Understanding debilitating symptom complexes attributed to ticks (DSCATT) in Australia to inform an evidence-based Clinical Pathway

Literature Review

WORKING DRAFT

31 May 2019

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CONTENTS

GLOSSARY

ACA – Acrodermatitis chronica atrophicans

ACIIDS – Australian Chronic Infectious and Inflammatory Disease Society

AHMAC – Australian Health Ministers' Advisory Council

ALLI – Australian Lyme-like Illness

ALS – Amyotrophic lateral sclerosis

BPG – Best practice guidance

CBT – Cognitive behavioural therapy

CCP – Cyclic citrullinated peptide

CDC – Centers for Disease Control and Prevention

CDNA – Communicable Diseases Network Australia

CFS – Chronic fatigue syndrome

CME – Continued Medical Education

CPC – Clinical Principal Committee

DSCATT – Debilitating Symptom Complexes Attributed to Ticks

EBG – Evidence-based guidelines

EIG – Evidence-informed guidance

ELISA – Enzyme Linked Immuno-sorbent Assay

EM – Erythema migrans

ESR – Erythrocyte sedimentation rate

ESR – Erythrocyte sedimentation rate

GI – Glycaemic Index

GP – General Practitioner

IDSA – Infectious Diseases Society of America

IgG – Immunoglobulin G

IgM – Immunoglobulin M

ILADS – International Lyme and Associated Disease Society

IOM – Institute of Medicine

LDAA – Lyme Disease Association of Australia

LTT – Lymphocyte Transformation Test

MCAD – Mast Cell Activation Disorder

MCNSW – Medical Council of New South Wales

MDT – Multi-disciplinary team

ME/CFS – Myalgic encephalomyelitis/Chronic fatigue syndrome

MND – Motor neurone disease

MRI – Magnetic resonance imaging

MS – Multiple sclerosis

NAAT – Nucleic Acid Amplification Techniques

NATA – National Association of Testing Authorities

NATA – National Association of Testing Authorities Australia

NICE – National Institute for Health and Care Excellence

PBS – Pharmaceutical Benefits Scheme

PCR – Polymerase chain reaction

PFAPA – Periodic Fever, aphthous Stomatitis, Pharyngitis, Adenitis

PHLN – Public Health Laboratory Network

POTS – Postural orthostatic tachycardia syndrome

RA – Rheumatoid arthritis

RACGP – Royal Australian College of General Practitioners

RACP – Royal Australian College of Physicians

RCPA – Royal College of Pathologists of Australasia

RCPA – Royal College of Pathologists of Australia

SLE -Systemic lupus erythematosus

STI – Sexually transmitted infection

TLG – Therapeutic Guidelines Ltd

US – United States

VZV – Varicella-Zoster Virus

WHO – World Health Organization

Tables

Figures

uidance on how to read this report

This report is a narrative literature review. It contains two main parts:

1. The *Key Findings* section provides a summary of the findings of this literature review presented by the research questions. A summary of the evidence and quality assessments is also provided.
2. The main report provides detailed findings on the research questions. Relevant data from all primary studies is included in evidence tables.

Appendix A: Quality assessment includes the quality assessment tables for quantitative research based on GRADE for Systematic Reviews and CASP for Randomised Control Trials, Case Control Studies, and Diagnostic Checklists. Appendix B includes the quality assessment tables for qualitative research based on COREQ [to add in next version].

A detailed methodology of the Literature Search is set out in a separate 'Literature Search Report'.

KEY FINDINGS

[to add in next version]

Methodology

[to add in next version – drawing on literatures search report]

Summary by research question

Question 1: What is the clinical epidemiology of DSCATT in Australia?

Key findings about prevalence, demographics and geographic distribution of DSCATT in Australia

- As Lyme-like illness (DSCATT) is not clearly defined and not formally reported, available statistics on its prevalence among Australian patients is limited, with much of the available evidence being self-reported.
- Reported prevalence and prevalence estimates for Lyme-like illness/DSCATT among Australian patients varies widely, ranging from hundreds to many thousands affected, through to an 'undiagnosed epidemic'.
- Submissions and analysis of submissions indicate that, while children and adults of all ages report having been diagnosed with Lyme-like illness/DSCATT, the illness appears to be more common in adults around the age of 40 years and more common among females.
- No information is available on the ethnicity of patients with DSCATT.
- The majority of patients diagnosed with Lyme-like illness reported they had never left Australia.
- Evidence was analysed on over 500 reports of Lyme-like cases in Australia between 1982 and 2015. This analysis showed that the diagnostic methods in the published case reports were unreliable, and therefore the evidence for Australian Lyme-like cases remains "*quite unsubstantial and unconvincing.*"
- While evidence suggests cases of Lyme-like illness/DSCATT have been reported across all States and Territories, DSCATT appears to consistently be most prevalent in New South Wales, with Queensland, Western Australia and Victoria also affected but to a lesser degree.

Key findings on the symptoms and clinical signs associated with DSCATT reported by Australian patients and treating medical professionals

- Overall, evidence from patients, analysis of submissions and treating medical professionals highlights that while some patients experience acute symptoms, particularly after a tick bite, most patients suffering from DSCATT are experiencing chronic debilitating symptoms.

- According to analysis of over 600 patient submissions (Brown, 2018 and Chalada et al., 2016), patients suffering Lyme-like illness often experience a range of symptoms and signs; while patients describe a large number of symptoms, overall the most common symptoms associated with DSCATT are fatigue, disordered thinking and sensory disturbance.
- Patients generally report experiencing multiple symptoms, with analysis of submissions indicating nearly six symptoms per patient on average.
- Patients generally report experiencing symptoms of DSCATT for many years; with around 10 years being average, but reports of up to 47 years.
- Acute symptoms and clinical signs of DSCATT/Lyme-like illness typically include flu-like symptoms, fever and rashes of various descriptions; some patients have the bullseye (erythema migrans) rash.
- ACIIDS, a group of doctors who treat patients with tick-borne diseases and Lyme-like illness advise there are multiple symptoms and clinical signs of chronic DSCATT/ Lyme-like illness; most commonly these include fatigue, headache, muscle and joint pain and cognitive impairment, with clinical signs involving the neurological, cardiovascular, gastrointestinal and musculoskeletal systems.

Question 2: What information is available on diseases or disorders Australian patients experiencing DSCATT symptoms have been diagnosed with and what are the most likely differential diagnoses?

Key findings on diseases and disorders Australian patients experiencing DSCATT have been diagnosed with and what are the most likely differential diagnoses

- From limited evidence, patients diagnosed with Lyme-like illness report having been diagnosed with infections and co-infections from ticks, the most common infection being Borrelia, followed by Bartonella, Babesia and Rickettsia.
- The very limited anecdotal evidence from medical professionals treating patients with DSCATT varies on the number of organisms from ticks that patients may be infected with; however, there are as yet no published clinical studies to confirm the evidence.
- From limited available information, a high proportion of patients diagnosed with DSCATT appear to have been diagnosed with Lyme disease in non-NATA/RCGP laboratories in Australia or by overseas laboratories.
- Limited information indicates around fifty diagnoses of non-tick borne diseases or conditions have been given by medical professionals to patients with Lyme-like illness, with multiple sclerosis, CFS/ME, rheumatoid arthritis, and motor neurone disease being most common; however, many patients have been given a diagnosis of depression, anxiety or mental/psychological disorder.
- Concerns have been raised about the risks and harms of misdiagnosis, with potentially treatable conditions being diagnosed as Lyme-like illness.
- There are established diagnostic avenues and pathways to assist clinicians when a patient presents with a tick bite and symptoms in Australia; taking a travel history from the patient is a critical part of the diagnostic pathway along with symptoms.

- While patients and treating doctors report confirmed diagnoses of Lyme disease and *Borrelia,* there is currently no evidence that *B. burgdorferi* or any other kinds of *Borrelia* are infecting humans in Australia.
- Current evidence is that the only systemic bacterial infections known to be transmitted by tick bites in Australia are Rickettsial (*Rickettsia* spp.) infections which include Queensland tick typhus, Flinders Island spotted fever and Australian spotted fever and Q fever (*Coxiella burnetii)* and there are no definite tick-borne viral illnesses in Australia currently.
- However, while ticks are suspected to be possibly responsible for symptoms of DSCATT and there are known tick borne diseases in Australia there are a lot of unknowns about Australian ticks and the diseases they do or might transmit; a range of other possible causes for DSCATT including parasitic and viral causes, as well as environmental toxins and other potential medical explanations have been suggested.
- From the limited information available, while many diagnoses have been given to patients with DSCATT, several non-infectious diagnosable and treatable diseases and conditions consistently stand out as differential diagnoses that should be considered high priority in patients presenting with DSCATT, including multiple sclerosis, motor neurone disease, rheumatoid arthritis, Parkinson's disease, fibromyalgia, autoimmune diseases and chronic pain syndromes. Chronic fatigue syndrome is also high on the list for differential diagnoses

Question 3: What are the issues associated with diagnostic testing for Lyme disease both in Australia and by overseas laboratories?

Key findings on issues associated with diagnostic testing for Lyme disease both in Australia and by overseas laboratories

- The Australian guidelines on the diagnosis of overseas acquired Lyme disease are for the diagnosis of classical Lyme disease only and do not apply to Lyme-like illness acquired in Australia.
- There are three laboratory techniques for diagnosis of Lyme disease, including culture of the organism, molecular detection of DNA and serology. All laboratory techniques have challenges – serology is the mainstay technique currently used.
- Most serological diagnostic protocols in the US and Europe use a two-tier system; the Australian guideline uses the two-tier system.
- The interpretation of serology tests, including for Lyme disease, depends on the sensitivity and specificity of the test, and how common the disease is among people being tested.
- The issue of diagnostic testing, whether Lyme disease can be contracted in Australia and discordant results for Lyme disease testing between accredited and non-accredited laboratories, was the most contentious issue to emerge in the 2016 Senate Inquiry.
- The Senate Inquiry noted the contradictory evidence about the reliability of the two-tier testing protocol, including the sensitivity of ELISA and false positives versus false negatives and its use in immunocompromised patients.

- Australian laboratories are accredited for medical testing by the National Association of Testing Authorities Australia (NATA) in conjunction with the Royal College of Pathologists of Australasia (RCPA). The Australian guideline for diagnosing overseas-acquired Lye disease states tests should be performed in an accredited laboratory.
- The use of non-accredited Australian laboratories and overseas laboratories has caused controversy and can cause significant confusion and frustration for patients.
- From limited available evidence a high proportion of patients with Lyme-like illness have tested positive to Lyme disease in non-accredited Australian or overseas laboratories.
- 'Lyme-literate' practitioners use non-accredited Australian laboratories and overseas laboratories for three reasons and consider these laboratories are better placed to accurately test for *Borrelia.*
- However, medical authorities suggest results from overseas laboratories should be interpreted with caution and that in the absence of a known causative agent for DSCATT in Australia a positive test is likely to be a false positive.
- Investigation of the performance of assays for Lyme disease in Australia by the National Serology Reference Laboratory in 2017 determined the tests used by Australian laboratories to diagnose Lyme disease had equivalent reliability to tests used in overseas laboratories.

Question 4: What are the treatment modalities that have been provided to patients (including subgroups of patients) with DSCATT in Australia and what is the evidence base to support these treatment modalities?

Key findings about effective treatment modalities that have been provided to patients with DSCATT in Australia

- There are no published peer-reviewed publications of clinical studies on the treatment of Lyme-like illness in Australia.
- From the limited evidence available, while numerous treatments and treatment regimens are reported by patients diagnosed with Lyme, Lyme-like illness, antibiotics, diet, supplements and herbs are the most common treatments.
- Evidence from ACIIDS doctors providing treatments to patients with Lyme-like illness include that patients are sometimes treated with long-term antibiotics, mainly orally, but because they have so many sick patients doctors are performing a lot of intravenous therapies as well, including intravenous antibiotics for long periods of time.
- Most patients obtain treatment in Australia with the USA being the second most common location for treatment.

Key findings on the evidence base for the treatment modalities provided to Australian patients suffering DSCATT

- ACIIDS advises the use of long-term antibiotics was evidence-based and in many cases has assisted patients to get better, but there are no published studies on clinical treatments or treatment outcomes conducted in Australia on patients with DSCATT to verify the anecdotal evidence.

- Serious concerns have been raised by multiple Australian medical professionals, medical professional bodies and medical professional regulatory authorities about overuse and long-term use of antibiotic treatment and antimicrobial resistance.
- Concerns have also been raised by Australian medical professionals and government health authorities over other treatments provided to patients with DSCATT, including unconventional therapies that are not evidence-based.
- The 2018 NICE Lyme disease guidelines are the most recently published guidelines available and aim to standardise antibiotic treatment and provide a consistent framework for good practice in Lyme disease. However, NICE advises evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme disease is of poor quality, out-dated and often based on small studies.

NICE recommendations on treatment

- The 2018 NICE Lyme disease guideline recommends that longer courses of 21 days of treatment should be offered as standard antibiotic treatment for erythema and/or non-focal symptoms.
- In patients with non-focal symptoms of Lyme disease (symptoms such as fever, sweats and muscle pain, which are not specific to an organ system) the NICE Lyme disease 2018 guideline recommends that patients should be given the same treatment as people with erythema migrans.
- For managing ongoing symptoms of Lyme disease after a course of antibiotics, the NICE Lyme disease 2018 guideline recommends that patients should not be routinely offered more than two courses of antibiotics because of a lack of evidence of benefit.
- For the management of Lyme neuroborreliosis, the NICE 2018 guideline recommends as first treatment antibiotics taken orally for 21 days for the management of Lyme disease affecting the cranial nerves and peripheral nervous system and antibiotics administered intravenously for 21 days for the management of Lyme disease affecting the central nervous system. Care of children and young people under 18 should be discussed with a specialist.
- Additionally, for neuroborreliosis, the Cochrane database of systematic reviews published in 2016 a systematic review of antibiotics for the neurological complications of Lyme disease; this review indicated that treatment with any of the four antibiotics produced similarly good outcomes for treatment of neurological Lyme disease in Europe, but a second treatment with amoxicillin does not appear to provide added benefit to ceftriaxone.
- For the management of Lyme arthritis, the NICE 2018 Lyme disease guidelines recommends oral antibiotic therapy for 28 days; longer courses of treatment (28 days) are appropriate when treating Lyme arthritis because it is difficult for antibiotics to penetrate to the synovium and synovial fluid. Care of children and young people under 18 with Lyme disease and focal symptoms such as carditis should be discussed with a specialist.
- For management of acrodermatitis chronica atrophicans the NICE 2018 Lyme disease guideline recommendations are the same as for Lyme arthritis and a 28 day course of

antibiotic treatment. Care of children and young people under 18 with Lyme disease and non-erythema migrans presentations should be discussed with a specialist.

- For the management of Lyme carditis, the NICE 2018 Lyme disease guidelines recommended course of antibiotic treatment is 21 days. Care of children and young people under 18 with Lyme disease and focal symptoms such as carditis should be discussed with a specialist.
- For management of women with Lyme disease during pregnancy and their babies NICE 2018 Lyme disease guideline recommends pregnant women should be treated following usual practice, and babies should receive treatment if they have serology showing IgM antibodies specific to Lyme disease or symptoms that might be caused by Lyme disease. NICE advises that while that mother-to-baby transmission of Lyme disease is possible in theory, there was an absence of evidence, and the risk appears to be very low. Women could be reassured that pregnancy and their baby are unlikely to be affected and NICE highlighted the importance of completing treatment.
- NICE reported no evidence was found for transmission of Lyme disease through sexual contact or blood products.

2010 German guideline recommendations on treatment

- German guidelines 'Diagnosis and Treatment of Lyme borreliosis' published in 2010 recommend either a monotherapy or combined therapy of antibiotics, however, the guideline notes the efficiency of a combined antibiotic therapy has not been scientifically attested to date. The authors note the guideline was prepared with great care but no liability whatever can be accepted for its accuracy, especially in relation to dosages.

2014 ILADS guidelines recommendations on treatment

- ILADS guidelines in 2014 found the available evidence regarding the treatment of known tick bites, erythema migrans (EM) rashes and persistent disease is limited and was of very low quality due to limitations in trial designs, imprecise findings, outcome inconsistencies and non-generalizability of trial findings. As such, optimal treatment regimens for the management of known tick bites, EM rashes and persistent disease has not yet been determined.
- ILADS recommended clinicians should not use a single 200 mg dose of doxycycline following a tick bite as prophylaxis for Lyme disease; The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis. The recommendation was based on very low quality evidence.
- ILADS recommends 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. For adults, 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. Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. The recommendation was based on very low-quality evidence.
- ILADS recommends clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease; 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. 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.

The ILADS Working Group guidelines (2004)

- The ILADS Working Group (2004) Evidence-based guidelines for the management of Lyme disease does not recommend hyperbaric oxygen therapy for routine use and notes patient's interest in alternative therapies

2006 IDSA guidelines recommendations on treatment

- The Infectious Diseases Society of America (IDSA) guidelines published in 2006 is the guideline promulgated in the Australian guideline on the diagnosis of overseas acquired Lyme disease.
- The voluntary review of the IDSA 2006 guidelines in 2008 vetted by an ombudsman concluded that the recommendations contained in the 2006 guidelines were medically and scientifically justified on the basis of all of the available evidence and that no changes to the guidelines were necessary. The Review Panel concluded that *in the case of Lyme disease* inherent risks of long-term antibiotic therapy were not justified by clinical benefit.

Question 5: What current guidelines and approaches to investigation and ongoing syndromic management of symptoms associated with DSCATT have been found effective internationally?

Key findings on current guidelines and approaches to investigation and ongoing syndromic management of symptoms associated with DSCATT that have been found effective internationally

- There are many other useful "guidelines" or "guidance" documents that are produced that contain references to scientific studies, but they do not specifically detail the methodology used for their development, which makes it difficult to assess their rigor of development.
- There are currently no evidence-based guidelines that directly address the debilitating symptom complexes attributed to tick bites in Australia.
- On the basis of the international literature on fatigue, it is recommended in a patients presenting with fatigue-like symptoms a comprehensive history and examination is taken, as well as a consideration of a period of watchful waiting in the absence of red flags and the judicious use of tests once the decision to investigate is made.
- ME/CFS has been identified as a differential diagnosis for Lyme disease.
- Pain management is likely to be an important component in the care of people with DSCATT.

- Rheumatoid arthritis (RA) guidelines recommend early diagnosis of RA and referral to a rheumatologist if the patient has persistent swelling beyond 6 weeks, even if RA is not confirmed. Early referral enables aggressive intervention with disease modifying drugs, reducing long term damage and disability.
- In the Clinical Pathway for the Screening, Assessment and Management of Depression in Adult Cancer Patients the Psycho-oncology Co-operative Research Group advises that unlike other common symptoms (for example, fatigue), anxiety and depression are readily treatable, and a strong evidence base for intervention exists. Early identification and treatment of anxiety and depression leads to better outcomes.
- Emerging evidence reported by the NHMRC reports that structured family programs may be helpful in reducing grief and burden of care, and in improving family members' sense of control over their situation.

Assessment of evidence table summary

[to add in next version]

1. INTRODUCTION

1.1. The Australian Government's position statement on DSCATT

The Australian Government acknowledges that there is a group of Australian patients suffering from the symptoms of a chronic debilitating illness, which many associate with a tick bite. The Australian Government has chosen to describe this patient group as having Debilitating Symptom Complexes Attributed to Ticks (DSCATT). This term was carefully considered to appropriately acknowledge this patient group and the multifaceted illness they are experiencing, whilst moving away from the stigma and controversy associated with the use of "Lyme Disease", "Lyme disease-like Illness" and "Chronic Lyme Disease" that has previously been used to describe this patient group.

Many of these patients experiencing debilitating symptom complexes are living in turmoil as their illness is poorly understood, making accurate diagnosis and treatment difficult. It is imperative for government health authorities, clinicians and patients alike to remain open minded as to the causes of these symptoms and work together to achieve a patient-centred multidisciplinary approach to their care.

The Australian Government is currently working with key stakeholders to investigate an evidence-based and flexible multidisciplinary care model that can be applied in both private and public healthcare settings. It is hoped that this model will provide patients with a comprehensive assessment of their symptoms and ensure that a potential diagnosis is not overlooked. Because of the imprecise nature of the symptom complexes some patients will remain undiagnosed; therefore, ways to manage ongoing symptoms through a comprehensive patient-centred care plan will also be investigated.

The Australian Government continues to support research into determining the cause of these debilitating symptom complexes along with innovative health care models to support the needs of this patient group. It is hoped that the National Health and Medical Research Council's $3.0 million targeted call for research into debilitating symptom complexes attributed to ticks will encourage researchers to further investigate this complex issue.

Unfortunately, some patients presenting with classical Lyme disease or debilitating symptom complexes have not had positive experiences in the Australian health care system, largely due to the controversy and stigma attached to Lyme disease in Australia.

To ensure that both the general public and health professionals have current evidence-based information and can distinguish between classical Lyme disease and DSCATT, the Australian Government will undertake to raise the awareness of both these illnesses. It is hoped that this information will help patients and health professionals better understand tick borne illnesses, keep an open mind to the cause of debilitating symptom complexes and result in a positive and consistent approach to diagnosis, treatment and ongoing management.

1.2. The Senate Community Affairs References Committee

The Senate Community Affairs References Committee (the committee) Inquiry and reports on the *Growing evidence of an emerging tick-borne disease that causes a Lyme -like illness for many Australians* and the recommendations of the committee are key documents included in this literature review. The committee's views and recommendations and the public submissions that

informed this inquiry are woven throughout this literature review. A brief overview of the Senate Inquiry, including the terms of reference and the public submission process and outcomes is included below.

The Senate referred 'the growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients' to the Community References Affairs Committee (the committee) on 12 November 2015, for inquiry and report. The terms of reference for this 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.

The committee invited submissions and as of 3 May 2016 had accepted and published 1171 submissions and undertaken three public hearings in Perth, Brisbane and Canberra. The committee published an Interim Report on 4 May 2016 (Senate Inquiry Interim Report, May 2016), containing a summary of the evidence heard as of 3 May 2016. The Senate was dissolved due to the federal election; however, on 13 September 2016, the Senate agreed to readopt the inquiry with the same terms of reference. While the committee did not call for any further submissions, noting it had received and considered over 1200 submissions prior to tabling its interim report, it did hold an additional public hearing in Sydney and published a Final Report in November 2016 (Senate Inquiry Final Report, November 2016), including 12 recommendations.

The committee reported in its Interim Report that it had received over 1000 submissions to the inquiry. Submissions from medical practitioners, medical authorities, and Commonwealth, state and territory governments made up a small proportion of submissions with the majority of submissions (1017) from or on behalf of Australians who were suffering from chronic debilitating symptoms. Additionally, the committee reported it received over 250 short statements from the families and friends of patients expressing their support for the inquiry and urging changes to better assist patients to access appropriate treatment (Senate Inquiry Interim Report, May 2016).

The Senate Affairs Final Report (November 2016) noted that for clarity, patients [who had provided submissions to the inquiry] were divided into four clear groups:

- those who acquired and were diagnosed with classical Lyme disease in an endemic area;
- those who acquired their illness overseas but weren't diagnosed;
- 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 have not been bitten by a tick or other insect.

Indeed, as referred to above, the committee in its Interim Report (Senate Inquiry, Interim Report, May 2016) noted there was considerable debate in Australia and internationally about the terms 'Lyme disease' and 'Lyme -like-illness' and considered the evidence from submissions and verbal evidence on the differing views on the terms 'classical Lyme disease', 'chronic Lyme disease' and 'Lyme-like illness'.

These various terms used to describe the symptoms experienced or the diagnosis received by Australian patients is of relevance to this literature review as the Interim Report noted the committee heard that patient advocacy groups use the term 'Lyme-like illness' to describe the diagnosis by 'Lyme-literate' practitioners of a range of infections that include *Borrelia,* and co-infections such as *Babesia, Bartonella, Ehrlichia, Anaplasma and Mycoplasma pneumoniae.* Additionally, the report noted that the LDAA, in their submission used the terms 'Lyme disease', Lyme-like-illness' or simply 'Lyme' to describe this diagnosis.

The committee's view was:

> *"The committee recognises that using the terms classical Lyme disease or chronic Lyme disease risks limiting the scope of the committee's inquiry. For the purposes of this inquiry, the committee prefers the use of the term 'Lyme-like illness' to describe the range of chronic debilitating symptoms experienced by submitters. The committee recognises this is not a formal acknowledgement of 'Lyme-like illness' as a single entity, but as a broad descriptor for the possible condition or conditions than manifest in chronic debilitating symptoms".*

The committee, in its Final Report:

> *"Noted the weight of evidence on the relationship between tick bites and people becoming ill".*

1.3. Purpose and scope of this literature review

The Australian Department of Health (the Department) has commissioned Allen and Clarke Policy and Regulatory Specialists Limited (*Allen + Clarke*) to develop an evidence-based clinical pathway and multidisciplinary care model (the Clinical Pathway) for patients suffering from debilitating system complexes attributed to ticks (DSCATT) that can be flexibly applied in both private and public health settings.

The literature review will inform the development of an evidence-based approach to developing a draft Clinical Pathway. The draft Clinical Pathway will then be further developed in consultation with key stakeholders to ensure it is fit for purpose and acceptable to the majority of stakeholders, including the Australian Health Ministers' Advisory Council (AHMAC) and its subcommittees, the Australian Health Protection Principal Committee (AHPPC) and Clinical Principal Committee (CPC).

The Clinical Pathway will contribute to fulfilling the Australian Government's response to Recommendation 5 of the Senate Community Affairs References Committee Final Report: *Inquiry into the growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients,* where the Australian Government agreed to consult with key stakeholder groups to develop a cooperative multidisciplinary framework which can accommodate patient and medical needs. The development of the Clinical Pathway will build on the consultation about the concept of multidisciplinary care previously undertaken through consultation forums with

medical professionals, state and territory health authorities and patient groups in April and July 2018.

This literature review focuses on debilitating symptom complexes attributed to ticks only. As discussed above, the Australian Government has chosen to describe this patient group as having Debilitating Symptom Complexes Attributed to Ticks (DSCATT) with this term being only very recently adopted in Australia. A preliminary PubMed search revealed there is no published academic literature using this term.

For this literature review, therefore, we had to revert to the terminology most commonly used to describe this set of symptoms in Australia and internationally, including Lyme-like disease, Lyme-like illness, chronic Lyme disease and Australian Lyme disease. While extensive literature and literature reviews exist for classical Lyme disease (particularly from Europe and North America), DSCATT and "Lyme-like" disease in the Australian literature is more limited and less restricted to peer-reviewed medical and scientific literature. Additionally, other terms are also used to describe the condition suffered by these patients internationally, including, but not limited to, chronic arthropod-borne neuropathy (in the UK) and multiple systemic infectious diseases syndrome.

This literature review is not a systematic review. No original meta-analysis or other pooled analysis was completed.

We identified and reviewed Australian (as a priority) and international peer reviewed research and evidence-based practice/guideline documents and literature (including primary studies and secondary research) to support the development of the Clinical Pathway, in addition to key documents provided by the Department of Health.

1.4. Ongoing research

[to add in next version]

1.5. Interdependencies

Classical Lyme disease

Regarding classical Lyme disease, the Senate Inquiry Interim Report noted *Lyme borreliosis* is a tick-borne disease caused by various closely related species of *Borrelia* bacteria and is found in parts of the United States, of America, Europe and Asia with the most common vectors of the *Borrelia* bacteria known to cause Lyme disease being the *Ixodes* species of ticks. The committee noted the Scoping Study by McKenzie (McKenzie, 2013) which showed patients with classical Lyme disease commonly display key symptoms depending on the stage of illness: early disease; early disseminated disease; and late stage.

Stage of classical Lyme disease	Key Symptoms
Early disease	Erythema migrans (EM- a rash, sometimes in a bulls-eye shape) and an influenza-like illness
Early disseminated disease	Multiple EMs, meningitis, cranial nerve palsies and carditis
Late stage	Primarily arthritis

The Interim Report noted the submission of the Communicable Diseases Network of Australia (CDNA), a Standing Committee of the Australian Health Protection Principal Committee (AHPPC) which stated classical Lyme disease is a "*well-defined clinical entity*", with a "*clear case definition*", that can be confirmed by laboratory, clinical and epidemiological evidence. The Interim Report also noted the Australian Department of Health's guideline (Lum, Hood, and Wright, 2015) on diagnosing a case of classical Lyme disease acquired overseas in an endemic area.

Chronic Lyme disease

Of chronic Lyme disease, the committee noted in the Interim Report that there is considerable debate, both in Australia and globally about the definition of what some practitioners refer to as 'chronic' Lyme disease, whereas classical Lyme disease is clearly defined. Referring to the Department of Health submission, the Report noted that the controversy about 'chronic' Lyme disease rests on whether or not an ongoing, active *Borrelia* bacterial infection can result in chronic, debilitating symptoms, with the debate divided on two key questions:

- whether the symptoms described as 'chronic' Lyme disease are caused by an ongoing infection with *Borrelia* bacteria; or
- whether these symptoms are the result of a separate condition, or range of conditions, with a different underlying cause such as residual damage from a previous infection.

A brief overview of the differing opinions by submitters from Australia on chronic Lyme disease included:

- the submissions by patient advocacy groups and some medical practitioners in Australia and overseas that argue chronic Lyme disease is caused by an active ongoing *Borrelia* infection, often with a number of other co-infections;
- the submissions by some Australian medical practitioners, such as those associated with the Chronic Infectious and Inflammatory Disease Society (ACIIDS) who argue if classical, or acute Lyme disease is not treated, it can become chronic, and that treatment for 'chronic' Lyme disease is different to classical Lyme disease. The symptoms of Ly
- me-like illness reported in the ACIIDS submission are described later in Section **Error! Reference source not found.**;
- the verbal submission by Dr Gary Lum, Principal Medical Advisor in the Department of Health, who advised Australian medical authorities (like their counterparts in the US) do not support the term 'chronic' Lyme disease and do not accept that the cause is an active, ongoing *Borrelia* infection;
- submissions from Australian medical authorities that do not support the use of the term 'chronic' Lyme disease and do not agree that the chronic debilitating symptoms described by Australian patients are caused by an ongoing infection of *Borrelia* bacteria. Of relevance to this section on differential diagnosis, the committee cited the submission of NSW Health in which the health authority stated:

> *"Although chronic Lyme disease can encompass post-Lyme disease syndrome in regions with endemic B. burgdorferi disease, it also includes a broad array of illnesses or symptom complexes for which there is no reproducible or convincing scientific evidence of any relationship to B. burgdorferi infection. Chronic Lyme disease is increasingly used as a diagnosis for patients with persistent pain, neurocognitive symptoms,*

> *fatigue, or all of these symptoms. With or without clinical or laboratory evidence of previous early or late Lyme disease".*

The Australian Government position on 'chronic Lyme disease' is (Australian Government Position Statement: Lyme disease in Australia):

> *"Some Australians and healthcare providers believe that classical Lyme disease can be acquired from ticks in Australia, or that a form of 'chronic Lyme disease' exists. Globally, 'chronic Lyme disease' is a disputed diagnosis which lack sufficient supporting evidence."*

2. METHODOLOGY

Summary

- This literature review provides an integrative review of the published peer-reviewed literature and grey literature on and relevant to debilitating symptom complexes attributed to ticks (DSCATT). Information was drawn from systematic reviews, narrative literature reviews, RCTs, case-control studies, prospective studies, observational studies, official Australian reports and government inquiries including submissions within relevant Senate Inquiry reports, (inter)national authority and intergovernmental reports and guidelines and international and Australian guidelines produced by clinical and professional bodies.
- As DSCATT was adopted very recently (in 2018) as the term to describe the symptoms suffered by this patient group in Australia, for this literature review we had to revert to the terminology most commonly used to describe this set of symptoms in Australia and internationally, including Lyme-like disease, Lyme-like illness, chronic Lyme disease and Australian Lyme disease.
- This literature review is not a systematic review. We have provided statements about the quality of the evidence included in this review. No primary research or pooled analysis was undertaken.
- The following databases were searched:
  - Discover (CINAHL Complete, Medline and PsycINFO)
  - Cochrane Library database
  - National Institute for Health and Clinical Excellence
  - PubMed
  - ProQuest (including Sociological Abstracts), and
  - Guidelines International Network (www.g-i-n.net) guideline library.
- Additionally, a range of other websites reporting on Lyme-like illness were also reviewed.

2.1. Objectives

This literature review of selected relevant literature and key documents is to support the development of an evidence-based approach to developing the Clinical Pathway. The Clinical Pathway must, at a minimum:

- Assist with a differential diagnosis; including the ruling out of obvious diagnosable conditions, including classical Lyme disease, other tick-borne illnesses and other obvious chronic debilitating conditions.
- Determine the composition of a multidisciplinary care approach or multidisciplinary care team (MDT) in terms of the skill mix required to comprehensively assess patients once obvious diagnosable conditions have been ruled out.

- Provide advice on when a patient should be referred to a multidisciplinary care approach or MDT, for example: the nature/duration of particular symptoms, absence of diagnosis from prior tests, diagnoses previously being considered and excluded prior to referral to MDT.
- Incorporate an agreed primary care management plan for those patients without a diagnosis that includes relevant ongoing support from their GP, allied health, and/or clinical specialists.
- Be flexible enough to be incorporated into existing public and private health care systems.

2.2. Research questions

The research questions were designed to inform the evidence-based approach to the development of the Clinical Pathway for patients suffering with DSCATT. The research questions are based around high-level themes of epidemiology, diagnosis, evidence-based treatment and management and expressed patient needs.

The eight research questions are described in Table 1 below.

Table 1: Research questions

Research questions
Research Question 1 What is the epidemiology of DSCATT in Australia? *Supplementary Questions* • What information is available on the prevalence, demographics and geographic distribution of patients experiencing DSCATT in Australia? • What information is available on the symptoms and clinical signs that have been associated with DSCATT as reported by Australian patients and treating physicians?
Research Question 2 What information is available on diseases or disorders Australian patients experiencing DSCATT symptoms have been diagnosed with and what are the most likely differential diagnoses?
Research Question 3 What are the current issues associated with diagnostic testing for Lyme disease both in Australia and by overseas laboratories?
Research Question 4 What are the treatment modalities that have been provided to patients (including subgroups of patients) with DSCATT in Australia and what is the evidence base to support these treatment modalities?
Research Question 5 What current guidelines and approaches to investigation and ongoing syndromic management of symptoms associated with DSCATT have been found effective internationally?

2.3. Literature search

A detailed description of how the Literature search was conducted can be found in the separate "Literature Search Report". A brief overview of the Literature search is provided below:

- A range of scientific and medical databases were searched between early March and mid-April 2019;
- From the results of the search, literature was prioritised according to a number of criteria, including official Australian reports, published, peer-reviewed literature, currency (published after 1 January 2008), relevance to the primary research questions, and full article available in English language;
- The literature review excluded non-peer reviewed material (other than that associated with the Senate Inquiry and 2018 DSCATT forum reports), any material that did not relate to the research questions, non-English language sources, and material published before 31 December 2007.

[this section to be aligned with literature search report]

3. CLINICAL EPIDEMIOLOGY OF DSCATT AMONG AUSTRALIAN PATIENTS

This section provides the findings of the literature reviewed to answer research question 1:

What is the clinical epidemiology of DSCATT in Australia?

Specifically, we have sought to reveal:

- The prevalence, demographics and geographic distribution of patients experiencing DSCATT in Australia (Section 3.1); and
- The symptoms and clinical signs associated with DSCATT as reported by Australian patients and treating physicians (Section 0).

Set within the context of Lyme-like illness/DSCATT not being clearly defined and not formally reported on in Australia, this section presents the available information and evidence on the epidemiology and symptomology of Lyme-like illness, now described as DSCATT in Australia.

The evidence reviewed, particularly the Senate Inquiry reports, the submissions from patient advocacy groups and patients and further analysis of published submissions, provides some understanding of the self-reported number of patients and geographic location of the patient group suffering with symptoms described as DSCATT.

3.1. Prevalence, demographics and geographic distribution of patients experiencing DSCATT in Australia

Evidence reviewed

To answer the research question '*What information is available on the prevalence, demographics and geographic distribution of patients experiencing DSCATT in Australia?*' we reviewed 13 articles, reports or submissions. Evidence was only included if it specifically related to Australian patients.

Systematic reviews	None
Narrative literature reviews and reviews	1 literature review: Chalada et al. (2016)
Observational studies	6 studies: Brown (2018); Mayne (2015); Mayne et al. (2014); Maud and Berk, 2013; Mayne (2012); Mayne (2011)
Official Australian reports and government inquiries including submissions within relevant Senate Inquiry reports	3 reports: Senate Inquiry Interim Report, May 2016; Senate Inquiry Final Report, November 2016; Commonwealth of Australia, Inquiry into Chronic Disease Prevention and Management in Primary Health Care, May 2016 3 submissions: ACIIDS submission 370, 2016; LDAA submission 528, March 2016; LDAA Supplementary submission, November 2016
(Inter)national authority and intergovernmental reports and guidelines	None

Available statistics on DSCATT prevalence among Australian patients is limited and much of the available evidence is limited to self-reported data

Much of the available information on the prevalence of Lyme-like illness/DSCATT comes from submissions to the Senate Inquiry, particularly from the Lyme Disease Association of Australia (LDAA) and the Australian Chronic Infectious and Inflammatory Disease Society (ACIIDS).

The Senate Community Affairs Reference Committee (the committee) requested submissions include information on the prevalence and geographic distribution of Lyme-like illness in Australia. In reporting on the findings from submissions the committee noted the prevalence of Lyme-like illness in Australia:

> *"As Lyme-like illness is not clearly defined and not formally reported on, available statistics on its incidence in Australia are limited. The committee notes that there is no official data on the number of classical Lyme disease cases acquired overseas or Lyme-like illness acquired in Australia".* (Senate Inquiry Interim Report, May 2016)

This statement was informed by:

- the submission from the Communicable Diseases Network Australia (CDNA) which advised it had reviewed whether Lyme disease should be added to the National Notifiable Diseases List, with the Joint Criteria Assessment Group having concluded that *"…inclusion was not warranted as Lyme disease did not satisfy a majority of the endorsed criteria and there was no definitive evidence of Lyme disease being acquired in Australia"*; and
- the submissions by medical authorities, including the Victorian Department of Health and Human Services, in which medical authorities stated *"that without a clear and agreed definition, the prevalence of Lyme-like illness cannot be accurately estimated"*.

It is noted that the submissions by patient advocacy groups stated that "*Lyme-like illness should be made a notifiable disease, and that the CDNA decision should be reviewed in light of the increasing number of patient groups being diagnosed with the condition*" (Senate Inquiry Interim Report, May 2016).

As noted in the Introduction, the Senate Inquiry received over 1200 submissions, with the majority of submissions (1017) from or on behalf of Australians who were suffering from chronic debilitating symptoms.

Analysis of those submissions, as reported by the LDAA in their supplementary submission to the Senate Inquiry and in the published paper by Brown (2018), provides additional insight into the prevalence, gender and geographic distribution of DSCATT among Australian patients. Also in 2016, the House of Representatives Standing Committee into Health 2016 included a Case Study on Tick-borne and Lyme-like diseases in its inquiry and report 'Inquiry into Chronic Disease Prevention and Management in Primary Health Care' (May 2016), which, like the Senate Inquiry, considered and reported on evidence from a number of submitters.

Additional information that contributes to the evidence base on the prevalence of Lyme-like illness comes from the published, peer reviewed paper by Chalada et al. (2016) in which the authors reviewed cases of Lyme-like illness reported in the literature between 1982 and 2015.

The available evidence on prevalence overall is presented in this subsection, with relevant information on gender and geographic distribution from the submissions and submissions analysis, and published papers presented later.

Key findings about prevalence, demographics and geographic distribution of DSCATT in Australia

- As Lyme-like illness (DSCATT) is not clearly defined and not formally reported, available statistics on its prevalence among Australian patients is limited, with much of the available evidence being self-reported.
- Reported prevalence and prevalence estimates for Lyme-like illness/DSCATT among Australian patients varies widely, ranging from hundreds to many thousands affected, through to an 'undiagnosed epidemic'.
- Submissions and analysis of submissions indicate that, while children and adults of all ages report having been diagnosed with Lyme-like illness/DSCATT, the illness appears to be more common in adults around the age of 40 years and more common among females.
- No information is available on the ethnicity of patients with DSCATT.
- The majority of patients diagnosed with Lyme-like illness reported they had never left Australia.
- Evidence was analysed on over 500 reports of Lyme-like cases in Australia between 1982 and 2015. This analysis showed that the diagnostic methods in the published case reports were unreliable, and therefore the evidence for Australian Lyme-like cases remains "*quite unsubstantial and unconvincing.*"
- While evidence suggests cases of Lyme-like illness/DSCATT have been reported across all States and Territories, DSCATT appears to consistently be most prevalent in New South Wales, with Queensland, Western Australia and Victoria also affected but to a lesser degree.

3.1.1. Prevalence

Reported prevalence and prevalence estimates vary widely ranging from hundreds to many thousands affected through to an 'undiagnosed epidemic'

The reported prevalence and prevalence estimates vary widely, primarily depending on the source of the information. In addition, much of the data collected is subject to significant limitations, which makes the reliability of reporting questionable.

More than 500 cases of Lyme-like illness have been reported in the scientific literature over the last 25 years; however, the evidence for Australian Lyme-like illness remains quite unsubstantial and unconvincing

The highest level of evidence reviewed in this section was the literature review by Chalada and colleagues (Chalada et al. 2016) who undertook a review of 156 papers to assess the current situation of the *"controversial Lyme or Lyme-like illness reported by some to be present in Australia".* This review contains findings of relevance to many of the sections in this literature review. Of relevance to this research question on the prevalence of DSCATT among Australian patients, Chalada and colleagues undertook a literature search that included only Academic Journals to review the evidence on Lyme-like cases reported in Australia. They identified 10 papers published between 1982 and 2015 in which they reported at least 525 human cases [79-82, 84-89] and two bovine cases [28] of Lyme-like illness have been mentioned in the scientific literature.

In the Abstract, Chalada and colleagues stated:

> *"In the last twenty-five years there have been over 500 reports of an Australian Lyme-like syndrome in the scientific literature. However, the diagnoses of Lyme Borreliosis made in these cases have been primarily by clinical presentation and laboratory findings of tentative reliability and the true cause of these illnesses is unknown"* (Chalada et al. 2016)

The studies in reviewed by Chalada et al. (2016) are outlined in

Table 2 below for completeness, noting that several of them are outside the timeframe for this literature review. While they have not been reviewed again for the purpose of this report, they are important to recognise.

Table 2: Studies reviewed by Chalada et al. (2016)

Date	Title	Author and publication
2015	Clinical determinants of Lyme Borreliosis, babesiosis, bartonellosis, anaplasmosis, and ehrlichiosis in an Australian cohort.	P.J. Mayne Int. J. Gen. Med. 8 (2015) 15.
2014	Evidence for Ixodes holocyclus (Acarina: Ixodidae) as a vector for human Lyme Borreliosis infection in Australia.	P. Mayne, S. Song, R. Shao, J. Burke, Y. Wang, T. Roberts J. Insect Sci. 14 (2014) 271.
2013	Neuropsychiatric presentation of Lyme disease in Australia.	C. Maud, M. Berk. Aust.N. Z. J. Psychiatry 4 (2013) 397–398
2012	Investigation of Borrelia burgdorferi genotypes in Australia obtained from erythema migrans tissue.	P.J. Mayne Clin. Cosmet. Investig. Dermatol. 5 (2012) 69.
2011	Emerging incidence of Lyme Borreliosis, babesiosis, bartonellosis, and granulocytic ehrlichiosis in Australia.	P.J. Mayne Int. J. Gen. Med. 4 (2011) 845.
1998	Culture-positive Lyme Borreliosis.	B.J. Hudson, M. Stewart, V.A. Lennox, M. Fukunaga, M. Yabuki, H. Macorison, et al., Med. J. Aust. 168 (1998) 500–503.
1987	Lyme Borreliosis — A Case Report for Queensland.	N. Stallman, 21CDI, 1987 8–9.
1986	Lyme disease on the NSW central coast.	R. Lawrence, R. Bradbury, J. Cullen, Med. J. Aust. 145 (1986) 364.
1986	Lyme disease on the NSW south coast.	McCrossin Med. J. Aust. 144 (1986) 724.
1982	Lyme arthritis in the Hunter Valley.	Stewart, J. Glass, A. Patel, G. Watt, A. Cripps, R. Clancy Med. J. Aust. 1 (1982) 139.

Chalada et al. (2016) noted in their literature review that the majority of the reported cases were Lyme-*like* cases that were suspected, but not confirmed, to represent cases of Lyme Borreliosis, and cautioned that:

> *"Unreliability of the published case reports in their diagnostic methods means the evidence for Australian Lyme-like cases remains quite unsubstantial and unconvincing".*

Official reports and some medical professionals also conclude that the incidence of tick-borne or Lyme-like illness in Australia is difficult to determine

In 2016, the House of Representatives Standing Committee into Health included a Case Study on tick-borne and Lyme-like diseases in its inquiry and report 'Inquiry into Chronic Disease Prevention and Management in Primary Health Care' (Commonwealth of Australia, Inquiry into Chronic Disease Prevention and Management in Primary Health Care, May 2016). The committee reported on evidence from a number of submitters and concluded the incidence of tick-borne or Lyme-like illness in Australia is difficult to determine. Informing this conclusion were:

- the submission by Dr Richard Schloeffel who identified a "tentative projection of 102,000 [people] in Australia with chronic borrelial infection", that "we have no idea how many people may have symptoms that fit this category" and that he currently has "400 patients with borreliosis or related illnesses";
- the submission by the Karl McManus Foundation which stated that *"part of the difficulty of determining incidence of tick-borne or Lyme-like diseases is due to the non-specific symptoms and unreliable diagnostics of these diseases"*;
- the submission by the Department of Health which included that tick-borne or Lyme-like disease had previously been assessed and was not added to the list of nationally notifiable diseases due to a lack of a good case definition and consensus about the cause of the disease, and
- the submission by the Royal Australian College of General Practitioners (RACGP) that indicated it could not know how widespread tick-borne or Lyme-like disease is as no research had been undertaken into the disease in the Australian context.

At the April 2018 Forum, Professor Lindsay Grayson, Director, Department of Infectious Diseases & Microbiology, Austin Health, University of Melbourne presented on 'A multi-dimensional program for patients with "Lyme-like" illness and reported 'the Austin experience with "LLI"' involved more than 50 patients [exact numbers not provided]. Professor Grayson reported that of the patients in the program,

> *"Australian Reference Lab results – 1-2 +ve for borreliosis"*

No further information was provided in the presentation as to whether these patients had travelled to endemic areas for classical Lyme disease.

While this presentation provides some insight into numbers of patients with Lyme-like illness investigated in the Austin Health program there was no further information about whether the patients in the program were only from Melbourne or wider Victoria, or from other jurisdictions.

There is no official data to qualify the size of the 'Lyme' problem in Australia, but data from some patient advocacy groups and doctors indicate that there could be "*undiagnosed epidemic*"

Well prior to the Senate Inquiry, the LDAA published the report 'Lyme disease: Australian patient experience in 2012', noting this was the first report to examine the Lyme disease situation in Australia from a patient perspective (. The report presented the findings of an online survey conducted by the LDAA from 1 July 2011 to 26 July 2012 and was summarised in the LDAA's submission in March 2016 (LDAA, Submission 528, March 2016).

This report indicated that in 2012, out of a total of 339 respondents, 224 reported they resided in Australia and as of July 2012 had been formally diagnosed with Lyme disease. The LDAA promoted the survey on its own News page, through its emailing list and posting links on the LDAA Facebook group page. Additionally, online support groups 'AussieLyme' on Yahoo; 'Aussie Lyme' and 'Lyme Australia and Friends' on Facebook posted information about the survey and provided survey links to their members. Participation, while voluntary, was limited to those who could access the survey online, with no paper surveys provided to respondents.

In March 2016, in their submission to the Senate Inquiry, regarding information on prevalence, the LDAA noted there is no official data to help quantify the size of the 'Lyme' problem in Australia, and that (LDAA, March 2016):

- "*For four years the LDAA been working to highlight the plight of more than a thousand people who have been diagnosed with an illness that resembles Lyme disease*";
- "*…the LDAA's work must be counted as the evidence*"; and
- "*Our data suggests we are looking at a large scale undiagnosed epidemic*".

Similarly, regarding the prevalence of Lyme-like illness, ACIIDS stated that: "*[i]t is difficult to gauge the prevalence of this illness in Australia*" and estimated that there are *"tens of thousands of patients in Australia suffering from this illness"* (ACIIDS, Submission 370).

The LDAA reported it had been collecting and compiling Australian data since 2011 to establish the prevalence of Lyme-like illness through detailed on-line surveys. Survey respondents were restricted to those who had been diagnosed with a Lyme -like illness by a medical practitioner.

While ACIIDS reported that many people are becoming unwell, sometimes very unwell, after a tick bite in Australia, the Society also noted most people who are bitten by a tick in Australia do not develop Lyme-like illness and that *"ACIIDS believes the proportion of Australian ticks that carries the causative organism is small".*

In their submission, the LDAA reported that since 2012, 1,051 patients reported having this illness.

The LDAA and ACIIDS presented further evidence to support the incidence of Lyme-like illness in Australia, including:

- ACIIDS doctors at the time of the submissions actively treating Lyme-like illness reported their case load was in the order of 1,500 patients and that ACIIDS doctors had treated over 4,000 patients for Lyme-like illness. The ACCIDS submission went on to report that most of these patients had positive blood tests for Borrelia in Australia and/or overseas laboratories (noting the overseas laboratories were fully accredited in their respective countries);

- ACIIDS also noted that they have treated approximately 300 patients with positive tests for Borrelia who have never left Australia;
- in addition to the patients treated by members of ACIIDS, ACIIDs reported there are other patients who have been treated by doctors who are not members of ACIIDS, patients who have been incorrectly diagnosed with other illnesses by other doctors, and patients who have sought help from naturopaths rather than doctors;
- the LDAA had seen an increase of over 400 percent of 'followers' in the two years since the organisation started tracking its Facebook page, with 10,795 'followers' in January [2016];
- the LDAA answer more than 280 emails per month generally to support patients who are newly diagnosed with Lyme-like illness; and
- the LDAA asserted that Australia's incidence of tick-borne illness be placed in the context of the international Lyme epidemic, noting that the Centers for Disease Control (CDC) had revised its annual estimate of Lyme disease cases in the USA from 30,000 to 300,000 in 2013, an increase of 900 percent.

Dr Richard Schloeffel, OASM, Prymble Grove Health Centre, in his presentation on Vector-borne disease (VBD) in Australia (at the April 2018 Forum), noted VBD is one of the fastest growing diseases internationally. Regarding prevalence of VBD in Australia, Dr Schloeffel reported:

- over 4,000 patients had been treated by ACIIDS doctors over the past six years;
- 1,500 patients were currently under treatment with thousands on wait lists; and
- undiagnosed cases may exceed tens of thousands.

The LDAA provided its estimate of the number of Lyme-like cases in Australia based on several scenarios involving international prevalence and incidence rates for Lyme disease. The LDAA's estimates are summarised in Table 3 below. Based on the CDC's revised annual estimate of Lyme disease cases in the USA, the LDAA estimated that if the 900 percent increase was to be applied to the current 'self-reporters' (1,051 as per the LDAA's 2013/14 data as described above), there would be 9,459 cases of Lyme-like illness in Australia per year and "*that is on the low end of the scale*".

Table 3: LDAA estimates of Lyme-like illness in Australia based on international estimates

Applying international estimates	LDAA's estimates of Lyme-like illness in Australia
CDC: 900 percent increase in Lyme disease	9,469 cases per year
Prevalence rate of Lyme disease reported in the USA	Up to 426,542 Australians with Lyme disease over the last 20 years Equals 1.78% of the population = 22,656 cases annually in 2015 (16,539 female; 6,117 male)
Incidence of Lyme disease in other countries – mean incidence of 5.804% in 39 countries examined by the LDAA	Potential estimated incidence rate of 1.3 million people in Australia with Lyme-like illness

Limitations to the data collected means that prevalence reports and estimates are not reliable

While the LDAA report does provide analysis of data from 224 respondents (LDAA, March 2016), from the promulgation of the survey, along with the survey being limited to participants who could access the survey online, the methodology would highly likely impact on the representativeness of the survey findings. The LDAA noted the limitations of the survey being restricted to people who have online access and that a cohort of patients may therefore be missed, and commented of these findings that:

> *"Our data under-reports the growing incidence of Lyme-like illness in Australia; we believe these figures to be the tip of the iceberg when it comes to the real incidence of Lyme-like illness in Australia".*

Analysis of submissions indicates that several hundred people are affected by tick-borne illness

Two analyses of submissions made by patients to the Senate Inquiry have been undertaken.

The LDAA provided a Supplementary Submission to the Senate Inquiry in November 2016 (LDAA, Supplementary Submission, November 2016), where the organisation presented an analysis of a subset of submissions made to the Senate Inquiry. The LDAA's analysis included 432 (34 percent) of the 1268 submissions, of which 349 were made by individuals who either provided their names or withheld their names.

In 2018, Brown reviewed and analysed responses of all public, first-person submissions made to the Australian Senate Inquiry in 2016 to describe the epidemiology, symptoms and outcomes of patients diagnosed and treated with Lyme disease in Australia (Brown, 2018). While not a prevalence study, the number of published submissions to the Senate Inquiry from Australian people who identified as suffering from Lyme disease or Lyme-like illness was 698 in 2016, indicating that several hundred people are affected.

3.1.2. Demographics

Additional detail from studies published after 2008 and reviewed by Chalada et al (2016) are described below, particularly where there was relevant information about patient characteristics.

Evidence indicates that DSCATT is more common in adults around the age of 40 years

A patient advocacy survey, submissions and analysis of submissions indicate that while Lyme-like illness/DSCATT has been reported to affect all age groups, it is more common in adults around the age of 40 years, and is more common among females, but little is known about children.

The LDAA reported that of the 224 respondents who reported they resided in Australia and as of July 2012 had been formally diagnosed with Lyme disease, the majority were female (73 percent), and predominantly adults over 18 years of age (90 percent) with the highest proportion being 46 or older (LDAA, March 2016), as shown in Table 4 below.

Table 4: Age and gender profile of respondents

Age groups	Female	%	Male	%	Total	%
0-18	16	7.14%	6	2.68%	22	9.82%
19-35	22	9.82%	11	4.91%	33	14.73%
36-45	53	23.66%	8	3.57%	61	27.223%
46-55	42	18.75%	21	9.38%	63	28.13%
56 and over	31	13.84%	14	6.25%	45	20.09%
Total	**164**	**73.21%**		**26.79%**	**24**	**100.00%**

Source: Table 1 page 10 LDAA 2012

Regarding children, the LDDA's survey revealed that in 2012, the lowest prevalence of diagnosed Lyme disease was among children aged 0 to 18 years. The LDAA commented the figures reported in their survey varied widely compared to other parts of the world where the Lyme disease age and gender profile is different, particularly in relation to children, and that "*it is highly probable that children are underrepresented in this survey*". The LDAA also noted that as the data collection method for the survey was online only, it was likely to be skewed to females due to the preponderance for female participation in social networking sites, citing evidence for this (LDAA, march 2016)

In their submission, the LDAA reported that since 2012, 1,051 patients reported having this illness (LDAA, March 2016). The prevalence data by age group as reported by the LDAA is presented below in

Table 5, with additional analysis undertaken for this literature review to assess the proportion of patients reported having this illness by age group.

Table 5: Age profile of Australian patients

Age group (years)	Total	Proportion of patients by age group
0-18	**87**	**8.3%**
19-35	**237**	**22.5%**
36-45	**265**	**25.2%**
46-55	**259**	**24.6%**
56 and over	**203**	**19.3%**
Total	**1051**	**99.9%**

Source: Figure 2 page 13 LDAA March 2016

It appears from the LDAA survey data that the prevalence among patients aged between 36 to 55 years is slightly higher than those aged 19-35 years and 56 years and over; however, the proportion of patients from 19 to 56 years and over is relatively similar. While patients under 18 years had the lowest prevalence at 8.3 percent, this does indicate that nearly one in ten participants in the LDAA survey were children. The prevalence of Lyme disease among children aged 0-18 years in this later survey by LDAA is lower (8.3 percent) than findings reported for the same age group in the 2012 LDAA survey in which 9.82 percent were reported to have been diagnosed with Lyme disease (LDAA, March 2016). As noted above, the LDAA had raised the high probability that children were underrepresented in their 2012 survey; either the proportion of children with a diagnosis of Lyme disease in this age group has reduced between 2012 and 2014 or the lower prevalence is due to lower participation by patients in this age group or their families reporting for them.

Evidence also indicates that DSCATT may be more common among females, although this could be due to data gathering methods

Of the survey data collected, the LDAA noted 73 percent of affected patients were female and 27 percent were male. The LDAA noted that studies of the prevalence of Lyme disease in the USA [not further defined] indicate a similar gender discrepancy to the LDAA data of Australian patients but that there had been no international study at the time the LDAA presented their submission that might explain the gender discrepancy. Table 6 below reproduces data presented in the LDAA submission (LDAA, March 2016).

Table 6: Demographic profile of Australian patients

Age group (years)	Female	Male
0-18	55	32
19-35	177	60
36-45	217	48
46-55	177	82
56 and over	138	65
Total	**764**	**287**

Source: Figure 2 page 13 LDAA March 2016

In the LDAA's supplementary submission to the Senate Inquiry described previously (LDAA, Supplementary Submission, November 2016), where the organisation presented an analysis of a 432 (34 percent) of the 1268 submissions made to the Senate Inquiry, LDAA classified the gender of 160 of the 349 individual submitters. The majority (120, 75 percent) were female.

In the submissions analysed by Brown, less than half of patients (259, 37.2 percent) reported data about their age (Brown, 2018). Of those who did, ages ranged from 15 to 84 years with the median age of patients suffering from Lyme disease being 44 years (Brown, 2018). While this data provides some insight into the ages of patients affected by DSCATT, given the majority (62.8 percent) of submissions did not include data on age, the findings regarding age should be taken cautiously and may not be representative of patients with Lyme-like illness/DSCATT generally.

In Brown's analysis, just over half of all submissions (381, 54.6 percent) were from females, 13.3 percent (93) were from males and about one third (32.1 percent) were from patients who did not disclose their sex. Where data on sex was reported, most (381, 80.4 percent) submissions were from females, with only 19.6 percent (n=93) being from males. Brown noted submissions had *"a striking female preponderance"*.

Regarding the high proportion of Australian females represented in the submissions to the Senate Inquiry, Brown cited evidence published in 2013 and 201, that indicated Lyme disease has a slight male preponderance in endemic areas, with Brown noting this was most likely attributed to males being more likely to engage in at risk occupations or hobbies. This comment by Brown is in contrast to that of LDAA noted earlier in which LDAA reported studies of the prevalence of Lyme disease in the USA [not further defined] indicate a similar gender discrepancy to LDAA data of Australian patients (the higher prevalence among females).

Brown's analysis revealed most (58.8 percent) of submissions did not comment on a tick bite, but where submitters did comment, the majority (257, 89.5 percent) reported a positive history.

Table 7 below presents Brown's analysis on the characteristics of patients who made submissions to the Senate Inquiry.

Table 7: Analysis of patient demographics

	Number (%) or median (range) of all patients	Number (%) of patients who reported data
Age	44 (range 15-84)	259 (37.2%)
Sex		
Male	93 (13.3%)	93 (19.6%)
Female	381 (54.6%)	381 (80.4%)
Tick bite		
Yes	257 (36.9%)	257 (89.5%)
No	30 (4.3%)	30 (10.5%)

In the literature review by Chalada et al. (2016) described earlier, the largest study of Lyme-like illness in Australian reviewed by the authors was the paper by Mayne published in 2015, in which he examined the clinical presentation of Lyme borreliosis, babesiosis, bartonellosis, anaplasmosis and ehrlichiosis from patient records of 500 across all states in Australia over the course of five years. In his paper Mayne reported the majority of patients were female (62 percent), with the

average age of onset being in the mid-thirties and average age at presentation being 41 years (Mayne, 2015).

The epidemiological parameters Mayne extracted from the dataset are presented below (Mayne, 2015)

Table 8: Epidemiological parameters

Demographic, epidemiologic, and clinical parameters	Number	Percentage	Total number
Age at presentation	Average = 41 years Median = 42 years Standard deviation = 18 years		500
Age at onset of illness	Average = 35 years Median = 35 years SD = 9.5 years		500
Sex, female	310	62%	500
Tick bites recorded	240	71%	340

The other recent studies reviewed by Chalada et al. (2016) on cases of Lyme-like illness involved small or relatively small numbers of patients and are discussed in the next section on geographic distribution and reported location of acquisition.

3.1.3. Geographic distribution and reported location of acquisition

DSCATT appears to consistently be most prevalent in New South Wales, with Queensland, Western Australia and Victoria also affected but to a lesser extent

The Senate Inquiry Interim Report noted that most submissions from patients who were experiencing chronic debilitating conditions came from NSW, Queensland, Victoria and Western Australia (Senate Inquiry, Interim Report, May 2016).

The table below outlines the distribution by jurisdiction of 1017 submitters to the Senate Inquiry and is reproduced from the Senate Inquiry Interim Report. The report notes that this number indicates those submitters who provided their postal address and whose submissions were accepted and published by 30 April 2016. This includes all submissions from each jurisdiction, including over 900 personal submissions, 28 submissions from organisations and a number of submissions from medical practitioners.

Table 9: Geographical distribution of submissions by jurisdiction at 30 April 2016

Jurisdiction	Number of submissions	Proportion of total submissions (%)
NSW	344	34.1
Queensland	201	19.9
Victoria	200	19.8
Western Australia	193	19.1
Other (SA, ACT, NT, Tasmania)	71	7.0
Total	**1,009**	

Source: Page 13 Senate Inquiry Interim Report 2016

In the 698 first-person published submissions to the Senate Inquiry reviewed by Brown and described above, the majority of patients (477, 68.3 percent) who provided submissions reported data about the location they acquired DSCATT with all states and territories implicated but to varying degrees. New South Wales, Queensland, Western Australian and Victoria had the highest reported prevalence for acquisition at 38.3 percent, 22.2 percent, 15.9 percent and 11.8 percent respectively. Only 9.5 percent of patients reported they had acquired their Lyme disease or Lyme-like illness overseas, as shown in

Table 10: Location of illness acquisition

Table 10: Location of illness acquisition

Location acquired*	Number (%) of all patients	Number (%) of patients who reported data
Any	477 (68.3%)	477 (100%)
NSW	185 (26.5%)	185 (38.3%)
QLD	106 (15.2%)	106 (22.2%)
WA	77 (11.0%)	77 (15.9%)
Vic	57 (8.2%)	57 (11.8%)
Tas	6 (0.9%)	6 (1.2%)
NT	6 (0.9%)	6 (1.2%)
SA	3 (0.4%)	3 (0.6%)
Overseas	46 (6.6%)	46 (9.5%)

*Seventeen reported more than one possible location and were counted in each location
Source: Table 1 page 424 Brown 2018

While the data on distribution by jurisdiction in the Senate Inquiry Interim Report presented above is reasonably concordant regarding prevalence pattern with the findings of Brown (2018), Brown's analysis was based on a portion (n= 698) of the submissions to the Senate Inquiry, and only on first-person submissions by patients who identified as suffering from Lyme disease or Lyme-like illness. In Brown's analysis, the proportion of submissions from patients in Victoria appears to be about eight percentage points lower than in the proportions of submissions in the Senate Inquiry reported data, above.

In their 2012 report, the LDAA presented data on locality of acquisition of respondents who reported they resided in Australia and as of July 2012 had been formally diagnosed with Lyme disease (LDAA, March 2016)

Of the participants who reported they recalled a tick or other bite, 133 respondents (79 percent) indicated they were bitten in Australia. Figure 1 below reports the geographic locations of bites as reported by respondents.

Figure 1: Geographic locations when bitten

Source: Figure 3 Page 13 LDAA 2012

Table 11 below presents data on the number of respondents who reported being bitten by a tick or experiencing another bite, by state.

In 2012, nearly six out of ten respondents (59 percent) reported being bitten in New South Wales, while just over a quarter (27 percent) reported being bitten in Queensland.

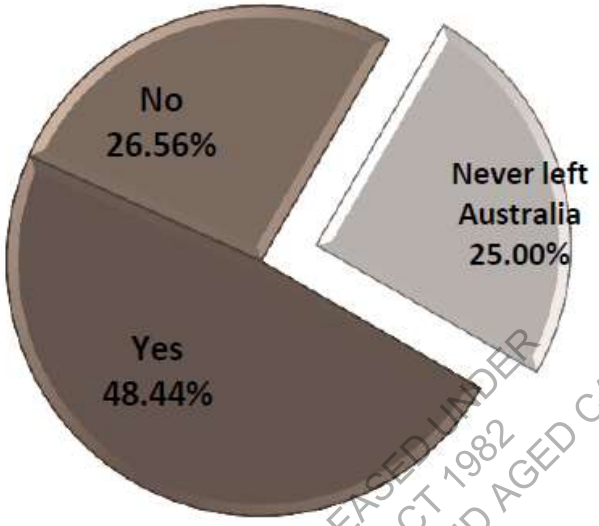
Table 11: Respondents who reported tick bites by state

State	Respondents
NSW	78
QLD	36
WA	10
Vic	6
NT	2
Tas	1
Total	**133**

Source: Figure 3 Page 13 LDAA 2012

Of the respondents who reported being bitten by a tick or other vector and who reported they were bitten in Australia, about half (66, 51.5 percent) reported 'No' when asked if they had ever been out of Australia prior to becoming ill, while 62 (48.4 percent) reported they had been out of Australia prior to becoming ill. Additionally, LDAA reported exactly 25 percent of respondents reported never leaving the country. Figure 2 shows the stakeholders who reported that they had left Australia.

Figure 2: Travel status of Australian Lyme patients



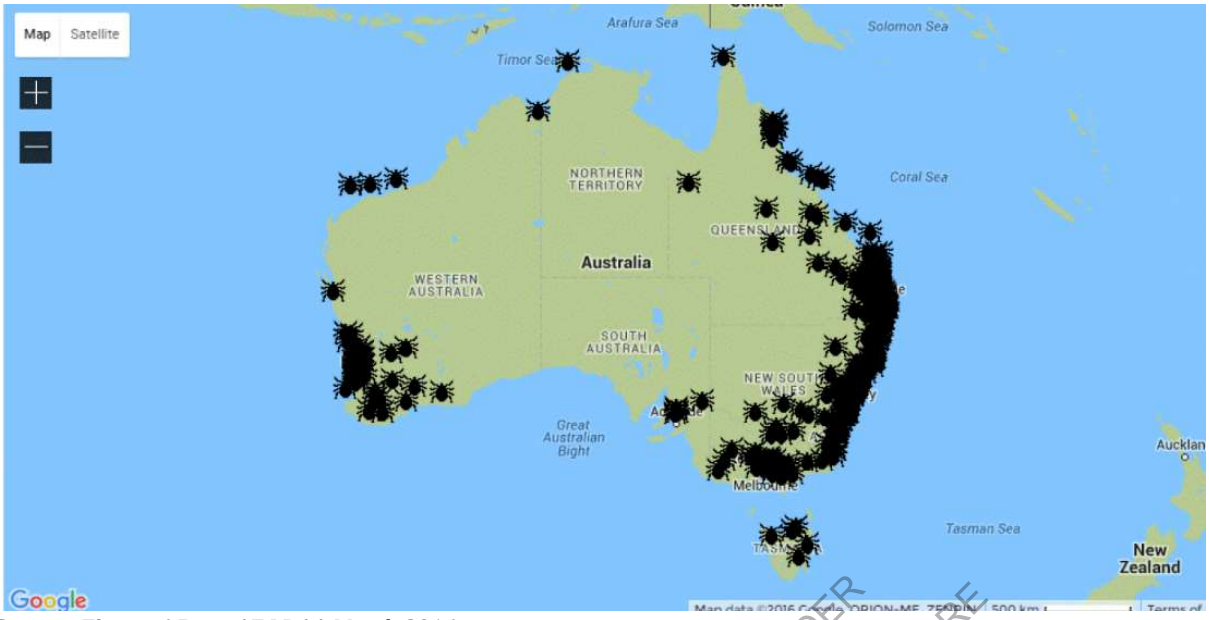
Source: Figure 3 Page 13 LDAA 2012

The LDAA's survey revealed that in 2012 there was a cohort of patients in Australia with 'overseas' acquired Lyme disease, 35 respondents (20.8 percent) having reported being bitten while travelling overseas (14 in Europe; 11 in America (North); six in Asia; two in Africa; and two in Oceania). The LDAA noted that this cohort of patients *"are in the minority (21%) of Australian patients who participated in the survey"*.

In their submission to the Senate Inquiry (LDAA, March 2016), the LDAA provided a tick plot map from data collected in their Lyme disease count survey (shown below at Figure 4). The tick plot map showed the geographical spread of Lyme -like disease in Australia and the distribution of ticks where people reported they acquired a tick bite that led them to becoming ill.

The LDAA noted that the tick plot map provided in their submission included 910 bite locations, and that plot data had increased by 143.97 percent since they commenced mapping in early 2014. The LDAA also noted that from their surveys 684 (68 percent) of people had told the LDAA that they knew of other people in their area who have been diagnosed with a Lyme-like illness.

Figure 3: Location of reported tick bites from patients with Lyme disease



Source: Figure 6 Page 17 LDAA March 2016

The LDAA reported in their Supplementary Submission (LDAA, November 2016) they documented any place of acquisition of Lyme -like illness reported in the submissions reviewed and classified the location by state in their analysis of 349 individual submissions to the Senate Inquiry (described earlier). The LDAA reported the majority of submitters (199, 73 percent) stated they had acquired their illness in Australia, while a smaller number of submitters (37, 13 percent) reported they acquired their illness overseas or reported the location of their acquisition of a Lyme-like illness was unknown (37, 13 percent).

Table 12: Acquisition of illness by location

Place of Acquisition	Total
NSW	75
VIC	19
QLD	58
SA	2
WA	26
NT	2
TAS	4
Australia (State unknown)	13
USA	16
Europe	8
Asia	6
Africa	2
Pacific	3
Unknown	37

While ACIIDS noted in their submission and reported above, that is was difficult to gauge the prevalence of Lyme-like illness in Australia, the Society reported Lyme-like illness is most common on the east and west coasts, but confirmed cases have been reported from every state and territory (ACIIDS, Submission 370, March 2016).

Chalada and colleagues in their review of the literature on Lyme-like cases reported in Australia described earlier provided a map of locations of Lyme-like cases reported in the scientific literature. As reported above, Chalada et al. identified that at least 525 human cases and two bovine cases of Lyme-like illness have been reported in the literature dating back to 1982. Figure 4 is reproduced from Chalada et al (2016). The authors noted that only the Lyme-like cases with specified locations were included in the diagram. The majority of cases were in NSW.

Figure 4: Locations of Australian Lyme-like cases published in the scientific literature. 🟢 Specific location based on town, suburb or GPS coordinates. 🟩 Approximate location based on broad location description, e.g. "rural Victoria" or "Hunter Valley"

Source: Figure 1 Page 145 Chalada et al. 2016

Chalada et al. also outlined information on location of cases of Lyme-like illness as reported in the literature reviewed, shown below in Table 13. The majority of cases from 1982 onwards are located in NSW.

Table 13: Lyme-like illness reported in literature

Reference	Location
Mayne (2011)	4 cases: NSW; Armstrong beach, Queensland; Queensland; Mid-north coast of NSW
Maud and Burk (2013)	Rural Victoria
Mayne (2012)	4 cases: 152.8E, 31.32S; 151.3E, 33.74S; 152.7E, 31.73S; 152.8E, 31.66S
Hudson et al. (1998)	Pittwater Shire, Sydney
Lawrence et al. (1986)	Gorokan, NSW
McCrossin (1986)	2 cases: North Bendalong (between Nowra and Ulladulla), NSW; Geurilla Bay near Moruya, NSW
Stewart et al. (1982)	Lower Hunter Valley, NSW

The study by Mayne in 2015 was a large study, and the author concluded *"the study suggests there is considerable presence of borreliosis in Australia and a highly significant burden of coinfections accompanying borreliosis transmission"*, only 83 (17 percent) of the cohort reported never leaving Australia (Mayne, 2015).

The study by Mayne et al. (2014) involved two patients who presented to the lead author's medical practice in New South Wales in 2012 with erythema migrans and attached ticks. No further information about the two patients was however, provided in the paper (Mayne et al., 2014).

The correspondence article by Maud and Berk (2013) on neuropsychiatric presentation of Lyme disease in Australia presented the case of an 18-year-old woman who had always lived with her parents in rural Victoria and who had been actively involved in caring for the animals and was a keen horsewoman. The patient was reportedly tested for Lyme disease amongst other laboratory tests and diagnosed with Lyme disease (results: B. burgdorferi IgG titre = 80 and IgM titre = 10), the authors reporting that this indicated past Lyme disease (Maud and Berk, 2013).

The study by Mayne published in 2012 involved four patients who presented to the author's medical practice in New South Wales, over a one-year period from mid- 2010 to mid-2011. No information about patient's age or gender was provided (Mayne, 2012).

In the 2011 paper by Mayne, the author used serology and molecular testing to investigate the incidence of *Borrelia burgdorferi*, and *Babesia, Bartonella* and *Ehrlichia* species (spp) among 51 patients who had either self-referred or were referred to his medical practice. While no information about age or gender of patients was provided, Mayne did report on four patients who reported never having travelled outside Australia, one of whom was a child (no age given) and three of whom were adults (no age given) (Mayne, 2011).

3.2. Symptoms and clinical signs associated with DSCATT

As noted in the preceding section on prevalence, demographics and geographic distribution of patients experiencing DSCATT in Australia, the situation with DSCATT is complex. The Australian Government in its Position Statement: Debilitating Symptom Complexes Attributed to Ticks notes that the illness experienced by patients with debilitating symptom complexes is poorly understood, making accurate diagnosis and treatment difficult and that because of the imprecise nature of the symptom complexes some patients will remain undiagnosed. (Australian Government Position Statement: Debilitating Symptom Complexes Attributed to Ticks, 2018)

Evidence reviewed

To answer the research question *'What information is available on the symptoms and clinical signs that have been associated with DSCATT as reported by Australian patients and treating physicians?'* we reviewed 10 articles, reports or submissions. Evidence was only included if it specifically related to Australian patients.

Systematic reviews	None
Narrative literature reviews and reviews	1 literature review: Chalada et al. (2016)
Observational studies	2 studies: Brown (2018); Mayne (2015)
Official Australian reports and government inquiries including submissions within relevant Senate Inquiry reports	2 reports: Senate Inquiry Interim Report, May 2016; Senate Inquiry Final Report, November 2016; 3 submissions: ACIIDS submission 370, 2016; LDAA submission 528 March 2016; LDAA Supplementary submission, November 2016
(Inter)national authority and intergovernmental reports and guidelines	1: Australian Government Position Statement: Debilitating Symptom Complexes Attributed to Ticks, 2018

In the available literature reviewed, symptoms and clinical signs are often combined. Furthermore, symptoms and signs can be more specific to acute illness, often following a tick bite, or more related to chronic debilitating illness, or both, for some symptoms. Therefore, we have provided a general overview of the findings on symptoms and signs and followed this, where possible, with more specific findings on symptoms and clinical signs associated with acute illness and with chronic illness.

Key findings on the symptoms and clinical signs associated with DSCATT reported by Australian patients and treating medical professionals

- Overall, evidence from patients, analysis of submissions and treating medical professionals highlights that while some patients experience acute symptoms, particularly after a tick bite, **most patients suffering from DSCATT are experiencing chronic debilitating symptoms.**
- According to analysis of over 600 patient submissions patients suffering Lyme-like illness often experience a range of symptoms and signs; while patients describe a large number of symptoms, overall the **most common symptoms associated with DSCATT are fatigue, disordered thinking and sensory disturbance**.
- Patients generally report experiencing **multiple symptoms**, with analysis of submissions indicating nearly six symptoms per patient on average.
- Patients generally report experiencing symptoms of DSCATT for **many years**; with around 10 years being average, but reports of up to 47 years.
- Acute symptoms and clinical signs of DSCATT/Lyme-like illness typically include **flu-like symptoms, fever and rashes of various descriptions**; some patients have the bulls-eye (erythema migrans) rash.
- ACIIDS, a group of doctors who treat patients with tick-borne diseases and Lyme-like illness advise there are **multiple symptoms** and clinical signs of chronic DSCATT/ Lyme-like illness; most commonly these include **fatigue, headache, muscle and joint pain and cognitive impairment**, with **clinical signs involving the neurological, cardiovascular, gastrointestinal and musculoskeletal systems**.

3.2.1. Acute and chronic symptoms

While some patients experience acute symptoms, particularly after a tick bite, most patients suffering from DSCATT experience chronic debilitating symptoms.

The Senate Inquiry sought submissions on the signs and symptoms that Australians with Lyme-like illness are enduring. In its report, the committee noted a common theme throughout the submissions of patients presenting to their local GP or medical practitioner with chronic and debilitating symptoms. The committee was concerned at the evidence from a large number of submitters experiencing a range of chronic debilitating illness, particularly regarding the impact of these symptoms on children. (Senate Inquiry Interim Report, May 2016).

Submitters suffering chronic debilitating symptoms were divided into four main groups:

1. Those who acquired and were diagnosed with classical Lyme disease in an endemic area overseas;
2. Those who acquired their illness overseas but were not diagnosed;
3. Those who became ill following a tick bite in Australia; and
4. 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.

For this literature review we have focused on the committee's findings for illness acquired in Australia, as these findings are relevant to DSCATT, rather than the committees' findings from submitters who acquired their illness overseas or were diagnosed with classical Lyme disease overseas.

The majority of submitters to the Senate Inquiry stated they acquired their illness in Australia. Submitters who stated they became ill immediately following a tick bite in Australia described symptoms that included a rash around the bite and a range of symptoms including fatigue, arthritis and chronic pain. The largest group of submitters were people who had experienced a long-term chronic illness: in many cases these submitters could not recall being bitten by a tick; however, in cases where a tick bite could be recalled this may have predated the onset of their illness by a number of years (Senate Inquiry Interim Report, May 2016).

ACIIDS members who reported treating approximately 1,500 patients with Lyme-like illness and having treated approximately 4,000 patients in total at the time of the Senate Inquiry advised that (ACIIDS, 2016):

- the symptoms of Lyme-like illness were similar to symptoms experienced by patients diagnosed with Lyme disease in the United States and Europe;
- it is important to differentiate between acute symptoms experienced within 48 hours of a tick bite, and symptoms of chronic Lyme-like illness experienced months or years after the tick bite;
- not all patients develop acute symptoms and patients sometimes do not develop symptoms until months or years after the tick bite;
- the infection 'Lyme-like illness' can sometimes lie dormant or latent for an extended period; and
- if the disease is left untreated patients often develop chronic Lyme-like Illness; this illness can cause a wide variety of symptoms and in some cases profound disability.

3.2.2. Range, number and duration of signs and symptoms

Patients often experience a range of symptoms and signs, with the most common symptoms associated with DSCATT being fatigue, disordered thinking and sensory disturbance

In their literature review, Chalada et al. (2016) reported the symptoms described, where available, in the peer-reviewed studies regarding the evidence on Lyme-like cases in Australia.

As can be seen in Table X below, the range of symptoms are diverse. For several of the studies where specific symptoms were reported, the erythema migrans (EM) rash is common, alongside headache, arthralgias and myalgias, lethargy and malaise, while two patients only had the EM rash and no systemic illness. From the studies where the symptoms are described more generically as 'Lyme-like presentation', it is not possible to comment further on individual symptoms.

Table 14: Geographic distribution of Australian Lyme-like cases from peer-reviewed scientific literature

Location	Travel history	Symptoms	Reference
Lower Hunter Valley, NSW	No data	Insect bite followed by EM with secondary lesions, relapsing arthritis with swelling and pain in the knee and left hip, behavioural change, headaches, memory loss, urinary retention, tachycardia	Stewart et al. (1982)
Guerilla Bay near Moruya, NSW	No data	Insect bite followed by EM. Weeks after treatment EM recurred.	McCrossin (1986)
North Bendalong (between Nowra and Ullladulla), NSW	No data	One-month EM, lassitude, polyarthralgia, headaches	McCrossin (1986)
Gorokan, NSW	No data	3 weeks of increasing lethargy, malaise, intermittent fevers, multiple EM, severe occipital headache, sore throat	Lawrence et al. (1986)
Pittwater Shire, Sydney	17 months prior to tick bite, visited 3 countries in Europe known to be endemic for Lyme. Did not recall any tick bites or exposure to ticks. EM appeared at the site of the Australian tick bite.	EM at tick bite. Mild headache, malaise, and low-grade fever, non-pruritic rash, insomnia, generalised arthralgias, myalgias, insomnia, difficulty with memory and "thinking clearly", secondary EM lesions. Duration > 18 months.	Hudson et al. (1998)

Location	Travel history	Symptoms	Reference
152.8E,31.66S	Yes	EM, no systemic illness	Mayne (2012)
152.7E 31.73S	Never left Australia	EM, systemic illness	Mayne (2012)
151.3E, 33.74S	Yes	EM, fever, menigism, severe headache worse with coughing and shaking of head, photophobia and retro-orbital pain	Mayne (2012)
152.8E, 31.32S	Never left Australia	EM, no systemic illness	Mayne (2012)
Rural Victoria	No data	Fever, regular presumed viral illness, chronic fatigue syndrome, severe arthritis in hands, auditory hypercussis, poor concentration, irritability and emotional lability, episodic sleep disturbances, two episodes of severe generalised body pain without cause, one episode of auditory hallucinations and paranoid ideas. Duration: 8 years.	Maud & Burk (2013)
Mid-north coast of NSW	Travelled from Byron Bay NSW to Eastlakes Victoria. No overseas travel	Lyme-like presentation	Mayne (2011)
QLD	Travelled to northern NSW and Sydney, NSW; Melbourne, Victoria; Hobart Tasmania. No overseas travel.	Lyme -like presentation	Mayne (2011)
Armstrong beach, QLD	Karratha, WA. No travel.	Lyme-like presentation	Mayne (2011)
NSW	Victoria, Queensland, South Australia. No overseas travel	Lyme-like presentation	Mayne (2011)

Source: Table 1 page 49 Chalada at al. 2016

The analysis by Brown in 2018 of first-person submissions made to the Senate Inquiry by people who self-identified as having Lyme disease in Australia provides the most recent insights into the range of symptoms affecting patients with DSCATT (Brown, 2018). This paper also demonstrates the wide range of symptoms reported by patients suffering from DSCATT. Of the 698 submissions published, 656 patients reported having at least one symptom. Of those patients who reported at least one symptom, Brown identified **nineteen symptoms,** as described by the patients.

Fatigue was the most common symptom reported by patients with two in three (66.6 percent) affected, followed by disordered thinking (including 'brain fog', 'memory loss' or loss of mental acuity) (55.2 percent), and sensory disturbance (49.1 percent) of patients. Nearly half of patients were affected by arthralgia and headaches.

The symptoms and prevalence of symptoms reported by patients in their submissions is in Table 15.

Table 15: Symptoms reported by patients

Symptoms	Number (%) of patients who reported at least one symptom (*n* = 656)*
Fatigue	437 (66.6)
Disordered thinking ('brain fog', 'memory loss' or loss of mental acuity	362 (55.2)
Sensory disturbance	322 (49.1)
Arthralgia	299 (45.6)
Headache	292 (44.5)
Myalgias	240 (36.6)
Rash	224 (34.1)
Mood disturbance	195 (29.7)
Visual disturbance	182 (27.7)
Dizziness	173 (26.4)
Pain	168 (25.6)
Fever	163 (24.8)
Nausea	147 (22.4)
Palpitations	120 (18.3)
Insomnia	118 (18.0)
Seizures	105 (16.0)
Diarrhoea	86 (13.1)
Tremor	85 (13.0)
Personality change	27 (4.1)

*34 patients who did not report symptoms were not included.
Source: Table 2 page 242 Brown 2018

Patients generally report experiencing multiple symptoms, with analysis of submissions almost 6 symptoms per patient on average

In Brown's analysis of patient submissions discussed above, of the 656 patients who reported having at least one symptom, on average, patients had 5.7 symptoms (Brown, 2018). While papers such as that by Mayne (2015) discussed above and other sources of information throughout this section indicate patients experience multiple symptoms, the paper by Brown (2018) was the only source of information we found that reported on the number of symptoms experienced per patient.

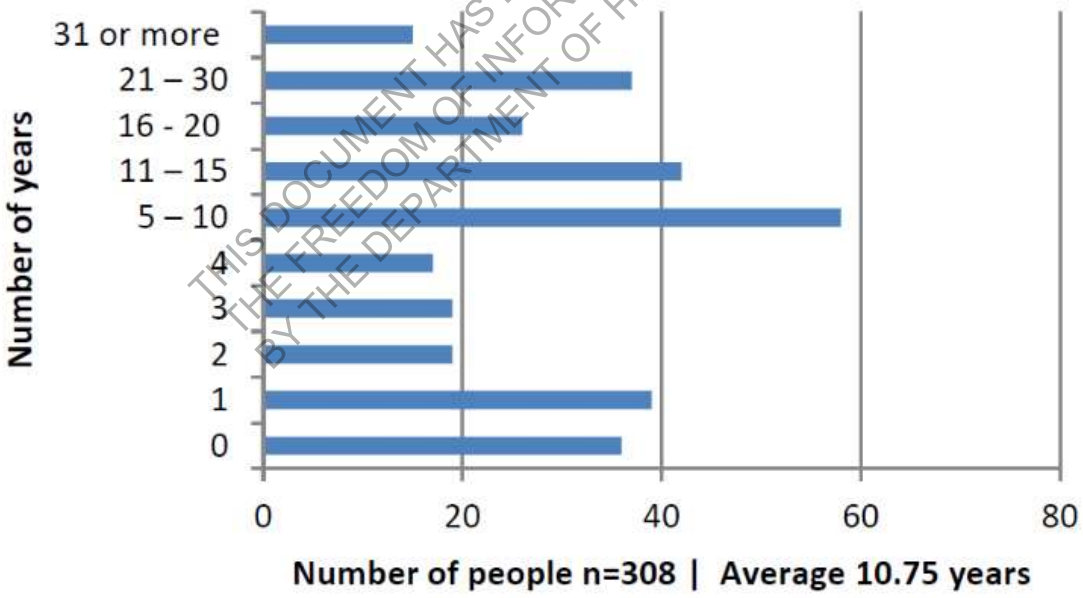
Patients generally report experiencing symptoms of DSCATT for many years, with around 10 years being average

Two studies and one submission reported relatively consistent findings regarding the many years that patients experienced symptoms of Lyme-like illness/DSCATT. Brown, in his analysis for the Senate Inquiry of the 656 patients who reported having at least one symptom, found the median duration of symptoms reported by patients was 10 years (Brown, 2018). The LDAA stated a similar timeframe, set out in

Figure 5 below (LDAA, March 2016):

> *"Given the time it takes for Australian patients to reach a diagnosis for their Lyme-like illness (10.75 years …) this means that the majority of patients are in chronic/late stage disease.*

Figure 5: Length of time from bite to diagnosis



Source: Table 1 page 24 LDAA March 2016

Chalada et al. (2016) reviewed the study by Mayne (2015) of Lyme-like cases in Australia. Mayne found from analysis of records of 500 patients across all states in Australia over the course of five years that the average length of illness at time of presentation was 7.4 years, with a minimum of 0.17 years and a maximum of 47 years (Mayne, 2015).

3.2.3. Acute signs and symptoms

Acute symptoms and clinical signs of Lyme-like illness typically include flu-like symptoms, fever and rashes, with some patients having the bulls-eye (EM) rash

The available information about symptoms and signs of acute Lyme-like illness comes from the submissions of ACIIDS and LDAA and the patient experience survey conducted by LDAA in 2012. While Brown's analysis of patient submissions discussed above was not organised into acute and chronic symptoms, many of the symptoms described by patients are similar to those described by ACIIDS.

ACIIDS provided the following symptoms and clinical signs of acute Lyme-like illness in their submission (ACIIDS, 2016), shown below in Table 16.

Table 16: Signs and symptoms of acute Lyme-like illness

Stage of Lyme-like illness	Symptoms	Signs
Acute Lyme-like illness	Typically: • fever • fatigue • headache • joint pain and muscle pain • the distinctive erythema migrans rash in some patients ("bulls-eye" rash) Occasionally: • encephalitis • meningitis	Can include: • fever • skin rash Occasionally: • Signs of acute neurological involvement with signs of encephalitis or meningitis

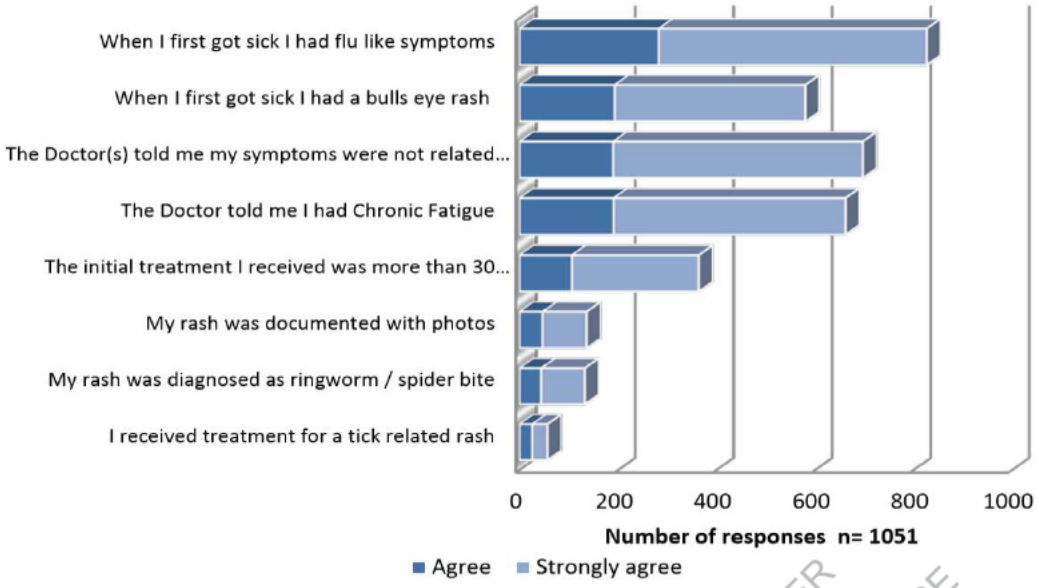
Source: ACIIDS 2016

The LDAA anlysed data of surveys from 2012-2014 they had conducted that explored the symptoms of Australian patients (LDAA, March 2016).

Figure 6: Common symptoms of Australian patients is reproduced from LDAA's submission. The responses are reported from 1,051 patients who were asked to rank a range of statements, providing a profile of the symptoms associated with Lyme-like illness. Of relevance to this section on symptoms and signs are the results for *'When I first got sick I had flu-like symptoms'* and *'When I first got sick I had a bull-eye rash'.*

Figure 6: Common symptoms of Australian patients

Source: Figure 13 page 58 LDAA March 2016



In their 2012 report, the LDAA presented the findings of clinical symptoms and rashes as reported by the 224 respondents who resided in Australia and as of July 2012 had been formally diagnosed with Lyme disease (LDAA, March 2016). Of these respondents, 84 percent reported the presence of flu-like symptoms at onset, while 50 percent reported having a rash (29 percent did not have a rash and 21 percent did not remember). The rash type of the 113 respondents reporting a rash was categorised by type by LDAA and is reproduced in Table 17 in decreasing order of frequency.

Table 17: Reported rash types

Type of rash	Number
Circular, red	38
Bullseye	31
Red, spots	7
Red, welts	5
Red, itchy	4
Red, lump	3
Red, blistered	3
Rosacea	3
Urticaria	2
Red, hot like sunburn	1
Red, scaly	1
Scabies like	1
Shingles like	1
Similar to hives	1
Total	**101**

Source: Table 6 page 17 LDAA 2012 report

3.2.4. Chronic signs and symptoms

According to ACIIDS, there are multiple symptoms and clinical signs of chronic Lyme-like illness, most commonly fatigue, headache, muscle and joint pain and cognitive impairment, with clinical signs involving the neurological, cardiovascular, gastrointestinal and musculoskeletal systems

Specific information relating to the symptoms and clinical signs of chronic Lyme-like illness comes from ACIIDS (ACIIDS, 2016). While Brown's analysis of patient submissions discussed above was not organised into acute and chronic symptoms, many of the symptoms described by patients are similar to those described by ACIIDS.

Table 18: Signs and symptoms of chronic Lyme-like illness

Stage of Lyme-like illness	Symptoms	Signs
Chronic Lyme-like illness	Most common symptoms: • fatigue • headache • muscle and joint pain • cognitive impairment ("brain fog") with poor memory and concentration Other symptoms can include: • sharp pains • numbness or pins and needles in the limbs • sensitivity to light and sound • sore throat • swollen glands • sleep disturbance • palpitations • limb weakness • muscle twitching • non-specific seizures • anxiety • depression • panic attacks • constipation • dizziness • vertigo fainting episodes • double vision • tinnitus (ringing in the ears)	Neurological system: • signs of cranial nerve involvement (such as Bell's palsy) • peripheral nerve signs such as reduced sensation in the extremities and absent reflexes, nystagmus, fasciculation, poor coordination, muscle weakness, ataxia, difficulty walking, positive Babinski response, clonus Cardiovascular system: • ECG changes, arrhythmias due to borrelia carditis; Postural Orthostatic Tachycardia Syndrome (POTS) Dermatological system: • skin rash of acrodermatitis chronic atrophicans (ACD) • dermatological manifestations of bartonellosis may be seen Gastrointestinal system: • enlarged liver or spleen • gastroparesis • loaded colon due to slow transition constipation Musculoskeletal system: • swollen joints • muscle weakness • muscle tenderness and trigger points.

Source: ACIIDS 2016

ACIIDS also noted that some patients suffering from severe Lyme-like illness have committed suicide and provided two reasons why patients with Lyme-like illness develop severe depression:

- the infection can have a direct effect on the brain causing depression, anxiety, panic attacks, personality disorders and psychosis (referencing a 1994 paper by Fallon and Nields 'Lyme disease: a neuropsychiatric illness'); and
- patients often become depressed after having seen many doctors and receiving no diagnosis or treatment despite experiencing debilitating symptoms.

4. DIAGNOSED DISEASES AND DISORDERS AND LIKELY DIFFERENTIAL DIAGNOSES

This section reports on the literature reviewed to answer the research question:

> *What information is available on diseases or disorders Australian patients experiencing DSCATT symptoms have been diagnosed with and what are the most likely differential diagnoses?*

There are complexities regarding the situation of DSCATT which are of relevance to this section on diagnosis. There is considerable debate about the terms 'Lyme disease' and 'Lyme-like' illness, both in Australia and internationally. Furthermore, patient advocacy groups advised the Senate Committee (the committee) they use the terms 'Lyme disease', 'Lyme-like illness' or simply 'Lyme' interchangeably. (Senate Inquiry, Interim Report, May 2016). The use of these words interchangeably makes the appraisal of evidence more difficult, particularly when classical Lyme disease is an internationally recognised tick-borne disease in humans.

With regard to classical Lyme disease in Australia, the Australian Government position is that while some Australians and healthcare providers believe that classical Lyme disease can be acquired from ticks in Australia or that a form of 'chronic Lyme disease' exists, the Australian Government cannot support the diagnosis of locally acquired Lyme disease in Australia without the causative organism of classical Lyme disease (*Borrelia burgdorferi* sensu lato) or a competent vector being identified in Australia. The Australian Government also notes that, globally, 'chronic Lyme disease' is a disputed diagnosis which lacks sufficient supporting evidence. (Australian Government Position Statement: Lyme disease, 2018).

With respect to DSCATT, the Australian Government notes that the illness experienced by patients with debilitating symptom complexes is poorly understood, making accurate diagnosis and treatment difficult and that because of the imprecise nature of the symptom complexes some patients will remain undiagnosed. Its Position Statement therefore stresses it is imperative for government health authorities, clinicians and patients to remain open-minded as to the causes of these symptoms. It also acknowledges that some patients presenting with classical Lyme disease or debilitating symptom complexes have not had positive experiences in the Australian health care system, and this has been largely due to the controversy and stigma attached to Lyme disease in Australia. (Australian Government Position Statement: Debilitating Symptom Complexes Attributed to Ticks)

Acknowledging these complexities, this section reports on the findings from the evidence reviewed of the diagnoses given to patients who have reported experiencing symptoms of DSCATT. This section also reports on the most likely diagnosable conditions which DSCATT may mimic and must be ruled out when a patient presents with systemic symptoms with or without a history of tick bite and that cannot be attributed to diagnosable overseas-acquired Lyme disease or vector-borne illnesses in Australia.

Evidence reviewed

To answer the research question '*What information is available on diseases or disorders Australian patients experiencing DSCATT symptoms have been diagnosed with and what are the most likely differential diagnoses?* we reviewed 31 articles, reports or submissions. Evidence was only included if it specifically related to Australian patients.

Systematic reviews	None
Narrative literature reviews and reviews (8)	Graves & Stenos (2017); Kwak (2018); Banks & Hughes (2019) Beaman (2016); Chalada et al. (2016); Collignon et al. (2016); Dehhaghi et al. (2019); Lowbridge et al. (2011)
Observational studies (12)	Brown (2018); Senanayake et al. (2012); Dawood et al. 2013; Gofton et al. (2015b); Gofton et al. (2015a), Graves et al. (2016); Vilcins et al (2009); Loh et al. (2016a); Loh et al. (2017); Whiley et al. 2016); Irwin et al. (2017)
Official Australian reports and government inquiries including submissions within relevant Senate Inquiry reports (8)	5 reports: Senate Inquiry Interim Report, May 2016; Senate Inquiry Final Report, November 2016; DSCATT Forum, April 2016; Inquiry into Chronic Disease Prevention and Management in Primary Health Care, May 2016, McKenzie, 2013 3 submissions: ACIIDS submission 370, 2016; LDAA submission 528, March 2016; LDAA Supplementary submission, November 2016
(Inter)national authority and intergovernmental reports and guidelines	None

Key findings on diseases and disorders Australian patients experiencing DSCATT have been diagnosed with and the most likely differential diagnoses

- From limited evidence, patients diagnosed with Lyme-like illness report having been diagnosed with infections and co-infections from ticks, the most common infection being *Borrelia*, followed by *Bartonella*, *Babesia* and *Rickettsia*.
- The very limited anecdotal evidence from medical professionals treating patients with DSCATT varies on the number of organisms from ticks patients may be infected with; however, there are as yet no published clinical studies to confirm the evidence.
- From limited available information, a high proportion of patients diagnosed with DSCATT appear to have been diagnosed with Lyme disease in non-NATA/RCGP laboratories in Australia or by overseas laboratories.
- Limited information indicates around fifty diagnoses of non-tick borne diseases or conditions have been provided by medical professionals to patients with Lyme-like illness, with multiple sclerosis, CFS/ME, rheumatoid arthritis, and motor neurone disease being most common; however, many patients have been given a diagnosis of depression, anxiety or mental/psychological disorder.
- Concerns have been raised about the risks and harms of misdiagnosis, with potentially treatable conditions being diagnosed as Lyme like illness.
- There are established diagnostic avenues and pathways to assist clinicians when a patient presents with a tick bite and symptoms in Australia; taking a travel history from the patient is a critical part of the diagnostic pathway along with symptoms.
- While patients and treating doctors report confirmed diagnoses of Lyme disease and *Borrelia,* there is currently no evidence that *B. burgdorferi* or any other kinds of *Borrelia* are infecting humans in Australia.
- However, while ticks are suspected to be possibly responsible for symptoms of DSCATT and there are known tick borne diseases in Australia there are a lot of unknowns about Australian ticks and the diseases they do or might transmit; a range of other possible causes for DSCATT including parasitic and viral causes, as well as environmental toxins and other potential medical explanations have been suggested.
- Current evidence is that the only systemic bacterial infections known to be transmitted by tick bites in Australia are Rickettsial (*Rickettsia* spp.) infections which include Queensland tick typhus, Flinders Island spotted fever and Australian spotted fever and Q fever (*Coxiella burnetii).*
- There are no definite tick-borne viral illnesses in Australia currently.
- Some infectious tick-borne diseases can present like or mimic Lyme Borreliosis, including Australian Rickettsiosis.
- From the limited information available, while many diagnoses have been given to patients with DSCATT, several non-infectious diagnosable and treatable diseases and conditions consistently stand out as differential diagnoses. These should be considered high priority in patients presenting with DSCATT, including multiple sclerosis, motor neurone disease, rheumatoid arthritis, Parkinson's disease,

fibromyalgia, autoimmune diseases and chronic pain syndromes. Chronic fatigue syndrome is also high on the list for differential diagnoses.

4.1. Diagnosed diseases and disorders

4.1.1. From limited evidence, patients diagnosed with Lyme-like illness report having been diagnosed with infections and co-infections from ticks, the most common infection being *Borrelia*, followed by *Bartonella*, *Babesia* and *Rickettsia*

The majority of submitters to the Senate Inquiry stated they had acquired their illness in Australia, with many submitters having had no history of travel to an endemic area for classical Lyme disease (Senate Inquiry, Interim Report, May 2016).

Among submitters who had become ill following a tick bite, the Interim Report noted that:

- some submitters stated they became ill immediately following a tick bite in Australia, with submitters describing symptoms such as a rash around the bite and a range of symptoms including fatigue, arthritis and chronic pain;
- in some cases, submitters were diagnosed with other known tick-borne infections, such as Q fever, Spotted Fever, Rickettsia, Queensland Tick Typhus or allergy to tick toxin, and received treatment; and
- in most cases, submitters stated that medical practitioners were not able to identify or diagnose the illness or offer any effective treatment.

The largest group of submitters were those who had experienced a long-term chronic illness. In many cases, the submitters could not recall being bitten by a tick; where submitters could recall a tick bite, according to the Interim Report, this may have predated the onset of their symptoms by a number of years (Senate Inquiry, Interim Report, May 2016).

LDAA analysed a subset of submissions (432 or 34 percent of the 1,268 submissions,) made to the Senate Inquiry for **type of infection or co-infection** reported. (LDAA, Suppl. Submission, November 2016) LDAA noted 156 people reported having more than one infection with LDAA commenting that this makes treatment much more complicated. The types of infections and co-infections identified by LDAA, and ordered by prevalence are listed below in

Table 19.

Table 19: Types of infections and co-infections identified by LDAA

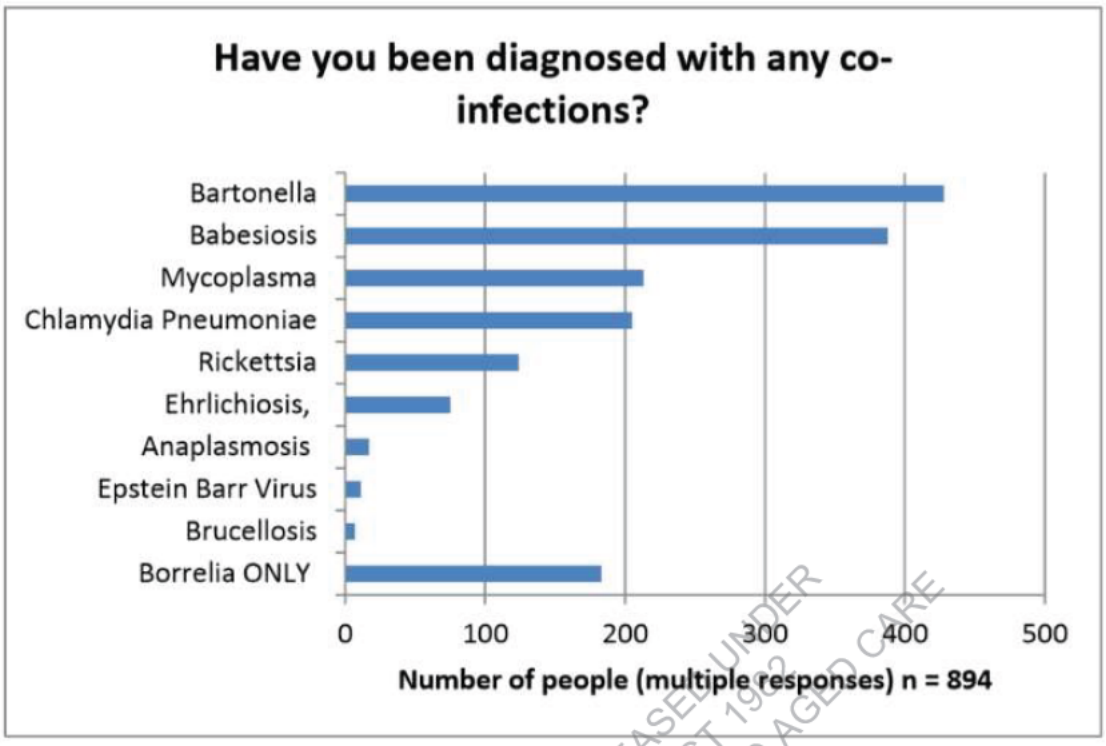
Infections reported	
Borrelia	181
Bartonella (henselae)	76
Babesia (unstated strain)	64
Rickettsia Spotted fever group	50
Mycoplasma	30
CPN	23
EBV	22
Ehrlichia, Ross River Fever	12
Babesia duncani	10
Typhus	7
Barmah Forest virus, CMV, Q Fever	5
Blastocystis hominis, Cocksackie virus	4
HSV/Zoster, Hashimoto disease, Mycoplasma fermentans, Parvo, Pyrroluria, Strep, Toxoplasmosis	3
Diantomoeba fragilis (parasite)	2
Anaplasma, *Babesia microti,* Brucella, *Coxiella burnetiae*, EMV	1
Other	22

Source: Figure 10, LDAA Supplementary Submission to Senate Inquiry (LDAA, November 2016)

LDAA noted that their research supported emerging international research that shows Lyme disease is rarely ever found in isolation of other pathogens. LDAA also noted the limitations of the term Lyme disease and that the term is being widely used as *"the catch all for a constellation of pathogens transmitted from ticks to humans".*

The graph below of common co-infections reported by patients completing LDAA's online surveys (2012-2014) has been reproduced from Figure 14 (page 59) of LDAA's submission (LDAA, Submission 528, May 2016). LDAA noted that a minority (183 patients, 20 percent) of the 894 patients who responded (with multiple responses available according to the graph legend) reported being infected solely with *Borrelia.* The most common co-infections reported by patients completing the surveys were Bartonella, Babesiosis, Mycoplasma and Chlamydia pneumoniae, followed by Rickettsia and Ehrlichiosis.

Figure 7: Common co-infections reported



Source: Figure 14, page 59 LDAA, March 2016

LDAA also submitted evidence on co-infections to the Inquiry into Chronic disease prevention and management in primary health care, including that 55% of patients with tick-borne or Lyme-like disease reported being diagnosed with at least one co-infection and that this is a much higher rate than that reported in the USA. (Australian Government Inquiry into Inquiry into Chronic disease prevention and management in primary health care, 2016).

Brown found in his analysis of all public, first-person submissions made to the Australian Senate Inquiry in 2016 that the majority (58.8 percent) of submissions did not comment on a tick bite, but where submitters did comment, the majority (257, 89.5 percent) reported a positive history. In about half (357, 51.5 percent) of all submissions analysed, patients reported having been diagnosed with co-infections (not further defined).

Table 20: Number of patients who reported a tick bite

	Number (%) or median (range) of all patients	Number (5) of patients who reported data
Tick bite		
Yes	257 (36.9%)	257 (89.5%)
No	30 (4.3%)	30 (10.5%)

Source: Brown, 2018

4.1.2. The very limited anecdotal evidence from medical professionals treating patients with DSCATT varies on the number of organisms from ticks patients may be infected with; however, there are as yet no published clinical studies to confirm the evidence

Professor Graves from Austin Health, University of Melbourne, reported after extensive investigation, of more than 50 patients with Lyme-like illness in the Austin Health ID Program, no evidence of babesiosis or rickettsiosis, based on laboratory evidence or failure to respond to medical therapy that is usually effective against these two diseases (DSCATT Forum, April 2016).

In contrast, Dr Schloeffel listed nine infective organisms found in Australian patients with Vector Borne Diseases (DSCATT Forum, April 2016). These were:

- Anaplasmosis;
- Babesia;
- Bartonella;
- Borrelia including relapsing fever;
- Coxiella Burnetti;
- Ehrlichiosis;
- Mycoplasmas;
- Rickettsias; and
- Viruses.

Dr Schloeffel also submitted evidence on co-infections to the Inquiry into Chronic disease prevention and management in primary health care. The report stated Dr Schloeffel lists ten groups of co-infections associated with tick-borne of Lyme -like disease, including relapsing fever, *rickettsias,* and chronic viral infections including HIV. (Australian Government, Inquiry into Chronic disease prevention and management in primary health care. 2016).

4.1.3. From limited information, a high proportion of patients diagnosed with DSCATT appear to have been diagnosed with Lyme disease in non-NATA/RCGP laboratories in Australia or by overseas laboratories

In his analysis of submissions by patients to the Senate Inquiry Brown also reported on diagnosis, including the diagnostic testing laboratory, and other methods of diagnosis.

Regarding the diagnostic testing laboratory that had supported submitters diagnoses, Brown reported that of the 137 submissions that disclosed a NATA/RCPA-accredited diagnostic pathology test, only 14 (10.2 percent) reported positive serology, which represented 2.8 percent of all submissions that reported pathology and 2.0 percent of all submissions. Of the 14 that reported positive serology, ten patients had travelled overseas while the four other patients who had either not travelled overseas or did not mention travel did not report the result of confirmatory (Western blot) serological testing. Additionally, two patients reported they had contracted Lyme disease overseas (USA and France) and another two patients who reported travel also reported explicitly that only first-tier testing was positive. Brown commented only a small proportion of patients reported a positive Lyme disease serology test from a NATA/RCPA accredited laboratory and that a proportion of these may be positives from overseas exposure unrelated to their current illness.

Table 21: Diagnostic information reported in submissions

Diagnostic method	Number (%) of all patients	Number (%) of patients who reported data
Diagnostic laboratory testing		
Any	508 (72.8%)	508 (100%)
Pos NATA/RCPA	14 (2.0%)	14 (2.8%)
Neg NATA/RCPA	123 (17.6%)	123 (24.2%)
Pos non-NATA/RCPA	454 (65.0%)	454 (89.4%)
Neg non-NATA/RCPA	27 (3.9%)	27 (5.3%)
Neg NATA/RCPA, Pos non-NATA/RCPA	83 (11.9%)	83 (16.4%)

Source: Brown, 2018

Additionally, nearly one in ten patient submissions (68, 9.8 percent) reported having self-diagnosed with Lyme disease after media reports, with a similar proportion (67, 9.8 percent) reported having self-diagnosed with Lyme disease by research or on the internet. Two submissions (0.3 percent) reported Lyme disease was acquired congenitally (Brown, 2018).

LDAA also provided data about where patients had their diagnostic testing performed, reporting (page 42) that their aggregated survey data from 2012-2014 showed that 57 percent of laboratory tests patients pay for are conducted in overseas laboratories

Table 22: Testing laboratories used by Australian patients

In which Laboratory have you tested positive to Lyme disease through a blood or other specimen test?	
Australian Laboratory	**Number**
Australian Biologics, Sydney	260
Australian Rickettsial Reference Laboratory, Geelong	30
Local collection centre	71
PaLMS, Sydney	20
University of Newcastle	3
Westmead Hospital, Sydney	6
Overseas Laboratory	
IGeneX, Palo Alto, USA	396
InfectoLab, Germany	114
Blank / unsure	129
Total	**1029**

Source: LDAA, 2016

4.2. Differential diagnoses

Limited information indicates around fifty diagnoses of non-tick borne diseases or conditions have been given by medical professionals to patients with Lyme-like illness, with multiple sclerosis, CFS/ME, rheumatoid arthritis, and motor neurone disease being most common; however, many patients have been given a diagnosis of depression, anxiety or mental/psychological disorder The available information on non-infectious diagnoses given to patients with Lyme-like illness comes from analyses of submissions to the Senate Inquiry by Brown (2018) and LDAA (LDAA, Supplementary Submission, November 2016).

One in ten (73, 10.5 percent) of the 698 submitters who self-identified to the Senate Inquiry as having Lyme disease in Australia and included in Brown's analysis reported being given another diagnosis that could explain their physical symptoms (Brown, 2018). The diagnoses included:

- Twenty-three who reported multiple sclerosis (MS);
- nineteen who reported rheumatoid arthritis (RA);
- ten who reported systemic lupus erythematosus (SLE)
- seven who reported Crohn's disease;
- four who reported motor neurone disease (MND); and
- fourteen patients who reported 'Other'.

Four patients reported more than one diagnosis (Brown, 2018).

LDAA's analysis of a smaller number of submissions (432) to the Senate Inquiry, provides more detail of diseases and conditions reported by patients as differential diagnoses they had been given. LDAA found that of the 349 submissions that provided information on differential diagnosis, fifty diseases, disorders or conditions were reported as differential diagnoses with CFS/ME, depression, fibromylgia, MS and anxiety, being the five most prevalent diagnoses reported by submitters.

Table X below shows the list of diagnoses provided by medical professionals as reported in the 349 individual submissions and analysed by LDAA, ordered by prevalence.

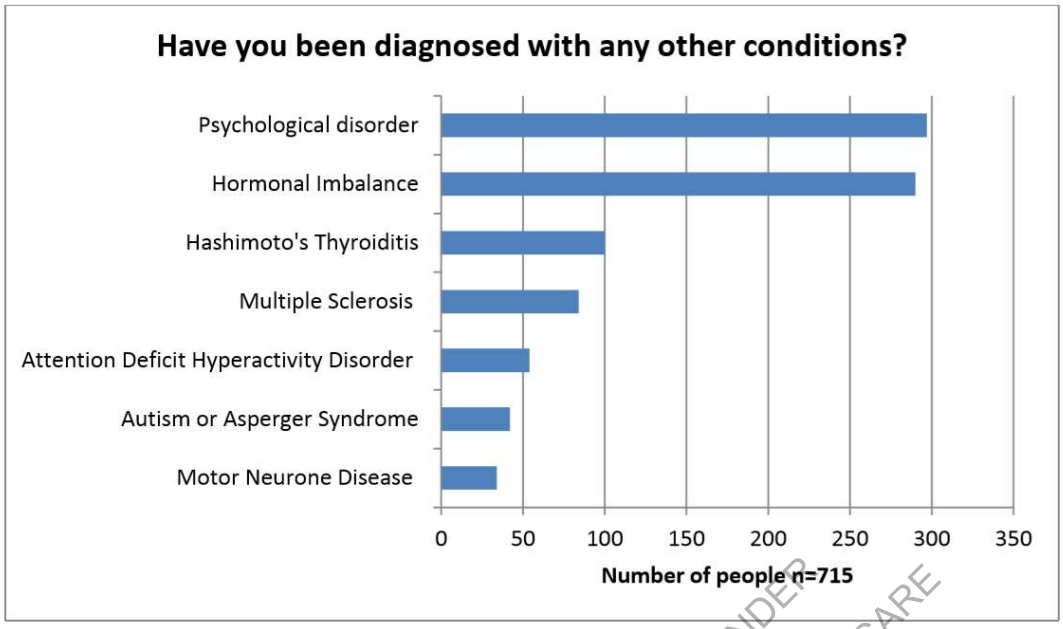
Table 23: Testing laboratories

Diagnosis provided by medical profession	
CFS/ME	87
Depression	42
Fibromyalgia	42
MS	28
Anxiety	21
Mental Disorder	18
EBV	16
Rheumatoid Arthritis	15
Adrenal fatigue, Post Viral Fatigue	13
Irritable Bowel Syndrome	12
Lupus	11
Migraine	10
Ross River Fever	9
ADD/ADHD, Thyroid/Graves	8
Hashimoto's, Poly arthroplasty/myalgia	7
Conversion Disorder	6
Blood pressure low, Diabetes, Meningitis, Osteoarthritis, PTSD	5
Costochondritis, Gastritis, Pyrrole's Disorder, Reactive Arthritis	4
Autonomic nervous system dysfunction, Bipolar Disorder, CCSVI, Active imagination, Parkinson's, Psoriatic Arthritis	3
B12 deficiency, Dengue Fever, Lattice Degeneration, Meniere's, Pancreatitis, Peri-Menopausal, Psoriasis, Postural Tremors	2
Coeliac disease, CREST, Cushing's disease, Folliculitis, Hernia, Hyperesthesia, MSID, Rheumatic Fever	1

Source: Figure 9 (LDAA, Supplementary Submission, November 2016)

The LDAA also reported the findings of commonly reported conditions that are often associated with chronic Lyme disease that patients participating in their online surveys 2012-2014 had reported being given. Of the 715 people who provided answers the most common conditions patients reported being diagnosed with were a psychological disorder and hormonal imbalance.

Figure 8: Other conditions Lyme patients are diagnosed with



Source: LDAA, March 2016

4.2.1. Concerns have been raised about the risks and harms of misdiagnosis, with potentially treatable conditions being diagnosed as Lyme-like illness

The Medical Board of Australia (MBA) and Australian Health Practitioner Regulation Agency (AHPRA) raised in their submission concerns related to Lyme disease or Lyme-like illness that had led to an investigation of a medical practitioner (Senate Inquiry, Interim Report, May 2016). These included:

- the use of unconventional diagnostic techniques such as kinesiology to diagnose Lyme--like illness;
- the reliance on non-accredited laboratories to diagnose Lyme-like disease;
- not referring patients with complex diagnoses to specialists, where this would have been appropriate;
- not managing other co-existing medical conditions once Lyme-like disease was diagnosed; and
- diagnosis of a large proportion of a medical practitioner's patients with Lyme-like disease without considering or excluding other conditions, with the 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.

In addition to the risks raised by the MBA and AHPRA in the Interim Report, which was again highlighted in the Final Report, the risk of misdiagnosis was also highlighted by other organisations, with the submission by the Medical Council of New South Wales (MCNSW) drawing 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"* (Medical Council of New South Wales, Submission 935)

A similar concern was echoed by Professor Graves from Austin Health, University of Melbourne, who after extensive investigation of more than 50 patients with Lyme-like illness in the Austin Health ID Program, found

- about 30-50 percent of patients had potentially serious medical conditions that have been either:
  - previously undiagnosed;
  - diagnosed but inappropriately treated; or
  - diagnosed but denied by the patient such that no treatment was sought/given; and
- 10-20 percent have a serious defined psychiatric illness needed specialist care.

The Royal College of Pathologists of Australia in the Position Statement *'Diagnostic Laboratory testing for Borreliosis ('Lyme Disease' or similar syndromes) in Australian and New Zealand*' (RCPA, March 2016), also raises concerns about misdiagnosis of potentially treatable conditions in patients presenting with symptoms resembling Lyme disease, stating:

> *"When a patient presents with symptoms resembling Lyme Disease and no history of overseas exposure, although it is not entirely possible to rule in or rule out locally acquired Borreliosis on the basis of a series of negative results, it is important that patients are not diagnosed erroneously as having Lyme Disease, when they may well have some other, potentially treatable, conditions: examples include chronic pain syndromes including fibromyalgia; complex neurodegenerative disorders such as motor neurone disease; or psychiatric illness such as major depression with somatisation"*

Brown, in discussing his findings on diagnoses given to patients who provided submissions to the Senate Inquiry, noted the potential harm of missed diagnoses and treatment of concurrent serious illnesses. He cited evidence about cancers being misdiagnosed as 'chronic Lyme disease' in Australia and overseas. He highlighted that 10.5 percent of submissions in his study had reported a previous significant diagnosis such as RA, SLE, MND or MS (Brown, 2018).

LDAA also notes that Lyme disease can mimic many other diseases, stating:

> *"Lyme disease is frequently called 'the great imitator' because it can mimic many other diseases such as Multiple Sclerosis, Parkinson's disease, Motor Neurone disease, Chronic Fatigue Syndrome, Fibromyalgia, Guillain-Barre Syndrome, Juvenile Rheumatoid Arthritis, Lupus, Alzheimer's disease etc. Lyme disease can affect any organ in the body including muscles and joints, the heart, gastro-intestinal system and neurological system (including the brain)"* (LDAA, Lyme disease: Australian patient experience in 2012).

In their supplementary submission, LDAA raise the potential for Borrelia infection in the United States, to be associated with other degenerative diseases, providing the following evidence to the Senate Inquiry:

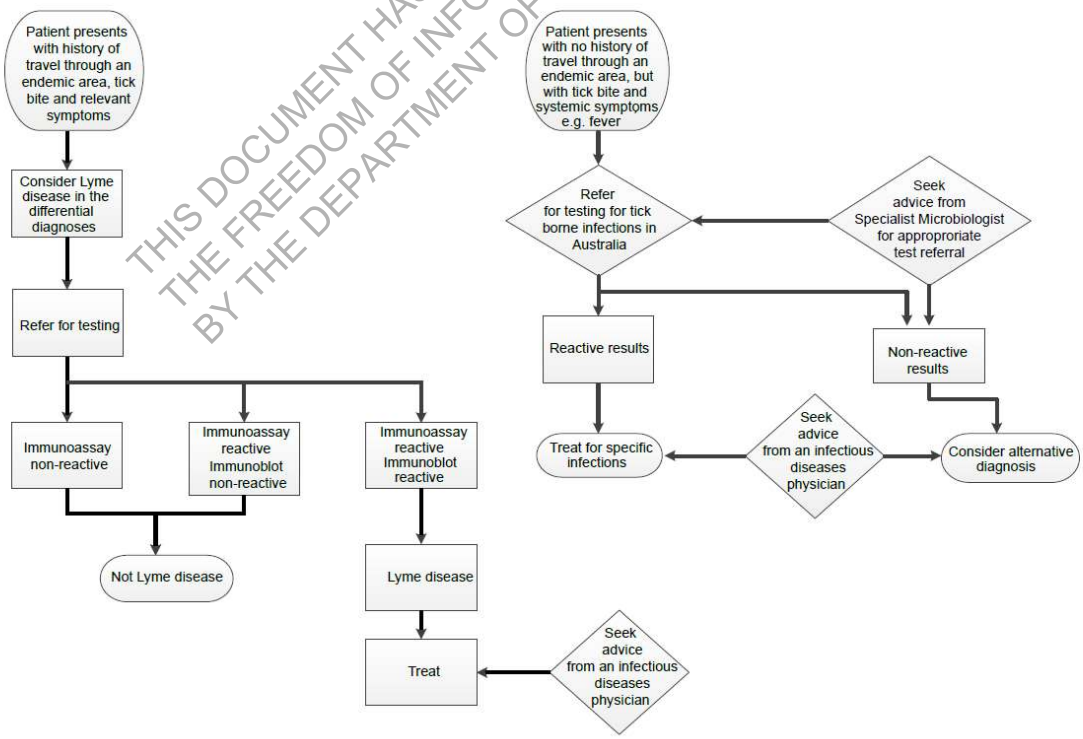
> *"There is considerable speculation that some patients with other degenerative diseases like Alzheimer's, Amyotrophic Lateral Sclerosis (ALS), Motor Neurone Disease, Parkinson's disease, and MS could be misdiagnosed. In fact, Dr Klinghardt, a specialist Lyme physician in the USA tells us in Under our Skin, a documentary on Lyme disease, that he has never had a patient with Alzheimer's, ALS, Parkinson's or MS who tested negative for Borrelia"* (Senate Inquiry, Final Report, November 2016)

4.2.2. There are established diagnostic avenues and pathways to assist clinicians when a patient presents with a tick bite and symptoms in Australia; taking a travel history from the patient is a critical part of the diagnostic pathway along with symptoms

There are two diagnostic pathways in the Australian guideline on the diagnosis of overseas-acquired Lyme disease.

- For patients presenting with a history of travel through an endemic area for classical Lyme disease, tick bite and relevant symptoms – consider Lyme disease in the differential diagnoses and follow the diagnostic pathway for overseas acquired Lyme disease.
- For patients presenting with no history of travel through an endemic area, but with tick bite and systemic symptoms (e.g. fever) – refer for testing for tick borne infections in Australia, treat for specific infections if results are reactive and if the results are non-reactive, consider an alternative diagnosis (Department of Health Australian Guideline-diagnosis of overseas-acquired Lyme disease, 2015).

Figure 9: Flow chart for an Australian diagnostic guideline for overseas acquired Lyme disease



Source: Lum, Hood and Wright, 2015

4.2.3. While patients and treating doctors report confirmed diagnoses of Lyme disease and *Borrelia,* there is currently no evidence that *B. burgdorferi* or any other kinds of *Borrelia* are infecting humans in Australia

As noted previously the Australian Government position is it cannot support the diagnosis of locally-acquired Lyme disease in Australia without the causative organism of classical Lyme disease (*Borrelia burgdorferi* sensu lato) or a competent vector being identified in Australia (Australian Government Position Statement: Lyme disease, 2018). It noted it is imperative for government health authorities, clinicians and patients to remain open minded as to the causes of these symptoms (Australian Government Position Statement: Debilitating Symptom Complexes Attributed to Ticks).

The Royal College of Pathologists of Australia, in its Position Statement, answered the question 'Is there endemic Borreliosis ('Lyme disease' or similar) in Australia?' with:

> "*There are several important human infectious diseases not thought to be present in Australia, including some transmitted by ticks. With respect to Lyme Disease in Australia, there is a spectrum of opinion (both medical and lay) on whether Lyme Disease is endemic in Australia or not. The number of cases of Lyme disease in Australian patients remains small and previous research efforts in Australia have failed to demonstrate the presence of Lyme Disease-causing Borrelia in Australian ticks. There are Ixodes genus ticks present in Australia, but none of the overseas Ixodes species known to carry Borrelia spp. occur in Australia. The examination of Australian ticks to date (February 2016), has not detected ticks that contain any of the Borrelia spp that are known to cause Lyme Disease elsewhere in the world. Further investigations of Australian patients (with symptoms similar to those of Lyme Disease) and Australian ticks (especially Ixodes spp) may clarify the issue. Only a genuine case in a non-travelling Australian patient would confirm the disease as being present in Australia." (RACP, Position Statement, March 2016)*

With regard to an indigenous form of classical Lyme disease in Australia, Collignon and colleagues cited evidence that since the early 1990s, the Australian medical community, especially specialist microbiologists and infectious diseases physicians, have debated whether an indigenous form of classic Lyme diseases occurs in Australia. This is especially in areas with high rates of tick bites, noting this interest motivated some of the early tick surveys. They stated:

> *"In 1991, B. burgdorferi s.l. could not be confirmed in any of 176 tick species examined. The findings of more recent surveys have also been negative".* (Collignon et al. 2016).

In the previous chapter on clinical epidemiology, we reported on Chalada and colleague's review of over 500 cases of Lyme-like illness mentioned in the scientific literature. The authors noted that the majority were Lyme-*like* cases that are suspected, but *not confirmed* to represent cases of Lyme Borreliosis, with diagnoses being "*highly questionable due to significant flaws in the diagnostic process or presentation of results.*

Chalada and colleagues reported four studies, published between 1991 and 2015 have investigated the potential for *B. burgdorferi* s.l. in ticks. The studies employed culture with and without PCR and in the most recent studies next generation sequencing. The four studies are detailed below?

Wills and Barry 1991

In a letter to the editor of The Medical Journal of Australia in 1991, Wills and Barry published preliminary results of their investigations into the presence of *Borrelia* in Australian ticks. *I. holocyclus and H. longicornus* ticks (177 ticks in all) were collected from the Hunter Valley and Manning River districts of coastal New South Wales and their midguts were cultured in BSK-II media. At least four of the spirochaetes isolated shared antigenic epitopes with *B. burgdorferi* as demonstrated by ELISA, immunofluorescence and Western blotting, suggestive of *Borrelia* species. However, Chalada et al. noted details of the laboratory methods were not published and the organisms recovered were not made for confirmation by another laboratory, rendering the experiment unable to be replicated. Chalada et al. also commented that false positives in the ELISA, immunofluorescence and western blotting cannot be ruled out, no PCR or sequencing has been conducted to confirm the identity of the isolates and positive *Borrelia* cultures from Australian ticks have not been reproduced to date. No follow up report to the preliminary findings was published in the scientific literature. Chalada et al. stated *"The use of molecular techniques, especially sequencing, would be ideal for confirmation or dismissal of any SLOs [spirochaete-like objects] as Borrelia".* (Chalada et al. (2016).

Evidence was presented to the Senate inquiry by LDAA that Dr Wills had her findings of spirochaetes and their isolates validated as positive *Borrelia* species by Professor Alan Barbour. Professor Barbour was then at the Department of Microbiology and is now Professor of Microbiology and Molecular Genetics, at the University of California (LDAA, Supplementary Submission, November 2016).

Russell et al. 1994 (as reported in Chalada et al. 2016)

Russell and colleague's (Russell et al. (1994) study of approximately 1,200 ticks collected over three years along the New South Wales coast contradicted the findings of Wills and Barry (1991). According to Chalada et al. (2016), the Russell study found no definitive evidence for the existence in Australia of *B. burgdorferi,* the causative agent of true Lyme Borreliosis, or for any other tick-borne spirochaete that may be responsible for a local syndrome being reported as Lyme disease. Chalada et al. concluded:

> *"The conclusion of Russell et al.'s study – that no spirochaetes were able to be identified through culture or molecular methods in Australian ticks – therefore seems more plausible than the conclusions of Wills and Barry" (Chalada et al. 2016)*

Gofton et al. 2015a (as reported in Chalada et al. 2016)

Gofton et al. found no *B. burdorferi* s. l. in 109 Australian *I.* holocyclus ticks from around New South Wales collected over a 10-year period but did detect a novel relapsing fever group Borrelia from a single Australian *I. holocyclus* taken from an echidna. Chalada et al. commented:

> *"This work provides further evidence that the cause of the Lyme-like illness in Australia may not be a member of the B. burgdorferi s. l. complex. The finding of a novel relapsing fever Borrelia in an Australian monotreme does provide evidence for the presence of Borrelia in Australia, but it is not known if this organism can infect humans, and should it do so, it is likely that it would present as a relapsing fever illness rather than with Lyme-like symptoms. These factors limit the likelihood that this novel Borrelia species is the cause of the Lyme-like illnesses seen in Australia".*

Chalada et al. noted a number of limitations of the study including the relatively low number of ticks sampled, the limited geographic range from which they were collected and that no data was presented regarding the distribution of collection sites (urban, rural or wilderness) within that state. (Chalada et al. 2016).

Gofton et al. 2015b

Chalada et al. reported that in this study Gofton et al. collected 460 ticks from below the tropic of Capricorn, in Western Australia, and the seaboard Eastern Australia (one from inland Queensland was also included). The ticks were identified as *I. holocyclus (n* = 279), *Amblyomma triguttanum (*n= 167), *H. bancrofti (n*= 7) and *H. longicornis* (*n* = 7). The midguts of all ticks were subjected to 16s ribosomal RNA PCR and next generation sequencing and a *Borrelia* genus specific *flab* nested PCR was also performed on all ticks recovered. Gofton et al. found none of the ticks concerned yielded and *Borrelia* sequences or products (Chalada et al. 2016).

Chalada et al. also reviewed the evidence on serology, culture and molecular detection from the published papers on Australian Lyme-like cases, and this is discussed in greater detail in Chapter 3. However, of the evidence and of relevance to this section was their conclusion:

> *"B. burgdorferi s. l. has never been cultured from an Australian patient that could not have acquired the infection overseas and therefore there is currently no proof that B. burgdorferi s. l. or any other kinds of Borrelia species are infecting humans in Australia. If there is a Lyme like disease that exists in Australia it may well be of a different aetiology".*

Earlier, in 2013, McKenzie, had noted, similarly to Chalada et al.'s findings that while Lyme borreliosis has been reported in Australia, but the vast majority of cases were patients who had travelled to Lyme endemic areas. The author also mentioned that confirmatory testing is required for patients with no travel history and where additional testing of putative positive specimens has been done in NATA- accredited laboratories, the results could not be confirmed to international standards to Lyme disease. (McKenzie, J. Scoping study to develop a research project(s) to investigate the presence or absence of Lyme disease in Australia, September 2013).

In 2017 Graves and Stenos in their review of tick-borne infectious diseases in Australia noted a *Borrelia* species has been detected in the Australian echidna tick (*Bothriocroton concolor).* However, this bacteria belongs to a unique clade unrelated to the *Borrelia* species responsible for causing Lyme disease and the tick in not known to bite humans. Additionally, the authors noted a *Borrelia* species detected in native rats was not virulent for a human after experimental challenge. They concluded Lyme disease bacteria are probably not present in Australian ticks (Graves and Stenos, 2017). Another review of Australian data on Lyme Borreliosis concluded that Lyme Borreliosis vectors are not found in Australia and Lyme Borreliosis has not been found in Australia vectors, animals or patients with autochthonous illnesses (Beaman, 2016).

In the most recent review of human tick-borne diseases in Australia, the authors reviewed Lyme and Lyme-like diseases (Dehhaghi et al. 2019). The authors noted the evidence for a potential Lyme Borreliosis pathogen in Australia is limited and there has been no research since 1994. They commented;

> *"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".*

In reviewing the evidence they concluded there is no evidence for transmission of *B. burgdorferi* sensu lato complex with Australian ticks and that while 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 (Dehhaghi et al. (2019). The findings of this latest literature review concur with other reviews (Chalada et al, 2016, Beaman, 2016) and the Australian Government Position Statement on Lyme disease.

In addition to the reviews noted above, Irwin and colleagues reported their study provided further evidence that Lyme borreliosis does not exist in Australia. They noted that in studies conducted in Europe and the United States, dogs have been used as sentinels for tick-associated illness in people since they readily contact ticks that may harbour zoonotic pathogens. Applying this principle, Irwin et al. used a combination of serological assays to test dogs living in tick 'hot spots' and exposed to the Australian paralysis tick, Ixodes holocyclus, for evidence of exposure to *B. burgdorferi* (s.l.) antigens and other vector-borne pathogens. The authors concluded:

> *"Except for a single dog presumed to have been exposed to Anaplasma platys, infection with Anaplasma spp. B. burgdorferi (s.l.), Ehrlichia spp., and Dirofilaria immitis, was not detected in the cohort of Australian dogs evaluated in this study. These results provide further evidence that Lyme borreliosis does not exist in Australia but that cross-reacting antibodies (false positive results) are common and may be caused by the transmission of other tick-associated organisms".*

4.2.4. Current evidence is that the only systemic bacterial infections known to be transmitted by tick bites in Australia are Rickettsial (*Rickettsia* spp.) infections which include Queensland tick typhus, Flinders Island spotted fever and Australian spotted fever and Q fever (*Coxiella burnetii)* and there are no definite tick-borne viral illnesses in Australia currently

The Senate Inquiry reported that ticks are hosts and vectors of a number of parasites, bacteria and viruses. The main organisms that may be transmitted by ticks and associated with disease known in Australia are outlined below:

- **Anaplasma –** causes disease in cattle (bovine anaplasmosis, or 'bovine tick fever') and dogs (canine anaplasmosis);
- **Babesia** – a significant cause of disease in cattle (Bovine babesiosis) and dogs (Canine babesiosis);
- **Bartonella –** causes disease in domestic and wild animals including cats and kangaroos – uncertain whether it can cause human disease;
- **Ehrlichia –** causes disease in dogs worldwide but has not been recognised in Australia;
- **Francisella –** relatively rare and no evidence to suggest pathogenic for humans; and
- **Rickettsia** – causes several diseases in humans including Queensland tick typhus (*Rickettsia australis*), Flinders Island spotted fever (*Rickettsia honei*), variation of spotted fever (*R. marmionii*) and Q fever (*Coxiella burnetii* –rarely tick-borne) (Senate Inquiry Interim Report, May 2016).

In 2013, McKenzie reported on co-transmission of tick-borne organisms in Australia, noting that ticks are hosts and vectors of a number of parasites, bacteria and viruses and are able to transmit more than one organism per blood meal.

In 2017, Graves and Stenos in their review of tick-borne infectious diseases in Australia reported that the only systemic bacterial infections that are known to be transmitted by tick bites in Australia are Rickettsial (Rickettsia spp.) infections which include Queensland tick typhus, Flinders Island spotted fever and Australian spotted fever and Q fever (Coxiella burnetiid). The authors also reported there are no definite tick-borne viral infections of humans yet in Australia.

Table 24 below presents information on Australian tick-borne organisms as reported by McKenzie (2013) and other possible bacterial organisms causing Rickettsial illness as reported by Graves and Stenos (2017).

Table 24: Australian tick-borne organisms

Organism	Mc Kenzie (2013)	Graves & Stenos (2017)
Anaplasma and Ehrlichia	• Two Anaplasma species occur in Australia, *A. platys* and *A. marginale*. Neither are known to infect humans. • *Ehrlichia* species have not been recognised in Australia. • *E. canis* is an infection found in dogs worldwide, except in Australia due to effective quarantine regulations, but it is not known whether any species occur in native wildlife.	• *Anaplasma* and *Ehrlichia* have been detected by molecular means in paralysis ticks and ornate kangaroo ticks in Australia. • Certain species of these bacterial genera are known to be human pathogens. • There is a possibility that these Australian bacteria may also be human pathogens.
Babesia	• Two species of *Babesia* cause bovine tick fever in Australia. • Three species of canine *Babesia* spp occur in Australia. • A *Babesia* species has been identified in the blood of wild captured woylies in Western Australia and a similar species has been found in ticks in eastern Australia. • First report of locally-acquired case of human babesiosis caused by *Babesia microti* was in a 56-year-old man who had never travelled and had no history of blood transfusions. • The origin of the aetiological agent is uncertain: the patient was either bitten by an imported tick or a local tick might have transmitted an autochthonous infection, presumably orginating from one or more species of introduced rodent. • If it was a local tick, the most likely candidate would be *I. holocyclus* as *Ixodes* species are the usual vector overseas.	• A single case of human babesiosis caused by *B. microti* was described in an Australian man who lived in close proximity to dogs but who did not recall being bitten by a tick and had not travelled outside Australia for nearly 40 years. • While this was thought to have been a locally acquired infection, there have been **no** subsequent cases of human babesiosis diagnosed in Australia.
Candidatus *Neoehrlichia mikuensis*	• A newly recognised human pathogen. • Shown to cause human infection in China and Germany and co-infection of *I. Ricinus* ticks Sweden, Denmark Switzerland. • Organism has not been found in Australia *"but it almost certainly hasn't been looked for at this stage"*	• Recent Australian studies demonstrated the presence of *Candidatus* Neoehrlichia spp. in paralysis ticks but their presence on Australian patients is yet to be shown.

Organism	Mc Kenzie (2013)	Graves & Stenos (2017)
Francisella	• First evidence in Australia was in the Northern Territory followed by a case in Tasmania. • No evidence to suggest these organisms are pathogenic for humans.	• *Francisella* spp are tick-transmitted bacteria that cause classic tularaemia. • A case of localised *Franiscella infection* following a bite from a ring-tail possum has been reported. • The tropical reptile tick from northern Australia which is not known to bite humans has been shown to contain DNZ from this bacterium. • It is not yet clear whether tularaemia is a tick-transmitted infection in Australia.
Rickettsia	• Several rickettsial diseases occur in humans in Australia but not all are tick borne. • Tick-borne human pathogens are Queensland tick typhus, Flinders Island spotted fever and Q fever. • Q fever (Coxiella burnetii) is carried by several tick species but most human cases are acquired by aerosol. • While most human infections with Q fever are acquired by aerosol, the potential exists for transmission from wildlife through a tick bite. • The most interesting of these tick-borne pathogens is *R. marmionii,* which has apparently wide distribution but may also be associated with occasional chronic diseases, including a chronic fatigue-like illness.	
Viruses	• Various viruses have been isolated from ticks in Australia and Australian territories, especially from sea bird ticks. Two flaviviruses, Gadgets Gully and Samaurez Reef have been described in Australia and Australian territories. The role (if any) that these seabird-associated tick-borne viruses play in human disease is unknown except for the antibodies to Gadgets Gully virus in some residents of Great Barrier islands.	

Regarding concerns about co-infections, McKenzie cited evidence that co-infection between *B. burgdorferi.* S. l. complex species and other tick-borne organisms may lead to different and varied

clinical manifestations and different levels of disease severity with abnormal laboratory test results frequently observed. He noted co-infections are very often underdiagnosed although they occur frequently.

In patients with unusually severe or atypical features of Lyme disease, concurrent infection should be considered. McKenzie cited evidence that in humans infected with Lyme disease and babesiosis patients appear to have more intense and prolonged symptoms than those with Lyme borreliosis alone. (McKenzie, 2013).

The most recent review on human tick-borne diseases in Australia noted that there are 17 human-biting ticks known in Australia but knowledge on Australian ticks and tick-borne diseases is in its infancy. Key findings from this review, as reported by Dehhaghi et al. (2019) are presented below in Table 25.

Table 25: Human tick-borne disease 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).
• 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.

Lowbridge and colleagues also published a short review on tickborne diseases which noted, as in the other reviews above, the three tick-borne diseases in Australia: Queensland tick typhus, Flinders Island spotted fever and Q fever (Lowbridge et al. 2011). They noted that while Q fever has been isolated from ticks, transmission to humans has not been proven (note above that Q fever is primarily transmitted by aerosol McKenzie, 2013). They note that Queensland tick typhus and Flinders Island spotted fever respond well to antibiotics (not further described) (Lowbridge et al. 2011)

Other Australian published literature on Australian ticks is covered only briefly below at Table 26, as the papers have been included in the literature reviews by Chalada et al. (2016), Dehhaghi et al. (2019), Graves and Stenos (2017), or McKenzie (2013).

Table 26: Australian published literature on Australian ticks

Authors	Results/ Conclusion
Vilcins et al. (2009)	Molecular detection of *Rickettsia, Coxiella* and *Rickettsia* DNA in three native Australian tick species. Hosts included twelve koalas, two echidnas and one wombat. *"These results represent the first detection of the three genera in each rick species and identify a high level of previously undetected bacterial diversity in Australian ticks".*
Senanayake et al. (2012)	*"This is the first report of a human case of babesiosis in Australia, which we believe was locally acquired".*
Dawood et al. (2013)	Observation of a novel *Babesis* spp. in Eastern Grey Kangaroos in Australia. *"The phylogenic position of this new kangaroo Babesia sp. As a sister species to the new Australian woylie Babesia sp. Suggests a close affinity to the described Afro-Eurasian species Babesia orientalis and Babesia occultans suggesting perhaps a common ancestor for the Babesia in kangaroos".*
Gofton et al. (2015 a)	See Chalada et al. (2016) above for further information on this paper.
Gofton et al. (2015b)	See Chalada et al. (2016) above for further information on this paper.
Graves et al. (2016)	*Ixodes holocyclus* tick-transmitted human pathogens in Northern New South Wales, Australia. *"It appears that persons bitten by I. holocyclus in NE NSW, Australia have an approximate one in six risk of being infected with R. Australia. Risks of Q fever were also high in this region but this may have been due to exposure by aerosol from the environment rather than by tick bite. A subset of 74 I. holocyclus ticks were further examined for DNA from Borrelia spp., Anaplasma spp. and Ehrlichia spp. but none was found positive".*
Loh et al. (2016)	Novel *Borrelia* species detected in echidna ticks, *Bothriocroton concolor,* in Australia *"We conclude that the novel Borrelia sp. identified in this study does not belong to the Borrelia burgdorferi (sensu lato) complex, and that the phylogenetic analysis of the partial 16S gene sequences suggests it forms a unique monophyletic cluster in the genus Borrelia, potentially forming a fourth major group in this genus associated with monotremes in Australia. However, a thorough molecular characterisation will be required to confirm the phylogenetic position of this unique Borrelia sp. The zoonotic potential and pathogenic consequences of this novel Borrelia sp. are unknown at the current time".*

Authors	Results/ Conclusion
Whiley et al. (2016)	*Rickettsia* detected in the reptile tick *Bothriocroton hydrosauri* from the lizard *Tiliqua rugosa* in South Australia. *"Rickettsiosis is a potentially fatal tick borne disease. It is caused by the obligate intracellular bacteria Rickettsia, which is transferred to humans through salivary excretions of ticks during the biting process... This study is the first to use PCR to positively identify Rickettsia from South Australian Bothriocroton hydrosauri ticks collected from Tiliqua rugosa (sleepy lizard) hosts. These findings suggest that B. hydrosauri may be a vector of multiple Rickettsia spp. Also as all 41 tested B. hydrosauri ticks were positive for Rickettsia this indicates an extremely high prevalence within the studied area in South Australia".*
Low et al. (2017)	Molecular characterisation of *'Candidatus* Borrelia tachyglossi' (family *Spirochaetaceae)* in echidna ticks, *Bothriocroton concolor.* *"The presence of the glpQ gene, which is absent in the Lyme Borreliosis group spirochaetes, further emphasises that the novel species of the genus Borrelia characterized in the present study does not belong to this group. Phylogenetic analyses at multiple loci produced consistent topographies revealing the monophyletic grouping of this bacterium, therefore providing* *strong support for its species status. We propose the name 'Candidatus Borrelia tachyglossi', and hypothesize that this species of the genus Borrelia may be endemic to Australia. The pathogenic potential of this bacterium is not yet known".*

We reviewed one additional paper that was very recently published and was not included in the latest review by Dehhaghi et al. (2019). This paper was by Kwak (2018). Kwak reported on the first record of human infestation and feeding by the native tick species *Ixodes australiensis,* based on a specimen from an adult male who had been bushwalking approximately eight kilometres east of the town of Denmark in Western Australia. After the tick was removed the patient reported itchiness around the feeding site followed by pustular discharge; however, no disease development was associated in the human host during or after tick removal.

Kwak also reviewed human infestation by *Ixodidae* and *Argasidae* ticks in Australia covering publications from 1970 to 2017. The author noted that within Australia, there are 21 tick species divided between seven genera and two families that have been recorded to infest humans. As detailed studies on host preferences of many of these species had not been undertaken, it is difficult to ascertain how anthropophilic each species truly is.

Kwak reported the most significant tick-borne diseases in Australia are those caused by the genus *Rickettsia* including Flinders Island spotted fever and Queensland tick typhus. Tick-induced paralysis is also a significant concern in humans and an allergic condition dubbed 'tick-induced meat allergy' is an emerging disease of public health importance in Australia and is associated with the tick *Ixodes holocyclus.* The author noted 'tick induced meat allergy' is now being associated with a growing list of tick species internationally and will likely be associated with a wider range of Australia tick species as research continues.

4.2.5. However, while ticks are suspected to be possibly responsible for symptoms of DSCATT there are a lot of unknowns about Australian ticks and the diseases they do or might transmit or there may be a range of other possible causes for DSCATT including parasitic and viral causes, as well as environmental toxins and other potential medical explanations

The Senate Inquiry identified there are as yet a lot of unknowns, particularly around Australian ticks and that there may be a range of possible causes for DSCATT. In addition, the Lyme disease debate in Australia is pertinent to this section as the debate relates to two closely related questions:

- whether the causative agent for classical Lyme disease (either known *Borrelia* species such as *B. burgdorferi* or an as yet unidentified *Borrelia* species) is endemic to Australia (i.e. has been identified in Australia); and
- consistent with the international debate about 'chronic' Lyme disease, whether the chronic debilitating symptoms experienced by Australian patients are caused by an ongoing active infection of *Borrelia* and associated co-infections, or another as yet unidentified underlying cause or causes.

The Interim Report noted the agreement between many submitters that research into chronic debilitating symptoms must be broader than seeking to identify *Borrelia* bacteria as the symptoms may reflect a number of interactions between multiple pathogens causing a number of chronic illnesses. The submission of the Communicable Diseases Network Australia was highlighted and reproduced as below:

> *"Given the constellation of symptoms it is likely that there are multiple different diseases with different causes within the widely inclusive term 'Lyme-like illness'. The search for a causative agent for 'Lyme-like illness' should not assume or be narrowed to 'a unique local causative agent'. It is possible the causative agent(s) or clinical determinants are multiple and may not be unique to Australia. As 'Lyme-like illness' may not be caused by an infectious agent, investigation should not be limited to infectious agents. It is likely there are multiple underlying causes for the constellations of symptoms experienced by these patients, many of which are not infectious, such as hormonal, metabolic, neuromuscular and psychological disorders".*

Other possible causes for Lyme-like illness were raised at the Senate Inquiry, with the Chief Medical Officer stating that 'other vectors and routes of transmission are postulated, but yet to be demonstrated', and Dr Gary Lum stating:

> *"In the context of evolving Australian research data, we need to consider that the cause may not be limited to a single bacterial species. Parasitic and viral causes, as well as environmental toxins, should be considered for investigation, as well as other potential medical explanations"* (Senate Inquiry, Interim Report, May 2016).

Collignon and colleagues noted similar themes stating:

> *"Given the lack of evidence that Australia has either the aetiological agent or competent vector required for classic Lyme disease, many advocates have adopted the new label, "Lyme disease-like illness". The problem with this term is that it suggests that chronic Lyme disease is a recognised medical*

> *diagnosis, whereas its validity remains contentious. Another description used is "multi-systemic infectious diseases syndrome" (MSIDS), despite the fact that it has not been established that the illness denoted by this term is infectious, nor that its constellation of non-specific symptoms is postinfectious. Environmental toxins and psychological bases have not been excluded as explanations. Moreover, many patients are initially diagnosed with neurological disorders, including motor neurone disease, Parkinson's disease, multiple sclerosis and Alzheimer disease, and some advocates claim that these chronic neurological conditions are also caused by Lyme borreliosis"* (Collignon et al. 2016).

Regarding the potential cause of Lyme-like illness among Australian patients, Chalada et al. (2016) stated:

> *"A number of animals have been introduced to Australia that may act as B. burgdorferi s.l. reservoirs in Lyme endemic countries, and there are some Australian Ixodes spp. And Haemaphysalis spp. Ticks whose geographical distribution matches that of the Lyme-like cases. Four published studies have searched for Borrelia in Australian ticks, with contradicting results. The cause of the potential Lyme-like disease in Australia remains undefined".*

Graves and Stenos, in their review of tick-borne diseases concluded much about Australian ticks and the medical outcomes following tick bites remains unknown. They noted that while Rickettsial infections are currently the most commonly known, it is likely that ongoing research will reveal new tick-borne viral, bacterial and protozoan infections, including the possibility of zoonotic transmission from wild and domestic mammals and birds bitten by ticks (Graves & Stenos, 2017).

4.2.6. Some infectious tick-borne diseases can present or mimic Lyme Borreliosis, including Australian Rickettsiosis

Chalada et al. reviewed the literature regarding infectious and non-infectious disease to be considered under differential diagnoses. Of infectious diseases the authors commented:

> *"Indeed, it is unusual that not more acute Lyme Borreliosis cases are identified in humans and animals within Australia if the organism causing the illness was indeed B. bergdorfei s.l. Any putative agent of the Lyme-like disease would be capable of producing a syndrome similar to Lyme Borreliosis, with a clinical presentation including flu-like symptoms followed by arthralgic, neurological, dermatological and/or cardiac complications. Some Australian bacteria, parasites and viruses individually, or in co-infection with other pathogens, might produce such a syndrome".*

The following table includes the symptoms and clinical manifestations of tick-borne diseases in Australia, reported by Chalada et al. from the evidence reviewed. It appears that all the tick-borne diseases in Australia have the potential to mimic Lyme Borreliosis.

Table 27: Symptoms and clinical manifestations of tick-borne diseases in Australia

Infectious disease	Characteristics and clinical presentations
Australian Rickettsioses	• **Atypical presentations may mimic acute Lyme Borreliosis** • Symptoms include headache, chills, malaise, fever, lymphadenopathy, maculopapular rash and an eschar at the tick bite site • Arthralgias and myalgias can sometimes be present • Eschars may be absent in some cases; the rash may appear as varicelliform or petechial • In rare cases, the rash will not develop at all • **Rickettsial infections presenting without a maculopapular rash could be mistaken for Lyme-like illness**
Babesia	• First case of definitive Babesiosis acquired in Australia reported in 2012 and caused by *Babesia microti;* to date *B. microcoti* has not been identified in any Australian ticks • *Babesia* infection can be atypically associated with rheumatoid muscular pains and nervous complications including incoordination of lags and hysteria, restlessness and nervousness • **Appears that *Babesia* is capable of mimicking Lyme-like syndrome** • *Babesia* is also capable of establishing long-term persistent infection, like *B. berdorferi* s.l
Coxiella burnetti (Q fever)	• May also be considered in patients with tick bite history and reporting Lyme-like symptoms • Majority of cases of *C. burnetti* infections are asymptomatic • In symptomatic infections, the most prevalent acute symptoms include fever (95%), headaches (53%) and myalgia (38%); other

Infectious disease	Characteristics and clinical presentations
	manifestations may include hepatitis, pneumonia, meningitis, meningoencephalitis, pericarditis, and myocarditis • Chronic infection may manifest as endocarditis, vascular infections, osteoarticular infections, chronic hepatitis, pericarditis and very rarely as adenopathies, lung or splenic pseudotumours, or chronic neuropathy • **Q fever may therefore sometimes present as an infection similar to Lyme carditis or Lyme neuroBorreliosis**
Bartonella	• At the time of publication, Chalada et al. reported presently only *Bartonella henselae* and *Bartonella quintana* have been reported to cause disease in Australian residents; however, several other *Bartonella* species on unknown clinical significance had been identified in Australian animals and their parasites • *B. henselae* (cat scratch disease) is typically associated with isolated lymphadenopathy with fever without any other symptoms**; it has been associated with erythema marginatum rashes that may be mistaken for an erythema migrans rash** • Now recognised that *Bartonella* may cause a wide spectrum of atypical manifestations even in immunocompetent patients; **atypical manifestations may mimic a Lyme-like illness including rheumatic manifestations, fibromyalgia and chronic fatigue syndrome, neurological disease and endocarditis** • *B. henselae* is capable of sustaining chronic infection, like *B. bergdorferi* s.l.
Candidatus Neoehrlichia	• Symptoms from 11 human cases in Europe included fever, myalgia, arthralgia, neutrophilia, and anaemia combined with vascular events such as transient ischaemic attacks and deep vein thrombosis; all but one patient was actively immunosuppressed and most were asplenic • While some of these symptoms may be confused with a Lyme-like illness, further work must be performed to determine the host range infectivity and clinical presentation of the novel *Ca. Neoehrlichia* species detected in Auatralian *I. holocyclus* ticks before these may be confirmed as potential Lyme-like candidates

Most recently in 2019 Banks and Hughes published a review of the evidence for potential impacts on black rats (*Rattus rattus*) on wildlife and humans in Australia, noting the black rat carries several diseases known to affect humans and they also carry a large diversity of ectoparasites, including ticks, mites and fleas that act as vectors for transmitting disease causing agents between animals or humans (Banks and Hughes, 2019). This paper provides some helpful information about the symptoms of diseases transmitted by rats, many of which are similar to symptoms reported by patients with DSCATT.

Regarding bacteria, rats harbour species of Rickettsia, which are responsible for several distinct rat typhus groups. Table 28 below describes the potential impacts on black rats, as reviewed by Banks and Hughes.

Table 28: Impacts on black rats

Disease	Impacts
Rickettsia	• *Rickettsia* tick typhus or spotted fever caused by *Rickettsia australis* is transmitted by the Australian paralysis tick *Ixodes holocyclus.* • Symptoms of spotted fever include fever, headache and muscles aches, with a stiff neck, vomiting and mental confusion also being possible. • Spotted fever is common in subtropical and tropical areas of Queensland extending down the eastern coast to East Gippsland in Victoria. • Flinders Island spotted fever is caused by *Rickettsia honei.* This disease also occurs in Tasmania. • A third species *Rickettsia felis* has been recorded in Victoria. Humans infected with this bacterium suffer a prolonged illness of more than 12 months (no further detail was provided).
Scrub typhus	• Spread via rat-borne mites. • Symptoms include a rash, pneumonia and potentially fatal encephalitis if not diagnosed and treated. • Scrub borne typhus primarily occurs in north-eastern Australia, including Cape York, and also the Northern territory and Western Australia.
Q fever	• Rats may also harbour the tick *Amblyomma triguttatum triguttatum* which is a natural host for the *Coxiella burnetii* bacterium and causes Q fever in humans. • Symptoms of Q fever in humans includes acute flu-like symptoms and occasionally heart failure.
Salmonella and *Leptospira*	• Leptospirosis, a notifiable disease is all states and territories in Australia, can lead to death of left untreated. • Symptoms more commonly include severe fever, headache, chills, myalgia, sweats, arthralgia and vomiting.

4.2.7. Allergy, paralysis, autoimmunity and post-infection fatigue following tick bites

Several papers reviewed commented on allergy, paralysis and autoimmunity in response to tick bites.

Dehhaghi et al. (2019) commented that there are an increasing number of allergic, inflammatory and potentially autoimmune illnesses attributed to ticks with *I. holocyclus, O. capensis,* and *O. gurneyi* being three tick species that trigger such complications in humans and are also present in Australia. Within Australia, Dehhaghi and colleagues report that currently, only some areas in Northern Territory and South Australia may be free from human-biting ticks and tick-borne diseases; however, tick-borne infections and illness have been reported in all other states including New South Wales, Queensland, Tasmania, Victoria, and Western Australia (Dehhaghi et al. 2019).

Chalada et al. (2016) noted that antigens to *I. holocyclus* saliva alone may cause an erythematous rash to develop in bitten patients and that such a hypersensitivity rash may be easily mistaken for

an erythema migrans rash in patients recently bitten by *I. holocyclus* ticks. The authors commented:

> *"These findings do raise a question as to whether the Australian presentation of a Lyme-like illness may in some cases be an allergic response by some individual patients to antigens found local tick saliva".*

Graves and Stenos noted local allergic reaction to ticks is not uncommon and may present as urticaria, or induration (due to tick saliva), scrub itch (due to infestations of nymphs) or rash. Allergic reaction may occasionally be systemic including wheezing, anaphylaxis and even death, with sever allergy having been recently described following prior sensitisation of a patient due to ingestion of red meat.

Regarding paralysis following tick bites, *I. holocyclus* – known as the paralysis tick – injects a mixture of neurotoxins similar to botulinum toxin into the host when it bites. Native animals, family pets and occasionally humans are affected, if they are small. The toxins may cause ataxia followed by an ascending, symmetrical, flaccid paralysis similar to Guillain-Barré syndrome, and cranial nerves may also be involved leading to facial paralysis or ophthalmoplegia. Human deaths due to tick toxin have occurred but not for many years (Graves & Stenos, 2017).

Regarding autoimmunity following tick bites, Graves and Stenos reported that one report of Graves' disease developing in a patient bitten by an unknown species of Australian tick in Western Australia exists in the literature. However, the patient also had a mild rickettsial infection following the tick bite and it was hypothesised that molecular homology between the thyroid secreting hormone receptor of the patient and the rickettsial ATPase enzyme resulted in the synthesis of an antibody that cross-reacted with the host thyroid receptor, leading to increased synthesis of thyroid hormones (Graves & Stenos, 2017).

Post-infection fatigue is a well-known consequence of several infections including Ross River virus, Q fever and Epstein-Barr virus; however, the antecedent infection may not be clearly identified in the patient 9Graves & Stenos, 2017). While not yet widely recognised as a problem following rickettsial infection, it has been suggested by a study involving two large cohorts or fatigued and non-fatigued patients, and a case report (Graves & Stenos, 2017).

4.2.8. From the limited information available, while many diagnoses have been given to patients with DSCATT, several non-infectious diagnosable and treatable diseases and conditions consistently stand out as differential diagnoses that should be considered high priority in patients presenting with DSCATT, including multiple sclerosis, motor neurone disease, rheumatoid arthritis, Parkinson's disease, fibromyalgia, autoimmune diseases and chronic pain syndromes. Chronic fatigue syndrome is also high on the list for differential diagnoses

Several sources of evidence and information are available regarding non-infectious diagnosable and treatable conditions associated with DSCATT. These sources are submissions by patients and LDAA, analysis of patient submissions to the Senate Inquiry and submissions and presentations by ACIDDS doctors treating patients with DSCATT. When several sources of evidence are compared there are common diagnoses of diagnosable and treatable conditions that appear to occur in patients with DSCATT, with multiple sclerosis, motor neurone disease, rheumatoid arthritis, Parkinson's disease fibromyalgia, autoimmune diseases and chronic pain syndromes being the most common. Chronic fatigue syndrome is also a very common diagnosis.

Table 29 below sets out the sources of evidence and information available regarding non-infectious diagnosable and treatable conditions that may be associated with DSCATT.

Table 29: Evidence and information regarding non-infectious diagnosable and treatable conditions associated with DSCATT

ACIIDS (ACIIDS, Submission 370, May 2016)	Dr Schloeffel (DSCATT Forum, April 2016)	Brown (2018)	LDAA submission analysis (LDAA, Supplementary submission, November 2016)
Multiple sclerosis	Multiple Sclerosis	multiple sclerosis	Yes
Amyotrophic lateral sclerosis (ALS)	Motor Neurone Disease (ALS)	motor neurone disease	
Parkinson's disease	Parkinson's Disease		Yes
Alzheimer's disease	Alzheimer's Disease		
Chronic Fatigue Syndrome	Chronic Fatigue Syndrome		Yes
Fibromyalgia	Fibromyalgia		Yes
Rheumatoid arthritis		Rheumatoid arthritis (RA)	Yes
Polymyalgia rheumatica			
Polymyositis			
Autism	Autistic Spectrum Disorders		
Complex regional pain syndrome	Chronic Pain Syndromes		
	Autoimmune Disease		
		Systemic lupus erythematosus (SLE)	
		Crohn's disease	
		'Other'	
			Mental disorder

In addition, Dr Schloeffel in his evidence to the Senate Inquiry was reported to have explained that diagnosis is neither quick nor simple and is evidence based (Senate Inquiry Final Report November 2016), and was quoted as stating:

> *"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 to 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 the disease".* (Senate Inquiry Final Report, November 2016).

Of the non-infectious diseases, Chalada et al. noted fibromyalgia, chronic fatigue syndrome, delusional parasitosis and multiple sclerosis as some examples of conditions that may be misdiagnosed as a Lyme-like disease, particularly in Australia where the infectious aetiology for Lyme-like illness has not been elucidated. The authors cited a 1989 paper that reported antigens in *I. holocyclus* saliva alone may cause an erythematous rash to develop in bitten patients, in most cases the rash being 50mm or more in diameter and persisting for seven days or more. They commented such a hypersensitivity rash might easily be mistaken for an erythema migrans lesion in patients recently bitten by *I. holocyclus* ticks, with the findings raising the questions as to whether the Australian presentations of Lyme-like illness may in some cases be an allergic response by some individual patients to antigens found within local tick saliva.

Chalada and colleagues also discussed fibromyalgia and chronic fatigue syndrome in relation to Lyme-like illness with key points presented below in

Table 30.

Table 30: Fibromyalgia and chronic fatigue syndrome in relation to Lyme-like illness

Non-infectious disease	Symptoms
Fibromyalgia	• Widespread musculoskeletal pain, hyperalgesia, fatigue, insomnia, memory loss and poor concentration, headache and irritable bowel syndrome • Diagnosed based on widespread musculoskeletal pain, sensitivity in a number of "tender spots", and the presence of other associated symptoms such as headaches, sleep disturbances and memory loss. • It is possible for fibromyalgia to be mistaken for Lyme Borreliosis and *vice versa* as diffuse arthralgia, cognitive difficulties and fatigue are common in chronic Lyme Borreliosis. • Fibromyalgia may present as sequelae of infections with *C. burnetti, Chlamydophilia pneumoniae,* Epstein-Barr virus and Parvo-virus B19.
Chronic fatigue syndrome (CFS)	• Very similar to fibromyalgia in that it is a syndrome of unknown aetiology characterised by persistent fatigue, musculoskeletal pain, insomnia and cognitive impairment and headaches. • CFS and fibromyalgia commonly co-occur with evidence suggesting that the two syndromes are merely symptom amplification of the same somatic syndrome. • Both syndromes are more common in women than men • CFS diagnosis is based on onset of unexplained persistent or relapsing chronic fatigue that is not substantially alleviated by rest, accompanied by symptoms including short term memory or poor concentration, sore throat or lymph nodes, muscle or joint pain and headaches. • CFS may present as sequelae of infections with *C. burnetti, Chlamydophilia pneumoniae,* Epstein-Barr virus and Parvo-virus B19.

Regarding fibromyalgia and CFS, Brown also commented the most commonly reported symptoms by patients to the Senate Inquiry (fatigue, disordered thinking, or 'brain fog', arthralgia and myalgia, sensory disturbance and headache), along with submissions showing a *"striking female preponderance"* (80.3 percent when reported), were prominent components of fibromyalgia and chronic fatigue syndrome (CFS), two of the most prominent MUPS ('medically unexplained physical syndrome'). He further commented that the non-specific symptoms, female preponderance and lack of confirmatory laboratory testing suggested patients are more likely to be experiencing a MUPS disorder (such as CFS) than an active or latent infection, citing evidence from 2015 that investigators of 'chronic Lyme disease' in the USA had reached the same conclusion from actively comparing healthy, CFS and 'alternatively diagnosed Lyme' groups.

Regarding the high proportion of Australian females represented in the submissions to the Senate Inquiry, Brown cited evidence published in 2013 and 2015, that indicated Lyme diseases has a slight male preponderance in endemic areas, with Brown noting this was most likely attributed to males being more likely to engage in at risk occupations or hobbies. However, as noted by LDAA earlier, they suspect their survey was skewed towards females, due to females being more active on social media sites. Given Brown noted that Lyme advocacy groups requested sufferers make submissions and provided standardised templates, this may have possibly had an impact on the

gender distribution of submissions from patients identifying as suffering from Lyme disease or Lyme-like illness.

5. ISSUES ASSOCIATED WITH DIAGNOSTIC TESTING FOR LYME DISEASE IN AUSTRALIA AND BY OVERSEAS LABORATORIES

This section reports on the literature reviewed the answer the research question:

> *What are the issues associated with diagnostic testing for Lyme disease both in Australia and by overseas laboratories?*

The section highlights the complexity in being able to distinguish between the illnesses classical Lyme disease, an infectious disease, and DSCATT. The Australian Government notes that while some Australians and healthcare providers believe that classical Lyme disease can be acquired from ticks in Australia or that a form of 'chronic Lyme disease' exists, the Australian Government cannot support the diagnosis of locally acquired Lyme disease in Australia without the causative organism of classical Lyme disease (*Borrelia burgdorferi* sensu lato) or a competent vector being identified in Australia (Australian Government Position Statement: Lyme Disease in Australia, 2018).

The complexity and controversy is very evident in the available literature. This section focuses on the issues of diagnostic testing in Australia for Lyme disease, a recognised and documented infectious disease, caused by the bacteria *Borrelia burdorferi* s. l. endemic in the US, Europe and Asia. As noted above in the Government's position statement, the causative agent or vector for 'chronic Lyme disease' or DSCATT in Australia has not been identified and therefore there is no diagnostic test for Lyme-like illness or DSCATT.

The complexity and controversy is this: on the one hand there is a diagnostic test that is used in Australia to detect and support diagnosis of classical Lyme disease in patients who have travelled outside Australia to Lyme endemic areas and have come back with symptoms of classical Lyme disease. On the other hand the Senate Inquiry investigated the diagnostic tests for overseas acquired Lyme disease in relation to its inquiry into Lyme-like illness and where the diagnostic test for classical Lyme disease had been applied to patients where the cause of Lyme-like illness/DSCATT has not been determined but believe they have locally acquired Lyme disease or classical Lyme disease. This led to significant controversies and differences in views by medical professionals and patient advocacy groups about the reliability of the diagnostic test and protocol designed to aid in the diagnosis of overseas-acquired classical Lyme disease.

To navigate this complexity, we first present the findings on the diagnostic tests for overseas-acquired Lyme disease when applied to patients who have been to Lyme endemic areas, and then present the controversies about diagnostic testing raised in the Senate Inquiry. We follow the controversies section with the National Serology Reference Laboratory Australia (NRL) investigation of the performance of assays for Lyme disease in Australia that occurred following the concerns and controversies raised in the Senate Inquiry about the ability of Australian accredited laboratories to detect classical Lyme disease compared to overseas laboratories. We then present the findings of international research on the diagnostic accuracy of tests of Lyme disease.

Evidence reviewed

To answer this research question, we reviewed 18 articles, reports or submissions. We prioritised evidence that is specifically related to treatment modalities provided in Australia.

Systematic reviews (2)	Leeflang et al. 2016; NICE 2018 Lyme disease: diagnosis and management [C] Evidence reviews for diagnostic tests.
Narrative literature reviews and reviews (3)	Chalada et al. (2016); Collignon et al. 2016; McManus and Cincotta (2015)
Observational studies (1)	Brown (2018);
Official Australian reports and government inquiries (4) **including submissions within relevant Senate Inquiry reports (5)**	Senate Inquiry Interim Report, May 2016; Senate Inquiry Final Report, November 2016; NRL, May 2017; Department of Health NRL Q&A 2018). CDNA, Submission 531, 2016; Public Health Laboratory Network (PHLN), Submission 319, as reported in Senate Inquiry Interim Report, May 2016; Dr Richard Horowitz, Submission 936 as reported in Senate Inquiry Final Report, November 2016); LDAA, submission 512 May 2016;ACIIDS submission 370, 2016
(Inter)national authority and intergovernmental reports and guidelines (2)	Department of Health Australian Guideline- diagnosis of overseas-acquired Lyme disease, 2015. NICE guideline Lyme disease, 2018
International and Australian guidelines produced by clinical and professional bodies (1)	RCPA Position Statement Diagnostic Laboratory testing for Borreliosis, 2016).

Key findings on Issues associated with diagnostic testing for Lyme disease in Australia and by overseas laboratories:

- The Australian guidelines on the diagnosis of overseas acquired Lyme disease are for the diagnosis of classical Lyme disease only and do not apply to Lyme-like illness acquired in Australia.
- There are three laboratory techniques for diagnosis of Lyme disease, including culture of the organism, molecular detection of DNA and serology. All laboratory techniques have challenges – serology is the mainstay technique currently used.
- Most serological diagnostic protocols in the US and Europe use a two-tier system; the Australian guideline uses the two-tier system.
- The interpretation of serology tests, including for Lyme disease, depends on the sensitivity and specificity of the test, and how common the disease is among people being tested.
- The issue of diagnostic testing, whether Lyme disease can be contracted in Australia and discordant results for Lyme disease testing between accredited and non-accredited laboratories, was the most contentious issue to emerge in the 2016 Senate Inquiry.
- The Senate Inquiry noted the contradictory evidence about the reliability of the two-tier testing protocol, including the sensitivity of ELISA and false positives versus false negatives and its use in immunocompromised patients.
- Australian laboratories are accredited for medical testing by the National Association of Testing Authorities Australia (NATA) in conjunction with the Royal College of Pathologists of Australasia (RCPA). The Australian guideline for diagnosing overseas-acquired Lye disease states tests should be performed in an accredited laboratory.
- The use of non-accredited Australian laboratories and overseas laboratories has caused controversy and can cause significant confusion and frustration for patients.
- From limited available evidence a high proportion of patients with Lyme-like illness have tested positive to Lyme disease in non-accredited Australian or overseas laboratories.
- 'Lyme-literate' practitioners use non-accredited Australian laboratories and overseas laboratories for three reasons and consider these laboratories are better placed to accurately test for *Borrelia.*
- However, medical authorities suggest results from overseas laboratories should be interpreted with caution and that in the absence of a known causative agent for DSCATT in Australia a positive test is likely to be a false positive.
- Investigation of the performance of assays for Lyme disease in Australia by the National Serology Reference Laboratory in 2017 determined the tests used by Australian laboratories to diagnose Lyme disease had equivalent reliability to tests used in overseas laboratories.

5.1. Diagnostic tests for overseas-acquired Lyme disease

5.1.1. The Australian guidelines on the diagnosis of overseas-acquired Lyme disease are for the diagnosis of classical Lyme disease only and do not apply to Lyme-like illness acquired in Australia

The Senate Inquiry Interim Report in the section on diagnostic testing for Lyme-like illness reported on diagnostic testing for Lyme disease. Key findings of the Senate Inquiry on the diagnosis of overseas acquired Lyme disease are included here.

The Department of Health had released Australian guidelines on the diagnosis of overseas-acquired Lyme disease in 2015, emphasising that these guidelines are for the diagnosis of classical Lyme disease only and do not apply to Lyme-like illness acquired in Australia (Department of Health Australian Guideline- diagnosis of overseas-acquired Lyme disease, 2015).

These Australian guidelines noted a confirmed case of Lyme disease requires laboratory definitive evidence of culture, DNA or serological assays, clinical and epidemiological evidence. Epidemiological evidence was highlighted as important in determining whether a patient has Lyme disease; determining a travel history and tick exposure-prone activities are essential.

In the Australian guideline, testing follows a two-tiered approach involving a screening immunoassay and a confirmatory immunoblot (Department of Health Australian Guideline-diagnosis of overseas-acquired Lyme disease, 2015).

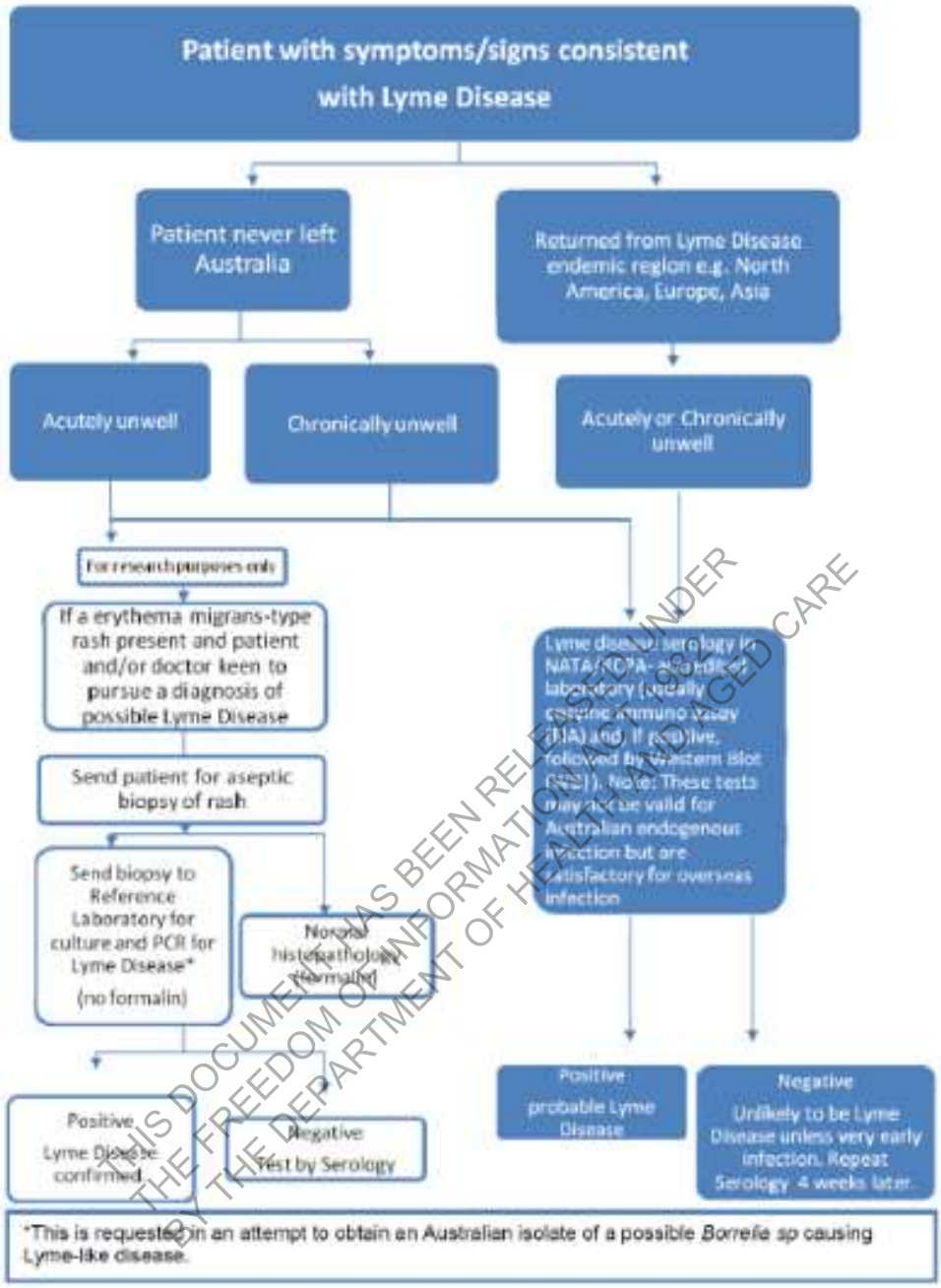
The Senate Inquiry noted diagnostic protocols in the Australian guideline were consistent with the 2014 position statement of the RCPA *Diagnostic testing for Borreliosis ('Lyme Disease' or similar syndromes) in Australia and New Zealand* and that submissions from medical authorities and state and territory governments supported the RCPA's position statement and that the diagnostic protocol should be followed for diagnosing Lyme disease or any similar syndromes (Senate Inquiry Interim Report, May 2016).

The Communicable Diseases Network Australia (CDNA) advocates the process for diagnosis as delineated in the Australian guideline and the RCPA. (CDNA, Submission 531, 2016).

Chalada et al. (2016) in their review of the evidence regarding the relevance of diagnostic tests in Australia noted that the CDC diagnostic serological method used for *B. burdorferi* s. s. is inappropriate for use in the Australian context except for patients with a travel history to endemic areas. The authors commented it is possible that any theoretical Australian *B. burgdorferi* s. l. species would cause a different serological response in a Lyme Borreliosis patient than the American, Asian or European species and such antigenic differences could result in false negative results.

Regarding accreditation of Australian laboratories, the Senate Inquiry Interim Report noted Australian laboratories are accredited for medical testing by the National Association of Testing Authorities Australia (NATA) in conjunction with the RCPA. According to the Department, NATA-accredited laboratories can readily test for Lyme disease acquired overseas where patients have travelled to an endemic area (Senate Inquiry Interim Report, May 2016). This protocol is reproduced in Figure 10 below.

Figure 10: Recommended protocol for laboratory testing of patients with suspected Lyme disease in Australia



5.1.2. There are three laboratory techniques for diagnosis of Lyme disease, including culture of the organism, molecular detection of DNA and serology. All laboratory techniques have challenges - serology is the current technique used

Laboratory definitive evidence for Lyme disease can be collected through culture, DNA or serological assays.

> *"The best independent confirmation of any reactive antibody result is demonstrating the microorganism itself. This usually involves culturing the microbe or detecting its genome by polymerase chain reaction (PCR)"* (Collignon et al. 2016).

Culture

The 'gold standard' for specificity of *Borrelia* infection is culture of spirochaetes from patient specimens (Senate Inquiry Interim Report, May 2016). The culture of *Borrelia* bacteria is difficult, the number of spirochaetes in clinical specimens is low; and culture is used/attempted usually only in reference laboratories (Collignon et al. 2016;Department of Health Australian Guideline-diagnosis of overseas-acquired Lyme disease, 2015; RCPA Position Statement Diagnostic Laboratory testing for Borreliosis, 2016; CDNA Submission 531, 2016).

Chalada et al. (2016) in their review of the evidence regarding culture from patients reported that while biopsies of erythema migans had been taken from numerous Australian patients for histology or PCR (McCrossin, 1986; Stewart et al. 1982; Lawrence, 1986; Mayne, 2012), there has only been one published report of *Borrelia* culture being successful (Hudson et al. 1998). The authors noted that although the disease appeared to follow the tick bite contracted in New South Wales, the patient had also travelled to three Lyme-endemic countries in Europe 17 months before the onset of symptoms and that while this published case demonstrated a culture confirmed Lyme Borreliosis causing *Borrelia* isolate in an Australian patient, Australian acquisition could not be confirmed.

Of the evidence Chalada et al. (2016) concluded:

> *"B. burgdorferi s. l. has never been cultured from an Australian patient that could not have acquired the infection overseas and therefore there is currently no proof that B. burgdorferi s. l. or any other kinds of Borrelia species are infecting humans in Australia. If there is a Lyme like disease that exists in Australia it may well be of a different aetiology".*

DNA

The Senate Inquiry noted molecular detection of *Borrelia* bacteria using a Polymerase Chain Reaction (PCR) test in patient specimens may also be used. However, citing evidence from Mackenzie (2013) the Senate Report noted these tests are not regarded as reliable as the bacteria are difficult to detect and appropriate samples are difficult to obtain (Senate Inquiry Interim Report, May 2016). RCPA also noted the assay for molecular detection of DNA from *Borrelia sp* in patient specimens is only available in Reference Laboratories and suffers from the difficulty of obtaining appropriate samples from the patient. (RCPA Position Statement Diagnostic Laboratory testing for Borreliosis, 2016).

Regarding PCR Collignon et al. (2016) reported, citing evidence:

> *"PCR targeting various gene targets (flaB, 16SrRNA, recA, p66, ospA, 5SrRNAe23SrRNA gene spacer region) can provide highly specific evidence of B. burgdorferi nucleic acid, but the very low organism load means that even the sensitivity of PCR in this context is not great. Further, if too many PCR cycles are undertaken, specificity is lost; there is also the possibility of contamination".*

Regarding the evidence on molecular detection of *B. burgdorferi* s. l. from patients with Lyme-like illness in Australia, Chalada et al. reported *Borrelia burgdorferi* s. l. DNA has been detected and sequenced in five Australian patients presenting with Lyme-like disease. The papers reviewed were Mayne et al. 2014; Mayne, 2012; Mayne, 2015). Issues raised by Chalada et al. of the three studies included primer sequences not being published, some patients having travelled overseas non-specific amplification possibly leading to a positive PCR reaction, and a laboratory at the time of Chalada et al.'s paper being submitted having not shared their primer sequences or any DNA or isolates with researchers for independent verification.

Serology

The Senate Inquiry more common way for diagnosing Lyme disease is through testing for antibodies to *Borrelia* bacteria through serological assays (Senate Inquiry Interim Report 2016). The Senate Inquiry noted the United States (US) Centers for Disease Control and Prevention (CDC) notes that serological test results need to be interpreted according to strict criteria, including whether Lyme disease is endemic to a particular area and whether the patient exhibits clinical symptoms. (Senate Inquiry Interim Report, May 2016).

The RACP Position statement notes serology is currently the mainstay of laboratory diagnostics for Lyme disease with important variables including:

- the stage of disease, antigenic variation between different *Borrelia spp*; and
- the origin of the Borrelia antigens utilised in the assay and immunoglobulin isotypes (e.g. IgM, IgG) being detected in the serum.

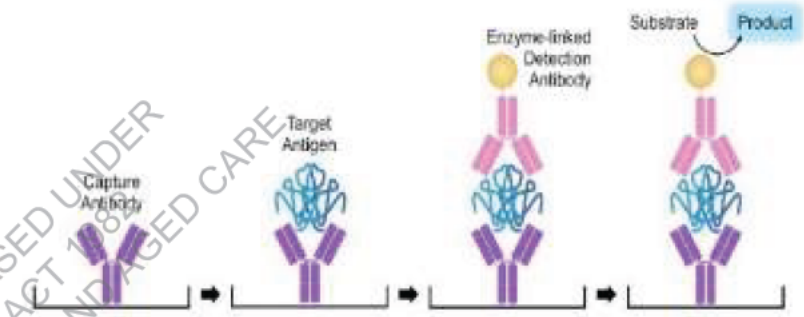
The RACP also advises that patients with early infection may have negative serology, although this is very unlikely in those with long-standing symptoms. IgM positivity alone may be a false positive result unless IgG sero-conversion is demonstrated subsequently (RCPA Position Statement Diagnostic Laboratory testing for Borreliosis, 2016).

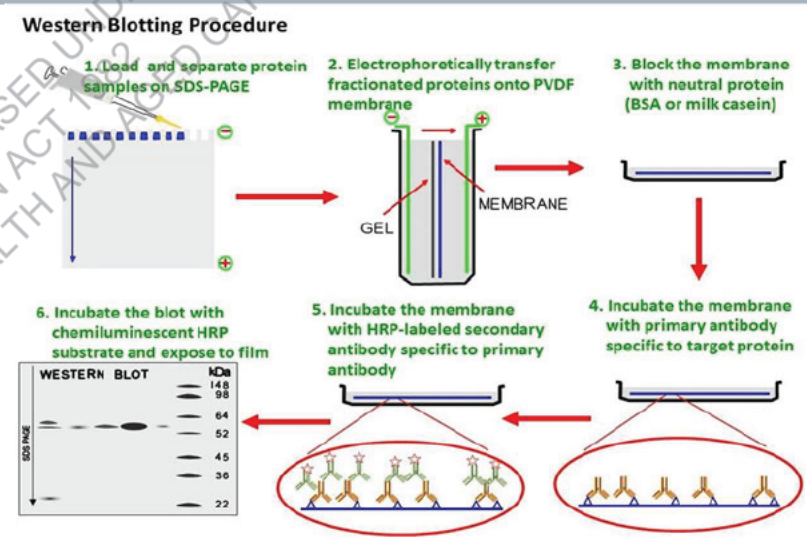
The CDNA submission also provided additional information on serology testing noting that as spirochaetes including *Borrelia* species may inhabit the human gastrointestinal tract:

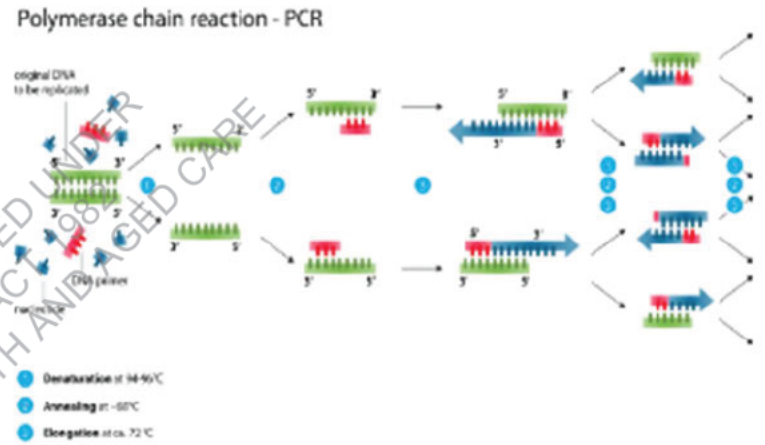
> *"it is important any tests for any 'Lyme-like illness' causative organism, if such an organism exists, do not cross react with antibodies in the normal flora. Cross reactions can also occur due to autoimmune diseases"* (CDNA submission 531, 2016).

Further detail about the advantages, disadvantages and limitations of diagnostic tests for Lyme disease are in Table 31 below.

Table 31: Diagnostic tests for Lyme Disease Adapted (with additions) from Lindsay, (2014)

	Advantages	Disadvantages	
Enzyme immunoassay (EIA)			
An enzyme immunoassay is used as a screening test to detect IgM and/or IgG antibodies in serum that are directed against the bacterium that causes Lyme Disease. Commercial kits, such as an enzyme-linked immunosorbent assay, rely on the use of whole-cell preparations of *B. burgdorferi* and/or recombinant antigens (e.g. C6 peptide). While most enzyme immunoassays are highly sensitive, they may lack specificity (i.e. false positives can occur as a result of other conditions).	High sample throughput and relatively easy to perform. Generates objective numerical values compared with other subjective measures (e.g. immunofluorescent assays).	Lower sensitivity in early stage disease. Variation in sensitivities and specificities of different commercial kits. Autoimmune disorders, EBV, bacterial endocarditis, syphilis, other spirochete infections, anaplasmosis or *Helicobacter pylori* infection may cause false-positive results. Some tests cannot discriminate between antibodies produced against North American versus European/Asian genospecies of *Borrelia.* Genotype of *B. burgdorferi* may reduce	

		sensitivity in early Lyme disease. Cannot differentiate a previous infection from re-infection with *B. burgdorferi.*	
Western blot			
Used as the corroborative test, has greater specificity than the enzyme immunoassay. Detects antibodies directed against electrophoretically separated antigen extracts and recombinant antigens native to *B. burgdorferi*. Commercial kits test for antibodies to individual genospecies of *Borrelia* and to differentiate IgM from IgG antibodies. A positive WB result is required to confirm exposure to *B. burgdorferi* , and seroconversion from IgM to IgG.	High specificity such that these tests can be used to rule out other etiologic agents. Able to determine reactive immunoglobulin classes (IgG vs. IgM) and help differentiate early from longer-standing infections.	Interpretation of results is subjective (e.g. scoring band position and intensity) for Western blot assays that do not use an automated reader. Significant cross-reactivity occurs among European genospecies. LgM antibodies are inherently cross-reactive, which may lead to false-positive results. False-negative IgG Western blot results may occur early in the course of infection or as a result of antibiotic treatment.	

WB antibodies provides definitive evidence of a recent infection.			
Polymerase Chain reaction (PCR)			
Several formats of PCR testing are used to amplify a variety of *Borrelia*-specific genetic targets in clinical specimens. Positive results are most frequently seen in the early phase of the disease. The sensitivity of PCR on cerebrospinal fluid is low or variable and of limited use in evaluating patients with neurological signs. Although these assays can identify an infection sooner than serological testing, their use is mostly restricted to research studies	Able to detect *B. burgdorferi* DNA after antibiotic treatment has started, therefore able to distinguish an ongoing infection from persistent symptoms due to an immunologic mechanism. *Borrelia* DNA can be detected in EM lesions before the appearance of serum antibodies and without the delay associated with bacterial culture / isolation.	Poor sensitivity due to low bacterial load in some clinical samples. Lack of standardization with respect to target genes. Specialist and scrupulous laboratory practice essential. High cost	

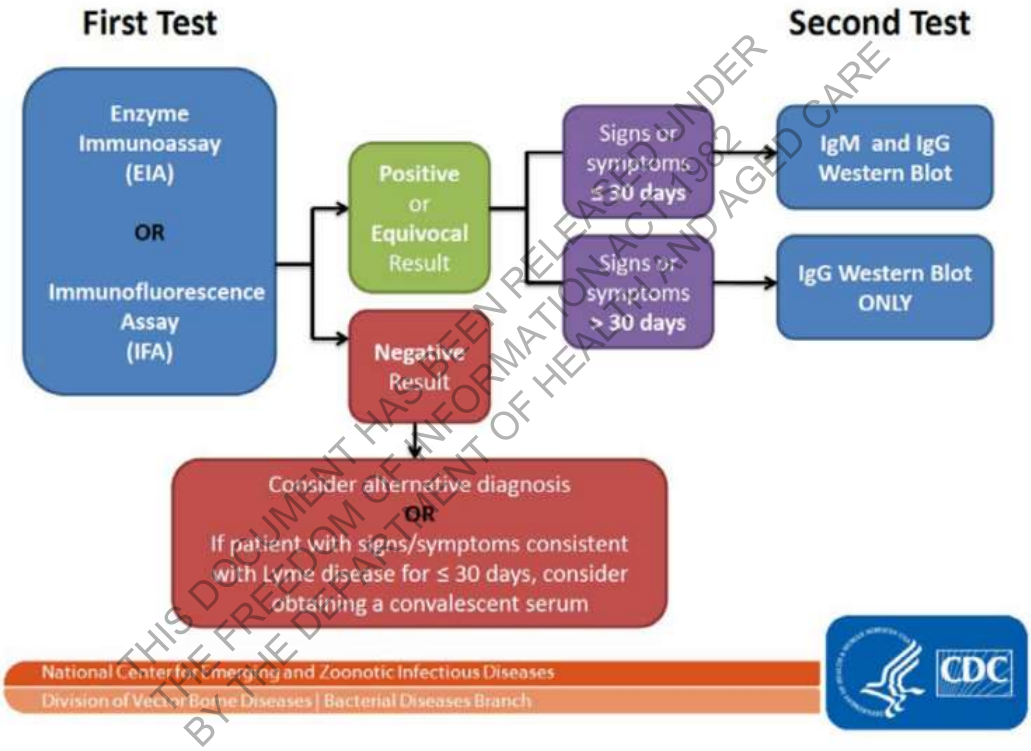
5.1.3. Most serological diagnostic protocols in the US and Europe use a two-tier system; the Australian guideline uses the two-tier system

The first stage is most commonly an enzyme-linked immunosorbent assay (ELISA), followed by a Western blot. Western blots are interpreted using standardised criteria. These criteria differ between the US and Europe depending on the different genospecies of *B. burgdorferi* in different regions (Senate Inquiry Interim Report, May 2016).

The RCPA's position statement recommends the use of the two-tiered system and highlights that Western blot tests 'must be interpreted with caution, especially in the absence of an Australian *Borrelia sp'*. (Senate Inquiry Interim Report, March 2016).

The figure below is reproduced from the Senate Inquiry Interim Report with the source of the diagram being the CDC.

Figure 11: Two-tiered testing for Lyme disease



5.1.4. The interpretation of serology tests, including for Lyme disease, depends on the sensitivity and specificity of the test, and how common the disease is among people being tested

The submission from the Public Health Laboratory Network had noted in evidence that the interpretation of serology tests depends on three key factors:

- the sensitivity of the test (the percentage of people with the disease who will have a positive test);
- the specificity of the test (the percentage of people without the disease who will have a negative test); and
- the pre-test likelihood of the person having the disease, based on the prevalence of the disease in the population being tested (Public Health Laboratory Network (PHLN), Submission 319, as reported in Senate Inquiry Interim Report, May 2016).

Additional evidence from the Communicable Diseases Network Australia (CNDA) gives further explanation to the last point highlighted above by PHLN regarding how common the disease is among the people being tested. CDNA stated:

> *"The accuracy of a laboratory test depends not only on the test itself and whether the testing laboratory is appropriately compliant with ISO 15189, but also on how common the disease is among the people being tested. Even with a laboratory test that is able to detect the disease in over 95% of the people who have the disease, and detect the absence of disease in over 95% of people who do not have the disease, it is inevitable that some people who do not have the disease will have a positive laboratory test (a false positive); the chance of this happening is increased if the disease is uncommon. Lantos et al. demonstrated that is an area of the United States of America where Lyme disease is uncommon, less than one in five patients with a positive test actually had Lyme disease. Lyme disease is rarer in the Australian context*

The Senate Inquiry Interim report noted that as classical Lyme disease is considered to have a low prevalence in Australia, locally acquired cases are considered likely to return negative results for *Borrelia*. The PHLN had noted that positive results for locally acquired Lyme disease are likely to be 'false positives' and are not uncommon in patients suffering other conditions:

> *"… a positive result is more likely to be a false-positive if the test is performed on a person with a low pre-test likelihood of having the condition, such as testing for Lyme disease in Australia. There are two factors at play here – the first is that when less stringent interpretative criteria are used … the results will be skewed to more patients with the disease. The other factor is that the assays were developed for classical Lyme disease, so for patients in a low prevalence population with nonspecific symptoms, the predictive value is low and reactive results are more likely to reflect absence of disease while nonreactive results likely reflect true absence of disease. False positive results for Lyme disease are not uncommon in patients suffering from other conditions"* (Public Health Laboratory Network Submission 319, as reported in Senate Inquiry Interim Report, May 2016).

Chalada et al., in reviewing the evidence on cases of Lyme-like illness, reviewed the evidence on serology from patients diagnosed as having likely Lyme Borreliosis in Australia (Rothwell et al.

1989; Maud and Burk, 2013; Mayne, 2011; Mayne, 2015; Stallman, 1887). Chalada et al. noted serology has a low positive predictive value in non-endemic areas and cannot be relied upon for diagnosis. They concluded:

> *"In summary, none of the published Lyme-like illness cases from Australian patients diagnosed by serology alone have met the minimum criteria for serological diagnosis of Lyme Borreliosis as described in Section 3.1" [in Lyme Borreliosis endemic Unites States of America].* (Chalada et al. 2016)

Chalada et al. (2016) noted that in areas not endemic for Lyme Borreliosis, the positive predictive value of the serology test will be low. The authors cited evidence that in endemic areas, patients with other illness and even healthy donors may display at least 5 of the 10 bands required for a positive anti-B. burgdorferi IgG western blot result. In the non-endemic setting of Papua New Guinea, 50 percent of 84 individuals screened for Lyme Borreliosis fitted the CDC serological criteria for Lyme Borreliosis, leading the authors of the cited study to think the false positive Lyme serology results were the consequence of high levels of immunoglobulin or cross-reactive antibodies residents of tropical regions. Taking such evidence into account Chalada and colleagues stated:

> *"It is possible this same phenomenon may occur in Australia. While the causative agent of the putative Lyme-like disease remains unknown, any positive or negative Lyme serology results are unreliable".*

Additionally, Chalada et al. (2016) pointed out that evidence from the CDC noted that the ELISA or IFA tests may give false-positive reactions in the presence of other infectious, autoimmune or inflammatory conditions, while not performing the ELISA or IFA step will increase the likelihood of false positives in the immunoblot.

The Senate Inquiry Final Report noted the two-tier testing protocol is considered to be world-class and reliable and accredited laboratories in Australia have only returned positive results for Lyme disease acquired overseas, reinforcing the understanding that the pathogens responsible for Lyme disease are not endemic to Australia (Senate Inquiry Interim Report, May 2016 as reported in the Senate Inquiry Final Report, November 2016). However, concerns about the reliability of the two-tier diagnostic protocol were raised in the Senate Inquiry (see Section 5.2). In response to those concerns Professor Graves of the Royal College of Pathologists of Australasia provided the following evidence to the Senate Inquiry regarding how and why the two tiers of testing ensure accuracy.

- '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.
- 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.
- 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.
- By going straight to a Western Blot assay, there is a possibility that some Lyme cases could be missed, as it is a less sensitive assay than the ELISA.

- In practice however, both assays can give false-positive results and also false-negative results. By having the two 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'. (Senate Inquiry Final Report, November 2016)

Regarding false positives vs false negatives of ELISA, Professor Graves stated:

> *"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"* (Senate Inquiry Final Report, November 2016).

Another paper published in 2016 showed similar themes to Professor Graves' comments. Antibody testing in a large Australian diagnostic laboratory over a 23-month period between September 2014 and July 2016 found that nearly all (5,372, 95.5 percent) of tests from 5,395 patients returned negative results for Lyme disease, with the authors commenting that to minimise the risk of a false positive result, tests should be requested only when there is a well-founded clinical suspicion of Lyme disease and not in situations of low-test probability (Collignon et al. 2016). In this study test referrals came from all Australian states, with most from New South Wales (45 percent) and Queensland (27 percent) with women aged 30-50 years being the largest group tested. Seventy-nine samples (one percent of all samples) returned positive results for both the screen immunoassay and initial immunoblot. Of these 79 patients, 29 who had a low pre-test probability of infection such as no symptoms or epidemiological risk factors were negative on a second immunoblot. The total number of true positive tests was therefore 50 (0.9 percent of all tests) from a total of 43 patients. Additionally, the total number of false positives was 206 of 256 positive screening tests (80.5 percent). The authors noted that a travel history was available for 37 of the 43 patients with true positive results and all had returned from countries in which Lyme disease is endemic (Collignon et al. 2016)

Professor Graves also provided evidence that the accuracy of the two-tiered protocol in use by the majority of laboratories is not impeded by hypervariable genomes, indicating this was not particular to *Borrelia* but could be said of all microbes. He stated:

> *"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!" (Senate Inquiry Final Report, November 2016)

5.2. Issues raised in the Senate Inquiry about diagnostic testing for Lyme disease and Lyme-like illness in Australia

5.2.1. The issue of diagnostic testing, whether Lyme disease can be contracted in Australia and discordant results for Lyme disease testing between accredited and non-accredited laboratories was the most contentious issue to emerge in the Senate Inquiry

"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" (Senate InquiryFinal Report, November 2016).

Both the Senate Inquiry Interim and Final Reports explored diagnostic testing. In the Interim Report the diagnostic process by which patients come to be diagnosed with Lyme-like illness was examined. This report also explored the discordant results for Lyme disease testing between accredited laboratories in Australia, and laboratories overseas and non-accredited laboratories in Australia. The Senate Inquiry Final Report noted that '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'.

Key issues raised and articulated in the Senate Inquiry Final Report included:

- the questioning of the reliability of laboratory tests used to diagnose or rule out Lyme-like illness, classical and chronic Lyme disease; and
- test quality, understanding which testing protocol is optimal and how tests are to be interpreted (Senate Inquiry Final Report November 2016).

5.2.2. The Senate Inquiry noted the contradictory evidence about the reliability of the two-tier testing protocol, including the sensitivity of ELISA and false positives versus false negatives and its use in immunocompromised patients

The evidence regarding the reliability of the two-tier serology test used to diagnose overseas acquired Lyme disease has been discussed above. However, the Senate Inquiry noted a considerable number of submitters and witnesses questioned the reliability of the protocol, with positions 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
- 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.

ACIIDS in its submission to the Senate Inquiry raised their specific concerns regarding the two-tier protocol including the following.

- IDSA and CDC maintain the "two-tier protocol" should be used for the laboratory diagnosis of borreliosis, and that according to the protocol the diagnosis of borreliosis can only be made if both ELISA and Western Blot/Immunoblot are positive.
- The two-tier protocol for testing for Borrelia is not universally accepted; the protocol having been established for disease surveillance; but, pathologists and infectious disease specialists have misused the surveillance criteria for diagnosis.
- ILADS and ACCIIDS consider the two-tier protocol should be abandoned because of the poor sensitivity of the ELISA test; the ELISA is not sensitive enough to detect most cases of borreliosis.
- Recent studies for the College of American Pathologists concluded that currently available ELISA tests do not have adequate sensitivity to meet the two-tiered approach recommended by the CDCD for surveillance.
- The CDC has cautioned that this surveillance case definition was developed for national reporting of Lyme disease and that it is not appropriate for clinical diagnosis. The CDC noted 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 or reimbursement.'
- 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.
- The test performed by most Australian laboratories for borreliosis is the ELISA test. This is one of the reasons that borreliosis is under-diagnosed in Australia.
- The members of ILADS and ACIIDS also consider that polymerase chain reaction (PCR) testing is valuable in the diagnosis of borreliosis. (ACIIDS Submission 370, March 2016).

These concerns were raised and elaborated on by Dr Hugh Derham, Dr Adam Nuttall, Dr Peter Dobie and Dr Richard Schloeffel in the hearing of evidence regarding the accreditation of Australian laboratories (Senate Inquiry Interim Report, May 2016).

Dr Schleoffel in evidence to the Senate Inquiry as the chairperson of ACIIDS was reported to have argued that diagnosis should begin with observation, which in this case is that Australian ticks are making people sick, and highlighted the importance of clinical diagnosis, making the point that pathology should be used to verify, not a guide a doctor's clinical diagnosis. He was stated as saying in evidence:

> *"A pathology test should only confirm your thought process, not the other way around. …The tests are inadequate because the patient is 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. It is not helpful; it is not good medicine….Forget about ELISA test versus Western Blot and all these other things"* (Senate Inquiry Final Report, November 2016).

Dr Richard Horowitz concluded the ELISA lacks the necessary sensitivity to detect ongoing infection, stating in his submission:

> *"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%.*
>
> *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".* (Dr Richard Horowitz, Submission 936 as reported in Senate Inquiry Final Report, November 2016)

In addition, the Karl McManus Foundation stated:

> *"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"* (Senate Inquiry Final Report, November 2016).

Dr Mualla McManus of the Karl McManus Foundation also raised concerns about the US CDC criteria used to interpret serological tests in accredited Australian laboratories, including that the CDC criteria are not appropriate for identifying other possible Australian species of *Borrelia.* She stated to the Senate Inquiry:

> *"The government only thinks of Lyme disease, and follows CDC criteria…. We have Borrelia burgdorferi, and a subset of that is Lyme disease. We have relapsing fever, and it has over 20 genospecies already. 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. …We could have a unique class of borrelia"* (Senate Inquiry Interim Report, May 2016).

Regarding hypervariable genomes, mentioned above and discussed by Professor Graves, Dr McManus raised the concern that *Borrelia* as complex and possessing considerable capacity for mutation makes testing difficult, stating:

> *"The testing is problematic because the bacteria Borrelia has got very variable, hypervariable genomes. Basically, it can mutate inside you…… 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".* (Senate Inquiry Final Report, November 2016).

The issue of the tests being of little use in immunocompromised patients was raised by Dr Schloeffel, and the Director of Australian Biologics, the latter stating:

> *"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" (Senate Inquiry Final Report, November 2016).

In addition to submissions to the Senate Inquiry, the paper by McManus and Cincotta (2015) raised, as Dr Schloeffel had, the effects of *Borrelia* on the immune system and its consequences for diagnostics. The key points of the paper were:

- Interpretation of indirect diagnostics of Borreliosis can be complicated due to immune dysregulation by *Borrelia* and other tick borne pathogens
- Serology testing of Borreliosis patients can result in false negatives (ELISA and Western blot) due to production of low affinity IgG subclasses and reduced total IgG.
- Prolonged IgM response observed could be due to relapsing fever *Borrelia* infection or inhibition of isotype switching prevention of the IgG response (McManus and Cincotta, 2015).

The following table on comparison of diagnostic tests for Borreliosis is reproduced from McManus and Cincotta, 2015). The authors stated *"Indirect tests that rely on an immune response are contraindicated in immunocompromised individuals".*

Table x: xxx

	Advantages	Limitations
Indirect Diagnostic Test		
ELISA – Enzyme Linked Immuno-sorbent Assay	• Inexpensive • Gives an indication of whether IgM or IgG immunoglobulins can be detected against *Borrelia* antigens	• Sensitivity species dependent • Cross-reactivity of some antigens (Flagellin) • Not distinguish from active and past infection clearly • A specific prolonged IgM response for relapsing fever can be interpreted as false positive
Western blot	• Higher specificity than ELISA • Allows discrimination between genus and species specific antigens	• Sensitivity can be species dependent e.g.; relapsing fever • Borrelia vs Lyme Borrelia • Not distinguish between active or past infection • Prolonged IgM response for relapsing fever may be interpreted as a false positive • Immunogenic diversity in genospecies makes it difficult to use one criterion (>5 bands) for positive response.
ELISPOT – Lymphocyte Transformation Test – LTT	• Earlier detection of T cell response compared • to IgG	• T cell response may not be specific

	Advantages	Limitations
	• Can measure treatment outcomes	
LTT-MELISA (Memory Enzyme Linked Immuno Stimulation Assay)	• Earlier detection of T cell response compared to IgG • Can measure treatment outcomes	• T cell recognition may not be specific
C6 antigen assay – WisE C6 peptide assay	• C6 antigen is highly immunogenic • Inexpensive	• Sensitivity is dependent on the C6 antigen expressed in VlsE. • Segmental recombination adds greater diversity and sensitivity varies with genospecies
Direct Diagnostic Test		
Culture	• Detects active infection • Growth and better detection using PCR, and labelling and microscopy • Highest sensitivity with skin biopsy • 40% EM, 22% ACA, 24% lymphocytoma	• Long incubation time due slow replication time (12 h or longer) • Fastidious growth requirements difficult to culture • Low levels in CSF, blood, synovium (<10%) • EM rash may not occur, depended on genospecies • Only for patients who have not had antibiotic therapy
Microscopy	• Detects active infection • Direct visualisation • Can be confirmed monoclonal antibody or DNA confirmation with PCR)	• Specimen collection during periods of high activity e.g. high spirochaetaemia in Relapsing fever • Confirmation with PCR or monoclonal fluorescent antibody • required.
Nucleic Acid Amplification Techniques – NAAT (PCR)	• Sensitive, specific and is a fast • Detects recent infection • Narrow sensitivity and high specificity • DNA sequences can be obtained • Quantification using rtPC • Monitoring levels of	• Not detecting all genospecies due to high diversity among genospecies • Inhibition of PCR process due to sample contents • Possible contamination if control/strict procedures are not abided to. Sequencing of all amplicons would detect contamination

5.3. Issues raised at the Senate Inquiry about discrepancies in serology results for Lyme disease between accredited, non-accredited and overseas laboratories

5.3.1. Australian laboratories are accredited for medical testing by the National Association of Testing Authorities Australia (NATA) in conjunction with the RCPA

Australian laboratories are accredited for medical testing by the National Association of Testing Authorities Australia (NATA) in conjunction with the RCPA. According to the department, NATA accredited laboratories can readily test for Lyme disease acquired overseas where patients have travelled to an endemic area (Senate Inquiry Interim Report, May 2016).

The Department of Health's 'An Australian guideline on the diagnosis of overseas-acquired Lyme disease/Borreliosis' states:

> *'Testing should be performed in a laboratory that has Lyme disease testing in its scope of accreditation and which is compliant with AS ISO 15189 Medical laboratories — Particular requirements for quality and competence or in nationally accredited laboratories in the location where the patient was infected. Commercial serological assays used in Australian laboratories with AS ISO 15189 medical testing accreditation are suitable for testing for Lyme disease acquired overseas in endemic regions. Consideration should be given to storing positive serum specimens for research and quality assurance purposes.*
>
> *Clinical specimens that produce repeatedly equivocal results, indeterminate results and results from laboratories without AS ISO 15189 medical testing accreditation should be considered cautiously and expert advice from a specialist microbiologist should be obtained. It may be necessary to refer patient specimens to a suitably certified laboratory such as the US Centers for Disease Control and Prevention".* (Department of Health Australian Guideline- diagnosis of overseas-acquired Lyme disease, 2015).

Regarding the accreditation for innovative laboratory processes such as PCR, (as used by Australian Biologics, see below), NATA representatives advised the Senate Inquiry that the threshold for evidence is higher than for usual accreditation, stating:

> *"For new and innovative methods for which the availability of appropriate validation is limited or where standard methods have been modified or, indeed, used outside their design parameters, the threshold of evidence for acceptance naturally becomes higher. The soundness of evidence provided is judged by relevant experts and professional bodies, not by employees of NATA. NATA must seek the best advice from expert sources, peers of the laboratory, before it commits to a precedent that will impact on the health and safety of the Australian population".* (Senate Inquiry Interim Report, May 2016).

'Lyme-literate' practitioners suggested to the Senate Inquiry that NATA should recognise the overseas accreditation of these specific laboratories overseas, through such measures as the International Laboratory Accreditation Cooperation Mutual Recognition Arrangement (MRA). Additionally, some advocacy groups also suggested that NATA should acknowledge that the

overseas laboratories in question are accredited to the international standards for medical testing (ISO 15189) and should therefore recognise results from these laboratories, in particular the German laboratory Infectolab. In response NATA confirmed Infectolab had achieved international recognition for medical testing (ISO 15189) in January 2016 under the MRA; however, the effect of MRA recognition is the equivalence of overseas testing methods – it does not expect or require laboratories or medical authorities in Australia to recognise another country's specific requirements or context. (Senate Inquiry Interim Report, May 2016).

5.3.2. The use of non-accredited Australian laboratories and overseas laboratories has caused controversy and can cause significant confusion and frustration for patients

The Senate Inquiry Interim Report noted that many submitters who reported having acquired their Lyme-like illness in Australia stated that when their blood samples were sent to an accredited Australian laboratory to test for *Borrelia* bacteria, the results have come back negative. However, on consulting a Lyme-literate practitioner, it was recommended their blood samples be sent to either a non-accredited laboratory in Australia or laboratories in the US or Germany (Senate Inquiry Interim Report, May 2016).

5.3.3. From limited available evidence a high proportion of patients with Lyme-like illness have tested positive to Lyme disease in non-accredited Australian or overseas laboratories

In the previous section on diagnoses and differential diagnoses, we reported that available evidence indicated a high proportion of patients diagnosed with DSCATT appear to have been diagnosed with Lyme disease in non-NATA/RCGP laboratories in Australia or by overseas laboratories (Brown, 2018; LDAA, submission 512 May 2016). We have included the information again as it is of relevance to this section on diagnostic issues.

Regarding the diagnostic testing laboratory that had supported submitters' (to the Senate Inquiry) diagnoses, Brown reported that of the 137 submissions that disclosed a NATA/RCPA-accredited diagnostic pathology test, only 14 (10.2 percent) reported positive serology, which represented 2.8 percent of all submissions that reported pathology and 2.0 percent of all submissions. Of the 14 that reported positive serology, ten patients had travelled overseas while the four other patients who had either not travelled overseas or did not mention travel did not report the result of confirmatory (Western blot) serological testing. Additionally, two patients reported they had contracted Lyme disease overseas (USA and France) and another two patients who reported travel also reported explicitly that only first-tier testing was positive. Brown commented only a small proportion of patients reported a positive Lyme disease serology test from a NATA/RCPA accredited laboratory and that a proportion of these may be positives from overseas exposure unrelated to their current illness.

Table 32: Diagnostic information reported in submissions

Diagnostic method	Number (%) of all patients	Number (%) of patients who reported data
Diagnostic laboratory testing		
Any	508 (72.8%)	508 (100%)
Pos NATA/RCPA	14 (2.0%)	14 (2.8%)
Neg NATA/RCPA	123 (17.6%)	123 (24.2%)
Pos non-NATA/RCPA	454 (65.0%)	454 (89.4%)
Neg non-NATA/RCPA	27 (3.9%)	27 (5.3%)
Neg NATA/RCPA, Pos non-NATA/RCPA	83 (11.9%)	83 (16.4%)

Source: Brown, 2018

LDAA also provided data about where patients had their diagnostic testing performed, reporting that their aggregated survey data from 2012-2014 showed that 57 percent of laboratory tests patients pay for are conducted in overseas laboratories. LDAA information also indicates several Australian laboratories are used, the most frequent being Australian Biologics. (LDAA submission 512, May 2016).

Figure 12: Testing laboratories used by Australians

In which Laboratory have you tested positive to Lyme disease through a blood or other specimen test?	
Australian Laboratory	**Number**
Australian Biologics, Sydney	260
Australian Rickettsial Reference Laboratory, Geelong	30
Local collection centre	71
PaLMS, Sydney	20
University of Newcastle	3
Westmead Hospital, Sydney	6
Overseas Laboratory	
IGeneX, Palo Alto, USA	396
InfectoLab, Germany	114
Blank / unsure	129
Total	**1029**

5.3.4. 'Lyme-literate' practitioners use non-accredited Australian laboratories and overseas laboratories for three reasons and consider these laboratories are better placed to accurately test for Borrelia

The Senate Inquiry noted arguments from 'Lyme literate' practitioners that the tests for *Borrelia* conducted by accredited Australian laboratories are not appropriate, and the criteria by which they are interpreted are inadequate. These practitioners assert that the two-tier process recommended by the RCPA and the US CDC does not adequately detect *Borrelia* and other co-infections acquired in Australia (Senate Inquiry Interim Report, May 2016)

Following on from ACIIDS concerns about the two-tier testing mentioned above, ACIIDS also provided evidence to the Senate Inquiry that Australian doctors treating borreliosis frequently use overseas laboratories for testing, with three reasons given:

- only two Australian laboratories (Australian Biologics and Australian Rickettsial Reference Laboratory) will perform Western Blot/Immunoblot testing without first performing the ELISA test;
- only two Australian laboratories (Australian Biologics and Australian Rickettsial Reference Laboratory) will perform PCR testing for borreliosis; and
- patients with Lyme-like illness should be tested for co-infections as well as Borrelia. These co-infections include babesiosis, bartonellosis, Mycoplasma, Rickettsia, human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA). Comprehensive testing for bartonellosis and babesiosis is not available in Australia. (ACIIDS submission 370, March 2016)

ACIIDS went on to state the three overseas laboratories most commonly used are IGenX (USA), Arminlabs (Germany) and BCA-Labs (Germany) (formerly known as Infectolab) with these laboratories being fully accredited in their countries.

Of these laboratories, ACIIDS reported the information set out in

Table 33 (ACIIDS submission 370, March 2016).

Table 33: Other accredited laboratories

IGenX	• Reference laboratory recognised by the American College of Pathologists • Clinical Laboratory Improvement Amendments (CLIA) approved with approval of CLIA overseen by FDA and CDC • Medicare and Medicaid approved • Met licencing requirements for testing in states that require additional licencing: California, Florida, Maryland, New York, Pennsylvania.
Arminlabs and BCA-Lab	• Accredited with DAKKS, the German accreditation authority

ACIIDS noted the mutual recognition arrangement between DAKKS and NATA with both being signatories to the International Laboratory Accreditation Cooperation (ILAC). ACIIDS stated *"Thus there is no justification for Australian doctors to reject results from Infectolab, BCA-Lab or Arminlabs"* (ACIIDS submission 370, March 2016).

Regarding Australian laboratories, ACIIDS stated the following *"ACIIDS considers Australian Biologics (Sydney) to be an excellent laboratory, with high standards. We suspect the reasons why NATA accreditation has not been granted to Australian Biologics are political"* (ACIIDS submission 370, March 2016).

A statement by Dr Hugh Derham, described in the Interim Report as a Lyme-literate practitioner in Western Australia, was highlighted to exemplify that test results from these [non-accredited laboratories in Australia or overseas laboratories] laboratories have returned a positive result for *Borrelia* often with a number of other co-infections such as *Bartonella* and *Babesia.* These results are used by "Lyme-literate' practitioners to confirm their clinical diagnosis*:*

> *"Almost all of my patents have a clinical diagnosis of Lyme disease and reasonable to excellent laboratory evidence as well, and at least half of them have some laboratory evidence from an accredited laboratory, either accredited by or recognised by NATA. I do not have hundreds of patients who believe they have Lyme disease; their belief is founded on good evidence".* (Senate Inquiry Interim Report, May 2016).

Also from ACIIDS, Dr Peter Dobie advised the Senate Inquiry that the ELISA test is not sensitive enough to detect Lyme-like illness and should be 'abandoned'. He states that the main reason 'Lyme-literate' practitioners use overseas laboratories is that these will do the Western blot test if requested, whereas Australian laboratories will only do so if the ELISA test is positive. (Senate Inquiry Interim Report, 2016).

The Director of Australian Biologics stated in evidence to the Senate Inquiry that through their testing process the laboratory had identified evidence of *Borrelia* in Australian paralysis ticks. In contrast to Australian accredited laboratories, Australia Biologics uses PCR assays to test for the presence of *Borrelia* DNA in human samples, and also uses different serological tests from Germany. In their submission, the Senate Inquiry noted Australian Biologics asserted that the serological tests used by other Australian laboratories are not effective for patients with a chronic infection of *Borrelia* and that PCR and German serological tests are more effective. (Senate Inquiry Interim Report, May 2016).

5.3.5. However, medical authorities suggested results from overseas laboratories should be interpreted with caution and that in the absence of a known causative agent for DSCATT in Australia a positive test is likely to be a false positive

Some medical authorities raised concerns about results from overseas laboratories, suggesting that results from overseas laboratories should be interpreted with caution, as each test has its own sensitivity and specificity based on the composition of the causative agent. According to these submitters, in the absence of a known causative agent in Australia, a positive test result is likely to indicate a false positive due to cross reactions from other bacteria. The RCPA highlights an example:

> *If caused by a tick-born microbe, the causative microbe has not yet been identified and thus its antigenic make-up is unknown. Without knowing its antigenic make-up, it is impossible to design a proper serological test with measurable sensitivity and specificity. Cross-reactivity between patient antibodies and Borrelia antigens from overseas Borrelia used in vitro in Australian diagnostic assays are hard to predict.*
>
> *There are many species of spirochetes (including Borrelia spp.) present in the normal human gastrointestinal tract (including the oral cavity) and some of these may potentially cause cross-reacting antibodies to be produced by the patient"*

The RCPA also raised concerns that it is difficult to assess the accuracy of results from serological tests conducted in overseas laboratories that are not accredited to Australian standards and warned that overseas laboratories favoured by 'Lyme literate' practitioners are not used by 'mainstream' practitioners in their own countries and are likely to return false positive results (Senate Inquiry Interim Report, May 2016).

Additional concerns raised to the Senate Inquiry by Dr Lum included that tests conducted in non-NATA accredited laboratories in Australia and laboratories overseas may produce different results to accredited Australian laboratories because they may not interpret their results according to the criteria set by the US CDC and the European Society of Clinical Microbiology and Infectious Diseases (Senate Inquiry Interim Report, May 2016).

The Committee view in the Final Report regarding diagnostic testing and whether classical Lyme disease can be contracted in Australia included:

- 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.
- However, while 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.

- 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 (Senate Inquiry Final Report November 2016).

5.3.6. NRL Investigation determined the tests used by Australian laboratories to diagnose Lyme disease had equivalent reliability to tests used in overseas laboratories

The Senate Inquiry stated in its report in May 2016 *"The issue of discordant results between accredited laboratories in Australia, and non-accredited Australian and overseas laboratories needs further inquiry".* (Senate Inquiry Interim Report, May 2016).

In its final report it was noted that the Department of Health had contracted the National Serology Reference Laboratory (NSRL) to conduct a review of serological assays used to diagnose Lyme disease. (Senate Inquiry Final Report, November 2016).

The NRL '*Final Report: Investigation of the performance of assays for Lyme disease in Australia*' was published in May 2017. The report noted the project was designed to determine the ability of *in vitro* diagnostic devices IVDs ("tests" uses for testing individuals for Lyme disease) to detect *Borrelia burgdorferi* sensu lato and not other *Borrelia* species. Objectives of the project were:

- to evaluate the IVDs used to test Australian individuals for Lyme disease both in Australian and overseas laboratories to the extent possible within the resources available; and
- to show whether Lyme disease testing performed by Australian laboratories was of high quality (NRL, May 2017).

Eight institutions provided serum specimens of sufficient volume to the project, four in Australia and four overseas. In Australia, the institutions were:

- Sullivan and Nicolaides Pathology (SNP);
- Pacific Laboratory Medicine Services at Royal North Shore Hospital (PaLMS);
- Australian Biologics; and
- Australian Red Cross Blood Service (ARCBS).

The overseas laboratories were:

- Rare and Imported Pathogen Laboratory (RIPL);
- Public Health England (PHE);
- InfectoLab, Germany;
- Armin Labs, Germany; and
- IGeneX Inc. USA.

NRL's conclusions were as follows:

- The report found that results reported by medical testing laboratories using the test kits in Australia were consistent with those from international laboratories. There can be confidence that infections with *Borrelia burgdorferi sl* are appropriately detected or excluded using these tests more than 80 per cent of the time.
- Two step testing with an immunoassay followed by an immunoblot test on positive results provides the best diagnostic accuracy. Confirmatory immunoblots should be read using scanning software rather than read by eye to limit inconsistency.
- There was reasonable 'test to test' correlation between the different IVDs (a true positive on one test was generally positive on another test).
- Test kits varied in their performance and generally IVDs that use native proteins are less reliable than other IVDs and are best avoided (NRL, May 2017; Department of Health NRL Q&A 2018).

Regarding the relevance of the findings to positive test results for Lyme disease in people who have not travelled to areas where Lyme disease is widespread, the report stated:

> *"The investigation was designed to evaluate the tests for Lyme disease. It did not evaluate the use of the test in individual patients. The research confirms that false positive results can occur in individuals who have not been exposed to Borrelia burgdorferi sl. A positive test result in someone who has not travelled to an overseas region with Lyme disease is likely to be a false detection of antibody to Borrelia burgdorferi sl. In these cases, other causes of the symptoms should be sought, or at least the test repeated.*
>
> *For any illness, results from tests must be interpreted in the clinical context of the patient and the test must be performed for the correct indications. When there is discordance between the patient's clinical history and examination and a serology test result, the test result must be considered cautiously" (Department of Health NRL Q&A 2018).*

5.4. Recent international assessments of diagnostic tests for Lyme disease

In 2016 Leeflang et al. systematically reviewed the accuracy of serological tests from 78 studies for the diagnosis of Lyme borreliosis in Europe. The included studies had evaluated an ELISA or an immunoblot assay against a reference standard of clinical criteria. The authors concluded:

> *"We found no evidence that ELISAs have a higher or lower accuracy that immunoblots; neither did we find evidence that two-tiered approaches have a better performance than single tests. However, the data in this review do not provide sufficient evidence to make inferences about the value of the tests for clinical practice. Valid estimates of sensitivity and specificity for the tests as used in practice require well-designed cross-sectional studies, done in the relevant clinical patient populations. Furthermore, information is needed about the prevalence of Lyme borreliosis among those tested for it and the clinical consequences of a negative or positive test result. The latter depend on the place of the test in the clinical pathway and the clinical decisions that are driven by the test results or not.* (Leeflang et al. 2016)

NICE (2018)

The NICE recommendations for Laboratory investigations in the NICE guideline for Lyme disease published in 2018 shown below.

Table 34: NICE recommendations for laboratory investigations

The committee agreed that laboratory testing is unnecessary for people presenting with erythema migrans, because the rash is very specific to Lyme disease and prompt treatment will prevent further symptoms developing. However, most other symptoms associated with Lyme disease have other more common causes, so testing may be helpful to ensure accurate diagnosis and appropriate treatment.
Based on the evidence on test accuracy, the committee agreed that test results need careful interpretation alongside clinical assessment to guide diagnosis. Because of the limitations of tests, Lyme disease should not be ruled out by negative tests if it is strongly suggested by the clinical assessment. The committee decided that treatment could be started at the same time as testing if clinical assessment strongly suggests Lyme disease, because prompt treatment is important.
The committee agreed a strategy of two-tier testing (an initial and confirmatory test), which the evidence indicated was potentially cost saving. Initial testing with a combination IgM and IgG enzyme-linked immunosorbent assay (ELISA) for Lyme disease should be offered because the evidence generally showed better accuracy (both sensitivity and specificity) for combined tests compared to IgM-only and IgG-only tests. The evidence was best for tests based on purified or recombinant antigens derived from the VlsE protein or its IR6 domain peptide (such as a C6).
For people with a negative ELISA result who continue to have symptoms, the committee agreed that clinical review would ensure that alternative diagnoses are not missed. In addition, because antibodies take some time to develop, repeat testing would be warranted for people who may have had the initial test too early, before an immune response has developed. If symptoms have been present for 12 weeks, the committee agreed that an immunoblot would help rule out or confirm diagnosis where uncertainty remains.

The committee agreed that testing should be done in UKAS-accredited laboratories and that any tests used for diagnosis should be validated before they are used to diagnose Lyme disease to avoid unreliable and misleading results, which may lead to misdiagnosis.
Based on their knowledge and experience, the committee agreed that *Borrelia burgdorferi sensu lato (sl)* infection does not behave differently in children than adults, but acknowledged that a young child's immune responses might not be as rapid and effective. The limited evidence in children did not show a noticeable difference in test accuracy compared with adults. Therefore, the committee decided that separate recommendations for testing in children were unnecessary.
The committee considered it important that people being tested for Lyme disease understand how the tests work, their limitations and the importance of basing decisions on tests that are valid.

The recommendations were informed by a diagnostic evidence review Lyme disease: diagnosis and management [C] Evidence reviews for diagnostic tests.

To be completed if required

Cook and Purie(2016)

Wilske et al. (2007)

Leeflang et al. (2016)

Aguero-Rosenfeld and Wormser (2015)

6. TREATMENT MODALITIES PROVIDED TO PATIENTS WITH DSCATT IN AUSTRALIA AND THE SUPPORTING EVIDENCE BASE

This section provides the findings of the literature reviewed to answer research question 4:

> *What are the treatment modalities that have been provided to patients (including subgroups of patients) with DSCATT in Australia and what is the evidence base to support these treatment modalities?*

The situation with DSCATT is complex and this section sits within this complexity. Regarding being able to distinguish between the illnesses classical Lyme disease, an infectious disease, and DSCATT, the Australian Government notes that while some Australians and healthcare providers believe that classical Lyme disease can be acquired from ticks in Australia or that a form of 'chronic Lyme disease' exists, the Australian Government cannot support the diagnosis of locally acquired Lyme disease in Australia without the causative organism of classical Lyme disease (*Borrelia burgdorferi* sensu lato) or a competent vector being identified in Australia (Australian Government Position Statement: Lyme Disease in Australia, 2018).

With respect to DSCATT, the Australian Government notes that the illness experienced by patients with debilitating symptom complexes is poorly understood, making accurate diagnosis and treatment difficult and that because of the imprecise nature of the symptom complexes some patients will remain undiagnosed. The Position Statement therefore stresses it is imperative for government health authorities, clinicians and patients to remain open minded as to the causes of these symptoms (Australian Government Position Statement: Debilitating Symptom Complexes Attributed to Ticks, 2018).

6.1. Treatment modalities provided to patients with DSCATT in Australia

Evidence reviewed

To answer the research question '*What information is available on the prevalence, demographics and geographic distribution of patients experiencing DSCATT in Australia?*' we reviewed ten articles, reports or submissions. We prioritised evidence that is specifically related to treatment modalities provided in Australia.

Systematic reviews (0)	-
Narrative literature reviews and reviews (2)	Beaman, 2016; Chalada et al. (2016)
Observational studies (1)	Brown (2018)
Official Australian reports and government inquiries (3) **including submissions within relevant Senate Inquiry reports (3)**	Senate Inquiry Interim Report, May 2016; Senate Inquiry Final Report, November 2016; Commonwealth of Australia, Inquiry into Chronic Disease Prevention and Management in Primary Health Care, May 2016 ACIIDS submission 370, 2016; LDAA submission 528, March 2016; LDAA Supplementary submission, November 2016
(Inter)national authority and intergovernmental reports and guidelines (0)	-
International and Australian guidelines produced by clinical and professional bodies (0)	-
Patient advocacy group reports (1)	LDAA, Lyme disease: Patient experience in Australia in 2012, LDAA, 2012)

Key findings about effective treatment modalities that have been provided to patients with DSCATT in Australia

- There are no published peer-reviewed publications of clinical studies on the treatment of Lyme-like illness in Australia.
- From the limited evidence available, while numerous treatments and treatment regimens are reported by patients diagnosed with Lyme, Lyme-like illness, antibiotics, diet, supplements and herbs are the most common treatments.
- Evidence from ACIIDS doctors providing treatments to patients with Lyme-like illness include that patients are sometimes treated with long-term antibiotics, mainly orally, but because they have so many sick patients doctors are performing a lot of intravenous therapies as well, including intravenous antibiotics for long periods of time.
- Most patients obtain treatment in Australia with the USA being the second most common location for treatment.

6.1.1. There are no published peer-reviewed publications of clinical studies on the treatment of Lyme-like illness in Australia

While the debate about classical Lyme disease being acquired from ticks in Australia dates back several decades, and evidence from ACIIDS described earlier in this review indicates that over 4,000 patients have been treated for Lyme-like illness with and without co-infections, there are no published peer-reviewed studies of treatments provided to Australian patients with Lyme-like illness and the clinical outcomes of those treatments. Therefore, the available evidence on treatments provided to patients in Australia is limited to self-reported, analysis of self-reported or anecdotal evidence.

6.1.2. Antibiotics, diet, supplements and herbs appear to be the most common treatments

The Senate Affairs committee asked for submissions to the Senate Inquiry to provide information on 'the signs and symptoms Australians with Lyme-like illness are enduring and the treatment they receive from medical professionals. The signs and symptoms reported by submitters to the Senate Inquiry have been discussed previously.

The majority of available evidence comes from Brown's 2018 analysis of first-person patient submissions to the Senate Inquiry, submissions by LDAA presenting information from patients, the submission from ACIIDS presenting information from groups of Australian doctors, primarily general practitioners who specialise in the treatment of tick-borne diseases, and from a survey LDAA conducted in 2012. Additionally, evidence was presented to the Inquiry into Chronic Disease Prevention and Management in Primary Health Care in 2016, which included a case study on tick-borne and Lyme-like diseases.

Much earlier than the 2016 Senate Inquiry, LDAA reported data from a 2012 online survey in which they examined the Lyme disease situation from a patient perspective (LDAA, Lyme disease: Australian patient experience in 2012, November 2012). We described this survey more fully in Chapter X: clinical epidemiology). Of relevance to this section is the self-reported information on

how patients are being treated once they have a formal diagnosis of Lyme disease. is reproduced from the 2012 Australian patient experience report. All of the respondents (n=224) answered the question 'Are you currently undergoing treatment?

Table 35: Patients currently undergoing treatment

Are you currently undergoing treatment?	Number
Yes	193
No	29
Blank	2
Total	**224***

Source: LDAA, Lyme disease: Australian patient experience in 2012, November 2012, page 27.

*Total number of respondents in the survey- All respondents answered this question

The majority (n=193, 86 percent) reported they were currently undergoing treatment for Lyme disease. The two respondents who left the answer blank reportedly sought advice on how to locate a doctor to treat them. Of those who reported not being under treatment, LDAA concluded from the free text answers provided by many participants a significant number were in the process of locating a suitable doctor to treat them for Lyme disease.

Participants in the survey were also asked to describe their treatment regimens and were provided with a list of common treatments, as detailed in

Table 36 below. We have reorganised the data in decreasing order of prevalence. Natural supplements, antibiotics and diet were, in 2012, the most common treatments for patients undergoing treatment for Lyme disease.

Table 36: Treatment regimens

What does your treatment regime include?	Count
Natural supplements	147
Antibiotics	137
Diet	122
Salt and Vitamin C combination	28
Adrenal treatment	25
Hormone treatment	21
Heavy metal chelation treatment	16

Source: LDAA, Lyme disease: Australian patient experience in 2012, November 2012, page 28.

In addition to the common treatment specified in the table above participants were able to select a category of 'other treatments' they were currently undergoing. The additional treatments and therapies are reproduced from the LDAA 2012 report and reported in Table 37 below.

Table 37: Additional treatments and therapies

Other treatments in use	Count
Herbs/herbal treatment	5
Vitamin B/C/D	5
Detoxification (FIR sauna, Mud packs, Epsom salts bath)	3
Exercise	3
Probiotics	3
RIFE	2
Homeopathy	2
Anti-inflammatory drugs/food	1
Antivirals, anti-fungal lozenges	1
Anxiety medication	1
Bicillin injections	1
Blood thinners	1
Colonics	1
Hyperbaric O_2 therapy	1
Holistic dentistry	1
IV Vitamin C and IV Glutathione	1
Lymphatic drainage and massage	1
Marshall Protocol	1
Opiates	1
Osteopathy	1
Ozone/oxygen therapy	1

Other treatments in use	Count
Physiotherapy/chiropractic support	1
Traditional Chinese Medicine (TCM)	1

Source: LDAA, Lyme disease: Australian patient experience in 2012, November 2012, page 28.

Brown's analysis of 698 first person submissions to the Senate Inquiry from Australian people who identified as suffering from Lyme disease or Lyme-like illness found respondents had seen a median of 13 doctors for diagnosis and treatment of their illness. Table 38 details the findings on management as reported by Brown (2018).

Table 38: Diagnosis and treatment management

Management	Number (%) or median (range of all patients	Number (%) of patients who reported data
Doctors seen	13 (range 1-100)	261 (37.4%)
Saw 'Lyme literate doctor'	291 (41.7%)	-
Received antibiotics	348 (49.9%)	-
Received oral antibiotics	319 (45.7%)	-
Received IV/IM antibiotics	116 (16.6%)	-

Source: Brown, A description of 'Australian Lyme disease' epidemiology and impact: ana analysis of submissions to an Australian senate inquiry, page 424.

Brown noted that, as above 348 (49.9 percent) of submissions mentioned antibiotic therapy and that only two patients denied using antibiotics.

While the findings do demonstrate the prevalence of patients receiving oral antibiotics is much higher (2.75 times) than for those receiving IV/IM antibiotics, the analysis does not report on the number of patients receiving both oral and IM/IV. However, it is noteworthy that a reasonable number of patients diagnosed with Lyme disease had received IV/IM antibiotics, particularly with respect to the discussion in the following section on the evidence base for treatments.

LDAA's supplementary submission to the Senate Inquiry provides additional information to Brown's analysis of treatments provided by patients who made submissions to the Senate Inquiry. While LDAA's analysis is of a smaller number of submissions (349) than Brown's analysis (698), LDAA provided an analysis of treatment type, where it had been reported in the 349 patient submissions provided to the Senate Inquiry (LDAA, Suppl. Submission, November 2016). LDAA noted antibiotics were the most commonly reported type of treatment obtained, followed by supplements and herbs.

Table 39: Type of treatment

Type of treatment undertaken	Number of submitters* reporting this type of treatment
Antibiotics	101
Supplements	52
Herbs	45
Other	34
Hypothermia	15
Ozone	5
Oils	3
RIFE	2
Bio-resonance	2

Source: LDAA, Senate Inquiry Supplementary Submission, November 2016, page 26.

*Out of 349 submissions analysed by LDAA

In the above table we note LDAA has used the term 'hypothermia'. This term is at variance to information reported later in this chapter about alternative treatments provided in Australia, where the term 'hyperthermia' is used. In the table above we have reported LDAA's wording as it appeared in the supplementary submission.

6.1.3. Patients are sometimes treated with long-term antibiotics, mainly orally, but long-term intravenous therapies are common too

The available information on treatments provided by medical professionals in Australia to patients with Lyme-like illness comes from the Australian Chronic Infectious and Inflammatory Disease Society (ACIIDS), and from evidence from Dr Schloeffel given to the Senate Inquiry and the Inquiry into Chronic Disease Prevention and Management in Primary Health Care. For this specific section, the evidence from Dr Richard Schloeffel to the Senate Inquiry provides the best information on antibiotic treatments provided to Australian patients with Lyme-like illness. Dr Schloeffel stated:

> *"We have treated 4 000 patients in five years. We are currently treating only 1 500 patients. Of the other 2 500 patients we have treated, most are better. They are getting better because they are having an appropriate diagnosis and appropriate treatment, sometimes with long- term antibiotics – oral in the main. But because we have so many sick patients we are doing a lot of intravenous therapies as well, including intravenous antibiotics for long periods of time, which is leading to a positive outcome, but under the same rigor that any intensive therapy would require, and we are doctors who are extremely qualified to do this work"*

ACIIDS advised it has formulated consensus-based treatment guidelines: *the ACIIDS Australian Chronic Infectious Disease Society Guidelines Version 1.51 (2014) Guidelines for the management of borreliosis, babesiosis, bartonellosis, theileriosis and associated disease* (ACIIDS submission 370, March 2016, Attachment 24). We understand that this guideline is now obsolete, although it remains on the internet. Our search did not reveal a current publicly available ACIIDS guideline. As such, the now obsolete ACIIDS guideline is not discussed further in this literature review.

6.1.4. Most patients obtain treatment in Australia with the USA being the second most common location for treatment

The LDAA (LDAA, Supplementary Submission, November 2016) provided an analysis of location of treatment and treatment type, where location had been reported in the 349 patient submissions LDAA analysed (LDAA, Supplementary Submission, November 2016).

Most submitters who reported obtaining treatment did so in Australia with the USA being the second most common location for treatment. LDAA noted, of the submitters who reported they had obtained treatment, seven percent reported they had undergone treatment in more than one location, and *"worryingly, some reported that they had never been treated".*

The following table is reproduced from the LDAA supplementary submission (LDAA, Suppl. Submission, November 2016).

Table 40: Location of treatment

Location of treatment	Number of submitters reporting treatment in this location
Australia	153
Belgium	1
India	1
Indonesia	1

Location of treatment	Number of submitters reporting treatment in this location
USA	14
UK	2
None	9

Source: LDAA, Senate Inquiry Supplementary Submission, November 2016, page 26.

6.2. Evidence base to support these treatment modalities

This subsection presents a review of the evidence regarding the treatment modalities provided to patients in Australia diagnosed with DSCATT. There are however, no published peer-reviewed studies of clinical treatments provided to patients in Australia with DSCATT and the outcomes of those treatments.

While the preceding subsection (4.1) on treatment modalities provided to patients included an extensive list of treatment modalities including prescription (antibiotics) and alternative treatments, section 4.2 focuses primarily on the evidence base around prescribing of antibiotics to Australian patients diagnosed with Lyme-like illness/DSCATT.

This literature review is not intended to be a review of the evidence base on the treatment of classical Lyme disease; however, we have reviewed the latest evidence for antibiotic prescribing for classical Lyme disease in endemic areas However, from submissions by treating medical professionals from ACIIDS that state that the symptoms of Lyme-like illness in Australia are similar to those experienced by patients diagnosed with Lyme disease in the United States and Europe (ACIIDS Submission 370, March 2016), antibiotic treatments provided to patients with DSCATT in Australia appear to be based on international guidelines for classical Lyme disease. These submissions are supported by evidence from LDAA. However, there is no available Australian evidence on how long patients are treated for, what antibiotics or combinations of antibiotics are prescribed and clinical outcomes of regimens of antibiotic therapy.

This literature review does not review the evidence base for other treatment modalities reported as having been provided to patients diagnosed with Lyme-like illness/DSCATT. However, we have reviewed the latest evidence on the management of non-specific symptoms that may be related to Lyme disease and the management of ongoing symptoms related to Lyme disease

Evidence reviewed

To answer the research question *'What is the evidence base to support these treatment modalities?'* we reviewed 35 articles, reports or submissions. Evidence was only included if it specifically related to Australian patients.

Systematic reviews (9)	Cadavid et al. (2016) Lantos & Wormser (2014) NICE guideline 95 Evidence review [D]: Evidence review for the management of erythema migrans, April 2018). NICE guideline 95 Evidence review [L] Evidence review for the management of ongoing symptoms related to Lyme disease NICE guideline Lyme disease, [F] Evidence review on the management of neuroborreliosis, April 2018). NICE guideline Lyme disease, [G] Evidence review for the management of Lyme arthritis, April 2018). NICE guideline Lyme disease, [H] Evidence review for management of with Acrodermatitis chronica atrophicans, April 2018). NICE guideline Lyme disease, [I] Evidence review for management of Lyme carditis, April 2018). NICE guideline Lyme disease, [I] Evidence review for management of Lyme carditis, April 2018).
Narrative literature reviews and reviews (3)	Borchers et al. (2015);Collignon et al. (2016); Perronne (2015)
Randomised control trials (1)	Berende et al (2016)
Observational studies (8)	Brown (2018); Cameron et al. (2009); Dersch et a. (2007;)Horowitz & Freeman (2019); Horton et al. (2016); Lantos et al. (2010); Middelveen et al. (2018); Steuer (2016)
Official Australian reports and government inquiries (3) including submissions within relevant Senate Inquiry reports (3)	Senate Inquiry Interim Report, May 2016; Senate Inquiry Final Report, November 2016; Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016 ACIIDS submission 370, 2016; LDAA submission 528, March 2016; LDAA Supplementary submission, November 2016
(Inter)national authority and intergovernmental reports and guidelines (4)	Australian Government Position Statement: Debilitating Symptom Complexes Attributed to Ticks, 2018 Australian Government Position Statement: Lyme disease, 2018 NICE guideline Lyme disease, April 2018 Mygland et al. (2010)
International and Australian guidelines produced by clinical and professional bodies (3)	British Infection Association (2011) Wormser et al. (2006) Cameron et al. (2014) The ILADS Working Group (2004)

Patient advocacy reports (1)	LDAA, Lyme disease: Australian patient experience in 2012. LDAA, 2012

Key findings on the evidence base for the treatment modalities provided to Australian patients suffering DSCATT

- ACIIDS advises the use of long-term antibiotics was evidence-based and in many cases has assisted patients to get better, but there are no published studies on clinical treatments or treatment outcomes conducted in Australia on patients with DSCATT to verify the anecdotal evidence.
- Serious concerns have been raised by multiple Australian medical professionals, medical professional bodies and medical professional regulatory authorities about overuse and long-term use of antibiotic treatment and antimicrobial resistance.
- Concerns have also been raised by Australian medical professionals and government health authorities over other treatments provided to patients with DSCATT, including unconventional therapies that are not evidence-based.
- The 2018 NICE Lyme disease guidelines are the most recently published guidelines available and aim to standardise antibiotic treatment and provide a consistent framework for good practice in Lyme disease. However, NICE advises evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme disease is of poor quality, out-dated and often based on small studies.

NICE recommendations on treatment

- The 2018 NICE Lyme disease guideline recommends that longer courses of 21 days of treatment should be offered as standard antibiotic treatment for erythema and/or non-focal symptoms.
- In patients with non-focal symptoms of Lyme disease (symptoms such as fever, sweats and muscle pain, which are not specific to an organ system) the NICE Lyme disease 2018 guideline recommends that patients should be given the same treatment as people with erythema migrans.
- For managing ongoing symptoms of Lyme disease after a course of antibiotics, the NICE Lyme disease 2018 guideline recommends that patients should not be routinely offered more than two courses of antibiotics because of a lack of evidence of benefit.
- For the management of Lyme neuroborreliosis, the NICE 2018 guideline recommends as first treatment antibiotics taken orally for 21 days for the management of Lyme disease affecting the cranial nerves and peripheral nervous system and antibiotics administered intravenously for 21 days for the management of Lyme disease affecting the central nervous system. Care of children and young people under 18 should be discussed with a specialist.
- Additionally, for neuroborreliosis, the Cochrane database of systematic reviews published in 2016 a systematic review of antibiotics for the neurological complications of Lyme disease; this review indicated that treatment with any of the four antibiotics produced similarly good outcomes for treatment of neurological Lyme disease in Europe, but a second treatment with amoxicillin does not appear to provide added benefit to ceftriaxone.
- For the management of Lyme arthritis, the NICE 2018 Lyme disease guidelines recommends oral antibiotic therapy for 28 days; longer courses of treatment (28 days)

are appropriate when treating Lyme arthritis because it is difficult for antibiotics to penetrate to the synovium and synovial fluid. Care of children and young people under 18 with Lyme disease and focal symptoms such as carditis should be discussed with a specialist.

- For management of acrodermatitis chronica atrophicans the NICE 2018 Lyme disease guideline recommendations are the same as for Lyme arthritis and a 28 day course of antibiotic treatment. Care of children and young people under 18 with Lyme disease and non-erythema migrans presentations should be discussed with a specialist.
- For the management of Lyme carditis, the NICE 2018 Lyme disease guidelines recommended course of antibiotic treatment is 21 days. Care of children and young people under 18 with Lyme disease and focal symptoms such as carditis should be discussed with a specialist.
- For management of women with Lyme disease during pregnancy and their babies NICE 2018 Lyme disease guideline recommends pregnant women should be treated following usual practice, and babies should receive treatment if they have serology showing IgM antibodies specific to Lyme disease or symptoms that might be caused by Lyme disease. NICE advises that while that mother-to-baby transmission of Lyme disease is possible in theory, there was an absence of evidence, and the risk appears to be very low. Women could be reassured that pregnancy and their baby are unlikely to be affected and NICE highlighted the importance of completing treatment.
- NICE reported no evidence was found for transmission of Lyme disease through sexual contact or blood products.

2010 German guideline recommendations on treatment

- German guidelines 'Diagnosis and Treatment of Lyme borreliosis' published in 2010 recommend either a monotherapy or combined therapy of antibiotics, however, the guideline notes the efficiency of a combined antibiotic therapy has not been scientifically attested to date. The authors note the guideline was prepared with great care but no liability whatever can be accepted for its accuracy, especially in relation to dosages.

2014 ILADS guidelines recommendations on treatment

- ILADS guidelines in 2014 found the available evidence regarding the treatment of known tick bites, erythema migrans (EM) rashes and persistent disease is limited and was of very low quality due to limitations in trial designs, imprecise findings, outcome inconsistencies and non-generalizability of trial findings. As such, optimal treatment regimens for the management of known tick bites, EM rashes and persistent disease has not yet been determined.
- ILADS recommended clinicians should not use a single 200 mg dose of doxycycline following a tick bite as prophylaxis for Lyme disease; The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis. The recommendation was based on very low-quality evidence.
- ILADS recommends 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. For adults, 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. Clinicians should continue antibiotic therapy for patients who have not fully recovered by the completion of active therapy. The recommendation was based on very low quality evidence.

- ILADS recommends clinicians should discuss antibiotic retreatment with all patients who have persistent manifestations of Lyme disease; 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. 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.

The ILADS Working Group guidelines (2004)

- The ILADS Working Group (2004) Evidence-based guidelines for the management of Lyme disease does not recommend hyperbaric oxygen therapy for routine use and notes patient's interest in alternative therapies

2006 IDSA guidelines recommendations on treatment

- The Infectious Diseases Society of America (IDSA) guidelines published in 2006 is the guideline promulgated in the Australian guideline on the diagnosis of overseas acquired Lyme disease.
- The voluntary review of the IDSA 2006 guidelines in 2008 vetted by an ombudsman concluded that the recommendations contained in the 2006 guidelines were medically and scientifically justified on the basis of all of the available evidence and that no changes to the guidelines were necessary. The Review Panel concluded that *in the case of Lyme disease* inherent risks of long-term antibiotic therapy were not justified by clinical benefit.

[Placeholder for key findings from papers/guidelines still being reviewed]

6.2.1. There are no published studies on clinical treatments or treatment outcomes conducted in Australia on patients with DSCATT to verify the anecdotal evidence

In their submission to the Senate Inquiry ACIIDS stated:

> *"The members of ACIIDS, who are primarily general practitioners, are the Australian experts in the diagnosis and treatment of tick-borne diseases and LLI [Lyme-like illness]. We have more expertise and experience in this field than any other doctors in this country".*

Information in the ACIIDs submission of relevance to this section includes:

- many of these patients [with Lyme-like illness] have positive tests for tick-borne infections such as Borrelia, Rickettsia, babesiosis, bartonellosis, ehrlichiosis and anaplasmosis
- 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
- it is the experience of ACIIDS doctors that most patients with Australian LLI respond to the same treatment as is used internationally for the treatment of Lyme disease.
- Most cases of borreliosis and Australian LLI can be treated with oral antibiotics, but there is a role for intravenous antibiotics upon failure or oral medications in patients with persistent, recurrent or refractory illness, and in cases where there is neurological involvement.

ACIIDS also advises that coinfections that may require treatment in patients suffering from LLI include Bartonella, Babesia, Rickettsia, ehrlichiosis, anaplasmosis and Mycoplasma, the principal treatment for these co-infections being antibiotics. ACIIDS advise that in some patients it appears the bulk of their symptoms are due to co-infections rather than borreliosis.

Regarding treatment rationale and protocols by ACIIDS doctors, ACIIDS also noted in their submission (ACIIDS, Submission 370, March 2016), that in addition to the now obsolete ACIDs guideline mentioned above ACIIDs doctors also refer to the guidelines laid down by the International Lyme and Associated Disease Society (ILADS), German Lyme specialists, and Drs Joseph Burrascano and Richard Horowitz, noted by ACIIDS to be two of the leading Lyme disease specialists in the United States.

ACIIDS noted two principal differences in views on the treatment of Lyme disease between the Infectious Diseases Society of America (IDSA) and the International Lyme and Associated Diseases Society (ILADS). Specifically, that:

- IDSA claims that no case of Lyme disease requires more than four weeks of treatment with antibiotics, whereas ILADS considers that much longer courses of antibiotics are needed in case of chronic Lyme disease; and
- IDSA claims that there is never a need to use more than one antibiotic at a time to treat Lyme disease, whereas ILADS doctors hold the opinion that it is often necessary to use a combination of antibiotics. (ACIIDS, Submission 370, March 2016).

ACIIDs view was that IDSA does not address the issue of the patient who acquires Lyme disease from a tick bite but does not receive initial treatment, stating *"This is a glaring omission".* ACIIDS advised that four weeks of antibiotics is probably sufficient if patients are treated soon after the

tick bite, but patients who acquire the infection and do not receive initial treatment will often develop chronic Lyme disease. (ACIIDS, Submission 370, March 2016),

Regarding long term antibiotic treatment, ACIIDS advised ACIIDs doctors are aware of the possible dangers of long-term antibiotic treatment, such as the development of hepatoxicity, pseudomembranous colitis or drag resistance, with patients being monitored and any side effects of antibiotic treatment being dealt with in the early stages before they become problematic.

Regarding treatment of Lyme-like illness, ACIIDS stated view was:

> *"ACIIDS considers that the risk of not treating this illness is greater than the risk of potential adverse reactions to treatment"* (ACIIDS, Submission 370, March 2016),

As noted earlier in this section, Dr Richard Schloeffel, a member of ACIIDS, presented the following evidence to the Senate Inquiry:

> *"We have treated 4 000 patients in five years. We are currently treating only 1 500 patients. Of the other 2 500 patients we have treated, most are better. They are getting better because they are having an appropriate diagnosis and appropriate treatment, sometimes with long- term antibiotics – oral in the main. But because we have so many sick patients we are doing a lot of intravenous therapies as well, including intravenous antibiotics for long periods of time, which is leading to a positive outcome, but under the same rigor that any intensive therapy would require, and we are doctors who are extremely qualified to do this work"* (Senate Inquiry, Final Report, November 2016)

Dr Schloeffel also provided evidence on antibiotics for the case study on tick-borne and Lyme-like diseases as part of the Inquiry into Chronic Disease prevention and management in primary health care (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 145). Dr Schloeffel stated in evidence that there are two approaches in the USA to treatment Lyme disease: the Centres for Disease Control (CDC) recommending a short course of treatment while the ILADS recommends a longer period of therapy. In addition to the report noting that Dr Schloeffel emphasised the importance of not 'bombarding' with doses of antibiotics that are too high, the following statement by Dr Schleoffel was highlighted (page 145):

> *"The type of treatment that we do is not just about throwing antibiotics at patients…. It is about management and giving the patient an understanding of their illness, making a proper diagnosis, sorting out their mental state and making sure they have carers and community support. It is about providing them with advice about how they should change their diet or improve their eating patterns, providing adequate supplementation for foods and for things that they may require as part of the treatment but also as a result of the treatment. So they will be on vitamins and supplements and other things, which they have often already started because they have already seen six or seven naturopaths before they see you. Then depending on their diagnosis, very gently and slowly, there is an antibiotic protocol. I have many antibiotic protocols, because every patient is different".* (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 145).

Dr Mualla McManus provided evidence to the Senate Inquiry regarding the difficulty in eradicating *Borrelia* infection, stating:

> *"The significance of Borrelia infection in 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 samples from the synovium, the knew joint, and they actually could actually 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"* (Senate Inquiry Final Report, November 2016).

LDAA also provided evidence regarding antibiotic treatment of patients with Lyme-like illness in Australia to both the Senate Inquiry and the Inquiry into Chronic Disease prevention and management in primary health care. LDAA's view is that:

> *"It's probable that any Australian doctor that chooses to treat Lyme -like disease will be investigated, given they administer antibiotics for a longer period of time than the one month treatment protocol and operate outside the ATGs [Australian Therapeutic Guidelines]"*(Senate Inquiry, Interim Report, May 2016).

Additionally, LDAA was reported to have stated that international Lyme experts and Lyme-treating doctors in Australia agree that 'four weeks is simply not long enough' (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 146).

6.2.2. Serious concerns have been raised by multiple Australian medical professionals, medical professional bodies and medical professional regulatory authorities about overuse and long-term use of antibiotic treatment and antimicrobial resistance

The rationale for this review of the evidence on treatment modalities provided to Australian patients diagnosed with Lyme-like illness/DSCATT sits within the context of concerns raised by medical professional, medical professional bodies and Australian medical regulatory bodies at the Senate Inquiry, and in scientific publications regarding the long term prescribing and over use of antibiotics among patients diagnosed in Australia with DSCATT, and the impact on antimicrobial resistance. Concerns raised by the committee in the Interim Report included:

- not only expensive treatments that were unaffordable to people receiving welfare or pension payment with some submitters not able to afford prescribed treatments. In some cases, prescribed treatments were not available in Australia, such as 'hyperthermia treatment' available in Germany where the body is heated to kill off bacteria and costing approximately $30,000 per course. Other patients had been referred to expensive treatments in the US or ozone therapy in Indonesia; and
- the appropriateness of some of the treatments offered by Lyme-literate practitioners such as side effects from antibiotics, infections from intravenous catheters (such as PICC lines) and potential toxins from unregulated medications.

Examples of specific concerns raised included from the Communicable Diseases Network Australia and state and territory health departments, with the submission by the WA Department of Health highlighted in the Interim Report:

> *"There is no evidence to support the use of combination antibiotics, immunoglobulin, hyperbaric oxygen, specific nutritional supplements, or prolonged courses of antibiotics for the management of Lyme disease"* (WA Department of Health, Submission, 529, p5).

Additionally, the Australian College of Dermatologists provided evidence from a randomised trial of long-term antibiotic therapy for symptoms attributed to Lyme disease in Europe that concluded:

> *"In patients with persistent symptoms attributed to Lyme disease, longer term antibiotic treatment did not have additional beneficial effects on health-related quality of life beyond those with shorter-term treatment".*

Negative effects of long-term antibiotic use for individuals and the broader community was raised by Royal College of Pathologists of Australasia (RCPA):

> *"Unproven long term broad spectrum antibiotic treatment is not only potentially harmful to the individual patient due to side-effects up to and including death, it is harmful to the patient and the Australian community in general because it promotes the proliferation of multi-drug resistant organisms. This resistance renders all antibiotics ineffective against common (non-Lyme disease) infections and is a genuine crisis in modern healthcare"* (RCPA Submission 532).

The Medical Board of Australia (MBA) and Australian Health Practitioner Regulation Agency (AHPRA) raised in their submission, and of relevance to this section on treatment modalities,

concerns related to Lyme disease or Lyme-like illness that had led to an investigation of a medical practitioner. These included:

- *"Treating Lyme-like illness with long-term antibiotic treatment, in the absence of an identified infection, is of concern. The 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)"*; and
- treatment for Lyme-like disease resulting in complications and interacting or interfering with other treatments, for example, use of large lines (e.g. PICC lines) to administer long-term antibiotics which can result in infections and thrombosis, and antibiotics interacting with other necessary treatments.

Concerns about prolonged antibiotic treatment were also raised by the Infectious Diseases Department of Austin Health, in that 80-90 percent of the cohort of patients who believe they have Lyme-like illness and who were referred to the Infectious Diseases Department of Austin Health, Melbourne, have undergone substantial hardship paying for investigations from unaccredited laboratories and in some cases, prolonged antibiotic treatment that has had no (or minimal) objective evidence of benefit (Infectious Disease Department, Austin Health, Submission 820).

Beaman in his review 'Lyme disease: why the controversy' reviewed the evidence on treatments for Lyme disease stated:

> *"Australian experiences include patients paying many thousands of dollars for non-specialist consultations and transportation of specimens for testing at overseas laboratories using non-approved protocols that have resulted in misdiagnoses associated with experimental treatments, which have caused serious complications including line sepsis, pancreatitis and pseudomembranous colitis(reported through the national ASID-OzBug bulletin board)"* (Beaman, 2016).

Beaman provided the following advice in his paper under *Frequently asked questions: Should patients receive empirical multidrug therapies for years?:*

> *"No. The first principle of medicine is non-maleficence, that is, 'primum non nocere' (probably Hippocrates, but first documented by Sydenham). These non-scientific empirical protocols have not been proven to be efficacious by randomised controlled treatment trials. They have been shown to have the potential for serious, even fatal, adverse effects and are extremely expensive for desperate patients to afford. Their use should only be offered as part of an experimental protocol after informed consent has been obtained, at no cost to the patient".*

In its Final Report the Senate Affairs committee noted issues with regard to access to treatment including lack of treatment options driving many Australian sufferers to seek treatment for Lyme-like illness overseas coupled with treatment locally and overseas often being expensive and thus leaving vulnerable patients open to financial exploitation (Senate Inquiry, Final Report, November 2016)

The Committee also noted that while appropriate treatment for patients with Lyme-like illness was a contentious issue, the committee did not receive any submissions disputing the call for medical treatment to be ethical and safe. The committee stated:

> *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 the one hand, there is a risk of misdiagnosis, as there is with any illness. On the other hand, denial of treatment in the absence of certainty around the diagnosis may arguably also contribute to an adverse outcome.*

In the case study on tick-borne and Lyme-like diseases conducted as part of the Inquiry into Chronic Disease prevention and management in primary health care in 2016, the Australasian Society of Infectious Diseases (ASID) stated:

> *"…it is of no benefit to the patients to treat them long term with antibiotics, which can be potentially harmful and certainly will not help chronic symptoms that are not due to bacterial infection. In the absence of a specific diagnosis, this, I would suggest, is malpractice, if it is not supported by a laboratory diagnosis*" (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 145).

ASID also provided evidence that most professional bodies in endemic areas have guidelines advising 'short-term antibiotic therapy usually for two weeks' in which time the 'vast majority of patients' will improve (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 145).

Concerns about antimicrobial resistance to prolonged use of antibiotics were also raised by the Karl McManus Foundation and by Royal Australasian College of General Practitioners (RACGP), the latter stating:

> *"… we have to be concerned about antimicrobial resistance, as already mentioned, in conditions which may be related to the overuse of antibiotics. Although people are seemingly getting some benefit from this anecdotally, we also have to be aware that some patients will be having adverse effects because of the long-term antibiotic use"* (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 145/146).

In addition to the issues raised in the Senate Inquiry reports, in the published scientific literature the difference in views on the prescribing of antibiotics for Lyme disease between IDSA and ILADS, (noted previously from the ACIIDS submission) was raised. Collignon and colleagues noted that internationally, the concept of chronic Lyme disease polarises opinion, with key protagonists in the debate in the United States being the Infectious Diseases Society of America (IDSA), an association of physicians and medical scientists, and the public advocacy group, the International Lyme and Associated Diseases Society (ILADS) (Collignon et al. 2016). Regarding the prescribing of antibiotics, Collignon et al. (2016) stated:

> *"Consistent with its model of persistent infection, ILADS and practitioners who share its views advocate long term treatment with oral antibiotics and sometimes prolonged use of intravenous antibacterial agents and associated complementary therapies, such as probiotics and natural and alternative therapies, for managing the adverse effects of long term antimicrobial administration".*

The authors cited evidence that:

- many people who believe they have Lyme disease or Lyme disease-like illness, as well as some of their medical practitioners, also believe that prolonged antibiotic therapy, including intravenous antibiotics, may cure their disease; and
- where classic Lyme disease is endemic, evidence from the US and Europe do not confirm this view. In particular, prolonged intravenous antibiotic therapy (longer than one month) does not seem to significantly improve symptoms (Collignon et al. (2016).

On the issue of antimicrobial resistance raised by submitters to the Senate Inquiry, Collignon et al. (2016) also commented on the major problem of antibiotic resistance resulting from the unnecessary and prolonged use of broad spectrum antibiotics (for example, ceftriaxone), including that antibiotic resistance not only harms the person receiving the agent (who will often be colonised by more resistant bacteria) but also the broader community: when resistant bacteria develop or multiply in an individual, they can be spread to family members and to the wider public.

Regarding long term antimicrobial therapy and the potential dangers of taking antibiotics unnecessarily, Collignon and colleagues made two statements:

> *"Further, advocates of long term antibiotic therapy for "Lyme disease" do not appreciate that generalisations cannot be made when treating infections caused by different genera and species of bacteria".*
>
> *"Other potential hazards of taking antibiotics unnecessarily include their toxicity, potential hypersensitivity reactions and even anaphylaxis (allergy), and predisposition to infection with Clostridium difficile and antibiotic-resistant bacteria."*

6.2.3. Concerns have been raised about other treatments provided to patients with DSCATT, including unconventional therapies that are not evidence-based

The only other treatment modality provided to Australian patients with DSCATT for which there is some information in the literature was for hyperthermia.

Evidence to the committee highlighted not only expensive treatments that were unaffordable to people receiving welfare or pension payment with some submitters not able to afford prescribed treatments. In some cases, prescribed treatments were not available in Australia, such as 'hyperthermia treatment' available in Germany where the body is heated to kill off bacteria and costing approximately $30,000 per course. Other patients had been refereed to expensive treatments in the US or ozone therapy in Indonesia (Senate Inquiry Interim Report, May 2016).

Additional information about hyperthermia came via Dr Schloeffel who presented evidence in the case study on tick-borne and Lyme-like diseases as part of the that in addition Inquiry into Chronic Disease prevention and management in primary health care and reported to antibiotic treatment, he is also involved in treatment using hyperthermia in which the body is treated for nine hours to 41.7 degrees in an intensive care unit. Dr Schloeffel was reported to have stated that over 1000 Australians have travelled to Germany to receive this particular treatment, which 'seems to be very effective' (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 146),

The committee examined the appropriateness of some of the treatments offered by Lyme-literate practitioners such as side effects from antibiotics, infections from intravenous catheters (such as PICC lines) and potential toxins from unregulated medications. The Communicable Diseases Network Australia and state and territory health departments noted concerns with the following statement highlighted in the Interim Report:

> *"There is no evidence to support the use of combination antibiotics, immunoglobulin, hyperbaric oxygen, specific nutritional supplements, or prolonged courses of antibiotics for the management of Lyme disease"* (WA Department of Health, Submission, 529, p5). (Senate Inquiry Interim Report, May 2016).

The RACGP in its evidence into the case study on tick-borne and Lyme-like diseases as part of the Inquiry into Chronic Disease prevention and management in primary health care, was reported to have stated that as it advocates for evidence based practice, it 'cannot support many of the treatment currently being used or advocated' , regardless of 'whatever success individual doctors have with their patients'. (Australian Government Inquiry into Chronic Disease prevention and management in primary health care, 2016, page 146).

The Australian Government Department of Health has provided the following advice to constituents who have enquired about the funding or appropriateness of various treatments:

> *"With respect to treatment, the Government is aware that some patients and medical practitioners are utilising and advocating for unconventional therapies such as the long-term use of antimicrobials, ozone therapy and various infusions. The Government and state and territory health services only support and provide treatment that is evidence-based"* (Department of Health, 20 May 2019).

6.2.4. NICE advice: evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme disease is of poor quality, out-dated and often based on small studies

The NICE Lyme disease guideline published in April 2018 covers diagnosing and managing Lyme disease, and aims to raise awareness of Lyme disease should it be suspected and ensure people have prompt and consistent diagnosis and treatment. The recommendations aim to standardise antibiotic treatment and to provide a consistent framework for good practice in managing Lyme disease (NICE guideline, Lyme disease, April 2018).

The guideline recommendations for antibiotic therapy are presented for a range of presentations of Lyme disease, including Lyme disease without focal symptoms and Lyme disease with focal symptoms with recommendations for each presentation informed by evidence reviews. As the clinical signs reported by ACIIDS for patients with Lyme-like illness are similar to the clinical signs of classical Lyme disease and the non-focal and focal presentations in the NICE Lyme disease guideline, we have presented an overview of the antibiotic treatment recommendations for each presentation. While we have presented an overview of the findings of the evidence reviews for each of the presentations, we refer the reader to the specific evidence reviews detailed in the sections below for further detail.

In forming the recommendations NICE asked the research question "*What are the most clinically and cost-effective treatment options for different clinical presentations of Lyme disease?*"

Of the evidence reviewed NICE stated:

> *"The evidence on the effectiveness of antimicrobial treatment regimens used in different presentations of Lyme diseases is of poor quality, out-dated and often based on small studies. No relevant cost-effectiveness evidence was identified. A series of prospective multicentre studies is needed to compare the clinical and cost effectiveness of different dosages and length of treatments needed and the clinical and cost effectiveness of oral compared with intravenous treatments for different presentations of Lyme disease. This is felt to be of high priority because it has enormous implications for people with Lyme disease and for NHS costs.*
>
> *There is currently insufficient quality evidence on the most effective drug and dose, and the effectiveness of extended treatment or retreatment regimens in those with continuing symptoms remains uncertain, leading to multiple referrals in search of alternative diagnoses. Clarification could improve outcomes, reduce costs and may minimise unnecessary treatment"* (NICE guideline, Lyme disease, April 2018).

While the NICE recommendations for the management of Lyme disease are aimed to provide consistency in managing Lyme disease, NICE does highlight health professionals' responsibility to make decisions appropriate to the circumstances of the individual, stating:

> *"The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the*

individual, in consultation with them and their families and carers or guardian" (NICE guideline, Lyme disease, April 2018).

6.2.5. The 2018 NICE Lyme disease guidelines make many relevant recommendations on treatment modalities

The National Institute for Health and Care Excellence (NICE) guideline on Lyme disease published in April 2018, covers diagnosing and managing Lyme disease in the UK, to ensure people have prompt and consistent diagnosis and treatment. The recommendations by NICE are informed by systematic reviews of the literature. In this section, we present the recommendations for antibiotic treatment of Lyme disease without focal symptoms (that is, erythema migrans and/or non-focal symptoms).

Longer courses of 21 days of treatment should be offered as standard antibiotic treatment for erythema and/or non-focal symptoms

The NICE recommendation for antibiotic treatment for adults and young people (aged 12 and over) diagnosed with Lyme disease without focal symptoms (that is, erythema migrans and/or non-focal symptoms) is:

- Treatment: Oral doxycycline 100mg twice daily or 200mg once daily for 21 days;
- First alternative: Oral amoxicillin 1g three times daily for 21 days; and
- Second alternative: Oral azithromycin 500 mg daily for 17 days.

For children aged 9-12 years the NICE recommendations for antibiotic treatment for diagnosed with Lyme disease without focal symptoms (i.e., erythema migrans and/or non-focal symptoms) are:

- Treatment: for children 9-12 years:
  - Oral doxycycline for children under 45 kg: 5mg/kg divided on doses on day 1 followed by 2.5 mg/kg daily in one or two divided doses for a total of 21 days;
  - For children 9-12 years with severe infections: up to 5mg/kg daily for 21 days ;
- First alternative: oral amoxicillin for children 33 kg and under: 30 mg/kg three times for day for 21 days; and
- Second alternative: Oral azithromycin for children 50kg and under: 10,g/kg daily for 17 days.

For children under 9 years the NICE recommendations for antibiotic treatment for diagnosed with Lyme disease without focal symptoms (that is, erythema migrans and/or non-focal symptoms) are:

- Treatment: Oral amoxycillin for children 33 kg and under: 30mg/kg three times daily for 21 days; and
- First alternative: Oral azithromycin for children under 50kg and under: 10mg/kg for 17 days.

Additional advice included:

- to ask women (including young women under 18) if they might be pregnant before offering antibiotic treatment for Lyme disease; and

- if symptoms worsen during treatment for Lyme disease, assess for an allergic reaction to the antibiotic, and be aware that a Jarisch-Herxheimer reaction may cause exacerbation of symptoms but does not usually warrant stopping treatment.

The committee's recommendations were informed by an evidence review for the management of erythema migrans developed by the National Guideline Centre (NICE guideline 95 Evidence review D: Evidence review for the management of erythema migrans, April 2018). A PICO table (reproduced below in Table 41) informed the review question *'What is the most clinically and cost effective treatment for people with ban erythema migrans?'*

Table 41: PICO characteristics of review question

Population	People with erythema migrans
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins - Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) • Rifampicin (oral, IV)
Comparisons	Antimicrobial agents compared with each other • If data are available consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of EM) 3. Reduction of EM symptoms 4. EM relapse **Important:**

	5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

Twenty studies were included in the evidence review; 18 were RCTs and two were non-randomised comparative studies, these two studies were included as no RCT evidence could be found for the comparison of different doses of doxycycline in adults and azithromycin with amoxicillin in children.

- The studies in adults included in the review ranged from 1990 to 2012 and were: Barsic, 2000; Breier, 1996; Cerar, 2010; Dattwyler 1990; Dattwyler, 1997; Luft 1996; Luger, 1995; Massarotti, 1992; Nadelman, 1992; Steere, 1983; Strle, 1992; Stupica, 2012; Weber, 1990; Weber, 1993; Wormser, 2003.
- The studies in children included in the review ranged from 199 to 2015 and were Arnez 1999; Arnez, 2002; Arnez, 2015; Eppes, 2002; Nizič, 2012.

In interpreting the evidence the committee considered cure (resolution of symptoms), reduction in symptoms, symptom relapse, and quality of life as *critical* outcomes to decision making. Adverse events were considered to be *important* to decision making.

The committee's interpretation of the overall quality of the evidence is set out in

Table 42 below.

Table 42: Overall quality of the evidence

The evidence was of Low to Very Low quality due to risk of bias, imprecision, inconsistency and indirectness. There were particular concerns about a lack of blinding of study participants, healthcare professionals who administered the treatment, and outcome assessors. There were also issues regarding randomisation with many studies not fully reporting on what method of randomisation had been used. Many outcomes and the time point at which they were assessed were poorly defined in the included studies making a clear interpretation of the evidence difficult. In particular, it was not clear whether cure or reduction of symptoms referred to the resolution or improvement of the erythema migrans rash or of any Lyme disease symptoms. Similar ambiguity existed for the outcomes of reoccurrence of symptoms. Studies also varied in the outcomes they reported.
Most of the included studies used low, probably sub-therapeutic, doses of antibiotics, which made the interpretation of their effectiveness difficult. Two studies included an indirect intervention as people received probenecid in addition to amoxicillin to increase the concentration of amoxicillin. There was no consistency in comparisons of dose or lengths of treatments used between included studies, or throughout the literature.
Two studies had an indirect population, that is, people had symptoms in addition to the erythema migrans rash. In 1 study, people had acute disseminated Lyme disease, which included multiple erythema migrans lesions or flu-like symptoms, heart block, facial palsy or radiculitis of less than 3 months' duration, and acute large-joint arthritis. The second study was in people with an erythema migrans rash and flu-like symptoms.
The lack of evidence meant that, for most comparisons, no meta-analyses could be conducted. Ten of the 20 included studies were relatively small and included less than 100 participants. For some antibiotics listed in the review protocol, no evidence could be found.

The table below provides the rationale and why the committee made the recommendations on antibiotic treatment (NICE Lyme disease guidelines, April 2018).

Table 43: Rationale for recommendations on antibiotic treatment

Erythema migrans	Rationale for the committee's recommendations on antibiotic treatment
Studies and quality of studies	A number of studies examined antibiotic treatment of Lyme disease with erythema migrans using different antibiotics, doses and durations of treatment. However, many of the studies did not reflect current prescribing practices and the evidence was of poor quality.
Adults	There was evidence that doxycycline is more clinically effective than some other antibiotics. However, the evidence showed no clear difference in effectiveness between doxycycline, an amoxicillin/probenecid combination and azithromycin. The evidence also showed no benefit of intravenous or intramuscular cephalosporin over doxycycline. It was noted that doxycycline and amoxicillin are able to penetrate the blood–cerebrospinal fluid barrier and pass into the central nervous system, whereas azithromycin cannot. This may be important to prevent the development of further symptoms. Doxycycline can also be taken in a single daily dose, which may help with adherence. Based on these factors, along with their knowledge and experience, the committee agreed on doxycycline as the initial treatment for adults and young people (aged 12 and over), with amoxicillin as an alternative, and azithromycin as a third option when both doxycycline and amoxicillin are contraindicated.
Children	The committee acknowledged that infectious disease specialists currently treat Lyme disease in children aged 9 and above with doxycycline, although it is not licensed in the UK for children under 12, and it is contraindicated in this age group because of side effects, such as teeth staining. Based on their experience and knowledge, feedback from stakeholders, and the evidence for adults, the committee agreed that doxycycline is the most effective treatment for Lyme disease and that the risk of dental problems in children is low when it is used for short-term treatment (28 days or less). Therefore, doxycycline can be used as the initial treatment for Lyme disease in children aged 9 and above. The committee agreed on doxycycline doses based on their knowledge and experience of current practice both in the UK and the US. The use of doxycycline in children under 9 years is currently limited by licensing and clinical experience. There was some evidence that amoxicillin and azithromycin were equally effective in children. Because of its ability to penetrate the blood–cerebrospinal fluid barrier, the committee agreed that children under 9 should be offered amoxicillin as the initial treatment, with azithromycin as an alternative treatment option, and that doses should be adjusted by weight.
Duration of treatment	Current guidelines give ranges for treatment duration, generally between 10 and 21 days, without guidance on when to use a longer or shorter course. The committee agreed that this is not clear enough for generalists. The evidence for treatment duration

Erythema migrans	Rationale for the committee's recommendations on antibiotic treatment
	was limited. The committee decided that longer courses of 21 days of treatment should be offered as standard because of their concern at low cure rates in some studies and the lack of clear evidence for shorter courses. They also agreed that a longer course may be reassuring for people being treated for Lyme disease who continue to have symptoms. The evidence showed adverse event rates were not increased for longer courses.

For more detail we refer the reader to the evidence review: NICE guideline 95 Evidence review D: Evidence review for the management of erythema migrans, April 2018.

Patients with non-focal symptoms of Lyme disease (symptoms such as fever, sweats and muscle pain, which are not specific to an organ system) should be given the same treatment as people with erythema migrans

The NICE guideline for Lyme disease provided recommendations for managing Lyme disease in people with non-focal symptoms (symptoms such as fever, sweats and muscle pain, which are not specific to an organ system). An evidence review informed the committee's recommendations (NICE guideline 95, [E] Evidence review for the management of non-specific symptoms related to Lyme disease. April 2018).

While no studies were identified comparing different antibiotics for managing Lyme disease in people with non-focal symptoms, the committee in reviewing the evidence available for treating other symptoms and based on this and their knowledge and experience agreed that people with non-focal symptoms should be given the same treatment as people with erythema migrans. However, due to the uncertainties about diagnosis and management the committee agreed that care of children and young people under 18 years with Lyme disease and non-erythema migrans presentations should have their care assessed with a specialist.

The evidence review noted:

> *"People with Lyme disease may present with non-specific or non-focal symptoms such as headache, fatigue, dizziness and muscle pain, which can be distressing and impact their quality of life. This review question is important to understand the most appropriate antibiotic and duration of treatment for these presentations.*
>
> *These people might not have the typical erythema migrans (EM) rash at the site of the tick bite and there is currently no standardised management approach for these people"* (NICE guideline 95, [E] Evidence review for the management of non-specific symptoms related to Lyme disease. April 2018).

The PICO characteristics of the research question for the evidence review *'What is the most clinically and cost effective treatment for people who have non-specific symptoms that may be related to Lyme disease?* are shown in Table 44 below.

Table 44: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with Lyme disease determined by a diagnostic test or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins - Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) • Rifampicin (oral, IV)
Comparisons	Antimicrobial agents compared with each other • If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination)

	• Antimicrobial agents compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Study design	• Randomised control studies (RCT) • Cohort studies (if no RCT evidence is found)

No relevant RCTs and cohort studies that assessed the effectiveness of antimicrobial therapy in people with solely non-specific symptoms and no prior antibiotic treatment of Lyme disease were identified.

For managing ongoing symptoms of Lyme disease after a course of antibiotics, patients should not be routinely offered more than two courses of antibiotics because of a lack of evidence of benefit

The NICE Lyme disease guideline 2018 advises that current treatment of Lyme disease is a single course of antibiotics; however, people who have had treatment for Lyme disease sometimes report ongoing symptoms, the cause of which is often not clear and includes reinfection, or organ damage caused by Lyme disease which may take a long time to heal or may even be permanent (NICE guideline Lyme disease, April 2018).

An evidence review developed by the National Guideline Centre [L] Evidence review for the management of ongoing symptoms related to Lyme disease informed the recommendations of the committee.

The committee's recommendations and the effect on clinical practice for ongoing symptoms of Lyme disease after a course of antibiotics are presented below in

Table 45.

Table 45: Recommendations and effect on clinical practice

The evidence available for treating ongoing symptoms did not show benefit from prolonged treatment with antibiotics. However, based on their knowledge and experience, the committee agreed that treatment failure could occur and that a second course of an alternative antibiotic might sometimes be appropriate. The committee noted the importance of considering alternative diagnoses to prevent inappropriate antibiotic treatment and misdiagnosis.
The committee agreed that people with ongoing symptoms should not routinely be offered more than 2 courses of antibiotics because of lack of evidence of benefit. However, discussion with a specialist or referral should be considered for some people, and discussion with the UK national reference laboratory might be helpful, for example, if a different tick-borne disease is possible.
People who have a slow recovery from Lyme disease may need additional support and access to social care. The committee agreed that it was important that healthcare professionals help people with long-term symptoms related to Lyme disease to access support if needed.
Current treatment for Lyme disease is a single course of antibiotics. Treatment for ongoing symptoms is unclear and practice varies. Further antibiotic treatment is now recommended as an option if persisting infection is a possibility. This will standardise practice, but may cause an increase in antibiotic prescribing in a small number of patients. The committee agreed that this change in practice would not result in a significant resource impact given the small number of people with treatment failure.

The evidence review noted:

- If Lyme disease is treated early, most people recover completely, but studies show that some people have ongoing symptoms following antibiotic treatment. It is not known whether these symptoms are due to persisting infection, tissue damage, autoimmune reaction or some other process. There is currently no test that helps determine this. It is important to assess whether repeat or longer courses of antibiotics might help.
- The term 'ongoing symptoms' was preferred for the guideline as it does not attribute cause of symptoms. Terms such as chronic Lyme disease imply possible chronic infection and may be misleading. (NICE guideline Lyme disease [L] Evidence review for the management of ongoing symptoms related to Lyme disease, April 2018).

For this evidence review, the PICO characteristics of the review question *'What is the most clinically and cost effective treatment for people who have non-specific symptoms that may be related to Lyme disease?'* are detailed below in

Table 46.

Table 46: PICO questions for review question

Population	People with Lyme disease determined by a diagnostic test or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins - Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) • Rifampicin (oral, IV)
Comparisons	Antimicrobial agents compared with each other • If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer

	• Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Study design	• Randomised control studies (RCT) • Cohort studies (if no RCT evidence is found)

Source: NICE guideline Lyme disease [L] Evidence review for the management of ongoing symptoms related to Lyme disease, April 2018

The evidence review reported that:

- for included studies, the evidence reviews conducted for antibiotic management of Lyme disease did not pre-specify for how long a person with symptoms related to Lyme disease had those symptoms but was organised by symptom complex;
- the review question on the management of non-specific symptoms related to Lyme disease did not identify any studies in people with non-specific symptoms in the early stages of Lyme disease; and
- the five studies from six papers identified were in adults in whom all or the majority had received antibiotic treatment prior to enrolment (NICE guideline Lyme disease [L] Evidence review for the management of ongoing symptoms related to Lyme disease, April 2018).

The five studies were published between 2001 and 2016 and were: Berende, 2016 (PLEASE trial); Cameron, 2008; Fallon, 2008; Klempner, 2001 and Kaplan 2003; Krupp, 2003.

The committee agreed these studies would inform recommendations about treating people with symptoms ongoing after treatment. All participants in the PLEASE trial received 2 grams intravenous ceftriaxone for 14 days prior to the study interventions. One treatment arm in this trial also used an indirect intervention as people received hydroxychloroquine in addition to clarithromycin (NICE guideline Lyme disease [L] Evidence review for the management of ongoing symptoms related to Lyme disease, April 2018).

Of the quality of the evidence, the guideline committee noted:

- The evidence was generally of Moderate to Very Low quality due to risk of bias, indirectness and imprecision. There were particular concerns around a lack of outcome assessor blinding for subjective outcomes, such as quality of life, high participant dropout rates and differences between treatment groups in outcomes at baseline. One treatment arm in the PLEASE trial also used an indirect intervention as people received hydroxychloroquine in addition to clarithromycin.
- One outcome, improvement in fatigue for the comparison of intravenous ceftriaxone versus placebo, was of High quality.
- There were no concerns regarding the risk of bias for any of the outcomes reported by the PLEASE trial. However, all participants in the trial received a 2-week course of open-

label intravenous ceftriaxone before their assigned study drug. This antibiotic treatment might have resulted in people experiencing a quality of life improvement.

- There was a general lack of evidence with only single, small studies identified for most comparisons. The committee agreed that while the evidence had to be interpreted with caution, there was a trend suggesting that continuous long-term treatment did not provide an additional benefit.

The recommendations from the evidence review are set out below in Table 47.

Table 47: Recommendations from the evidence review

L.6 Offer regular clinical review and re-assessment to people with ongoing symptoms, including people who have no confirmed diagnosis.
L7. Explore any ongoing symptoms with the person and offer additional treatment if needed following usual clinical practice.
L8. Be alert to the possibility of symptoms related to Lyme disease that may need assessment and management including: • chronic pain • depression and anxiety (see NICE's guideline on common mental health disorders) • fatigue • sleep disturbance.
L9. Support people who have ongoing symptoms after treatment for Lyme disease by: • encouraging and helping them to access additional services, including referring to adult social care for a care and support needs assessment, if they would benefit from these • communicating with children and families social care, schools and higher education, and employers about the person's need for a gradual return to activities, if relevant.

For the management of Lyme neuroborreliosis, the NICE 2018 guideline recommends as first treatment antibiotics taken orally for 21 days for the management of Lyme disease affecting the cranial nerves and peripheral nervous system and antibiotics administered intravenously for 21 days for the management of Lyme disease affecting the central nervous system. Care of children and young people under 18 should be discussed with a specialist.

The symptoms and signs reported by Australian patients with Lyme-like illness and ACIIDs doctors treating these patients cognitive impairment, with clinical signs involving the neurological systems. While this NICE guideline is specific to diagnosed classical Lyme disease, we have included the NICE guidelines for Lyme disease affecting the cranial nerves and peripheral nervous system as the guidelines specify the evidence-based recommended antibiotics, route of administration and length of course for managing these focal symptoms.

For Lyme disease in adults and young people (aged 12 and over) who have focal symptoms affecting the cranial nerves or peripheral nervous system the 2018 NICE guideline recommends:

- Treatment: Oral doxycycline 100mg twice daily or 200 mg once daily for 21 days; and
- First alternative: Oral amoxicillin 1g three times daily for 21 days.

For Lyme disease in adults and young people (aged 12 and over) who have focal symptoms affecting the central nervous system, the 2018 NICE guideline recommends:

- Treatment: Intravenous ceftriaxone 2g twice daily or 4 g once daily for 21 days (when an oral switch is being considered, use doxycycline); and
- First alternative: Oral doxycycline 200 mg twice daily or 400 mg once daily for 21 days.

For children aged 9-12 years who have focal symptoms affecting the cranial nerves or peripheral nervous system, the NICE 2018 Lyme disease guidelines recommend:

- Treatment:
  - Oral doxycycline for children under 45 kg: 5mg/kg divided doses on day 1 followed by 2.5 mg/kg daily in one or two divided doses for a total of 21 days;
  - For children 9-12 years with severe infections: up to 5mg/kg daily for 21 days; and
- First alternative: oral amoxicillin for children 33 kg and under: 30 mg/kg three times for day for 21 days.

For children aged 9 under years who have focal symptoms affecting the cranial nerves or peripheral nervous system, the NICE 2018 Lyme disease guidelines recommend:

- Treatment: Oral amoxicillin for children 33kg and under: 30mg/kg three times daily for 21 days

For children aged 9-12 years who have focal symptoms affecting the central nervous system, the NICE 2018 Lyme disease guidelines recommend:

- Treatment: Intravenous ceftriaxone for children under 50 kg: 80mg/kg (up to 4kg) once per day for 21 days;
- First alternative: Oral doxycycline for children under 45 kg: 5mg/kg divided doses on day 1 followed by 2.5 mg/kg daily in one or two divided doses for a total of 21 days:
  - For severe infections: up to 5mg/kg daily for 21 days.

For children aged 9 under years who have focal symptoms affecting the central nervous system, the NICE 2018 Lyme disease guidelines recommend:

- Treatment: Intravenous ceftriaxone for children under 50 kg: 80mg/kg (up to 4kg) once per day for 21 days.

The NICE recommendations for antibiotic treatment for Lyme disease affecting the cranial nerves, peripheral nervous system or central nervous system were informed by and evidence review (NICE guideline Lyme disease, [F] Evidence review on the management of neuroborreliosis, April 2018).

For this evidence review, the PICO characteristics of the review question *'What is the most clinically and cost effective treatment for people with symptoms consistent with neuroborreliosis?'* are detailed below in Table 48. NICE guideline Lyme disease, [F] Evidence review on the management of neuroborreliosis, April 2018).

Table 48: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with clinical presentations consistent with neuroborreliosis, such as: • peripheral nervous system - radiculopathy - mononeuritis multiplex - peripheral neuropathy or polyneuropathy - myopathy (for example, myositis) - cranial nerve lesions including facial nerve (VII) palsy - autonomic nerve dysfunction • central nervous system - white matter lesions - meningitis - encephalitis - seizures - optic neuritis - transverse myelitis - movement disorders (for example, chorea, ataxia) • psychiatric - psychosis - depression - cognitive decline including dementia
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins

	- Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) • Rifampicin (oral, IV) • Steroids (corticosteroids)
Comparisons	Any type of intervention compared to each other • If data are available consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment or steroids compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of neuroborreliosis) 3. Reduction of clinical symptoms related to neuroborreliosis 4. Relapse of neuroborreliosis symptoms **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

Six studies (7 papers) published between 1989 and 2016 were included in the review and were: Jowett, 2016; Karlsson, 1994; Kohlhepp, 1989; Ljostad, 2008; Lyostad, 2010; Pfister, 1989; Pfister, 1991.

Of the overall quality of the evidence, the authors stated:

> *"The evidence came from six studies with small sample sizes and was on Moderate to Very Low quality due to risk of bias, imprecision and indirectness"* (NICE guideline Lyme disease, [F] Evidence review on the management of neuroborreliosis, April 2018).

The committee's advice from the evidence review as reported in the NICE guidelines for Lyme disease (NICE guidelines Lyme disease, April 2018) is set out in below.

Table 49: Recommendations from the evidence review

The evidence for antibiotic treatment of Lyme disease affecting the nervous system was limited. One study showed a greater benefit with oral doxycycline than intravenous ceftriaxone in treating Lyme disease affecting the peripheral nervous system. However, both treatments showed low rates of cure (full resolution of neurological symptoms). The committee also noted that the study used a 14-day course of antibiotics, which is below the maximum treatment durations recommended by some current guidelines.
The committee agreed that people presenting with meningitis or encephalitis (before a diagnosis of Lyme disease) would receive treatment with intravenous ceftriaxone, and that intravenous treatment would achieve adequate concentrations in the central nervous system more rapidly than oral treatment.
The committee also discussed the management of neurosyphilis, which has similar central nervous system involvement. The committee considered that, although the evidence was limited, central nervous system symptoms in Lyme disease should be treated with a similar antibiotic dose to that recommended for neurosyphilis.
Once-daily ceftriaxone has the advantage of being given more easily as an outpatient treatment than other intravenous options, which allows completion of the course as an outpatient.
Taking these factors into account and based on their knowledge and experience, the committee agreed on a 21-day course of intravenous ceftriaxone 4 g daily as the initial treatment for adults and young people (aged 12 and over) with Lyme disease affecting the central nervous system, with a 21-day course of doxycycline 400 mg daily recommended as an alternative treatment. The higher dose (4 g) is the recommended dose for bacterial meningitis. For Lyme disease affecting the cranial nerves or the peripheral nervous system, the committee agreed on a 21-day course of doxycycline 200 mg daily as the initial treatment for adults and young people (aged 12 and over), with amoxicillin recommended as an alternative treatment.
No studies were identified for nervous system symptoms in children. However, the committee agreed that the evidence for adults and young people could be used to support similar treatment for children aged 9 to 12 years, with the same antibiotics and duration of treatment but with doses adjusted by weight. The use of doxycycline in children under 9 years is currently limited by licensing and clinical experience.
Because of the importance of diagnosis and management, the committee also agreed that care of children and young people under 18 should be discussed with a specialist.

6.2.6. 2016 Cochrane findings relevant to treatment

Additionally, for neuroborreliosis, the Cochrane database of systematic reviews published in 2016 a systematic review of antibiotics for the neurological complications of Lyme disease; this review indicated that treatment with any of the four antibiotics produced similarly good outcomes for treatment of neurological Lyme disease in Europe, but a second treatment with amoxicillin does not appear to provide added benefit to ceftriaxone

In 2016, Cadavid and colleagues review of antibiotics for the neurological complications of Lyme disease was published in the Cochrane Library Cochrane Database of Systematic Review (Cadavid et al. 2016). An overview of the findings of the systematic review is provided in Table 50 below. For further detail, we refer to the reader to the full article.

Table 50: Findings of the systematic review

Objectives	To assess the effects of antibiotics for the treatment of Lyme neuroborreliosis
Selection criteria	Randomised clinical trials of antibiotic treatment of Lyme neuroborreliosis in adults and children that compared any antibiotic treatment, including combinations of treatment, versus any other treatments, placebo or no treatment. Studies of entities considered as post-Lyme syndrome were excluded.
Study characteristics	Seven randomised studies involving 450 European participants with LNB were identified; no trials conducted in the US were found. Marked heterogeneity among the studies prevented meta-analysis. None of the studies included a placebo control on the initial antibiotic treatment and only one was blinded. None were delayed-start studies. All were active comparator studies, and most were not adequately powered for non-inferiority comparison. The trials investigated four antibiotics: penicillin G and ceftriaxone in four studies, doxycycline in three studies, and cefotaxime in two studies. One study tested a three-month course of oral amoxicillin versus placebo following initial treatment with intravenous ceftriaxone; one study was limited to children. The trials measured efficacy using heterogeneous physician- or patient-reported outcomes, or both. In some cases cerebrospinal fluid analysis was included as an indirect biomarker of disease and outcome. None of the studies reported on our proposed primary outcome, 'Improvement in a measure of overall disability in the long term (three or more months).' None of the trials revealed any between-group differences in symptom resolution in response to active treatment. In general, treatment was tolerated well. The quality of adverse event reporting, however, was low.

Key results	The seven studies were too different for their results to be combined, so the author's analysed them individually. None of the studies provided clear evidence that one antibiotic was better than another. One study failed to find evidence that a second and longer treatment with an oral antibiotic (amoxicillin) offered any extra benefit following initial intravenous treatment with ceftriaxone. As none of the other studies used a dummy treatment (placebo), the extra benefit offered by antibiotic treatment over recovery that occurs naturally is unknown. In general, the treatment was tolerated well, although the quality of adverse event reporting in most studies appeared to be low. The results indicate that treatment with any of the four antibiotics produced similarly good outcomes for treatment of neurological Lyme disease in Europe. A second treatment with amoxicillin does not appear to provide added benefit to ceftriaxone. We found no trials of antibiotics for treatment of neurological Lyme disease in the United States.
Author's conclusions	There is mostly low- to very low-quality clinical evidence from a limited number of mostly small, heterogeneous trials with diverse outcome measures, comparing the relative efficacy of central nervous system-penetrant antibiotics for the treatment of LNB. The few existing randomized studies have limited power and lack consistent and well-defined entry criteria and efficacy endpoints. It is not possible to draw firm conclusions on the relative efficacy of accepted antibiotic drug regimens for the treatment of LNB. The majority of people are reported to have good outcomes, and symptoms resolve by 12 months regardless of the antibiotic used. A minority of participants did not improve sufficiently, and some were retreated. These randomized studies provide some evidence that doxycycline, penicillin G, ceftriaxone, and cefotaxime are efficacious in the treatment of European LNB. No evidence of additional efficacy was observed when, in one study, an initial antibiotic treatment with intravenous ceftriaxone was followed by additional longer treatment with oral amoxicillin. There is a lack of evidence identified through our high-quality search strategy on the efficacy of antibiotics for treatment of LNB in the United States.

Studies included in Cadavid and colleagues' systematic review were published between 1989 and 2008. They are set out in

Table 51: Studies included in the systematic review

Summary of study	Full citation
Karlsson 1994 {published data only}	Karlsson M, Hammers-Berggren S, Lindquist L, Stiernstedt G, Svenungsson B. Comparison of intravenous penicillin G and oral doxycycline for treatment of Lyme neuroborreliosis. *Neurology* 1994;**44**(7):1203–7. PUBMED: 8035916]
Kohlhepp 1989 {published data only}	Kohlhepp W, Oschmann P, Mertens H-G. Treatment of Lyme borreliosis, randomized comparison of doxycycline and penicillin G. *Journal of Neurology* 1989;**236**(8):464–9. PUBMED: 2614491]
Ljostad 2008 {published data only}	Ljostad U, Skogvoll E, Eikeland R, Midgard R, Skarpaas T, Berg A, et al. Oral doxycycline versus intravenous ceftriaxone for European Lyme neuroborreliosis: a multicenter, non-inferiority, double-blind, randomized trial. *Lancet Neurology* 2008;**7**(8):690–5. PUBMED: 18567539]
Mullegger 1991 {published data only}	Mullegger RR, Millner MM, Stanek G, Spork KD. Penicillin G sodium and ceftriaxone in the treatment of neuroborreliosis in children-a prospective study. *Infection* 1991;**19**(4):279–83. PUBMED: 1917046]
Oksi 2007 {published and unpublished data}	Oksi J. VS: Cochrane Review: Neuroborreliosis. Email to: P Auwaerter 9 November 2012. _Oksi J, Nikoskelainen J, Hiekkanen H, Lauhio A, Peltomaa M, Pitkaranta A, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a doubleblind, randomized, placebo-controlled, multicenter clinical study. *European Journal of Clinical Microbiology & Infectious Diseases* 2007;**26**(8):571–81. PUBMED: 17587070]
Pfister 1989 {published data only}	Pfister HW, Preac-Mursic V, Wilske B, Einhaupl KM. Cefotaxime vs penicillin G for acute neurologic manifestations in Lyme borreliosis. A prospective randomized study. *Archives of Neurology* 1989;**46**(11): 1190–4. PUBMED: 2684107]
Pfister 1991 {published data only}	Pfister HW, Preac-Mursic V, Wilske B, Schielke E, Sorgel F, Einhaupl KM. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. *Journal of Infectious Diseases* 1991;**163**(2):311–8. PUBMED: 1988514]

For additional detail of this systematic review, we refer the reader to the original paper (Cadavid et al. 2016)

NICE advice: Lyme arthritis Lyme is for oral antibiotic therapy for 28 days; longer courses of treatment (28 days) are appropriate when treating Lyme arthritis because it is difficult for antibiotics to penetrate to the synovium and synovial fluid. Care of children and young people under 18 with Lyme disease and non-erythema migrans presentations should be discussed with a specialist.

ACIIDs advised in its submission to the Senate Inquiry that doctors treating patients with Lyme-like illness in Australia observe **clinical signs involving the musculoskeletal system, including swollen joints** (ACIIDS, Submission 370, March 2016)

While this NICE guideline is specific to diagnosed classical Lyme disease we have included the NICE guidelines for Lyme disease arthritis as the guideline specifies the evidence-based recommended antibiotics, route of administration and length of course for managing these focal symptoms.

The 2018 NICE guideline for antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) with Lyme arthritis is:

- Treatment: Oral doxycycline 100mg twice daily or 200 mg once daily for 28 days;
- First alternative: Oral amoxicillin 1g three times daily for 28 days; and
- Second alternative: Intravenous ceftriaxone: 2g once per day for 28 days.

For children aged 9-12 years the 2018 NICE guideline for antibiotic treatment for Lyme disease with Lyme arthritis is:

- Treatment: Oral doxycycline for children under 45kg: 5mg/kg in 2 divided doses on day 1 followed by 2.5mg/kg daily in 1 or 2 divided doses for a total of 28 days;
    - For severe infections, up to 5mg/kg daily for 28 days;
- First alternative: Oral amoxicillin for children 33 kg and under: 30mg/kg three times daily for 28 days; and
- Second alternative: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2g) once per day for 28 days.

For children aged under 9 years, the 2018 NICE guideline for antibiotic treatment for Lyme disease with Lyme arthritis is:

- Treatment: Oral amoxicillin for children 33 kg and under: 30mg/kg three times daily for 28 days; and
- First alternative: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2g) once per day for 28 days.

The NICE recommendations for antibiotic treatment for Lyme disease arthritis were informed by an evidence review (NICE guideline Lyme disease, [G] Evidence review for the management of Lyme arthritis, April 2018).

For this evidence review, the PICO characteristics of the review question *'What is the most clinically and cost effective treatment for people with arthritis related to Lyme disease?'* are detailed below in Table 52 (NICE guideline Lyme disease, [G] Evidence review for the management of Lyme arthritis, April 2018).

Table 52: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with symptoms consistent with arthritis related to Lyme disease
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin + clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins - Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) • Rifampicin (oral, IV) • Steroids (corticosteroids; systemic, local injections) • Dexamethasone (local injection, IV) • Hydrocortisone (local injection, IV) • Methylprednisolone (local injection, IV) • Prednisolone (local injection, IV) Non-steroidal anti-inflammatory drugs (NSAIDs) Hydroxychloroquine sulfate (Plaquenil, Quinoric; oral)
Comparisons	Any type of intervention compared to each other • If data are available consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial treatment, steroids or NSAIDs compared to no treatment /placebo

Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme arthritis) 3. Reduction of clinical symptoms related to Lyme arthritis 4. Relapse of symptoms related to Lyme arthritis **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

Three RCTs were included in the review. The studies were published between 1985 and 1994 and were:

Caperton, 1990; Steere, 1985; Steere, 1994.

Of the quality of the evidence, the authors made the following statements:

"The evidence came from 3 RCTs comprising 140 people and was of Low to Very Low quality due to risk of bias, imprecision and indirectness. There were particular concerns regarding the lack of blinding, which could have had a confounding effect on subjective outcomes, such as signs and symptoms that could not be measured by objective tests.

Many outcomes and the time point at which they were assessed were poorly defined in the

included studies. In particular, it was not clear whether cure or reduction of symptoms referred to the resolution or improvement of the arthritic symptoms or of any Lyme disease symptoms. Similar ambiguity existed for the outcomes of reoccurrence of symptoms. Studies also varied in the outcomes they reported.

One of the studies included an indirect intervention. People in the amoxicillin group also received 500 mg probenecid, which was used to increase the effective body concentration of amoxicillin. Meta-analysis was not possible due to the different treatments regimens given in the studies". (NICE guideline Lyme disease, [G] Evidence review on the management of Lyme arthritis, April 2018).

The committee's recommendation for the antibiotic treatment of Lyme disease arthritis in the NICE guideline Lyme disease (Nice guideline, Lyme disease, April 2018)) is outlined in

Table 53.

Table 53: Recommendation for antibiotic treatment

The studies identified looked at antibiotic treatment in children, young people and adults with Lyme arthritis (inflammation affecting 1 or more joints). Evidence from 1 study showed that a 30-day course of doxycycline resulted in fewer symptom relapses and adverse events than 30 days of amoxicillin plus probenecid.
The committee agreed that longer courses of treatment are appropriate when treating Lyme arthritis because it is difficult for antibiotics to penetrate to the synovium and synovial fluid.
Taking these factors into account, the committee decided that a 28-day course of antibiotics would be appropriate and also practical, because antibiotics are available in weekly packs.
Because the evidence was limited, the committee also took into account evidence for other presentations of Lyme disease. Based on this, along with their knowledge and experience of current practice, the committee agreed that doxycycline should be offered to adults and young people (aged 12 and over) as the initial treatment, with amoxicillin recommended as an alternative treatment. The committee also agreed that if oral doxycycline and amoxicillin are contraindicated or unsuitable, 28 days of intravenous ceftriaxone should be offered.
Although there was no evidence for treating Lyme arthritis in children, the committee agreed that the evidence for adults and young people could be used to support similar treatment for children aged 9 to 12 years, with the same antibiotics and duration of treatment but with doses adjusted by weight. The use of doxycycline in children under 9 years is currently limited by licensing and clinical experience.
Because of the importance of correct diagnosis and management, the committee agreed that care of children and young people under 18 with Lyme disease and non-erythema migrans presentations should be discussed with a specialist.

Placeholder: Brockensted and Wormser (2014)- Unravelling Lyme disease – evidence base [for treatment outcomes in Lyme arthritis]

[This section is under construction]

For management of acrodermatitis chronica atrophicans NICE 2018 Lyme disease guideline recommendations are the same as for Lyme arthritis Care of children and young people under 18 with Lyme disease and non-erythema migrans presentations should be discussed with a specialist.

ACIIDs advised in its submission to the Senate Inquiry that doctors treating patients with Lyme-like illness in Australia observe **clinical signs involving the dermatological system, including** Acrodermatitis chronica atrophicans.

The 2018 NICE guideline recommendations for antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) with Acrodermatitis chronica atrophicans is the same as for Lyme arthritis and is:

- Treatment: Oral doxycycline 100mg twice daily or 200 mg once daily for 28 days
- First alternative: Oral amoxicillin 1g three times daily for 28 days
- Second alternative: Intravenous ceftriaxone: 2g once per day for 28 days

For children aged 9-12 years the 2018 NICE guideline for antibiotic treatment for Lyme disease with Acrodermatitis chronica atrophicans is the same as for Lyme arthritis and is:

- Treatment: Oral doxycycline for children under 45 kg:5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 28 days
  - For severe infections, up to 5 mg/kg daily for28 days
- First alternative: Oral amoxicillin for children 33 kg and under: 30mg/kg three times daily for 28 days
- Second alternative: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2 g) once per day for 28 days

For children aged under 9 years, the 2018 NICE guideline for antibiotic treatment for Lyme disease with Acrodermatitis chronica atrophicans is the same as for Lyme arthritis and is:

- Treatment: Oral amoxicillin for children 33 kg and under: 30mg/kg three times daily for 28 days
- First alternative: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2 g) once per day for 28 days

The NICE recommendations for antibiotic treatment for Lyme disease with acrodermatitis chronica atrophicans were informed by an evidence review (NICE guideline Lyme disease, [H] Evidence review for management of with Acrodermatitis chronica atrophicans, April 2018).

For this evidence review, the PICO characteristics of the review question *'What is the most clinically and cost effective treatment for people with acrodermatitis chronica atrophicans related to Lyme disease?'* are detailed below in

Table 54 (NICE guideline Lyme disease, [H] Evidence review for management of with Acrodermatitis chronica atrophicans, April 2018).

Table 54: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with symptoms consistent with acrodermatitis chronica atrophicans related to Lyme disease
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins - Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) - Rifampicin (oral, IV)
Comparisons	Antimicrobial agents compared with each other • Type of antimicrobial agent • Route of administration • Duration of treatment: 1 month versus longer Monotherapy versus polytherapy (any combination) Antimicrobial agents compared to no treatment
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of ACA symptoms) 3. Reduction of ACA symptoms 4. Relapse of ACA symptoms **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

The review included only one cohort study by Aberer published in 1996. No randomised trials were identified. Of the quality of the evidence, the committee stated:

> *"The evidence came from 1 study with a small sample size and was of Very Low quality due to the non-randomised study design, risk of bias and imprecision. There were particular concerns about the selection of people, the general lack of blinding to the treatment allocation, and inadequately defined outcomes"* (NICE guideline Lyme disease, [H] Evidence review for management of with Acrodermatitis chronica atrophicans, April 2018).

The committee's recommendations and advice for the antibiotic treatment of Lyme disease with acrodermatitis chronica atrophicans in the NICE guideline Lyme disease (Nice guideline, Lyme disease, April 2018)) from the evidence review are set out in

Table 55.

Table 55: Recommendations and advice for antibiotic treatment

One study suggested that a 30-day course of doxycycline was better for treating acrodermatitis chronica atrophicans than a 20-day course of treatment. Oral doxycycline given for 30 days was also more effective than a 15-day course of intravenous ceftriaxone. The committee agreed that a longer course of treatment might be beneficial because it is difficult for antibiotics to penetrate the affected skin. They also took into account evidence for Lyme arthritis, which justified a longer treatment course to allow penetration into joints. The committee decided that a 28-day course of antibiotics would be appropriate and practical, because antibiotics are available in weekly packs.
The evidence for antibiotics was very limited, so the committee also took into account evidence for other presentations of Lyme disease and their experience and knowledge of current practice. The committee agreed that doxycycline should be offered to adults and young people (aged 12 and over) as the initial treatment, with amoxicillin recommended as an alternative treatment. The committee also agreed that if oral doxycycline and amoxicillin are contraindicated or unsuitable, intravenous ceftriaxone could be offered.
Although there was no evidence for treating acrodermatitis chronica atrophicans in children, the committee agreed that the evidence for adults and young people could be used to support similar treatment for children aged 9 to 12 years, with the same antibiotics and duration of treatment but with doses adjusted by weight. The use of doxycycline in children under 9 years is currently limited by licensing and clinical experience.
Because of the importance of correct diagnosis and management, the committee agreed that care of children and young people under 18 with Lyme disease and non-erythema migrans presentations should be discussed with a specialist.

For the management of Lyme carditis, the recommended course of antibiotic treatment is 21 days. Care of children and young people under 18 with Lyme disease and focal symptoms such as carditis should be discussed with a specialist.

ACIIDs advised in its submission to the Senate Inquiry that doctors treating patients with Lyme-like illness in Australia observe **clinical signs involving the cardiovascular system, including** ECG changes, arrhythmias due to borrelia carditis; Postural Orthostatic Tachycardia Syndrome (POTS) (ACIIDS, Submission 370, March 2016).

While the 2018 NICE guideline Lyme disease is specific to diagnosed classical Lyme disease, we have included the NICE guidelines for Lyme disease carditis as the guidelines specify the evidence-based recommended antibiotics, route of administration and length of course for managing these focal symptoms.

The 2018 NICE guideline recommendations for antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) with Lyme carditis is:

- Treatment: Oral doxycycline 100mg twice daily or 200mg once daily for 21 days; and
- First alternative: Intravenous ceftriaxone: 2g once per day for 21 days.

The 2018 NICE guideline recommendations for antibiotic treatment for Lyme disease in adults and young people (aged 12 and over) with **Lyme carditis and who are haemodynamically unstable** is:

- Treatment: Intravenous ceftriaxone: 2g once per day for 21 days (when an oral switch is being considered, use doxycycline).

For children aged 9-12 years the 2018 NICE guideline for antibiotic treatment for Lyme disease with **Lyme carditis and who are haemodynamically stable** is:

- Treatment: Oral doxycycline for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days:
  - For severe infections, up to 5 mg/kg daily for 21 days; and
- First alternative: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2 g) once per day for 21 days.

For children aged under 9 years, the 2018 NICE guideline for antibiotic treatment for Lyme disease with **Lyme carditis and who are haemodynamically stable** is:

- Treatment: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2 g) once per day for 21 days.

For children aged 9-12 years the 2018 NICE guideline for antibiotic treatment for Lyme disease with **Lyme carditis and who are haemodynamically unstable** is:

- Treatment: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2 g) once per day for 21 days; and
- First alternative: Oral doxycycline for children under 45 kg: 5 mg/kg in 2 divided doses on day 1 followed by 2.5 mg/kg daily in 1 or 2 divided doses for a total of 21 days:
  - For severe infections, up to 5 mg/kg daily for 21 days.

For children aged under 9 years, the 2018 NICE guideline for antibiotic treatment for Lyme disease with **Lyme carditis and who are haemodynamically unstable** is:

- Treatment: Intravenous ceftriaxone for children under 50kg: 80mg/kg (up to 2 g) once per day for 21 days.

The NICE recommendations for antibiotic treatment for Lyme disease with Lyme carditis were informed by an evidence review (NICE guideline Lyme disease, [I] Evidence review for management of Lyme carditis, April 2018).

For this evidence review, the PICO characteristics of the review question *'What is the most clinically and cost effective treatment for people with carditis related to Lyme disease?'* are detailed below in **Error! Reference source not found.**. (NICE guideline Lyme disease, [I] Evidence review for management of Lyme carditis, April 2018).

Table 56: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years) and children (under 12 years) with symptoms consistent with carditis related to Lyme disease
Interventions	Antimicrobials, including but not limited to: • Penicillins - Amoxicillin (oral, IV) - Ampicillin (oral, IV) - Benzylpenicillin sodium / Penicillin G (IV) - including Augmentin (Amoxicillin and clavulanic acid; oral, IV) - Phenoxymethylpenicillin / Penicillin V (oral) • Tetracyclines - Doxycycline (oral) - Minocycline (oral) • Cephalosporins - Cefotaxime (IV) - Ceftriaxone (IV) - Cefuroxime axetil (oral) • Macrolides - Azithromycin (oral) - Clarithromycin (oral, IV) • Fluoroquinolones - Ciprofloxacin (oral, IV) - Levofloxacin (oral, IV) - Moxifloxacin (oral, IV) - Nalidixic acid (oral) - Norfloxacin (oral) - Ofloxacin (oral, IV) • Rifampicin (oral, IV) • Steroids (corticosteroids; oral, IV)
Comparisons	Any type of intervention compared to each other • If data are available, consider: - Type of agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer Monotherapy versus polytherapy (any combination) Antimicrobial treatment or steroids compared to no treatment / placebo
Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms related to Lyme carditis) 3. Reduction of clinical symptoms related to Lyme carditis 4. Relapse of symptoms related to Lyme carditis **Important:** 5. Adverse events
Study design	• RCTs • Cohort studies (if no RCT evidence is found)

The review did not identify any relevant RCTs and cohort studies comparing the effectiveness of antibiotics and steroids versus each other or placebo as treatment for people with carditis related to Lyme disease.

From the evidence review the committee provided the advice and recommendations set out in Table 57 on the management of Lyme carditis.

Table 57: Advice and recommendations

No studies of antibiotic treatment for heart problems caused by Lyme disease were identified. Therefore, the committee reviewed the evidence available for treating other symptoms of Lyme disease and used this, their experience of current practice and their knowledge of care for people with heart problems, to develop the recommendations.
The committee decided that a 21-day course of doxycycline would be appropriate as the initial treatment for adults and young people (aged 12 and over) with carditis who are stable, with a 21-day course of intravenous ceftriaxone recommended as an alternative treatment.
The committee noted that people with severe heart problems are likely to need treatment in hospital from cardiologists. They agreed that intravenous ceftriaxone for 21 days would therefore be suitable as the initial treatment for people with carditis who are haemodynamically unstable.
Because of the lack of evidence for treatment in children, the committee agreed that the evidence for adults and young people could be used to support similar treatment for children aged 9 to 12 years, with the same antibiotics and duration of treatment but with doses adjusted by weight. The use of doxycycline in children under 9 years is currently limited by licensing and clinical experience.
Because of the importance of correct diagnosis and management, the committee agreed that care of children and young people under 18 with Lyme disease and focal symptoms such as carditis should be discussed with a specialist.
The committee also noted that azithromycin should not be used to treat people with cardiac abnormalities because of its effect on the QT interval.

For management of women with Lyme disease during pregnancy and their babies NICE recommends pregnant women should be treated following usual practice, using antibiotics suitable in pregnancy and babies born to women with Lyme disease should be discussed with a paediatric infectious disease specialist. The risk of mother-to-baby transmission of Lyme disease appears to be very low. No evidence was found for transmission of Lyme disease through sexual contact or blood products

The committee made recommendations in the NICE guideline Lyme disease, April 2018 regarding management of women with Lyme disease during pregnancy and their babies, set out in Table 58.

Table 58: Recommendations regarding management of women during pregnancy

The committee acknowledged that mother-to-baby transmission of Lyme disease is possible in theory. There was an absence of evidence, but the risk appears to be very low. The committee decided that women could be reassured that pregnancy and their baby are unlikely to be affected and highlighted the importance of completing treatment. It was also agreed that pregnant women should be treated following usual practice but using antibiotics suitable in pregnancy.
Given the absence of evidence and the lack of a standard approach to care, the committee agreed that care of babies born to mothers with Lyme disease during pregnancy should be discussed with a paediatric infectious disease specialist if the mother has concerns about her baby. In addition, to ensure that babies with Lyme disease do not go untreated, the committee agreed that babies should receive treatment if they have serology showing IgM antibodies specific to Lyme disease or symptoms that might be caused by Lyme disease.
No evidence was found for transmission of Lyme disease through sexual contact or blood products and the committee agreed that they could not make recommendations in these areas.

The NICE recommendations for management for women with Lyme disease during pregnancy and their babies were informed by an evidence review (NICE guideline 95 Lyme disease: diagnosis and management [M] Evidence review for person-to-person transmission, Intervention evidence review, April 2018).

The evidence review noted the possibility of person-to person spread of Lyme disease has been raised and developing Lyme disease during pregnancy is of concern to women who are pregnant. The committee therefore included person-to-person transmission in the scope of the guideline to assess what evidence was available. (NICE guideline 95 Lyme disease: diagnosis and management [M] Evidence review for person-to-person transmission, Intervention evidence review, April 2018).

In the earlier section on clinical epidemiology, patients had reported in submissions that they had acquired Lyme-like illness congenitally or via their mother (Brown, 2018). Therefore, this evidence review is of relevance to the evidence base of transmission of DSCATT, however, still acknowledging the definitive cause of Lyme-like illness in Australia is yet to be found.

For this evidence review, the PICO characteristics of the review question *'What are the patterns of person-to- person transmission of Lyme disease?* are detailed below in Table 59. (NICE guideline 95 Lyme disease: diagnosis and management, [M] Evidence review for person-to-person transmission, April 2018).

Table 59: PICO characteristics of review question

Population	Adults (18 years and over), young people (12 to 17 years), children (under 12 years), neonates or new-borns (under 28 days old) and stillbirths with suspected (or under investigation for) Lyme disease.
Study design	Observational studies that report an incidence or prevalence estimate of Lyme disease through 1 of the following ways of transmission: • vertical transmission • sexual transmission • transmission through blood products
Statistical measures	Transmission risk of Lyme disease, defined as the number of effective contacts per unit of time (that is, people infected through the contact measured) divided by the total number of contacts between infectious and susceptible individuals per time unit. In the absence of reliable transmission risk data, incidence and prevalence data will be included in this review. Incidence of Lyme disease (any clinical presentation related to Lyme disease), defined as the number of new cases within a specified time period divided by the size of the population initially at risk. The prevalence of Lyme disease (any clinical presentation related to Lyme disease) is defined as the number of individuals with the disease divided by the number of individuals tested in the population at risk.
Review strategy	Titles and abstracts will be reviewed to identify papers that mention transmission of Lyme disease, transmission risk or any models used to generate such estimates. The full text of the identified articles will then be assessed and studies on vector-borne transmission (that is, infections through a tick bite) will be excluded from the review. Stratum: • By way of transmission Appraisal of methodological quality: • The methodological quality of each study will be assessed using an adaptation of a checklist for prevalence and incidence studies published by the Joanna Briggs Institute Synthesis of data: • Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined)

6.2.7. 2010 German guidelines 'Diagnosis and Treatment of Lyme borreliosis' recommendations on treatment

Recommend either a monotherapy or combined therapy of antibiotics, however, the guideline notes the efficiency of a combined antibiotic therapy has not been scientifically attested to date. The authors note the guideline was prepared with great care but no liability whatever can be accepted for its accuracy, especially in relation to dosages

As mentioned above in this section, ACIIDS doctors refer to the German guidelines to inform the treatment of patients with Lyme-like illness in Australia. The guidelines Deutsche Borreliose-Gesellschaft e. V. 'Diagnosis and treatment of Lyme borreliosis (Lyme disease) were provided as an attachment to ACIIDS submission (ACIIDS submission 370, Attachment 2, March 2016).

The German guidelines were published in April 2008, with a revised second addition in December 2010. The guideline notes that the recommendations were revised in 2009/10 by a working party, this being followed by a repeated anonymous consultation process in which all ordinary members of the German Borreliosis Society (Deutsche Borreliose-Gesellschaft (DGB)) and external experts were able to submit, comment and vote on suggested amendments. The authors noted they had no conflicts of interest, being physicians in their own practices, working for a medical laboratory, a clinic or in retirement. They also noted there were no economic, political, academic or scientific conflicts of interest. The guideline includes 162 references.

The guidelines state:

> *Guidelines are presented as recommendations. They are intended to help physicians to arrive at decisions. They are neither legally binding on physicians nor do they form grounds for substantiating or indemnifying from liability.*
>
> *This guideline, "Diagnosis and Treatment of Lyme borreliosis" was prepared with great care. However, no liability whatever can be accepted for its accuracy, especially in relation to dosages, either by the authors or by the German Borreliosis Society"* (Deutsche Borreliose-Gesellschaft e. V. 'Diagnosis and treatment of Lyme borreliosis (Lyme disease), 2010)

The guidelines noted the scientific basis for antibiotic treatment is still inadequate at this time, with the exception of the localised early stages (EM). The authors cited evidence for statements:

- There are now a few studies available which provide evidence of the positive effect and the safety of long term antibiotic therapy
- Additional factors are involved in vivo which lie in the capability of Borrelia to evade the immune system specifically under the influence of various antibiotics.
- Hypothetically the persistence of Borrelia is attributed to its residency within the cell and to the development of biologically less active permanent forms (sphaeroplasts, encystment) among other things

The Deutsche Borreliose-Gesellschaft guidelines advised the treatment of Lyme borreliosis can be conducted either as a monotherapy or with a synchronous combined therapy and that:

> *"; this form of treatment is based on microbiological findings The efficiency of a combined antibiotic therapy has not been scientifically attested to date and on empirical data that have not so far been systematically investigated".*

(Deutsche Borreliose-Gesellschaft e. V. 'Diagnosis and treatment of Lyme borreliosis (Lyme disease), 2010)

For monotherapy, the guidelines advise antibiotic treatment should be adjusted for weight as a matter of principle. Table X below shows the Antibiotic monotherapy of Lyme borreliosis from the guideline. In this table, we note duration of antibiotic treatment is 'dependent on clinical progress at least 4 weeks.

Table 60: Antibiotic monotherapy of Lyme borreliosis

In the early stage (localised)	
Doxycycline	400 mg daily (children of 9 years old and above)
Azithromycin	500 mg daily on only 3 or 4 days/week
Amoxicillin (pregnant women, children)	3000-6000 mg/day
Cefuroxime axetil	2 x 500 mg daily
Clarithromycin	500-1000 mg daily
Duration dependent on clinical progress at least 4 weeks. If ineffective with regard to EM maximum 2 weeks/ then change antibiotic.	
In the early stage with dissemination and late stage	
Ceftriaxone	2 g daily
Cefotaxime	2-3 x 4 g
Minocycline	200 mg daily, introduced gradually
Duration dependent on clinical progress. If ineffective, change antibiotic, at the earliest after 4 weeks.	
Alternatives in the late stage	
Benzathine benzylpenicillin	1.2 Mega 2x/week or 2 x 1.2 Mega 1x/week
Metronidazole	400-1200 mg daily, whenever possible parenterally 6-7 days, max. 10 days, also repeatedly in particular well-fonded cases

For combined therapy, the guideline states:

- In a combined therapy, two, or sometimes three, antibiotics are used at the same time, usually in the form of synchronously combined long-term antibiotic treatment.
- The action of macrolides and possibly also of tetracyclines is intensified by the simultaneous administration of hydroxychloroquine, which, like metronidazole, acts on encysted forms of Borrelia.
- Third-generation cephalosporins can be combined with minocycline (enters the CSF) alternating between the two, that is, each substance alone on 3 days a week each. Both can be combined with hydroxychloroquine. Hydroxychloroquine can be tested for tolerability, for example given as a single drug within the first 3 days of therapy. The dosage of minocycline should be increased gradually. If minocycline is not tolerated, it can be replaced with doxycycline or clarithromycin.
- Doxycycline and minocycline can be combined with azithromycin and hydroxychloroquine. To make it easier to identify drug intolerance, the treatment should not be started with the individual antibiotics given simultaneously. It is preferable to add

the other antibiotics staggered over time, say at intervals of one to two weeks. (Deutsche Borreliose-Gesellschaft e.V. 'Diagnosis and treatment of Lyme borreliosis (Lyme disease), 2010).

Table 61 below is reproduced from the guidelines and show antibiotics for a combined therapy of Lyme borreliosis.

Table 61: Antibiotics for a combined therapy of Lyme borreliosis

Betalactams	
Ceftriaxone	2 g daily
Cefotaxime	3 x 4 g daily
Tetracyclines	
Minocycline*	200 mg daily
Doxycycline	400 mg daily
Macrolides	
Azithromycin	500 mg daily on 3 or 4 days/week
Clarithromycin	2 x 500 mg daily
Others	
Metronidazole	400-1200 mg daily, whenever possible parenterally, 6-7 days, max. 10 days, also repeatedly in particular well-fonded cases
Hydroxychloroquine	200 mg daily or every other day (cumulative)
Duration in the late and disseminated early stage: 3 months and more. Recurrence is treated again as necessary, but generally in cycles of shorter treatment times, e.g. 3 days – 3 weeks. *Take special note of particulars of risks with minocycline!	

6.2.8. 2014 ILADS guidelines recommendations on treatment

The available evidence regarding the treatment of known tick bites, erythema migrans (EM) rashes and persistent disease is limited and was of very low quality due to limitations in trial designs, imprecise findings, outcome inconsistencies and non-generalizability of trial findings. As such, optimal treatment regimen for the management of known tick bites, EM rashes and persistent disease has not yet been determined.

ACIIDS stated ACIIDS doctors also refer to the guidelines laid down by ILADS when treating patients in Australia for Lyme-like illness (ACIIDS Submission 370, March 2016). ACIIDS provided two attachments of ILADS guidelines with their submission, Attachment 25, the 2014 ILADS guidelines 'Evidence assessment and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease (Cameron et al. 2014) and Attachment 34 -The 2004 International Lyme and Associated Diseases Society Evidence based guidelines for the management of Lyme disease.

The guideline (Cameron et al. 2014) 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.

The guideline cited 213 references and notes it presents evidence-based treatment recommendations which follow the Grading of Recommendations Assessment, Development and Evaluation system. However, the authors note *"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"* (Cameron et al. 2014).

Key issues stated in the guideline specific to treatment are set out in

Table 62.

Table 62: Key issues specific to treatment

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.
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.

Source: Cameron et al. (2014) page 1129

ILADS recommended clinicians should not use a single 200 mg dose of doxycycline following a tick bite as prophylaxis for Lyme disease; The preferred regimen is 100–200 mg of doxycycline, twice daily for 20 days. Other treatment options may be appropriate on an individualized basis. The recommendation was based on very lo- quality evidence

For the question *'Does a single 200 mg dose of doxycycline following a tick bite provide effective prophylaxis for Lyme disease?* ILADS (Cameron et al. 2014) made the recommendations set out in Table 63

Table 63: Dose recommendations

Recommendation	Role of patient preferences
Recommendation 1a Clinicians should not use a single 200 mg dose of doxycycline for Lyme disease prophylaxis (Recommendation, **very low-quality evidence**).	**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**).	**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**).	**Low** The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

ILADS recommends shorter courses of antibiotic treatments of 10 or 20 days depending on antibiotic are not recommended for patients with EM rashes because failure rates in the clinical trials were unacceptably high.

For the question *'Should the treatment of an EM rash be restricted to 20 or fewer days or oral azithromycin, cefuroxime, doxycycline and phenomethylpenicillin/amoxicillin?* ILADS (Cameron et al. 2014) made the recommendations set out in Table 64.

Table 64: Recommendations for treatment length

Recommendation	Role of patient preferences
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**).	**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	**Moderate** See recommendation 2a.

Recommendation	Role of patient preferences
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**).	
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**).	**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	**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

Recommendation	Role of patient preferences
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**).	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	**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	Role of patient preferences
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**).	
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**).	**Low** The benefits of educating patients about potential disease manifestations clearly outweigh any attendant risks associated with education.

ILADS recommends that for patients who have persistent manifestations of Lyme disease, if antibiotic retreatment is undertaken, clinicians should initiate treatment with 4–6 weeks of the selected antibiotic

For the question '*Should patients with persistent manifestations of Lyme disease be retreated with antibiotics*?' ILADS (Cameron et al. 2014) made the recommendations set out in Table 65.

Table 65: Recommendations for patients with persistent manifestations

Recommendation	Role of patient preferences
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	**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	Role of patient preferences
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).	
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	**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	Role of patient preferences
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**).	
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	**High** See Recommendation 3b.

Recommendation	Role of patient preferences
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**).	

Regarding the difference in view between ILADS and IDSA raised above by ACIIDS (ACIIDS Submission 370, March 2016), ILADS made the following comments:

> *"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]."* (Cameron et al. 2014)

6.2.9. The ILADS Working Group (2004) Evidence-based guidelines for the management of Lyme disease does not recommend hyperbaric oxygen therapy for routine use and notes patient's interest in alternative therapies

This report was completed in November 2003, dated 2004. While it is out of the literature review data range, we have included it as it relates to the 2014 guideline and provides some information about symptomatic treatment modalities that patients with DSCATT report having received.

ILADS advised hyperbaric oxygen therapy (HBOT) is under study but is not recommended for routine use.

Of alternative therapies, the only advice ILADS provided in the guideline was that as patients are becoming more interested in alternative therapies (for example, traditional Chinese medicine, anti-oxidants, hyperthermia, bee venom, naturopathy and homeopathy), physicians should be prepared to address questions regarding these topics.

6.2.10. 2006 Infectious Diseases Society of America (IDSA) guidelines recommendations on treatment

The IDSA guideline is promulgated in the Australian guideline on the diagnosis of overseas acquired Lyme disease

The Australian guideline on the diagnosis of overseas acquired Lyme disease refers to the treatment advice of the Infectious Diseases Society of America. This guideline is *'The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America'* (Wormser, 2006).

IDSA recommendations for treatment of early Lyme disease

The following treatment recommendations (Table 66) were based on 10 in vitro studies that have shown *B. burgdorferi* is highly susceptible to several antimicrobial classes including tetracyclines, most penicillins and many second and third generation cephalosporins and at least nine randomised, prospective trials addressing the treatment of early Lyme disease in the United States.

Table 66: Treatment recommendations

The management options considered included oral antimicrobial therapy for patients with a single erythema migrans skin lesion and oral versus parenteral therapy for patients with clinical evidence of early disseminated infection (i.e., patients presenting with multiple erythema migrans lesions, carditis, cranial nerve palsy, meningitis, or acute radiculopathy). In view of the high frequency of travel between North America and Europe, borrelial lymphocytoma was addressed, despite its rarity in North America. Its primary etiologic agent is *B. afzelii,* one of the exclusively Eurasian species of Lyme borrelia, which are often referred to as *B. burgdorferi* sensu lato.
The panel was unable to provide a recommendation on treatment of seropositive patients without erythema migrans believed to have an acute viral-like illness due to *B. burgdorferi* infection because of lack of data, although recommended therapies for the treatment of erythema migrans would likely b eadequate.
Doxycycline (100 mg twice per day), amoxicillin (500 mg 3 times per day), or cefuroxime axetil (500 mg twice per day) for 14 days (range for doxycycline, 10–21 days; range for amoxicillin or cefuroxime axetil, 14–21 days) is recommended for treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans in the absence of specific neurologic manifestations (see Early Neurologic Lyme Disease) or advanced atrioventricular heart block (tables 2 and 3) (A-I). Ten days of therapy is sufficient if doxycycline is used; however, given the much shorter half life of b-lactam drugs, such as amoxicillin or cefuroxime axetil, it is unclear whether a 10-day course of these drugs would be as effective. Therefore, for uniformity, a 14-day course of therapy is recommended for all of the first-line oral agents. Each of the recommended antimicrobial agents has been shown to be highly effective in the treatment of erythema migrans and associated symptoms in prospective studies. Doxycycline has the advantage of being effective for treatment of HGA (but not for babesiosis), which may occur simultaneously with early Lyme disease. Doxycycline is relatively contraindicated during pregnancy or lactation and in children 18 years of age. For children, amoxicillin, cefuroxime axetil, or doxycycline (if the patient is _8 years of age) is recommended (tables 2 and 3)(A-II).
Macrolide antibiotics are not recommended as first line therapy for early Lyme disease (E-I). When used, they should be reserved for patients who are intolerant of, or should not take, amoxicillin, doxycycline, and cefuroxime axetil. Patients treated with macrolides should be closely observed to ensure resolution of the clinical manifestations.
First-generation cephalosporins, such as cephalexin, are ineffective for treatment of Lyme disease and should not be used (E-II). When erythema migrans cannot be reliably distinguished from community-acquired bacterial cellulitis, a reasonable approach is to treat with either cefuroxime axetil or amoxicillin clavulanic acid (dosage of amoxicillin–clavulanic acid for adults, 500 mg 3 times per day; dosage for children, 50 mg/kg per day in 3 divided doses [maximum of 500 mg per dose]), because these antimicrobials are generally effective against both types of infection (A-III)
Ceftriaxone, while effective, is not superior to oral agents and is more likely than the recommended orally administered antimicrobials to cause serious adverse effects. Therefore, ceftriaxone is not

recommended for treatment of patients with early Lyme disease in the absence of neurologic involvement or advanced atrioventricular heart block (E-I).
Pregnant or lactating patients may be treated in a fashion identical to nonpregnant patients with the same disease manifestation, except that doxycycline should be avoided (BIII).
Because of a lack of biologic plausibility, lack of efficacy, absence of supporting data, or the potential for harm to the patient, the following are not recommended for treatment of patients with any manifestation of Lyme disease: firstgeneration cephalosporins, fluoroquinolones, carbapenems, vancomycin, metronidazole, tinidazole, amantadine, ketolides, isoniazid, trimethoprim-sulfamethoxazole, fluconazole, benzathine penicillin G, combinations of antimicrobials, pulsed-dosing (i.e., dosing on some days but not others), long-term antibiotic therapy, anti-*Bartonella* therapies, hyperbaric oxygen, ozone, fever therapy, intravenous immunoglobulin, cholestyramine, intravenous hydrogen peroxide, specific nutritional supplements, and others (see table 4) (EIII).
Coinfection with *B. microti* or *A. phagocytophilum* or both may occur in patients with early Lyme disease (usually in patients with erythema migrans) in geographic areas where these pathogens are endemic (see the sections below on post-Lyme disease syndromes, HGA, and babesiosis). Coinfection should be considered in patients who present with more severe initial symptoms than are commonly observed with Lyme disease alone, especially in those who have high-grade fever for 148 h, despite antibiotic therapy appropriate for Lyme disease or who have unexplained leukopenia, thrombocytopenia, or anemia (A-III). Coinfection might also be considered in patients who have resolved their erythema migrans skin lesion but have had no improvement or worsening of viral infection–like symptoms (B-III).

[A review of the management of early neurologic Lyme disease IDSA is in progress]

6.2.11. A voluntary review of the IDSA 2006 guidelines in 2008 concluded the 2006 guidelines were medically and scientifically justified and that no changes to the guidelines were necessary. The Review Panel concluded that *in the case of Lyme disease* inherent risks of long-term antibiotic therapy were not justified by clinical benefit

An investigation to determine whether the IDSA violated antitrust laws in the promulgation of the IDSA's 2006 Lyme disease guidelines mentioned above was initiated in November 2006 by Connecticut Attorney General Richard Blumenthal. In April 2008, the Connecticut Attorney General reached an agreement to end the investigation, with the IDSA agreeing to convene an independent review panel to determine whether the 2006 Lyme disease guidelines were based on sound medical and scientific evidence and whether these guidelines should be changed or revised (Lantos et a. 2010).

Lantos et al. concluded:

> *"The Review Panel finds that the 2006 Lyme disease guidelines were based on the highest-quality medical and scientific evidence available at the time and are supported by evidence that has been published in more recent years. The Review Panel did not find that the 2006 guidelines authors had failed to consider or cite relevant data and references that would have altered the published recommendations. In addition to the review by this*
>
> *panel, the recommendations in the 2006 IDSA guidelines are further corroborated by guidelines and statements by other independent bodies from the United States and Europe. It is expected that the IDSA will review the 2006 Lyme disease guidelines on a regular basis to consider any new evidence that would warrant a substantive change to the current recommendations".*

Regarding post-Lyme disease syndromes, and the controversial and public profile nature of this subject the Review Panel reviewed numerous sources of evidence including large volumes of case reports, case reports submitted by ILADS, journal correspondence, patient testimony and the available randomised, placebo-controlled, clinical trials of long-term antibiotic therapy for symptoms attributed to Lyme disease and made the following conclusions:

- The prospective, controlled clinical trials of extended antibiotic treatment of Lyme disease have demonstrated considerable risk of harm, including potentially life-threatening adverse events, attributable both to antibiotic treatment and to intravascular access devices. Such events include intravenous catheter infection, including septicemia (line sepsis), venous thromboembolism, drug hypersensitivity reactions, and drug induced cholecystitis. Minor adverse events, such as diarrhea and candidiasis, were also more common among antibiotic treated patients [9–13]. In a recent cohort of 200 patients, catheter-associated adverse events, such as thrombosis and infection, occurred a mean of 81 days into therapy, underscoring the cumulative risk of adverse events with increasing time [14].
- Prospective, controlled clinical trials have demonstrated little benefit from prolonged antibiotic therapy. Nearly all primary outcome measures failed to demonstrate an advantage to prolonged antibiotic therapy. Statistically significant improvements in treatment groups were not demonstrated across studies, were nonspecific, were of

unclear clinical importance, and in one case, were not sustained at the end of the trial [9–13].

- The risk/benefit ratio for prolonged antibiotic therapy discourages prolonged antibiotic courses for Lyme disease. Several presenters in the 30 July hearing argued that patients with symptoms attributed to chronic Lyme disease confer considerable societal cost. This argument, however, was not accompanied by quantitative evidence from controlled trials that prolonged antibiotic therapy could even partly reduce this cost. The Review Panel concluded that a societal benefit was at best hypothetical based on current evidence.

7. GUIDELINES AND APPROACHES TO INVESTIGATION AND ONGOING SYNDROMIC MANAGEMENT OF SYMPTOMS ASSOCIATED WITH DSCATT THAT HAVE BEEN FOUND EFFECTIVE INTERNATIONALLY

This section provides the findings of the literature reviewed to answer research question 5:

> *What current guidelines and approaches to investigation and ongoing syndromic management of symptoms associated with DSCATT have been found effective internationally?*

As mentioned previously, the situation with DSCATT in Australia is complex. The Australian Government notes that while some Australians and healthcare providers believe that classical Lyme disease can be acquired from ticks in Australia or that a form of 'chronic Lyme disease' exists, the Australian Government cannot currently support the diagnosis of locally acquired Lyme disease in Australia.

Evidence reviewed

To answer the research question, we reviewed 14 articles, reports or guidelines. We prioritised official and government-published evidence.

International guidance on Lyme disease (6)	NICE Guideline – Lyme Disease 2018; Infectious Diseases Society of America (IDSA) Guidelines 2006; EFNS Guidelines on the diagnosis and management of European Lyme neuroborreliosis 2009; Deutsche Borreliosis-Gesellschaft (DBG), Diagnosis and Treatment of Lyme borreliosis Guidelines 2010; The International Lyme and Associated Diseases Society 2004 (ILADS); Australian Guideline on the Diagnosis of overseas-acquired Lyme disease/ borreliosis by Lum G et al (2015).
Australian guidelines and guidance (8)	DOHa, 2018; DOHb, 2018; Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Advisory Committee, 2018; Holliday et al., 2018; EIG, 2107; EIG, 2019; Chalada et al., 2016; Wilson et al., 2014; Moulds and van Driel, 2013;

Key findings about Guidelines and approaches to investigation and ongoing syndromic management of symptoms associated with DSCATT that have been found effective internationally

- There are many other useful "guidelines" or "guidance" documents that are produced that contain references to scientific studies, but they do not specifically detail the methodology used for their development, which makes it difficult to assess their rigor of development.
- There are currently no evidence-based guidelines that directly address the debilitating symptom complexes attributed to tick bites in Australia.
- On the basis of the international literature on fatigue, it is recommended in a patients presenting with fatigue-like symptoms a comprehensive history and examination is taken, as well as a consideration of a period of watchful waiting in the absence of red flags and the judicious use of tests once the decision to investigate is made.
- ME/CFS has been identified as a differential diagnosis for Lyme disease.
- Pain management is likely to be an important component in the care of people with DSCATT.
- Rheumatoid arthritis (RA) guidelines recommend early diagnosis of RA and referral to a rheumatologist if the patient has persistent swelling beyond 6 weeks, even if RA is not confirmed. Early referral enables aggressive intervention with disease modifying drugs, reducing long term damage and disability.
- In the Clinical Pathway for the Screening, Assessment and Management of Depression in Adult Cancer Patients the Psycho-oncology Co-operative Research Group advises that unlike other common symptoms (for example, fatigue), anxiety and depression are readily treatable, and a strong evidence base for intervention exists. Early identification and treatment of anxiety and depression leads to better outcomes.
- Emerging evidence reported by the NHMRC reports that structured family programs may be helpful in reducing grief and burden of care, and in improving family members' sense of control over their situation.

7.1. International guidelines

Many documents produced to guide clinical practice are described by the authors as "guidelines".

7.1.1. Definition of guidelines and standard for appraisal

The US Institute of Medicine (IOM) defines clinical practice guidelines as "*statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternate care options*" (IOM Clinical Practice Guidelines We Can Trust, 2011). For the purpose of this literature review, we will refer to guidelines meeting the IOM description, as "*evidence-based guidelines*" (EBG). An example of an evidence-based guideline is the Lyme Disease Guidelines produced by the National Institute for Health and Care Excellence in the UK (NICE 2018).

The standard for the appraisal of these explicit, evidence-based guidelines in the AGREE II Instrument (AGREE Trust). AGREE II is used to assess guidelines for their scope and purpose; stakeholder involvement; rigor of development (such as describing systematic methods for searching for evidence, listing criteria for selecting evidence, describing the limitations of the body of evidence and having explicit links between recommendations and the supporting evidence), clarity of presentation, applicability including supporting tools to promote implementation of recommendations, and editorial independence.

There are many other useful "guidelines" or "guidance" documents that are produced that contain references to scientific studies, but they do not specifically detail the methodology used for their development. This makes it difficult to assess their rigor of development. They often do not describe the body of evidence from which recommendations are formed. However, they frequently contain practical, best practice advice as well as evidence informed advice. For the purposes of this literature review, such documents are identified as "*evidence-informed guidance*" (EIG). Examples of EIG include guidelines produced by Therapeutic Guidelines Ltd (TGL). TGL reviews international literature assessed by local Australian experts and includes a practical distillation of current evidence and opinion.[1]

Position statements and consensus guidelines can provide useful best practice advice and are also sometimes referred to as guidelines. Such documents do not always provide scientific rationale for their recommendations or positions and do not describe the processes used in the formation of these statements. For the purposes of this literature review, they have been described as "*best practice guidance*" (BPG).

[1] https://www.tg.org.au/the-organisation/production-process/

7.1.2. Findings from International Guidelines on Lyme disease

A 2015 study of the methodological quality of guidelines for the management of Lyme neuroborreliosis (Dersch 2015) reviewed eight international guidelines for the treatment of Lyme disease published between 1999 and 2012. The study assessed the guidelines using the AGREE II tool. They showed considerable variability in the methodological quality across the guidelines and reported that many of the guidelines had contradicting recommendations and were based on limited evidence.

To inform this literature review, AGREE II assessments were undertaken on the above guidelines. The AGREE II assessments highlight the wide variation in the methodologies used to develop guidelines. The results are included in Appendix B: AGREE II Score.

Key clinical areas covered in the guidelines and guidance documents associated with Lyme disease are included in Table 67.

Table 67: Key clinical areas covered in the guidelines

Guideline Title	Type of Guideline	Recommendations/ topics covered in Guideline			
Nice		Diagnosis	AB Treatment	Symptom Management & Other Treatment	Other areas
NICE Lyme disease 2018	EBG	*	*	Chronic pain, fatigue, depression, sleep disturbance	Care of pregnant women & babies
EFNS 2009	EBG	*	*	Post Lyme disease syndrome (PLDS) described	
Deutsche Borreliose-Gesellschaft 2010	EIG	*	*	Prevention of tick bites	
IDSA 2006	EIG	*	*	Prevention of tick bites, PLDS, HGA, Babesiosis	
ILADS 2004	EIG	*	*	Persistent Lyme disease	Hyperbaric oxygen therapy
Australia Guideline on the diagnosis of overseas acquired Lyme disease/ borreliosis	EIG	*	No – refers to IDSA for treatment advice		

Details of best practice diagnosis and treatment derived from these guidelines are described in earlier chapters of this literature review.

The NICE Lyme disease guidelines for antibiotic treatment and ongoing management and the systematic reviews that inform those recommendations are outlined in Section 6. NICE also recommends regular assessment and review to people with ongoing symptoms or no confirmed

diagnosis. They also highlight the importance of being alert to the possibility of symptoms related to Lyme disease that may need assessment and management, including:

- chronic pain;
- depression and anxiety (see NICE's guideline on common mental health problems);
- fatigue; and
- sleep disturbance.

NICE recommends providing support for people who have ongoing symptoms after treatment for Lyme disease by:

- encouraging and helping them to access additional services, including referring to adult social care for a care and support needs assessment, if they would benefit from these; and
- communicating with children and families' social care, schools and higher education, and employers about the person's need for a gradual return to activities, if relevant.

The NICE Lyme disease guideline developers also acknowledged that mother-to-baby transmission of Lyme disease is possible in theory. There was an absence of evidence, but the risk appears to be very low. The developers decided that women could be reassured that pregnancy and their baby are unlikely to be affected and highlighted the importance of completing treatment. It was also agreed that pregnant women should be treated following usual practice but using antibiotics suitable in pregnancy. No evidence was found for transmission of Lyme disease through sexual contact or blood products.

An example of how evidence-based guidelines and guidance documents can be developed from the NICE and the ILADS guideline recommendations, is the UK's Royal College of General Practitioners Lyme Disease Toolkit. The College collaborated with the UK's Clinical Innovation and Research Centre, to produce a user-friendly, evidence-informed resources that combine evidence-based recommendations with public health advice and local policies and processes.

7.2. Australian guidelines and guidance

There are currently no evidence-based guidelines that directly address the debilitating symptom complexes associated with tick bites in Australia.

Other guidance identified through the searches included a range of evidence-informed or good practice guidelines that provide a mix of referenced clinical advice and good practice points. For example, there is clinical guidance produced in Australia that is used by general practitioners and primary care providers – the eTG Toxicology (EIG) and Wilderness Guidelines and the Remote Primary Health Care Manuals (2017), as well as the Clinical Procedures Manual for Remote and Rural Practice (4th edition) (EIG) to assess their advice on Australian tick bites. Both documents focus on the prevention of tick bites and the removal of ticks. These guidelines do not provide specific advice on how to treat bites from Australian ticks, although the eTG guideline notes that mild to moderate tick paralysis usually requires no intervention except observation and serial neurological examination for 48 hours (note that tick bite prevention is outside the scope of this literature review).

The eTG antibiotics guidelines (EIG, 2019) refer to overseas acquired Lyme disease and references the Royal College of Pathologists of Australasia position statement on Lyme disease in Australia (DOHa, June 2018) and the IDSA guidelines for treatment.

7.2.1. Managing complex symptoms and chronic conditions

The Australian Government acknowledges that there is a group of Australian patients suffering from the symptoms of a debilitating illness which many associate with a tick bite (DOHb, June 2018). The Government sees it as imperative for government health authorities, clinicians and patients alike to work together to achieve a patient-centered multi-disciplinary approach to their care.

The Australian Commission on Safety and Quality in Health Care actively promotes and encourages patient and consumer centered care to ensure that health information and services meet people's needs. Patient-centered care is health care that is respectful of and responsive to, the preferences, needs and values of patients and consumers. The widely accepted dimensions of patient-centered care are respect, emotional support, physical comfort, information and communication, continuity and transition, care co-ordination, involvement of family and carers, and access to care.

People with DSCATT reported to the Senate Inquiry that they experience a number of debilitating symptoms. These symptoms include fatigue, disordered thinking/cognitive impairment, sensory disturbance, headaches, myalgias, pain (including joint and muscle pain), sleep disturbance, anxiety, depression, seizures, fainting, panic attacks, vertigo, rash, encephalitis or meningitis, neurological involvement, palpitations, sore throat, swollen glands, constipation and or diarrhea, enlarged liver or spleen, acrodermatitis chronic atrophicans etc.

Outside of the formal search and appraisal of literature for this review, the Department of Health supplied links to the following Australian guidelines and best practice guidance that, while not specifically designed to address issues attributed to Australian tick bites, could be of assistance in providing care or treatment to address a range of these DSCATT symptoms, including:

- fatigue;
- ME/ chronic fatigue syndrome;
- pain;

- rheumatoid arthritis;
- depression and anxiety;
- medically unexplained illness; and
- interventions that meet the needs of families', partners' and carers' needs.

Fatigue

Wilson et al., (Wilson et al., 2014) reference the eTG's fatigue guidelines (EIG) as the most useful reference for Australian GPs. The eTG fatigue guidelines (Moulds and van Driel, 2013) describe fatigue as an enduring feeling of tiredness, where the constant subjective sensation of weariness is usually not relieved by rest. Patients and their families, however, may use a variety of terms to describe fatigue including 'tiredness', 'weakness', 'sluggishness', 'sleepiness', 'feeling flat', 'lethargic' or 'knackered'. The guideline recommends a practical approach to the patient presenting with fatigue: a comprehensive history and examination, consideration of a period of watchful waiting in the absence of red flags and the judicious use of tests once the decision to investigate is made.

Red flags which raise the suspicion of serious underlying disease include:

- recent onset of fatigue in a previously well older patient;
- unintentional weight loss;
- abnormal bleeding;
- shortness of breath;
- unexplained lymphadenopathy;
- fever; and
- recent onset or progression of cardiovascular, gastroenterological, neurological or rheumatological symptoms.

The guidelines advise that after excluding significant organic disease and psychological illness, many patients remain troubled by some degree of persistent fatigue, often accompanied by other somatic symptoms. Some will consult multiple doctors and alternative health practitioners seeking explanations for their symptoms. A second opinion by an experienced physician to minimise nagging doubts of having missed something may support plans for practical management and reassure patients, families and carers. Referral may also help to address the thorny question of whether it is 'chronic fatigue syndrome' (CFS).

Myalgic encephalomyelitis and Chronic fatigue syndrome (ME/CFS)

ME/CFS is one of many labels for a poorly understood condition, which features persisting fatigue and a variety of somatic and cognitive symptoms. Chalada et al. (2016) identified ME/CFS as a differential diagnosis for Lyme disease.

Diagnosis requires the presence of unexplained persistent or relapsing fatigue for six months or more that is not attributable to exertion, not improved by rest and causes substantial functional impairment. Fatigue must be accompanied by at least four of eight additional symptoms, including:

- post-exertional malaise lasting more than 24 hours;

- unrefreshing sleep;
- impaired memory or concentration;
- muscle pain;
- joint pain without swelling or erythema;
- headache of a new type or severity, tender cervical or axillary lymph nodes, and sore throat (EIG, 2011).

The 2011 Australian therapeutic guidelines (EIG, 2017) also report that CFS appears to affect all age groups with a peak incidence in adults between their twenties and forties and is twice as common in women. The extensive search for causes of CFS over many decades has pursued possible triggers including viral infections, altered immune function, neuropsychological factors, environmental toxins and immunisation reactions. There remains no firm scientific evidence for any of these. The inherent heterogeneity of the CFS patient population with regard to severity, duration of symptoms and associated conditions makes prognostication difficult.

Patients with persistent unexplained fatigue value support from a solid, compassionate therapeutic relationship with their primary care physician. It is often difficult for patients and their carers and families to accept that persisting fatigue might be unexplained and that it sometimes resolves spontaneously.

Further work to understand and treat people with ME/CFS has recently been commissioned. In December 2018, a report to the NHMRC Chief Executive Officer from the Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Advisory Committee identified the following key issues and challenges (Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Advisory Committee, 2018):

- inconsistent use of diagnostic criteria has led to inadequately defined research cohorts and inconsistent findings in both pathophysiology and treatment;
- estimates of the Australian prevalence and burden of disease are dated and would benefit from updated prevalence estimation and morbidity assessment;
- ME/CFS diagnosis is hampered by the lack of knowledge of its pathophysiology and aetiology;
- defining and diagnosing ME/CFS is challenging given the heterogeneity of symptoms and the lack of diagnostic investigations;
- ME/CFS patients have described experiencing stigma, isolation and lack of effective or supportive care and this has been attributed to ME/CFS being a misunderstood and poorly recognised condition;
- controversial treatments such as graded exercise therapy have created a disparity in approaches and some disengagement between patients and clinicians; and
- understanding and acknowledging patient concerns are critical in moving forward with the diagnosis, treatment and management of what can be a highly debilitating condition.

NHMRC has recently received $3m to fund research into ME/CFS in Australia.

NICE is currently in the process of updating its chronic fatigue syndrome/myalic encephalomyelitis guideline (CFS/ME). The 2007 CFS/ME guideline outlines a patient centered care approach to the diagnosis, and this is expected to be incorporated into the updated guideline. Reports from a recent guideline scoping meeting indicate that the revision will address ways to

make an early diagnosis, how to manage co-existing conditions such as fibromyalgia, irritable bowel symptomology, migraine type headaches and osteoporosis. The guidelines will also address symptoms such as sleep disturbance, pain, orthostatic intolerance and exercise physiology.

Pain

Pain management is likely to be an important component in the care of people with DSCATT. The Australian Pain Management Association reports on its website (EIG) that chronic pain is complex because it involves the nerves and nervous systems, including the central nervous system made up of the brain and spinal cord.

Chronic pain occurs because of changes to the nerves or nervous system which keeps the nerves firing and signalling pain. However, there are likely to be other precipitating factors with chronic pain including genetics, gender and previous episodes of acute pain. Chronic pain can be intense and unrelenting, and lead to various degrees of disability if it is not managed well.

Chronic pain is a condition in its own right because changes in the nervous system can be unrelated to the original diagnosis or injury, if there was one.

NPS Medicinewise's advice recommends that pain management is enhanced by a broad, 'whole person' assessment. The psychosocial dimension includes assessment of mood, cognitions, trauma, suicide risk and the social context of the presenting problems (for example, workers' compensation, family issues). Additional components incorporate physical activity, sleep patterns, nutrition, and past or current use of addictive substances including prescription drugs. Explaining the neuroscience of pain has actually been shown to improve pain, movement and fear-avoidance, especially when provided with active strategies such as encouraging the patient to gradually resume normal activities in a paced manner and assistance with sleep disturbance.

Holliday et al., concluded that although most pain care is delivered outside specialist centres by GPs and other non-pain specialists, they are often not trained or confident in delivering this care (Holliday et al., 2018).

The Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine regularly publishes an Acute Pain Management: Scientific Evidence report (EBG). While this guideline addresses acute pain management strategies, it also has some useful insights in providing culturally responsive pain care for culturally and linguistically diverse patients in Australia. The 2015 4th Edition reports on a systematic review that looked at the effect of patient race and ethnicity on pain assessment and management (Cintron 200). Marked disparities in effective pain treatment were reported. The report authors state that to ensure culturally responsive care, it is imperative that health professionals continually improve their cultural competence by increasing their cross-cultural knowledge, skills and self-awareness. The Scientific Evidence Report highlights the following key messages:

- Disparities in assessment, analgesic requirements and effective treatment of pain exist across ethnic groups;
- Pain expression in Aboriginal and Torres Straits Islander peoples may not reflect that which is expected by health professional's cultural background. This places the onus on the health professional to understand nuances of pain expression and beliefs within such population;

- The verbal descriptor scale may be a better choice of pain measurement tool than verbal numerical ratings in Aboriginal and Torres Strait Islander peoples; and
- Medical co-morbidities such as renal impairment are more common in Aboriginal and Torres Strait Islander peoples and may influence the analgesic agent.

Rheumatoid arthritis

Rheumatoid arthritis guidelines, published by the Royal Australian College of General Practitioners (RACGP) and NHMRC in 2009, provide recommendations for adults (over 16 years of age) for general practitioners diagnosing rheumatoid arthritis (RA) and providing management options (RACGP, 2009). These guidelines recommend early diagnosis of RA and referral to a rheumatologist if the patient has persistent swelling beyond 6 weeks, even if RA is not confirmed. Early referral enables aggressive intervention with disease modifying drugs, reducing long term damage and disability.

The more recent 2017 eTG Rheumatology guidelines recommend urgent referral of any patient with suspected rheumatoid arthritis to a specialist.

Features suggesting rheumatoid arthritis include:

- family history of inflammatory arthritis;
- early morning stiffness lasting longer than 1 hour;
- swelling in five or more joints;
- symmetry of the areas affected;
- bilateral compression tenderness of the metatarsophalangeal joints;
- RF positivity;
- anti-CCP antibody test positivity;
- symptoms present for longer than 6 weeks;
- bony erosions evident on X-rays of the wrists, hands or feet (uncommon in early disease);
- raised inflammatory markers, such as CCP (cyclic citrullinated peptide) or erythrocyte sedimentation rate (ESR), in the absence of infection; and
- presence of rheumatoid nodules.

Depression and anxiety

Many DSCATT patients report symptoms of depression and anxiety. The Beyond Blue website (beyondblue.org.au) provides evidence-based resources for people with depression, including adolescents and young people and women and mothers.

Many people with chronic conditions also report feelings of depression and anxiety. For example, Clinical Pathway for the Screening, Assessment and Management of Depression in Adult Cancer Patients, Psycho-oncology Co-operative Research Group, Australia advise that unlike common symptoms (for example, fatigue), anxiety and depression are readily treatable, and a strong evidence base for intervention exists. Early identification and treatment of anxiety and depression leads to better outcomes (Psycho-oncology Co-operative Research Group, 2017).

Medically unexplained illness

An Australian Family Physician article by Louise Stone on managing medically unexplained illness in general practice, reports that patients with medically unexplained symptoms are often very unwell, experience severe disability and require complex care (Stone, 2015). This is consistent with the paper by Brown (2018) discussed in Section 4 of this review which commented on the high female prevalence and MUPS.

Management strategies include:

- establishing and maintaining a healthy therapeutic relationship;
- explicitly validating the patient's experience;
- establishing a common ground explanation; and
- maximising general health.

Stone also recommends co-ordinating care to avoid duplication of investigations, exacerbation of iatrogenic harm; offering symptom relief and practical support to address disability (for example, home help, workplace assessment); encouraging physical therapies (for example, massage, physiotherapy, hydrotherapy); and managing co-morbidities as effectively as possible.

Harm minimisation strategies for managing medically unexplained illness include balancing the risks and benefits of investigations and procedures and advocating for patients at risk of harm from untried investigations or therapies. The RACGP's position on responding to patient requests for tests not considered clinically appropriate is that "*the patient's wellbeing must be the primary consideration in determining whether to order particular tests. Testing can be painful and anxiety-provoking, and can lead to unnecessary, expensive, and potentially dangerous treatment*" (RACGP, 2019).

Stone advises that all patients need support to manage distressing symptoms and the disability that accompanies them. GPs are in a unique position to provide tenacious care for illness in the absence of disease, and for monitoring potential red flags that herald the emergence of a known diagnosis.

Interventions to meet families, partners' and carers needs

One of the important components of patient-centered care is ensuring that families and support people are actively engaged in understanding the patient or consumer's health condition, treatment and options. This is discussed briefly in the NICE Lyme disease guideline. Another Australian guideline that has undertaken systematic searches and appraisal of literature on interventions offered to families and carers was the Australian Clinical Practice Guideline for the Management of Borderline Personality Disorder (NHMRC, 2012). That guideline reported emerging evidence suggesting that structured family programs may be helpful in reducing grief and burden of care, and in improving family members' sense of control over their situation.

[still to add: Sutcliffe, HorowitzBaggio-Yoshinari guidelines]

APPENDIX A: QUALITY ASSESSMENT

APPENDIX B: AGREE II SCORE

AGREE II Domains	NICE	EFNS	DBG	ILADS	IDSA	LUM
Scope and Purpose	100%	72%	33%	83%	67%	67%
Stakeholder involvement	100%	11%	61%	61%	39%	50%
Rigor of development	100%	71%	33%	38%	42%	15%
Clarity of presentation	100%	83%	56%	22%	83%	44%
Applicability	100%	0%	42%	25%	17%	25%
Editorial independence	100%	83%	25%	33%	75%	25%
Overall quality						

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