicable to the US patients	Very low

†Several comparative studies described differing durations of therapy.
EM: Erythema migrans; ITT: Intention to treat.

(1). These were not considered further. An additional 15 trials were excluded because additional review demonstrated that they were either retrospective studies (2); incompletely randomized (1); used a symptom list during post-treatment assessments that did not include commonly reported symptoms of the disease (7) or had a non-completion rate of 20% or higher (5). Thus, nine trials met the requirements for this GRADE analysis and were evaluated in detail (Tables 4 & 5) [46–49,53,74,88,91,92].

Rating the quality of the evidence

Bias

None of the trials compared all four antibiotic classes (azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin). The nine trials had significant differences in design elements including: antibiotic agents investigated, duration of therapy, outcome definitions, length of observation period and longitudinal data methods; these differences potentially biased findings in favor of one or more agents and make it difficult to draw broad conclusions regarding the effectiveness of the various agents.

Observation periods ranged from 3 to 24 months. 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 [32,33,93]. For example, one trial reviewed here reported a relapse at 20 months [46] and Logigian *et al.* found that in their subjects (all of whom had neurologic manifestations of Lyme disease), the median time from EM to chronic CNS symptoms was 26 months, with a range of 1–168 months. Thus, trials with longer observation periods are more likely to capture disease relapse and subsequently report lower success rates. Therefore, variations in the length of the observation period may bias efficacy findings in favor of agents that were investigated in trials utilizing short observation periods.

Recognizing this, investigators in two of the EM trials cited the need for longer observation periods in their discussions [47,74]; one suggested that to accurately compare agents, observation periods would need to extend 2 years post-treatment [47]. Of the nine trials reviewed by the panel, only one [46] met this suggested standard and, given that relapse may occur even later, 2 years may not be sufficient.

The lack of standardized outcome definitions also introduces bias. The trials used broad definitions of treatment success that differed by trial [46–49,53,74,88,91,92]. All required the complete resolution of EM and an absence of new findings but, to varying degrees, each trial allowed subjects with improved yet persistent symptoms and subjects who had developed new symptoms consistent with Lyme disease during the observation period to be included within the success group. Thus, treatment success was not synonymous with the full restoration of the pre-Lyme disease health status and prevention of late manifestations of Lyme disease and, therefore, all of the trials were biased toward finding treatment to be effective.

The choice of longitudinal data methods may bias findings by either overstating or understating success rates [94] and the nine trials employed different methods for handling subjects who did not complete the study as designed [46–49,53,74,88,91,92]. Seven trials used complete-case methodology [46–48,53,74,88,91], one reported results in both complete-case and last observation

Table 5. Summary of findings regarding the effectiveness of treating an erythema migrans rash with 20 or fewer days of antibiotics based on a re-analysis of the original trial data to reflect patient-centered outcomes.

Duration of treatment, in days	Outcome	Number of trials, success rate by agent†			
		Azith	*Cefur*	*Doxy*	*PMP/Amox*
≤10 days	Return to baseline without relapse	6 trials [46–49,53,74] 230/298 (77.8%)	No trials	1 trial [53] 14/22 (63.6%)	2 trials [48,53] 11/52 (78.8%)
11–19	Return to baseline without relapse	No trials	1 trial [92] 110/140 (78.6%)	3 trials [46,47,49] 77/115 (67.0%)	1 trial [46] 12/23 (52.2%)
20	Return to baseline without relapse	No trials	2 trials [88,91] 48/78 (61.5%)	No trials	2 trials [74,91] 114/135 (84.4%)
5–20	Adverse events	Serious adverse events, defined as allergic reactions, *Clostridium difficile* infections, any adverse event resulting in withdrawal from study or change in therapeutic agent, and any adverse event labeled by the investigators as 'serious' occurred in 21 of 1068 subjects (2.0%) [46–49,53,74,88,91,92]. None of the adverse events was specifically categorized as allergic reactions. The majority of serious adverse events involved the skin (13), including non-specific skin rash (6) [74], drug eruptions (6) [53] and serious photosensitivity reaction (1) [46]. Gastrointestinal adverse events were also common, including poor medication palatability in pediatric subjects (2) [91], nausea and vomiting (1) [48] and diarrhea (5) [49,74,88]. A single subject was treated for *C. difficile* infection shortly after completing treatment [91]. No deaths were reported.			

†CIs for the individual trials are available in Supplementary Appendix III.
Azith: Azithromycin; Cefur: Cefuroxime; Doxy: Doxycycline; PMP/Amox: Phenoxymethylpenicillin/amoxicillin.

carried forward [92] and one trial employed an intention-to-treat (ITT) approach [49].

Complete-case methodology is likely to overstate treatment success because subjects who leave the trial prematurely due to treatment ineffectiveness or intolerance are excluded from outcome calculations [94,95]. Thus, the trials that used this approach were biased towards finding higher treatment success rates. Last observation carried forward completes the data set for missing subjects by imputing the value from the most recent visit to all subsequently missed observation points, implying outcomes are static [94,95]. Because relapses occur in Lyme disease, this methodology may overstate treatment success; thus, the trials that used last observation carried forward were likely biased towards finding higher treatment success rates.

ITT models evaluate subjects by their assigned treatment, regardless of compliance [94,95]. These models also impute data for the missing and the chosen values reflect assumptions regarding the likelihood that certain potential outcomes actually occurred [95]. Potential assumptions range from worst-case to best-case scenarios. In general, ITT methodology is thought to better represent clinical realities, where patients may inadvertently or purposefully supplement treatment with other interventions that affect outcomes or elect to abandon ineffective treatment altogether [94,96]. The EM trial that employed ITT methodology assumed that missing subjects fulfilled the worst case scenario, that is, had failed [49], biasing the trial toward finding treatment less successful. However, adopting a conservative approach to efficacy determinations avoids the potential harms associated with overstating treatment success and understating treatment failures.

Precision

The number of trials that investigated a given antibiotic was limited and sample sizes in the individual trials were small. Trial numbers per agent ranged from 3 to 5 and median sample sizes per agent ranged from 28 to 63. Small sample sizes are susceptible to random chance and small study bias [97–99].

Only three of the nine trials reported CIs for treatment efficacy [74,88,92]; a fourth reported CIs for the risk of a drug eruption [53].

Consistency

Outcomes, as originally reported by the nine trials, were inconsistent. Two trials simultaneously evaluated the effectiveness of azithromycin, doxycycline and phenoxymethylpenicillin/amoxicillin plus probenecid [46,53]. Strle *et al.* reported that 28% of subjects, overall, had post-treatment signs/symptoms. By agent, 15% of azithromycin, 26% of doxycycline and 43% phenoxymethylpenicillin subjects had post-treatment manifestations [46]. In contrast, Massarotti *et al.* reported that azithromycin, doxycycline and amoxicillin plus probenecid were equally efficacious [53].

Seven trials compared two of the three agents, although the pairings differed [48,49,74,88,91,92,100]. Weber *et al.* found that

azithromycin and phenoxymethylpenicillin were comparable, while Luft *et al*. found amoxicillin to be more efficacious for preventing late disease than azithromycin [48,74]. Azithromycin was more efficacious than doxycycline in the 1993 trial by Strle *et al*., but Barsic *et al*. found the two agents equivalent [47,49].

In a separate analysis, success rates for the individual agents were determined after uniform patient-centered outcome definitions and longitudinal data methods were applied to the original data (see Benefits section below and Table 5). These results were also inconsistent. Success, in relation to treatment duration, demonstrated inter- and intra-agent inconsistencies. For example, when the treatment duration was 11–19 days, cefuroxime (78.6%) outperformed phenoxymethylpenicillin/amoxicillin (52.2%) but for 20 days of treatment, success for phenoxymethylpenicillin/amoxicillin (84.4%) was greater than that of cefuroxime (61.5%). Success rates for individual agents were also inconsistent; both cefuroxime and phenoxymethylpenicillin/amoxicillin had higher success rates with shorter, rather than longer, treatment durations.

Directedness (generalizability)

Findings are applicable to patients with EM rashes, without evidence of CNS dissemination. It cannot be assumed that findings are applicable to patients with Lyme disease inclusive of CNS dissemination, other tick-borne diseases or immunocompromised states [101]. Nor can it be assumed that findings are applicable to non-EM early Lyme disease [102]. Given the clinical variations between the genospecies [103,104], results from European trials, where *Borrelia afzelii* is the dominant cause of EM rashes [102], may not be applicable to the US patients.

Evidence quality, in aggregate

The quality of the evidence addressing the effectiveness of 5–20 days of antibiotics for the treatment of EM is very low, implying that the true effectiveness of a 5–20 day course of antibiotics for the treatment of an EM rash is likely to be substantially different from the trials' reported effectiveness rate.

Benefits

The limitations of the evidence from the original trials reduce the reliability of their findings. Given that no trial directly compared all classes of agents (azithromycin, cefuroxime, doxycycline and phenoxymethylpenicillin/amoxicillin) and direct comparisons between individual trials are hampered by differences in outcome definitions, length of the observation periods and longitudinal data methodologies, the ability to draw valid conclusions regarding the relative effectiveness of commonly prescribed antibiotic regimens is impaired.

To provide comparative information on patient-centered outcomes by agent – information of clinical import to clinicians and patients – the original trial data were reanalyzed. To minimize biases due to variations in trial design, standardized, patient-centered definitions of treatment success and failure and uniform statistical methodology, utilizing the conservative approach of Barsic *et al*. [49], were applied to the original trial data. To avoid overstating the effectiveness of the investigated antibiotics, the panel specifically chose to assume that those who failed to complete the trial were treatment failures.

Success was defined as the complete resolution of EM and all associated symptoms and findings, without evidence of disease relapse or the development of new manifestations consistent with Lyme disease during the observation period. The panel viewed this outcome definition as the outcome that would matter most to patients and thought it was consistent with the expectation that the appropriate treatment of an EM rash should restore the patient to their pre-morbid baseline.

Failure included any outcome short of that. Subjects described by the investigators as failures and those who were retreated (regardless of the post-retreatment outcome) were considered failures for the purpose of this outcome analysis. Subjects who had ongoing symptoms at the final end point, including those described as 'partial responders', were also considered failures. In some instances, this resulted in subjects being re-categorized as failures. Subjects who were 'unevaluable', wrongly enrolled, non-compliant, withdrawn prematurely due to adverse reactions to their assigned antibiotic or lost to follow-up were also considered failures for the purpose of this analysis.

Success rates across the nine trials differed significantly. The lowest, 52.2% (CI: 30.6, 73.3), was in the phenoxymethylpenicillin arm of the 1992 trial by Strle *et al*. and the highest, 93.3% (CI: 68.1, 99.8), was in the high-dose cefuroxime arm in the trial by Eppes and Childs (see Supplementary Appendix III). The two arms with the highest success rates had exceptionally small sample sizes; one arm had 13 subjects, the other had 15 [91]. The two arms with the lowest success rates also had small samples sizes, 23 subjects in one and 26 in the other [46,53].

Success rates were subsequently regrouped by agent and treatment duration and weighted average success rates for the various regimens were then calculated. The outcome results from arms which had non-completion rates equal to or exceeding 20% were excluded from the calculations. As shown in Table 5, success rates for a given treatment duration vary by antibiotic class. Twenty days of phenoxymethyl-penicillin/amoxicillin had the highest overall success rate of all of the regimens, 84.4%, while 11–19 days of these same agents had the lowest success rate, 61.5%.

Harms

Serious adverse events, defined as allergic reactions, *C. difficile* infections, any adverse event resulting in withdrawal from study or change in therapeutic agent and any adverse event labeled by the investigators as 'serious' occurred in 20 of 1068 subjects (1.9%) (Table 5). None of the adverse events was specifically categorized as allergic reactions. The majority of serious adverse events involved the skin (11), including non-specific skin rash (6) [74], drug eruptions (4) [53] and serious

photosensitivity reaction (1) [46]. Gastrointestinal adverse events were also common, including poor medication palatability in pediatric subjects (2) [91], nausea and vomiting (1) [48] and diarrhea (5) [49,74,88]. A single subject was treated for *C. difficile* infection shortly after completing treatment [91]. No deaths were reported.

Although the panel did not consider a Jarisch–Herxheimer reaction an adverse event, four EM trials reported a Jarisch–Herxheimer reaction in 60 of 351 subjects (17.1%) (range 12.1–18.7%) [47,53,88,91].

Risk–benefit assessment

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.

Although it is generally assumed that antibiotic regimens of shorter duration will be associated with a lower rate of significant adverse events, adverse event rates for oral antibiotics are generally quite low regardless of the duration of use [105–107]. The panel concluded that while antibiotic treatment regimens of 20 or fewer days may result in slightly fewer significant adverse events compared with regimens of longer duration, that benefit does not offset the potential harms associated with the unacceptably high failure rates resulting from this treatment approach. Furthermore, as previously noted, the concomitant use of probiotics should reduce the risk of *C. difficile* colitis and antibiotic-associated diarrhea [44,45].

Values

The panel placed a high value on avoiding both: the unnecessary progression from a potentially curable infection to one that is chronic and the morbidity and costs associated with chronic disease. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong and compelling evidence to the contrary.

Recommendation 2a

Treatment regimens of 20 or fewer days of phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline and 10 or fewer days of azithromycin are not recommended for patients with EM rashes because failure rates in the clinical trials were unacceptably high. Failure to fully eradicate the infection may result in the development of a chronic form of Lyme disease, exposing patients to its attendant morbidity and costs, which can be quite significant. (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: Although many patients will value avoiding the risk of treatment failure over a potentially modest increase in the risk of significant adverse events that may be associated with longer treatment durations, others may prefer to avoid the additional risks of longer treatment. Clinicians should inform patients that the combined failure rate for the individual agents investigated in the previously discussed EM trials were judged by this panel to be unacceptably high when antibiotic treatment was restricted to 20 or fewer days; the evidence supporting the use of longer treatment durations is limited and of low quality [41–43] and increases in antibiotic duration may increase the risk of antibiotic-associated adverse events, although the risks associated with oral antibiotics are low and some of this risk can be mitigated by the concomitant use of probiotics [44,45,108]. Treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2b

Clinicians should prescribe amoxicillin, cefuroxime or doxycycline as first-line agents for the treatment of EM. Azithromycin is also an acceptable agent, particularly in Europe, where trials demonstrated it either outperformed or was as effective as the other first-line agents [46–49]. Initial antibiotic therapy should employ 4–6 weeks of amoxicillin 1500–2000 mg daily in divided doses, cefuroxime 500 mg twice daily or doxycycline 100 mg twice daily or a minimum of 21 days of azithromycin 250–500 mg daily. Pediatric dosing for the individual agents is as follows: amoxicillin 50 mg/kg/day in three divided doses, with a maximal daily dose of 1500 mg; cefuroxime 20–30 mg/kg/day in two divided doses, with a maximal daily dose of 1000 mg and azithromycin 10 mg/kg on day 1 then 5–10 mg/kg daily, with a maximal daily dose of 500 mg. For children 8 years and older, doxycycline is an additional option. Doxycycline is dosed at 4 mg/kg/day in two divided doses, with a maximal daily dose of 200 mg. Higher daily doses of the individual agents may be appropriate in adolescents.

Selection of the antibiotic agent and dose for an individual patient should take several factors into account. In the absence of contraindications, doxycycline is preferred when concomitant Anaplasma or Ehrlichia infections are possibilities. Other considerations include the duration and severity of symptoms, medication tolerability, patient age, pregnancy status, co-morbidities, recent or current corticosteroid use [54,55], cost, the need for lifestyle adjustments to accommodate certain antibiotics and patient preferences. Variations in patient-specific details and the limitations of the evidence imply that clinicians may, in a variety of circumstances, need to select therapeutic regimens utilizing higher doses, longer durations or combinations of first-line agents. (Recommendation, very low-quality evidence)

Role of patient preferences

Moderate: See Recommendation 2a.

Recommendation 2c

Clinicians should provide ongoing assessments to detect evidence of disease persistence, progression or relapse or the presence of other tick-borne diseases. Lacking a test of cure, ongoing assessments are crucial for determining if treatment has been clinically effective (see remarks following Recommendation 2f). The first assessment should immediately follow the completion of therapy and subsequent evaluations should occur on an as-needed basis. (Recommendation, very low-quality evidence)

Role of patient preferences

Low: The benefits of monitoring the response to treatment clearly outweigh any attendant risks associated with monitoring.

Recommendation 2d

Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. 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 (see remarks following Recommendation 2f). There is a wide range of options and choices must be individualized, based on the strength of the patient's initial response. Dosage ranges for oral agents are as noted in Recommendation 2b.

Strong-to-moderate responses favor extending the duration of therapy of the initial agent at the same dosage. Modest responses may prompt an increase in the dosage of the initial antibiotic or a switch to a different first-line agent. Tetracycline, with a total daily dose of 1000–1500 mg in three or four divided doses, is an additional option [50,109]. Due to its favorable pharmacokinetics, tetracycline may be more effective than doxycycline when initial therapy is non-curative [109].

Minimal or absent responses suggest a need for a combination of first-line agents, which includes at least one antibiotic that is able to effectively reach intracellular compartments [109,110]. Injectable penicillin G benzathine (Bicillin LA), totaling 1.2–3.6 million units weekly, or iv. agents such as ceftriaxone are other options. Intramuscular (IM) benzathine penicillin avoids the risks associated with gaining iv. access and it was effective in seemingly recalcitrant Lyme arthritis [111]. Ceftriaxone, 2 g iv. per day is known to be effective [16,17,32,33,54,112] and iv. cefotaxime [113], another cephalosporin, has also been recommended. iv. penicillin is less effective and requires more frequent dosing [114]. Additional iv. cell wall agents from the carbapenem and monobactam classes were effective *in vitro*, but have not been studied clinically [115].

Disease progression or recurrence suggests that the iv. agents or injectable penicillin G benzathine, as discussed above, may be required. For patients requiring antibiotic therapy beyond the initial treatment period, subsequent decisions regarding the modification or discontinuation of treatment should be based on the therapeutic response and treatment goals. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis (see remarks following Recommendation 2f). (Recommendation, very low-quality evidence).

Role of patient preferences

Moderate: While most patients will place a high value on the potential of regaining their pre-morbid health status and preventing chronic illness by continuing treatment, a substantial portion may also value avoiding unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2e

Clinicians should retreat patients who were successfully treated initially, but subsequently relapse or have evidence of disease progression. Support for retreatment is drawn from the EM trials themselves. In seven of the nine trials reviewed in this analysis [46,48,53,74,88,91,92], subjects who had evidence of treatment failure during the observation period were offered retreatment. Regimens used either oral [46,48,53,74,88,91,92] or iv. antibiotics [48,53,74,88,92], with the choice of agent and route apparently reflecting the investigators' clinical assessments and treatment preferences.

Therapeutic options include repeating the initial agent, changing to another oral agent or instituting injectable penicillin G benzathine or iv. ceftriaxone therapy. The previously listed dosage ranges for the individual agents would be appropriate. Choices must be individualized and based on several factors, including: the initial response to treatment; the time to relapse or progression; the current disease severity and the level of QoL impairments.

Prior to instituting additional antibiotic therapy, the original diagnosis should be reassessed and clinicians should evaluate patients for other potential causes that would result in the apparent relapse or progression of symptoms and/or findings (see remarks following Recommendation 2f).

The presence of other tick-borne diseases, in particular, should be investigated if that had not already been done. *I. scapularis* transmits several pathogens and the resulting infections may produce symptoms similar to those of Lyme disease. Thus, apparent relapse or disease progression following antibiotic therapy for Lyme disease may be indicative of a concurrent co-infection and not the failure to eradicate *B. burgdorferi*. The presence of other *Ixodes*-borne infections may increase the severity and duration of Lyme disease symptoms [116,117]. Treatment of dually infected patients has not been studied, therefore, the optimal antibiotic regimen for the Lyme disease component is unknown. The possibility of co-infections should not be casually dismissed. Two published surveys of Lyme disease patients found that many respondents were infected with more than one tick-borne pathogen [118,119]. A survey of 3090 patients diagnosed with Lyme disease found that laboratory confirmed cases of babesiosis and anaplasmosis were reported by 32.3 and 4.8% of respondents, respectively [119].

Following a long period of disease latency, minimal manifestations causing little deterioration in the patient's QoL favor continued observation or repeating therapy with the initial

agent; mild manifestations or QoL impairments may prompt a switch to a different first-line agent, tetracycline [50,109], or a combination of first-line agents (which includes at least one antibiotic that is able to effectively reach intracellular compartments) [109,110,120]. Intravenous or IM antibiotics such as injectable penicillin G benzathine or iv. ceftriaxone are other options.

Disease relapse or progression with mild manifestations or QoL impairments occurring within a few months of treatment suggests a need for longer regimens using either a combination of oral first-line agents, injectable penicillin G benzathine or iv. ceftriaxone. Regardless of the duration of disease latency, when disease manifestations or QoL impairments are significant or rapidly progressive, injectable penicillin G benzathine or iv. ceftriaxone may be required. Subsequent decisions regarding the modification or discontinuation of a patient's treatment should be based on the individual's therapeutic response and preferences (Recommendation, very low-quality evidence).

Role of patient preferences

High: While most patients will place a high value on the potential of regaining their pre-morbid health status and improving their QoL and preventing chronic disease through continued antibiotic treatment, a substantial portion will also value avoiding potentially unnecessary antibiotics. Hence, treatment risks, benefits and options should be discussed with the patient in the context of shared medical decision-making.

Recommendation 2f

Clinicians should educate patients regarding the potential manifestations of Lyme disease, carefully explaining that disease latency can be prolonged. Education should also include information on preventing future bites, the manifestations of the other tick-borne diseases that they may have contracted as well as the symptoms and signs of a *C. difficile* infection and the preventative effect of probiotics. Patients should be encouraged to immediately report the occurrence of any recurrent or newly developing manifestation of Lyme disease as well as those suggestive of other tick-borne diseases or a *C. difficile* infection. Clinicians should emphasize that the need to report manifestations of tick-borne diseases never expires. (Recommendation, very low-quality evidence)

Role of patient preferences

Low: The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

Remarks

This patient-centered analysis of the evidence from nine clinical trials of EM treatment demonstrates that treatment regimens which used 20 or fewer days of antibiotics were often ineffective. The findings of this analysis are consistent with those from a recently published observational study of EM. In the study by Aucott *et al.*, the authors reported that 21 of 63 (33.3%) patients treated with three weeks of doxycycline met the study's definition of post-treatment Lyme disease syndrome in that they experienced disease manifestations during the 3–6 month post-treatment interval [121]. Furthermore, reports of neurocognitive problems were 9% higher at the 6-month end point than at baseline.

Identifying patients at higher risk for treatment failure and offering them more extensive treatment may improve outcomes. Outcomes might also be improved by assessing the immediate post-treatment response and taking appropriate action. Several studies suggested that certain clinical presentations are associated with a higher risk of treatment failure. Results from two trials suggested that patients who remained symptomatic at the completion of therapy [74] or 1 month post-treatment [88] were at higher risk for long-term failure. These findings form the basis for Recommendation 2c. Other high-risk presentations included: increased severity of initial symptoms [50], paresthesia [88], dysesthesias [53], irritability [52], arthralgia [52], multiple EM [88] and the presence of co-infections [117]. In such circumstances, clinicians should consider lengthening the initial phenoxymethylpenicillin, amoxicillin, cefuroxime or doxycycline therapy to a minimum of 6 weeks or extending azithromycin treatment to a minimum of 4 weeks.

Relapse and/or disease progression may occur at any time and this analysis notes that longer observation periods increase the likelihood of detecting disease relapse, which would decrease the long-term efficacy noted in these trials. This conflicts with the oft stated position that success rates improve with time [71]. In a trial frequently cited in support of this position, success rates did increase over time when calculated on a complete case basis (the trial's chosen methodology for handling longitudinal data) [122]. However, the ITT data supplied in Table 3 of that paper documented that the absolute numbers of successfully treated subjects declined significantly between the 12- and 30-month visits. In the 10-day doxycycline arm, complete success peaked at 12 months, with 44 of 61 (72.1%) returning to their pre-Lyme disease baseline while at 30 months, only 35 of 61 (57.4%) were categorized this way [122]. Readers should note that while Table 3 of the study is entitled 'Clinical Response Based on an Intention-To-Treat Analysis of Patients for Whom Information Was Available*', this was not an ITT analysis. Calculating response rates based on a portion of the group rather than on all who were randomized to a particular arm is contrary to ITT principles.

Additionally, given that prior *B. burgdorferi* infections do not provide durable immunoprotection [123], clinicians should consider the possibility that the patient was re-infected and seek information to confirm or dispel that this occurred [124]. 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.

Disease manifestations may appear to relapse and/or progress for reasons unrelated to Lyme disease. 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 and sleep apnea. (*Note*: this list is not intended to be exhaustive and patient-specific circumstances will guide the physician in determining whether other potential etiologies of relapsing or progressive manifestations need to be investigated.)

Q3. Should patients with persistent manifestations of Lyme disease be retreated with antibiotics?

Evidence

The panel conducted a Medline search on 5 March 2013 for RCTs investigating the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease following treatment considered by some to be standard and appropriate antibiotic therapy for their stage of illness. The search used this strategy: chronic Lyme disease OR Lyme encephalopathy OR persistent Lyme disease AND antibacterial Agents/administration & dosage and this filter: clinical trial.

Five RCTs conducted in the USA were identified. Four met the inclusion criteria for this analysis [16–18]. A fifth trial had a non-completion rate in excess of 20% [87] and was excluded from this analysis on that basis. A Swedish trial was also excluded due to excessive incomplete data [125].

The four trials had unique designs. In one trial, Klempner *et al.* exclusively enrolled seropositive subjects and treatment consisted of 30 days of iv. ceftriaxone followed by 60 days of oral doxycycline or an identical placebo regimen [18]. A second trial by that same group used an identical design except enrolled subjects were exclusively seronegative [18]. Krupp *et al.* enrolled seropositive subjects with severe fatigue; participants received either 30 days of iv. ceftriaxone or an identical placebo [17]. Fallon *et al.* enrolled seropositive subjects with Lyme encephalopathy; treatment consisted of either 10 weeks of iv. ceftriaxone or an identical placebo [16].

Bias

The designs of three of the four trials introduced the potential for type II errors [126,127], which biased the trials against antibiotic retreatment. Type II errors occur when there is a failure to reject a false null hypothesis. With regard to treatment trials, type II errors would wrongly label effective treatment as ineffective.

Type II errors may arise when the designated treatment effect for a trial is too large. The primary end point in the trials by Klempner *et al.* was improvement in QoL, as measured by gains in the 36-item short-form health survey (SF-36) mental and physical component summary scores [18]. A biostatistical review of those trials noted that the minimal clinically important difference (MCID) in SF-36 scores have not been established for Lyme disease and it demonstrated that the designated treatment effect sizes for categorizing subjects as 'improved' likely exceeded the MCIDs of the SF-36 scores by several-fold [126].

The enrollment criteria and subsequent data analysis of the trials by Klempner *et al.* also raise the possibility of a type II error [127]. Subjects were not required to meet a specific level of symptom severity, which allowed for the recruitment of subject groups with baseline heterogeneity on the primary end point. Due to outcome averaging, studies failing to account for such baseline heterogeneity in their sample population are more apt to report no treatment effect. Of the four trials, only the trials by Klempner *et al.* failed to address baseline heterogeneity issues and these were the only trials which failed to find a treatment effect on any end point. In contrast, the subjects in the study by Krupp *et al.* were homogeneous with regard to fatigue and the *post hoc* analysis of Fallon *et al.* addressed baseline heterogeneity on this end point as well, with both trials finding a positive treatment effect on fatigue [16,17].

Delayed processing speed was not an inclusion criterion for the trial by Krupp *et al.* and subjects had minimal baseline deficits on this end point. The designated treatment effect, which was based on earlier studies of Lyme patients [128], called for an increase in processing speed that was unrealistically high for this group of subjects in that meeting the designated treatment effect would have required the subjects' processing speed to exceed healthy population norms [126]. Thus, the trial was biased on this end point [126].

All four trials enrolled subjects who had previously received extensive antibiotic treatment for Lyme disease yet remained ill. The presence of treatment refractory subjects biased the trials against finding treatment to be effective.

Krupp *et al.* also investigated an experimental biologic marker of current disease, namely, the presence of outer surface protein A (OspA) in the cerebrospinal fluid of Lyme patients. Although the trial was designed with clearance of OspA from the cerebrospinal fluid as a primary end point [17], only 16% of the subjects had OspA in their baseline cerebrospinal fluid [17], making it impossible to demonstrate a treatment effect in 84% of the subjects. Accordingly, this trial failed to validate the use of OspA as a surrogate marker and the trial was biased against finding treatment to be effective on this end point.

Results can be biased if unmasking occurs. Although they had no direct evidence that this occurred, Krupp *et al.* raised the concern that masking in their study may have been compromised as subjects in the ceftriaxone arm were more likely to correctly guess their treatment group than the placebo subjects. However, two reviews of the NIH-sponsored retreatment trials noted that the correct guesses could reflect that the subjects in the ceftriaxone arm were feeling better and, therefore, properly attributed this change to being on active therapy [126,127].

Precision

Sample sizes in the individual trials were small, ranging from 37 to 78 [16–18]. Small sample sizes are susceptible to random chance and small study bias [97–99].

The trial by Fallon *et al.* was underpowered. It enrolled 37 patients, yet its design required 45 subjects to achieve at least 80% power to detect an effect size of 1.1 with a two-sided test with $\alpha < 0.05$ [16]. The mental processing speed end point in the trial by Krupp *et al.* was designed with only 74% power [17].

Although the trials by Klempner *et al.* were sufficiently powered, the trials called for an unrealistically large treatment effect that likely exceeded the MCID for changes in the SF-36 scores of Lyme disease patients [126]. The selection of a smaller, and more appropriate, effect size would have required significantly larger sample sizes to achieve sufficient statistical power [126].

Consistency

Krupp *et al.* found retreatment provided a clinically meaningful reduction in severe fatigue and the *post hoc* analysis by Fallon *et al.* corroborated this finding [16,17]. In the treatment response rates in the trial by Krupp *et al.*, 64% improved in the treatment arm versus 18.5% in the placebo arm ($p < 0.001$) was similar to the response rates of Fallon *et al.*, where 66.7% of treated subjects improved versus 25% of the placebo group ($p < 0.05$) [16,17].

Cognitive benefits were evaluated by Krupp *et al.* and Fallon *et al.* [16,17]., but consistency cannot be judged because the trial by Krupp *et al.* was inadequately designed for this end point (see bias and precision sections above).

The trials by Klempner *et al.*, in contrast to those of Krupp *et al.* and Fallon *et al.*, reported finding no benefit from antibiotic retreatment [18]. As discussed above, the trials by Klempner *et al.* were inadequately designed, calling for a treatment effect that likely exceeded the MCID [126]. As such, the absence of a treatment benefit in these trials is uninformative.

Directness (generalizability)

The directness (generalizability) of the evidence is limited because entrance criteria led to the enrollment of subjects who are not representative of the full clinical spectrum of patients with persistent symptoms. Trial subjects had been ill for prolonged periods of time and had received extensive antibiotic treatment prior to enrollment [16–18]. Subjects in the antibiotic arms of the trials by Klempner *et al.* and Fallon *et al.* had been ill, on average, for 4.7 and 9.0 years, respectively [16,18]. Thirty-three percent of the subjects in the trials by Klempner *et al.* had been treated with 30 days of iv. ceftriaxone and subjects in the trial by Krupp *et al.* had received, on average, 7.2 weeks of antibiotic therapy, with 47.3% having been previously treated with a minimum of 2 weeks of iv. ceftriaxone [17,18]. Prior antibiotic treatment in the subjects by Fallon *et al.* was significantly higher. The average duration of therapy was 9.5 months, which included 2.3 months of iv. ceftriaxone use [16].

The trials also excluded patients with characteristics commonly seen in clinical practice. All four trials excluded patients with co-infections or confounding illnesses/conditions [16–18]. Fallon excluded patients who were negative on current ELISA and western blot testing and Krupp *et al.* excluded those who lacked both a history of a physician-documented EM and serologic confirmation of late manifestations [16,17]. However, seronegative status would not necessarily deter clinicians from offering antibiotic therapy [87,75]. Once subjects were enrolled, trial designs restricted the investigators' ability to prescribe non-antibiotic therapy to subjects, which is a common clinical practice. For example, the need for pain medication resulted in one subject being dropped from the trial by Fallon *et al.* [16]. Investigators' primary responsibility is to the trial and not potential enrollees, while clinicians are chiefly concerned with providing care to ill patients and thus they may choose to employ broader treatment criteria. Highly selective research entry criteria and treatment restrictions, like those employed in the four retreatment trials, serve the purpose of ensuring internal validity, but may do so at the expense of external validity, undermining the generalizability of the results to the population of patients clinicians see in practice.

Evidence quality, in aggregate

The quality of the evidence regarding the effectiveness of antibiotic retreatment in patients with persistent symptoms following standard and appropriate antibiotic therapy for Lyme disease is very low (Table 6), implying that the true effectiveness of retreatment is likely to be substantially different from the effectiveness rates seen in the four NIH-sponsored retreatment trials.

Benefits

Retreatment with ceftriaxone was effective in two of the four trials (Table 7). Krupp *et al.* found that 28 days of ceftriaxone was more effective than placebo (64 vs 18.5%; $p < 0.001$) for producing a clinically significant reduction in severe fatigue, a primary outcome [17]. The effect size was moderate to large [127]. Fallon *et al.* found that subjects treated with 70 days of iv. ceftriaxone achieved a moderate improvement (effect size = 0.81) in generalized cognitive function at 2 weeks post-therapy compared with those in the placebo arm (effect size = 0.30) ($p = 0.053$), although the preferential effect of drug versus placebo was not sustained at 14 weeks post-therapy [16]. The mechanisms leading to the subsequent loss of the cognitive gains are unknown; however, this long-term outcome may indicate that the offered therapy was incomplete. A planned secondary analysis demonstrated an interaction effect between baseline impairments and treatment, such that the ceftriaxone effect increased with higher baseline severity; this was demonstrated for the measures of pain and physical dysfunction at week 12 and sustained to week 24 [16]. On *post hoc* analysis, Fallon *et al.* also demonstrated a positive treatment effect on severe fatigue. Of the subjects in the trial by Fallon *et al.*, who met the fatigue entrance criteria of the trial by Krupp *et al.*, those who received ceftriaxone experienced significant

Table 6. Quality of the evidence, in aggregate, that supports antibiotic retreatment in patients with persistent symptoms of Lyme disease.

No. of studies	Limitations	Precision	Consistency	Indirectness	Evidence quality
4	Designated treatment effects were excessive [17,18] Unsupported design assumptions [17,18] Lack of pertinent inclusion criteria [17] Enrollment of treatment-refractory subjects	Small sample sizes (range 37–78) [16–18] Underpowered trial/end point [16,17]	Consistent finding of treatment effectiveness on fatigue in the trials by Krupp *et al.* and Fallon *et al.* [16,17]. Inconsistent findings on treatment effectiveness between the trials by Krupp *et al.*, Fallon *et al.* and Klempner *et al.* [16–18].	Subjects had prolonged illnesses [16,18] Subjects had a history of extensive antibiotic treatment [16–18] Excluded subjects with co-morbidities and medication use commonly seen in practice [16–18] Restricted use of non-antibiotic medications, limiting practice [16–18]	Very low

reductions in the level of their fatigue compared with those who received placebo (66.0 vs 25.0%; $p < 0.05$).

Harms

The NIH-sponsored retreatment trials described 15 serious adverse events among the 221 subjects (6.8%) [16–18]. Each event was associated with ceftriaxone itself or the need for venous access; 60 days of oral doxycycline therapy was not associated with any significant adverse event. Six individuals experienced allergic reactions [16–18], including one case of anaphylaxis [17]. Seven events were related to the iv. line [16–18], four cases involved line-related infections (all on placebo) [16,17], two cases involved thrombi [16] and one subject developed a pulmonary embolus [18]. Additionally, there was one case of cholecystitis [16] and one case of gastrointestinal bleeding with fever and anemia [18].

Risk–benefit assessment

The clinical population of patients with persistent manifestations of Lyme disease is heterogeneous; therefore, the risk–benefit assessment needs to be done on an individualized basis, taking into account the severity of an individual's persistent disease, their responsiveness to treatment, their ability to tolerate side effects associated with additional and potentially long-term treatment as well as their willingness to accept the risk associated with antibiotic treatment or, conversely, the level of their desire to avoid treatment-associated risk.

The scientific evidence regarding potential etiologic mechanisms for the development of persistent manifestations of Lyme disease continues to evolve. Proposed mechanisms include immune dysregulation of various types, tissue injury, infection-induced secondary conditions, unrecognized or undertreated co-infections and persistent infection [129,130]. Of these, we think the weight of the evidence supports persistent infection, although other mechanisms may co-exist and the exact etiology for persistent manifestations may vary from patient to patient. Given this uncertainty, the panel concluded that the evidence at hand regarding persistent infection and the potential benefits of retreatment are adequate to support those who wish to treat but is not overwhelming enough to mandate treatment.

The panel also determined 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 and thus it is inappropriate to constrain clinicians from exercising their clinical judgment.

In making these determinations, the panel considered the strength of the evidence addressing the effectiveness of antibiotic retreatment, the burden of disease and the risks associated with various antibiotic options. The panel weighed each in light of the marked heterogeneity within this patient population.

Potential benefits include the restoration of health, improved QoL and prevention of further decline in health status. While complete restoration of health was not identified in any of the four retreatment trials, the moderate-to-large treatment effect on severe fatigue demonstrated in the trial by Krupp *et al.* and the sustained interaction effects between baseline severity and improvements in pain and physical functioning seen in the trial by Fallon *et al.* suggested to the panel that retreatment may improve the QoL of some patients.

Others have reached a similar conclusion. In a recent review of the four retreatment trials, Fallon *et al.* make the point that guidelines restricting the use of antibiotics in patients with persistent manifestation of Lyme disease are based on the erroneous dismissal of the treatment efficacy demonstrated in two of

Table 7. Summary of findings regarding the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease.

Assessment[†]	Trial	N	Measure	Outcome		Comments	Ref.
				Treatment	*Placebo*		
Impairment: fatigue							
FSS[‡]	Krupp *et al.*	55	% improved	64%	18.5%	*Ad hoc* success	[17]
FSS[‡]	Fallon *et al.*	37	% improved	66.7%	25%	*Post hoc* success in the subset of subjects who had a baseline FSS-11 score of 4.0 or higher	[16]
Impairment: pain							
MPQ[§]	Fallon *et al.*	37	Mean drop	5.2	5.6	Secondary analysis – Patients with more joints in pain at baseline had a preferential improvement with ceftriaxone on measures of pain ($p = 0.07$) at week 24	[16]
VAS[¶]	Fallon *et al.*	37	Mean drop	1.4	0.9		
Impairment: neurocognitive dysfunction							
Index[#]	Fallon *et al.*	37	Mean gain index	1.1	0.72	Secondary analysis – Patients with more joints in pain at baseline had a preferential improvement with ceftriaxone on cognitive index measures at week 24 ($p = 0.04$)	[16]
A-A[††]	Krupp *et al.*	48	N/total (%)	2/26 (8)	2/22 (9)	The authors noted that baseline cognitive deficits 'were relatively mild which may have contributed to the lack of a treatment effect on cognition'.	[17]
*****Impairment: QoL physical functioning***							
SF-36 PCS[‡‡]	Klempner *et al.*, seropositive	78	N/total (%)	11/35 (31%)	10/25 (29%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]
SF-36 PCS[§§]	Klempner *et al.*, seronegative	51	N/total (%)	9/22 (41%)	5/23 (22%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]
SF-36 PCS[¶¶]	Fallon *et al.*	37	Mean gain	4.9	3.3	Secondary analysis – sustained improvement in physical functioning to week 24 could also be seen when baseline severity of impairment was not included as a covariate ($p = 0.09$) at week 24	[16]
Impairment: QoL mental health							
SF-36 MCS[‡‡]	Klempner *et al.*, seropositive	78	N/total (%)	11/35 (31%)	16/35 (46%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]

[†]Outcome for measures described in Table 1.
[‡]The FSS assesses the impact of fatigue on everyday functioning [210].
[§]The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively.
[¶]VAS [16].
[#]Neurocognitive dysfunction index
[††]A-A
[‡‡]The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].
[§§]The MCS on the SF-36 measure of QoL is a measure of mental health, role emotional, social function and vitality [209].
FSS: Fatigue severity scale; GI: Gastrointestinal; MCS: Mental component of health; MPQ: McGill Pain Questionnaire; PCS: Physical component of health; VAS: Visual analog scale; QoL: Quality of life.

Table 7. Summary of findings regarding the effectiveness of antibiotic retreatment in patients with persistent manifestations of Lyme disease (cont.).

Assessment[†]	Trial	N	Measure	Outcome		Comments	Ref.
				Treatment	*Placebo*		
Impairment: QoL mental health (cont.)							
SF-36 MCS[§§]	Klempner *et al.*, seronegative	51	N/total (%)	8/22 (36%)	6/23 (26%)	Due to design deficiencies, the lack of a demonstrable treatment effect is uninformative	[18]
SF-36 MCS[¶¶]	Fallon *et al.*	37	Mean gain	2.9	6.6		[16]
Adverse events							
	Klempner *et al.*, Krupp *et al.* and Fallon *et al.*	221	Fifteen serious adverse reactions among the 221 subjects (6.8%) [16–18]. Six subjects experienced allergic reactions [16–18], including one case of anaphylaxis [17]; four developed line-related infections (all on placebo) [16,17], two developed thrombi [16] and there was one case of each of the following: pulmonary embolus [18], cholecystitis [16], GI bleed with fever and anemia [18]				[16–18]

[†]Outcome for measures described in Table 1.
[‡]The FSS assesses the impact of fatigue on everyday functioning [210].
[§]The MPQ estimates the sensory and affective elements of pain, both qualitatively and quantitatively.
[¶]VAS [16].
[#]Neurocognitive dysfunction index
[††]A-A
[‡‡]The PCS on the SF-36 measure of QoL is a measure of physical health, role physical, bodily pain and general health [209].
[§§]The MCS on the SF-36 measure of QoL is a measure of mental health, role emotional, social function and vitality [209].
FSS: Fatigue severity scale; GI: Gastrointestinal; MCS: Mental component of health; MPQ: McGill Pain Questionnaire; PCS: Physical component of health; VAS: Visual analog scale; QoL: Quality of life.

the trials [127]. The authors state that such guidelines 'are not helpful to clinicians and patients' [127].

In addition to the NIH-sponsored retreatment trials, retreatment was also shown to be beneficial in clinical trials of EM treatment and in a case series involving the treatment of late neurologic disease. Investigators in seven of the nine EM trials discussed above retreated subjects who failed initial therapy [47,48,53,74,88,91,92]. Decisions to retreat were often based on symptoms alone and investigators frequently reported on the success of retreatment. In three trials, biopsy specimens from the EM site were culture-positive for *B. burgdorferi* 1–3 months post-treatment [47,48,92]. In two of these, subjects were retreated with oral antibiotics and follow-up cultures 3 [47] or 4 months later [92] were negative. Thus, these trials simultaneously demonstrated persistent infection following standard therapy and the value of retreatment.

In a study by Logigian *et al.*, one subject relapsed at 8 months post-treatment, was retreated, became well once again and remained so for the remainder of the study [33]. Several observational studies also demonstrated benefits from antibiotic retreatment [87,109,110,131].

The panel also considered the risk of withholding antibiotics from patients with a potentially treatable *B. burgdorferi* infection. Currently available laboratory tests are unable to confirm or deny persistent infection on a routine basis yet persisting infection has been demonstrated in patients with Lyme disease by PCR and culture [47,113,132–136]. A recently published xenodiagnostic study in humans demonstrated positive results in one of eight subjects with post-treatment manifestations of Lyme disease; a subsequent xenodiagnostic specimen obtained from the same subject 8 months later was also positive [137]. Animal studies have corroborated the human findings, documenting bacterial persistence by culture, PCR and histopathologic testing of post-treatment necropsy specimens and by xenodiagnosis [76,138,139]. Given these realities, withholding antibiotic retreatment risks allow an infection to continue unchecked.

The panel weighed the burden of chronic illness that Lyme disease imposes on patients. In the four retreatment trials analyzed here, the subjects' QoL was consistently worse than that of control populations and reductions in employment or educational activities were common [16–18]. A community-based trial of antibiotic retreatment found the QoL of its subjects was the same or worse as that of individuals with depression, diabetes, heart disease, osteoarthritis and rheumatoid arthritis [87]. Surveys of Lyme disease patients further document the negative impact of persistent manifestations. One survey of openly recruited Lyme disease patients identified 2424 patients whose initial clinical diagnosis of Lyme disease was confirmed with positive serology and who had persistent manifestations of Lyme disease despite antibiotic treatment [140]. Of this cohort, 25% had received public support or disability benefits and the majority of respondents in this subset received these payments for 2 or more years. A second online survey identified 1087 respondants diagnosed with Lyme disease (based on the presence of an EM rash or positive two-tier testing that used the CDC interpretive criteria) who had ongoing manifestations of Lyme disease for 6 or more months [119]. Using a CDC metric of health-related QoL, the survey found that this group averaged 19.6 and 15.5 days/month of poor physical and mental health days, respectively. Not surprisingly, 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 and the survey findings corroborate those of the community-based retreatment trial mentioned above. By comparision, in a general population with an average age of 46, only 16% rated their health as fair or poor [119]. The respondants also reported significant economic impacts – 39.4% stopped working and an additional 28.3% reduced their work hours or role; 37.3% spent at least US$5000 in out-of-pocket Lyme-related expenses.

Given the severity of the QoL impairments, the panel viewed the need for clinical intervention as high.

Additionally, the panel considered that antibiotic risk varies by agent and route of administration. Although all of the regimens in the NIH-sponsored retreatment trials incorporated iv. ceftriaxone, the use of iv. antibiotics is discretionary and should be based on an individualized risk–benefit assessment. The risks associated with iv. antibiotics have two main origins. The first is the medication itself and includes allergic reactions and other adverse events, such as cholecystitis from ceftriaxone. The second source of risk is the iv. access device.

The risks associated with iv. access are well known. A meta-analysis of the risks associated with iv. access, in general, found that risks varied by access type; peripheral iv. catheters caused 0.5 bloodstream infections per 1000 intravascular device days, while surgically implanted long-term central venous devices – cuffed and tunneled catheters – caused 1.6 infections per 1000 intravascular device days [141].

Combined, there were seven device-related adverse events among the four retreatment trials and approximately 8110 days of device use, yielding 0.86 device-related adverse events per 1000 intravascular device days, which is lower than the rate found in the meta-analysis. Although the risk associated with iv. antibiotics is significant, in situations where the QoL impairments are substantial, retreatment with iv. antibiotics may be wholly appropriate.

There is substantial evidence on the clinical safety of amoxicillin, cefuroxime axetil, doxycycline and azithromycin, which are commonly used to treat Lyme disease [105,106]. In a community-based trial, none of the subjects randomized to amoxicillin experienced a serious adverse event [87]. Similarly, the trials by Klempner *et al*. confirmed the safety of oral doxycycline for longer-term use [18]. Regardless of treatment agent and route of administration, it is expected that the concomitant use of probiotics would reduce the risk of *C. difficile* colitis and antibiotic-associated diarrhea [44,45].

Values: The panel placed a high value on reducing the morbidity associated with chronic Lyme disease and improving the patient's QoL as well as on the need for individualized risk/benefit assessment and informed shared decision-making. The panel also placed a high value on the ability of the clinician to exercise clinical judgment. In the view of the panel, guidelines should not constrain the treating clinician from exercising clinical judgment in the absence of strong compelling evidence to the contrary.

Recommendation 3a

Clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease. These discussions should provide patient-specific risk–benefit assessments for each treatment option and include information regarding *C. difficile* infections and the preventative effect of probiotics (although none of the subjects in the retreatment trials developed a *C. difficile* infection). (Strong recommendation, very low-quality evidence. *Note*: In GRADE, a strong recommendation may be made in the face of very low-quality evidence when the risk–benefit analysis favors a particular intervention such that most patients would make the same choice.)

Role of patient preferences: low

The benefits of educating patients about the potential benefits of retreatment and the risks associated with various treatment options, including not treating, clearly outweigh any attendant risks associated with education.

Recommendation 3b

While continued observation alone is an option for patients with few manifestations, minimal QoL impairments and no evidence of disease progression, in the panel's judgment, antibiotic retreatment will prove to be appropriate for the majority of patients who remain ill. Prior to instituting antibiotic retreatment, the original Lyme disease diagnosis should be reassessed and clinicians should evaluate the patient for other potential causes of persistent disease manifestations. The presence of other tick-borne illnesses should be investigated if that had not already been done. Additionally, clinicians and their patients should jointly define what constitutes an adequate therapeutic trial for this particular set of circumstances.

When antibiotic retreatment is undertaken, clinicians should initiate treatment with 4–6 weeks of the selected antibiotic; this time span is well within the treatment duration parameters of the retreatment trials. Variations in patient-specific details and the limitations of the evidence imply that the proposed duration is a starting point and clinicians may, in a variety of circumstances, need to select therapeutic regimens of longer duration.

Treatment options are extensive and choices must be individualized. Each of these options would benefit from further study followed by a GRADE assessment of the evidence and consideration of associated risks and benefits, but until this information is available, clinicians may act on the currently available evidence.

In choosing between regimens, clinicians should consider the patient's responsiveness to previous treatment for Lyme disease, whether the illness is progressing and the rate of this progression; whether the patient has impaired immune system functioning or has received immunosuppressant corticosteroids [54,114] and whether other co-morbidities or conditions would impact antibiotic selection or efficacy. The possibility of co-infections should be investigated (see Recommendation 2e for discussion regarding co-infections complicating the diagnosis and treatment of Lyme disease).

Clinicians should also weigh the extent to which the illness interferes with the patient's QoL, including their ability to fully participate in work, school, social and family-related activities and the strength of their initial response against the risks associated with the various therapeutic options. Antibiotic selection should also consider medication tolerability, cost, the need for lifestyle adjustments to accommodate the medication and patient preferences.

For patients with mild impairments who had a strong-to-moderate response to the initial antibiotic, repeat use of that agent is favored. Patients with moderate impairments or only a modest response to the initial antibiotic may benefit from switching to a different agent or combination of agents; the latter to include at least one agent that is able to effectively reach intracellular compartments [109,110]. Injectable penicillin G benzathine or iv. agents such as ceftriaxone are other options.

For patients with significant impairments and/or a minimal or absent therapeutic response, a combination of oral antibiotics or injectable penicillin G benzathine or iv. ceftriaxone alone, or in combination with other agents, is preferred. For patients who experienced disease progression despite earlier therapy, treatment with injectable penicillin G benzathine or an iv. agent, such as ceftriaxone, alone or in combination with other antibiotics, is advisable. Additionally, minimal or absent responses and disease progression require a re-evaluation of the original diagnosis. (Recommendation, very low-quality evidence)

Role of patient preferences

High: The heterogeneous nature of the patient population seen in clinical practice, particularly with regard to variations in disease severity, QoL impairments and aversion to treatment-related risk, is likely to affect the risk–benefit assessment. Although many patients will value the opportunity to improve their individual QoL through antibiotic treatment over the risk of adverse events, others may prefer to avoid the risks associated with treatment. Hence, treatment options, including their associated risks and benefits, should be discussed with the patient in the context of shared medical decision-making.

Recommendation 3c

Clinicians should re-assess patients immediately following the completion of the initial course of retreatment to evaluate the effectiveness of retreatment and the need for therapeutic adjustments. Reassessment may need to be done much earlier and with greater scrutiny in patients with severe disease or when the therapeutic intervention carries substantial risk.

For patients who improve yet continue to have persistent manifestations and continuing QoL impairments following 4–6 weeks of antibiotic retreatment, decisions regarding the continuation, modification or discontinuation of treatment should be based on several factors. In addition to the factors listed in Recommendation 3b, the decision to continue treatment may depend on the length of time between the initial and subsequent retreatment, the strength of the patient's response to retreatment, the severity of the patient's current impairments, whether diagnostic tests, symptoms or treatment response suggest ongoing infection and whether the patient relapses when treatment is withdrawn.

In cases where the patient does not improve after 4–6 weeks of antibiotic retreatment, clinicians should reassess the clinical diagnosis as well as the anticipated benefit. They should also confirm that other potential causes of persistent manifestations have been adequately investigated prior to continuing antibiotic retreatment. Decisions regarding the continuation, modification or discontinuation of treatment should consider the factors noted above as well as the definition of an adequate therapeutic trial.

Whenever retreatment is continued, the timing of subsequent follow-up visits should be based on the level of the therapeutic response, the severity of ongoing disease, the duration of current therapy and the need to monitor for adverse events (see remarks section below). (Recommendation, very low-quality evidence).

Role of patient preferences

High: See Recommendation 3b.

Remarks

The lack of pharmaceutical interest and its concomitant funding does not encourage the innovative research that is essential to improving care for patients with Lyme disease. When pharmaceutical interest is lacking, clinical practices often become the source of therapeutic innovation, preceding rather than following clinical trials.

The US FDA recognizes the important role that clinical innovation plays in patient care, stating: 'Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations [142]'. In providing clinicians with therapeutic flexibility, the agency makes room for clinicians to fashion patient-centered care, with treatment decisions being driven by the specific circumstances of an individual's illness. The benefits related to therapeutic flexibility are quite evident in orphan diseases, where an estimated 90% of all prescribed medications represent off-label use and if not for that practice, clinicians would often have no effective therapies to employ [143]. In this respect, patient care in Lyme disease is like that of other research-orphaned diseases, relying heavily on innovative clinicians to develop treatments that improve health and reduce morbidity.

Innovative therapies may employ unconventional dosages of standard medications, novel combinations of currently accepted practices, new applications of standard interventions or may use accepted therapy or approved drugs for non-approved indications [144]. Unlike research, the primary purpose of innovative care is to benefit the individual patient [144]. Clinicians

employing innovative therapies need to verify that the innovation is intended to be in the patient's best interest and recognize that informed consent requires that the patient understand that the recommended therapy is not standard treatment [144]. In this context, the panel concluded that it is necessary for clinicians to provide patients with treatment options and engage in shared medical decision-making.

This determination is in keeping with the approach used by other physician-developed guidelines. The American Academy of Pediatrics guidelines recognize that in the face of low-quality evidence or where the risk–benefit equilibrium is balanced, 'guideline developers generally should not constrain the clinician's discretion [9]'. Guideline developers commonly consider not only RCTs, but also observational trials, animal model studies, expert opinion, clinical experience, patient values and judgments regarding the potential harms of an intervention as well as the potential harms of inaction [19]. Moreover, when the condition in question poses great risk or QoL impairments, guideline panels may recommend an intervention even when the evidence base is uncertain, mixed or incompletely developed [19].

The panel endorses the view that informed choice is the ethical ideal in circumstances involving scientific uncertainty because it recognizes the patient's right to self-determination [19]. Patients with significant QoL or functional impairments may be willing to take on a far greater degree of risk than those who are relatively unaffected by ongoing disease manifestations. However, because the degree of relative risk aversion varies significantly among patients, it is important that patients be given sufficient information to make a meaningful choice regarding treatment options.

The demonstrated persistence of *B. burgdorferi* in specific individuals [42,47,48,133–135,145,146] and animal models [76,138,139,147] suggests a need for treatment regimens which address the mechanisms underlying bacterial persistence yet these mechanisms may not be fully identified and those that have been are not fully understood. Emerging evidence supports potential roles for these mechanisms: immune evasion via physical seclusion of Bb within immunologically protected tissue sites such as the CNS, joints and eyes [147–149], collagen-rich tissues [150], cells [151–154] and biofilms [155]; alterations in Osp profiles through antigenic variation [156–159], phasic variation [160] and alteration in Bb morphology (including cell-wall deficient forms, spherocytes and 'cyst' forms) [161–166]; immune modulation via alterations in complement [167–169], neutrophil and dendritic cell functioning [170,171], and changes in cytokine and chemokine levels [129,172,173] and innate antibiotic tolerance of some *B. burgdorferi* populations [174].

In the absence of a clear scientific understanding of persistent infection, different views regarding whether and how to address potential mechanisms have developed [175,176]. While some clinicians may elect to wait for more definitive answers, other clinicians, given the QoL impairments some patients bear, may elect to provide innovative care based on the information at hand. Antibiotic options for treating persistent manifestations include all agents known to be effective against *B. burgdorferi* [87,54,75,109,110,112]. While the use of agents proven to be effective in clinical research trials may be preferred, clinicians may choose antibiotics based on their clinical experiences and those of others [177–181]. While agents with favorable *in vitro* findings may also merit consideration, antibiotics that were ineffective in clinical trials are best avoided.

Treatment regimens may employ either a sole agent or combinations of antibiotics, depending on which mechanisms of persistence the clinician is attempting to thwart. The delivery method – oral, iv., IM – is dependent on the agents selected, disease severity and patient preferences. It is reasonable to start with dosages examined in clinical trials, but clinicians may decide to adjust dosages in individual patients with the goal of improving outcomes by achieving adequate drug levels in all infected tissues.

Oral antibiotics which demonstrated effectiveness in clinical trials include the cell wall agents amoxicillin [74,91], phenoxymethylpenicillin [46,48] and cefuroxime axetil [88,91,92]. Other cell wall agents may also be clinically useful; however, first-generation cephalosporins are known to be ineffective [182]. Oral agents within the tetracycline and macrolide classes, which disrupt ribosomal function and are capable of entering cellular compartments, are also effective in Lyme disease. Individual agents include doxycycline [53,183–190], tetracycline [109], azithromycin [49,74,190,191] and clarithromycin [110,192]. However, erythromycin, which performed well *in vitro*, was ineffective *in vivo* [50,193] and the macrolide telithromycin has been linked to drug-induced liver injury [194]. Several of the EM trials reviewed earlier in this document used higher antibiotic dosages than suggested by the panel in Recommendation 2b [47–49,74,88]. For example, Luft *et al*. and Weber *et al*. prescribed azithromycin 500 mg/day [74,191]. Strle *et al*. and Barsic *et al*. prescribed azithromycin 500 b.i.d. on day 1 followed by 500 mg daily [47,49]. Nadelman prescribed doxycycline 100 mg t.i.d. [88]. In certain circumstances, clinicians may decide that higher doses are required.

Metronidazole and tinidazole effectively kill cell wall deficient forms of *B. burgdorferi in vitro* [195,196], but their effectiveness *in vivo*, in either oral or iv. form, has not been investigated in clinical trials.

Ceftriaxone, 2 g iv. per day is known to be effective [16,17,32,33,54,112] and iv. cefotaxime [113], another cephalosporin, has also been recommended. Intravenous penicillin is less effective and requires more frequent dosing [114]'. Additional iv. cell wall agents from the carbapenem and monobactam classes were effective *in vitro*, but have not been studied clinically [115].

IM benzathine penicillin is another useful cell wall agent and it avoids the risks associated with gaining iv. access. A case report noted its effectiveness in antibiotic resistant Lyme arthritis [111].

If the initial course of antibiotic retreatment does not produce a complete response, clinicians should consider various options. Patients who had an incomplete response with one

agent may be responsive to another; thus, switching agents may prove successful. Alternatively, combination therapy may be appropriate in select patients. Examples include those with known or suspected co-infections and patients who had incomplete responses to single-agent therapy.

Aside from antibiotics, few therapeutic strategies have been employed to address non-infectious mechanisms of ongoing disease yet individual patients have benefitted from non-antibiotic therapies. For example, some patients with 'antibiotic-resistant' Lyme arthritis obtained a localized (joint-specific) benefit from synovectomy [197,198]. The rationale being that ongoing synovitis is a reflection of an auto-immune process [198]. Additionally, an autoimmune-mediated polyneuropathy that was secondary to a proven *B. burgdorferi* infection of the CNS improved following IVIG therapy, whereas prior antibiotic interventions failed to halt the progression of the polyneuropathy [199]. Other methods of immunomodulation may prove useful in the future, especially if it can be established that immune dysregulation is the specific mechanism underlying an individual's persistent disease. However, unless an ongoing infection can be definitively ruled out, caution is required because immunomodulation could cause an occult infection to flare.

Reconciling divergent guidelines

The ILADS panel recommendations differ from those of the IDSA. Different guideline panels reviewing the same evidence can develop disparate recommendations that reflect the underlying values of the panel members, which may result in conflicting guidelines [200,201]. The IOM explains that conflicting guidelines most often result 'when evidence is weak; developers differ in their approach to evidence reviews (systematic vs non-systematic), evidence synthesis or interpretation and/or developers have varying assumptions about intervention benefits and harms' [200]. Conflicting guidelines exist for over 25 conditions and there is no current system for reconciling conflicting guidelines [200]. Supplementary Appendix 1 reconciles the differences between the ILADS and IDSA treatment recommendations by clinical situation.

Expert commentary & five-year view

Lyme disease is a complex illness and patients may experience both acute and persistent manifestations. The science regarding disease mechanisms is limited, uncertain and evolving. However, the profoundly negative impact that persistent manifestations exert on patients' wellbeing as measured on validated QoL assessment tools is well documented. Therefore, critical treatment goals include: disease prevention, treating to cure where possible and otherwise improving patient QoL and preventing disease progression. Following the GRADE model, ILADS recommends that patient goals and values regarding treatment options be identified and strongly considered during a shared decision-making process. Because the GRADE process for formulating evidence-based treatment recommendations fosters transparency and recognizes that patient values may play a pivotal role, GRADE is particularly useful when addressing questions marked by significant scientific uncertainty.

Looking forward over the next 5 years, significant advances are expected in both technology and clinical research that may significantly impact the quality of patient care in Lyme disease. Since the discovery of Lyme disease in 1981, researchers have identified more than 15 new tick-borne pathogens. Progress in identifying new tick-borne pathogens and in understanding the clinical ramifications of simultaneous tick-borne diseases may help improve both the diagnosis and treatment of tick-borne diseases. Advances in genomics and proteonomics should permit researchers to identify differences in *B. burgdorferi* species and strains and explore their clinical implications. Significant advances in diagnostic testing may permit clinicians to distinguish the infected from the non-infected and cured and provide clinicians with a laboratory measure of therapeutic progress. Finally, advances in information technology as well as the methodology for conducting large-scale clinically relevant trials will provide evidence that addresses topics that clinicians and patients deem meaningful to improving patient QoL. These fundamental changes may change the clinical landscape and enable optimal care treatment regimens to be established.

Disclaimer

The state of the evidence in the diagnosis and treatment of Lyme disease is limited, conflicting and evolving. Accordingly, the recommendations in these guidelines reflect an evidence-based, patient-centered approach that many clinicians will find helpful; they are not intended to be viewed as a mandate or as a legal standard of care. Guidelines are not a substitute for clinical judgment. The International Lyme and Associated Diseases Society encourages clinicians to consider the specific details of an individual patient's situation when determining an appropriate treatment plan.

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Key issues

- Lyme disease is a complex illness and patients may experience both acute and persistent manifestations.
- Persistent manifestations may produce profound quality-of-life impairments, yet the mechanisms that produce persistent manifestations are poorly understood.
- The available evidence regarding the treatment of known tick bites, erythema migrans (EM) rashes and persistent disease is limited.
- Grading of Recommendations Assessment, Development and Evaluation-based analyses found the evidence regarding these scenarios was of very low quality due to limitations in trial designs, imprecise findings, outcome inconsistencies and non-generalizability of trial findings.
- It is impossible to state a meaningful success rate for the prevention of Lyme disease by a single 200 mg dose of doxycycline because the sole trial of that regimen utilized an inadequate observation period and unvalidated surrogate end point.
- Success rates for treatment of an EM rash were unacceptably low, ranging from 52.2 to 84.4% for regimens that used 20 or fewer days of azithromycin, cefuroxime, doxycycline or amoxicillin/phenoxymethylpenicillin (rates were based on patient-centered outcome definitions and conservative longitudinal data methodology).
- In a well-designed trial of antibiotic retreatment in patients with severe fatigue, 64% in the treatment arm obtained a clinically significant and sustained benefit from additional antibiotic therapy.
- The optimal treatment regimen for the management of known tick bites, EM rashes and persistent disease has not yet been determined. Accordingly, it is too early to standardize restrictive protocols.
- Given the number of clinical variables that must be managed and the heterogeneity within the patient population, clinical judgment is crucial to the provision of patient-centered care.
- Based on the Grading of Recommendations Assessment, Development and Evaluation model, International Lyme and Associated Diseases Society recommends that patient goals and values regarding treatment options be identified and strongly considered during a shared decision-making process.
- Research is needed to better define the disease process, to identify variables associated with poor outcomes and to establish highly effective therapeutic regimens for known tick bites, EM rashes and persistent disease.

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Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients

Final report

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Senator Carol Brown	Tasmania, ALP
Senator Katy Gallagher	Australian Capital Territory, ALP
Senator the Hon Bill Heffernan (from 4 February to 15 March 2016)	New South Wales, LP
Senator Joanna Lindgren (to 4 February 2016)	Queensland, LP
Senator James Paterson (from 15 March 2016)	Victoria, LP

Participating members for this inquiry

Senator Scott Ludlam	Western Australia, AG
Senator John Madigan	Victoria, IND
Senator Claire Moore	Queensland, ALP
Senator Linda Reynolds	Western Australia, LP
Senator Zhenya Wang	Western Australia, PUP

TABLE OF CONTENTS

Appendix 2

ABBREVIATIONS

ACIIDS	Australian Chronic Infectious and Inflammatory Disease Society
AHPRA	Australian Health Practitioner Regulation Agency
AMA	Australian Medical Association
CDC	US Centers for Disease Control and Prevention
DAkkS	Deutsche Akkreditierungsstelle
Department	Department of Health
ELISA	Enzyme-linked immunosorbent assay
IDSA	Infectious Diseases Society of America
ILADS	International Lyme and Associated Diseases Society
KMF	Karl McManus Foundation
LB	Lyme Borreliosis
MBA	Medical Board of Australia
MCNSW	Medical Council on New South Wales
MSIDS	Multiple Systemic Infectious Disease Syndrome
NATA	National Association of Testing Authorities
NHMRC	National Health and Medical Research Council
NSRL	National Serology Reference Laboratory
NSW	New South Wales
PCR	Polymerase Chain Reaction
POTS	Postural orthostatic tachycardia syndrome
QCMD	Quality Control Molecular Diagnostics
US	United States of America

LIST OF RECOMMENDATIONS

Recommendation 1

2.90 The committee recommends that the Australian Government Department of Health engage with stakeholders following the publication of the National Serology Reference Laboratory review to discuss the findings of the review and any bearing those may have on testing for Lyme disease in Australia.

Recommendation 2

2.91 The committee recommends that the Australian Government increase funding for research into tick-borne pathogens as a matter of urgency. This funding should include:

- **funding for research on pathogens which may cause infection;**
- **funding for research on whether newly-identified pathogens can cause illness in humans; and**
- **funding for the development of diagnostic tests which can detect infection by any newly-identified pathogens endemic to Australia.**

Recommendation 3

3.54 The committee recommends that government medical authorities, in consultation with stakeholders including the Australian Chronic Infectious and Inflammatory Diseases Society (ACIIDS) and the Karl McManus Foundation, establish a clinical trial of treatment guidelines developed by ACIIDS with the aim of determining a safe treatment protocol for patients with tick-borne illness.

Recommendation 4

3.55 The committee recommends that the Australian Government allocate funding for research into medically-appropriate treatment of tick-borne disease, and that medical authorities measure the value of treatment in terms of patient recovery and return to health. The best treatment options must then be developed into clinical treatment guidelines.

Recommendation 5

3.56 The committee recommends that the Australian Government Department of Health facilitate, as a matter of urgency, a summit to develop a cooperative framework which can accommodate patient and medical needs with the objective of establishing a multidisciplinary approach to addressing tick-borne illness across all jurisdictions.

Recommendation 6

3.57 The committee recommends that federal, state and territory health agencies, through the Council of Australian Governments Health Council, develop a consistent, national approach to addressing tick-borne illness.

Recommendation 7

3.58 The committee recommends that the Australian Government Department of Health urgently undertake an epidemiological assessment of the prevalence of suspected tick-borne illness in Australia, the process and findings of which are to be made publicly available.

Recommendation 8

3.59 The committee recommends that the Australian Government Department of Health establish the prevalence and geographical distribution of overseas-acquired Lyme disease in Australia.

Recommendation 9

3.60 The committee recommends that Australian medical authorities and practitioners addressing suspected tick-borne illness:

- **consistently adopt a patient-centric approach that focusses on individual patient symptoms, rather than a disease label; and**
- **remove 'chronic Lyme disease', 'Lyme-like illness' and similar 'Lyme' phrases from diagnostic discussions.**

Recommendation 10

3.61 The committee recommends that, to help the referral of patients for guided and comprehensive pathology testing, medical practitioners work with pathologists, especially microbiologists, immunologists, chemical pathologists and hæmatologists to optimise diagnostic testing for each patient.

Recommendation 11

3.62 The committee recommends that the Australian Government Department of Health work closely with the Australian Medical Association and Royal Australian College of General Practitioners to ensure that general practitioners have a better understanding of how to treat patients who present with complex symptoms.

Recommendation 12

3.63 The committee recommends that treatment guidelines developed by Australian medical authorities emphasise the importance of a multidisciplinary, case conference approach to patient care, involving consultation between general practitioners and specialists with expertise in neurology, psychiatry, rheumatology, immunology, infectious diseases and microbiology.

Chapter 1
Patients first

> People often say to me that I have coped with my situation with bravery and an astonishing amount of grace, but it is not really true. It is just that my fury has made me quiet.[1]

1.1 The existence of tick—or other vector—borne, Lyme-like illness endemic to Australia is a controversial, polarising question. The committee considered evidence provided by many qualified professionals articulating considered, plausible, yet contradictory views. This evidence, presented over the course of two parts to this inquiry, mirrored the tangled public discourse which has been going around in circles for years: do pathogens responsible for Lyme disease exist in Australia, which pathology results are reliable, who do we believe?

1.2 The committee heard many moving personal accounts from patients over the course of this inquiry: eroding health, excruciating pain, complex manifestations, desperation, exasperation—in a few cases, even death. Ordinary, previously high-functioning members of the community rendered helpless and exhibiting symptoms many say are consistent with tick-borne illness. Years—sometimes decades—spent struggling just to get up and get on with life. It is undeniable that people are suffering.

1.3 Given that the committee accepts that the human toll is real, it is clearly necessary to go back to first principles—people are unwell, and they must be helped. It is therefore the committee's primary objective, in this, its final report on this inquiry, to put the patients first.

1.4 With this in mind, this report builds on the committee's interim report, tabled in May 2016, and seeks to define why there is so much confusion and disagreement. The committee hopes to establish how some progress can be made by cutting through the controversy and identifying areas of agreement. Put simply, why don't we know exactly what these patients have, and how do we help people suffering from an unrecognised, unidentified, but real illness?

1.5 These are the questions at the core of this inquiry.

Inquiry background

1.6 The inquiry into emerging evidence of a tick-borne disease was first referred to the committee on 12 November 2015, with a reporting date of 20 June 2016.[2]

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1 Ms Fiona Caskie, *Committee Hansard*, Sydney, 2 November 2016, p. 32.

2 *Journals of the Senate*, No. 126–12 November 2015, p. 3380.

1.7 The terms of reference for the inquiry were:

a. the prevalence and geographic distribution of Lyme-like illness in Australia;

b. methods to reduce the stigma associated with Lyme-like illness for patients, doctors and researchers;

c. the process for diagnosis of patients with a Lyme-like illness, with a specific focus on the laboratory testing procedures and associated quality assurance processes, including recognition of accredited international laboratory testing;

d. evidence of investments in contemporary research into Australian pathogens specifically acquired through the bite of a tick and including other potential vectors;

e. potential investment into research to discover unique local causative agents causing a growing number of Australians debilitating illness;

f. the signs and symptoms Australians with Lyme-like illness are enduring, and the treatment they receive from medical professionals; and

g. any other related matters.[3]

1.8 Due to the federal election, however, the inquiry lapsed at the dissolution of the Senate on 9 May 2016, by which time the committee had held three hearings, in Perth, Brisbane and Canberra. Given the large volume of evidence received, the committee tabled a comprehensive interim report on 4 May 2016, just prior to the dissolution of the Senate.[4]

Interim report

1.9 The committee's interim report was a wide-ranging analysis of the evidence presented, and recognised that there is considerable debate in Australia and internationally about what constitutes Lyme disease and Lyme-like illness.

1.10 A large number of submissions were made by individuals detailing their personal experience, or that of others close to them. Many submissions were also received from doctors treating patients and researchers looking at tick-borne pathogens. The report detailed this experience, the trajectory of illness, access to medical treatment, and, in some cases, journey to recovery. For clarity, patients were divided into four clear groups:

- those who acquired and were diagnosed with classical Lyme disease in an endemic area overseas;
- those who acquired their illness overseas but weren't diagnosed;

3 *Journals of the Senate*, No. 126–12 November 2015, p. 3380.

4 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016.

- those who became ill following a tick or other insect bite in Australia; and
- those who have experienced a long-term chronic illness in Australia and may or may not have been bitten by a tick or other insect.[5]

1.11 The committee noted the weight of evidence on the relationship between tick bites and people becoming ill.

1.12 The committee was concerned by reports of stigma attached to Lyme-like illness and the treatment of those patients potentially suffering the illness, and noted that more could be done to educate the public and medical professionals about the risk of tick bites and tick-borne illnesses in Australia, as well as classical Lyme disease acquired overseas.[6]

1.13 The committee also looked at diagnostic testing processes for Lyme disease and the recommended protocol for laboratory testing of patients with suspected Lyme disease. Testing, evidence suggested, was at the centre of the heated debate on whether or not Lyme disease itself can be contracted in Australia. Discordant laboratory results between accredited laboratories in Australia and non-accredited Australian and overseas laboratories, the committee concluded, were the cause of considerable confusion and frustration for patients.[7]

1.14 Although the committee's interim report was comprehensive and examined key evidence in detail, the committee identified a number of issues warranting further investigation.

1.15 Three recommendations were made:

Recommendation 1

4.52 The committee recommends that the Community Affairs References Committee continue its inquiry into this matter in the 45th Parliament.

Recommendation 2

4.56 The committee recommends that the Department of Health further develop education and awareness strategies for:

- the public about the prevention of tick bites and seeking medical attention; and

5 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 19.

6 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 31.

7 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 58.

- the medical profession about how to diagnose and treat classical Lyme disease acquired overseas and known tick-borne illnesses acquired in Australia.

Recommendation 3

4.58 The committee recommends that the Chief Medical Officer continue to consult with the medical and patient communities through mechanisms such as the Clinical Advisory Committee on Lyme Disease, and for the Department of Health to continue to facilitate meetings with medical and patient representatives.[8]

Conduct of the inquiry

1.16 In light of the truncating effect the dissolution of Parliament had on the committee's inquiry, on 13 September 2016 the Senate agreed to re-adopt the inquiry with the same terms of reference and a reporting date of 30 November 2016.[9]

1.17 The committee did not call for further evidence upon re-adoption of this inquiry, having already received and considered over 1200 submissions prior to tabling its interim report. The committee did, however, hold an additional public hearing on 2 November 2016, in Sydney.

Structure of the report

1.18 This report is divided into three chapters:

- **Chapter 1** provides a background to the committee's inquiry and overview of evidence considered by the committee in its interim report.
- **Chapter 2** looks at diagnostic testing processes for Lyme disease, with the objective of establishing why these processes and test results are so controversial.
- **Chapter 3** examines treatment options available for patients suffering Lyme-like illness. The chapter examines the evidence around non-mainstream treatment, the position Australia's medical authorities take on such treatment, and how the existing impasse might be breached.

Acknowledgements

1.19 The committee thanks witnesses and submitters for their engagement with this inquiry, and recognises that a number of witnesses attended hearings at short notice on more than one occasion. The committee thanks them for their time, professionalism and evident commitment to acting in the best interests of the community.

8 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. ix.

9 See inquiry homepage, available at: http://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Community_Affairs/Lymelikeillness45 (accessed 14 November 2016).

1.20 The committee also extends particular gratitude and recognition to the individuals who came forward to relate their difficult personal experiences. The committee was deeply moved by these accounts, and by the patients' determination in having their voices heard and contributing in a positive way to the wider community's understanding of tick-borne disease.

Chapter 2
Testing for infection

> Scientific folk want evidence of causative agents to enable disease; patients want focus on their symptoms, their illness, while science works on the details. Both groups make equally valid points, but lives are at risk and people are suffering.[1]

2.1 The question of pathology testing is perhaps the most contentious issue to emerge from this inquiry, and is at the root of the frequently-posed and incessantly debated question: can Lyme disease be contracted in Australia? The committee explored this issue at length in its interim report but found that conclusive answers were elusive. In this, its final report, the committee aims to identify a few areas where some progress may be made.

2.2 Evidence presented to the committee over the course of this inquiry suggests three principal points of contention:

1. A lack of an agreed definition and understanding of what constitutes Lyme-like illness and how, if at all, it differs from Lyme disease.
2. Disagreement over laboratory testing protocols and results when looking for the pathogens responsible for Lyme disease.
3. The lack of conclusive, accepted scientific evidence linking tick bites in Australia to Lyme-like illness.

2.3 This chapter will examine all three.

Lyme, or Lyme-like?

2.4 The illnesses discussed throughout this inquiry are Lyme disease, chronic Lyme disease and Lyme-like illness. The terms are often used interchangeably, and generate considerable disagreement.

Classical Lyme disease

2.5 In its interim report, the committee outlined known epidemiological facts about Lyme disease in detail.[2] Classical Lyme disease, or Lyme borreliosis, is a tick-borne disease caused by a number of closely related species of *Borrelia* bacteria. Lyme disease is recognised as one of the most common tick-borne diseases in

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1 Ms Elaine Kelly, Secretary, Sarcoidosis Lyme Australia, *Committee Hansard*, 14 April 2016, p. 9.

2 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 3.

humans, and is known to be present in parts of the United States of America (US), Europe and Asia. Lyme disease is named after the town of Lyme in Connecticut where it was first recognised in the early 1970s.[3]

2.6 There are a number of common species of *Borrelia* known to cause Lyme disease. In the US, the most common of these is *Borrelia burgdorferi*. Different species of *Borrelia* have been identified as Lyme pathogens in Europe and Northern Asia, such as *Borrelia afzelii* and *Borrelia garinii*. Although different, these species are related and referred to as the '*Borrelia burgdorferi* sensu lato complex'.[4]

Chronic Lyme disease

2.7 If classical Lyme disease is understood to be an acute infection, one that is treated with readily available antibiotics,[5] the concept of chronic Lyme disease, on the other hand, is a controversial one. This is in part because the symptoms some patients experience after an acute Lyme infection are not easily defined. As put by the Department of Health (department):

> In some patients, a post-treatment late Lyme disease syndrome occurs, with patients experiencing non-specific symptoms like headache, fatigue, and muscle and joint pain. These symptoms are generally not regarded as persistence of active infection but more as post infectious problems.[6]

2.8 There is much debate about whether post-infection symptoms constitute chronic Lyme disease, whether such a disease even exists. This debate, as set out in the committee's interim report, is not unique to Australia. Disagreement revolves around whether an ongoing *Borrelia* infection can manifest as chronic, debilitating illness once the acute state of infection has subsided:

> The department is aware of the controversy in endemic areas overseas about the diagnosis of chronic Lyme disease. That controversy which focuses on persistent infection rather than post infectious sequelæ as the cause of ongoing symptoms is relevant to the Australian context because the Australian advocacy groups for a Lyme disease-like illness support the concept of persistent infection.[7]

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3 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 3. Department of Health, *Submission 495*, p. 2.

4 See Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 3. The committee notes that there are other, known *Borrelia* species which cause different illnesses in humans and animals, but not Lyme disease.

5 Department of Health, *Submission 495*, p. 3.

6 Department of Health, *Submission 495*, p. 2.

7 Department of Health, *Submission 495*, p. 2.

2.9 Australian medical authorities do not support the use of the term 'chronic Lyme disease', nor do they accept that its associated symptoms are the result of ongoing *Borrelia* infection:

> The issue of chronic Lyme disease assumes that there is persistent, active infection. That is what is so contentious. The mainstream conventional position is that the sequelae that we see after an infection is post-infectious and not active infection … So, in Australia, like in many other countries that we would be like-minded with in terms of medicine, the experts in microbiology and infectious disease will not readily accept that there is chronic Lyme disease or chronic persistent active infection. So, for that reason, and because of the association between what is happening in Australia with chronic Lyme disease, most of the medical profession expert in this field do not accept that it is Lyme disease.[8]

2.10 This view was, however, challenged by submitters such as Dr Mualla McManus, a scientist with credentials and expertise in immunology, pharmacology, pharmacy, neuroscience and molecular biology:

> The significance of *Borrelia* infection is that once you are infected with it, you have to be treated early so that it does not disseminate. Once disseminated, it becomes chronic. It is very hard to eradicate…after 20 years of antibiotic treatment on a patient, they took the samples from the synovium, the knee joint, and they could actually identify the *Borrelia burgdorferi*—after 20 years of treatment. So you are looking at a unique pathogen that is emerging, but the problem with this pathogen is that it is emerging very slowly.[9]

2.11 The notion of chronic Lyme disease is also important to understanding the debate around laboratory testing results, to be discussed later in this chapter.

Lyme-like illness

2.12 Whereas Lyme disease is caused by known pathogens, and later stages of infection are sometimes referred to as chronic Lyme disease, the term 'Lyme-like illness' has been used to describe a constellation of symptoms thought to be caused by a variety of tick-borne pathogens. As these symptoms are closely connected to those exhibited by patients with classical Lyme disease, the terms 'Lyme disease', 'Lyme-like illness' and 'chronic Lyme disease' are often used interchangeably by patients and their advocates.

2.13 Public discourse on Lyme-like illness is problematic in part due to a lack of agreement or understanding around terminology:

> The department [Department of Health WA] notes that there is no widely published or accepted definition of Lyme-like illness. It is not possible, therefore, to determine the prevalence or geographical distribution of

8 Dr Gary Lum, Principal Medical Adviser, Office of Health Protection, Department of Health, *Committee Hansard*, Canberra, 20 April 2016, p. 10.

9 Dr Mualla McManus, Director, Karl McManus Foundation, University of Sydney, *Committee Hansard*, 15 April 2016, p. 28.

> Lyme-like illness in Australia or even to be certain that different groups discussing Lyme-like disease are referring to the same concept.[10]

2.14 Patient advocacy groups, such as the Lyme Disease Association of Australia, similarly recognise the lack of clear definition. From their perspective, however, the semantic debate is unhelpful:

> There is considerable contention around these two simple words 'Lyme' and 'disease'. On their own they do not offend, used together they invoke very powerful, often emotive shifts in the demeanour, language and behaviours of others. Depending on your perspective, we either have it in Australia or we don't – it's binary.
>
> It is impossible to find a precise and consistent definition of the term in Australia. It is used by the medical community to describe a very specific strain of a biological organism, or sometimes organisms; even they can't decide. It is used by the rest of the world to describe a suite of symptoms and infections caused by a number of organisms.
>
> …We don't know what people have. We do know that some people become seriously ill, sometimes after the bite of a tick, and that their symptoms closely resemble that of internationally defined Lyme disease.[11]

2.15 Given that the pathogens which cause Lyme disease overseas are known, Australian authorities are firm in the view that the term 'Lyme disease' is misused in the local context. This is because the pathogens responsible for Lyme disease overseas were identified some time ago, and have not been identified locally:

> The term is used to describe a variety of symptoms and clinical features ranging from well-defined illnesses to non-specific chronic symptoms. However, there is no evidence to indicate that infection with *Borrelia burgdorferi* sensu lato, resulting in Lyme disease, has been acquired within Australia. In addition, there is no convincing scientific evidence to date that tick bites from native Australian ticks result in Lyme-like disease.[12]

2.16 Critics of this position, however, challenge both the assertion that a) *Borrelia* known to cause Lyme disease have not been found in Australia, and b) only bacteria known to be part of the *Borrelia burgdorferi* sensu lato complex can cause Lyme disease.

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10 Professor David Forbes, Office of the Chief Medical Officer, Department of Health Western Australia, *Committee Hansard*, Perth, 14 April 2016, p. 1.

11 Lyme Disease Association of Australia, *Submission 528*, p. 5.

12 Professor David Forbes, Office of the Chief Medical Officer, Department of Health Western Australia, *Committee Hansard*, Perth, 14 April 2016, p. 1.

Lack of consensus on the name or the cause

2.17 If symptoms of Lyme-like illness in Australia lack clear definition, its cause is similarly very poorly understood and in dispute. As put by Dr McManus, exclusive focus on *Borrelia burgdorferi* as a causative agent for Lyme-like disease may be counterproductive:

> We need to change our view. The government only thinks of Lyme disease, and follows the CDC [US Center for Disease Control] criteria. I have an explanation for *Borrelia*…There is *Borrelia burgdorferi* sensu lato group, and a subset of that is Lyme disease *Borrelia*. There is relapsing fever, which has over 20 genospecies known today. We have reptilian *Borrelia*, but the infection has not yet been found in humans. So if we concentrate on Lyme disease we are missing out on 80 per cent of other *Borrelia* infections, and that is really dangerous. We are being short-sighted. Some of the relapsing fever genospecies can produce 80 per cent of their infections neurologically, but there is no research, because relapsing fever is a poor-country disease. It is endemic in Africa, Asia, India, Indonesia and Vietnam. All the focus is in Lyme disease; everyone makes such a fuss about it. Lyme disease, *Borrelia burgdorferi* sensu stricto, is much easier to treat that relapsing fever. This is something that has not been understood.[13]

2.18 Dr Richard Horowitz, who spoke to the committee in a private capacity, suggested that Lyme disease itself is far more complex than first imagined. The fact that Lyme disease is still poorly understood, Dr Horowitz believes, contributes in large part to the controversy over its diagnosis and treatment:

> I think some of the controversy is happening because we are not understanding the definition of what Lyme disease really is. The patients that I see with Lyme disease do not just have *Borrelia burgdorferi* sensu latu. What they end up having is many other species of bacteria, viruses and parasites because the ticks are now containing many of these different species and are rapidly spreading.[14]

2.19 The evidence supplied by Dr Horowitz is not easily dismissed. He is one of the founding members, as well as past president, of the International Lyme and Associated Diseases Society (ILADS), has published a large number of peer-reviewed articles on the subject and has engaged with a number of governments—including the US, Chinese, UK, French and Belgian—on the subject of Lyme and related diseases.[15]

2.20 On the basis of his own research and that of others cited in his submission, Dr Horowitz in fact advocates a move away from the term "Lyme disease", submitting that the Lyme diagnosis fails to capture the chronic symptoms and multiple infections exhibited by many patients:

> One of the first and most basic problems we face is in helping Australian patients is defining “chronic Lyme disease” or “Lyme-like illness”. Patients

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13 Dr Mualla McManus, *Committee Hansard*, 15 April 2016, p. 29.

14 Dr Richard Horowitz, *Committee Hansard*, 2 November 2016, p. 1.

15 Dr Richard Horowitz, *Submission 936*, pp. 25–33.

> with chronic symptoms who see me, either before or after classical treatment for Lyme disease, have multifactorial causes for their illness. I call this syndrome Lyme-MSIDS. MSIDS stands for Multiple Systemic Infectious Disease Syndrome, and represents sixteen potential overlapping medical problems contributing to persistent symptoms in the Lyme patient.
>
> …
>
> The first point on the MSIDS map is infections. Ticks are now containing multiple bacterial, viral and parasitic infections which can be transmitted simultaneously with *Borrelia burgdorferi*, the agent of Lyme disease. Patients infected with Lyme disease and associated co-infections are much sicker and resistant to standard therapies.[16]

2.21 Dr McManus similarly pointed to multiple infections as an impediment to straightforward diagnosis and treatment:

> The scientific community is not in a state to understand the multiple infections. Over 100 years ago, Koch's postulates were formulated to say, 'You have one infection, one specific set of symptoms—we give you one antibiotic.' That was the treatment. But then you come to something with four or five infections—which one do you treat first? Which is the prominent one that produced the symptoms?
>
> Doctors do not know, we do not know. There are no clinical trials, no investigations into it, because most of the research community thinks that it is too hard to handle. Most of the research on Lyme disease or any species of *Borrelia* looks at acute disease because it is easier to follow. You have got one tick bit, you have got history and you can detect it because the immune system is competent and you can follow it through and treat it. But when it comes to chronic—I have talked to IDSA members; they do not know what to do. ILADS try to treat with long-term antibiotics.[17]

Where to from here?

2.22 Despite considerable disagreement around most aspects of tick-borne illness in Australia, this inquiry also highlighted important areas of agreement. The committee chose to focus on these, as they are a clear indication that progress on the issue is possible.

2.23 Importantly, the committee noted a promising level of interest in further research and examination of the issues from authorities, such as this statement from the department indicating its preparedness to work towards broadening and deepening understanding of tick-borne illness:

> We acknowledge that the cause of these tick-bite-associated, chronic debilitating symptoms may not be limited to a single bacterial species. Parasitic and viral causes as well as environmental toxins should also be investigated.

16 Dr Richard Horowitz, *Submission 936*, p. 2.

17 Dr Mualla McManus, *Committee Hansard*, 15 April 2016, p. 29.

> As part of the department's work in communicable diseases in states and territories, we are developing an awareness of newer genomic technology that is using specimens from patients to look for bacterial and viral nucleic acid, in an attempt to find commonalities in patient specimens. It may reveal a common pathogen or pathogens which can be further considered.[18]

Committee view

2.24 The committee notes that the term 'Lyme-like illness' is in use to describe a constellation of symptoms and what may very well be a number of different illnesses. In the committee's view debate around what to call tick-borne illness in Australia has impeded progress on establishing its cause and optimising treatment. The scope of what scientists and clinicians are grappling with—tick-borne infections, co-infections and post-infection symptoms—is not yet well defined, but appears to be considerable. Australia's understanding of what is in our ticks, and how it might be making some people sick, is clearly at a very nascent stage.

2.25 The committee notes the department's commitment to exploring tick-borne illness and identifying the pathogens involved:

> Through regular communication and correspondence, the department has gained a deeper appreciation and real concern for those Australians experiencing these chronic debilitating symptoms, which they associate with a tick bite. The department remains engaged with the patient and medical community to continue to find, share and understand the evidence associated with this medical conundrum. The department hopes our work with diagnostic pathology and research communities will result in answers and relief for patients and their families.[19]

2.26 The committee is encouraged by this and calls on medical authorities to engage with the research presented during the course of this inquiry.

Diagnosing Lyme disease

2.27 Diagnostic testing of samples—usually blood—taken from patients suspected of having Lyme-like illness is perhaps the most controversial issue to emerge from this inquiry, and one that evidence returned to time and again.

2.28 Much—if not most—of the evidence presented was contradictory, and most of it was confidently articulated by qualified, experienced and respected professionals. It is therefore necessary to establish from the outset that the committee is not in a position to arbitrate a scientific debate. Instead, the committee's objective is to broadly define the parameters of the disagreement around laboratory testing, and identify how some progress can be made.

2.29 As outlined in the committee's interim report, a number of prominent and experienced doctors have questioned the reliability of laboratory tests used to

18 Department of Health, *Submission 495*, p. 2.

19 Department of Health, *Submission 495*, pp. 1–2.

diagnose or rule out Lyme-like illness—classical and chronic Lyme disease or other Lyme-like illnesses. Broadly, the question can be seen from two perspectives:

1. Classical Lyme disease, caused by *Borrelia* bacteria, cannot be contracted in Australia. This position is held by the Australian medical authorities and many experts in relevant fields, and supported by the fact that accredited Australian laboratories return negative results when testing for Lyme disease.
2. An illness with considerable similarities to Lyme disease can and has been contracted in Australia, and pathogens which cause Lyme disease do exist here. This position is held by some doctors and scientists, and supported by the fact that patients who have not travelled overseas have had positive laboratory test results when tested for Lyme disease by some Australian and overseas laboratories.

2.30 A key part of the matter is the issue of test quality—understanding which testing protocol is optimal and how test results are to be interpreted.

2.31 This section will build on evidence already explored by the committee's interim report. Evidence already examined by the interim report is only referred to again where necessary.

The two-tier testing protocol

2.32 As previously described, classical Lyme disease is caused by a number of known, closely related species of *Borrelia* bacteria. The *Borrelia* strains known to cause Lyme disease in Europe, for example, are different to the strains responsible for Lyme disease in the United States (US)—together the bacteria make up the *Borrelia burgdorferi* sensu lato complex. It is antibodies to these bacteria that most laboratories test for when doctors send patients for pathology tests, looking to diagnose or rule out Lyme disease.

2.33 The committee's interim report detailed the protocol used for testing and diagnosis.[20] In brief, most Australian laboratories accredited with the National Association of Testing Authorities (NATA)[21] use a two-tier serological diagnostic protocol, as is also the case with accredited US and European laboratories.

2.34 The first tier is most commonly an enzyme-linked immunosorbent assay (ELISA). If the ELISA test returns a positive result, laboratories will then conduct a Western blot test. The committee understands that laboratories can, but will rarely run a Western blot test in the absence of a positive ELISA result.

2.35 This testing protocol is considered to be world-class and reliable. Accredited laboratories using the protocol in Australia have only returned positive results for

20 For details, see Chapter 3 of Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016.

21 NATA Australia provides assessment, accreditation and training services to laboratories. Accreditation with NATA provides assurance of laboratory competence. See www.nata.com.au (accessed 16 November 2016).

Lyme disease acquired overseas, reinforcing the understanding that the pathogens responsible for Lyme disease are not endemic to Australia.[22]

2.36 Seeking to understand the logic behind the two-tier testing system, the committee questioned why the ELISA test was routinely performed first. Professor Stephen Graves, spokesman on Lyme disease for the Royal College of Pathologists Australasia, described how and why the two tiers of testing ensure accuracy:

> The Western Blot assay is more "reliable" than the ELISA in that it is more specific, at least when the IgG class of antibodies is being tested for. This means it is less likely to give a false-positive result. i.e. mis-call some other illness as Lyme Disease.
>
> The ELISA assay is more sensitive than the Western Blot and will detect almost all patients with antibodies to the Lyme bacteria, but it is less specific and some of the antibodies it detects are not the result of Lyme Disease. These are cross-reacting antibodies. The ELISA assay can therefore give false-positive results.
>
> By going straight to a Western Blot assay, there is a possibility that some Lyme cases could be missed, as it a less sensitive assay than the ELISA.
>
> The logic for this serological testing pattern is that the ELISA is a "screening" assay that will detect all cases of Lyme Disease [and some non-case also] and the Western Blot is a "specific" assay and will differentiate the true Lyme cases from the non-Lyme cases, as it is a more specific assay than the ELISA.
>
> In practice however, both assays can give false positive results and also false-negative results. By having the 2 assays the lab is more likely to obtain the correct result.
>
> If a lab went straight to the Western Blot assay they are likely to miss some genuine cases of Lyme Disease.[23]

2.37 However, a considerable number of submitters and witnesses questioned the reliability of the protocol. These ranged from patients and their advocates, to respected members of the medical and scientific community—each provided evidence in stark contrast to that presented by Professor Graves. Their positions can be broadly divided into two categories:

- those who hold that the ELISA test is not sensitive enough, can therefore only detect antibodies to Lyme disease in some patients, and cannot rule infection out; and

22 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, pp. 47–49.

23 Professor Stephen Graves, Spokesman on Lyme Disease, Royal College of Pathologists of Australasia, answer to question on notice, received 15 November 2016.

- those who hold that Lyme-like illness is in Australia caused by an as-yet unidentified pathogen, perhaps a species of *Borrelia* unique to Australia, and therefore testing for *Borrelia* which are endemic overseas is redundant.

2.38 A small sample of the evidence presented in support of a move away from ELISA-led testing is cited below.

ELISA sensitivity

2.39 Dr Peter Dobie, Secretary of the Australian Chronic Infectious and Inflammatory Disease Society (ACIIDS), told the committee that Lyme disease and Lyme-like illness were underdiagnosed in Australia due to over-reliance on ELISA, which in his experience is not sensitive enough to detect the presence of infection:

> [M]ost Australian pathology laboratories are doing the wrong blood test for Lyme disease. This is one reason why Lyme disease and Lyme-like illness are underdiagnosed in Australia. Most laboratories are using a test called the ELISA test. This test is not sensitive enough to detect most cases of this illness. There is a large body of scientific opinion that this test should be abandoned because of the high rate of false negatives.[24]

2.40 Mr Christopher Walker, Acting Chief Executive Officer of the Karl McManus Foundation, was unequivocal in his assessment of the two-tier protocol:

> The complicated nature of Borrelia infections makes it highly possible for laboratory tests to miss an infection, for multiple reasons. One of the biggest flaws in the current Australian Borrelia or Lyme disease testing is the singularity presumption—that is, a presumption that a negative test result is a positive confirmation that one does not have a Borrelia infection. Permit me to repeat that: there is a presumption that a negative test result is a positive confirmation that one does not have a Borrelia infection.[25]

2.41 Dr Richard Horowitz similarly questioned the logic behind the protocol, concluding that ELISA lacks the necessary sensitivity to detect ongoing infection:

> According to these guidelines, an immunoblot is not to be performed if the ELISA is negative, despite the poor sensitivity of ELISA tests ranging from 34 to 70.5%.[26]
>
> The problem with that is if you look at the scientific literature carefully, the scientific literature is supporting that the ELISA test is not reliable…these organisms can persist. I think the literature is there.[27]

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24 Dr Peter Dobie, Secretary, Australian Chronic Infectious and Inflammatory Disease Society (ACIIDS, formerly the Australian Chronic Infectious Disease Society, ACIDS), *Committee Hansard*, 15 April 2016, p. 19.

25 Mr Christopher Walker, Acting Chief Executive Officer, Karl McManus Foundation, *Committee Hansard*, 2 November 2016, p. 45.

The Karl McManus Foundation is a charity funding research into tick-borne diseases.

26 Dr Richard Horowitz, *Submission 936*, p. 10.

27 Dr Richard Horowitz, *Committee Hansard*, 2 November 2016, p. 4.

2.42 Dr McManus concurred, describing *Borrelia* as complex and possessing a considerable capacity for mutation which makes testing difficult:

> The testing is problematic because the bacteria *Borrelia* has got very variable, hypervariable genomes. Basically, it can mutate inside you. If I had a rat injected in one leg with one genome species of *Borrelia* and I took blood from the other leg, I can get a different genospecies. That is not normal; you do not normally find that. If I inject a rat with a *staph. aureus*, or a golden staph, I get the golden staph, but a different strain, not a different genospecies. The reason for this is that this bacteria: (1) can mutate a lot; and (2) it as a lot of phages, or bacterial viruses. I can give you an example. Golden staph has got only one phage, and it is very difficult to eradicate from hospitals because of the way it develops a tolerance to all the treatment protocols. You have a *Borrelia*, the *burgdorferi* one in the US has 21 phages. That means it can dress itself in so many different ways that it can hide in your body—it can change from vector to vector; it can be in a tick; it can be in a deer; it can be in a human—because it has the capacity to change itself so enormously. I do not think that is really understood by the scientific community or by the clinicians.[28]

2.43 The committee put this to Professor Graves. He indicated that having hypervariable genomes was not particular to *Borrelia*, but instead could be said of all microbes. He reiterated that the accuracy of the two-tiered protocol in use by the majority of laboratories is not impeded by the hypervariable genomes:

> This problem doesn't apply to serological assays that detect antibodies, as a wide variety of antibodies of different specificities that are produced by a patient in response to an infectious agent.
>
> Those persons who believe that Lyme Disease occurs in Australia can always point to minor defects in certain assays that may result in the assay not detecting the occasional patient with Lyme Disease due to a rare variability in the patient or the bacterium. But this would not be the case for the majority of patients and the fact that no genuine patients have been detected, by a variety of laboratory assays, strongly points to the conclusion that this infection [Lyme Disease] does not occur naturally in Australia.
>
> The patients who claim to have Lyme Disease have something else wrong with them, whether an infection transmitted by tick bite or not remains to be seen. They clearly need help but giving them the wrong diagnosis does not help them![29]

2.44 The committee noted the contradictory evidence.

2.45 Dr Richard Schloeffel, Chairperson of ACIIDS, challenged the role which has been ascribed to laboratory testing, making the point that pathology should only be used to confirm a doctor's clinical assessment, not the other way around. The tests

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28 Dr Mualla McManus, *Committee Hansard*, 15 April 2016, p. 28.

29 Professor Stephen Graves, answer to question on notice, received 15 November 2016.

most commonly used, Dr Schloeffel, stated, were of little use in patients who are immunosuppressed:

> The tests are not good enough. The bugs are varied. There are viruses, parasites and bacteria. Pathology is very secondary. Sure, do no harm, but do not lie to your patient that they are not sick because the test was negative.[30]

2.46 This was supported by Ms Jennie Burke, Director of Australian Biologics, who clarified how the devastating effect *Borrelia* has on patients' immune system makes detection through ELISA, which looks for an immune response, uncertain:

> With tests that rely on an immune response, again Borrelia is difficult, as it has a devastating effect on the patient's immune system, which may lead to abhorrent effects in tests. With other infections you would expect the patient to produce IgM antibodies in the initial stage and, three to six months later, the antibodies to seroconvert to IgG antibodies. With Borrelia, however, patients may show no antibodies at all. They may not seroconvert and can remain IgM positive for greater lengths of time than usual.[31]

2.47 Australian Biologics does not use the two-tier protocol to detect *Borrelia* infection. This is explored below.

Other testing protocols

2.48 There are a number of laboratories which do not use the two-tier testing protocol, and which have reported positive results for Australian patients who have never travelled to known Lyme-endemic areas overseas. The laboratories most 'Lyme-literate'[32] doctors prefer to use are:

- Australian Biologics Testing Services, a Sydney-based laboratory which is not yet accredited with NATA;[33]
- ArminLabs, a German laboratory with a focus on Lyme disease which is in the process of accreditation with the German accreditation body, Deutsche Akkreditierungsstelle (DAkkS);[34]

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30 Dr Richard Schloeffel, Chairperson, ACIIDS, *Committee Hansard*, 2 November 2016, p. 55.

31 Ms Jennie Burke, Director, Australian Biologics, *Committee Hansard*, 2 November 2016, p. 12.

32 The term 'Lyme-literate' is used by some clinicians, patients and advocacy groups to denote doctors who have expertise in Lyme disease and Lyme-like illness beyond that of the mainstream medical establishment. For more see Chapter 2 of the committee's interim report.

33 It is important to note that discussion of laboratory competence should not be linked to discussion of NATA accreditation. NATA has stated that it makes no judgement about the competence of non-accredited laboratories. The committee understands that Australian Biologics is aiming to secure NATA accreditation in the near future. See Mrs Nicole Bailey, Assistant Stakeholder Relations Manager, NATA, *Committee Hansard*, 2 November 2016, p. 10; Dr Hugh Derham, *Submission 453*, p. 2; Dr Adam Nuttall, *Submission 601*, p. 2.

34 http://www.arminlabs.com/en. See Dr Hugh Derham, *Submission 453*, p. 2; Dr Adam Nuttall, *Submission 601*, p. 2.

- Infectolab in Germany, which is accredited by DAkkS;[35] and
- IGeneX, a US-based laboratory which specialises in Lyme Disease and associated tick-borne diseases.[36]

2.49 Australian Biologics offers three types of testing for *Borrelia*—DNA testing, or Polymerase Chain Reaction (PCR), an immunoblot test imported from Germany, and EliSpot testing, also from Germany. Australian Biologics uses these tests because of a perceived lack of sensitivity of ELISA testing:

> Earlier ELISA testing was known to have poor sensitivity whereas the newer ImmunoBlot assays using recombinant antigens have a much higher level of sensitivity. The EliSpot Lymphocyte Transformation Test is useful to show if an infection is active.[37]

2.50 A submission from Australian Biologics explains that the PCR test is the gold standard for the detection of bacterial infection:

> PCR is one of the most sensitive methods utilised to detect microbial pathogens in clinical specimens. This is particularly necessary when specific pathogens, difficult to culture in vitro or are known to be of low level in blood, tissue and other samples, are to be detected. The diagnostic value of PCR is known to be significant.[38]

False positives vs false negatives

2.51 The committee held an additional public hearing partly with the aim of clarifying the apparent discordance in test results obtained from different laboratories, however this failed to provide conclusive answers.[39] In short, evidence on the presence of *Borrelia* in Australia was once again contradictory. However, two laboratories testing for the same infection but getting different results cannot both be right—it is an issue of false positives versus false negatives.[40]

2.52 When asked about the rate of false negatives of ELISA, Professor Graves assured the committee the tests have a high degree of sensitivity and are not likely to miss infections. On the contrary, it appears ELISA is more likely to return a false positive than false negative:

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35 See Dr Hugh Derham, *Submission 453, Attachment 1*, p. 11; Dr Adam Nuttall, *Submission 601*, p. 2.

36 www.igenex.com. See Dr Richard Schloeffel, *Submission 2, Attachment 1*, p. 7.

37 Australian Biologics Testing Services, *Submission 545*, p. 1.

38 Australian Biologics, *Submission 545*, p. 2.

39 A detailed discussion of alternative testing protocols, including arguments presented for and against their use, is contained in the committee's interim report and is not repeated here.

40 A 'false positive' is a test result that indicates that a person has an illness when they do not; a 'false negative' is a test result that indicates that a person does not have a particular disease when they in fact do.

> Probably close to zero as it is a very sensitive assay and won't miss many cases. However, many of the "positive" results will not be genuine Lyme Disease as the assay has poor specificity.
>
> In my lab, the Australian Rickettsial Reference Laboratory, the genuine cases of Lyme Disease that we have diagnosed [all in travellers returning from overseas and infected in endemic countries] the ELISA assay has always been positive.[41]

2.53 Professor Graves suggested that Australian Biologics must be getting false positive results:

> I would never refer a specimen to a nonaccredited laboratory so I never refer specimens to Jenny because I do not think that her laboratory is doing the tests properly. I think she is getting a lot of false positives. That is where the difference is. I hear everybody laughing but that is the bottom line. I think that she is putting out a lot of false positives for Lyme disease, mycoplasma and whatever so I do not have confidence in her testing; therefore, I would not refer to her.[42]

2.54 However, the committee noted that there is no concrete evidence to support the conclusion that Australian Biologics is returning false positives.[43]

2.55 The committee sought to clarify, through a question taken on notice, whether testing protocols used by Australian Biologics were peer reviewed:

> Yes, we have swapped samples (both positives and negatives) with the Reference Laboratory for Borreliosis in the Czech Republic. We detected all the samples they sent us and they detected all the samples we sent them. The six research papers on Borrelia to which we contributed used our PCR testing and the same samples were also tested by Prof Eva Sapi at New Haven University. Prof. Sapi is well known for her work on Borrelia. We have also had correlations in PCR testing with Professor Vett Lloyd at Mt. Alison University and since 2012 we have participated in a Quality Assurance Programme offered by QCMD (Quality Control Molecular Diagnostics), based at Glasgow University. We now have 5 years of results showing 100% correct detection of Borrelia through QCMD. Dr. Peter Mayn published "Clinical Determinants of Lyme Borreliosis, babesiosis, bartonellosis, anaplasmosis, and ehrlichiosis in an Australian cohort" in 2014 (paper is attached) which compared our testing to that of Igenex. Our positivity rate for Borrelia was given as 59% and Igenex as 58%. This is very good confirmation of both laboratories' testing.[44]

2.56 Professor Graves suggested that his laboratory and Ms Burke's might do well to compare the assays they use in order to ascertain why they are getting different results:

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41 Professor Stephen Graves, answer to question on notice, received 15 November 2016.

42 Professor Stephen Graves, *Committee Hansard*, 2 November 2016, p. 16.

43 *Committee Hansard*, 2 November 2016, pp. 16–17.

44 Australian Biologics, answer to question on notice, received 17 November 2016, pp. 2–3.

> What usually happens in a situation like this is that different labs will compare their assays so we would take a common QAP, quality assurance process, sample. They would go to different laboratories and be tested to see whether or not they are getting the same results. That is how we normally do it. There may be, say, just for argument's sake, six or seven different assays for detecting antibodies for Lyme disease used in Australian laboratories. They will all have slightly different sensitivities and specificities but on the whole most of them will give the same answer—positive if it is truly positive or negative if it is truly negative. That is how we do it. Strictly speaking, what we should do is Jennie [Ms Burke, Director, Australian Biologics] and I should exchange specimens and methodologies and see why we are not getting the same results.[45]

2.57 Representatives of the Karl McManus Foundation suggested that some of the confusion could be alleviated if laboratories stated the parameters and limitations of their results when these are provided.[46]

2.58 Clarity around these issues may be within reach, however. As noted in the committee's interim report, the department has contracted the National Serology Reference Laboratory (NSRL) to conduct a review of serological assays used to diagnose Lyme disease. The review is looking at assays used in Australia and overseas.[47]

2.59 The NSRL provided an update on the status of the review:

- We have received approximately 650 specimens from the collaborators in UK, Germany, US and Australia, along with the results the collaborators obtained for those specimens.
- We have collected 308 specimens prospectively from Australian blood donors who have not travelled outside Australia.
- The collaborators have informed us of the serology assays they use to test for Lyme Disease.
- NRL has purchased sufficient of each of these assays to test all collaborator and blood donor specimens on all assays.
- We are in the process of testing the specimens now.
- The specimens are being tested in a blind manner. By that I mean that the specimens are labelled with an NRL identifier, not the identifier from the collaborator. Therefore we do not know the origin of the specimens or the results obtained by the collaborators

45 Professor Stephen Graves, *Committee Hansard*, 2 November 2016, p. 17.

46 Mr Christopher Walker, *Committee Hansard*, 2 November 2016, p. 45.

47 Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016, p. 57.

> as we are testing them. Therefore we cannot say anything at the moment about what the results are showing.[48]

Committee view

2.60 This inquiry has highlighted what is now decades-old disagreement on whether classical Lyme disease can be contracted in Australia. The committee acknowledges evidence provided by Australian medical authorities indicating that accredited laboratories—following established best-practice testing processes—have not found classical Lyme disease in Australian patients, with the exception of those who most likely contracted the disease overseas. This is what leads many in the medical profession to the conclusion that classical Lyme disease is not endemic to Australia.

2.61 However, while ever the issue of test quality remains contentious, the committee warns against ruling out the possibility that these bacteria are endemic to Australia. The committee is not satisfied that enough has been done to examine testing processes used by laboratories such as Australian Biologics. In the absence of such examination, the committee does not support an *a priori* conclusion that those test results are false positives.

2.62 Furthermore, the very fact that the reliability of the two-tiered testing protocol for Lyme disease is being questioned by respected doctors and scientists is, in the committee's view, reason enough for authorities to give careful consideration to these doctors' concerns. This notwithstanding, acknowledging the controversy does not in itself constitute proof of the inadequacy of the two-tiered testing protocol. The committee notes that work on developing new tests for Lyme disease is underway overseas and urges Australian medical authorities to remain appraised of the development of these tests.

2.63 The committee notes the NSRL review currently underway with interest. It is the committee's hope that this review will be conducted in a transparent manner and its findings published as anticipated. The committee expects that this review will provide some much-needed, conclusive answers, and enable the discourse on testing protocols to progress beyond the current impasse.

What is in our ticks?

2.64 Ticks in Australia, like ticks elsewhere, harbour a microcosm of bacteria, viruses and other pathogens. To reiterate, the department states that bacteria responsible for Lyme disease have not been identified in Australian ticks, and discovering such a bacterium is necessary before an evidence-based conclusion about the existence of Lyme disease in Australia—or a related illness—can be made:

> The conclusive finding of a bacterium that could cause Lyme disease or a Lyme disease-like illness in Australia has yet to be made. Such a finding

48 National Serology Reference Laboratory, answer to question on notice, received 18 November 2016, p. 1.

> would put beyond doubt the existence of Lyme disease, or a Lyme disease-like illness in Australia.[49]

2.65 Many submitters and witnesses concurred with this position, and suggested an alternative explanation: that another, as yet unidentified pathogen, may be the likely cause of tick-borne illness in Australia.

2.66 Others however challenged the assertion that bacteria causing Lyme disease were not present in Australian ticks, providing evidence to support their views.

2.67 Both positions are explored below.

Is Lyme Borreliosis endemic in Australia?

2.68 The committee was provided with excerpts from doctoral research dating back to the early 1990s which alludes to the likely presence in Australian ticks of *Borrelia* associated with Lyme disease. The objectives of the research were as follows:

> 1. To determine whether Australian ticks carry and transmit spirochaetes related to *Borrelia burgdorferi*.
> 2. To develop a specific and sensitive sero-diagnostic test to assess whether or not there is a correlation between clinical illness and the presence of *Borrelia burgdorferi* specific antibodies in likely Australian LB [Lyme Borreliosis] candidates.
> 3. To access the distribution of LB along the East Coast of Australia.[50]

2.69 The research project was initiated in 1989 and concluded in 1994. It began with a focus on the Manning Valley in New South Wales (NSW), but expanded to include the Sydney and Hunter Valley regions of NSW as well.

2.70 The paper concluded that Lyme Borreliosis does exist indigenously in Australia, because patients who had never left Australia tested positive for *Borrelia* antigens and displayed corresponding clinical symptoms.[51] Based on these findings, Dr Wills called for further research into:

> 1. Development of suitable cultural conditions for the growth and maintenance of Australian *B. burgdorferi*.
> 2. The molecular characteristics of Australian strains of *B. burgdorferi* so that a taxonomical comparison with existing genospecies can be obtained.
> 3. A more exact definition of the clinical manifestations of Australian Lyme disease and the immunological responses of patients.

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49 Department of Health, *Submission 495*, p. 2.

50 Dr Stuart King, *Submission 1289*, *Attachment 1*, p. 1.

51 Lyme Disease Association of Australia, *Submission 528.1*, pp. 7–9

4. Determination of epizootiology of LB in Australia, and the importance of LB in Australian wild and domestic animal populations.[52]

2.71 It is unknown to what extent this research has been pursued or reviewed. The department did, however, address this research in a scoping study conducted in 2013, concluding that the results were unable to be replicated:

> To this date, there has only been one report of *Borrelia* species being found in *I. holocyclus* ticks, but the cultures were not confirmed and were unsustainable (Wills and Barry 1991)…. Spirochaetes morphologically similar and antigenically related to *Borrelia burgdorferi* were cultured from the gut contents of *I. holocyclus* and *Haemophysalis spp.* ticks by Wills and Barry (1991), but the cultures weren't sustainable and these results have not been able to be repeated from ticks collected more recently.[53]

2.72 The committee notes that the department does not conclusively rule out the presence of classical Lyme disease in Australia. Instead, the department expresses a more nuanced position, stating that there is no evidence to suggest the presence of the bacteria:

> [T]he likelihood that Australia has an indigenous form of classical Lyme disease is questionable, given that a causative micro-organism with a competent vector is yet to be found. Whether a form of tick-borne human borreliosis exists in Australia is yet to be determined.[54]

A different Borrelia?

2.73 Some witnesses suggest that—accepting that Lyme disease is caused by members of the *Borrelia burgdorferi* sensu lato complex which have not been found in Australia—a different species of *Borrelia* might be present in Australia:

> On that basis, I would like to say that as far as I can see—from the patients' clinical symptoms, from the scientific research and from the preliminary results from the tick-borne disease unit—we do not have *Borrelia burgdorferi*, or Lyme disease, in Australia. What we have is a unique *Borrelia* infection. The problem with this disease is the symptoms are non-specific, so not every single Lyme patient ends up with the same set of symptoms. It is very hard to diagnose clinically. You can check the literature: every single publication will say the same thing. In the US they ask for a history of tick bite, and in certain areas like Connecticut it is common to have an EM rash, or the 'bull's-eye' rash, so diagnosis is easier. But in Australia the symptomology is much broader, and there are a lot more neurological symptoms. So you will end up with patients having seizures, patients having MS-like symptoms, patients having atypical Parkinson—atypical. Most of their symptoms are atypical, so a classical

52 Lyme Disease Association of Australia, *Submission 528.1*, p. 7.

53 Department of Health, *Submission 495, Attachment D*, pp. 8–14.

54 Dr Gary Lum, Department of Health, *Committee Hansard*, 2 November 2016, p. 58.

> neurologist cannot put them in the perfect box of multiple sclerosis or whatever they are familiar with.[55]

2.74 The plausibility of this theory is supported by other evidence. Dr Horowitz pointed out that identification of new strains of *Borrelia* is progressing at a rapid rate, suggesting that there may be far more species of *Borrelia* than are currently identified:

> So with inadequate diagnostic testing, and with the multiple species of bacteria and parasites that are spreading with environmental toxins, the problem is that with over 100 strains of Lyme borreliosis in the United States and 300 strains worldwide, although most of them are not pathogenic, we are finding new species every two years. There have been 15 new *Borrelia* species discovered in the last 20 years. The problem is that the testing has a difficult time keeping up with it.[56]

2.75 The committee notes that, as Dr Horowitz states above, most of the new species found are not pathogenic, they will not cause illness in humans. However, the identification of new strains of *Borrelia*, as well as other bacteria, in ticks around the world, including Australia, is of considerable significance to this inquiry, as it is possible that some will be found to be pathogenic.

2.76 The department noted the recent discovery of new *Borrelia* species in some Australian ticks, but cautioned against premature conclusions in the absence of thorough research:

> The department welcomes the finding of new *Borrelia* species from ticks found on echidnas. This new *Borrelia* probably represents a new clade.[57] It is different from the *Borrelia* in the Lyme disease group, the relapsing fever group and the reptile group. While this is a significant finding, it is important not to jump to conclusions. Whether these micro-organisms cause disease in humans requires research into transmission and human pathogenicity. The same research group has been able to readily identify *Borrelia burgdorferi* sensu lato species in ticks collected from endemic areas overseas. This demonstrates that, to date, with state-of-the-art technology, there remains no evidence of a cause of classical Lyme disease in Australian ticks. The Australian government has previously highlighted, in the scoping study it commissioned, the importance of research not only in ticks but also in patients, and of the need to draw evidence-based connections, if they exist.[58]

2.77 The committee looks at research underway in the next section.

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55 Dr Mualla McManus, *Committee Hansard*, 15 April 2016, p. 28.

56 Dr Richard Horowitz, *Committee Hansard*, 2 November 2016, p. 2.

57 A clade is a group of organisms, usually species, more closely related to one another than any group, implying a shared recent ancestor.

58 Dr Gary Lum, Department of Health, *Committee Hansard*, 2 November 2016, p. 59.

Committee view

2.78 The committee notes contradictory evidence received on the subject of *Borrelia* in Australian ticks, and reiterates that it is beyond the scope of this inquiry to establish whether *Borrelia* species which may cause Lyme disease are to be found in Australian ticks. The committee acknowledges the prevailing view that contracting Lyme disease in Australia is not possible, that our ticks have been studied and found not to harbour known Lyme disease-causing pathogens.

2.79 However, the committee also notes that evidence challenging this position has been presented during this inquiry. The committee refers particularly to the research of Dr Michelle Wills, which has been provided in evidence by more than one submitter, with consent from Dr Wills. The committee is persuaded that steps should be taken by the medical authorities to conduct a review of this evidence afresh if this has not already been done. To be authoritative and conclusive, such a review must be conducted by an independent, qualified team of scientists, with its methodology and results published in full.

More research is needed

2.80 Scientific research will play a critical part in identifying the pathogen, or pathogens, responsible for tick-borne illness in Australia. The committee's interim report outlined research currently underway. This was explored further at an additional hearing, with new evidence presented by Professor Peter Irwin, representing the Vector- and Water-borne Pathogen Research Group at Murdoch university, on recently discovered potential pathogens:

> Since the appearance of Professor Ryan and Dr Oskam before the committee, we have further characterised a number of bacteria which, in our opinion, represent potential candidates for tick-borne pathogens in Australia. These include *Neoehrlichia*, *Anaplasma*, *Ehrlichia* and *Borrelia*. Our work with *Borrelia* has confirmed that it is a unique Australian species. It is distinct from both the Lyme disease group and the relapsing fever disease group. Similar work with other bacterial species also reveals a unique phylogeny. Our conclusion, based on the evidence so far, is that Australian ticks harbour a relatively unique set of bacteria and therefore these are unknown to medical science in terms of their capacity to cause disease.[59]

2.81 Professor Irwin has emphasised that it is not appropriate to link these newly identified bacteria to illness in humans.[60] The next logical step in this research, Professor Irwin advised, will be to look at which, if any, of the newly identified organisms found in Australian ticks can be transmitted to humans. This, Professor Irwin concludes, is critical to determining causation.[61] Professor Irwin further

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59 Professor Peter Irwin, Principal, College of Veterinary Medicine, Murdoch University, *Committee Hansard*, 2 November 2016, p. 25.

60 Department of Health, *Submission 495*, p. 4.

61 Professor Peter Irwin, *Committee Hansard*, 2 November 2016, p. 25.

explained that after potential pathogens are identified, work will need to be done to assess the impact these may have on humans:

> There are several phases in this research. Ours is to form the building blocks of what is here in the ticks. The whole determination of disease causation by which of those bugs could cause disease in people is a further set of work that will require quite significant epidemiological type studies.
>
> We are actually intending to start work in that space. We intend to apply for an NHMRC grant next year—in the next main funding round—to support this work. We are starting to gather together collaborators—doctors in various parts of Australia who see patients with tick bites. We want to investigate them in a longitudinal fashion to follow those patients into the future.[62]

2.82 Professor Irwin reported having received a new grant which will fund some studies over the next three years, but called for an urgent increase in funding through the National Health and Medical Research Council (NHMRC):

> The NHMRC is the most relevant funding agency. However, an understanding of the importance, or relevance, of research into Lyme-disease-like illness may not be appreciated by all the reviewers and independent experts. We are aware of a grant application on this topic that was recently rejected by the NHMRC that scored relatively poorly for the category of 'significance'. I note also that Professor Kelso explained the NHMRC funding process in her submission to the committee in April, and I am encouraged by her comments that the NHMRC is putting in place targeted calls for research, which may recognise the priorities of not only government but also the wider Australian community. I believe that funding for research into tick-borne diseases in Australia is urgently needed.[63]

2.83 Research is also underway at the tick-borne diseases unit at Sydney University, which is currently conducting a study looking at whether ticks in Australia carry *Borrelia* or similar bacteria. The committee notes that the research has not been published yet, but that conclusive, direct evidence of *Borrelia* known to cause Lyme disease has not been found, but that other *Borrelia* have been found.[64]

2.84 Professor Irwin and Dr Ann Mitrovic[65] both extrapolated a further conclusion from the research already conducted: serological testing currently available, discussed earlier in this chapter, is quite likely ill-equipped to identify infection by the pathogens most likely at play in Australia:

> I heard the end of the discussion previously on serological testing, and, to my mind, it somewhat completely misses the point—that all the tests that are available at the moment are developed against known bacteria and

62 Professor Peter Irwin, *Committee Hansard*, 2 November 2016, p. 26.

63 Professor Peter Irwin, *Committee Hansard*, 2 November 2016, p. 25.

64 See discussion, *Committee Hansard*, 2 November 2016, pp. 25–26.

65 Dr Ann Mitrovic is a Research Fellow with the Tick-Borne Diseases Unit, School of Medical Sciences (Pharmacology), University of Sydney.

> disease. That is what they are designed for. I believe the Australian situation is completely different. We have organisms here that may be causing disease—we do not know what they are yet; we are working on that. In order to develop tests that are going to be more specific for what we have going on here, we need to isolate those organisms and develop tests from them.[66]

2.85 In making the same point, Dr Mitrovic brought the committee back to the issue of laboratory testing. In the US and Europe, where new strains of *Borrelia* are being discovered, these are not able to be detected by tests looking for infection with the *Borrelia burgdorferi* sensu lato complex.[67]

2.86 The committee notes evidence indicating that international bodies are expanding definitions around Lyme disease to include more than one strain of *Borrelia* and a number of co-infections.[68]

Committee view

2.87 The committee notes evidence outlined above indicating that unique pathogens have already been identified in Australian ticks, and that pathology tests currently conducted in Australia are not designed to look for those newly-identified pathogens. The committee is of the view that funding should be made available for this research to continue and be expanded as a matter of priority.

2.88 The committee is persuaded that it is possible that these unique pathogens may be causing Lyme-like illnesses and therefore further work is urgently needed to identify these pathogens and links to Lyme-like illnesses.

2.89 The committee however urges caution against extrapolating too much from the discovery of possible new pathogens, supporting the department's view that nothing should be assumed without further research.[69]

Recommendation 1

2.90 The committee recommends that the Australian Government Department of Health engage with stakeholders following the publication of the National Serology Reference Laboratory review to discuss the findings of the review and any bearing those may have on testing for Lyme disease in Australia.

Recommendation 2

2.91 The committee recommends that the Australian Government increase funding for research into tick-borne pathogens as a matter of urgency. This funding should include:

- **funding for research on pathogens which may cause infection;**

66 Professor Peter Irwin, *Committee Hansard*, 2 November 2016, p. 27.

67 Dr Ann Mitrovic, *Committee Hansard*, 2 November 2016, p. 27.

68 Ms Sharon Whiteman, President, Lyme Disease Association of Australia, *Committee Hansard*, 2 November 2016, p. 43.

69 See Department of Health, *Submission 495*, p. 4.

- **funding for research on whether newly-identified pathogens can cause illness in humans; and**
- **funding for the development of diagnostic tests which can detect infection by any newly-identified pathogens endemic to Australia.**

Chapter 3
Treating the illness

> My father taught me to swim with the rip, and that is how my children and I have survived. I am treading water, holding up two children. The medical system is stuck on the rocks. Way before Lyme I learnt that the medical profession does the best it can, but they are swamped and they do not know everything. I see the responses from authorities added to the inquiry. They are debating if the rip exists, how they can test if it is a true rip and who has the accreditation required to tell if it is a rip. I am so relieved to see people on the beach now, but I need to know that you are not just going to write a report about what you see. I need decisions to be made that will save my children from sinking. I want my children and I to please receive the critical, effective and timely treatment that we need.[1]

3.1 It will be some time before scientists are able to conclusively identify the pathogen, or pathogens, responsible for tick-borne illness in Australia. This is a critical step in the evolution of our understanding and response to tick-borne illness in Australia. For this reason, in the previous chapter the committee recommended that funding for research into tick-borne disease be prioritised. But the answers that research will bring may be years away, and people need action now.

3.2 Despite continued disagreement around the science, two important facts have emerged over the course of this inquiry: there is considerable evidence indicating that the illness we are looking at is tick-borne, and almost unanimous agreement that people with this illness must be helped.

3.3 The experiences patients have described are of great concern to the committee. Many report being dismissed by general practitioners and infectious disease specialists. Some report being turned away from hospitals and denied treatment upon mentioning the words 'Lyme disease'. Others report being shuttled from misdiagnosis to misdiagnosis over a number of years, eventually only to be told 'it's all in your head'.

3.4 This inquiry shows that there are too many people presenting with tangible symptoms for this assessment to be accurate. While the committee cannot independently verify patients' accounts, it has no reason to doubt their veracity. Put simply, this many people cannot be making themselves this sick.

3.5 Throughout this inquiry, the committee has sought to place patients who are unwell and in need of treatment front and centre.

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1 Ms Julianne Hansen, *Committee Hansard*, 15 April 2016, p. 42.

Existing treatment pathways

> Exactly seven years ago today I was in a hospital bed with my daughters at my side. Under my pillow was a letter telling them how much I love them and what good girls they were in case I died. Six months earlier I had over 20 nymph tick bites. I had fevers and sweats all night, and the next day the doctor gave one course of antibiotics. One week later, with heart symptoms, I was sent home from the hospital, told I had anxiety and given Valium, which I refused. After seeing every doctor and natural therapist I could for six months, barely able to walk, sleep or eat, I spent one week in hospital. Again, I was told I had anxiety and was sent home with Xanax. It was living hell.[2]

3.6 In its interim report the committee described treatment pathways available for people who acquired Lyme disease overseas, and treatment pathways for illness acquired in Australia. The committee recognised that many people, like the witness quoted above, felt let down by the health system, and that more should be done to educate the public and medical professionals about the risk of tick bites and tick-related illness.[3]

3.7 The committee also noted that Australia's health care system could be improved to better meet the needs of people with chronic illness, and that the illness in question would benefit from greater attention from the medical authorities.

3.8 The committee heard that a lack of treatment options and the resulting desperation was driving many Australian sufferers to seek treatment for Lyme-like illness overseas. On top of this, treatment locally and abroad is often expensive, and may leave vulnerable patients open to financial exploitation.[4]

3.9 Given the number of people suffering the chronic, debilitating symptoms associated with Lyme-like illness, it is clear that more must be done.

3.10 The following section of this report will look at evidence presented on treatment recommended by doctors who have diagnosed patients with Lyme-like illness, and who are at the frontline in the management of this disease.

First do no harm

3.11 As with most aspects of this inquiry, appropriate treatment for patients with Lyme-like illness was a contentious issue.

3.12 The Australian Medical Association (AMA), the nation's foremost membership organisation representing medical practitioners, explained that doctors

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2 Ms Dianne Ellis, *Committee Hansard*, 2 November 2016, p. 34.

3 Chapter 2, Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016.

4 Chapter 2, Senate Community Affairs References Committee, *Growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients*, Interim report, May 2016.

have a responsibility to rely on evidence to determine a diagnosis and treatment plan. The AMA set out its position in a submission to the committee:

> Medical practitioners do their utmost to accurately diagnose the cause of an illness and provide an appropriate treatment. Doctors support the patient in understanding their condition and what they might expect, define circumstances when patients' symptoms could have several causes, identify and advise on appropriate treatment or preventive options. A doctor's duty of care is to make an accurate diagnosis or state that there is insufficient evidence for a specific diagnosis…
>
> …To date there has been no evidence to support the existence of *Borrelia burgdorferi* (*Borrelia*) in Australia...In the absence of a conclusive aetiology of an indigenous vector for Lyme disease or a Lyme-like disease, diagnosis remains difficult and patients are frustrated when their illness is not easily diagnosed or treated. The AMA understands that this sentiment is genuine and that a failure to reach a conclusive diagnosis can be stressful, however the medical profession's role is to make clinically appropriate treatment recommendations based on the best available evidence. It is ethically and legally appropriate for doctors to refuse demands by patients, patients' family members or other third parties for tests, treatments or procedures that are not clinically appropriate.[5]

3.13 The committee did not receive any submissions disputing the call for medical treatment to be ethical and safe. The question of what constitutes clinically appropriate treatment for an illness with an undefined causative agent, however, can be seen from a number of perspectives. On one hand, there is a risk of misdiagnosis, as there is with any illness. On the other, denial of treatment in the absence of certainty around the diagnosis may arguably also contribute to an adverse outcome.

The risk of misdiagnosis

3.14 As seen above, the AMA highlights the responsibility of doctors to make evidence-based diagnoses. This is echoed by other organisations, such as the Medical Council of New South Wales (MCNSW). The MCNSW expressed concern about the harm caused by misdiagnosis and drew the committee's attention to complaints from the public and medical professionals about the performance of some doctors who have diagnosed Lyme-like illness in the absence of confirmation from an accredited laboratory:

> Additionally, in those patients with serious underlying diseases, including cancers, misdiagnosed as "Lyme-like illness" and treated for long periods with repeated courses of antibiotics there has been progression of the underlying disease in the absence of the patient receiving timely and appropriate therapy.[6]

3.15 A submission from the Medical Board of Australia (MBA) and the Australian Health Practitioner Regulation Agency (AHPRA) similarly indicated that medical

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5 Australian Medical Association, *Submission 456*, p. 1.

6 Medical Council of New South Wales, *Submission 935*, p. 2.

authorities are aware of concerns about treatment being administered for Lyme-like illness. Specifically, there is a concern that the diagnosis might be premature and as such may preclude more appropriate treatment for other conditions:

> There is a concern that patients may be deprived of the opportunity to have more appropriate treatment for another condition because the alternative condition is not considered once Lyme-like illness has been diagnosed. Treating Lyme-like illness with long-term antibiotic treatment, in the absence of an identified infection, is of concern. This management is at odds with advice from public health authorities regarding the dangers of antibiotic resistance. We understand that some practitioners are prescribing and administering antibiotics for years (whereas the treatment of Lyme disease is for weeks).[7]

3.16 A submission from the Infectious Diseases Department at Austin Health, Melbourne, describes work and treatment undertaken with a cohort of patients who believe they have Lyme-like illness and who were referred to Austin Health for assessment. It was determined that, of these patients:

- 30-50% have potentially serious medical conditions that have either been previously undiagnosed, diagnosed but inappropriately treated, or diagnosed but denied by the patient such that no treatment was sought.
- 10-20% have a serious defined psychiatric illness that requires specialist care
- 80-90% have undergone substantial financial hardship paying for investigations from unaccredited laboratories and, in some cases, prolonged antibiotic treatment that has had no (or minimal) objective evidence of benefit.
- The current specialty-based medical approach to managing these patients is inappropriate. Instead, a multi-disciplinary approach is required to better assess these patients, including specialist physicians (e.g. infectious diseases, rheumatology and oncology), psychiatrists (with a special expertise in so-called conversion disorders) and primary care physicians (GPs) with an interest in the long-term care of patients with chronic disease. A specific funding model should be considered since the current system is inhibitory to this approach.[8]

3.17 It is unclear how the sample of patients referred to Austin Health was selected; however, the conclusions infer a considerable instance of inappropriate diagnosis and treatment.

3.18 The committee's interim report discussed the stigma feared by doctors who treat tick-borne disease in Australia, citing numerous reports of threats and

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7 Medical Board of Australia and Australian Health Practitioner Regulation Agency, *Submission 533*, p. 3.

8 Infectious Disease Department, Austin Health, *Submission 820*, p. 2.

intimidation by the medical authorities. Patients reported feeling anxious that their doctors would have complaints made against them or be sanctioned for attempting to treat the illness.

3.19 The committee discussed complaints against practitioners who treat Lyme disease or Lyme-like illness with AHPRA and the MBA, and was informed that the vast majority of complaints do not result in regulatory action. Only three doctors currently 'have conditions on their practice relating to Lyme or Lyme-like illness.'[9]

3.20 The committee notes that despite these statistics, there are claims of intimidation by AHPRA.[10]

The risk of inaction

3.21 A number of medical practitioners with experience in treating the tick-borne illness in question discussed the risk of medical inaction and over-reliance on pathology tests. They argued that chronically ill patients need safe, appropriate treatment even when a definitive pathological cause is elusive. Medicine, as pointed out by the Karl McManus Foundation, 'is not static but constantly changing':[11]

> In a situation where the causative agent is not well characterised treatment protocols are not likely to be within the realm of mainstream medicine.[12]

3.22 Dr Richard Schloeffel, chairperson of the Australian Chronic Infectious and Inflammatory Diseases Society (ACIIDS), argued that diagnosis should begin with observation, which in this case is that Australian ticks are making people sick:

> We have to recognise there are things in our ticks that we have not fully identified yet. When you make an observation, what happens is the evidence will follow the observation. But chance favours only the prepared mind. If the mind is not prepared, you will not make that A equals B equals Z. You cannot join the dots if you are not able to make that transition. That is why it has not moved forward with the doctors. I do not think they are hearing the patient. This is a clinical diagnosis before anything else.[13]

3.23 Dr Schloeffel highlighted the importance of clinical diagnosis, making the point that pathology should be used to verify, not guide a doctor's clinical diagnosis:

> A pathology test should only confirm your thought process, not the other way around. We are clinicians. Doctors are properly trained, hard thinking and intelligent people who make a decision clinically, and then the test verifies our thought process. The tests are inadequate because the patient is immunosuppressed. The tests are not good enough. The bugs are varied.

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9 Associate Professor Stephen Bradshaw, Practitioner Member, Medical Board of Australia, *Committee Hansard*, 2 November 2016, p. 60.

10 Karl McManus Foundation, answer to question on notice, received 18 November 2016, p. 4.

11 Karl McManus Foundation, answer to question on notice, received 18 November 2016, p. 1.

12 Karl McManus Foundation, answer to question on notice, received 18 November 2016, p. 1.

13 Dr Richard Schloeffel, Chairperson, Australian Chronic Infectious and Inflammatory Diseases Society, *Committee Hansard*, 2 November 2016, p. 50.

> There are viruses, parasites and bacteria. Pathology is very secondary. Sure, do no harm, but do not lie to your patient that they are not sick because the test was negative. It is not helpful; it is not good medicine.[14]

> The most important thing when you have patients who are sick is to listen to the patient. If you do not listen to the patient you will not make a diagnosis. Forget about ELISA test versus Western Blot and all these other things. These patients come to me, referred to me by other specialists, other doctors. I have 800 people on a waiting list. I have letters like this one from people telling me their child is going to die if they do not have treatment.[15]

3.24 Dr Schloeffel described the magnitude of the situation and the urgent need for action, estimating that 40 000 to 50 000 Australians may have this illness.[16] He explained that diagnosis is neither quick, nor simple, and is evidence-based:

> I started looking at this disease 20 years ago. I have become very interested in it of late because we seem to have more and more patients with this. People are coming forward with motor neurone disease, chronic fatigue syndrome, fibromyalgia, autism spectrum disorder, dementia, multiple sclerosis, Parkinson's disease. I have seen all of those patients multiple times. I have had 17 of my patients die and I have three of them dying at the moment. They will die from this illness. They got a tick bite and they are going to die. Most of them talked to 20 or 30 doctors before they got to us. We diagnosed them with Australian testing and overseas testing and developed what we called levels of evidence. But it was in the clinical diagnosis and the absence of other disease that we decided this was this disease.[17]

3.25 Dr Richard Horowitz discussed tick-borne illness in Australia in a wider, international context, describing Lyme disease as a worldwide epidemic:

> The National Science Foundation and the World Health Organization consider Lyme disease to be one of the pandemic diseases that is spreading worldwide right now.[18]

3.26 Dr Christopher Walker, representing the Karl McManus Foundation, a charity funding research into tick-borne diseases, suggested that medical authorities' lack of focus on tick-borne illness and debates around terminology in the absence of an agreed causative agent were having an adverse effect on progress in terms of diagnosis and treatment for patients. This inaction and dearth of support from medical authorities in some cases leaves patients looking for a diagnosis themselves, making them vulnerable to misinformation and exploitation:

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14 Dr Richard Schloeffel, *Committee Hansard*, 2 November 2016, p. 55.

15 Dr Richard Schloeffel, *Committee Hansard*, 2 November 2016, p. 48.

16 Dr Richard Schloeffel, *Committee Hansard*, 2 November 2016, p. 49.

17 Dr Richard Schloeffel, *Committee Hansard*, 2 November 2016, p. 48.

18 Dr Richard Horowitz, *Committee Hansard*, 2 November 2016, p. 1.

> Currently health practitioners are being discouraged from diagnosis and treatment of tick-borne diseases. This appears to be linked to the Lyme disease terminology and has seen a significant reduction in treating doctors. This reduction of available medical practitioners is forcing desperate people to turn to the likes of 'Dr Google' for answers. It must be said that 'Dr Google' presents one of the most disruptive and destructive forces in diagnosis and treatment of any tick-borne disease. There exists a plethora of individuals and organisations who are quick to reproduce and repost advice without any qualification or validation. One of the most extreme, misguided 'Dr Google' discourses identified is the claim that Lyme disease can be contracted from eating too much kale. A claim of nonsense in the extreme, but nonetheless published in a women's health magazine, readily available on 'Dr Google' and easily believed by those who know no better. We need our medical profession to be actively involved in the diagnosis and treatment of these diseases, even at this confounding juncture, and put paid to such subterfuge ignorance and outright incompetence.[19]

3.27 Mr Mike Pym, Director of the Karl McManus Foundation, called for action based on current best practice, telling the committee that waiting for research to be conclusive would cause harm:

> [W]e have to have a treatment protocol for this 'new name' set of symptoms now. We cannot wait for more science. We have to work out what is best practice now, draw a line in the sand, acknowledge that that is what is good enough and then move on—but get all of the doctors using best practice now. We all know that it will not be perfect, but it is better than watching people die. Simply doing nothing is not doing no harm; it is letting people suffer and die on your watch.[20]

Committee view

3.28 The committee notes concerns expressed by medical authorities about the potential for misdiagnosis and inappropriate treatment in a situation where the cause of illness is not entirely clear. The committee shares these concerns.

3.29 At the same time, however, the committee recognises that complex, emerging diseases require treatment even in the absence of definitive research. As put by Dr Schloeffel, 'the science has not caught up, but the compassion needs to be there.'[21]

3.30 Recognising that it is not a medical body, the committee agrees in principle that in situations where other causes have been appropriately considered and ruled out, doctors should have access to the best available treatment guidelines for Lyme-like, tick-borne disease.

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19 Dr Christopher Walker, Acting Chief Executive Officer, Karl McManus Foundation, *Committee Hansard*, 2 November 2016, p. 46.

20 Mr Mike Pym, Director, Karl McManus Foundation, *Committee Hansard*, 2 November 2016, p. 47.

21 Dr Richard Schloeffel, *Committee Hansard*, 15 April 2016, p. 23.

3.31 The committee acknowledges the work and experience of medical professionals treating this illness, and supports calls for the treatment options they have developed to be trialled more broadly in consultation with medical authorities.

Establishing a treatment protocol

3.32 Aware of the need for medical professionals to balance the risks involved in addressing an unknown or emerging disease, the committee sought evidence on how patients can receive treatment in a safe environment.

3.33 To this end, the committee held an additional hearing on 2 November 2016, at which treatment was discussed with a number of witnesses. To establish what is current best practice, the committee consulted representatives from the Karl McManus Foundation, Dr Schloeffel representing ACIIDS, and Dr Horowitz, a US-based practitioner specialising in the treatment of Lyme disease and related infections. The evidence they presented was discussed with the department, the MBA and AHPRA.

3.34 The committee invited the AMA and Royal Australian College of General Practitioners to participate in this discussion, however representatives were not available at the time of the hearing.

Effective treatment

3.35 The Karl McManus Foundation described the lack of agreement in the medical community on how best to address tick-borne disease:

> Generally doctors in Australia are also split into two groups, the mainstream who will consider acute treatment and offer palliative care for chronic TBDs (ie: post Lyme syndrome). While holistic doctors are aware that when pathogens have disseminated into other tissues a broad approach may be needed which may require not only prolonged treatment of disseminated infections but also supporting the immune system and providing the right nutrients for patient recovery.[22]

3.36 Holistic doctors treat what they refer to as chronic illness. This, the committee heard, is because tick-borne disease is complex and often involves more than just one single, acute infection:

> The patients that I see with Lyme disease do not just have *Borrelia burgdorferi* sensu lato. What they end up having is many other species of bacteria, viruses and parasites because the ticks are now containing many of these different species and are rapidly spreading.[23]

3.37 In Australia, doctors treating the disease frequently see patients presenting with symptoms consistent with relapsing fever. Dr Schloeffel postulated that research would ultimately confirm this to be the case:

> Borreliosis is from a spirochete organism. It can cause all sorts of symptoms. It can go anywhere. There are multiple species. There is one in America called Lyme disease, but what we have here—I am sure a lot of

22 Karl McManus Foundation, answer to question on notice, received 18 November 2016, p. 4.

23 Dr Richard Horowitz, *Committee Hansard*, 2 November 2016, p. 1.

> the patients I see have a relapsing fever type of *Borrelia*. That would be consistent with what Peter Irwin is finding in those ticks. We just have to join the dots between what he finds in echidna ticks and what I see in my patients.[24]

3.38 The committee heard that the co-infections Dr Horowitz and Dr Schloeffel describe can in some cases lead to death if not adequately treated.[25] Treatment, however, is not simple, and involves more than fighting infection with antibiotics. Patients first of all need to be stabilised before antibiotics can be used to fight infection:

> Treatment is not throwing antibiotics at people. I totally agree with my colleagues about the overuse or the difficulty of giving just antibiotics. You have to resuscitate the patient. These people are sick. They get brain fog, fits and seizures. Some of them are psychotic and some of them are depressed. They get pounding, vice-like headaches, seizures, twitches, body pain and POTS [postural orthostatic tachycardia syndrome[26]]. Their blood pressure is really low and they cannot do anything—they stand up and they collapse. Their bowels do not work and they have racking pain in their body. Their body temperature is often 34—three degrees below normal—because their thyroids are failing and they get adrenal failure. If you give someone like that antibiotics to start with, they are just going to get much sicker. So we have to resuscitate the patients.[27]

3.39 The committee understands that Dr Schloeffel, together with colleagues Dr Peter Dobie and Dr Hugh Durham, is in the process of drafting new evidence-based guidelines for diagnosis and treatment of tick-borne illness in Australia:

> It will have no authority except we will try and get some backing from infectious disease specialists. I will show it to the chief medical officer and Gary Lum, because it is important that they have a look at it. But it will go out irrespective of how they think about it. It is not a dangerous document. It is a factual document based on evidence that we will present. It will be a guideline and it will be up to the individual doctors to make a decision but at least it is a guideline. If we start treating patients who get a tick bite, or something that bites, in the first instance they may not end up like this lot of people who have suffered.[28]

3.40 The committee understands that the guidelines will move away from the term 'Lyme' and refer instead to tick-borne illness as 'Multiple Systemic Infectious Disease

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24 Dr Richard Schloeffel, *Committee Hansard*, 15 April 2016, p. 49.

25 Dr Richard Schloeffel, *Committee Hansard*, 15 April 2016, p. 49.

26 Postural orthostatic tachycardia syndrome (POTS) is a condition in which sufferers experience an abnormal heart rate increase when they chance from a supine to an upright position.

27 Dr Richard Schloeffel, *Committee Hansard*, 15 April 2016, p. 49.

28 Dr Richard Schloeffel, *Committee Hansard*, 15 April 2016, p. 50.

Syndrome, as suggested by Dr Horowitz.[29] They will be peer reviewed by two infectious disease specialists, then forwarded to the department.[30]

3.41 The committee discussed these guidelines with the department, and was advised the department was aware of the draft and engaging with Dr Schloeffel on the content:

> In discussion with Dr Schloeffel, the department provided information on how he can modify the ACIIDS guidelines which he is currently writing to be included in the National Health and Medical Research Council's clinical guidelines portal. The department will also continue to encourage Dr Schloeffel, along with his ACIIDS members, to work with academic units in medical schools to develop NH&MRC grant applications for patient based research.[31]

3.42 The committee understands the new treatment guidelines will be complete and ready for dissemination by the end of 2016 or early 2017.[32]

3.43 The committee also approached the Karl McManus Foundation on the topic of treatment guidelines, and was informed that the Foundation had not validated any treatment protocols as yet and therefore could not recommend a particular protocol. The Foundation did, however, recognise that different treatment protocols may be required for acute and chronic disease:

> Keen to see current best practise to be implemented immediately the KMF recognise that the Infectious Diseases Society of America (IDSA) present best practise treatment protocol for treatment of ACUTE forms of Lyme disease while International Lyme and Associated Diseases Society (ILADS) have developed best practise protocol for CHRONIC conditions. It is noted that the ILADS practice of long term antibiotic therapy is disputed by some and the two societies are split over TBDs treatment.[33]

3.44 A submission from ACIIDS states that their views are closely aligned with those of ILADS and provided the committee with current treatment guidelines—the committee notes that these advocate cautious use of antibiotics where needed.[34]

3.45 ACIIDS reports a considerable patient recovery rate, with peer review of this treatment conducted in Europe and the US:

> In relation to the recovery rate of patients, of which the ACIIDS group of doctors have treated over 4,000, the general consensus is that 60-80% of

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29 Dr Richard Horowitz, see *Submission 936*, p. 1.

30 ACIIDS, answer to question on notice, received 17 November 2016, p. 2.

31 Dr Gary Lum, Principal Medical Adviser, Office of Health Protection, Department of Health, *Committee Hansard*, 2 November 2016, p. 59.

32 ACIIDS, answers to questions on notice, received 17 November 2016, p. 3.

33 Karl McManus Foundation, answer to question on notice, received 18 November 2016, p. 3.

34 ACIIDS, *Submission 370, Attachment 24*. ILADS treatment guidelines can be found at http://www.ilads.org/lyme/treatment-guideline.php (accessed 23 November 2016).

> our patients have considerable or complete recovery with appropriate treatment.[35]

3.46 The committee asked the department about its consultations with ACIIDS. The department provided the following on its engagement with the organisation:

> The department has met with medical practitioners who are treating patients. This has included meetings with members of the Australian Chronic Infectious and Inflammatory Diseases Society, separate meetings with Dr Richard Schloeffel and a treatment roundtable which brought together nine treating general practitioners along with other specialist medical practitioners to consider treatment options. Dr Lum has also attended a two-day meeting of the International Lyme and Associated Diseases Society.[36]

3.47 The committee welcomes this engagement, and notes Dr Schloeffel's call for government support:

> I am happy to have doctors sit in with me and I will teach them how to diagnose, treat and help these patients, but then someone else has to take them on. So we need funding for hospitals. We need an intellectual and a committed effort from the health departments, national and state, in our public system to help everybody who thinks they might have this illness…I do not think I am right or wrong; I am just seeing clinical evidence of a disease that needs to be managed…[I]t has got to come from the health minister, the Department of Health and the senior colleagues who direct policy and thought process, who have to say, 'Stop! We've got to stop. We've got to go over here. Maybe we got it wrong.' Admit you are wrong and come and talk to us. Actually make something happen. Support a pilot program with the Karl McManus Foundation. Let's look at 100 patients straight-up. Let's fund that. Let's do some proper medicine. Let's study that. Then we get 100 more. Then you will have 10,000 waiting in the queue. But they can be treated in all these peripheral hospitals, and doctors with interest and skill can start treating them. It is a process. I think that is the answer.[37]

Committee view and conclusion

3.48 The committee concludes its inquiry without clarity on diagnosis or treatment of this illness. Given the magnitude of the dispute around tick-borne illness in Australia this is perhaps unsurprising.

3.49 What is clear, however, is that potentially infectious pathogens are being transmitted by Australian ticks, and treatment for the ensuing illnesses is currently suboptimal. The committee therefore returns to its starting premise: people are sick, and they must be helped. That people report avoiding engagement with medical staff at Australian hospitals for fear of being branded 'crazy' is concerning. That some

35 ACIIDS, answer to question on notice, received 17 November 2016, p. 1.

36 Department of Health, answer to question on notice, received 21 November 2016, p. 5.

37 Dr Richard Schloeffel, *Committee Hansard*, 2 November 2016, p. 51.

patients are contemplating suicide as a result, in part, of their distress at not receiving what they believe to be proper medical attention and care, is profoundly disquieting. The committee has no cause to doubt the veracity of these accounts.

3.50 Any suggestion that doctors should only treat patients if and when they have pinpointed the cause of illness is troubling—whilst not being comprised of medical professionals, the committee is persuaded that emerging diseases require safe and responsible treatment even when the science is in progress. Notwithstanding the absence of definitive answers on what the responsible pathogens are, it is the committee's view that medical authorities and doctors have a responsibility to address and treat illness. The patients are not responsible for the absence of vital research establishing which pathogens carried by which vectors are responsible for Lyme-like illness—this evidence is needed, and urgently, but so is treatment for patients who are unwell now.

3.51 The best possible treatment protocols need to be established as a matter of priority, and medical professionals educated on their use. The committee urges medical authorities to take advantage of the momentum created by this inquiry and consult extensively with researchers and clinicians focusing on tick-borne disease. With the right commitment from medical professionals and authorities, these treatment protocols will be refined and improved over time.

3.52 For this reason, the committee is recommending that treatment guidelines currently in use by doctors who claim significant recovery rates in their patients be assessed and a clinical trial conducted to determine their effectiveness. In parallel with scientific research into possible pathogens which is currently underway, this clinical trial of treatment protocols will serve to inform an evolving, evidence-based response to tick-borne disease. The committee urges medical authorities to act on this recommendation without delay and in consultation with relevant stakeholders including the Karl McManus Foundation and ACIIDS.

3.53 Patients cannot be asked to wait. The science will catch up, and it is critical that funding be made available for this to happen.

Recommendation 3

3.54 The committee recommends that government medical authorities, in consultation with stakeholders including the Australian Chronic Infectious and Inflammatory Diseases Society (ACIIDS) and the Karl McManus Foundation, establish a clinical trial of treatment guidelines developed by ACIIDS with the aim of determining a safe treatment protocol for patients with tick-borne illness.

Recommendation 4

3.55 The committee recommends that the Australian Government allocate funding for research into medically-appropriate treatment of tick-borne disease, and that medical authorities measure the value of treatment in terms of patient recovery and return to health. The best treatment options must then be developed into clinical treatment guidelines.

Recommendation 5

3.56 The committee recommends that the Australian Government Department of Health facilitate, as a matter of urgency, a summit to develop a cooperative framework which can accommodate patient and medical needs with the objective of establishing a multidisciplinary approach to addressing tick-borne illness across all jurisdictions.

Recommendation 6

3.57 The committee recommends that federal, state and territory health agencies, through the Council of Australian Governments Health Council, develop a consistent, national approach to addressing tick-borne illness.

Recommendation 7

3.58 The committee recommends that the Australian Government Department of Health urgently undertake an epidemiological assessment of the prevalence of suspected tick-borne illness in Australia, the process and findings of which are to be made publicly available.

Recommendation 8

3.59 The committee recommends that the Australian Government Department of Health establish the prevalence and geographical distribution of overseas-acquired Lyme disease in Australia.

Recommendation 9

3.60 The committee recommends that Australian medical authorities and practitioners addressing suspected tick-borne illness:

- **consistently adopt a patient-centric approach that focusses on individual patient symptoms, rather than a disease label; and**
- **remove 'chronic Lyme disease', 'Lyme-like illness' and similar 'Lyme' phrases from diagnostic discussions.**

Recommendation 10

3.61 The committee recommends that, to help the referral of patients for guided and comprehensive pathology testing, medical practitioners work with pathologists, especially microbiologists, immunologists, chemical pathologists and hæmatologists to optimise diagnostic testing for each patient.

Recommendation 11

3.62 The committee recommends that the Australian Government Department of Health work closely with the Australian Medical Association and Royal Australian College of General Practitioners to ensure that general practitioners have a better understanding of how to treat patients who present with complex symptoms.

Recommendation 12

3.63 The committee recommends that treatment guidelines developed by Australian medical authorities emphasise the importance of a multidisciplinary, case conference approach to patient care, involving consultation between general practitioners and specialists with expertise in neurology, psychiatry, rheumatology, immunology, infectious diseases and microbiology.

Senator Rachel Siewert

Chair

APPENDIX 1

Submissions and additional information received by the Committee

Submissions

1	Mrs Alexandra Patsan
2	Dr Richard Schloeffel (plus twelve attachments)
3	Confidential
4	Name Withheld
5	Ms Marie Corby
6	Confidential
7	Name Withheld
8	Name Withheld
9	Mr Greg Watts
10	Mr Charlie Cohen
11	Name Withheld
12	Name Withheld
13	Confidential
14	Mr Jeremie Smith
15	Miss Emily O'Sullivan
16	Confidential
17	Confidential
18	Name Withheld

19 Name Withheld

20 Ms Bev McMillan

21 Confidential

22 Name Withheld

23 Name Withheld

24 Mr Nick Knottenbeld

25 Confidential

26 Ms Sara Franzoni

27 Mr Paul Fenwick

28 Name Withheld

29 Ms Kylie Gilbert

30 Ms Trudi Bareham

31 Ms Nell Anderson

32 Name Withheld

33 Confidential

34 Name Withheld

35 Chris Wilson

36 Name Withheld

37 Name Withheld

38 Ms Kamisha Seale-Woodberry

39 Mr John Woodberry

40 Mr Alan Williams

41 Confidential

42 Name Withheld

43 Ms Angela Muzzin

44 Confidential

45 Name Withheld

46 Confidential

47 Mr Sean O'Donoghue

48 Confidential

49 Name Withheld

50 Name Withheld

51 Ms Kathy Brierley

52 Ms Samantha Coates

53 Name Withheld

54 Name Withheld

55 Name Withheld

56 Confidential

57 Name Withheld

58 Name Withheld

59 Confidential

60 Name Withheld

61 Name Withheld

62 Name Withheld

63 Name Withheld

64 Name Withheld

65 Mr Brad Shepherd

66 Confidential

67 Name Withheld (plus seven attachments)

68 Name Withheld

69 Confidential

70 Ms Christine Linigen

71 Ms Gail Petherick

72 Name Withheld

73 Ms Emily Miklovic

74 Ms Marie Saurine

75 Mr Glenn Gilbert

76 Mr Mathew Gilbert

77 Name Withheld

78 Name Withheld

79 Name Withheld

80 Name Withheld

81 Mrs Bronwyn Bungey (plus two attachments)

82 Name Withheld

83 Ms Cate Moloney

84 Name Withheld

85 Mr Mark O'Meara (plus an attachment)

86 Name Withheld

87 Confidential

88 Confidential

89 Name Withheld

90 Ms Sharon King

91 Name Withheld

92 Ms Jill Marley

93 Confidential

94 Name Withheld

95 Name Withheld

96 Name Withheld

97 Name Withheld

98 Country Women's Association of NSW (plus an attachment)

99 Name Withheld

100 Confidential

101 Name Withheld

102 Confidential

103 Ms Cornelia Mortimer

104 Ms Tiffany Cameron

105 Name Withheld

106 Mr Brendan Witham

107 Confidential

108 Mr Ross Floate

109 Ms Karin Floate

110 Name Withheld

111 Name Withheld

112 Name Withheld

113 Confidential

114 Name Withheld

115 Confidential

116 Name Withheld

117 Confidential

118 Mr Daniel Larking

119 Confidential

120 Confidential

121 Name Withheld

122 Name Withheld (plus five attachments)

123 Name Withheld

124 Name Withheld

125 Name Withheld

126 Name Withheld

127 Mr Chris Willis

128 Ms Dona Stobie

129 Ms Michelle Wood (plus an attachment)

130 Name Withheld

131 Ms Val Wright

132 Ms Tammorae Williamson

133 Name Withheld

134 Mr Lachlan Monks

135 Mrs Sue Monks

136 Name Withheld

137 Confidential

138 Name Withheld

139 Name Withheld

140 Ms Natalie Young (plus three attachments)

141 Ms Krystle Krenske

142 Ms Di Ellis

143 Ms Heidi Adams

144 Name Withheld

145 Mrs Christina Sinnamon

146 Name Withheld

147 Ms Vicki Hain

148 Ms Angela Milroy

149 Ms Margaret Adams

150 Ms Steph Hammersley (plus an attachment)

151 Ms Georgina Burston

152 Name Withheld

153 Name Withheld

154 Name Withheld

155 Name Withheld

156 Name Withheld

157 Mrs Neeva Stephen

158 Confidential

159 Name Withheld

160 Name Withheld

161 Ms Anita Morrison

162 Name Withheld

163 Name Withheld

164 Name Withheld

165 Name Withheld

166 Confidential

167 Confidential

168 Name Withheld

169 Name Withheld

170 Name Withheld

171 Confidential

172 Name Withheld

173 Confidential

174 Name Withheld

175 Name Withheld

176 Name Withheld

177 Confidential

178 Name Withheld

179 Name Withheld

180 Confidential

181 Mr Marcus Hewitt

182 Name Withheld

183 Name Withheld

184 Name Withheld (plus four attachments)

185 Name Withheld

186 Name Withheld

187 Name Withheld

188 Confidential

189 Name Withheld

190 Mr Kim Rhodes

191 Name Withheld (plus an attachment)

192 Confidential

193 Confidential

194 Name Withheld

195 Name Withheld

196 Name Withheld

197 Name Withheld

198 Name Withheld

199 Name Withheld

200 Name Withheld

201 Name Withheld

202 Name Withheld

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228 Confidential

229 Confidential

230 Confidential

231 Name Withheld

232 Name Withheld

233 Name Withheld

234 Name Withheld

235 Name Withheld

236 Name Withheld

237 Name Withheld

238 Confidential

239 Name Withheld

240 Mr Des O'Sullivan

241 Name Withheld

242 Confidential

243 Name Withheld

244 Mrs Carolyn O'Sullivan

245 Confidential

246 Name Withheld (plus an attachment)

247 Name Withheld

248 Name Withheld

249 Confidential

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251 Name Withheld

252 Name Withheld

253 Name Withheld

254 Name Withheld

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256 Name Withheld

257 Name Withheld

258 Confidential

259 Name Withheld

260 Name Withheld

261 Ms Linda Jones

262 Name Withheld

263 Name Withheld

264 Name Withheld

265 Name Withheld

266 Name Withheld

267 Name Withheld

268 Name Withheld

269 Name Withheld

270 Confidential

271 Name Withheld

272 Name Withheld

273 Name Withheld

274 Confidential

275 Name Withheld

276 Name Withheld

277 Name Withheld

278 Mr Max Russell

279 Name Withheld

280 Name Withheld

281 Name Withheld (plus an attachment)

282 Name Withheld (plus an attachment)

283 Confidential

284 Name Withheld

285 Name Withheld

286 Confidential

287 Name Withheld

288 Name Withheld

289 Name Withheld

290 Name Withheld

291 Name Withheld

292 Name Withheld

293 Ms Lynn Rees

294 Confidential

295 Name Withheld (plus an attachment)

296 Name Withheld

297 Confidential

298 Name Withheld

299 Name Withheld

300 Ms Nickey Carroll

301 Name Withheld

302 Name Withheld

303 Name Withheld

304 Name Withheld

305 Name Withheld

306 Name Withheld

307 Name Withheld

308 Name Withheld (plus an attachment)

309 Name Withheld

310 Name Withheld

311 Mr Chris Hain (plus four attachments)

312 Confidential

313 Name Withheld

314 Mr Stephen Bloomer

315 Ms Melissa Pym

316 Name Withheld

317 Mr Ryan O'Dea

318 Name Withheld

319 Name Withheld

320 Mr Allen Main

321 Confidential

322 Name Withheld

323 Ms Alison Veitch

324 Name Withheld (plus a supplementary submission)

325 Name Withheld

326 Confidential

327 Name Withheld

328 Name Withheld

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336 Name Withheld

337 Name Withheld (plus an attachment)

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341 Name Withheld

342 Name Withheld

343 Name Withheld

344 Name Withheld

345 Name Withheld

346 Ms Karen Winter

347 Name Withheld

348 Name Withheld

349 Name Withheld

350 Name Withheld

351 Mr John Curnow

352 Ms Connie Conlon

353 Name Withheld

354 Name Withheld

355 Name Withheld

356 Name Withheld

357 Ms Nancy Weir

358 Name Withheld

359 Name Withheld

360 Name Withheld

361 Name Withheld

362 Name Withheld

363 Confidential

364 Confidential

365 Confidential

366 Confidential

367 Name Withheld

368 Name Withheld

369 Name Withheld

370 Australian Chronic Infectious and Inflammatory Disease Society (plus forty one attachments)

371 Confidential

372 Name Withheld

373 Confidential

374 Name Withheld

375 Confidential

376 Name Withheld

377 Name Withheld

378 Mr Shane Moloney

379 Name Withheld

380 Name Withheld

381 Name Withheld

382 Ms Joanne Cassam

383 Name Withheld

384 Ms Jasmin Moran

385 Name Withheld

386 Name Withheld

387 Name Withheld

388 Ms Lara Coleman

389 Ms Allison Alexander

390 Name Withheld

391 Ms Susie Brown

392 Name Withheld (plus six attachments)

393 Name Withheld

394 Name Withheld

395 Name Withheld

396 Name Withheld

397 Name Withheld

398 Name Withheld

399 Mr Michael Reid

400 Name Withheld

401 Name Withheld

402 Name Withheld

403 Name Withheld

404 Name Withheld

405 Name Withheld

406 Mr Alex Lange

407 Ms Emily Rosner

408 Name Withheld

409 Name Withheld

410 Name Withheld

411 Name Withheld

412 Name Withheld

413 Name Withheld

414 Name Withheld

415 Mrs Marie Huttley-Jackson

416 Mr Carl Jackson

417 Ms Chrissy Carter

418 Ms Lynne Hogan

419 Ms Beki Seekamp

420 Ms Vikki Seekamp

421 Ms Claire O'Dea

422 Name Withheld

423 Ms Tahlia Smith

424 Name Withheld

425 Name Withheld

426 Name Withheld

427 Name Withheld

428 Mr Ray Pignataro

429 Ms Sarah Belmomte

430 Name Withheld

431 Mrs Christine Humphries

432 Mr Stephen Humphries

433 Name Withheld

434 Name Withheld

435 Ms Tracey Payne

436 Ms Roz Moore

437 Mr Terry Rowlands

438 Ms Ronda Rowlands

439 Name Withheld

440 Name Withheld

441 Name Withheld

442 Ms Jacqui Judd

443 Name Withheld (plus a supplementary submission)

444 Name Withheld

445 Ms Robyn Williams

446 Ms Betty Quick

447 Name Withheld

448 Name Withheld

449 Ms Lauren and Ms Sarah Parker (plus an attachment)

450 Ms Margaret Stewart

451 Dr Margaret Hardy

452 Dr Lance Sanders (plus two attachments)

453 Dr Hugh Derham (plus two attachments)

454 Public Health Laboratory Network

455 Australasian College of Dermatologists

456 Australian Medical Association

457 NSW Health

458 Professor Peter Collignon AM (plus six attachments)

459 Australian Rickettsial Reference Laboratory Foundation

460 Name Withheld

461 Name Withheld (plus an attachment)

462 Name Withheld

463 Name Withheld

464 Name Withheld

465 Name Withheld

466 Name Withheld

467 Name Withheld

468 Name Withheld

469 Name Withheld

470 Confidential

471 Dr Ivan Hooper (plus twelve attachments)

472 Ms Dale Ryan

473 Name Withheld

474 Name Withheld

475 Name Withheld

476 Name Withheld

477 Confidential

478 Confidential

479 Confidential

480 Name Withheld

481 Ms Violet Moloney

482 Name Withheld

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487 Confidential

488 Name Withheld

489 Name Withheld

490 Name Withheld

491 Name Withheld

492 Name Withheld

493 Mr Anthony Docherty

494 Ms Kerry Mathews

495 Australian Government Department of Health (plus fourteen attachments)

496 Australasian Society for Infectious Diseases Inc (plus three attachments)

497 Murdoch University

498 Name Withheld

499 Confidential

500 Name Withheld

501 Name Withheld

502 Name Withheld

503 Name Withheld

504 Name Withheld

505 Name Withheld

506 Name Withheld

507 Confidential

508 Name Withheld

509 Name Withheld

510 Name Withheld

511 Name Withheld

512 Name Withheld

513 Name Withheld

514 Ms Isabelle Ghetti

515 Name Withheld

516 Name Withheld

517 Name Withheld

518 Name Withheld

519 Name Withheld

520 Mrs Valmae Price

521 Confidential

522 Name Withheld

523 Ms Annette Pollard (plus an attachment)

524 Ms Hellene Burling

525 Ms Diane Walker

526 Name Withheld

527 Country Women's Association of Australia

528 Lyme Disease Association of Australia (plus two supplementary submissions)

529 Western Australian Department of Health

530 Karl McManus Foundation

531 Communicable Diseases Network Australia

532 Royal College of Pathologists of Australasia

533 Medical Board of Australia and Australian Health Practitioner Regulation Agency

534 Dr Philip Stowell

535 Ms Carol Adams

536 Ms Michelle Nettle (plus two attachments)

537 Name Withheld

538 Mrs Linda Bourne

539 Name Withheld

540 Name Withheld

541 Ms Leanne Barsby

542 Name Withheld (plus an attachment)

543 Name Withheld

544 Name Withheld

545 Australian Biologics Testing Services Pty Ltd (plus a supplementary submission)

546 Professor Edward Holmes

547 Victorian Department of Health and Human Services

548 Name Withheld

549 Confidential

550 Name Withheld

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570 Name Withheld

571 Name Withheld

572 Name Withheld

573 Name Withheld

574 Dr Clare Middle

575 Name Withheld

576 Name Withheld

577 Name Withheld

578 Name Withheld

579 Confidential

580 Name Withheld

581 Mrs Daphne Bunt

582 Name Withheld

583 Name Withheld

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592 Confidential

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600 Confidential

601 Dr Adam Nuttall

602 Name Withheld

603 Ms Lisa Chatwin

604 Ms Jennifer Hall

605 Name Withheld

606 Name Withheld

607 Ms Jill Willis

608 Mr Ross McLagan

609 Ms Diane McLagan

610 Name Withheld

611 Ms Michelle Bowry

612 Ms Ellen Bailey

613 Name Withheld

614 Name Withheld

615 Name Withheld

616 Name Withheld

617 Name Withheld

618 Name Withheld

619 Ms Charlotte Markwick

620 Miss Amanda Petrie

621 Confidential

622 Name Withheld

623 Name Withheld

624 Mr Turker Sen

625 Name Withheld

626 Mr Philip Gardiner

627 Mrs Therese Perez

628 Name Withheld

629 Name Withheld

630 Mr Malcolm Gully

631 Name Withheld

632 Name Withheld

633 Ms Pam Rudd

634 Name Withheld

635 Dr Clifford Hawkins

636 Name Withheld

637 Name Withheld

638 Ms Jennifer Taylor

639 Name Withheld

640 Name Withheld

641 Ms Linda Epton

642 Ms Janine Clark

643 Name Withheld

644 Name Withheld

645 Name Withheld

646 Mr Anthony Jones

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651 Name Withheld

652 Confidential

653 Ms Michele Mora

654 Ms Noeleen Mora

655 Name Withheld

656 Confidential

657 Name Withheld

658 Ms Coreena Chenhall

659 Ms Belinda Mears

660 Mr Greg Haylen

661 Mr Rod Chenhall

662 Name Withheld

663 Name Withheld

664 Name Withheld

665 Name Withheld

666 Confidential

667 Name Withheld

668 Name Withheld

669 Name Withheld

670 Name Withheld

671 Name Withheld

672 Mrs Roberta Verey

673 Mrs Tanya Chapman

674 Name Withheld

675 Confidential

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677 Name Withheld

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679 Name Withheld

680 Name Withheld

681 Name Withheld

682 Name Withheld

683 Ms Patricia Davies

684 Dr Ariane Kersting (plus three attachments)

685 Confidential

686 Name Withheld

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691 Name Withheld

692 Name Withheld

693 Confidential

694 Name Withheld

695 Ms Janice Foster
Response from Department of Health
Response from Health Care Complaints Commission
Response from NSW Health
Response from Australian Medical Association

696 Confidential

697 Name Withheld

698 Name Withheld

699 Confidential

700 Name Withheld

701 Ms Deborah Davis

702 Confidential

703 Name Withheld

704 Name Withheld

705 Name Withheld

706 Name Withheld

707 Confidential

708 Ms Trudi Marchant

709 Name Withheld

710 Ms Josie Downes

711 Name Withheld

712 Ms Carolyn Ford

713 Name Withheld

714 Name Withheld

715 Name Withheld

716 Name Withheld

717 Name Withheld (plus a supplementary submission)

718 Name Withheld

719 Name Withheld

720 Name Withheld

721 Confidential

722 Confidential

723 Ms Pamela Connellan

724 Name Withheld (plus an attachment)

725 Name Withheld

726 Confidential

727 Ms Natalie Ross

728 Name Withheld

729 Name Withheld

730 Confidential

731 Name Withheld

732 Name Withheld

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734 Confidential

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736 Name Withheld

737 Name Withheld

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745 Name Withheld

746 Name Withheld

747 Name Withheld

748 Name Withheld

749 Name Withheld

750 Name Withheld

751 Confidential

752 Confidential

753 Name Withheld

754 Royal Australasian College of Physicians

755 Name Withheld

756 Name Withheld

757 Confidential

758 Mr Lindsay Neil

759 Combined Caravan Club of Victoria

760 Name Withheld

761 Name Withheld

762 Confidential

763 Name Withheld

764 Name Withheld

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778 Name Withheld

779 Name Withheld

780 Confidential

781 Australian Society for Microbiology

782 Confidential

783 Confidential

784 Name Withheld

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787 Confidential

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797 Name Withheld

798 Confidential

799 Confidential

800 Name Withheld

801 Name Withheld

802 ME/CFS and Lyme Association of WA Inc

803 Name Withheld

804 Wildlife Health Australia

805 Name Withheld

806 Name Withheld

807 Name Withheld

808 Confidential

809 Name Withheld

810 Confidential

811 Confidential

812 Name Withheld

813 Name Withheld

814 Name Withheld

815 Name Withheld

816 Name Withheld

817 Name Withheld

818 Confidential

819 Name Withheld

820 Infectious Diseases Department, Austin Health
Response from Australian Biologics Testing Services

821 Mr Nigel Say

822 Lyme Australia Recognition and Awareness; and Global Lyme and Invisible Illness Organisation Inc (plus three attachments)

823 Name Withheld

824 Name Withheld

825 Name Withheld

826 Name Withheld

827 Confidential

828 Confidential

829 Name Withheld (plus an attachment)

830 Name Withheld

831 Confidential

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837 Name Withheld

838 Name Withheld

839 Name Withheld

840 Name Withheld (plus an attachment)

841 Confidential

842 Confidential

843 Name Withheld

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845 Name Withheld

846 Confidential

847 Name Withheld

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850 Name Withheld

851 Name Withheld

852 Name Withheld

853 Name Withheld

854 Ms Jen Thwaites

855 Confidential

856 Confidential

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861 Name Withheld

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879 Name Withheld

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881 Name Withheld (plus an attachment)

882 Confidential

883 Name Withheld

884 Name Withheld

885 Name Withheld

886 Ms Magic Barclay

887 Name Withheld

888 Confidential

889 Name Withheld

890 Name Withheld

891 Name Withheld

892 Name Withheld

893 Name Withheld

894 Name Withheld (plus two attachments)

895 Name Withheld

896 Confidential

897 Name Withheld

898 Name Withheld

899 Confidential

900 Confidential

901 Name Withheld

902 Mr Ben Cavenagh

903 Name Withheld (plus an attachment)

904 Confidential

905 Name Withheld

906 Name Withheld

907 Name Withheld

908 Name Withheld

909 Confidential

910 Confidential

911 Confidential

912 Confidential

913 Name Withheld

914 Name Withheld

915 Name Withheld (plus four supplementary submissions)

916 Name Withheld

917 Dr David Weedon (plus two attachments)

918 Ms Janice Kruger

919 Name Withheld

920 Name Withheld

921 Ms Gillian Jones

922 Name Withheld

923 Ms Melitta Marr

924 Ms Melissa Turner

925 Mr Ryan Hollings

926 Name Withheld

927 Dr Joseph Dunn

928 Mr David Meyrick

929 Mrs Lesley Peterson

930 Ms Rochelle Meyrick (plus an attachment)

931 Ms Giovanna Triana Cuellar

932 Mr Dennis Johnson

933 Ms Colette Geier

934 Name Withheld

935 Medical Council of NSW

936 Dr Richard Horowitz

937 Ms Christina Cassar

938 Mr John Miller

939 Ms Leanne Bennie

940 Name Withheld

941 Confidential

942 Name Withheld

943 Name Withheld

944 Ms Jennifer Taylor (plus a supplementary submission)

945 Mr Donald Taylor

946 Ms Gloria Reddy

947 Name Withheld

948 Name Withheld (plus an attachment)

949 Confidential

950 Ms Marilyn Oldfield

951 Mr Joel Lange

952 Mr Rowen Privett

953 Mr John Eldred

954 Mrs Lisa Willis

955 Ms Lisa Oats

956 Ms Amanda Hogg

957 Confidential

958 Confidential

959 Mrs Vicki Ferguson

960 Name Withheld

961 Mrs Holly Sanders

962 Name Withheld

963 Name Withheld

964 Name Withheld

965 Ms Julieanne Ditchfield

966 Ms Janet Burgin

967 Name Withheld

968 Name Withheld

969 Name Withheld

970 Ms Naomi Hart

971 Name Withheld

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973 Name Withheld

974 Name Withheld

975 Name Withheld

976 Name Withheld

977 Name Withheld

978 Name Withheld

979 Name Withheld

980 Confidential

981 Ms Jenny Spencer

982 Name Withheld

983 Confidential

984 Confidential

985 Confidential

986 Name Withheld

987 Name Withheld

988 Name Withheld

989 Name Withheld

990 Name Withheld

991 Name Withheld

992 Australian Red Cross Blood Service

993 Name Withheld

994 Name Withheld

995 Ms Rhonda Johnson

996 Name Withheld

997 Name Withheld

998 Name Withheld

999 Confidential

1000 Confidential

1001 Name Withheld (plus an attachment)

1002 Ms Amanda Bramwell

1003 Confidential

1004 Confidential

1005 Name Withheld (plus a supplementary submission)

1006 Name Withheld

1007 Name Withheld

1008 Name Withheld

1009 Name Withheld

1010 Name Withheld

1011 Name Withheld

1012 Name Withheld

1013 Confidential

1014 Name Withheld

1015 Ms Sarah Limbrick

1016 Ms Elise Searson

1017 Confidential

1018 Name Withheld

1019 Name Withheld

1020 Name Withheld

1021 Name Withheld

1022 Name Withheld

1023 Name Withheld

1024 Name Withheld

1025 Confidential

1026 Name Withheld

1027 Name Withheld

1028 Name Withheld

1029 Name Withheld

1030 Mr Barry Gray

1031 Name Withheld

1032 Confidential

1033 Name Withheld

1034 Ms Emma Monteiro

1035 Name Withheld

1036 Name Withheld

1037 Name Withheld

1038 Name Withheld

1039 Confidential

1040 Confidential

1041 Name Withheld

1042 Name Withheld

1043 Name Withheld

1044 Name Withheld

1045 Name Withheld

1046 Ms Leanne Collingwood

1047 Mr Andrew Vilder

1048 Name Withheld

1049 Mr Jim Luxford

1050 Mr David Ellett

1051 Ms Karen New

1052 Ms Monika Gotthardt-Marshall

1053 Name Withheld

1054 Name Withheld

1055 Name Withheld

1056 Name Withheld

1057 Ms Ingeborg Kuiper

1058 Ms Tracey Pritchett

1059 Name Withheld

1060 Ms Julie Mills

1061 Name Withheld

1062 Confidential

1063 Name Withheld

1064 Ms Catherine Monteiro

1065 Name Withheld

1066 Name Withheld

1067 Ms Moira Martin

1068 Name Withheld

1069 Name Withheld

1070 Ms Deanne Powell

1071 Mr Michael and Ms Mary O’Neill

1072 Name Withheld

1073 Name Withheld

1074 Name Withheld

1075 Mr Phil Shaw

1076 Ms Emily Campbell

1077 Name Withheld

1078 Mr Frank Kipling

1079 Mr Alex Silva

1080 Name Withheld

1081 Ms Ailsa Burgess

1082 Ms Marian Slusny

1083 Name Withheld

1084 Ms Carole Adele (plus a supplementary submission)

1085 Name Withheld (plus an attachment)

1086 Name Withheld

1087 Ms Michelle Wheeler

1088 Mr Trevor Ryan

1089 Dr Karina Kennedy

1090 Ms Aydah Silva

1091 Mr Dave Main

1092 Name Withheld

1093 Name Withheld

1094 Name Withheld

1095 Ms Amanda Loren

1096 Mrs Lisette Studdert

1097 Ms Zowie Tydeman

1098 Name Withheld

1099 Mr Robert Cooper

1100 Name Withheld

1101 Name Withheld

1102 Name Withheld

1103 Name Withheld

1104 Ms Noela Hamilton

1105 Mr Simon Bremner

1106 Ms Kylie Hutcheon

1107 Ms Agnieszka Toole

1108 Dr Rachel Wells

1109 Name Withheld

1110 Name Withheld

1111 Ms Victoria Meyer

1112 Name Withheld

1113 Name Withheld

1114 Name Withheld

1115 Name Withheld

1116 Name Withheld

1117 Name Withheld

1118 Name Withheld

1119 Name Withheld

1120 Name Withheld

1121 Name Withheld

1122 Name Withheld

1123 Name Withheld

1124 Ms Elisha Parker

1125 Mr Laurie Seekamp

1126 Name Withheld (plus an attachment)

1127 Name Withheld

1128 Name Withheld

1129 Name Withheld

1130 Ms Molly Hannebery

1131 Mr Gerard Siero

1132 Name Withheld

1133 Ms Kristine Maunder

1134 Name Withheld

1135 Name Withheld

1136 Ms Clare Henry

1137 Name Withheld

1138 Name Withheld

1139 Ms Lisa-Jane Hunt

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1141 Name Withheld

1142 Ms Kathy Nastov

1143 Ms Belinda Elliott

1144 Mr Lee Salman

1145 Ms Rachael Brice

1146 Ms Deborah Gleeson

1147 Name Withheld

1148 Name Withheld

1149 Name Withheld

1150 Ms Margaret Wilson

1151 Ms Kate Miljons

1152 Name Withheld

1153 Name Withheld

1154 Ms Tara Stevens

1155 Confidential

1156 Name Withheld

1157 Ms Mandy Stevens

1158 Mr Glen Wilkie

1159 Name Withheld

1160 Confidential

1161 Ms Shekinah Yammacoona

1162 Name Withheld

1163 Name Withheld

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1166 Ms Bronwyn Smith

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Response from NSW Health

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1209 Name Withheld

1210 Name Withheld

1211 Name Withheld

1212 Mrs Sue Fuller

1213 Name Withheld

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1215 Name Withheld

1216 Name Withheld

1217 Ms Suzanne Clementi

1218 Ms Sue McFarlane

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1220 Name Withheld

1221 Mr Brett Jones
Response from Professor Stephen Graves

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1244 Mr Kevin Bryant

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1246 Dr James Read

1247 Name Withheld

1248 Ms Michelle Curry

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1274 Revd. Nikki Coleman

1275 Confidential

1276 Confidential

1277 Confidential

1278 Confidential

1279 Confidential

1280 Confidential

1281 Professor Noel Campbell

1282 Pluslife Perth Bone and Tissue Bank

1283 Confidential

1284 Confidential

1285 Confidential

1286 Confidential

1287 Confidential

1288 Confidential

1289 Dr Stuart King (plus two attachments)

Additional Information

1 Information, from Multiple Systemic Infectious Disease Syndrome Inc, received 9 May 2016

2 The Use of Dapsone as a Novel "Persister" Drug in the Treatment of Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome, journal article, from Dr Richard Horowitz, received 31 October 2016

3 Are Mycobacterium Drugs Effective for Treatment Resistant Lyme Disease, Tick-Borne Co-Infections, and Autoimmune Disease, journal article, July 2016, from Dr Richard Horowitz, received 31 October 2016

4 Does Lyme disease exist in Australia?, from Dr Gary Lum, received 1 November 2016

5 Transhemispheric Exchange of Lyme Disease Spirochetes by Seabirds, journal article, from Dr Ann Mitrovic, received 24 November 2016

Answers to Questions on Notice

1 Answers to Questions taken on Notice during 14 April public hearing, received from Australasian College of Dermatologists, 14 April 2016

2 Answers to Questions taken on Notice during 14 April public hearing, received from Australasian College of Dermatologists, 14 April 2016

3 Answers to Questions taken on Notice during 14 April public hearing, received from Professor John Mackenzie, 21 April 2016

4 Answers to Questions taken on Notice during 14 April public hearing, received from WA Department of Health, 22 April 2016

5 Answers to Questions taken on Notice during 14 April public hearing, received from WA Department of Health, 27 April 2016

6 Answers to Questions taken on Notice during 14 April public hearing, received from Lyme Disease Association of Australia, 27 April 2016

7 Answers to Questions taken on Notice during 15 April public hearing, received from Australian Health Practitioner Regulation Agency, 26 April 2016

8 Answers to Questions taken on Notice during 20 April public hearing, received from National Association of Testing Authorities Australia, 26 April 2016

9 Answers to Questions taken on Notice during 20 April public hearing, received from Department of Health, 6 May 2016

10 Answers to written Questions on Notice, received from Professor Peter Collignon, 2 May 2016

11 Answers to written Questions on Notice, received from Department of Health, 6 May 2016

12 Answers to Questions taken on Notice during 14 April public hearing, received from Multiple Systemic Infectious Disease Syndrome Inc, 9 May 2016

13 Answers to Questions taken on Notice during 2 November public hearing, received from Royal College of Pathologists of Australasia, 15 November 2016

14 Answers to Questions taken on Notice during 2 November public hearing, received from Australian Chronic Infections and Inflammatory Diseases Society, 17 November 2016

15 Answers to Questions taken on Notice during 2 November public hearing, received from National Serology Reference Laboratory, 17 November 2016

16 Answers to Questions taken on Notice during 2 November public hearing, received from Australian Biologics Testing Services, 17 November 2016

17 Answers to Questions taken on Notice during 2 November public hearing, received from Karl McManus Foundation, 18 November 2016

18 Answers to Questions taken on Notice during 2 November public hearing, received from National Association of Testing Authorities, Australia, 18 November 2016

19 Answers to Questions taken on Notice during 2 November public hearing, received from Department of Health, 21 November 2016

Correspondence

1 Response from Professor Peter Collignon to adverse comments made during the public hearing on 2 November 2016

Tabled Documents

1 Information, tabled by Lyme Disease Association of Australia, at Brisbane public hearing 15 April 2016

2 Diagram explaining Borrelia, tabled by Karl McManus Foundation, at Brisbane public hearing 15 April 2016

3 Journal article: Effects of Borrelia on host immune system: Possible consequences for diagnostics, tabled by Karl McManus Foundation, at Brisbane public hearing 15 April 2016

4 Information, tabled by Australian Biologics Testing Services, at Brisbane public hearing 15 April 2016

5 Opening statement, tabled by Department of Health, at Canberra public hearing 20 April 2016

6 Scientific papers, tabled by Department of Health, at Canberra public hearing 20 April 2016

7 Scientific papers, tabled by Department of Health, at Canberra public hearing 20 April 2016

8 Scientific papers, tabled by Department of Health, at Canberra public hearing 20 April 2016

9 Scientific papers, tabled by Department of Health, at Canberra public hearing 20 April 2016

10 Scientific papers, tabled by Department of Health, at Canberra public hearing 20 April 2016

11 Scientific papers, tabled by Department of Health, at Canberra public hearing 20 April 2016

APPENDIX 2

Public hearings

Thursday, 14 April 2016

International on the Water Hotel, Perth

Witnesses

Department of Health, Western Australia
MAK, Dr Donna, Public Health Physician, Communicable Disease Control Directorate
FORBES, Professor David Alan, Senior Clinical Adviser, Office of the Chief Medical Officer

Multiple Systemic Infectious Disease Syndrome Inc.
DANIELS, Ms Kathryn Mary (Kate), Chairperson

Sarcoidosis Lyme Australia
KELLY, Ms Elaine, Secretary

ME/CFS and Lyme Association of WA Inc.
LE PAGE, Mr Stephen George, Committee Member

Lyme Disease Association of Australia
VARY, Ms Rebecca Ellen, Volunteer

ASH, Ms Judith, Private capacity

BOWER, Ms Joanne, Private capacity

BROWN, Ms Natalie, Private capacity

BULL, Ms Rebecca, Private capacity

DOWNIE, Mrs Leanne, Private capacity

EBDEN, Ms Linda, Private capacity

HAMERSLEY, Ms Stephanie, Private capacity

MONKS, Ms Sue, Private capacity

STEPHEN, Ms Melinda, Private capacity

STEVEN, Mrs Meg, Private capacity

WEBB, Ms Leanne, Private capacity

WHITE, Ms Vicki, Private capacity

Australasian College of Dermatologists
ZAGARELLA, Associate Professor Samuel, Fellow

COLLIGNON, Professor Peter, Private capacity

DERHAM, Dr Hugh, Private capacity

NUTTALL, Dr Adam, Private capacity

ADAMS, Ms Carol, Private capacity

NETTLE, Ms Michelle, Private capacity

ERSEK, Ms Nikki, Private capacity

GUERINI, Ms Nicole, Private capacity

HUTTLEY-JACKSON, Ms Marie, Representative, Lyme Disease Association of Australia

KENT, Ms Jan, Private capacity

KURET, Ms Gabrielle, Private capacity

LIDDELL, Ms Carol, Private capacity

LIM, Mr Nick, Private capacity

SHEPHERD, Ms Val, Private capacity

WILLIAMS, Ms Amy, Private capacity

Vector and Waterborne Pathogens Group, Murdoch University

RYAN, Professor Una, Professor, Vector and Waterborne Pathogens Group, Murdoch University
OSKAM, Dr Charlotte, Lecturer, Murdoch University

MACKENZIE, Professor John Sheppard, Private capacity

Friday, 15 April 2016

Royal on the Park Hotel, Brisbane

Witnesses

Lyme Disease Association of Australia
WHITEMAN, Ms Sharon Lee, President

Global Lyme & Invisible Illness Organisation Inc; and Lyme Australia Recognition & Awareness
SMITH, Ms Karen Ann, Co-President; and Founder

CHANT, Mr Mathew William, Private capacity

SULLIVAN, Mrs Meaghan, Private capacity

Australian Chronic Infectious and Inflammatory Disease Society
SCHLOEFFEL, Dr Richard John, Chairperson
DOBIE, Dr Peter, Secretary

Karl McManus Foundation, University of Sydney
McMANUS, Dr Mualla, Director

CURNOW, Mr John Arthur, Veterinarian

HARDY, Dr Margaret, Private capacity

BAKER, Mrs Wanda, Private capacity

BALLARD, Ms Ailsa Victoria, Private capacity

BARSBY, Ms Leanne Bridget, Private capacity

BRADLEY, Mrs Rhonda Ruth, Private capacity

CHAPMAN, Mrs Wendy, Private capacity

ELLIS, Ms Dianne Elizabeth, Private capacity

EVANS, Ms Yvonne Denise, Private capacity

GRAY, Mr Barry, Private capacity

HANSEN, Ms Julieanne, Private capacity

SEEKAMP, Ms Vikki, Private capacity

SIMONSEN, Mr Jason Andrew, Private capacity

Public Health Laboratory Network
BATES, Mr John Robert, Chair

Royal College of Pathologists of Australasia; and Australian Rickettsial Reference Laboratory
GRAVES, Professor Stephen Roger, Spokesman on Lyme Disease

Australian Biologics Testing Services Pty Ltd
BURKE, Ms Jennie Maree, Director

Australian Health Practitioner Regulation Agency
FLETCHER, Mr Martin, Chief Executive Officer

Medical Board of Australia
BRADSHAW, Associate Professor Stephen, Practitioner Member

Wednesday, 20 April 2016

Parliament House, Canberra

Witnesses

Department of Health
LUM, Dr Gary David, Principal Medical Adviser, Office of Health Protection
APPLEYARD, Ms Sharon, First Assistant Secretary, Office of Health Protection
BARDEN, Mr Graeme, Assistant Secretary, Health Protection Policy Branch, Office of Health Protection

National Health and Medical Research Council
KELSO, Professor Anne, Chief Executive Officer

National Association of Testing Authorities, Australia
STYZINSKI, Mr John, General Manager, Operations and Technical
MITCHELL, Mr John Cameron, Manager, Government Relations
GRIFFIN, Mr Andrew James, Deputy Sector Manager, Legal and Clinical Services

Wednesday, 2 November 2016

Portside Centre, Sydney

Witnesses

HOROWITZ, Dr Richard, Private capacity

Australian Biologics Testing Services Pty Ltd
BURKE, Ms Jennie, Director

Royal College of Pathologists of Australasia
GRAVES, Professor Stephen Roger, Spokesman on Lyme Disease

National Association of Testing Authorities
GRIFFIN, Mr Andrew, Deputy Sector Manager, Legal and Clinical Services
MITCHELL, Mr John Cameron, Manager, Government Relations
BAILEY, Mrs Nicole, Assistant Stakeholder Relations Manager

National Serology Reference Laboratory
BEST, Ms Susan, Director

IRWIN, Professor Peter, Principal, College of Veterinary Medicine

MITROVIC, Dr Ann, Research Fellow, Tick-borne Diseases Unit, School of Medical Sciences (Pharmacology), University of Sydney

CASKIE, Ms Fiona, Private capacity

ELLIS, Ms Dianne, Private capacity

FITT, Ms Megan, Private capacity

FLOATE, Mr Ross, Private capacity

FOSTER, Ms Janice, Private capacity

GUMIENIUK, Ms Lisa, Private capacity

HAFOURI, Ms Rita, Private capacity

HUTTLEY-JACKSON, Ms Marie, Private capacity

KELLY, Ms Elaine, Private capacity

KNEVITT, MS Rachel, Private capacity

PARKINSON, Ms Dayna, Private capacity

STEVENS, Ms Tara, Private capacity

ATTWOOD, Ms Lani, Private capacity

CHADWICK, Mr Jesse, Private capacity

CLULOW, Mr Adrian, Private capacity

CONNELLAN, Ms Pamela, Private capacity

DAVIS, Mrs Deborah, Private capacity

DAVIS, Mr Peter, Private capacity

HOLBEN, Mrs Tania, Private capacity

KERMODE, Miss Vivienne, Private capacity

MOTT, Mr Bruce, Private capacity

NASH, Ms Joanne, Private capacity

PEPPER, Mrs Roanna, Private capacity

PYM, Mr Michael, Private capacity

TOOLE, Mr Daniel, Private capacity

WINNER, Miss Tracey, Private capacity

Lyme Disease Association of Australia
WHITEMAN, Ms Sharon, President

Karl McManus Foundation
WALKER, Mr Christopher Peter, Acting Chief Executive Officer
PYM, Mr Mike, Director

Australian Chronic Infections and Inflammatory Diseases Society
SCHLOEFFEL, Dr Richard John, Chairperson

Department of Health
LUM, Dr Gary, Principal Medical Adviser, Office of Health Protection

Australian Health Practitioner Regulation Agency
HARDY, Mr Matthew, National Director, Notifications

Medical Board of Australia
BRADSHAW, Associate Professor Stephen, Practitioner Member

Counterpoint: Long-Term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease

Raphael B. Stricker

International Lyme and Associated Diseases Society, Bethesda, Maryland

(See the point by Auwaerter on pages 143–8)

Background. Controversy exists regarding the diagnosis and treatment of Lyme disease. Patients with persistent symptoms after standard (2–4-week) antibiotic therapy for this tickborne illness have been denied further antibiotic treatment as a result of the perception that long-term infection with the Lyme spirochete, *Borrelia burgdorferi,* and associated tickborne pathogens is rare or nonexistent.

Methods. I review the pathophysiology of *B. burgdorferi* infection and the peer-reviewed literature on diagnostic Lyme disease testing, standard treatment results, and coinfection with tickborne agents, such as *Babesia, Anaplasma, Ehrlichia,* and *Bartonella* species. I also examine uncontrolled and controlled trials of prolonged antibiotic therapy in patients with persistent symptoms of Lyme disease.

Results. The complex "stealth" pathology of *B. burgdorferi* allows the spirochete to invade diverse tissues, elude the immune response, and establish long-term infection. Commercial testing for Lyme disease is highly specific but relatively insensitive, especially during the later stages of disease. Numerous studies have documented the failure of standard antibiotic therapy in patients with Lyme disease. Previous uncontrolled trials and recent placebo-controlled trials suggest that prolonged antibiotic therapy (duration, >4 weeks) may be beneficial for patients with persistent Lyme disease symptoms. Tickborne coinfections may increase the severity and duration of infection with *B. burgdorferi.*

Conclusions. Prolonged antibiotic therapy may be useful and justifiable in patients with persistent symptoms of Lyme disease and coinfection with tickborne agents.

Lyme disease is a controversial illness [1–6]. The classic features of the disease include receipt of a tick bite followed by the so-called erythema migrans or "bullseye" rash and significant joint swelling typical of arthritis. Unfortunately, the classic features of this tickborne disease are not always present. For example, only 50%–60% of patients with Lyme disease recall having received a tick bite, and often the erythema migrans rash is absent or not in the shape of a bullseye [5, 6]. According to health departments around the United States, the typical bullseye rash is only reported in 35%–60% of patients with Lyme disease [7, 8]. Furthermore, frank arthritis is only seen in 20%–30% of patients with Lyme disease [1, 2]. Thus, the classic features of the disease may be absent, and the diagnosis may be easily missed [1–4].

In the absence of typical features of Lyme disease, patients may go on to develop a syndrome with multiple nonspecific symptoms that affect various organ systems, including the joints, muscles, nerves, brain, and heart. The myriad symptoms prompt the question whether this is "post–Lyme disease syndrome," a poorly defined entity triggered by Lyme disease, or whether these symptoms are caused by persistent infection with the Lyme spirochete, *Borrelia burgdorferi.* To address this question, we must first examine the pathophysiology of the disease.

PATHOPHYSIOLOGY OF LYME DISEASE

B. burgdorferi is a fascinating bacterium [9, 10]. It has >1500 gene sequences with at least 132 functioning

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This is a modified version of a paper presented at the 44th Annual Meeting of the Infectious Diseases Society of America, Toronto, Canada, October 2006.

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DOI: 10.1086/518853

genes. In contrast, *Treponema pallidum,* the spirochetal agent of syphilis, has only 22 functioning genes. The genetic makeup of *B. burgdorferi* is quite unusual. It has a linear chromosome and 21 plasmids, which are extrachromosomal strands of DNA. This is 3 times more plasmids than any other known bacteria (*Chlamydia* comes in a distant second, with 7 plasmids). Plasmids are thought to give bacteria a kind of "rapid response" system that allows them to adapt very rapidly to changes in the environment, and the complex genetic structure of *B. burgdorferi* suggests that this is a highly adaptable organism [9, 10].

In addition to its complex genetic makeup, *B. burgdorferi* engages in so-called "stealth pathology" to evade the human immune response [11–50]. Stealth pathology involves 4 basic strategies: immunosuppression; genetic, phase, and antigenic variation; physical seclusion; and secreted factors (table 1). These strategies are outlined below.

IMMUNOSUPPRESSION

During a tick bite and before transmission of the Lyme spirochete, tick saliva containing analgesic, anticoagulant, and immunosuppressive factors is expressed into the wound, allowing the spirochete to penetrate the skin and evade the local immune response [11–13]. *B. burgdorferi* also induces immunosuppression by complement inhibition and induction of inhibitory cytokines, such as IL-10. In addition, the bacterium induces monocyte and lymphocyte tolerization and antibody sequestration in immune complexes—all mechanisms of evading the immune response [14–19].

GENETIC, PHASE, AND ANTIGENIC VARIATION

B. burgdorferi engages in genetic, phase, and antigenic variation that shares various features with other organisms [20–23]. For example, gene switching is similar to what is seen with trypanosomes, mutation and recombination are typical of HIV, variable antigen expression is seen with *Neisseria* species, autoinduction of dormant organisms occurs in mycobacterial infection, and fibronectin binding occurs with staphylococcal and streptococcal infection.

B. burgdorferi may assume a dormant state with cyst formation [24–29]. Although spirochetal persistence in the cyst form is a controversial issue, it has recently been shown that neutrophil calprotectin can induce a dormant state in the spirochete, allowing it to persist in tissue without replicating and providing the means to avoid antibiotics [30].

Although antibiotic resistance associated with gene mutation was previously thought to be rare in *B. burgdorferi* infection [31], recent studies have demonstrated gene mutations in the Lyme spirochete that confer in vitro resistance to various antibiotics [32, 33]. The clinical implication of these gene mutations is uncertain at present.

PHYSICAL SECLUSION

The Lyme spirochete uses physical seclusion at intracellular sites as a means of evading the immune response in multiple cell types, including synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and neuronal cells [34–43]. In culture, *B. burgdorferi* can be grown in fibroblasts for >8 weeks, suggesting that the organism can thrive over long periods of time in the right place and under the right conditions.

Physical seclusion at extracellular sites, including the joints, eyes, and CNS, may also promote survival of the Lyme spirochete. In addition, *B. burgdorferi* engages in "cloaking" mechanisms by binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin. These substances can mask the bacterium and make it invisible to the immune system [38–42].

SECRETED FACTORS

There are a number of factors that are secreted either by *B. burgdorferi* itself or in response to infection with the spirochete [44–51]. For a number of years, it has been known that *B. burgdorferi* secretes a hemolysin, although its function is uncertain [44]. More recently, the spirochete has been shown to elaborate porin and adhesin, 2 proteins that allow bacteria to adhere to cells and pierce the cell wall to gain entry [45].

Even more recently, *B. burgdorferi* was found to secrete pheromones, including AI-2, which is also secreted by mycobacteria [46–50]. This is the first time that a spirochete has been shown to secrete an autoinducer and suggests that the Lyme spirochete engages in autoresuscitation like other dormant organisms, such as the tubercle bacillus [46–50]. In addition, *B. burgdorferi* can induce secretion of aggrecanase, an enzyme that damages cartilage [51]. This may be a mechanism by which the bacterium induces damage and inflammation in joints. Armed with these weapons of "stealth pathology," the Lyme spirochete is a formidable infectious agent.

LABORATORY TESTING

Let's turn briefly to laboratory testing in Lyme disease. A major problem is that current commercial Lyme serologic tests are not sensitive enough for diagnosis, especially during the later stages of disease [52–64]. The Centers for Disease Control and Prevention (CDC) advocates a "2-tier" testing system using an ELISA or immunofluorescence assay as a screening test, followed by a Western blot for confirmation if the result of the ELISA or immunofluorescence assay is positive. The CDC cautions, however, that the 2-tier system should only be used for surveillance purposes and not for diagnosis, and the reason for this warning is clear: although the 2-tier system has a very high specificity (99%–100%), thus avoiding the false-positive results that are the bane of surveillance statistics, it has relatively poor

Table 1. "Stealth" pathology of *Borrelia burgdorferi.*

Immunosuppression
Tick saliva components
Complement inhibition
Inhibitory cytokine induction (IL-10)
Lymphocyte/monocyte tolerization
Antibody sequestration in immune complexes
Genetic, phase, and antigenic variation
Gene switching (trypanosomes)
Mutation/recombination (HIV)
Variable antigen expression (*Neisseria* species)
Dormant state, autoinduction (*Mycobacterium* species)
Fibronectin binding (*Staphylococcus* and *Streptococcus* species)
Physical seclusion
Intracellular sites
Multiple cell types (synovial cells, endothelial cells, fibroblasts, macrophages, Kupffer cells, and nerve cells)
Persistent infection in vitro (8 weeks)
Extracellular sites
Privileged sites (joints, eyes, and CNS)
Cloaking mechanisms (binding to proteoglycan, collagen, plasminogen, integrin, and fibronectin)
Secreted factors
Hemolysin (BlyB)
Porin (Oms 28)
Adhesin (Bgp)
Pheromones (DPD/AI-2)
Aggrecanase (ADAMTS-4)

NOTE. See text for explanation and references.

sensitivity (50%–75%), which limits its use as a diagnostic test for individual patients.

Other problems with current Lyme disease testing include omission of highly specific bands from the commercial Western blot, sex differences in test reactivity, and limitations of molecular testing, and these issues have been discussed in detail elsewhere [1, 56, 60–63]. Thus, the diagnosis of Lyme disease remains problematic, with as many as one-half of patients experiencing failure with the current 2-tier testing approach [52–64].

TREATMENT OF LYME DISEASE

With this background concerning the clinical diagnostic problems, complex pathophysiology, and testing difficulties related to *B. burgdorferi,* we arrive at the topic of this debate, which is treatment failure in Lyme disease. Documented treatment failure with culture-confirmed *B. burgdorferi* infection was first reported >17 years ago by Preac-Mursic et al. [65], so it was surprising to see a quotation in the *New York Times* by 2 members of the Infectious Diseases Society of America (IDSA) Lyme disease guidelines committee stating that "[there] is no credible scientific evidence for the persistence of symptomatic *B. burgdorferi* infection after antibiotic treatment" [66]. Let's review the "credible scientific evidence" for persistence of this infection taken from articles published over the past 17 years.

ANIMAL MODELS

We can start with animal models of Lyme disease [67–75]. In the mouse, one study found that "persistence of spirochetes within macrophages provides a possible pathogenetic mechanism for chronic or recurring Lyme disease" [67, p. 909]. In another study, "nine months after treatment, low levels of spirochete DNA could be detected by real time PCR in a subset of antibiotic treated mice" [68, p. 1430]. So at least in the mouse model, spirochetes may persist after appropriate treatment.

Next is the dog model—a particularly convincing model, because Straubinger et al. [69] revealed that, in dogs that had been experimentally infected with *B. burgdorferi* by tick exposure, treatment with high doses of amoxicillin or doxycycline for 30 days diminished persistent infection but failed to eliminate it. Furthermore, when dogs were observed for a 500-day postinfection period (the equivalent of 3–4 human years), *B. burgdorferi* DNA was detectable at low levels in multiple tissue samples obtained from the dogs, despite the administration of "adequate" antibiotic treatment [70].

Finally, in a model using our closest relative, the nonhuman primate macaque monkey, Pachner and colleagues [71–75] found that neurologic and cardiac disease were associated with persistent infection in these monkeys, and cytokine and gene expression related to persistent *B. burgdorferi* infection could be demonstrated >3 months after infection. In summary, these animal models provide "credible scientific evidence" for persistent infection in Lyme disease.

HUMAN STUDIES

Turning to human studies, there are a number of reports that show persistent symptoms of Lyme disease after short-term antibiotic therapy [76–96]. Persistent symptoms have been noted in 25%–80% of patients with Lyme disease after 2–4 weeks of antibiotic therapy [76–87]. Furthermore, infection that was determined to be persistent on the basis of either culture or PCR evidence has been documented in up to 40% of patients following receipt of the "adequate" antibiotic treatment recommended by the IDSA [88–96]. For example, positive culture and PCR results were found in synovium and synovial fluid specimens obtained from a patient 7 years after treatment [92], and a positive result was reported for a culture of an iris biopsy specimen obtained from a treated patient [93]. These reports suggest that short-term antibiotic therapy may suppress the Lyme spirochete but not eradicate it.

In another case, the patient's condition deteriorated despite receipt of repeated courses of antibiotic treatment over a 2-

Table 2. Results of placebo-controlled trials of antibiotic treatment in chronic Lyme disease.

Study	Year	Treatment	Results	Comments
Klempner et al. [101]	2001	IV Ctri for 4 weeks followed by oral doxycycline for 2 months vs. placebo	No improvement in fatigue or quality of life	Study was criticized because subjects had been sick an average of 4.7 years, and similar treatment had already failed; the treatment regimen was inadequate for degree of functional impairment [104]
Krupp et al. [102]	2003	IV Ctri for 4 weeks vs. placebo	SI in fatigue noted in 64% of treatment group, compared with 19% of control group; no improvement in cognition	The exact duration of illness was not stated (at least 6 months), and the treatment duration was relatively short; previously untreated patients fared significantly better than control subjects in terms of fatigue improvement (69% vs. 0%; $P<.01$)
Fallon [105]	2005	IV Ctri for 10 weeks vs. placebo	SI in cognitive and physical functioning at 12 weeks in treatment group, compared with control group	Improvement in physical functioning but not cognitive functioning was sustained in the treatment group at 24 weeks
Cameron [106]	2005	Oral amoxicillin for 3 months vs. placebo	SI in cognitive and physical functioning in treatment group, compared with control group	Treatment was successful in two-thirds of the patients who had the best initial quality of life, but it failed in one-third of the patients who had the worst initial quality of life

NOTE. IV Ctri, intravenous ceftriaxone; SI, significant improvement.

Table 3. Precedents for prolonged antibiotic therapy.

Disease	Organism	Treatment	Duration of treatment, months
Drug-susceptible tuberculosis	*Mycobacterium tuberculosis*	2–4 antibiotics	6–9
Multidrug-resistant tuberculosis	*M. tuberculosis*	3–5 antibiotics	18–24
Leprosy	*Mycobacterium leprae*	3–4 antibiotics	24
Atypical tuberculosis	*Mycobacterium chelonae*	Oral and intravenous antibiotics	6–12
Q fever endocarditis	*Coxiella burnetii*	2 antibiotics	36

NOTE. Data are based on [143–147].

year period. She received 12 months of intravenous antibiotic treatment, followed by 11 months of oral antibiotics, and her condition improved significantly [95]. Thus, this case report suggests that longer treatment may be beneficial in some patients with Lyme disease. Taken as a whole, these studies provide "credible scientific evidence" for persistence of *B. burgdorferi* infection after "adequate" short-term antibiotic treatment in humans.

That brings up the next question: does longer antibiotic treatment help in persistent Lyme disease? There have been a number of uncontrolled trials that support longer treatment of persistent disease symptoms [97–100]. The largest study included 277 patients who were treated with tetracycline for 1–11 months (mean duration, 4 months). The study showed that, after 2 months of therapy, 33% of patients had improvement in symptoms, but after 3 months of treatment, 61% of patients had decreased symptoms [97]. So this study suggests that longer treatment may result in better symptom outcome in Lyme disease. There have been other small, uncontrolled trials showing that longer treatment may have better symptom outcomes in patients with Lyme disease, including one trial that showed that patients who were re-treated with intravenous therapy had the greatest improvement in their symptoms [98–100].

In contrast to these uncontrolled trials, 2 randomized, placebo-controlled trials examined re-treatment of patients with persistent symptoms of Lyme disease (table 2) [101, 102]. Krupp et al. [102] studied 1 month of intravenous ceftriaxone, whereas Klempner et al. [101] studied 1 month of intravenous ceftriaxone followed by 2 months of oral doxycycline. The Krupp study showed improvement in fatigue with its 30-day treatment regimen, whereas the Klempner study showed no improvement in quality of life following re-treatment for 90 days. The main problem with these studies is that they included patients who had been symptomatic for an average of 4–5 years, and treatment with 1 month of intravenous antibiotics, with or without low-dose doxycycline, is insufficient for patients who have been sick this long [103, 104]. Thus, the generalizability of results in these highly selected patients with persistent Lyme disease is questionable [104].

In contrast to these studies, 2 placebo-controlled trials were presented in 2005 at the Columbia/Lyme Disease Association's annual meeting (table 2) [105, 106]. One study involved oral amoxicillin for 3 months versus placebo for previously treated patients, and re-treatment was successful for the two-thirds of patients with the best initial quality of life. A second study administered intravenous ceftriaxone for 10 weeks to patients with persistent neurologic symptoms of Lyme disease, and these patients had significant cognitive improvement with this treatment. We look forward to publication of these 2 placebo-controlled trials, which show that longer courses of antibiotic therapy are useful in patients with persistent Lyme disease.

COINFECTION WITH TICKBORNE AGENTS

In addition to infection with *B. burgdorferi,* tickborne coinfections are being recognized more frequently. If a patient is treated for Lyme disease and has symptoms that have persisted or worsened, the lack of improvement may be due to the presence of *Babesia, Anaplasma, Ehrlichia,* or *Bartonella* coinfection [107–126]. Coinfection with *Babesia* and *Ehrlichia* has been shown to exacerbate Lyme disease in mouse models [108–110] and also in humans [111–118]. Traditionally, *Babesia*, *Anaplasma*, *Ehrlichia* and *Bartonella* are thought to produce acute fulminant infections, but in fact these pathogens may cause low-grade infections that can increase the severity and duration of Lyme disease [119–125].

A disturbing study from New Jersey examined the prevalence of coinfections in *Ixodes* ticks that transmit Lyme disease [126]. In that study, the prevalence of *B. burgdorferi* infection was 33.6%, but the prevalence of *Bartonella* infection was 34.5%. Thus, *Bartonella* species were found more often than the Lyme spirochete in these ticks. This observation presages a greater problem with *Bartonella* infection associated with tick exposure in the near future.

TREATMENT APPROACH TO CHRONIC LYME DISEASE

What is the approach for a patient who presents with persistent symptoms of Lyme disease [127–140]? First, the Lyme Western blot should be repeated, and coinfection testing should be performed by a laboratory that is proficient in tickborne disease analysis. At the same time, other medical problems that could

cause persistent symptoms should be ruled out. Measurement of the CD57 natural killer cell level, which is an immunologic marker that can be used to monitor treatment in chronic Lyme disease, should be performed [129–131]. If neurologic symptoms are severe, a single-photon emission CT SPECT brain scan should be obtained, to see how much inflammation is present in the brain. Neuropsychiatric evaluation may also be helpful [132].

On the basis of these results, coinfections should be treated first, if any are present, and then oral or parenteral antibiotics should be used to treat symptoms of persistent Lyme disease. Antibiotic therapy should be administered in a rotating and open-ended manner, in conjunction with probiotics, to minimize adverse effects [133–136]. Monitoring of clinical symptoms, CD57 natural killer cell levels, and markers of inflammation should be performed in conjunction with treatment [137–140].

This approach differs from the recommendations of the current IDSA guidelines, which do not recognize persistent infection in chronic Lyme disease [141]. However, the treatment approach is consistent with the guidelines of the International Lyme and Associated Diseases Society, which mandates treatment for persistent infection in patients with chronic Lyme disease symptoms [142]. It is helpful to recall that *B. burgdorferi* shares certain pathophysiological features with mycobacterial infection and other chronic infections (table 1), that these infections may require prolonged antibiotic therapy (6–36 months), and that the risks of long-term treatment are considered justifiable in those situations (table 3) [143–147]. On the basis of the foregoing discussion, prolonged antibiotic therapy appears to be useful and justifiable in chronic Lyme disease.

In summary, >18,000 scientific articles have been written about Lyme disease. Some of these articles focus on the complex pathophysiology of *B. burgdorferi,* whereas others highlight the clinical uncertainty surrounding tickborne disease. Because the optimal therapy for this complicated illness is still in doubt, we must keep an open mind about the treatment of patients who present with persistent symptoms of Lyme and associated tickborne diseases.

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REVIEW
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Human Tick-Borne Diseases in Australia

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There are 17 human-biting ticks known in Australia. The bites of *Ixodes holocyclus, Ornithodoros capensis,* and *Ornithodoros gurneyi* can cause paralysis, inflammation, and severe local and systemic reactions in humans, respectively. Six ticks, including *Amblyomma triguttatum, Bothriocroton hydrosauri, Haemaphysalis novaeguineae*, *Ixodes cornuatus*, *Ixodes holocyclus*, and *Ixodes tasmani* may transmit *Coxiella burnetii, Rickettsia australis*, *Rickettsia honei,* or *Rickettsia honei* subsp. *marmionii*. These bacterial pathogens cause Q fever, Queensland tick typhus (QTT), Flinders Island spotted fever (FISF), and Australian spotted fever (ASF). It is also believed that babesiosis can be transmitted by ticks to humans in Australia. In addition, *Argas robertsi, Haemaphysalis bancrofti, Haemaphysalis longicornis, Ixodes hirsti, Rhipicephalus australis,* and *Rhipicephalus sanguineus* ticks may play active roles in transmission of other pathogens that already exist or could potentially be introduced into Australia. These pathogens include *Anaplasma* spp., *Bartonella* spp., *Burkholderia* spp., *Francisella* spp., Dera Ghazi Khan virus (DGKV), tick-borne encephalitis virus (TBEV), Lake Clarendon virus (LCV), Saumarez Reef virus (SREV), Upolu virus (UPOV), or Vinegar Hill virus (VINHV). It is important to regularly update clinicians' knowledge about tick-borne infections because these bacteria and arboviruses are pathogens of humans that may cause fatal illness. An increase in the incidence of tick-borne infections of human may be observed in the future due to changes in demography, climate change, and increase in travel and shipments and even migratory patterns of birds or other animals. Moreover, the geographical conditions of Australia are favorable for many exotic ticks, which may become endemic to Australia given an opportunity. There are some human pathogens, such as *Rickettsia conorii* and *Rickettsia rickettsii* that are not currently present in Australia, but can be transmitted by some human-biting ticks found in Australia, such as *Rhipicephalus sanguineus*, if they enter and establish in this country. Despite these threats, our knowledge of Australian ticks and tick-borne diseases is in its infancy.

Keywords: anaplasmosis, arbovirus, babesiosis, bartonellosis, Lyme-like disease, Q fever, rickettsial infection, tick paralysis

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BACKGROUND

Ticks and mosquitoes are recognized as the most important vectors in the transmission of bacterial and viral pathogens to humans and animals worldwide (Colwell et al., 2011). Ticks show marked genetic diversity with numerous species being mainly found in three families, *viz*. *Argasidae*, *Ixodidae*, and *Nuttalliellidae*. They can feed on various hosts and transmit or receive pathogenic bacteria, helminths, protozoa, and viruses to/from their host animals and humans. Although most studies have found that ticks and tick-borne illnesses are often limited to specific geographical regions, they may potentially be found anywhere in the world. International travel from endemic regions to non-endemic regions by people, animals and cargo can transport ticks. Whilst tick bites in Australia potentially can cause various diseases including bacterial and viral infections, paralysis, allergies, autoimmune disorders, post-infection fatigue and allegedly poorly quantified illnesses, the exact incidence of tick-borne disease in Australia is unknown (Graves and Stenos, 2017). Characterization of tick biology, tick-borne infections, and the distribution of ticks and tick-borne diseases can provide knowledge on their biological processes including tick immunity, reproduction, salivation, as well as tick-borne pathogens. This information is crucial for developing innovative strategies to control ticks and tick-borne disease. Understanding the microorganisms-host relationship could be exploited for our benefits (Dehhaghi et al., 2018). In case of tick-borne pathogens, such knowledge could be used for developing preventive mechanisms either for establishment of pathogens or their transmission. In this review, we will examine the geographical distribution of human-biting ticks in Australia, the reported tick-borne diseases, and potential of these ticks to carry emerging pathogens of humans and their possible transmission to humans. Allergic manifestations of tick bite are potentially life-threatening and not uncommon but are outside the scope of this paper.

AUSTRALIAN TICKS

There are 896 valid species of ticks worldwide, distributed in two main families of Argasidae (soft ticks) and Ixodidae (hard ticks) (Guglielmone et al., 2010; Barker et al., 2014). The major proposed events in the evolution of ticks are shown in **Figure 1** (Klompen et al., 1996; Dobson and Barker, 1999; Murrell et al., 2001; Mans et al., 2012; Barker et al., 2014). Australia has unique climatic and environmental conditions that are favorable for six of the eight subfamilies of ticks including *Amblyomminae, Argasinae, Bothriocrotinae, Haemaphysalinae, Ixodinae*, and *Ornithodorinae*. Despite this faunal richness, only ∼8% of all valid tick species are endemic to Australia, comprising 14 soft ticks and 58 hard ticks, mainly feeding on wildlife (Barker et al., 2014; Ash et al., 2017; Kwak et al., 2018). Of these, 17 species may attach and feed on humans and domestic animals (**Table 1**), whereas the remaining 55 ticks mainly feed on birds, wild reptiles, and wild mammals.

The overall aim of this review is to provide relevant information on tick-borne diseases in humans; as such, only those ticks which been proven as vectors of human pathogens are discussed. The classification of 17 human-biting ticks is shown in **Figure 2**. Amongst them, *Argas persicus*, *Haemaphysalis longicornis*, *Otobius megnini*, *Rhipicephalus australis*, and *Rhipicephalus sanguineus* have been accidentally introduced into Australia by humans (Barker et al., 2014).

Ornithodoros capensis, previously known as *Carios capensis*, feeds primarily on seabirds, although it can bite humans if the opportunity is provided. Off-shore islands are the most likely place that this tick bites humans because they provide nesting grounds for seabirds; therefore, campers, explorers, and those who participate in recreational and professional fishing are at higher risk. *Ornithodoros gurneyi* is exclusively a desert-dwelling tick in Australia that lives mainly in the wallows of desert-dwelling kangaroos and hence rarely encounters livestock or humans. However, this tick quests in soil and ambushes humans and other mammals if they rest under a desert-tree or in a desert-cave. The bites of *O. capensis* and *O. gurneyi* cause inflammation and severe local and systemic reactions in humans, respectively. In addition, a bite from the former tick species may cause blistering, dull ache, erythema, general lassitude and discomfort, intense pruritus, lesions, lymphangitis, rheumatic pain, and weeping; whereas the latter may cause headache, impaired vision, temporary blindness, swelling, and vomiting (Henary, 1938; Barker and Walker, 2014). *O. megnini* is eyeless and may feed on people who are in close contact with horses. There are no reports of transmission of any pathogens by this tick to its hosts. However, tick spines as well as feeding in the ear canal causes considerable irritation, inflammation, and tissue necrosis of the ear which may lead to bacterial infections.

Of the 18 valid species of *Amblyomma* in Australia, only *Amblyomma triguttatum* is regularly reported on domestic animals and has been taken from humans (Barker and Walker, 2014). *Bothriocroton auruginans* is a tick with an unknown life-cycle but its larvae and nymphs may attack domestic dogs without developing any illness. However, the adult tick is strictly host specific and to date its adult form has been only found on wombats (Barker and Walker, 2014). *Bothriocroton hydrosauri,* previously known as *Aponomma hydrosauri*, is one of the most commonly studied ticks in Australia. It feeds on reptiles in southern Australia as well as cattle, horses and humans. For many years, it was believed that *H. longicornis* is a possible vector of *Theileria orientalis* in New South Wales. However, despite the reports of its ability to transmit some bacteria and viruses in other parts of the world, it is not a known vector of any pathogens in Australia or has limited vectorial capacity of *T. orientalis* (Stewart et al., 1996; Barker and Walker, 2014).

Ixodes cornuatus, Ixodes hirsti, and *Ixodes holocyclus* can cause paralysis in their hosts. In Tasmania, *I. cornuatus* is the only tick that has been clinically associated with paralysis and is the most common tick found on domestic animals. In contrast, *I. holocyclus* is the most common tick that causes tick

Abbreviations: AG, Ancestral Group; ASF, Australian Spotted Fever; BSK-II, Barbour Stoenner Kelly II; DGKV, Dera Ghazi Khan Virus; FISF, Flinders Island Spotted Fever; HGA, Human Granulocytic Anaplasmosis; LCV, Lake Clarendon Virus; QTT, Queensland Tick Typhus; SREV, Saumarez Reef Virus; SLO, Spirochaete-Like Object; SFG, Spotted Fever Group; TBE, Tick-Borne Encephalitis; TBEV, Tick-Borne Encephalitis Virus; TRG, Transitional Group; UPOV, Upolu Virus; VINHV, Vinegar Hill Virus.

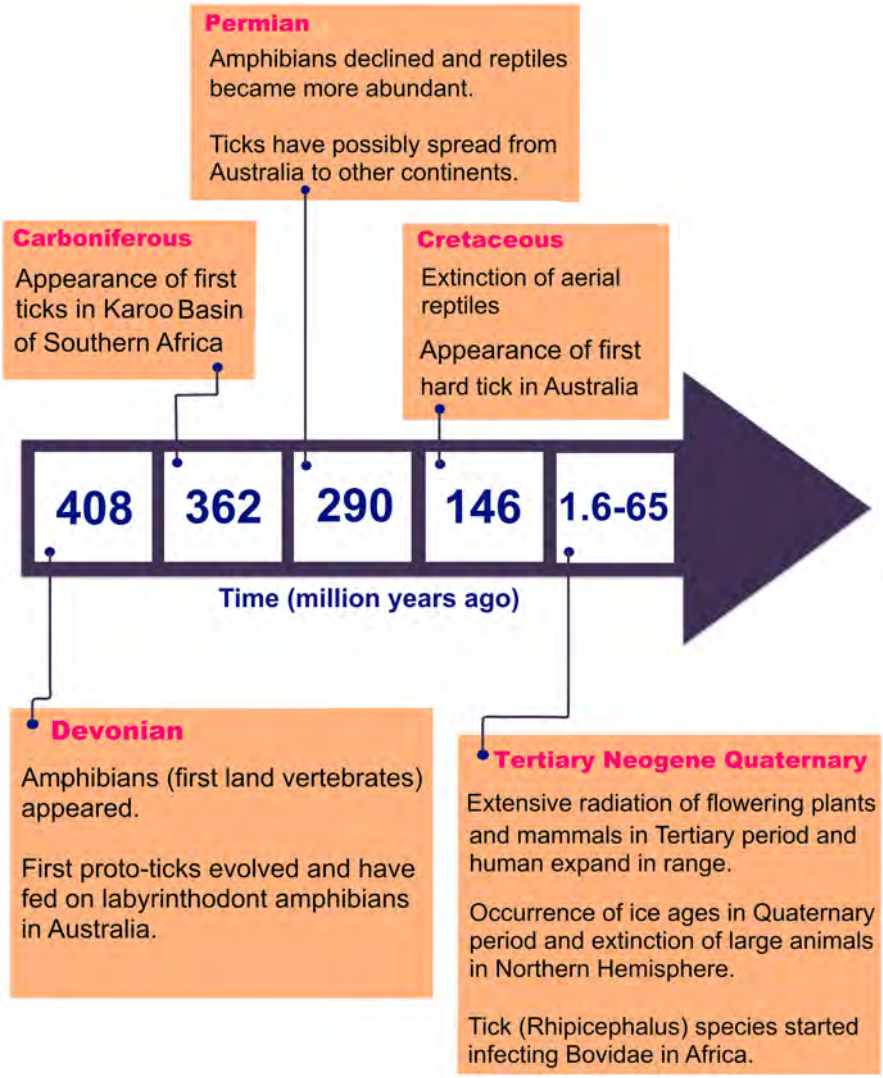

FIGURE 1 | Major events in tick evolution.

paralysis in domestic animals, humans, and wildlife in Australia. Although *I. holocyclus* feeds on various birds and mammals, it needs bandicoots to sustain its life cycle and population (Barker and Walker, 2014). *Ixodes tasmani* has the most widespread geographic distribution as well as the broadest range of hosts of any Australian tick. These three species of *Ixodes* ticks occur only in Australia, with the exception of *I. cornuatus* which is also found in Papua New Guinea (Arundel, 1988; Barker and Walker, 2014). *R. australis*, previously known as *Boophilus microplus*, primarily feeds on cattle, but its larvae and young adults, especially males, may feed on humans. However, the tick is usually removed by a human host due to local irritation and itching. There is a reported case (Green, 1971) of a female *R. australis* producing viable eggs following attachment to and feeding on a human host. *R. sanguineus* is the most widespread tick in tropical and sub-tropical areas of Australia owing to its specialized feeding on domestic dogs, which are its hosts for all life stages (Barker and Walker, 2014). When dogs are not available, this tick seeks other hosts such as cattle to maintain tick populations. Additionally, the immature forms of this tick may attach to humans. This tick species can carry different human health-threatening pathogens. Some of these pathogens include *Rickettsia cornii*, the cause of "boutonneuse fever," and *Rickettsia rickettsii*, the cause of Brazilian spotted fever and Rocky Mountain spotted fever, are not present in Australia yet.

In Australia, only six out of 17 human-biting ticks act as competent vectors for the transmission of pathogens to humans. They include *A. triguttatum, B. hydrosauri, Haemaphysalis novaeguineae*, *I. cornuatus*, *I. holocyclus*, and *I. tasmani* (Barker and Walker, 2014). **Figure 3** shows the geographical distribution of those six competent ticks and an additional four ticks that carry or have potential to carry human pathogens as

TABLE 1 | Human-biting ticks of Australia with their habitats and main hosts.

Species	Australian name	Region	Main host in Australia	References
Family *Argasidae*				
Argas persicus	Fowl or poultry tick	All states in Australia except Tasmania	Fowl	Roberts, 1970
Argas robertsi	Robert's bird tick	Lake Cowal, NSW[a]; South-western Qld[b]	Fowl, Great cormorant	Roberts, 1970
Ornithodoros capensis	Seabird soft tick	Along the coast from Perth, WA[c] to Sydney, NSW; Off-shore islands, particularly coral cays of the Great Barrier Reef, Qld	Seabirds, particularly terns, gulls, penguins	Barker and Walker, 2014
Ornithodoros gurneyi	Kangaroo soft tick	Desert area of Australia; Malchi, Gracemere, and Brisbane, Qld	Eastern gray and red kangaroos, wallaroos	Doube, 1975
Otobius megnini	Spinose ear tick	WA	Domestic horses	Barker and Walker, 2014
Family *Ixodidae*				
Amblyomma triguttatum	Ornate kangaroo tick	Northern NSW; Qld; WA; Yorke Peninsula, SA[d]	Kangaroos	Barker and Walker, 2014
Bothriocroton auruginans	Wombat tick	Armidale, Burrawang, and Tooloom, NSW; Benalla, Dargo (Gippsland), Healsville, Melbourne, Omeo, and Orbost, Vic[e]; Flinders Island, Deloraine, Gretna, and Tarraleah, Tasmania	Dogs, wombats	Barker and Walker, 2014
Bothriocroton hydrosauri	Southern reptile tick	Jenolan Caves and along the narrow state border with Vic, NSW; Eyre Peninsula and Southeastern SA; Along the coast from Bremer Bay to Albany and Margaret River area as well as along the coast from Cape Naturaliste to Cape Leeuwin, WA; Vic; Tasmania	Reptiles	Barker and Walker, 2014
Haemaphysalis bancrofti	Wallaby tick	Eastern-coast of Australia; Vic	Kangaroos, wallabies and their kin	Roberts, 1970; Barker and Walker, 2014
Haemaphysalis longicornis	Bush tick	A coastal area between Walpole and Denmark, WA; Buderim, Maleny, and Tamborine, Qld; Narrow coastal strip of eastern-coast of Australia; Taree-Wauchope region, NSW; Vic	Cattle, horses, sheep	Roberts, 1970; Barker and Walker, 2014
Haemaphysalis novaeguineae	-	Eastern half of Australia	Mammals	Unsworth et al., 2007
Ixodes cornuatus	Southern paralysis tick	Brownlee, NSW; Bullengarook, Daylesford, Donvale Warragul District, Lakes Entrance, Mallacoota, Noojee Neerim North, Orbost, Silvan, and Leongatha, Vic; Tasmania	Wide range hosts	Barker and Walker, 2014
Ixodes hirsti	Hirst's marsupial tick	Sub-coastal areas of southern Australia	Kangaroos and their kin, domestic dogs and cats, some birds	Barker and Walker, 2014
Ixodes holocyclus	Paralysis tick	Narrow coastal strip of eastern Australia; Normanton, Qld	Mammals (mainly bandicoots), Birds	Barker and Walker, 2014
Ixodes tasmani	Common marsupial tick	Central-eastern NSW; Qld; south-eastern SA; south-western WA; Tasmania; Vic	Australian marsupials, monotremes, rodents, domestic animals and humans	Roberts, 1970
Rhipicephalus australis	Australian cattle tick	Broad coastal band from north-eastern NSW to north-eastern WA	Cattle	Arundel, 1988; Barker and Walker, 2014
Rhipicephalus sanguineus	Brown dog tick	Most common in north of latitude 30°S; Occasionally as far as south as Sydney, NSW and Melbourne, Vic	Dogs	Roberts, 1965

[a] *New South Wales.*
[b] *Queensland.*
[c] *Western Australia.*
[d] *South Australia.*
[e] *Victoria.*

well as the distribution of tick-borne infections of humans in Australia. It is important to note in this context that the ability to carry pathogens is different from the ability to transmit them, and active transmission has yet to be established in some cases. New South Wales, Queensland, Tasmania, Victoria, and Western Australia are endemic to at least one tick-borne infection of humans. In contrast, no tick-borne infections of humans are known to occur in north, west, and south-west portions of South Australia as well as the Northern Territory States. Significantly, the tick fauna of all states in Australia

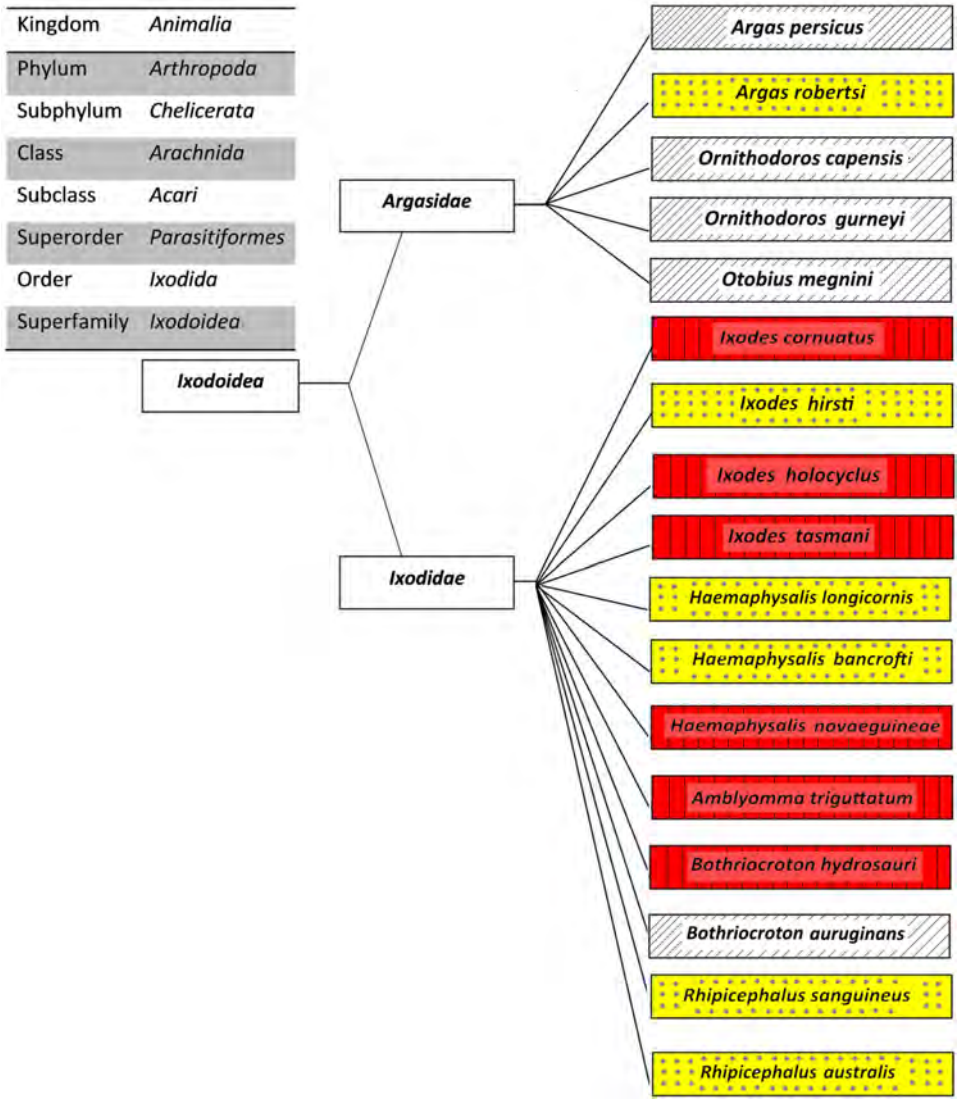

FIGURE 2 | Classification of Australian human-biting ticks. Tick-borne diseases of humans that are transmitted (red boxes with vertical lines), potential tick-borne diseases of humans that may be transmitted (yellow boxes with dots), and other human-biting ticks (white boxes with upward diagonals).

have potential to transmit new and emerging pathogens of humans. The only exceptions may be some areas within Northern Territory and South Australia States. It is unclear why no human-biting tick or tick-borne human infection has been reported from these areas. It may be because of tick density or simply lower number of field examinations. The sustainability of tick-borne pathogens within a specific geographical location is determined by tick population density, which itself is controlled by hosts population densities and tick mortality rates. The biotic (predation) and abiotic (climate including desiccation, drowning, extreme temperature) characteristics of any one location influence the host density. Moreover, environmental factors are a determinant for mortality rates of free-living tick; therefore, the suitability of specific habitat for tick population invasion, establishment, and persistence is important. For instance, larvae of *I. holocyclus* and, to lesser extent, its engorged nymphs are highly susceptible to desiccation which confines them to a narrow coastal strip with low temperatures, high humidity, and existence of hosts. It is important to emphasize that climatic patterns have direct influence on tick survival rates as mentioned earlier; critically, therefore, climate change may occasionally or permanently provide particularly favorable conditions for tick survival, increasing tick densities and exposing more humans to tick-borne pathogens. Hence, the epidemiology of ticks and tick-borne pathogens of humans also must be studied in respect to climate change and ecology. It should be also noted that any variation in fauna could change the transmission risk for tick-borne diseases

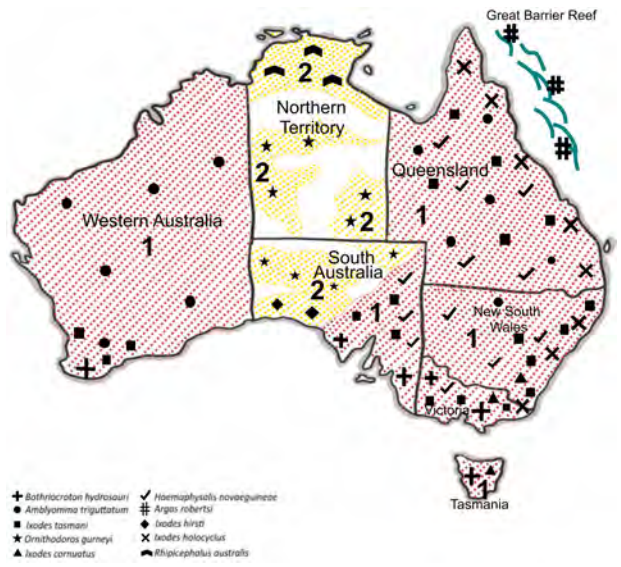

FIGURE 3 | Geographical distribution of 10 potentially human biting-ticks of Australia; Tick-borne diseases of humans that are transmitted (red and 1) and potential tick-borne diseases of humans that may be transmitted (yellow and 2).

through addition of new reservoir and/or amplification of the circulation of native or exotic pathogens (Marsot et al., 2013).

BACTERIAL TICK-BORNE INFECTIONS

Q fever and some rickettsial infections (see section -Q fever and Rickettsial infections) are the only bacterial diseases that are believed to be transmitted by human-biting ticks in Australia. However, ticks that bite humans may also be potential vectors for transmitting human pathogens that cause anaplasmosis, bartonellosis, Lyme-like disease, melioidosis, and tularemia in this country. The phylogenetic analysis of the causative pathogens of these diseases is shown in **Figure 4**.

Q Fever

Coxiella is a genus of bacteria of the family Coxiellaceae, order Legionellales, class Gammaproteobacteria, and phylum Proteobacteria. *Coxiella burnetii* is the causative agent of Q fever. It was previously classified as a *Rickettsia* species due to morphological similarities. However, it has now been placed into the gamma subdivision of Proteobacteria based on genetic and physiologic characteristics, with closer similarities to *Legionella* and *Francisella* than to *Rickettsia* (Roest et al., 2013). This obligate intracellular Gram-negative bacterium protects itself in hostile environments by forming spores which can survive for long periods, for example 586 days in tick feces at room temperature (Philip, 1948). In mammals, macrophages are unable to kill *Coxiella burnetii* and the pathogen may persist asymptomatically. Furthermore, *C. burnetii* demonstrates antigenic shift, a phenomenon that is the basis of serology tests used to differentiate acute from chronic Q fever (Million et al., 2010).

Q fever notification rates decreased over 50% from 2002 to 2005, following the introduction of a nationally funded Q fever vaccination program in Australia (Gidding et al., 2009). However, this vaccine has significant side effects in persons exposed to *C. burnetii* and therefore requires pre-vaccination screening (Madariaga et al., 2003; Gidding et al., 2009). This pathogen affects a large variety of domestic (e.g., cattle, cats, goats, sheep) and wild animals as well as humans. According to Australian government Department of Health, the incidence rate of Q fever in Australia in 2005 was 17.2 per each million of the population. Currently, this disease is the most reported zoonosis in Australia. However, it should be noted that many people suffering from Q fever remain asymptomatic or only show a self-limiting febrile illness and hence are not included in calculations of incidence rate. The geographical distribution of Q fever includes Queensland and northeast New South Wales; however, it is emerging in other regions, for examples, Northern Territory and southwest Western Australia (Gidding et al., 2009).

More than 40 species of ticks can carry *C. burnetii* worldwide; there is, however, controversy over their importance in epidemiology of Q fever (Duron et al., 2015) because inhalation of infectious aerosols or dust particles remains the main route of the disease transmission. Ticks, including *Haemaphysalis bispinosa*, *Haemaphysalis humerosa*, *I. holocyclus*, *Rhipicephalus microplus,* and *R. sanguineus* may have roles in Q fever epidemiology in Australia (Smith, 1941). Accordingly, *H. humerosa* and *I. holocyclus* are competent vectors for *C. burnetii* and can acquire the pathogen from an infected animal and transmit it to an uninfected animal, but for the other three ticks not enough information is available to assess the vector competency for this pathogen (Smith, 1941).

The pathogen is vertically transmitted trans-stadailly from larva to nymph and from nymph to adult in the abovementioned ticks, with the exception of *H. bispinosa* and *R. microplus*. *H. bispinosa* show trans-stadial transmission only from larva to nymph (Duron et al., 2015). No information has been provided on the ability of *H. bispinosa* and *R. sanguineus* to transmit *C. burnetii* to animals. However, studies showed that *I. holocyclus* and *R. microplus* could only transmit infection from these ticks to guinea pigs by feces and bite, respectively. Despite the demonstrated transmission of *C. burnetii* in experimental systems, ticks only occasionally transmit the pathogen in the field (Duron et al., 2015). No solid information is available on tick-borne Q fever in Australian populations. Occasional case reports only suggest the possibility. For example, a human case of acute Q fever with pericarditis north-east of Perth in Western Australia has been described (Beaman and Hung, 1989) as transmitted directly by *A. triguttatum* bite. Symptoms may include abdominal and thoracic pain, bradycardia, chills, headache, high fever, myalgia, and pharyngitis after a 2–4-week incubation period. Compared to rickettsial infections, Q fever is unlikely to be associated with a rash. Apparent lung involvement may be

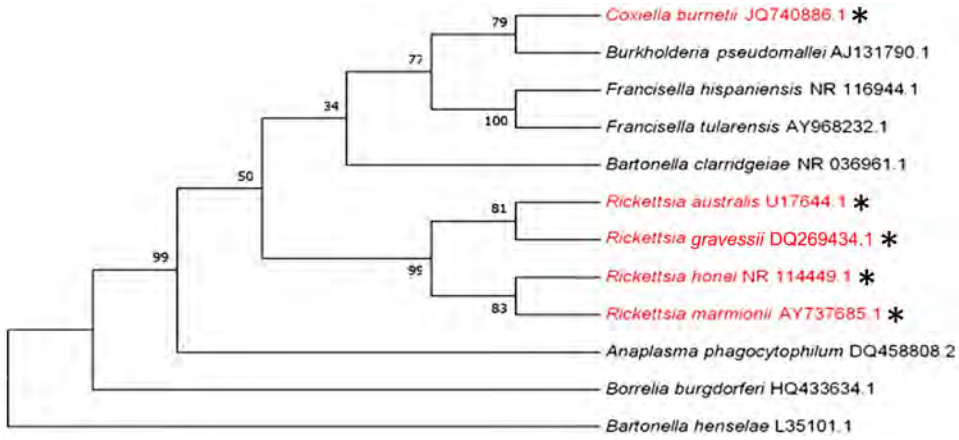

FIGURE 4 | Phylogenetic analysis of pathogenic bacteria of humans that are transmitted (red and *) or could potentially be transmitted by human-biting ticks (black) in Australia inferred using a Maximum Likelihood method based on the 16S rRNA gene sequence comparison (1,400 to 1,500 nucleotides).

absent as many cases present with fever, with no localizing signs, although hepatitis is common. Q fever is typically diagnosed by serology but can also be confirmed by more specialized, albeit less accessible, tests such as immunohistochemistry and polymerase chain reaction (PCR). Isolation of *C. burnetii* can only be performed in biosafety three (BSL-3) facilities, owing to its high infectivity.

Rickettsial Infections

Rickettsia is a genus of non-motile, non-spore forming, obligate intracellular, Gram-negative bacteria that belongs to family Rickettsiaceae, order Rickettsiales, class Alphaproteobacteria, phylum Proteobacteria. *Rickettsia* obtains energy by parasitising vascular endothelial cells and macrophages in mammalian target organs. This pathogen can be transmitted vertically between invertebrates through life stages or be transmitted horizontally from invertebrates to vertebrates or vice versa during feeding of the tick on its host (Weinert et al., 2009). It is serologically categorized into two major classes, namely, the spotted fever group (SFG) and the typhus group. SFG rickettsia has two new sister groups: the ancestral group (AG), and the transitional group (TRG). All the members in SFG and AG, as well as *Rickettsia australis* from TRG are transmitted by tick and together these organisms encompass more than 36 tick-borne species. Of these, 15 species have been implicated as causal agents for a variety of human illnesses.

In Australia, three species including *R. australis*, *Rickettsia honei* (including its novel strain *Rickettsia honei marmionii*), and *Rickettsia gravesii* can be transmitted by bite of one or more ticks species, including *A. triguttatum B. hydrosauri, H. novaeguineae, I. cornuatus, I. holocyclus,* and *I. tasmani*. Unfortunately, no incidence rate has been reported for rickettsial diseases in Australia, but the annual rate of SFG rickettsioses surged up to 8.5 folds from 2008 to 2012, reaching 14.3 cases per each million populations (Drexler et al., 2016). The symptoms of these infections include eschar, fatigue, fever, headache, myalgia, and rash (macular, popular, vesicular). They are typically seen in residents of endemic areas as well as campers, travelers, and hikers to endemic areas. The severity and duration of rickettsial diseases vary considerably. **Table 2** presents some information on different SFG rickettsial diseases in Australia.

The genetic variation in Australian SFG rickettsia has been classified into two populations (Baird et al., 1996). *R. australis* and *R. honei* were designated as etiological agents of Queensland tick typhus (QTT) and Flinders Island spotted fever (FISF), respectively. Furthermore, *R. honei* strain *marmionii* causes Australian spotted fever (ASF). Whilst, ASF, FISF and QTT diseases have similar clinical and serological characteristics, their causative pathogens have varying plaque-forming abilities on different culture media. Additionally, characterization of the gene responsible for encoding the genus-specific 17-kDa antigen of *R. australis* revealed a distinct nucleotide sequence, compared to those of *R. honei* (Baird et al., 1992).

Southern blot analysis of isolates from patients with FISF and QTT showed clear differences in banding patterns when a probe for the rRNA genes is used (Baird et al., 1992). Both species respond well to antibiotic therapy with doxycycline. A new possible class of Australian SFG rickettsia has been recently proposed, following reports of possible rickettsiosis among local workers (Owen et al., 2006; Sentausa et al., 2013; Abdad et al., 2017). According to these studies, *R. gravesii* can use *A. triguttatum* as a vector to infect humans. This tick-borne disease has been reported on Barrow Island in the north-west coast of Western Australia.

Although it is also found in *Amblyomma limbatum*, no confirmed report of transmission of *R. gravesii* by this tick has been published yet. QTT is an emerging public health threat along the whole eastern seaboard of Australia. Cases may occur throughout the year. The geographical distribution of the aetiologic agent, *R. australis*, is expanding due to changes in climate and human population demographics (Stewart et al., 2017). *I. cornuatus*, *I. holocyclus*, and *I. tasmani* have been identified as the main vectors of this pathogen. The first description of QTT was reported from Queensland in 1946

TABLE 2 | Spotted fever group rickettsia in Australia.

Disease	Pathogen	Vertebrate host	Tick species	Geographical distribution
QTT[a]	*Rickettsia australis*	Mammals (Native rats, bandicoots)	*Ixodes cornuatus* *Ixodes holocyclus* *Ixodes tasmani*	East coast of Australia with Queensland included
FISF[b]	*Rickettsia honei*	Native reptiles	*Bothriocroton hydrosauri*	Flinders Island in Tasmania; South-eastern Australia; south-western coastal of Western Australia in Salisbury Island and Walpole; south-eastern coastal region of South Australia near Adelaide
ASF[c]	*Rickettsia honei* subsp. *marmionii*	Unknown	*Haemaphysalis novaeguineae*	Eastern half of Australia
NA[d]	*Rickettsia gravesii*	Macropods and wild pigs	*Amblyomma triguttatum*	Barrow Island in north-west coast of Western Australia

[a] *Queensland tick typhus.*
[b] *Flinders Island spotted fever.*
[c] *Australian spotted fever.*
[d] *Not available.*

with subsequent similar cases reported in New South Wales and Victoria (Pinn and Sowden, 1998). Generally, QTT is considered as relatively mild illness with symptoms of enlarged lymph nodes, fever, headache, maculopapular or vesicular rash, and malaise. Other possible symptoms include chills, cough, eschar, and myalgia. In 1991, a study reported the incident of SFG rickettsial infections in East Gippsland in Victoria with no identification of the causative *Rickettsia* sp. (Dwyer et al., 1991). In the same year, information on 62 Australian cases of SFG rickettsial infections from New South Wales, Queensland, and Victoria were also reviewed (Sexton et al., 1991). This included a fatal case of a healthy 68-year-old male from Mossman in Queensland (Sexton et al., 1990). The authors concluded that *R. australis* was the causative agent of all cases.

In 2007, three suspected cases of QTT were reported. Each case displayed complications including renal failure and severe pneumonia (McBride et al., 2007). More recently, five cases of QTT were reported from southern coastal New South Wales (Fergie et al., 2017), in which illness was characterized by a cutaneous eruption of erythematous papules and pustules as well as lymphadenopathy. Acute delirium or acute kidney injury was observed in three of the five cases. Improved awareness of the condition and its complications amongst the community and its clinicians is imperative to enable early diagnosis and treatment.

R. honei is the etiological agent of FISF (Stenos et al., 1998) and is transmitted by *B. hydrosauri*. FISF was first described on Flinders Island in Tasmania in 1991 and the causative organism was characterized (Graves et al., 1991). Symptoms include cough, fever, headache, maculopapular rash, myalgia, and transient arthralgia. FISF was initially thought to be restricted to south-eastern Australia with highest prevalence in summer, but new cases from previously non-endemic areas for this infection, including south-western coastal areas of Western Australia in Salisbury Island and Walpole, and south-eastern coastal regions of South Australia near Adelaide have been reported (Graves et al., 1991, 1993; Dyer et al., 2005; Unsworth et al., 2007).

In 2007, seven cases of SFG rickettsial diseases similar to FISF were reported from eastern Australia (Unsworth et al., 2007). Genetic identification of the etiologic agent of the disease showed close genetic relationship to *R. honei*, with also low similarities to *R. australis*. Therefore, a new strain of *Rickettsia*, *R. honei* subsp. *marmionii*, was designated as the causative agent of the rickettsiosis (Unsworth et al., 2007). To distinguish infection caused by *R. honei marmionii* from that of caused by *R. honei*, the name ASF was adopted. Unfortunately, no information is available on the epidemiology and ecology of its tick vector, *H. novaeguineae,* within Australia yet.

Potential Bacterial Tick-Borne Infections

Several pathogenic bacteria have been isolated from human-biting ticks collected within Australia or have been transmitted in other parts of the globe by ticks of genera endemic in Australia. Some of these diseases, including anaplasmosis, bartonellosis, melioidosis, and tularemia have been discussed in this review. The incident rates of each of these potential disease has been provided in respect to Australia (if available) or other regions in the world to provide the readers a clue about their potential public health risks.

Anaplasmosis

Human granulocytic anaplasmosis (HGA), formerly known as human granulocytic ehrlichiosis, is an acute febrile disease caused by the rickettsial bacterium *Anaplasma phagocytophilum*, previously known as *Ehrlichia phagocytophilum*. This pathogen is transmitted by ticks, particularly the genera *Amblyomma*, *Dermacentor, Ixodes,* and *Rhipicephalus*. *A. phagocytophilum* is an obligate intracellular, Gram-negative bacterium in family *Ehrlichiaceae,* order *Rickettsiales*, class *Alphaproteobacteria*, and phylum *Proteobacteria*. This pathogen infects granulocytes and survives by suppressing or postponing vital antimicrobial mechanisms including apoptosis, oxidative burst, and phagocytosis as well as by reducing expression of defense genes in host cells. The clinical presentation is an acute, febrile, non-specific, viral-like disease with common early symptoms of headache, elevated hepatic transaminase, leukopaenia, myalgias, and thrombocytopaenia.

The incidence of HGA (cases/million/year) jumped from 1.4 in 2000 to 6.1 in 2010 and 6.3 in 2012. Although, there are as yet no reports of HGA in Australia, data is limited. Bacterial profiling of 460 ticks from four Australian human-biting tick species, namely, *A. triguttatum*, *Haemaphysalis bancrofti*, *H. longicornis*, and *I. holocyclus* were recently conducted (Gofton et al., 2015a). A novel *Anaplasma* sp. was identified in about 2% of *A. triguttatum* ticks. Other studies draw attention to the competence of *R. sanguineus* and *R. australis* in transmission of *Anaplasma* spp. (Bock et al., 1999; Rymaszewska and Grenda, 2008), both of which are also found in Australia. Further investigation is required to determine whether these ticks or other ticks within Australia can act as a vector for *A. phagocytophilum* and subsequently transmit *Anaplasma* to humans or not.

Bartonellosis

Bartonella is a genus of facultative intracellular, Gram-negative bacteria belonging to family *Bartonellaceae*, order *Rhizobiales*, class *Alphaproteobacteria*, phylum *Proteobacteria*. The three most common human diseases caused by this genus are Carrion's disease, cat scratch disease, and trench fever. The pathogenic agents of these diseases are *Bartonella bacilliformis, Bartonella henselae,* and *Bartonella quintana,* respectively. The only information about incidence of bartonellosis belongs to cat scratch disease in United States (94 cases/million people) between 2005 and 2013 (Nelson et al., 2016). These diseases are transmitted when humans are scratched by domestic or feral cats or by contact with arthropods including body louse, fleas, or sand flies. Symptoms and signs include a papule or pustule at the inoculation site, abdominal pain, bacillary angiomatosis (lesions in the skin, subcutaneous tissue, bone, or other organs), bacillary peliosis (vascular lesions in liver and spleen), bone pain, fever, enlarged lymph nodes, headache, rash, severe anemia, and subacute endocarditis. In Australia, *Bartonella clarridgeiae* and *Bartonella henselae* are found in cats, cat fleas and humans. *Bartonella henselae* sequence type 1 or strain Houston-1 is believed to be the major etiological agent of human bartonellosis and is distributed in up to 35% of the younger than 1-year cat population of Australia (Iredell et al., 2003; Arvand et al., 2007; Barrs et al., 2010; Kaewmongkol et al., 2011a). Additionally, novel *Bartonella* spp. have been identified in mammalian hosts in Australia. These include *Bartonella australis*, *Bartonella coopersplainsensis, Bartonella queenslandensis, Bartonella rattaustraliani*, *Candidatus Bartonella antechini*, isolated from eastern gray kangaroos (*Macropus giganteus*), *Uromys* spp., *Melomys* spp., *Rattus* spp., and mardo or yellow-footed antechinus (*Antechinus flavipes*), respectively (Dehio, 2008; Gundi et al., 2009; Kaewmongkol et al., 2011b).

At least eight *Bartonella* spp. are carried by some ticks within Australia, *viz. Bartonella rattaustraliani* by *Ixodes* spp., *Candidatus Bartonella antechini* n. sp. by *Ixodes antechini*, *Candidatus Bartonella woyliei* n. sp. by *Ixodes australiensis*, and five uncultured and unpublished *Bartonella* spp. (genotypes accession numbers EF662053 to EF662057) by perhaps *I. tasmani* (Vilcins et al., 2009; Kaewmongkol et al., 2011a). These ticks were collected from various animals, including koalas (*Phascolarctos cinereus*), rodents, woylies (*Bettongia penicillata*), or yellow-footed antechinus (*Antechinus flavipes*). Despite these findings, there is currently no convincing evidence that verifies tick-borne transmission of *Bartonella* infection to humans, in Australia. However, this possibility should not be excluded until tick-borne bartonellosis is either rejected or accepted by the performance of well-conducted, detailed studies of the relationship between humans, ticks and tick-associated *Bartonella* species (CDC, 2015).

Lyme and Lyme-Like Diseases

Lyme disease (or lyme borreliosis) is another tick-borne disease caused by genus *Borrelia* in family *Spirochaetaceae*, order *Spirochaetales*, and phylum *Spirochates* (Paster and Dewhirst, 2000) This spirochete is generally transmitted by *Ixodes* ticks with life-cycles that involve birds and non-human mammalian hosts (Chalada et al., 2016). The annual incidence rates of Lyme disease in England and Wales are <2 per 100,000 (Lorenc et al., 2017), whereas that of United States is higher than 300,000 (CDC, 2017b). According to the USA CDC, this rate is based on approximately one tenth of actual cases with most remaining undiagnosed or unreported in the United States. Importantly, there is no convincing evidence for the presence of locally acquired Lyme disease in Australia. The disease can be typically initiated with an erythema migrans rash (bull's eye) at the place of tick bite followed by arthritis, influenza-like signs, and neurological disorders (Chalada et al., 2016).

The causative *Borrelia* species are classified in the *Borrelia burgdorferi* sensu lato group (Shapiro, 2014). After the initial discovery of the causative species in north-eastern USA, a number of species have been shown to cause Lyme borreliosis (**Table 3**). The causative bacterial species in various geographic areas are different. This highly depends on climate change in various regions that affect the number of reservoir animals, survival, and activity of ticks. In fact, the incidence of different species of *Borrelia* is determined by abundance of an appropriate vector which is dependent on climate feature of each region (Khatchikian et al., 2012). Accordingly, various species of *Borrelia* have been introduced as the main causative agent of Lyme disease in different regions. For example, *B. burgdorferi* is the only species that causes Lyme disease in the United States while in Europe and Asia other species of *Borrelia* such as *Borrelia afzelii* and *Borrelia garinii* have been also reported as Lyme disease causative agents in addition to *B. burgdorferi.* which are collectively called *B. burgdorferi* sensu lato (Shapiro, 2014).

Ticks usually acquire *Borrelia* by feeding on infected mice, birds, and squirrels during their larval stage. Upon the entrance to their nymphal stage, these infected ticks feed on various animals, including rodents and small mammals, which can be considered as new reservoirs for spirochaetes. After molting into the adult stage, ticks feed on larger mammals. Notably, both nymphs and adults ticks can feed on humans and cause Lyme borreliosis (**Figure 5**) (Donahue et al., 1987; Tilly et al., 2008).

The presence of Lyme disease (Lyme borreliosis, LB) or Lyme-like disease in Australia is highly controversial. The Australian Government Chief Medical Officer convened a Clinical Advisory Committee on Lyme Disease in 2013 to advise on aspects of

TABLE 3 | Known species from Borrelia burgdorferi sensu lato complex with potential of human Lyme borreliosis.

Borrelia species	Vector	Geographical distribution
B. afzelii	*I. ricinus, I. persulcatus*	Asia, Europe
B. bavariensis	*I. ricinus*	Europe
B. bissettii	*I. ricinus, I. scapularis, I. pacificus, I. minor*	Europe, United States
B. burgdorferi sensu stricto	*I. ricinus, I. scapularis, I. pacificus*	Europe, United States
B. garinii	*I. ricinus, I. persulcatus, I. hexagonus, I. nipponensis*	Asia, Europe
B. kurtenbachii	*I. scapularis*	Europe, United States
B. lusitaniae	*I. ricinus*	Europe, North Aferica
B. spielmanii	*I. ricinus*	Europe
B. valaisiana	*I. ricinus, I. granulatus*	Asia, Europe

Lyme disease in Australia (DOH, 2018). The first report about the presence of *Borrelia* species in Australia dates back to 1956 when a species of *Borrelia* was isolated from a rat in northern-west Queensland (Mackerras and Mackerras, 1960). *Borrelia theileri* in Queensland and New South Wales and *Borrelia anserina* in Victoria and the Northern Territory were introduced via the agricultural industry. These species are the worldwide causative agents of bovine borreliosis and avian spirochaetosis, respectively (Mulhearn, 1946).

Evidence for a vector of a potential LB pathogen in Australia is limited and there has been no research into the issue since 1994. It is assumed that if the causative species of LB is/are transmitted by ticks within Australia, likely would be (not necessarily) from the *Ixodes* genus. Research on potential vectors of LB in Australia advises that *I. holocyclus* and *I. tasmani* are the two common ticks with the widest geographical distribution in Australia (Roberts, 1970).

The presence of *Borrelia* species in ticks of Australia has been studied using various methods, including direct culture, PCR, and next generation sequencing (NGS). Wills and Barry collected 167 ticks consisting of *I. holocyclus* and *H. longicornis* from the Hunter Valley and Manning River districts of coastal New South Wales. They found rigid spirochaete-like objects (SLOs) in 41.9% of all Australian collected ticks. In addition, ELISA, immunofluorescence, and western blotting revealed that at least four bacterial isolates had similar antigenic epitopes with *B. burgdorferi*. Crucially, however, the identity of isolates was not confirmed using PCR or further sequencing (Wills and Barry, 1991).

In another Australian study, 12,000 ticks consisting of *H. bancrofti, H. longicornis,* and *I. holocyclus* were collected from the New South Wales coast and their midguts were cultured on BSK-II media. In 92 cultures straight, rigid, non-motile SLOs were detected. Further studies using electron microscopy (EM) indicated aggregates of bacterial flagellae in SLOs. Of these, 18 SLOs showed positive binding results of polyclonal *B. burgdorferi* antibodies; however, no isolates showed positive binding of monoclonal *B. burgdorferi* antibodies (Russell et al., 1994). Gofton et al. (2015b) studied 109 *I. holocyclus* ticks from around the New South Wales to find the microorganisms using PCR method. They found no member of *B. burgdorferi* sensu lato group, but their results revealed the presence of a new relapsing fever group *Borrelia* (Gofton et al., 2015b).

Hence, there is no evidence for transmission of *B. burgdorferi* sensu lato complex with Australian ticks. Whilst patients in Australia with Lyme-like disease may occasionally have positive Lyme serology, finding the causative agent using PCR or direct culture is regarded as mandatory for confirmation of local acquisition of infection.

Melioidosis

Burkholderia pseudomallei is an aerobic, non-spore forming, saprophytic motile, Gram-negative bacterium in family *Burkholderiaceae,* order *Burkholderiales*, class *Betaproteobacteria*, and order *Proteobacteria*. This bacterium is the etiological agent of melioidosis, a disease with high mortality rate (21% in Australia) because of lack of vaccine as well as significant antibiotic resistance. The resistance against antibiotics is believed to be due to secretion of highly hydrated glycocalyx capsule that contributes to formation of slime and microcolonies. This disease is endemic in northern Australia and has an incidence rate of 58/million populations during 2001-2002 (Cheng et al., 2003). The Melioidosis has 1–21 (mean 9) days incubation period (Currie et al., 2000) and its symptoms include cellulitis, fever, pneumonia, and septicemia; however, the symptoms may be absent for decades. Australian melioidosis cases have also been described in which encephalomyelitis and prostatic abscesses are not uncommon. The biogeography of *B. pseudomallei* in Australia was studied and it found two populations with sequence type diversities from Northern Territory and Queensland (McRobb et al., 2014). More than 820 documented cases of melioidosis (13% fatality) have been reported in Northern Territory over 24-year duration (Currie et al., 2010; Parameswaran et al., 2012; McRobb et al., 2014). Although, the infection is commonly transmitted through inhalation of airborne particles or inoculation, tick-borne melioidosis is not unexpected due to the susceptibilities of a broad range of animal species. *B. pseudomallei* was successfully collected from *Haemaphysalis punctate* and *Rhipicephalus bursa* after the bacterium was transmitted from infected rabbits to those ticks (Kharbov et al., 1981). Three species of *Haemaphysalis* ticks (*H. bancrofti, H. longicornis, H. novaeguineae*) and two species of *Rhipicephalus* ticks (*R. australis, R. sanguineus*) can attach to and feed on humans in Australia. Despite these facts, the role of ticks as vectors of *B. pseudomallei* has been extensively ignored in Australia. Therefore, it is crucial to validate these ticks or other Australian human-biting ticks for their ability to act as vectors for this pathogen.

Tularemia

Tularemia is re-emerging in many parts of world. Unfortunately, there is no report of tularemia frequency in Australian population; however, it is currently considered as an infrequent disease in the Southern Hemisphere. Among European countries, the highest incidence rate of 52/million belonged to Kozovo

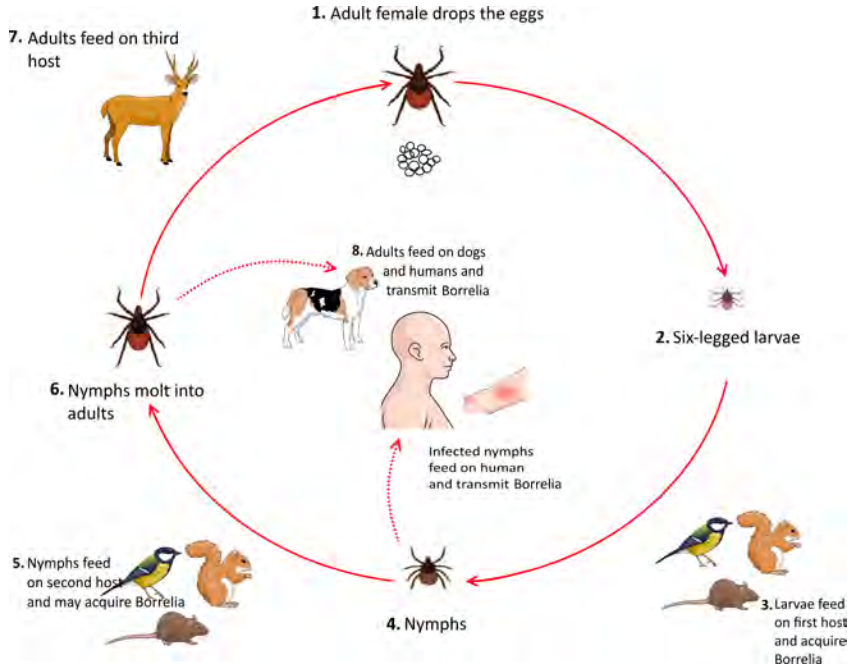

FIGURE 5 | Life cycle of *Borrelia* in tick *Ixodes* spp.

during 2001–2010. It was followed by (per million people) Sweden, 28; Finland, 11.9; Slovakia, 10.0; Czech Republic, 8.1; Norway, 4.2; Serbia-Montenegro, 4.0; Hungry, 3.6; Bulgaria, 2.1; and Croatia, 1.5. The rate for United States is 0.5–5 for same number of population (Gürcan, 2014).

Tularemia is caused by bacterium *Francisella tularensis* or its subspecies. The genus *Francisella* is a member of family *Francisellaceae* in order *Thiotrichales,* class *Gammaproteobacteria*, and phylum *Proteobacteria*. There are four subspecies of this aerobic, facultative, intracellular, non-motile, non-spore forming, Gram-negative bacterium, namely, *F. tularensis tularensis* (type A), *F. tularensis holarctica* (type B), *F. tularensis mediasiatica*, and *F. tularensis novicida*. Where present, it is a highly contagious pathogen in domestic animals and humans. It persists in soil and water and ubiquitously occurs in arthropod vectors as well as wildlife. Tularemia may be transmitted through direct contact, ingestion or inhalation, and indirectly through bites of infected deer flies, ticks, or even infected animal. The disease is categorized into six groups of glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, and ulceroglandular (CDC, 2017a). Symptoms may appear 3–5 days after exposure and include abdominal pain, anorexia, chest discomfort, cough, chills, diarrhea, fatigue, fever, headache, malaise, myalgia, sore throat, and vomiting. The bite of an infected tick or animal causes an ulceroglandular form of tularemia, in which pain and inflammation develops at the bite site accompanied by enlargement of nearby lymph nodes. In Australia, the ringtail possum (*Pseudocheirus peregrinus*) is, so far proven to be, the only natural host of tularemia.

In 2011, a case of infection with *F. tularensis holarctica* that was transmitted through bites of an infected ringtail possum in Tasmania was reported (Jackson et al., 2012). Six years later, *F. tularensis holarctica* was isolated from ringtail possums in Sydney (Eden et al., 2017). Additionally, two *Francisella* spp. were separately isolated from two infected women in Australia and both isolates were identified as *Francisella hispaniensis* (Whipp et al., 2003; Aravena Román et al., 2015). These studies proved the presence of *Francisella* spp. in New South Wales, Northern Territory, Tasmania, and Western Australia at least since 2003. The known tick vectors for tularemia are *Amblyomma americanum, Dermacentor andersoni,* and *Dermacentor variabilis*. Although these ticks are not present in Australia, ringtail possums are hosts for some ticks that bite humans e.g., *I. hirsti* and *I. holocyclus*. Therefore, researchers must thoroughly evaluate these ticks for their ability to acquire endemic *Francisella* spp. from ringtail possums and then transmit them to humans. Additionally, it will be important to evaluate whether additional animals, such as kangaroos or domestic animals, may act as possible hosts for *Francisella* sp. as well as the possibility of indirect transmission to humans by ticks which in Australia that have both humans and these animals as hosts.

VIRAL TICK-BORNE INFECTIONS

Arboviruses (arthropod-borne viruses) are a major public health concern in Australia, with more than 75 arboviruses identified in Australia, some of which are associated with human diseases, and are almost exclusively female mosquito-borne (Russell and Dwyer, 2000; Smith et al., 2011). Dera Ghazi Khan virus

(DGKV), *I. holocyclus* Iflavirus (IhIV), Lake Clarendon virus (LCV), Saumarez Reef virus (SREV), Upolu virus (UPOV), and Vinegar Hill virus (VINHV) are, to date, the only reported viruses endemic in Australia that have been isolated from human-biting ticks. DGKV was isolated from *Argas robertsi* in Darwin (Northern Territory), whereas LCV and VINHV were independently taken from the same tick species that were attached to and fed on the eastern subspecies cattle egrets (*Bubulcus ibis coromandus*) and the western cattle egrets (*Bubulcus ibis*) at Gatton in south-east Queensland, respectively (Doherty et al., 1976; St George et al., 1984; Gauci et al., 2017).

LCV belongs to genus *Orbivirus,* family Reoviridae (double-stranded RNA virus). DGKV and VINHV consist of three negative-sense, single-stranded RNA that classified in genus *Orthonairovirus*, family Nairoviridae, and order Bunyavirales. It is worthy of mention that the genus *Orthonairovirus* includes several viruses that are associated with severe infections in humans or other vertebrate hosts like Crimean-Congo haemorrhagic fever and Nairobi sheep disease. SREV and UPOV were independently isolated from *O. capensis* associated with sooty terns (*Onychoprion fuscatus*) on coral cays off the east coast of Queensland and on Upolu Cay in a coral atoll of Great Barrier Reef in Queensland, respectively (George et al., 1977).

SREV was also isolated from *Ixodes eudyptidis* associated with a dead silver gull (*Chroicocephalus novaehollandiae*) in Northern Tasmania. However, as *I. eudyptidis* does not attach to and feed on humans, it is not considered further in this review. SREV belongs to genus *Flavivirus* in the family *Flaviviridae* that possesses positive-sense single-stranded RNA. The genus *Flavivirus* includes arboviruses such as dengue virus, tick-borne encephalitis virus (TBEV), yellow fever virus, Zika virus, and West Nile virus that can cause severe illnesses in humans.

Tick-borne encephalitis (TBE) is caused by TBEV that is transmitted by consumption of unpasteurized/raw milk as well as bites of *Ixodes* ticks, although there is no evidence that it exists in Australia aside from those who have been infected overseas. TBE is a systemic disease of humans, with a pronounced effect on the central nervous system, and complications are not unusual (Brown, 1994). The virus may access the central nervous system by either haematogenous or neuronal routes. Since its first isolation in 1937, three virus sub-types have been described; namely, European or Western TBEV, Far eastern TBEV (previously known as Russian Spring Summer encephalitis virus), and Siberian TBEV (CDC, 2014). TBE was characterized in an Australian man following a 6-week trip traveling through Russia (Chaudhuri and Růžek, 2013).

Iflaviridae is another family that belongs to Group IV (positive-sense, single-stranded RNA) viruses with *Iflavirus* as the sole genus member. Recently, a novel member of this genus, i.e., IhIV has been identified from *I. holocyclus* populations from northern New South Wales and Queensland. Currently, no human disease has been caused by any members of family *Iflaviridae* (O'Brien et al., 2018). Almost 50 years after isolation of UPOV, an enveloped spherical virus, (Briese et al., 2014) provided clear demonstration that UPOV is a member of *Thogotovirus* in family *Orthomyxoviridae*. Its genome consists of six segments of negative-sense, single-stranded RNA (Group V). UPOV extensively infects African green monkey kidney, baby hamster kidney, human embryonic kidney 293 and is lethal to newborn mice when inoculated intracerebrally (Doherty et al., 1969; Briese et al., 2014). Despite the apparent lack of pathogenicity factor, UPOV can cause disease in humans. Furthermore, a novel *Thogotovirus* member, Bourbon virus, was most likely transmitted by tick bite to a healthy man on North America and took his life within 11 days under medical care due to cardiopulmonary arrest (Kosoy et al., 2015). He was unresponsive to doxycycline therapy and showed fatigue, fever, multiorgan failure, leukopenia, and thrombocytopenia.

Despite the isolation of all the aforementioned arboviruses more than 35 years ago, no information on their pathogenicity for humans is available. RNA viruses are abundant infectious agents that can be transmitted by about 10% of all species of tick in the world, owning to highly specific nature of the relationships among viruses, ticks, and vertebrate hosts. RNA viruses result in more fatalities than tick-borne microbes. Therefore, comprehensive surveillances and characterizations of these viruses to carefully monitor their potential as emerging pathogens in regard to virus survival and its ability to replicate and infect both tick and human cells are crucial. Metagenomic sequencing technology now offers a way of effectively screening samples for the presence of potential tick-borne human viruses. The potentially serious health consequences of infection with these viruses highlights the vital need for comprehensive surveillance for these viruses and any potential clinical illness caused by them, as more investigation is required to determine their potential to be emerging pathogens.

OTHER TICK-BORNE DISEASES

Babesiosis

Among more than 100 *Babesia* spp. reported worldwide, only a few species including *B. divergens*, *B. duncani, B. microti,* and *B.* MO-1 can cause disease in humans. Of these, *B. divergens* and *B. microti* have been identified in most human babesiosis. In Australia, *B. duncani* and *B. microti* have been identified through sequencing and/or serology (Sanjaya et al., 2012). The genus *Babesia* is classified in family *Babesiidae*, order *Piroplasmida*, class *Aconoidasida*, phylum *Apicomplexa*. This protozoan is transmitted by ticks, mainly *Ixodes scapularis* (not present in Australia), and is the most common cause of babesiosis in humans. It can either reproduce asexually in its mammalian host erythrocytes or sexually in its arthropod vector. No information on its incidence rate in Australia or in world is available; however, its incidence rate is lower than that of Lyme diseases due to higher difficulty in diagnosis, higher proportion of asymptomatic infection, inadequate physician awareness, lower tick infection rate, and more restricted geographic range (Vannier et al., 2015). This protozoan is the parasite of human red blood cells. Within these cells, trophozoites of *B. microti* reproduce by budding and undergo two successive divisions to form Maltese Cross (tetrad morphology). Then, merozoites are release into bloodstream, with simultaneous lysis of red blood cells, and attach to and invade other red blood cells. Although babesiosis is a well-documented infection of domestic animals

including cattle and dogs, there is, to date, only one human case has been reported from Australia. The case was identified on the south coast of New South Wales in 2012 (Sanjaya et al., 2012). This patient developed cholestatic liver function disorder, moderate-to-severe thrombocytopenia, pancytopenia with fluctuating anemia, multiorgan failure, and required ongoing blood product transfusions as well as haemodialysis. The patient did not recover from multiorgan failure, and severe thrombocytopenia led to acute gastrointestinal bleeding and a fatal asystolic arrest (Sanjaya et al., 2012). The causative agent was confirmed as *B. microti* through complete and partial sequencing of the 18S rRNA gene (18S rDNA) and the β-tubulin gene. Asymptomatic parasitaemia is common in babesiosis during primary infection and/or following treatment of systemic infection (Vannier et al., 2008; Sanjaya et al., 2012). This disease is primarily transmitted through the infected tick bites (commonly *Ixodes* spp.) with occasional transmission through the transfusion of blood products. Unlike several countries such as US, blood products are not screened for *Babesia* in Australia, which pose the danger of transmission through blood donation by unrecognized babesiosis patients (Ngo and Civen, 2009; Government, 2018). Patients may have fever, haemolytic anemia, influenza-like disease, and thrombocytopenia. Asplenics typically are susceptible to severe life-threatening illness.

Babesiosis may be suspected in Australia in patients with a history of overseas travel to an endemic area, with or without a documented history of tick bite, or a history of blood transfusion. A tick-borne route was assumed because the parasitaemia was neither transfusion related nor acquired overseas (Sanjaya et al., 2012). A later study (Storey Lewis et al., 2017) extracted DNA from 1,154 ticks that where collected from across Australia to characterize *Babesia* spp. However, no *B. microti* could be identified in these Australian ticks. Only several closely related sequences to *B. macropus* were reported from ticks of genera *Bothriocroton, Haemaphysalis,* and *Ixodes*. Therefore, the animal host and tick vector are yet to be identified in Australia.

Tick Paralysis

Tick paralysis is the only tick-borne disease that is not attributed to pathogens. The bite of a single tick is sufficient to paralyze one animal. The injection of chemical compounds, i.e., neurotoxins and paralysis is usually due to the attachment of an adult female *I. holocyclus,* mostly in the spring and summer months. Larva of *I. holocyclus* cannot feed on humans; however, their attachments to humans usually cause no more than localized dermatitis. For example, a larva of *I. holocyclus* was found attached to right temporal conjunctiva of a 10-year-old boy from Sydney in New South Wales (Teong et al., 2015). The only symptoms developed were eye itch and conjunctival vessel dilatation around the organism. In contrast to larva, nymphs and to a greater extent female *I. holocyclus*, frequently attach to humans and after several days can abundantly feed and engorge (Barker and Walker, 2014). During a blood meal, especially after day three of feeding, sufficient chemical compounds including neurotoxins (holocyclotoxin), secreted by female tick salivary glands, are injected into hosts. The neurotoxin may bind to the location where nerves meet muscles, i.e., neuromuscular junction and reduces the release of acetylcholine at the presynaptic membrane which may lead to acute anaphylactic shock and paralysis (Chand et al., 2016).

Tick paralysis extensively occurs in Australia and many researchers have reported human case studies. It is worth mentioning that the geographical distribution of such cases is highly restricted to the enzootic range of the paralysis tick. The most commonly affected group is children 1–5 years of age and infected children usually become subdued, refuse food, and sleep excessive periods (Grattan Smith et al., 1997). The typical presentation is a prodrome with the subsequent development of an unsteady gait followed by ascending, symmetrical, flaccid paralysis (Grattan Smith et al., 1997). The disease is characterized by early cranial nerve involvement, especially, with the presence of both internal and external ophthalmoplegia (Grattan Smith et al., 1997). It is noteworthy that the progress of paralysis commonly continues for 24–48 h after removal of Australian paralysis tick, unlike the short duration seen with North American ticks. Therefore, it is crucial to carefully observe the affected child during this period. Since the second-half of the twentieth century, death due to respiratory failure has been relatively uncommon if appropriate early diagnosis and supportive medical care are provided.

No documented fatality has been reported in Australia since 1945. Respiratory support may be needed for more than a week (Grattan Smith et al., 1997) and a recovering child requires several weeks to walk unaided. It should be pointed out that currently no study has ever been investigated tick paralysis recovery in a longitudinal pattern. In older children and adults, the initial symptoms may be difficulty in reading with double vision, nystagmus, or photophobia (Sutherland and Tibballs, 2001; Barker and Walker, 2014). According to these reports, there is no increase in body temperature unless the disease is complicated by bacterial infection.

There have been three exported cases of *I. holocyclus* attachments reported in the literature, although there are probably other cases that have occurred in the past but were not recognized. The first case was a Japanese man traveled to the Gold Coast in Queensland in late 2002 (Inokuma et al., 2003). After his return to Japan, he removed a semi-engorged female tick that had attached to his scalp 3 days earlier. The patient developed an illness consistent with SFG rickettsia, but without rash. Serology was positive for antibodies to SFG, but PCR did not detect rickettsia in the tick. The second case was reported in 2014 (Pietzsch et al., 2014) from an English traveler returning back to London from East coast of Australia. She displayed swelling and a small black lump in the groin area. The ticks were finally discovered and removed from her lower leg. Two years later, a paralysis tick was attached to a woman's right temporal region of scalp following a trip to Sydney (Pek et al., 2016). She presented to a Singapore Emergency Department (ED) with facial swelling, facial pain and a painful, swollen skin tag over her right temporal region, that proved to be a female adult *I. holocyclus* tick. She developed motor and sensory changes with weakness in the distribution of the temporal branch of the facial nerve with dysesthesiae over

scalp in the sensory distribution of that nerve (Pek et al., 2016).

CONCLUSIONS

The Australian climatic and environmental conditions provide suitable conditions for many ticks. Australia is known to be endemic for 70 of the known 896 tick species. At least 17 species of Australian ticks attach to and feed on domestic animals and humans. Although humans are accidental hosts for many of these ticks, tick bites may have negative influences on human health and quality of life. Whilst tick-borne pathogens of humans do not appear to contribute to Australia's overall communicable disease burden, this perception must be re-examined using new laboratory and epidemiological tools that we now have at our disposal. Against a true baseline estimate of the burden of illness associated with tick bite, we can then prepare for the future when changes in climate, lifestyle, human and animal populations will invariably impact on the likelihood that tick bite will likely increase in many parts of Australia. Introduced species of ticks, many of which harbor pathogens not previously seen in Australia, may adapt to and flourish in Australia. *A. persicus*, *H. longicornis*, *O. megnini*, *R. australis*, and *R. sanguineus* are good examples of species introduced into Australia because of human interventions. Human-biting ticks carry pathogens such as arboviruses (DGKV, LCV, SREV, TBEV, UPOV, VINHV) as well as *Anaplasma*, *Borrelia*, *Burkholderia*, *Francisella*, and *Rickettsia* species. These pathogens have been identified in some human-biting ticks such as *A. robertsi*, *H. bancrofti*, *H. longicornis*, *I. hirsti*, *R. australis*, and *R. sanguineus* that have been collected within Australia. Some of these introduced human-biting ticks that are now endemic to Australia can carry serious human pathogens that have not yet been detected in Australia but are well-known in other parts of the globe. *R. sanguineus* is a vector of *R. conorii* and *R. rickettsii*, both causes of SFG infections that have higher fatality rates than ASF. New pathogens may be introduced into and then established in Australia by many means that are not amenable to simple regulation, such as tourism, trade, bird or animal migration.

Aside from pathogen transmission, there are an increasing number of allergic, inflammatory and potentially autoimmune illnesses attributed to tick bites. *I. holocyclus*, *O. capensis*, and *O. gurneyi* are three tick species that trigger such complications in humans and are also present in Australia. Currently, only some areas in Northern Territory and South Australia may be free from human-biting ticks and tick-borne diseases. Tick-borne infections and illness have been reported in all other states including New South Wales, Queensland, Tasmania, Victoria, and Western Australia. Accordingly, Australia undoubtedly faces new disease threats associated with tick-bite, all of which can only be countered by improving our knowledge of the ticks, the pathogens and the epidemiology of tick bite and its consequences. There is an urgent need for a comprehensive study to determine the role of Australian human-biting ticks in the transmission of emerging pathogens to humans in Australia.

AUTHOR CONTRIBUTIONS

MD and HK wrote the manuscript and prepared the figures. EH, RS, BH, and GG have reviewed and corrected the manuscripts based on their respective expertise. All authors read and approved the final version of the manuscript.

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