Australian Government
Department of Health and Aged Care

Guidance Note for medical practitioners and hospitals

Overseas-acquired tick-borne diseases: Lyme disease

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List of abbreviations

Abbreviations	Description
AAN	American Academy of Neurology
AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
ACR	American College of Rheumatology
CDC	Centers for Disease Control and Prevention
DEET	N,N-Diethyl-meta-toluamide
DIY	Do it yourself
DSCATT	Debilitating Symptom Complexes Attributed to Ticks
ECDPC	European Centre for Disease Prevention and Control
EM	Erythema migrans
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
IDSA	Infectious Diseases Society of America
LLPI	Long-lasting permethrin-impregnated
MMA	Mammalian meat allergy
NATA	National Association of Testing Authorities, Australia
NICE	National Institute for Health and Care Excellence
OLE	Oil of lemon eucalyptus
PMD	Para-menthane-diol
PrEP	Pre-exposure prophylaxis
RCPA	Royal College of Pathologists of Australasia
RCT	Randomised-controlled trial
STARI	Southern tick-associated rash illness
UK	United Kingdom
US	United States

About this Guidance Note

Purpose and objective

This Guidance Note is part of a series of Guidance Notes on ticks, tick-borne diseases, tick-induced allergies, and Debilitating Symptom Complexes Attributed to Ticks (DSCATT).

In response to the 2016 Senate Community Affairs References Committee's Final Report *Inquiry into the growing evidence of an emerging tick-borne disease that causes a Lyme-like illness for many Australian patients,* the Australian Government commissioned the development of educational and awareness materials related to DSCATT, as well as a clinical pathway and multidisciplinary care model to support clinicians' decision-making on differential diagnosis and referral pathways for patients presenting with DSCATT. The purpose of the Guidance Notes is to provide evidence-based guidance for clinicians in community and hospital settings, as well as providing a reference source on DSCATT topics.

Topics covered in this Guidance Note

This Guidance Note covers overseas-acquired Lyme disease. It does not cover co-infections associated with Lyme disease or southern tick-associated rash illness (STARI) (pathogen unknown). Symptoms of STARI and early Lyme disease are similar, with STARI potentially being misdiagnosed as Lyme disease in areas with both lone star ticks and black-legged ticks.

This Guidance Note is based on information freely available to the public, from published peer-reviewed literature, and Australian and international guidance and guidelines, with a focus on literature published in the past 10 years. In this Guidance Note, where published peer-reviewed papers were not freely available to the public but are of high importance as they relate to the Australian situation, this literature was included. The percentages for various measures reported in this Guidance Note were included as they were reported by the authors of included literature; as such, there are a range of decimal places reported for percentages. Studies and publications cited by the authors of articles included in this Guidance Note are provided as in-text citations. This approach allows for articles published outside of the past 10 years and articles that are not freely available to the public to be acknowledged and provides easy access for readers who may wish to explore an article further.

In this Guidance Note and in the series of Guidance Notes on ticks, tick-borne diseases, tick-induced allergies and DSCATT, there is some repetition of content between the Guidance Notes and also within the Guidance Notes, where appropriate. This approach enables each Guidance Note to be read as a stand-alone document, rather than requiring the reader to read from start to finish. The repetition between sections within a Guidance Note allows the reader to read each section as a standalone section, rather than being referred to other sections within the Guidance Note. The Contents page of each Guidance Note is hyperlinked to sections within the Guidance Note to enable the reader to easily access information. Additionally, readers are also referred to other Guidance Notes in this series where additional information can be found.

Overview and summary

In Australia, Lyme disease should be considered in patients presenting with a travel history to Lyme disease endemic areas along with supporting symptoms and/or a known tick bite and appropriate *in vitro* diagnostic tests undertaken by pathology laboratories accredited by National Association of Testing Authorities, Australia (NATA) and the Royal College of Pathologists of Australasia (RCPA) (Australian Government Department of Health, 2018, 2020a).

Lyme disease is an infection that can be transmitted to humans who are bitten by certain species of *Ixodes* ticks carrying different species of *Borrelia* bacteria (spirochaetes) collectively known as *Borrelia burgdorferi* sensu lato. More than 19 spirochaete species comprise the *B. burgdorferi* s.l. complex, but only five are significantly pathogenic to humans. Four species are found only in North America, 11 species occur in and are restricted to Eurasia, and three species occur in North America and Europe.

The main species within this group that cause Lyme disease include:

- Borrelia burgdorferi sensu stricto (in North America, Europe)
- Borrelia afzelii (in Europe, China)
- Borrelia garinii (in Europe, Asia).

Lyme disease is the most prevalent tick-transmitted infection in temperate areas of Europe, North America and Asia, and its geographic distribution is increasing. Almost all confirmed cases of Lyme disease have occurred in the Northern Hemisphere.

The major vectors transmitting pathogenic *Borrelia* spp. all belong to the hard-bodied ticks of the genus *Ixodes. Ixodes* spp. ticks acquire Lyme disease spirochaetes through a blood meal; there is little or no transovarial transmission. Lyme disease spreading ticks are distributed throughout the Northern Hemisphere. In North America, the black-legged (deer) tick (*Ixodes scapularis*) and the western black-legged tick (*Ixodes pacificus*) are the vectors for the agents of Lyme disease. *I. scapularis* is widely distributed across the eastern United States (US) and vectors >95% of Lyme disease in North America. In Europe, the main vectors for Lyme disease are the castor bean tick (*Ixodes ricinus*) and taiga tick (*Ixodes persulcatus*). In China, the main vectors of Lyme disease are *I. persulcatus,* in Northern China, *Ixodes granulatus*, and *Ixodes sinensis* in Southern China, while *Haemphysalis bispinosa* ticks may act as the vector in Southern China.

While there are species of *Ixodes* ticks in Australia, the ticks that are the vectors for *B. burgdorferi* s.l. in the Northern Hemisphere are not present in Australia. Despite multiple studies which have searched for it in Australian ticks and patients, the organisms that cause Lyme disease have not, to date, been identified in Australian ticks, nor any other vector that could transmit the disease to humans. It is for this reason that the Australian medical profession does not support the diagnosis of locally acquired Lyme disease in Australia.

Transmission of Lyme disease occurs through the bite of infected ticks, both adults and nymphs, although most human infections of Lyme disease result from bites by nymphs. In endemic areas not all ticks will carry the Lyme disease bacterium, and not all bites from an infected tick will result in human Lyme disease. In Lyme disease endemic areas, the risk of *Borrelia* infection after the bite of an infected tick is low at only 1% and 3% in the United States, and 3% to 12% in Europe.

The duration of tick attachment is one of the most important predictors of subsequent Lyme disease, with infection more likely the longer a tick is attached to the skin. In most cases, in the

US, the tick must be attached for 36 to 48 hours or more before the Lyme disease bacterium can be transmitted. The risk of subsequent Lyme disease may exceed 20% when a tick has been attached for ≥72 hours. In Europe, studies suggest time to infection following a tick bite is shorter, with a number of reports having shown people in Europe became infected after a tick attachment of ≤24 hours.

There is no evidence that Lyme disease is transmitted from person-to-person, including via touching, kissing or through sexual contact. The risk of mother-to-baby transmission during pregnancy is very low and with appropriate treatment there is no increased risk of adverse pregnancy outcomes. There are no reports of Lyme disease being spread through breast milk. There is no evidence of transmission through blood products. There is no credible evidence that Lyme disease can be transmitted through air, food, water, or from the bites of mosquitoes, flies, fleas, or lice.

Lyme disease is a multisystemic disease that includes dermatological, neurological and cardiac manifestations. However, a *Borrelia burgdorferi* infection can be asymptomatic. A tick bite can be followed by an 'erythema migrans' (EM) rash, which is a circular target-like rash which is considered pathognomonic for Lyme disease[1] but can sometimes be mistaken for cellulitis or ringworm, delaying effective treatment. While the prevalence of EM is seen in about 70% of cases reported to the Centers for Disease Control and Prevention (CDC), ≥90% in cohorts of paediatric and adult US patients and in 70% to 95% in European epidemiological studies, central clearing of EM is seen only in 19% of US patients compared to almost 80% of European patients, thus illustrating the variation in clinical manifestation according to where the infection was acquired and, therefore the need to take a travel history.

If there is no EM rash or it is unnoticed, diagnosis can be difficult as the same symptoms may be caused by many other conditions as well as Lyme disease. Subjective complaints and symptoms that are usually more prominent early in the infection include fatigue, arthralgia, headache, stiff neck, and impaired concentration; symptoms that are common in many infectious and non-infectious diseases.

Lyme disease is customarily divided into three stages - early stage (stage 1), early dissemination (stage 2) and late disseminated stage (stage 3), with clinical manifestations varying in their occurrence and incidence depending on the infecting species and whether the infection was acquired in Eurasia or North America. Approximately 4% to 8% of patients develop cardiac findings, 11% develop neurologic findings and 40% to 60% of patients manifest arthritis, although surveillance data over the past 15 years documents a much lower annual incidence of 30% for Lyme arthritis in patients with untreated EM.

While some people believe that a form of 'chronic Lyme disease' exists in Australia, globally, 'chronic Lyme disease' is a disputed diagnosis which lacks sufficient supporting evidence.

The risk of infection with Lyme disease for travellers is generally low except for visitors to rural areas, particularly campers and hikers, in countries or areas at risk. In risk areas, 5% to 40% of ticks may be infected. Time spent in endemic areas, time spent outdoors, factors associated with tick density and the proportion of ticks carrying disease are risk factors. In risk areas,

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1 Note: an EM rash is considered to be pathognomic for Lyme disease in countries where this infection is endemic. In Australia, localised erythema around a tick attachment site is NOT an EM rash, as Lyme disease is not present in Australia. However, such a rash is sometimes seen and is associated with allergic reactions or rickettsial infection (Graves, S.R). It is not uncommon in Queensland tick typhus (Stewart et al., 2017a).

people involved in outdoor recreational or occupational activities are at an increased risk of being bitten by ticks.

People living in, or travelling to, areas endemic for Lyme disease and who also undertake activities that can increase their risk of coming into contact with ticks are at highest risk when nymphs are active. Nymphs can be active and feed from spring through autumn [fall] but their activity peaks in late spring and summer, which is when most cases of Lyme disease occur.

People who do not safely remove attached ticks without delay are at increased risk of Lyme disease.

The highest incidence rates for Lyme disease are seen in children aged five to nine years and in adults >50 years of age in both the US and Europe. Data suggests no significant differences in rates of Lyme disease between men and women.

In recent years, the worldwide burden of Lyme disease has increased and extended into regions and countries where the disease was not previously reported, with available data suggesting that Lyme disease cases will continue to increase. In addition to changes in geographic distribution of ticks and Lyme disease over recent years, changes have also been observed in the temporal distribution of ticks and Lyme disease. In Europe, ticks are spreading to higher altitudes and more northern latitudes and disease incidence is shifting towards spring and autumn.

The general factors driving the escalation of Lyme disease are similar in North America, Europe, and Asia irrespective of differences in habitat, hosts, and behaviour and include climate change, host and reservoir expansion, and enhanced monitoring, detection and reporting of *Ixodes* spp. and Lyme disease.

Lyme disease is not a notifiable disease in Australia. The Australian Government Department of Health advises that because there is no person-to-person transmission of Lyme disease, the risk to Australia and Australians is low. All confirmed cases of Lyme disease diagnosed in Australia to date have been in returned travellers.

Currently there is no licenced vaccine for Lyme disease; however, the CDC advises there are clinical trials of new vaccines for Lyme disease currently underway.2

In the absence of a vaccine, international guidance on preventing Lyme disease focuses on avoiding tick risk areas, being informed about and recognising early symptoms, wearing protective clothing, using tick repellents, checking the entire body daily for ticks, and correct removal of attached ticks before transmission of infection can occur. The Infectious Diseases Society of America (IDSA)/American Academy of Neurology (AAN)/American College of Rheumatology (ACR) advises healthcare professionals can play a very important role by increasing awareness and educating patients about ticks, tick-borne pathogens, and measures to reduce exposure, thereby increasing their confidence and likelihood to practice precautionary behaviours.

The Australian Government Department of Health advises people travelling overseas, including people travelling to Lyme disease endemic areas, to kill attached ticks in situ if an appropriate ether-containing product is available, and without delay, but otherwise follow local

2
https://www.cdc.gov/lyme/prev/vaccine.html#:~:text=A%20vaccine%20for%20Lyme%20disease,this%20vaccine%20decreases%20over%20time

guidance, for example, from the CDC.3 However, if Australian travellers are known to have a tick allergy, they should go to a hospital to have the tick removed. The Australian Government Department of Health advice to kill ticks *in situ* without delay is relevant, not only to managing tick bites in Australia, but to the ticks that can transmit Lyme disease in Lyme disease endemic areas, as some of these ticks are now recognised to be causative of tick anaphylaxis (*I. pacificus* and *I. ricinus*) and/or are responsible for the development of mammalian meat allergy (MMA) after tick bite (*I. ricinus*).

When traveling to a Lyme disease endemic area, using the Australian method to manage tick bites by killing ticks where they are and without delay will help prevent infection with Lyme disease as well as preventing tick-induced allergies.

A short video on how to remove a tick by killing the tick *in situ* with ether-containing sprays is available here:

> Important! Watch this video about how to safely remove a tick
> https://www.allergy.org.au/patients/insect-allergy-bites-and-stings

3 https://www.cdc.gov/ticks/removing_a_tick.html

Lyme disease

Lyme disease takes its name from the town of Lyme in Connecticut, US, where, in the mid-1970s, an unusual cluster of cases with an initial diagnosis of juvenile rheumatoid arthritis occurred (Steere et al. (1977) in Borchers et al., 2015). Originally called Lyme arthritis, when it became clear that arthritis was only one of the late manifestations of a multisystem disease that included dermatological, neurological and cardiac manifestations (Steere et al. (1983) in Borchers et al., 2015), the name was changed to Lyme disease (Borchers et al., 2015).

The peak of cases in summer and early autumn and its geographic clustering led to the hypothesis that an arthropod vector was transmitting an unknown agent (Steere et al. (1977) and Steere et al. (1978) in Stone et al., 2017).

In 1982, Burgdorfer and colleagues isolated a previously unidentified spirochaete from deer ticks (Ixodes dammini, now Ixodes scapularis,) (Burgdorfer et al. (1982) in Borchers et al., 2015; Burgdorfer et al. (1982), Benach et al. (1983) and Steere et al. (1983) in Stone et al., 2017). Burgdorfer and colleagues' data and other data demonstrated that this was the aetiological agent of Lyme disease (Burgdorfer et al. (1982), Steere et al. (1983) and Benach et al. (1983) in Borchers et al., 2015). The aetiological agent of Lyme disease was named Borrelia burgdorferi, in honour of its original discoverers (Johnson et al. (1984) in Borchers et al., 2015).

Lyme disease is the most prevalent tick-transmitted infection in temperate areas of Europe, North America and Asia, and its geographic distribution is increasing (European Centre for Disease Prevention and Control, 2015a).

Infectious agents

International situation

Lyme disease is a bacterial infection that can be transmitted to humans who are bitten by certain species of *Ixodes* ticks carrying different species of *Borrelia* bacteria (spirochaetes) collectively known as *Borrelia burgdorferi* sensu lato (Australian Government Department of Health, 2018; European Centre for Disease Prevention and Control, 2015a; Lantos et al., 2020; Mackenzie, 2013; National Institute for Health and Care Excellence, 2018c; Royal College of Pathologists of Australasia, 2019).

The B. burgdorferi complex comprises of at least 19 genospecies worldwide; only five are significantly pathogenic to humans (European Centre for Disease Prevention and Control, 2015a). Four species are found only in North America, 11 species occur in and are restricted to Eurasia and three species occur in North America and Europe (Mackenzie, 2013).

The main species within this group include:

- Borrelia burgdorferi sensu stricto (North America, Europe)
- Borrelia afzelii (in Europe, China)
- Borrelia garinii (in Europe, Asia) (Mackenzie, 2013; Royal College of Pathologists of Australasia, 2019).

Of the three main genospecies *B. garinii* and *B. afzelii* are antigenically distinct from *B. burgdorferi* s.s. which may account for the variation in clinical presentation in different geographic regions (Mackenzie, 2013).

Less-common species known to cause Lyme borreliosis include *B. bavariensis* (Europe), *B. bissetiae* (US, Europe), *B. lusitaniae* (Europe), *B. mayonii* (mid-west US), *B. spielmanii* (Europe), *B. valaisiana* (Europe, Asia) (Royal College of Pathologists of Australasia, 2019). *B. valaisiana* and *B. lusitaniae* rarely cause disease in humans (European Centre for Disease Prevention and Control, 2015a).

B. burgdorferi s.l. differ in pathogenicity, geographic location, Ixodidae vector, and preferred reservoir hosts(s) (Stone et al., 2017).

Inoculum size

Borchers et al., in their review of diagnostic criteria and treatment of Lyme disease, noted the minimal infective dose in humans is unknown; however, as only low numbers of spirochaetes (20-60/gland) can be detected in salivary glands of feeding ticks (Piesman et al. (1987), Ohnishi et al. (2001) and Piesman et al. (2001) in Borchers et al., 2015), Borchers et al. noted this suggests that a small inoculum is sufficient to cause infection and disease (Borchers et al., 2015).

In a study involving mice (mostly C3H), Borchers et al. reported that the "ID50 (infectious dose at which 50% of animals became infected, for subcutaneous needle inoculation of salivary gland extracts obtained from partially fed nymphal ticks was 18 spirochaetes" (Lima et al. (2005) in Borchers et al., 2015, p. 86). Other studies have shown that the ID50 values in syringe inoculation experiments are somewhat higher and greatly depend on the *B. burgdorferi* strain being investigated (Dunham-Ems et al. (2009), Hanson et al. (1998), and Lazarus et al. (2006) in Borchers et al., 2015).

Australia

Studies and reviews on Australian endemic and exotic ticks have not shown the presence of the tick vectors responsible for causing Lyme disease in the Northern Hemisphere, in Australia (Dehhaghi et al., 2019). See *Introduction to ticks, Australian ticks and tick-borne diseases and illnesses* Guidance Note for more information.

Despite multiple studies which have searched for it in Australian ticks and patients, the organisms that cause Lyme disease have not, to date, been identified in Australian ticks (Australian Government Department of Health, 2018; Beaman, 2016; Chalada et al., 2016; Collignon et al., 2016; Dehhaghi et al., 2019; Gofton, Doggett, et al., 2015; Gofton, Oskam, et al., 2015; Graves & Stenos, 2017; Harvey et al., 2019; Irwin et al., 2017; Loh et al., 2016, 2017; Mackenzie, 2013), nor any other vector that could transmit the disease to humans (Australian Government Department of Health, 2018; Graves & Stenos, 2017). It is for this reason that the Australian medical profession does not support the diagnosis of locally acquired Lyme disease in Australia (Australian Government Department of Health, 2018).

Vector

International situation

Borrelia spp. are maintained in a complex enzootic4 cycle involving one or more vertebrate host reservoir species and one or more tick species. The major vectors transmitting pathogenic *Borrelia* spp. all belong to the hard-bodied ticks of the genus *Ixodes* (Borchers et al., 2015). Lyme disease spreading ticks are distributed throughout the Northern Hemisphere (Stanek et al. (2012) in Stone et al., 2017). These ticks are:

- I. scapularis transmits B. burgdorferi in the east, mid-Atlantic and upper Midwest of the US
- I. pacificus transmits B. burgdorferi and B. bissettii in the western parts of the US
- I. ricinus is the major European vector for B. burgdorferi, B. afzelii, and B. garinii along with other potentially pathogenic and non-pathogenic Borrelia spp.
- I. persulcatus, is the main vector of B. afzelii and B. garinii in eastern regions of Europe and in Asia. The geographical distribution of I. persulcatus partially over laps with I. ricinus (Borchers et al., 2015).

There are other tick species that may be infected with and able to transmit *B. burgdorferi* s.l. including *Ixodes minor, Ixodes dentatus, Ixodes spinipalpis,* and *Haemaphysalis longicornis,* among others (Rudenko et al. (2011b) in Stone et al., 2017). While these tick species rarely bite humans, and therefore pose little risk of transmitting the Lyme disease pathogen, they do play an important role in maintaining *B. burgdorferi* in nature (James & Oliver (1980), Hornok et al. (2012) and Roome et al. (2017) in Stone et al., 2017).

Biology and ecology of Ixodes ticks

Ixodes spp. ticks pass through three life stages [post-egg]: larva, nymph, and adult, generally in a two-year cycle (Stone et al., 2017), but on average the life cycle takes three years to complete (Public Health England, 2018a). Each stage needs an animal host on which to feed before it can moult to the next stage, or in the case of the adult females, lay eggs (Public Health England, 2018a). When ticks search for a host on which to feed, they climb to the tips of vegetation and use special sensory organs on their front legs to detect stimulants such as carbon dioxide, changes in light and body heat [and odours] given off by hosts (Public Health England, 2018a). Some tick species can recognise a shadow (Centers for Disease Control and Prevention, 2020c). Ticks can't fly or jump, but many species wait in a position called 'questing' (Centers for Disease Control and Prevention, 2020c). As a host brushes past the vegetation, the tick climbs on. Once a suitable feeding site has been found on the host, the tick will take one continuous blood meal (lasting for a varying number of days, depending on the life stage of the tick). The tick will then detach and drop off into the vegetation to digest and moult to the next stage. After mating, adult female ticks will lay several thousand eggs at ground level before dying (Public Health England, 2018a).

Infection occurs through the bite of infected ticks, both adults and nymphs, although most human infections of Lyme disease result from bites by nymphs (Centers for Disease Control and Prevention, 2020a; Lantos et al., 2020; World Health Organization, n.d.). Many species of mammals can be infected, with deer acting as an important reservoir (World Health Organization, n.d.).

4 Enzootic = (of a disease) regularly affecting animals in a particular district or at a particular season.

Ixodes spp. ticks acquire Lyme disease spirochaetes through a blood meal; there is no transovarial transmission (Piesman et al. (1986), Patrician (1997) and Roll-end et al. (2013) in Stone et al., 2017).

Although both nymphs and adults can act as a vector for *B. burgdorferi*, nymphs are the main Lyme disease vectors due to their smaller size, and cryptic colouration that affords them lower detection probability, greater abundance, and their seasonality which coincides with higher levels of human outdoor activity (Mead (2015) in Lantos et al., 2020).

Adults are less important as vectors of Lyme disease for two main reasons:

- Adult male Ixodes spp. ticks do not attach or feed long enough to infect people (Falco et al. (1999) in Lantos et al., 2020)
- Adult females, which are reddish and larger than nymphs, are more quickly detected and removed before they transmit the infection (Lantos et al., 2020).

Therefore, the nymphal questing period poses the greatest risk. Nymphs can be active from spring through autumn, but their activity peaks in late spring and summer, which is when most cases of Lyme disease occur (Lantos et al., 2020).

Ticks are very sensitive to temperature and relative humidity, requiring areas with dense ground vegetation for survival, reproduction or establishment (Stone et al., 2017).

The geographic distribution of *Ixodes* spp. ticks is governed by the distribution of hosts and limited by temperature and humidity, with ticks preferring environments with warm, humid summers and mild winters (Ostfeld & Brunner (2015) in Stone et al., 2017). While deciduous and mixed forests provide leaf litter that maintain high relative humidity and are regarded as the classic microhabitat for ticks, several temperate biomes, including coniferous forests, grasslands and pastures contains microclimates that sustain *Ixodes* spp. ticks (Estrada-Pena (2001), Walker et al. (2001), Richter & Matuschka (2006), and Millins et al. (2016) in Stone et al., 2017). Additionally, some urban, peri-urban, and recreational environments and gardens support or are capable of supporting *Ixodes* spp. ticks (Public Health England, 2018a; Rizzoli et al. (2014), Mackenstedt et al. (2015) and Hansford et al. (2017) in Stone et al., 2017). Within these habitats, ticks are often highly abundant in ecotonal habitats, that is, transition zones between different habitats that are often used by wildlife (Public Health England, 2018a).

Stone et al. notes that an increase in temperature at northern latitudes would also expand suitable *Ixodes* spp. habitats, and that a longer spring and summer would lengthen the exposure window, as *Ixodes* spp. are most actively questing during warm, humid periods (Ogden et al. (2004) in Stone et al., 2017), making it likely that *Ixodes* spp. will extend northward within North America, Europe and Asia (Stone et al., 2017).

United States and North America

Figure 1: Adult female black-legged (deer) tick (Ixodes

	
Public domain: Photo courtesy of the Agricultural Research Service, the research agency of the United States Department of Agriculture. *Photo by Scott Bauer* *Image Number: K8002-3, {{PD-USGov-USDA-ARS}}* *https://commons.wikimedia.org/wiki/File:Adult_deer_tick.jpg*	*Public domain: CDC / Sue Partridge (2017)*

In North America, while there are several human-biting tick species, the black-legged (deer) tick (*I. scapularis*) (see Figure 1), and the western black-legged tick (*I. pacificus*) are the vectors for the agents of Lyme disease, *B. burgdorferi* s.s., and less commonly, *B. mayonii* (Centers for Disease Control and Prevention, 2020e; Lantos et al., 2020). *I scapularis* vectors >95% of Lyme disease in North America (Mead (2015) in Lantos et al., 2020). Most cases occur within its geographical range, with this tick being widely distributed across the eastern US (Centers for Disease Control and Prevention, 2020b; Lantos et al., 2020).

I. pacificus, the western black-legged tick, transmits *B. burgdorferi* and is found in the Pacific Coast states in the US (Centers for Disease Control and Prevention, 2020d). It is the vector of Lyme disease in California, and the west coast of the US and Canada (Stone et al., 2017), and it is the main vector west of the Rocky Mountains (Ogden et al., 2009).

Both I. scapularis and I. pacificus ticks have the three post-egg host-seeking life stages: the larvae, nymph, and adult. For Lyme disease risk assessment, not all life stages can transmit infection to people. Larvae hatch free of *B. burgdorferi* infection and are therefore not considered vectors of that pathogen (Rollend et al. (2013) in Lantos et al., 2020). However if larvae acquire *B. burgdoferi* while feeding on infected reservoir hosts, such as the white-footed mouse in the eastern U S, they can transmit the spirochaete as nymphs and adults (Lantos et al., 2020).

Figure 2: Starved, female castor bean tick (*Ixodes ricinus*)

Public domain: Walter (2021)

https://commons.wikimedia.org/wiki/File:Ixodes_ricinus_on_dry_grass.jpg

Figure 3: Taiga tick (Ixodes persulcatus) (Public domain)

Public domain: CC BY-SA 3.0: Lamiot

https://upload.wikimedia.org/wikipedia/commons/4/4c/Ixodes_persulcatusFL.jpg

In Europe the main vectors of Lyme disease are I. ricinus (the castor bean tick) (see Figures 2 and 4) and I. persulcatus (the taiga tick) (see Figure 3). In Russia, Borrelia spp. are transmitted almost exclusively by adult I. persulcatus ticks (Korenberg et al. (1996) in Borchers et al., 2015). In the United Kingdom (UK), I. ricinus, commonly known as the sheep, castor bean or deer tick, is the principal vector of Lyme disease and can be found feeding on humans (Public Health England, 2018a).

Figure 4: Castor bean tick (Ixodes ricinus) – Male Female (Public domain)

Public domain: Photo courtesy of CDC

Sensitive to climatic conditions, *I. ricinus* requires a relative humidity of 80% to survive during its off-host periods. As such it is restricted to areas of moderate to high rainfall with vegetation that retains high humidity (Medlock et al., 2013). Typical habitats vary across Europe, with optimal habitats being deciduous and coniferous woodland, but *I. ricinus* ticks can also be found in heathland, moorland, rough pasture, forests and in suburban and urban parks and gardens (European Centre for Disease Prevention and Control, 2015a; Medlock et al., 2013).

Asia

In China, the main vectors of Lyme disease are *I. persulcatus* in Northern China, *I. granulatus* and *I. sinensis* in Southern China, while *Haemphysalis bispinosa* ticks may act as the vector in Southern China (Niu et al. (2009) and Sun et al. (2003) in Wu et al., 2013).

Australia

While there are species of *Ixodes* ticks in Australia, the ticks that are the vectors for *B. burgdorferi* s.l. are not present in Australia, and as above, studies to date have not identified the organisms that cause Lyme disease in Australian ticks.

Reservoir

International

While *Ixodes* spp. are generalists when seeking a blood meal, they often like to feed on particular species at particular life stages; for example, adult ticks in both Europe and the northeastern US prefer deer as their feeding source (Ostfeld et al. (2006), Gilbert et al. (2012), Levi et al. (2012), and Pacilly et al. (2014) in Stone et al., 2017). In Eurasian areas endemic for Lyme disease, *B. burgdorferi* genospecies circulate between hard ticks of the *I. ricinus* complex and vertebrate hosts (European Centre for Disease Prevention and Control, 2015a), with research indicating there does not appear to be a single, predominant reservoir as a diverse population of rodents, small and medium mammals and birds serve as adequate reservoirs (Ger et al. (1998) in Stone et al., 2017).

United States and North America

I. scapularis has largely spread throughout most of the eastern US and into southern Canada during the 20th century, following the reforestation and reintroduction and proliferation of white-tailed deer (Randolph (2014) in Sonenshine, 2018). There is broad consensus that the white-tailed deer has been the main driver for the substantial increase in *I. scapularis* ticks in the northern parts of the eastern US over the past 40 years (Stafford (2007), Eisen & Dolan (2016), Spielman (1994) and Telford (2017) in Eisen, 2020). The white-tailed deer are also extending their range throughout Canada, due to changes in climate and land use (Dawe & Boutin (2016) in Stone et al., 2017). Ambient temperature constrains the establishment of *I. scapularis* in Canada to the warmer regions of southeastern Manitoba, southern Ontario and Quebec and some regions of the Maratimes (Ogden et al., 2009), however, climate change is projected to permit and accelerate the expansion of *I. scapularis* into Canada (Ogden et al. (2005), and Ogden et al. (2006) in Ogden et al., 2009).

The black-legged tick, I. scapularis, can be found in a variety of landscapes (urban, suburban, and rural) in a variety of habitats, however they are most abundant in or near wooded areas (Falco & Fish (1998) in Lantos et al., 2020), where wildlife hosts are ample and a sufficient layer of leaf litter reduces the risk of dessication and promotes their survival (Schulze (2002) in Lantos et al., 2020). While off-host I. scapularis have been shown in laboratory experiments to be highly susceptible to low temperature and dessication, established populations have been found in regions that experience frigid and dry winters, suggesting that microclimates are invaluable for I. scapularis survival (Stone et al., 2017).

The habitat in California, in particular, is different to that observed in the northeastern US, with mainly coastal oak forests and semi-desert scrub (Salkeld et al. (2014), and Salkeld et al. (2015) in Stone et al., 2017), with the mild climate allowing infected ticks to be active year-round (Salkeld et al. (2014) in Stone et al., 2017). Larvae and nymphs of the western black-legged tick, *I. pacificus,* often feed on lizards, birds, and rodents, and adults more commonly feed on deer (Centers for Disease Control and Prevention, 2020d). Stone et al. noted that while *I. pacificus* primarily feeds on lizards in California, (the western fence lizard and the southern alligator lizard), in addition to rodents, birds and mammals, (Castro & Wright (2007) in Stone et al., 2017), both lizards are refractory hosts for *B. burgdorferi* s.l. (Lane & Llye (1989), Lane & Quistad (1998), and Lane et al. (2013) in Stone et al., 2017). The presence of such refractory hosts decreases the prevalence of infected ticks and therefore the prevalence of Lyme disease (Stone et al., 2017).

Europe

I. ricinus is opportunistic and will feed on humans given the chance (Parola & Raoult (2001) in Medlock et al., 2013), making these ticks very efficient vectors of tick-borne human diseases (Medlock et al., 2013). All stages of *I. ricinus* quest for hosts using an ‘ambush’ technique (questing) in which they climb up vegetation and wait for a host to brush past (Medlock et al., 2013). This tick possesses light-sensitive cells on the dorsum and also sensory organs (Haller’s organs) at the tip of its appendages which enable it to detect changes in the environment including light levels, temperature, carbon dioxide, humidity and vibrations, which indicates the best time to quest and the presence of a host (Medlock et al., 2013).

I. ricinus feed on a wide range of warm- and cold-blooded vertebrate hosts including small rodents, lizards, passerines, and mammals such as hedgehogs, hares, squirrels, wild boar, deer and livestock (Medlock et al., 2013). Common hosts of *I. ricinus* vary in different geographical regions and habitats and infestation rates vary according to the seasonal pattern of questing activity and host availability (Medlock et al., 2013).

The immature stages of *I. ricinus* are found on hosts of all sizes, from birds, including ground feeding birds, and small mammals to ungulates (European Centre for Disease Prevention and Control, 2015a; Medlock et al., 2013). Adult stages feed more exclusively on larger hosts such as cattle and deer (Medlock et al., 2013), but also feed on sheep and other large ungulates, which are not reservoir-competent for *Borrelia*, but help to maintain the tick's reproductive stage (European Centre for Disease Prevention and Control, 2015a). Larger hosts are essential to maintain *I. ricinus* tick populations and where there is an absence of these animals, tick populations tend to be lower (Hoodless et al. (1998), Gray et al. (1992), and Medlock et al. (2008) in Medlock et al., 2013) as the local composition of fauna, and their abundance heavily affects the numbers of ticks being fed (Medlock et al., 2013).

In Europe there does not appear to be a single, predominant reservoir, as a diverse population of rodents, small and medium mammals, and birds all serve as adequate reservoirs (Gern et al. (1998) in Stone et al., 2017).

Asia

In Asia there does not appear to be a single, predominant reservoir as a diverse population of rodents, small and medium mammals, and birds all serve as adequate reservoirs (Gern et al. (1998) in Stone et al., 2017).

Mode of transmission

Transmission via ticks

The Lyme disease bacterium *B. burgdorferi* is spread through the bite of infected ticks, both adults and nymphs, of the genus *Ixodes* (Centers for Disease Control and Prevention, 2020a; World Health Organization, n.d., 2014).

In nature, the bacteria that cause Lyme disease are carried in the blood of wild animals, primarily small mammals and birds (Public Health England, 2018a). Ticks take one blood meal during each of the three stages of their life cycle, i.e. as larvae, nymphs, and adults. There is little to no transovarial transmission of Borrelia spp. infection. Therefore ticks become infected when larvae or nymphs feed on an infected host; infection is then maintained transstadially and can be passed on to the host providing the next blood meal, including humans (Borchers et al., 2015). More simply, ticks feeding on an infected animal will take in the bacteria, which remain in the tick for the rest of its life. When an infected tick bites and feeds on a human, the bacteria can be passed on via the tick's saliva (Public Health England, 2018a). In risk areas, as much as 5% to 40% of ticks may be infected (World Health Organization, 2014). However, not all ticks will carry the bacterium which causes Lyme disease and not all bites from an infected tick will result in human Lyme disease (Public Health England, 2018a).

See Guidance Notes on *Introduction to ticks, Australian ticks and tick-borne diseases and illnesses* for more information on the transmission of diseases via the tick feeding process.

Mechanism of transmission

Ixodes ticks live on the ground and climb 20-70 cm onto grasses and bushes where they wait for hosts (World Health Organization, 2014).

Ticks can attach to any part of the human body but are often found in hard-to-see areas such as the groin, armpits, and scalp (Centers for Disease Control and Prevention, 2020a). As ticks seek the more humid parts of the body, in addition to the groin and armpits, ticks may be found in the waistband area, under the breasts and behind the knees (World Health Organization, 2014). In young children, tick bites are more common on the head (including the scalp) and the neck (World Health Organization, 2014).

Most humans are infected through the bites of immature nymph ticks (Centers for Disease Control and Prevention, 2020a; Lantos et al., 2020; World Health Organization, n.d.).

Nymphs are tiny (less than 2 mm) and difficult to see; they feed during the spring and summer months in the Northern Hemisphere (Centers for Disease Control and Prevention, 2020a).

Adult ticks can also transmit Lyme disease bacteria, but they are much larger and are more likely to be discovered and removed before they have had time to transmit the bacteria (Centers for Disease Control and Prevention, 2020a).

The CDC advises the tick feeding process makes ticks very good at transmitting infection (Centers for Disease Control and Prevention, 2020a). CDC has provided the following advice:

- Depending on the tick species and its stage of life, preparing to feed can take from 10 minutes to two hours. When the tick finds a feeding spot, it grasps the skin and cuts into the surface. The tick then inserts its feeding tube. Many species also secrete a cement-like substance that keeps them firmly attached during the meal. The feeding tube can have barbs, which help keep the tick in place.
- Ticks can also secrete small amounts of saliva with anaesthetic properties, so that the animal or person (host) cannot feel that the tick has attached itself. If the tick is in a sheltered spot, it can go unnoticed.
- A tick5 will attach to its host and suck the blood slowly for several days. If the host animal has certain bloodborne infections, such as the bacteria that cause Lyme disease, the tick may ingest the pathogen and become infected. If the tick later feeds on a human, that human can become infected.
- After feeding, the tick drops off and prepares for the next life stage. At its next feeding, it can then transmit the infection to the new host. Once infected, a tick can transmit infection throughout its life.
- If a tick is removed within 24 hours, this can greatly reduce the chances of the host getting Lyme disease. It takes some time for the Lyme disease-causing bacteria to move from the tick to the host. The longer the tick is attached, the greater the risk of acquiring disease from it (Centers for Disease Control and Prevention, 2020a).

Duration of tick attachment and risk of infection

Not all ticks will carry the Lyme disease bacterium and not all bites from an infected tick will result in human Lyme disease (Public Health England, 2018a). In Lyme disease endemic areas, the risk of *Borrelia* infection after the bite of an infected tick is low at only 1% and 3% in the US (Sood et al. (1997), Shapiro et al. (1992) and Costello et al. (1989) in Borchers et al., 2015), and 3% to 12% in Europe (Maiwald & Oehme (1998), Huegli et al. (2011), Fryland et al. (2011), Nahimana et al. (2004) and Korenberg et al. (1996) in Borchers et al., 2015).

Infection rates are higher in adult ticks than in nymph ticks (Fingerle et al. (2008), Falco et al. (1999), and Rauter & Hartung (2005) in Borchers et al., 2015), but nymphs are more abundant, much smaller and more difficult to detect and therefore, are more likely to stay attached for longer (Huegli et al. (2011) in Borchers et al., 2015). Hence the importance of thoroughly checking the body for ticks after being outside as described in the section ‘Check the body for ticks after being outdoors’.

The duration of tick attachment is one of the most important predictors of subsequent Lyme disease, with infection more likely the longer a tick is attached to the skin (Borchers et al., 2015; Mackenzie, 2013; National Institute for Health and Care Excellence, 2018c; Lantos et

5 While the CDC reference was specifically for black-legged ticks in this reference, the information is consistent for ticks in general.

al., 2020). Unfed (that is, flat) and recently attached ticks do not pose a significant risk for *B. burgdorferi* infection (Lantos et al., 2020).

Spirochaetes reside in the midgut of unfed ticks. When the blood meal reaches the midgut, the spirochaetes begin to replicate and then disseminate via the hemocoel [feeding cavity] to the salivary glands (Dunham-Ems et al. (2009) in Borchers et al., 2015).

In most cases, the tick must be attached for 36 to 48 hours or more before the Lyme disease bacterium can be transmitted (Centers for Disease Control and Prevention, 2020a). Experimental data have demonstrated that *B. burgdorferi*–infected *I. scapularis* nymphs transfer considerable numbers of spirochaetes as early as 24 hours after attachment (Hodzic et al. (2002) in Borchers et al., 2015); however, in animal experiments, infection rarely occurs within 24 hours of tick attachment with peak infection rates not reached until 48 to 72 hours of attachment (Piesman et al. (1987), Piesman et al. (1991), Piesman (1993), des Vignes et al. (2001), Ohnishi et al. 2001), and Hojgaard et al (2008) in Borchers et al., 2015).

As studies indicated, the time required for infection to occur appears to depend on the target host species (Piesman et al. (1987), and Piesman et al (1991) in Borchers et al., 2015) as well as the infecting strain of *B. burgdorferi* (des Vignes et al. (2001) in Borchers et al., 2015). In accordance with these findings, the risk of infection for residents of endemic areas of the US was found to be minimal if ticks stayed attached for <72 hours, but that risk increased significantly with longer attachment duration (Sood et al. (1997), and Nadelman et al. (2001) in Borchers et al., 2015).

The risk of subsequent Lyme disease may exceed 20% when a tick has been attached for ≥72 hours (Sood et al. (1997) in Lantos et al., 2020).

Research indicates the risk of infection following a tick bite in Europe is different than in the US. A number of reports have shown people in Europe became infected after tick attachment of ≤24 hours (Huegli et al. (2011), Fryland et al. (2011), and Strle et al. (1996) in Borchers et al., 2015), particularly in Russia (Korenberg et al. (1996) in Borchers et al., 2015). IDSA/AAN/ACR also noted two European epidemiological studies, different to those cited by Borchers et al., had suggested that transmission of *B. burgdorferi* s.l. may occur within 24 hours of attachment of *I. ricinus* ticks (Hofhuis et al. (2013), and Wilhelmsson et al. (2016) in Lantos et al., 2020). Lantos et al. commented it was unclear whether differences in the tick or *Borrelia* species may be responsible for the faster transmission rate and that the travel history may therefore inform anticipatory guidance (Lantos et al., 2020).

Person-to-person transmission

International advice from the US and Europe is consistent - Lyme disease is not transmitted from person-to-person. The US CDC advises there is no evidence that Lyme disease is transmitted from person-to-person, and a person cannot get infected from touching, kissing, or through sexual contact with a person who has Lyme disease (Centers for Disease Control and Prevention, 2020a). Similarly the UK Government advises there is no reliable documented evidence of transmission by person-to-person contact (Health and Safety Executive, n.d.; Public Health England, 2018e).

Within Australia, the Australian Government Department of Health advises that as there is no person-to-person transmission of classical Lyme disease, the risk to Australia and Australians is low (Australian Government Department of Health, 2020b).

Transmission in pregnancy

International authority guidance from the US CDC and the National Institute for Health and Care Excellence (NICE) in the UK indicates the risk of mother-to-baby transmission is very low and that, with appropriate treatment, there is no increased risk of adverse pregnancy outcomes.

The CDC advised that:

- untreated Lyme disease during pregnancy can lead to infection of the placenta
- spread from mother-to-fetus is possible but rare
- with appropriate antibiotic treatment, there is no increased risk of adverse birth outcomes
- there are no published studies assessing developmental outcomes of children whose mothers acquired Lyme disease during pregnancy (Centers for Disease Control and Prevention, 2020a).

An evidence-based review (National Institute for Health and Care Excellence, 2018b) of person-to-person transmission of Lyme disease, to inform the 2018 NICE Lyme disease guideline, 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. NICE acknowledged that mother-to-baby transmission of Lyme disease is possible in theory. However, while there was an absence of evidence, the risk appears to be very low (National Institute for Health and Care Excellence, 2018b). While the NICE committee considered that vertical transmission is not impossible, no strong causal link between a maternal Lyme disease infection and adverse pregnancy outcomes could be found. The committee also found no evidence that a maternal infection resulted in a transmission of *Borrelia* spirochaete to the child.

Transmission through breast milk

The US CDC advises there are no reports of Lyme disease being spread to infants through breast milk (Centers for Disease Control and Prevention, 2020).

Transmission through sexual contact

International authority guidance from the US CDC and NICE in the UK confirms there is no credible evidence that Lyme disease is spread through sexual contact (Centers for Disease Control and Prevention, 2021a; National Institute for Health and Care Excellence, 2018c). The CDC noted published studies in animals do not support sexual transmission (Moody (1991) and Woodrum (1999) in Centers for Disease Control and Prevention, 2021a), and that the biology of the Lyme disease spirochaete is not compatible with this route of exposure (Porcella (2001) Centers for Disease Control and Prevention, 2021a).

The CDC did note, however, that the ticks that transmit Lyme disease are very small and easily overlooked. Consequently, it is possible for sexual partners living in the same household to both become infected through tick bites, even if one or both partners doesn’t remember being bitten (Centers for Disease Control and Prevention, 2021a).

Transmission through blood products

International authority guidance from the US CDC and NICE in the UK indicates that there is no evidence for transmission of Lyme disease through blood products (Centers for Disease Control and Prevention, 2020a; National Institute for Health and Care Excellence, 2018c). However, the CDC advises that although no cases of Lyme disease have been linked to blood transfusion, scientists have found that the Lyme disease bacteria can live in blood from a person with an active infection that is stored for donation. Therefore, the CDC advises that individuals being treated for Lyme disease with an antibiotic should not donate blood; however individuals who have completed antibiotic treatment for Lyme disease may be considered potential blood donors (Centers for Disease Control and Prevention, 2020a).

Transmission through other ways

The US CDC advises the following regarding whether there are other ways for people to get Lyme disease in the US:

- There is no credible evidence that Lyme disease can be transmitted through air, food, water, or from the bites of mosquitoes, flies, fleas, or lice.
- While dogs and cats can get Lyme disease, there is no evidence that they spread the disease directly to their owners. However, as pets can bring infected ticks into the home or backyard, people should consider protecting their pet, and possibly themselves, through the use of tick control products.
- People will not get Lyme disease from eating venison or squirrel meat, but in keeping with general food safety principles, meat should always be cooked thoroughly. Hunting and dressing deer or squirrels may bring people into close contact with infected ticks.
- Ticks not known to transmit Lyme disease include lone star ticks (Amblyomma americanum), the American dog tick (Dermacentor variabilis), the Rocky Mountain wood tick (Dermacentor andersoni), and the brown dog tick (Rhipicephalus sanguineus) (Centers for Disease Control and Prevention, 2020a).

Advice from Europe is that there are no known cases of transmission of Lyme disease by vectors other than ticks (Public Health England, 2018e).

Incubation period

The incubation period for Lyme disease is reported to range from three to 30 days in the US (Centers for Disease Control and Prevention, 2020d), UK (Health and Safety Executive, n.d.), and Europe (European Centre for Disease Prevention and Control, 2015a), with Asia reporting three to 32 days (Centre for Health Protection, Hong Kong Department of Health, n.d.).

Mackenzie noted that the incubation period between tick bite and appearance of an EM is typically seven to 14 days but may be as short as one day and as long as 30 days (Marques (2010) in Mackenzie, 2013).

Infectious period

There is no infectious period for Lyme disease. There is no evidence that Lyme disease is transmitted from person-to-person (Australian Government Department of Health, 2020b; Centers for Disease Control and Prevention, 2020a; Public Health England, 2018e).

Clinical presentation and outcome

Lyme disease is a multisystemic disease that includes dermatological, neurological and cardiac manifestations. *B. burgdorferi* infection can be asymptomatic (European Centre for Disease Prevention and Control, 2015a). Many people may not notice or remember a tick bite. A recent infection with *B. burgdorferi* s.l. can sometimes go unremarked, with mild symptoms that are ignored by the person. When symptoms occur, this is called Lyme disease.

A tick bite can be followed by EM rash, a circular target-like rash which is considered pathognomonic for Lyme disease6 (see Figures 5 and 6) but can sometimes be mistaken for cellulitis or ringworm, delaying effective treatment. EM is an erythematous rash that gradually expands from the site of the tick bite and is not significantly raised or painful (European Centre for Disease Prevention and Control, 2015a). EM can vary in form depending on where the infection was acquired. It can either be a single red area that gradually expands from the site of the tick bite or it can be a central spot surrounded by clear skin that is then surrounded by an expanding red rash ("bulls-eye") which is centred on the tick bite (Royal College of Pathologists of Australasia, 2019).

Figure 5: Some examples of Lyme disease rashes (Public domain)

"Classic" Lyme disease rash

Erythema migrans rash

Figure 6: An example of erythema migrans rash (Public domain)

Public domain: Photo courtesy of CDC

6 Note: An EM rash is considered to be pathognomic for Lyme disease in countries where this infection is endemic. In Australia, localised erythema around a tick attachment site is NOT an EM rash as Lyme disease is not present in Australia. However, such a rash is sometimes seen and is associated with allergic reactions or rickettsial infection (Graves, 2017). It is not uncommon in Queensland tick typhus (Stewart et al., 2017a).

While EM is seen in about 70% of the cases reported to the CDC, ≥90% in cohorts of paediatric and adult US patients and in 70% to 95% in European epidemiological studies, central clearing of EM is seen only in 19% of US patients compared to almost 80% of European patients (Borchers et al., 2015), thus illustrating the variation in clinical manifestation according to where the infection was acquired and, therefore the need to take a travel history.

In addition to the different prevalence and clinical manifestation of EM from different species of *B. burgdorferi* s.l., there can be other differences in clinical manifestation by species, again emphasising the need for a travel history. Of the three main genospecies, *B. garinii* and *B. afzelii* are antigenically distinct from *B. burgdorferi* s.s. which may account for the variation in clinical presentation in different geographic regions (Mackenzie, 2013). *B. afzelii* and *B. garinii* are the major pathogenic genospecies found in Europe, and are associated with skin and neurological complications respectively (European Centre for Disease Prevention and Control, 2015a).

B. burgdorferi s.s. (the only pathogenic genospecies found in North America) is present in some parts of Europe and can cause neurological and arthritic complications (European Centre for Disease Prevention and Control, 2015a). *B. burgdorferi* s.s. may cause Lyme arthritis, especially in large joints such as the knee (Royal College of General Practitioners, 2020).

Two other pathogenic genospecies have been identified in Europe: *B. bavariensis* is associated with neurological complications, and *B. spielmanii* (European Centre for Disease Prevention and Control, 2015a). Additionally, *B. valaisiana* and *B. lusitaniae* can cause disease in humans, but rarely (European Centre for Disease Prevention and Control, 2015a).

If there is no EM rash or it is unnoticed, diagnosis can be difficult, as the same symptoms may be caused by many other conditions as well as Lyme disease (National Institute for Health and Care Excellence, 2018c). Subjective complaints and symptoms that are usually more prominent early in the infection include fatigue, arthralgia, headache, stiff neck, and impaired concentration; symptoms that are common in many infectious and non-infectious diseases (Auwaerter et al., 2011).

The three stages of Lyme disease

Lyme disease is customarily divided into three stages, with clinical manifestations varying in their occurrence and incidence depending on the infecting species and whether the infection was acquired in Eurasia or North America (Borchers et al., 2015; Royal College of Pathologists of Australasia, 2019). Approximately 4% to 8% of patients develop cardiac findings, 11% develop neurologic findings and 40% to 60% of patients manifest arthritis (Borchers et al., 2015), although surveillance data over the past 15 years documents a much lower annual incidence of 30% for Lyme arthritis in patients with untreated EM (Lantos et al., 2019).

The three customary stages of Lyme disease are: early stage (stage 1), early dissemination (stage 2), and late dissemination (stage 3) (see Table 1).

Table 1: Stages of Lyme disease in patients who have travelled to Lyme disease endemic countries (Royal College of Pathologists of Australasia, 2019)

Early Stage (Stage I)

Constitutional (flu-like) signs and symptoms including headache, myalgia, arthralgia and fever may be present (Royal College of Pathologists of Australasia, 2019)

EM (usually around seven to 14 days post-infected tick bite) either as a single expanding area, or a central spot surrounded by clear skin that is in turn encircled by an expanding red rash (''bulls-eye'') which is centred on the tick bite, is the characteristic sign of early infection in ~80% of patients (Royal College of Pathologists of Australasia, 2019)

A rash, which is not EM, can develop as a reaction to a tick bite (National Institute for Health and Care Excellence, 2018c). This rash:

- usually develops and recedes during 48 hours from the time of the tick bite
- is more likely than EM to be hot, itchy or painful
- may be caused by an inflammatory reaction, or infection with a common skin pathogen.

Other common causes of rashes that can be mistaken for EM include:

- reaction to an insect bite
- cellulitis
- tinea corporis (ringworm)
- granuloma annulare
- erythema multiforme (if multiple lesions)
- nummular eczema (Public Health England, 2018c).

Early Dissemination (Stage 2)

- Early haematogenous dissemination to other sites
- Multiple EM lesions (~20%)
- Nervous system involvement (~15%) – headache, lymphocytic meningitis, mild neck stiffness, facial palsy
- Cardiac involvement (~5%) – acute onset of high-grade atrioventricular conduction defects, myopericarditis
- Joint involvement – a large joint oligoarthritis with brief attacks [not further defined] (Royal College of Pathologists of Australasia, 2019).

Late Dissemination (Stage 3)

This stage can potentially occur after months to several years following the initial infection though the pathologic mechanism is unclear. It is hypothesised that any ongoing symptoms are more immune related, which may or may not be a consequence of the initial infection. Ongoing infection is regarded a debatable diagnosis by the medical profession globally.

- ~60% present with rheumatologic involvement, intermittent attacks of joint swelling and pain in large joints, infiltration of mononuclear cells
- ~5% present with neuroborreliosis, peripheral neuropathy, spinal radicular pain, distal paresthesia, encephalopathy leading to subtle cognitive disturbances, intrathecal antibody production and, rarely, cerebrospinal fluid pleocytosis
- Acrodermatitis chronica atrophicans - a rare skin condition not seen in North American Lyme disease (Royal College of Pathologists of Australasia, 2019).

‘Chronic Lyme disease’

While some people believe that a form of ‘chronic Lyme disease’ exists in Australia, globally, ‘chronic Lyme disease’ is a disputed diagnosis which lacks sufficient supporting evidence (Australian Government Department of Health, 2018; Auwaerter et al., 2011; Lantos et al., 2010, 2020; Lantos & Wormser, 2014; Marzec et al., 2017; National Institute for Health and Care Excellence, 2018c; Wormser et al., 2006).

Within Australia, Collignon et al. noted Australian medical practitioners are faced with a difficult dilemma as growing numbers of patients, their supporters, some integrative medical practitioners, and politicians are demanding diagnoses and treatment according to the protocols of the “chronic Lyme disease” school of thought (Collignon et al., 2016).

NICE does not support the term ‘chronic Lyme disease’. In its evidence review for the management of ongoing symptoms related to Lyme disease (National Institute for Health and Care Excellence, 2018a), NICE advised the term ‘ongoing symptoms’ was preferred for the NICE Lyme disease guideline (National Institute for Health and Care Excellence, 2018c), as it does not attribute cause of symptoms, whereas terms such a ‘chronic Lyme disease’ imply possible chronic infection and may be misleading. Health Canada advised there is no definitive evidence that persistent symptoms represent ongoing infection (Public Health Agency of Canada, 2022a).

The clinical practice guidelines for the prevention, diagnosis and treatment of Lyme disease by the IDSA/AAN/ACR, published in 2020, noted the term ‘chronic Lyme disease’ lacks an accepted definition for either clinical use or scientific study (Lantos et al., 2020). However, in practice the term has been applied to a highly heterogeneous patient population, including patients who lack objective features of Lyme disease, many of whom prove to have other diagnosable and potentially treatable conditions, while many have “medically unexplained symptoms” (MUS) (Lantos et al., 2020).

The CDC (Marzec et al., 2017) advised in a Morbidity and Mortality Weekly Report that ‘chronic Lyme disease’ is a non-specific diagnosis without a consistent definition and is a term used by some health care providers as a diagnosis for constitutional, musculoskeletal, or neuropsychiatric symptoms (Feder et al. (2007) and Patrick et al. (2015) in Marzec et al., 2017). Marzec et al. noted many of these patients have experienced significant debilitation from their symptoms and have not found relief after consultation with conventional medical practitioners and, as a result, some seek treatment from practitioners who might identify themselves as Lyme disease specialists (‘Lyme literate’ doctors), or from complementary and alternative medicine clinics, where they receive a diagnosis of ‘chronic Lyme disease ‘(Lantos et al. (2015) in Marzec et al., 2017). Citing Feder et al. 2007 and Lantos 2015, the authors went on to explain that a diagnosis of ‘chronic Lyme disease’ might be based solely on clinical judgment and without laboratory evidence of *B. burgdorferi* infection, objective signs of infection, or a history of possible tick exposure in an area with endemic Lyme disease. They also noted a belief among persons who support the diagnosis and treatment of ‘chronic Lyme disease’ (Stanek et al. (2012) in Marzec et al., 2017) that *B. burgdorferi* can cause disabling symptoms even when standard testing is negative, despite evidence that the recommended two-tiered serologic testing is actually more sensitive the longer *B. burgdorferi* infection has been present, and, additionally, that some practitioners use tests or testing criteria that have not been validated for the diagnosis of Lyme disease (Feder et al. (2007) in Marzec et al., 2017). Marzec et al. highlighted that it is of significant concern to the CDC that after the diagnosis of ‘chronic Lyme disease’ is made, the actual cause of a patient’s symptoms might remain undiagnosed and untreated (Lantos et al. (2015), and Nelson et al. (2015) in Marzec et al., 2017).

Marzec (2017) advised treatment offered for the diagnosis of ‘chronic Lyme disease’, such as prolonged antibiotic or immunoglobulin therapy, lacks data supporting effectiveness. Serious complications can result from prolonged antibiotic therapy or immunoglobulin therapy, and so they are not recommended (Marzec et al., 2017). Marzec (2017) noted the various treatments prescribed to patients given a diagnosis of ‘chronic Lyme disease’, and for which there is often no evidence of effectiveness, include extended courses of antibiotics (lasting months to years), IV infusions of hydrogen peroxide, immunoglobulin therapy, hyperbaric oxygen therapy, electromagnetic frequency treatments, garlic supplements, colloidal silver, and stem cell transplants (Feder et al. (2007), and Lantos et al. (2015) in Marzec et al., 2017). Additionally, the CDC, in Marzec’s report, noted at least five randomised, placebo-controlled studies have shown that prolonged courses of IV antibiotics in particular do not substantially improve long-term outcomes for patients with a diagnosis of ‘chronic Lyme disease’ and can result in serious harm, including death (Feder et al. (2007), Wormser et al. (2006), Berende et al. (2016), and CDC in Marzec et al., 2017).

Five cases were described to illustrate complications resulting from unproven treatments, including septic shock, *Clostridium difficile* colitis, osteodiscitis, abscess and death (Marzec et al., 2017).

The CDC cautioned that in addition to the dangers associated with inappropriate antibiotic use, such as selection of antibiotic resistant bacteria, these treatments can lead to injuries related to unnecessary procedures, bacteraemia and resulting metastatic infection, venous thromboses, and missed opportunities to diagnose and treat the actual underlying cause of the patient’s symptoms. CDC advice was that patients and their healthcare providers need to be aware of the risks associated with treatments for ‘chronic Lyme disease’ (Marzec et al., 2017).

In their systematic review of chronic coinfections in patients diagnosed with ‘chronic Lyme disease’, Lantos and Wormser (2014) found the medical literature does not support the diagnosis of chronic, atypical tick-borne coinfections in patients with chronic non-specific illnesses. The authors noted the controversial and ill-defined diagnosis of ‘chronic Lyme disease’ is often given to patients with alternative diagnoses or prolonged, medically unexplained physical symptoms, with many of these patients also treated for chronic coinfections with *Babesia, Anaplasma,* or *Bartonella* in the absence of typical presentations, objective clinical findings, or laboratory confirmation of active infection. In addition, they noted active infection is characterised by objective clinical findings (for example, fever or laboratory abnormalities), but commented that practitioners who frequently offer the diagnosis of ‘chronic Lyme disease’ often do not rely on more accepted standards of clinical and laboratory testing, and in such circumstances, many patients also receive spurious diagnoses of chronic anaplasmosis, babesiosis and bartonellosis (Lantos & Wormser, 2014).

Auwaerter et al. (2011) in their article ‘Antiscience and ethical concerns associated with advocacy of Lyme disease’, published in Lancet Infectious Diseases, commented a belief system has emerged for some activists over the last 20 years, although unsupported by scientific evidence, that Lyme disease can cause disabling subjective symptoms even in the absence of objective signs of the disease, that diagnostic tests are often falsely negative, and that treatment with antibiotics for months or years is necessary to suppress the symptoms of the disease, which often recur despite prolonged antibiotic therapy. As a consequence, some individuals with MUS (Hickie et al. (2006) in Auwaerter et al., 2011) and others with more well defined conditions were diagnosed with, or self-attributed their symptoms to, Lyme disease, in the absence of supportive laboratory data. Auwaerter et al. (2011, p. 717) reported ‘concepts’ about Lyme disease that are either unsubstantiated or have been proven to be inaccurate, that the authors obtained from popular Lyme disease websites and from public statements and presentations by some ‘Lyme literate’ medical doctors and ‘chronic Lyme disease’ activists. Auwaerter et al. point out that one ‘concept’ is that Lyme disease causes autism, Morgellons disease, multiple sclerosis, Parkinson’s disease, amyotrophic lateral sclerosis, homicidal behaviour (‘Lyme rage’), immune dysfunction, birth defects, and Alzheimer’s disease. As such, Auwaerter et al. note many patients, believing they were chronically infected and who sought treatment from ‘Lyme literate’ medical doctors, and who receive long-term treatment, have no convincing evidence of having ever had *B. burgdorferi* infection, by history, (sometimes including never having been exposed to ticks, never having been in an endemic area, and never having had objective clinical findings suggestive of Lyme disease), physical examination, or laboratory test results (Feder et al. (2007) and Hassett et al. (2008) in Auwaerter et al., 2011).

Persons at increased risk of disease

International

World Health Organization advice is that the risk of infection with Lyme disease for travellers is generally low, except for visitors to rural areas -particularly campers and hikers, in countries or areas at risk (World Health Organization, n.d.). The European Centre for Disease Control and Prevention advises risk groups to be ‘All persons exposed to risk of tick bites are at risk of becoming infected’ [with Lyme disease] (European Centre for Disease Prevention and Control, 2015a).

Risk factors and risk activities

The risk of contracting a tick-borne infection such as Lyme disease is determined by the overall number of ticks in the area, the proportion of those carrying disease, and human behaviour (World Health Organization, 2014). Additional risk factors include time spent in endemic areas, time spent outdoors, and, as noted by the World Health Organization, factors associated with tick density (Berglund & Eitrem (1993), Finch et al. (2014) and Beytout et al. (2007) in Borchers et al., 2015). In risk areas, 5% to 40% of ticks may be infected (World Health Organization, 2014). Therefore, the most effective way to minimise *Borrelia* infection is to avoid tick habitats, such as wooded areas, shrubs, tall grass and particularly the edges where these types of vegetation meet (Borchers et al., 2015).

In risk areas, people involved in outdoor recreational or occupational activities are at an increased risk of being bitten by ticks. Examples of increased risk activities include:

- hunting
- fishing
- camping
- collecting mushrooms and berries
- farming
- military training (World Health Organization, 2014).

A study that investigated both environmental and behavioural risk factors identified a previous diagnosis of Lyme disease, along with age, as an independent predictor of *B. burgdorferi* infection (Finch et al. (2014) in Borchers et al. (2015). Borchers et al. noted that this probably reflects that the same population subgroups stay at risk of repeated infections due to the same behavioural or environmental factors that increased their original risk (Borchers et al., 2015).

Additionally, several cohort studies have confirmed that a previous history of Lyme disease constitutes a risk factor for reinfection (Bennet & Berglund (2002), Salazar et al. (1993), and Nowakowski et al. (2003) in Borchers et al., 2015). Borchers noted this means that previous infection does not protect from future infection. Mice develop immunity but it is strain-specific (Barthold (1999) in Borchers et al., 2015). Recent empirical data suggests that humans develop strain-specific immunity that lasts for ≥6 years (Khatchikian et al. (2014) in Borchers et al., 2015).

A 2019 systematic review and meta-analysis on spatial risk factors for *I. scapularis* tick bites and *I. scapularis* tick-associated diseases in eastern North America that investigated where risk is highest concluded interventions applied at the neighbourhood scale are most likely to protect human health (Fischhoff et al., 2019). From the 19 eligible studies representing 2,741 cases of tick-borne illness and 1,447 tick bites, the meta-analysis revealed significant disease risk factors in backyards (OR 2.6; 95%CI: 1.96–3.46), in the neighbourhood (OR 4.08: 95% CI: 2.14–6.68) and outside the neighbourhood (OR 2.03: 95% CI: 1.59–2.59) with analysis of variance revealing risk at the neighbourhood level was 57% greater than risk in the yard, and 101% greater than outside the neighbourhood (Fischhoff et al., 2019).

Risk areas overseas for Lyme disease

Lyme disease is found in high rates in endemic areas, mainly the northeast of the US, some areas of Europe including the UK and some parts of Asia (Aucott et al., 2017; Borchers et al., 2015; European Centre for Disease Prevention and Control, 2015a; World Health Organization, 2014). By inference, people who live in, or travel to, areas endemic for Lyme disease and who also engage in activities that increase the risk of coming into contact with ticks (described above) would be at increased risk of becoming infected with Lyme disease.

In the US, 14 states in the northeastern, mid-Atlantic, and north-central US, where infected questing nymphs are abundant, consistently account for >95% of all cases of Lyme disease reported to the CDC (Schwartz et al. (2017) in Lantos et al., 2020). The CDC reported that in 2015, 95% of Lyme disease cases were reported from the following 14 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin (Centers for Disease Control and Prevention, 2020e).

In Canada, *I. scapularis* ticks and human cases of Lyme disease have been identified in Long Point on the Ontario shore of Lake Erie, and in southern Ontario, Nova Scotia, south-eastern Manitoba and New Brunswick (Ogden et al. 2009). Additionally, active surveillance driven by risk maps has identified the possibility of additional emerging populations in southern Quebec (Ogden et al., 2009). Surveillance by the British Columbia Centre for Disease Control has suggested established populations of *I. pacificus* ticks and areas where *B. burgdorferi* is endemic are widely distributed in southern British Columbia (Ogden et al. 2009). More recently, official advice is that black-legged ticks are spreading to new areas in Canada in part due to climate change (Public Health Agency of Canada, 2022b). These ticks can sometimes be found in areas outside of where they are known to live. They can also spread by travelling on birds and deer. For Canada, Lyme disease risk areas maps available at https://www.canada.ca/en/public-health/services/diseases/lyme-disease/surveillance-lyme-disease.html.

In Canada, the risk of Lyme disease in endemic areas where *I. pacificus* is the vector is generally lower than where *I. scapularis* is the vector (Ogden et al., 2009).

In Europe, the regions with highest tick infection rates (nymphs >10%; adult ticks >20%) are located in central Europe and include Austria, Czech Republic, southern Germany, Switzerland, Slovakia and Slovenia (European Centre for Disease Prevention and Control, 2015a).

In the UK and Ireland, particularly high risk areas are the South of England and the Scottish Highlands (National Institute for Health and Care Excellence, 2018c).

Seasonal risk

People living in, or travelling to, areas endemic for Lyme disease, and who also engage in activities that increase their risk of coming into contact with ticks, are at greater risk of contracting Lyme disease during the Northern Hemisphere spring and summer.

In the US, the greatest risk of being bitten by *I. scapularis*, the black-legged (deer) tick, which is widely distributed across the eastern US, exists in the spring, summer, and fall [autumn] in the northeast, upper Midwest and mid-Atlantic. However, adult ticks may be out searching for a host any time when winter temperatures are above freezing. All life stages bite humans, but nymphs and adult females are most commonly found on people (Centers for Disease Control and Prevention, 2020d).

The nymphal questing period poses the greatest risk. In the US, nymphs can be active and feed from spring through fall but their activity peaks in late spring and summer, which is when most cases of Lyme disease occur (Centers for Disease Control and Prevention, 2020a; Schwartz et al. (2017), and Mead (2015) in Lantos et al., 2020). Adult *Ixodes* ticks are most active during the cooler months of the year (Centers for Disease Control and Prevention, 2020a). They are primarily active in fall and spring but also in winter, when temperatures exceed 4°C (Duffy & Campbell (1994) in Lantos et al., 2020).

In Canada, black-legged ticks are most likely to be encountered during the spring, summer and fall. However, ticks can be active at any time of the year when the temperature is consistently above freezing (Public Health Agency of Canada, 2022b).

In England, nymphal tick activity increases during spring, peaking during April to June (Public Health England, 2018a). During this period, the risk of acquiring a tick bite is highest. Activity reduces during the summer months, but can then pick up again in early autumn. Activity continues over the winter months but at a reduced level. Adult ticks can be active at all times of year, but in the UK, they are more active in summer, which is also the peak time for larval activity (Public Health England, 2018a).

Ticks remaining attached for >72 hours in the US or 24 hours in Europe

The risk of infection for residents of endemic areas of the US was found to be minimal if ticks stayed attached for <72 hours, but that risk increased significantly with longer duration of attachment (Sood et al. (1997), and Nadelman et al. (2001) in Borchers et al., 2015). The risk of subsequent Lyme disease may exceed 20% when a tick has been attached for ≥72 hours (Sood et al. (1997) in Lantos et al., 2020).

The risk of Infection following a tick bite in Europe appears to be different than in the US. A number of reports have shown people in Europe became infected after a tick attachment of ≤24 hours (Huegli et al. (2011), Fryland et al. (2011), and Strle et al. (1996) in Borchers et al., 2015), particularly in Russia (Korenberg et al. (1996) in Borchers et al., 2015). IDSA/AAN/ACR also noted two European epidemiological studies, different to those cited by Borchers et al., had suggested that transmission of *B. burgdorferi* s.l. may occur within 24 hours of attachment of *I. ricinus* ticks (Hofhuis et al. (2013), and Wilhelmsson et al. (2016) in Lantos et al., 2020).

Gender

In the US, CDC data suggest that males constitute slightly more than half of reported cases (51% overall and 61% of paediatric cases) (Lyme disease-United States, 2003-2005, (2007) in

Borchers et al., 2015). In Europe, data often suggest a slight female preponderance (Hubálek, (2009), Zeman & Benes (2013) and Bennet et al. (2006) in Borchers et al., 2015), but in some areas an even distribution has been reported ((Berglund et al. (2006), Altpeter et al. (2013) and Lesnyak et al. (1998) in Borchers et al., 2015).

In the UK, females and males are equally susceptible to Lyme disease (Public Health England, 2018a).

Age

The age distribution among cases with Lyme disease is generally bimodal: the highest incidence rates are seen in children aged five to nine years and in adults >50 years of age in both the US and Europe (Hubálek, (2009), Bacon et al. (2008), Lyme disease-United States, 2003-2005, (2007), Zeman & Benes (2013), Berglund et al. (1995) and Huppertz et al. (1999) in Borchers et al., 2015).

IDSA/AAN/ACR noted that adult ticks are primarily active in fall and spring but also in winter, when temperatures exceed 4°C (Duffy & Campbell (1994) in Lantos et al., 2020). IDSA/AAN/ACR also noted that while risk of Lyme disease is much lower at this time of year, studies, including one on *I. ricinus,* indicated risk appears to be more significant for children and older adults who may not as readily detect and remove ticks in time to prevent transmission (Falco et al. (1996), and Wilhelmsson et al. (2013) in Lantos et al., 2020).

In contrast, Public Health England reports that while people of all ages can be affected, the highest rates of Lyme disease occur in people aged between 24 and 64 years (Public Health England, 2018a).

Australia

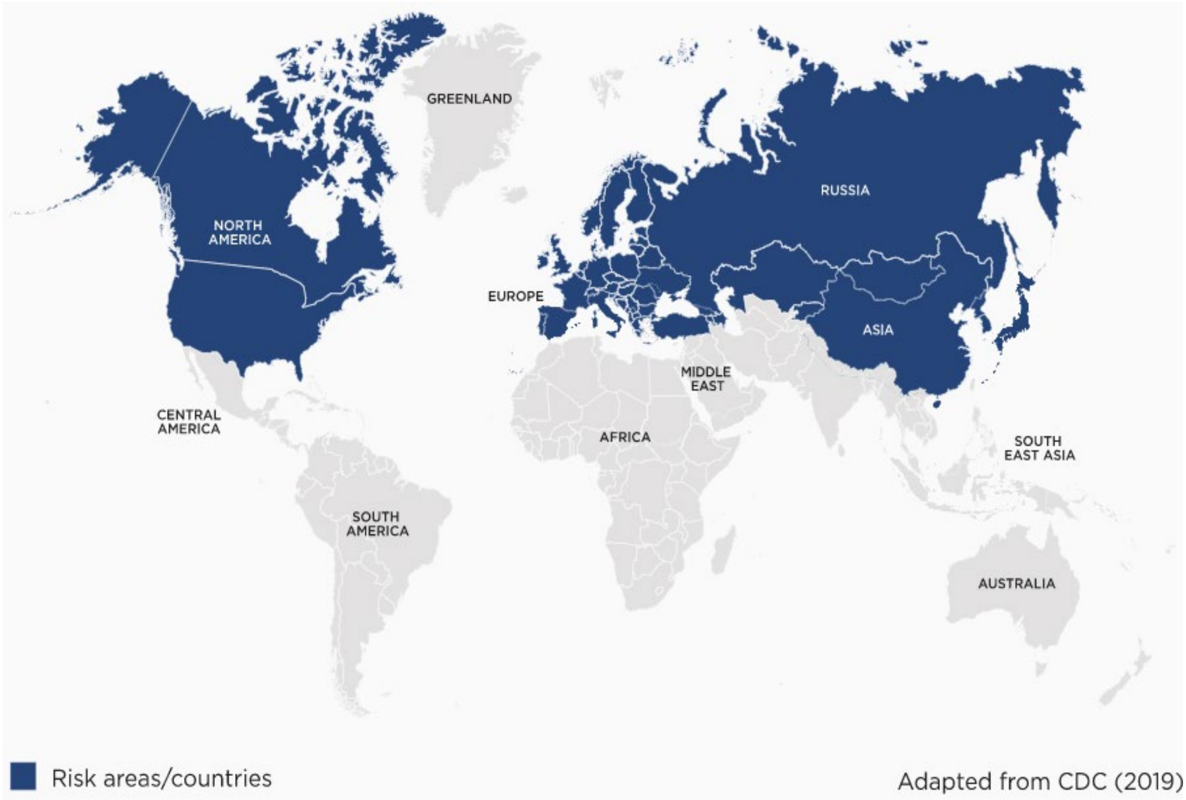
In Australia, Lyme disease should be considered in patients presenting with a travel history to Lyme disease endemic areas along with supporting symptoms and/or a known tick bite and positive serology results from a NATA/RCPA-accredited diagnostic laboratory (Australian Government Department of Health, 2018, 2020b).

Disease occurrence and public health significance

International occurrence of Lyme disease

Lyme disease is the most prevalent tick-transmitted infection in temperate areas of Europe, North America and Asia, and its geographic distribution is increasing (European Centre for Disease Prevention and Control, 2015a). It has been reported in more than 70 countries on five continents (Wu et al., 2013). Almost all confirmed cases of Lyme disease have occurred in the Northern Hemisphere (Hubálek (2009) in Borchers et al., 2015). Lyme disease is found in high rates in endemic areas, mainly the northeast of the US, some areas of Europe including the UK and some parts of Asia (Aucott et al., 2017; Borchers et al., 2015; European Centre for Disease Prevention and Control, 2015a; World Health Organization, n.d.) (see Figure 7 overleaf). The majority of cases come from the US and Europe (including the European part of Russia), with far fewer cases from Asia, and some from North Africa (Hubálek (2009) in Borchers et al., 2015).

Figure 7: Distribution of Lyme disease globally (Public domain)



Public domain: Photo courtesy of CDC

The most recent data from the World Health Organization, in its 'Global vector control response 2017-2030', reported the estimated or reported annual number of cases globally of Lyme disease as 532,125 (Kuehn (2013), and Sykes & Makiello (2016) in World Health Organization, 2017). Available data on the estimated annual disability adjusted life years was 10.5 (7.6 to 16.9) per 100,000 population in the Netherlands (van den Wijingaard et al. (2015) in World Health Organization, 2017).

In recent years, the worldwide burden of Lyme disease has increased and extended into regions and countries where the disease was not previously reported, with available data suggesting that Lyme disease cases will continue to increase (Stone et al., 2017). In addition to changes in geographic distribution of ticks and Lyme disease over recent years, changes have also been observed in the temporal distribution of ticks and Lyme disease (World Health Organization, 2014). In Europe, ticks are spreading to higher altitudes and more northern latitudes, and disease incidence is shifting towards spring and autumn (World Health Organization, 2014).

The general factors driving the escalation of Lyme disease are similar in North America, Europe, and Asia irrespective of differences in habitat, hosts, and behaviour (Manelli et al. (2012), Kulkarni et al. (2015), and Medlock & Leach (2015) in Stone et al., 2017). These factors include:

- climate change (Ostfeld & Brunner (2015) in Stone et al., 2017)
- host and reservoir expansion (Diuk-Wasser et al. (2012), Roy-Dufresne et al. (2013), and Roome et al. (2017) in Stone et al., 2017)

- enhanced monitoring, detection and reporting of Ixodes spp. and Lyme disease (Aenishaenslin et al. (2016) in Stone et al., 2017).

The World Health Organization notes that, in addition to climate change, factors such as changes in land cover and land use, changes in the distribution of tick hosts, and human-induced changes in the environment are involved in driving changes in the geographic and temporal distribution of the ticks and Lyme disease (World Health Organization, 2014).

However, in addition to increased awareness of the disease, climate change, changes in land use, and changes in residential distribution and human recreational behaviour attributing to the rise in incidence of Lyme disease in the US and Europe, Borchers et al. also notes there is potential error of a false positive diagnosis (Zeman & Benes (2013), Trager et al. (2013), Levy (2013), Brownstein et al. (2005), Randolph (2004), Lindgren et al. (2000) in Borchers et al., 2015).

Peak onset of Lyme disease occurs in both the eastern US and most parts of Europe during the summer months, when nymphal abundance is highest and nymphs are actively questing, whereas few cases occur during the late fall [autumn] and the first few months of the year when adult ticks actively seek a host (Berglund et al. (1995), Huppertz et al. (1999), Strle et al. (1996), Falco et al. (1999), and Smith et al. (2002) in Borchers et al., 2015). A secondary peak in the incidence of EM is seen late in the fall [autumn] (October, November) in some European countries suggesting that actively questing adults also contribute to human *Borrelia* infection (Strle et al. (1996), and Lipsker et al. (2002) in Borchers et al., 2015). In Russia, *Borrelia* spp. are transmitted almost exclusively by adult *I. persulcatus* ticks (Korenberg et al. (1996) in Borchers et al., 2015).

North America

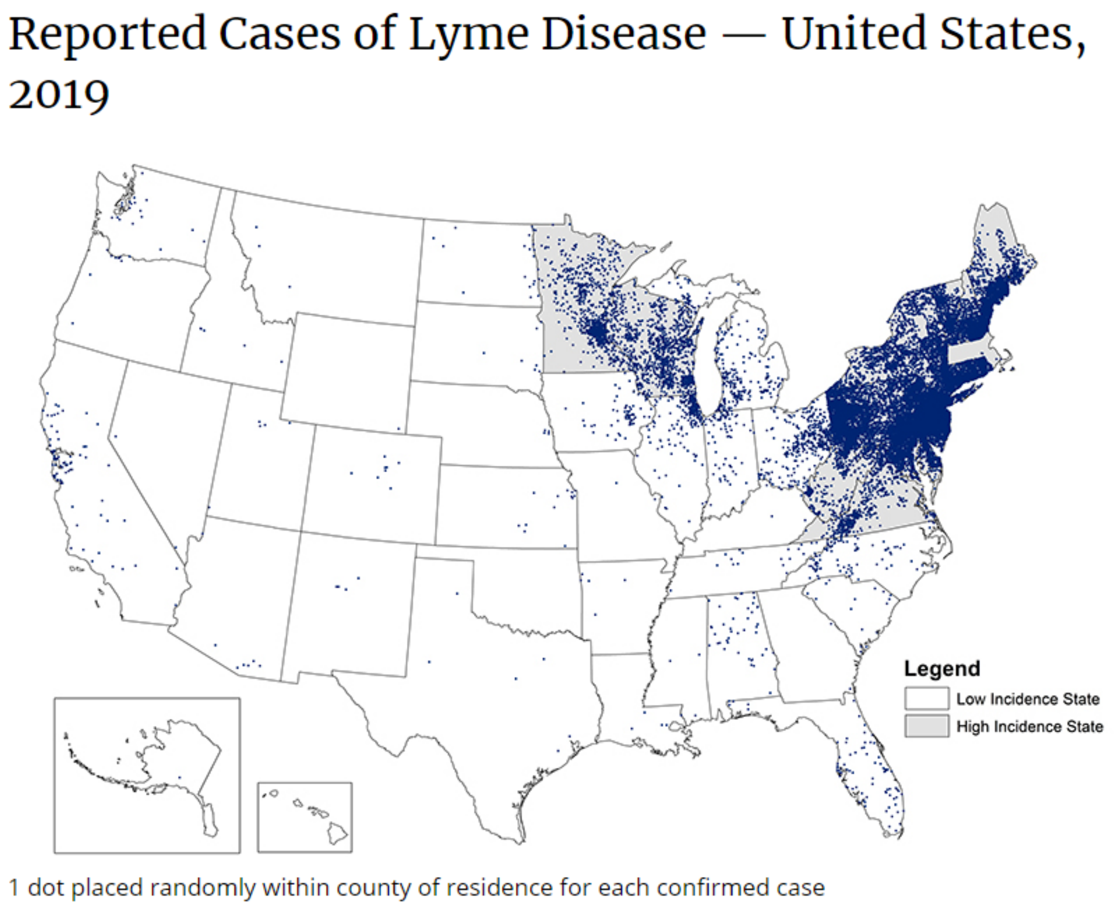
United States

Lyme disease became a nationally notifiable disease in the US in January 1991 (Centers for Disease Control and Prevention, 2019b) although, for reasons described below, the CDC advises there is no way of knowing exactly how many people get Lyme disease (Centers for Disease Control and Prevention, 2021b).

Lyme disease is the most common tick-borne disease in the US with approximately 300,000 new cases diagnosed each year (Hinckley et al., 2014 and Nelson et al., 2015 in Aucott et al., 2017). Lyme disease accounts for 82% of all US tick-borne disease cases (Aucott et al., 2017).

While approximately 30,000 cases of Lyme disease are reported to CDC by state health departments and the District of Columbia each year (see Figure 8 overleaf), this number does not reflect every case of Lyme disease that is diagnosed in the US every year. A recently released estimate based on insurance records suggests that each year approximately 476,000 Americans are diagnosed and treated for Lyme disease (Schwartz et al. (2021) and Kugeler et al. (2021) in Centers for Disease Control and Prevention, 2021b). The CDC advises that this number is likely an over-estimate of actual infections because patients are sometimes treated presumptively in medical practice; however, regardless, this number indicates a large burden on the health care system and the need for more effective prevention measures (Centers for Disease Control and Prevention, 2021b).

Figure 8: Reported cases of Lyme disease – US, 2019 (Public domain)



Public domain: Photo courtesy of CDC
https://www.cdc.gov/lyme/datasurveillance/maps-recent.html

While the most common tick-borne disease in the US, Lyme disease cannot be contracted just anywhere in the US, as it is spread through the bite of a black-legged tick (*I. scapularis* or *I. pacificus*) that is infected with *B. burgdorferi* (see Figure 9 overleaf). In the US, most infections occur in the following endemic areas:

- Northeast and mid-Atlantic, from northeastern Virginia to Maine
- North central states, mostly in Wisconsin and Minnesota
- West Coast, particularly northern California (Centers for Disease Control and Prevention, 2021a).

Figure 9: Reported tick populations in the US, 2018 (Public domain)

Western black-legged tick (Ixodes pacificus) populations

Public domain: Photo courtesy of CDC

Black-legged tick (Ixodes scapularis) populations

Public domain: Photo courtesy of CDC

As >95% of cases of Lyme disease in North America are vectored by *I. scapularis*, most cases occur within its geographical range, which is much of the eastern US. However, the distribution of Lyme disease risk is not uniform and corresponds closely to the distribution of *B. burgdorferi* – infected questing nymphs (Diuk-Wasser et al. (2012) in Lantos et al., 2020).

Fourteen states in the northeastern, mid-Atlantic, and north-central US where infected questing nymphs are abundant consistently account for >95% of all cases of Lyme disease reported to the CDC (Schwartz et al. (2017) in Lantos et al., 2020). In 2015, 95% of Lyme disease cases were reported from the following 14 states: Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, and Wisconsin (Centers for Disease Control and Prevention, 2020e).

The number of Us counties now considered to be of high incidence for Lyme disease has increased by more than 300% in northeastern states and by approximately 250% in north-central states (Aucott et al., 2017). In more southern states, where *I. scapularis* is widely established, the risk of exposure to *B. burgdorferi*- infected ticks is, however, much lower. Lantos et al. noted the difference in risk is due in part to:

- negligible or extremely low prevalence of infection in both nymphs and adult *I. scapularis*
- the rare tendency of southern nymphal black-legged ticks to quest above the leaf litter and feed on reservoir hosts, in contrast to their northern counterparts (Lantos et al., 2020).

The CDC is concerned about Lyme disease as it is the most common vector-borne disease in the US, and in addition to a large burden of illness, areas where Lyme disease is common are expanding. Due to these concerns, the CDC is developing better insect repellants; evaluating products used by the public; educating the public; funding collaborative approaches to understanding Lyme disease and other tick-borne diseases; discovering new tick-borne diseases; and understanding attitudes towards vaccination for Lyme disease (Centers for Disease Control and Prevention, 2021c).

Canada

Lyme disease has spread into neighbouring Canada with 917 cases reported in 2015 (Government of Canada (2016) in Stone et al., 2017). The number of documented endemic areas has increased recently; in the early 1990's only one geographically discrete population of *I. scapularis* ticks was known at Long Point on the Ontario shore of Lake Erie (Barker et al. (1992) in Ogden et al., 2009). Since 1997, populations of *I. scapularis* have been identified in southern Ontario, Nova Scotia, south-eastern Manitoba and New Brunswick (Ogden et al. (2005) in Ogden et al., 2009) through detection of human cases by vigilant clinicians and passive surveillance for ticks (Ogden et al. (2006) in Ogden et al., 2009). Additionally, active surveillance driven by risk maps has identified the possibility of additional emerging populations in southern Quebec (Ogden et al. (2008) in Ogden et al., 2009). Surveillance by the British Columbia Centre for Disease Control has suggested established populations of *I. pacificus* ticks and areas where *B. burgdorferi* is endemic are widely distributed in southern British Columbia (Ogden et al., 2009).

Health Canada monitoring data showed that between 2009 and 2021, provincial public health units have reported 14,616 human cases of Lyme disease across Canada (Public Health Agency of Canada, 2022b). In 2009, 144 cases were reported; preliminary data for 2021 indicated 2,851 cases of Lyme disease. Within this monitoring, reported Lyme disease cases are from those who became infected with Lyme disease while in Canada or while abroad (travel related). It was acknowledged that there is under-reporting as some cases are undetected or unreported (Public Health Agency of Canada, 2022b).

The risk of Lyme disease in endemic areas where *I. pacificus* is the vector is generally lower than where *I. scapularis* is the vector (Ogden et al., 2009). Studies have shown the prevalence of *B. burgdorferi* infection in host-seeking *I. pacificus* ticks is usually lower (typically less than 10% (Holden et al. (2006), and Lane et al. (2001) in Ogden et al., 2009) than that in *I. scapularis* (typically greater than 25% in the northeastern US and southeastern Canada (Kurtenbach et al. 2006), and Lindsay & Barker (1997) in Ogden et al., 2009).

Europe

Lyme disease is highly endemic in Europe where it is the most common tick-borne disease (Medlock et al., 2013; World Health Organization, 2014). In most of Europe, Lyme disease is not a notifiable disease and available data are less reliable (Borchers et al., 2015; Medlock et al., 2013), with a variety of active and passive surveillance methods used to arrive at the available estimates (Borchers et al., 2015). As such, trends in Europe are difficult to track, due to differences in agencies and reporting across the continent (Smith & Takkinen (2006) and Schotthoefer & Frost (2015) in Stone et al., 2017).

Between 1990 and 2010, the highest average incidence rates of Lyme disease among reporting countries were from Belarus, Belgium, Croatia, Norway, the Russian Federation and Serbia (<5 per 100,000), Bulgaria, Finland, Hungary, Poland and Slovakia (<16 per 100,000), the Czech Republic, Estonia, and Lithuania (<36 per 100,000) and Slovenia (<130 per 100,000) (World Health Organization, 2014). There is no more recent data, by European country, published by the World Health Organization. The ECDC publishes tick surveillance data, not Lyme disease incidence.

Estimated cases for all of Europe are approximately 85,000 cases per year (Lindgren & Jaenson (2006), Smith & Takkinen (2006), Schotthoefer & Frost (2015), and World Health Organization (2017) in Stone et al., 2017). The total number of annual cases in Europe is estimated to be about three-fold the number of cases reported to the CDC (Borchers et al., 2015).

Across Western Europe,7 the estimated number of cases per 100,000 persons is 22 (Sykes & Makiello (2016) in Stone et al., 2017).

Medlock et al. reported in 2013 that the incidence has increased in at least nine European countries over the past decade (Hofhuis et al. (2006), Hubalek (2009), and Rizzoli et al. (2011) in Medlock et al., 2013) with one plausible cause being the changing geographical distribution, density and activity of the principal vector tick *I. ricinus*, and/or changed activity that brings people into contact with ticks (Medlock et al., 2013). *I. ricinus* occurs throughout Europe, west to east from Ireland to the Urals in Russia, and north to south from northern Sweden to North Africa (Estrada-Peña (2001), and Estrada-Peña et al. (2012) in Medlock et al., 2013). The distribution of *I. ricinus* is known to be changing in Europe, at extremes of altitude and latitude as well as within its prior range (Medlock et al., 2013; World Health Organization, 2014).

Advice from the ECDC in 2015 was that the regions with highest tick infection rates (nymphs >10%; adult ticks >20%) are located in central Europe and include Austria, Czech Republic, southern Germany, Switzerland, Slovakia and Slovenia (European Centre for Disease Prevention and Control, 2015a). A 2018 study that represents the largest analysis of the distribution of the pathogen in questing nymphs of *I. ricinus* in Europe, found from their meta-analysis of more than 82,000 nymphs that *B. afzelii*, *B. garinii* and *B. valaisiana* largely overlap across Europe (Estrada-Peña et al., 2018). The highest prevalence of *B. burgdorferi* in questing nymphs of *I. ricinus* in areas of 280°–290°K8 of mean annual temperature (around central Europe and southern parts of Nordic countries) and a slow spring rise of temperature, together with high mean values and a moderate spring rise of vegetation vigor. Low prevalence of *B. burgdorferi* in questing nymph *I. ricinus* was found to occur in colder areas with abrupt annual changes of vegetation. Models used by the authors, based on support vector machines, yielded a correct classification rate of the habitat and prevalence of 89.5%. The authors concluded there is an environmental niche driving the prevalence of the most commonly reported species of bacteria of the *B. burgdorferi* s.l. complex in questing nymph *I. ricinus* ticks. In this study, the authors reported that only data from questing nymphs was used due to the unreliability of reports in ticks collected and processed while feeding; additionally, questing nymphs are also the more abundantly collected stage of *I. ricinus* (Estrada-Peña et al., 2018).

Medlock et al. noted that many factors are involved in the latitudinal and altitudinal spread of *I. ricinus* as well as in changes in the distribution within its prior endemic zones (Medlock et al., 2013). They explained that the drivers can be divided into those directly related to climatic change, those related to changes in the distribution of tick hosts particularly roe deer and other cervids, or other ecological changes and anthropogenically induced changes. To illustrate this, Medlock et al. developed a conceptual framework of drivers for change in geographical distribution on *I. ricinus* (Medlock et al., 2013). Their framework is reproduced as Figure 10. The drivers can be divided into those directly related to: climatic change (blue), ecological changes (green), anthropogenic change (brown), and others (red). The colour of the outline indicates the indirect effect of one driver upon the other.

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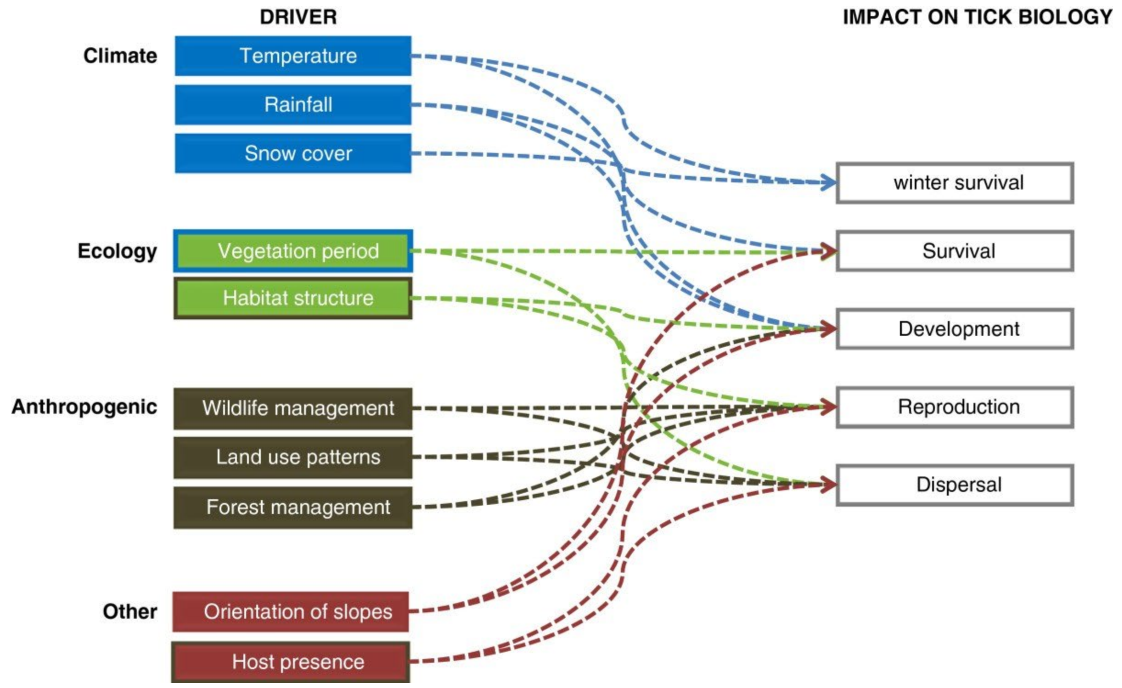
7 'Western Europe' in this paper were those countries defined as in Western Europe by the World Bank: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxenbourg, The Netherlands, Norway, Portugal, Spain (La Rioja), Sweden, Switzerland, UK (England and Wales, Scotland).

8 280–290°K equates to 6.85–16.85°C.

Figure 10: Conceptual framework of drivers for change in geographical distribution of castor bean tick (Ixodes ricinus) (Public domain)



Public domain: Figure 1 of Medlock et al. (2013).

https://doi.org/10.1186/1756-3305-6-1

United Kingdom

Infected ticks are found throughout the UK and Ireland, with particularly high risk areas being the South of England and the Scottish Highlands (National Institute for Health and Care Excellence, 2018c). Peak incidence of Lyme disease occurs in June, with a smaller peak in September, reflecting increased tick activity in the early summer and autumn, coinciding with times when people are more likely to be outdoors (Royal College of General Practitioners, 2020).

Lyme disease is monitored in England and Wales through routine surveillance (Public Health England, 2018d). Data is published in the quarterly Health Protection Report and annually in the UK Zoonoses Report. Cases of Lyme disease are not statutorily notifiable by medical practitioners in England, Wales and Northern Ireland. However, since October 2010 under the Health Protection (Notification) Regulations 2010, every microbiology laboratory (including those in the private sector) in England is required to notify all laboratory diagnoses of Lyme disease to Public Health England (Public Health England, 2018d).

The UK Government advises Lyme disease is not common, with an estimated 2,000 to 3,000 new cases each year in England and Wales (Public Health England, 2018b). While estimated to be approaching 3,000 cases annually, the number of reported cases is much lower (Public Health England (2013), and Schotthoefer & Frost (2015) in Stone et al., 2017). Approximately 1,000 laboratory confirmed cases are reported annually in England and Wales, with around 15% of these cases acquired overseas (Public Health England, 2018a). People of all ages can be affected and both sexes are equally susceptible. Highest rates occur in people aged between 24 and 64 years. Cases have been reported from most counties in England and Wales, but more frequently from the southern counties (Public Health England, 2018a).

Additionally, the UK Government advises that only a small minority of ticks in the UK are infected with the bacteria that cause Lyme disease, and being bitten by a tick does not necessarily result in Lyme disease (Public Health England, 2018b).

To highlight the Scottish Highlands as an area of high endemicity, between 2008 and 2013, the prevalence of Lyme disease in all of Scotland was 6.8 cases per 100,000 persons, while in the Highland region it was 44.1 per 100,000 (Mavin et al. (2015) and Munroe et al. (2015) in Stone et al., 2017).

Additionally, the Tayside region adjacent to the Highlands has seen a dramatic rise in Lyme disease cases recently, with the increase attributed to changes in climate (Slack et al. (2011) in Stone et al., 2017).

Asia

Japan

Lyme disease was classified as a Category IV infectious disease under the Infectious Diseases Control Law in 1999 in Japan. Doctors are required to notify the Ministry of Health of any diagnosed cases (Infectious Diseases Surveillance Center (2011) in Centre for Health Protection, Hong Kong Department of Health, n.d.).

From April 2006 to 2010, 49 cases were reported, with an incidence rate of 0.008 per 100 000 population (Infectious Diseases Surveillance Center (2011) in Centre for Health Protection, Hong Kong Department of Health, n.d.; Infectoius Diseases Surveillance Center (2011) in Stone et al., 2017).

Additional information about Lyme disease in Japan from the Infectious Disease Surveillance Center for Lyme disease included that:

- about 84% of the cases were acquired locally
- the male to female ratio was 1.6:1
- among the local cases, nearly half of the patients were aged over 60, and most cases were diagnosed in the summer season
- no case was reported in the winter season from December to March
- about half of the cases were acquired in Hokkaido, 12% in Nagano with the rest of the cases acquired in other regions such as Kanagawa, Niigata, Gifu and Fukuoka respectively
- around 16% of cases were imported from other countries, which included the US, Germany, and the Switzerland (Infectious Diseases Surveillance Center 2011 in Centre for Health Protection, Hong Kong Department of Health, n.d.).

Hong Kong

In Hong Kong, Lyme disease is not a statutory notifiable disease. No confirmed human case has been reported to the Department of Health (Centre for Health Protection, Hong Kong Department of Health, n.d.).

Korea

Lyme disease remains rare in Korea[9] (Lee & Cho (2004) in Stone et al., 2017).

China

Lyme disease was first reported in China in 1985, in a forest region in Hailin County, Heilongjiang (Meng et al. (2004) in Wu et al., 2013).

The Hong Kong Department of Health cited a 1998 paper (citation in Chinese) that described Lyme disease as being widely distributed in China, particularly in the northeast region and Inner Mongolia, with the incidence of Lyme disease in China 'roughly estimated' at over 10,000 cases annually (Centre for Health Protection, Hong Kong Department of Health, n.d.).

Human cases of Lyme disease caused by genospecies *B. garinii, B. afzelli,* and *B. valaisiana* have been reported in most provinces of mainland China (Fang et al. (2015) in Stone et al., 2017), although Stone et al. noted the exact numbers of cases are unclear as the disease is likely underreported due to lack of surveillance, lack of awareness by most physicians, and the lack of appropriate diagnostic facilities (Fang et al. (2015) in Stone et al., 2017).

An earlier paper by Wu et al. (2013) was more specific, noting human cases of Lyme disease have been confirmed in 29 provinces/municipalities. Wu et al. reported that, as demonstrated by the occurrence of Lyme disease, its natural foci is present in at least 19 provinces/municipalities in China (Wu et al., 2013). These provinces/municipalities are Anhui, Beijing, Chongqing, Fujian, Gansu, Guangdong, Guangxi, Guizhou, Hebei, Heilongjiang, Henan, Hubei, Hunan, Inner Mongolia, Jiangsu, Jiangxi, Jilin, Liaoning, Ningxia, Shandong, Shaanxi, Shanxi, Sichuan, Tianjin, Tibet, Qinghai, Xinjiang, Yunnan, Zhejiang (Hein et al. (2012), Niu et al. (2009), Wang et al. (2011) and Pan et al. (1996) in Wu et al., 2013 Table 1). The 1998 paper cited by the Hong Kong Department of Health mentioned above indicated a higher number of affected provinces than reported by Wu et al., with previous seroprevalence studies indicating Lyme disease had occurred in the forest areas of more than 26 provinces and autonomous areas (Centre for Health Protection, Hong Kong Department of Health, n.d.).

The major endemic areas for Lyme disease in China are forests in the northeast and northwest and some areas in North China (Wu & Jiang (2007) in Wu et al., 2013). Over 3 million people suffer tick bites annually in Heilongjiang, Jilin, Liaoning, and Inner Mongolia, and of those, approximately 30,000 people become infected with Lyme disease (Wang et al. (2011) in Wu et al., 2013). The Hong Kong Department of Health cited another study, dated 1999 (citation in Chinese), that had reported seroprevalence of antibodies to *B. burgdorferi* was the highest (over 10%) in the population of mountainous areas. In forest areas such as Southern region of Qinling forest area, the seroprevalence was relatively lower (ranging from 5% to 10%), with the prevalence the lowest (below 5%) in flatlands (Centre for Health Protection, Hong Kong Department of Health, n.d.).

While Wu et al. reported the peak incidence of Lyme disease in China appears to occur from June to August (Wu et al., 2013), the Hong Kong Department of Health, based on the 1998 paper mentioned above, indicated that Lyme disease was more commonly diagnosed in summer season from April to August in the northeast forest area, coinciding with the tick activities. The 1998 paper had also reported that few cases were observed beyond April-August, all ages and sexes were susceptible but higher attack rate appeared in young adults,

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9 The author is based in South Korea and we assume that this information refers only to South Korea rather than the Korean Peninsula.

and occupation of patients was usually related to forestry workers and other workers exposed to forests (Centre for Health Protection, Hong Kong Department of Health, n.d.).

Australia

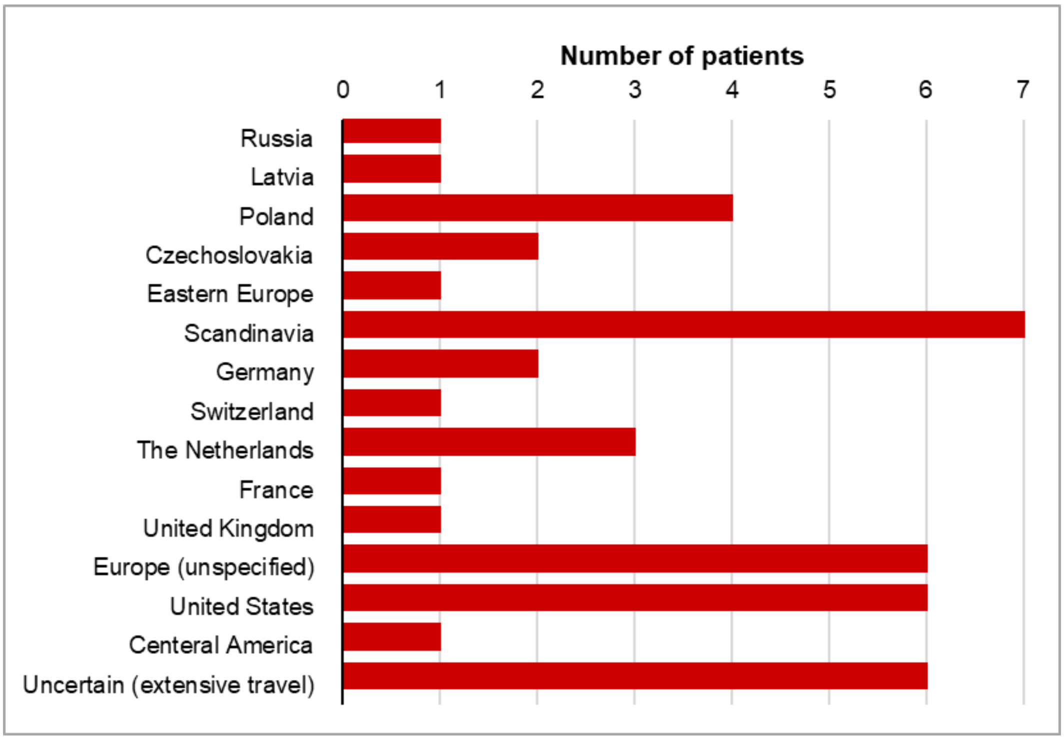
Lyme disease is not a nationally notifiable disease in Australia (Australian Government Department of Health, 2021). The Australian Government Department of Health advises that because there is no person-to-person transmission of classical Lyme disease, the risk to Australia and Australians is low (Australian Government Department of Health, 2020b).

Lyme disease has been diagnosed in Australia in overseas travellers, with all confirmed cases to date in Australia having been in returned travellers (Subedi et al. (2015) in Graves & Stenos, 2017). Subedi et al. (2015) reported on the first case of Lyme neuroborreliosis in a returned Australian traveller, a 58-year-old woman who had spent three months in Lithuania where she was bitten by a tick during a trip to a pine forest near Vilnius. Her symptoms started one month after returning to Australia. This case report demonstrates that Australian clinicians and laboratories can accurately support diagnosis of Lyme disease using internationally validated serology testing protocols. For more detail about this paper see the literature review that supports the DSCATT Clinical Pathway (Subedi et al. (2015) in Allen + Clarke, 2020).

More recently, in 2018, Doolan et al. described a case of Lyme disease in a recent migrant, highlighting the infrequent skin disease in the Australian setting (Doolan et al., 2019). This case was in a 43-year-old woman who presented with a four-month history of an erythematous, enlarging, annular lesion consistent with EM rash on her lower calf and a three-month history of localised dysaesthesia, and constitutional symptoms including intermittent flu-like illness, lethargy and arthralgia. She had moved from Switzerland to Australia five months earlier. Further detail about this case report is also available in the literature review that supports the DSCATT Clinical Pathway (Doolan et al. (2019) in Allen + Clarke, 2020).

In an analysis of diagnostic testing for Lyme disease conducted by a large private laboratory in Australia, over a 23-month period (September 2014 – July 2016) nearly all (95.5%) of the tests performed in 5,395 patients returned negative results. A travel history was available for 37 of the 43 patients with true positive results. All had returned from countries in which Lyme disease is endemic. The analysis found most Lyme disease acquired overseas but diagnosed in Australia was European in origin (30 of 43 cases, or 70% of cases). The following graph (see Figure 11 overleaf) is reproduced from Collignon et al. (2016) to demonstrate the countries where travellers had travelled to prior to returning to Australia and being diagnosed with Lyme disease via positive serological testing.

Figure 11: Travel history for patients in Australia with positive serological test results for Lyme disease (Collignon et al., 2016) (Public domain)



Routine prevention activities

Lyme disease vaccine – none currently but some are in clinical trials

There is no prophylaxis for Lyme disease (World Health Organization, n.d.), and no licensed vaccine for Lyme disease is currently available (Centers for Disease Control and Prevention, 2020f). The CDC advises that the only vaccine previously marketed in the US, LYMERix® was discontinued by the manufacturer in 2002, citing insufficient consumer demand. As protection provided by this vaccine decreases over time, the CDC advises that if people received this vaccine before 2002, they are probably no longer protected against Lyme disease (Centers for Disease Control and Prevention, 2020f).

However, clinical trials of new vaccines for Lyme disease are currently underway, but no specific dates for vaccine availability from these trials was available.10 In 2020, the CDC provided the following advice on the clinical trials for new Lyme disease vaccines:

- Valneva and Pfizer have developed a Lyme disease vaccine candidate, VLA15, that is currently in Phase 2 human trials. VLA15 is a multivalent, protein subunit vaccine that targets the outer surface protein A (OspA) of Borrelia. This vaccine is designed to protect people against North American and European strains of the Lyme disease bacterium [not further specified].
- The University of Massachusetts Medical School's MassBiologics has developed a human monoclonal antibody designed to be used as pre-exposure prophylaxis (PrEP) for Lyme disease. Human trials are expected to begin soon. This approach would provide seasonal protection against Lyme disease. It would likely consist of a single shot that people would

10 https://www.cdc.gov/lyme/prev/vaccine.html#:~:text=A%20vaccine%20for%20Lyme%20disease,this%20vaccine%20decreases%20over%20time

get each year at the beginning of the tick season (Centers for Disease Control and Prevention, 2020f).

Additionally, the CDC is currently conducting research to understand what concerns healthcare providers and the public may have about any potential Lyme disease vaccines. Once a Lyme disease vaccine is approved as safe and effective by the Food and Drug Administration (FDA), CDC will work with the Advisory Committee on Immunization Practices (ACIP) to develop recommendations about where in the US the public might benefit from a Lyme disease vaccine. CDC will communicate these recommendations to increase awareness of a vaccine among the public and clinicians to prevent Lyme disease in the US (Centers for Disease Control and Prevention, 2020f).

International authority advice and education to prevent Lyme disease

Australians travelling to Lyme disease endemic areas need to know how best to prevent tick bites and, therefore how to prevent Lyme disease. Guidance from international authorities and international medical professional associations on preventing or reducing the risk of Lyme disease consistently focusses on avoiding or limiting exposure to ticks, preventing tick bites and early removal of attached ticks, in the absence of a currently available vaccine (Centers for Disease Control and Prevention, 2020e; European Centre for Disease Prevention and Control, 2015a; Lantos et al., 2020; Public Health England, 2018b; World Health Organization, n.d., 2014).

Tick-borne diseases are preventable and an integrated approach to avoiding tick bites and preventing infection is necessary (World Health Organization, 2014). This includes avoiding tick risk areas, being informed about how to recognise early symptoms of tick-borne diseases, wearing protective clothing (long trousers and long-sleeved shirts), using tick repellents on one's skin and clothes, checking the entire body daily for ticks, and removing attached ticks before transmission of infection can occur (European Centre for Disease Prevention and Control, 2015a; World Health Organization, 2014).

Topics covered by the international guidance and advice on preventing tick bites includes personal protective strategies to prevent tick bites on people, and preventing tick bites on pets and in the backyard.

Personal protective strategies to prevent tick bites on people

The 2020 IDSA/AAN/ACR Lyme disease guideline for the prevention, diagnosis and treatment of Lyme disease notes that in the absence of vaccines, the risk of Lyme disease and other tick-borne diseases can be reduced by preventing exposure to ticks. Furthermore, the IDSA/AAN/ACR advises healthcare professionals can play a very important role by increasing awareness and educating patients about ticks, tick-borne pathogens, and measures to reduce exposure, thereby increasing their confidence and likelihood to practice precautionary behaviours (Richardson et al. (2019) in Lantos et al., 2020).

Regarding personal protective measures,the IDSA/AAN/ACR recommends:

Individuals at risk of exposure should implement personal protective measures to reduce the risk of tick exposure and infection with tick-borne pathogens (Good practice statement) (Lantos et al., 2020).

Prior to going outdoors

Be informed – know where to expect ticks.

Knowing which tick species and life stages are vectors, and when and where they are most likely to be active, can help people avoid ticks in the first place or take proper precautions to prevent bites when in risky habitats (Lantos et al., 2020). Ticks live in grassy, brushy, or wooded areas, or even on animals. Spending time outside walking a dog, camping, gardening, or hunting could bring people in close contact with ticks. Many people get ticks in their own yard or neighbourhood (Centers for Disease Control and Prevention, 2019a).

Avoid wooded and brushy areas with high grass and leaf litter (Centers for Disease Control and Prevention, 2019a) and walk in the center of trails or on clearly defined paths to avoid brushing against vegetation where ticks may be present (Centers for Disease Control and Prevention, 2019a; Public Health England, 2018a).

Wear light-coloured protective clothing

Wearing light coloured clothing helps people see ticks crawling on clothing so they can be spotted and brushed off. Wearing long sleeved tops and long trousers and tucking pants into socks reduces the tick's direct exposure to a person's skin and therefore makes it more difficult for the tick to find a suitable area to attach (European Centre for Disease Prevention and Control, 2015a; Lantos et al., 2020; Public Health England, 2018a).

Use repellants to prevent tick bites

The IDSA/AAN/ACR provided the following advice about efficacy and safety of repellants used to prevent tick bites.

To improve efficacy and safety, repellents should:

- always be applied to targeted areas of the body and/or clothes according to the manufacturers' instructions and EPA label
- only be applied to exposed skin or clothing and should not be sprayed under clothing (Lantos et al., 2020).

To maintain efficacy, repellents may need to be reapplied after swimming, washing, or heavy perspiration. The use of products that combine sunscreen and N,N-Diethyl-meta-toluamide (DEET) is discouraged because frequent application of the sunscreen may exceed the recommended exposure to the repellent. Furthermore, sunscreen may increase the absorption of DEET through the skin (Ross et al. (2004) in Lantos et al., 2020). Consequently, the FDA recommends that sunscreen be applied before DEET (Lantos et al., 2020).

The 2020 IDSA/AAN/ACR recommendation on repellants to prevent tick bites is:

For the prevention of tick bites, we recommend N,N-Diethylmeta-toluamide (DEET), picaridin, ethyl-3-(N-n-butyl-Nacetyl) aminopropionate (IR3535), oil of lemon eucalyptus (OLE), p-methane-3,8-diol (PMD), 2-undecanone, or permethrin (strong recommendation, moderate-quality evidence) (Lantos et al., 2020).

The CDC advise people to use Environmental Protection Agency (EPA)-registered insect repellents containing DEET, picaridin, IR3535, oil of lemon eucalyptus (OLE), para-menthane-diol (PMD), or 2-undecanone. Always follow product instructions. Do not use products containing OLE or PMD on children under three years of age (Centers for Disease Control and Prevention, 2019a).

In laboratory and field experiments involving human subjects, the use of DEET, picaridin, IR3535, OLE, PMD (the synthetic active ingredient in oil of lemon eucalyptus), 2-undecanone, and permethrin reduced the number of ticks detected crawling on or attached to subjects compared with controls (Buchel et al. (2015), Carrol et al. (2010), Solberg et al. (1995), Schreck et al. (1986), Gardulf et al. (2004), and Bissinger et al. (2014) in Lantos et al., 2020).

DEET, picaridin, IR3535, OLE, PMD, and 2-undecanone can be applied directly to skin and clothing (Lantos et al., 2020). Different concentrations and preparations affect their efficacy and duration of activity. In general, products with higher concentrations provide greater and/or longer periods of efficacy compared with lower concentrations (Buchel et al. (2015), Carrol et al. (2010), Solberg et al. (1995), Schreck et al. (1986), Gardulf et al. (2004), and Bissinger et al. (2014) in Lantos et al., 2020). However, research shows that products containing >50% DEET (Katz et al. (2008) in Lantos et al., 2020) do not offer a meaningful increase in protection time over lower concentrations (Lantos et al., 2020).

Additionally, adults should supervise the application of repellents on children. The IDSA/AAN/ACR notes that the EPA has approved DEET for use on children with no age restriction, however, because of a lack of safety data, the American Academy of Pediatrics (AAP) and the CDC only recommend DEET for infants at least two months of age and above. The AAP, CDC, and EPA do not recommend OLE and PMD for children under three years of age (Lantos et al., 2020).

Regarding the safety of DEET, the IDSA/AAN/ACR noted that despite public concern over DEET, decades of use have shown there is a very low risk of adverse effects when used as labelled (Osimtz et al. (2010), Veltri et al. (1994), Osimitz & Murphy (1997), Antwi et al. (2008), Bell et al. (2002), Chen-Hussey et al. (2014), Koren et al. (2003), Gready et al. (2001), and Sudakin & Trevathan (2003) in Lantos et al., 2020). IDSA/AAN/ACR noted some reported cases of encephalopathy following DEET application were likely due to improper application, an excessive dose, or unintentional ingestion (Osimitz et al. (2010), Veltri et al. (1994), and Bell et al. (2002) in Lantos et al., 2020). IDSA/AAN/ACR also noted that despite hundreds of millions of annual applications of DEET, reports of encephalopathy are rare and may not differ from the background rate in the general population (Veltri et al. (1994), and Osimitz & Murphy (1997) in Lantos et al., 2020).

For people with frequent occupational or recreational exposure, IDSA/AAN/ACR advises that a feasible option is to wear permethrin-treated clothing and to apply a repellent to exposed skin, if additional protection is desired (Lantos et al., 2020). For those who prefer an alternative to conventional synthetic repellents, IR3535, OLE, PMD, 2-undecanone are all considered by the EPA as biopesticides (derived from natural materials). IDSA/AAN/ACR noted there was more information, and to decide which repellent to recommend, there are resources at the websites of the EPA, CDC, and many state agencies (Lantos et al., 2020).

Commercially available products not recommended as repellants to prevent tick bites by IDSA/AAN/ACR due to insufficient evidence include botanical agents and essential oils (for example essential oils of rosemary, cinnamon leaf, lemongrass, nootkatone, geraniol (Bissinger et al. (2014) in Lantos et al., 2020) and carvacrol (Jordan et al. (2012) in Lantos et al., 2020)).

Treating clothing and gear

CDC advice is to treat clothing and gear with products containing 0.5% permethrin. Permethrin can be used to treat boots, clothing and camping gear and remain protective through several washings. Alternatively, people can buy permethrin-treated clothing and gear (Centers for Disease Control and Prevention, 2019a).

IDSA/AAN/ACR noted permethrin (0.5%) kills ticks on contact but must be applied to clothing. Field studies had indicated that clothes sprayed with permethrin or made with pretreated, permethrin-impregnated material provide highly effective protection against tick bites (Schreck et al. (1986), Evans et al. (1990), Vaughn et al. (2014), and Faulde et al. (2015) in Lantos et al., 2020) and are more effective compared with clothes treated with DEET (Schreck et al. (1986), and Evans et al. (1990) in Lantos et al., 2020).

A pilot study that assessed the effectiveness of long-lasting permethrin-impregnated (LLPI) clothing in the field for the prevention of tick bites in outdoor workers in North California, US, found the participants wearing Insect Shield-treated clothing had a 93% reduction ($p < .0001$) in the total incidence of tick bites compared to participants using standard tick-bite prevention measures (Vaughn & Meshnick, 2011). The authors noted Insect Shield had developed a factory-based method for long-lasting permethrin impregnation of clothing that allows clothing to retain effective repellent activity for over 70 washes and that clothing treated with Insect Shield had undergone extensive safety testing and has been registered by the USEPA for use among people of all ages, with no exclusion for pregnant women and children (Insect Shield, USEPA (2009) in Vaughn & Meshnick, 2011).

More recently, a two-year randomised-controlled trial (RCT) investigated the protective effectiveness of LLPI (clothes treated with permethrin at the Insect Shield facility) against tick-bites in a Lyme disease endemic setting among outdoor workers frequently exposed to bites from *I. scapularis* (Mitchell et al., 2020). The factory-impregnated clothing was found to significantly reduce risk of tick bites by 65% in the first year of the study, and by 50% in the second year, compared to the control group, who wore untreated clothing. The two-year protective effect was 58%. No treatment-related adverse outcomes were reported in the treatment arm of the study. The authors noted prior studies had shown factory permethrin impregnation of uniforms to be highly effective at preventing tick bites from the lone star tick among outdoor workers (Vaughn & Meshnick (2011), and Vaughn et al. (2014) in Mitchell et al., 2020), but that their study was the first RCT to field test LLPI clothing among outdoor workers where *I. scapularis* – the vector of the three most frequently reported tick-borne diseases in the US –- was the predominant human biting tick. While the authors noted a number of limitations of the study, they commented their study showed that LLPI clothing provides significant levels of protection from bites of black-legged ticks among outdoor workers, retains moderate protective effectiveness through two years of routine fieldwork and laundering, and that factory permethrin impregnation of clothing is safe (Mitchell et al., 2020).

In addition to applying permethrin products to clothing, clothing commercially treated with permethrin is available in Australia. While not a study conducted in Lyme disease endemic areas, a recent (2020) Australian study that was the first to investigate the toxicity and persistence of permethrin-impregnated clothing against the Australian paralysis tick, *Ixodes holocyclus,* found that the pre-impregnated product was more effective in repelling *I. holocyclus* ticks than the DIY permethrin impregnation kit, but that the efficacy of the pre-impregnated product degrades notably after 10 washes (Panthawong et al., 2020). See *Prevention and management of tick bites in Australia* Guidance Note for more detail about this study.

After coming indoors

Check clothing for ticks

Ticks may be carried into the house on clothing. Any ticks that are found should be removed (Centers for Disease Control and Prevention, 2019a). Tumble dry clothes in a dryer on high heat for 10 minutes to kill ticks on dry clothing after people come indoors (Centers for Disease Control and Prevention, 2019a; Lantos et al., 2020). If the clothes are damp, additional time may be needed (Centers for Disease Control and Prevention, 2019a). Placing clothes directly in a dryer on high heat for at least 10 minutes is highly effective for killing *I. scapularis*, though up to 60 minutes may be required for other tick species (Nelson et al. (2016), and Carroll (20013) in Lantos et al., 2020). If the clothes require washing first, hot water is recommended, as hot water will kill *I. scapularis* (Centers for Disease Control and Prevention, 2019a; Nelson et al. (2016) in Lantos et al., 2020). Cold and medium temperature water will not kill ticks (Centers for Disease Control and Prevention, 2019a).

Examine gear and pets

Ticks can ride into the home on gear and pets, then attach to a person later, so carefully examine pets and daypacks (Centers for Disease Control and Prevention, 2019a). Because companion animals (e.g. dogs and cats) that spend time outdoors may bring unattached ticks into the home, IDSA/AAN/ACR (Falco & Fish (1988) in Lantos et al., 2020) note they should also be checked regularly for ticks, even if they are treated with tick control products, to prevent subsequent tick attachment to humans (Jones et al. (2018) in Lantos et al., 2020).

However, IDSA/AAN/ACR noted that although there is an association between companion animal ownership and tick exposure, there is no direct evidence that companion animal ownership increases the risk of falling ill with a tick-borne disease (Lantos et al., 2020).

Check the body for ticks after being outdoors

People should check their body and the bodies of their children for attached ticks after being outdoors (Centers for Disease Control and Prevention, 2019a; European Centre for Disease Prevention and Control, 2015a, 2015b; Public Health England, 2018a).

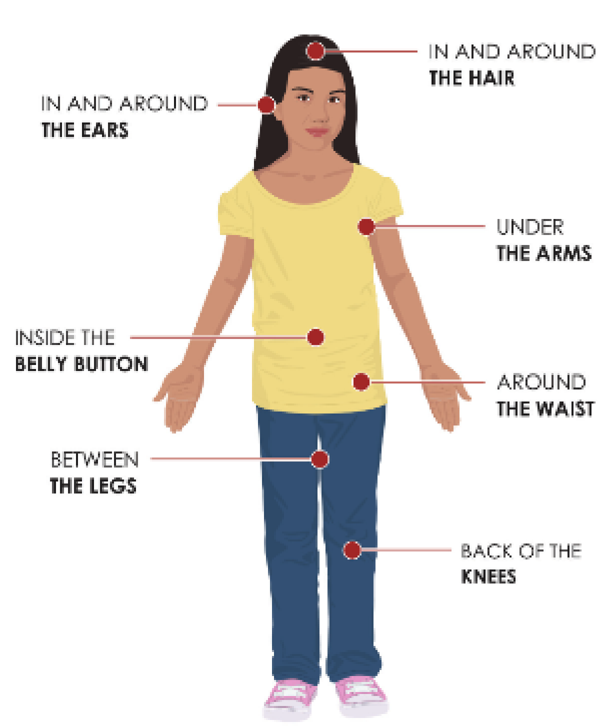
As ticks are very small and their bites do not usually hurt, ticks can easily be overlooked on the body (European Centre for Disease Prevention and Control, 2015b). A tick bite usually looks like a small dark freckle, [or mole] on the skin. A magnifying glass may be helpful (European Centre for Disease Prevention and Control, 2015b).

A tick check is carried out by looking and feeling for ticks that may have attached to the skin. By performing a tick check, the chance of infection is reduced because feeding ticks are spotted and removed early (Public Health England, 2018a).

A full body check for attached ticks should be conducted upon returning from potentially tick-infested areas, including peoples' own backyards. People can use a hand-held or full-length mirror to view all parts of their body (Centers for Disease Control and Prevention, 2019a).

- To do a full body check for ticks, the following parts of adults' and childrens' bodies should be checked as per Figure 12 below (Centers for Disease Control and Prevention, 2019a; European Centre for Disease Prevention and Control, 2015a):
- The head- in and around the hair and ears, the scalp and neck area. The head and neck area of young children should be checked carefully, as tick bites are relatively more common at these sites in this age group.
- Skin-folds- groins, armpits, under breasts, waistband area, backs of knees. Pay particular attention to skin-folds as ticks seek out more humid areas for attachment.
- Inside the belly button.
- Between the legs.
- Legs, arms, and back for nymphal ticks (Wilhelmsson et al. (2013), and Falco & Fish (1988) Lantos et al., 2020).

Figure 12: Where to check for ticks (Public domain)



Public domain: Photo courtesy of CDC

Bathe or shower soon after being outdoors

Bathing or showering within two hours of outdoor activity can significantly reduce the risk of Lyme disease (Centers for Disease Control and Prevention, 2019a; Connally et al. (2009) in Lantos et al., 2020) and may be effective in reducing the risk of other tick-borne diseases (Centers for Disease Control and Prevention, 2019a). Showering may help wash off unattached ticks and it is a good opportunity to do a tick check (Centers for Disease Control and Prevention, 2019a; Lantos et al., 2020)

Preventing tick bites on pets

People travelling to areas where Lyme disease is endemic may visit or stay at properties where they come into contact with pets, or look after pets during their stay. Generic information (that is, not specific to Lyme disease) about preventing tick bites on pets is available from the CDC (Centers for Disease Control and Prevention, 2019a). As above, the IDSA/AAN/ACR noted that although there is an association between companion animal ownership and tick exposure, there is no direct evidence that companion animal ownership increases the risk of falling ill with a tick-borne disease (Lantos et al., 2020).

The CDC advises dogs are very susceptible to tick bites and tick-borne diseases. Vaccines are not available for most of the tick-borne diseases that dogs can get, and they do not keep the dogs from bringing ticks into people's home. For these reasons, the CDC advises it is important to use a tick preventive product on one's dog (Centers for Disease Control and Prevention, 2019a).

Tick bites on dogs may be hard to detect. Signs of tick-borne disease may not appear for seven to 21 days or longer after a tick bite. CDC advice is for people to watch their dog closely for changes in behaviour or appetite if it is suspected that the dog has been bitten by a tick.

CDC advise people to talk with a veterinarian about the best tick prevention products for their dog and tick-borne diseases in their area. To further reduce the chances that a tick bite will make a dog sick, the CDC advises that people should:

- check dogs for ticks daily, especially after they spend time outdoors
- remove a tick right away if found on the dog
- reduce tick habitat in the area.

The CDC cautions that cats are extremely sensitive to a variety of chemicals, and strongly advises people not to apply any tick prevention products to cats without first consulting a veterinarian (Centers for Disease Control and Prevention, 2019a).

Preventing tick bites in the backyard

People travelling to Lyme disease endemic areas may come into contact with ticks in the backyards of properties where they stay or visit. The CDC advises people create a Tick-Safe Zone through Landscaping (Centers for Disease Control and Prevention, 2019a). The CDC notes people can make their yard less attractive to ticks depending on how they landscape. Some simple landscaping techniques that can help reduce tick populations offered by the CDC include:

- clearing tall grasses and brush around homes and at the edge of lawns
- placing a 3-foot [~1 metre] wide barrier of wood chips or gravel between lawns and wooded areas and around patios and play equipment. This will restrict tick migration into recreational areas
- mowing the lawn frequently and keeping leaves raked
- stacking wood neatly and in a dry area (discourages rodents that ticks feed on)
- keeping playground equipment, decks, and patios away from yard edges and trees and placing them in a sunny location, if possible
- removing old furniture, mattresses, or rubbish from the yard that may give ticks a place to hide.

The CDC also issued the following advice on applying pesticides outdoors to control ticks:

- Use of acaricides (tick pesticides) can reduce the number of ticks in treated areas of your yard. However, you should not rely on spraying to reduce your risk of infection.

If you have concerns about applying acaricides:

- check with local health officials about the best time to apply acaricide in your area
- identify rules and regulations related to pesticide application on residential properties (EPA and your state determine the availability of pesticides)
- consider using a professional pesticide company to apply pesticides at your home (Centers for Disease Control and Prevention, 2019a).

Remove attached ticks safely and without delay using the Australian-developed technique

People travelling to Lyme disease endemic areas may be bitten by a tick that carries the Lyme disease bacterium. The duration of tick attachment is one of the most important predictors of subsequent Lyme disease, with infection more likely the longer a tick is attached to the skin (Borchers et al., 2015; Mackenzie, 2013; National Institute for Health and Care Excellence, 2018c; Lantos et al., 2020).

The latest Australian guidance on tick removal from the Australian Government Department of Health, as published in the DSCATT Clinical Pathway, is based on recent Australian research. The guidance states the following:

- If a tick has embedded in the patient's skin and remains in situ, enquire whether the patient suffers from allergies to ticks before attempting to remove the tick. It is vital that anyone with a known tick allergy summon urgent medical attention as soon as they are aware of an attached tick and not attempt to remove it without medical help. For patients with known tick allergies, removing the tick must occur in a medical facility with capacity to initiate advanced life support in the event of anaphylaxis.
- Once a tick is found attached, patients should be advised not to touch, scratch or try to remove the tick, which should be left as undisturbed as possible. Several years of experience at Sydney hospital emergency departments using ether-containing sprays to freeze attached adult ticks has proven highly successful in killing ticks in situ and substantially reducing the risk of allergy/anaphylaxis (Australian Government Department of Health, 2020a).

The Australian Government Department of Health advises overseas travellers, including people travelling to Lyme disease endemic areas, to kill attached ticks *in situ* by freezing them if an appropriate ether-containing product is available (and without delay), but otherwise follow local guidance, for example, from the CDC.[11] However, if Australian travellers are known to have a tick allergy, they should go to a hospital to have the tick removed. Refer to the *Prevention and management tick bites in Australia* Guidance Note for further information on the Australian-developed technique to remove ticks using ether-containing sprays that freeze attached adult ticks and kill them *in situ.*

The Australian Government Department of Health advice to kill ticks *in situ* without delay is relevant, not only to managing tick bites in Australia, but to the ticks that can transmit Lyme disease in Lyme disease endemic areas as some of these ticks are now recognised to be causative of tick anaphylaxis (*I. pacificus* and *I. ricinus*) and/or are responsible for the development of MMA after tick bite (*I. ricinus*).

See *Tick-induced allergies: tick anaphylaxis and mammalian meat allergy/anaphylaxis, and tick-associated toxicosis and paralysis* Guidance Note for more information.

For advice on how to safely remove a tick by killing the tick *in situ* with ether-containing sprays, see https://www.allergy.org.au/patients/insect-allergy-bites-and-stings. See the DSCATT Clinical Pathway and *Prevention and management of tick bites in Australia* Guidance Note for more advice.

Diagnosis

More information on the diagnosis of Lyme disease in Australia is available in the DSCATT Clinical Pathway (Australian Government Department of Health, 2020a).

Treatment

More in formation on the treatment of Lyme disease is available in the DSCATT Clinical Pathway (Australian Government Department of Health, 2020a).

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11 https://www.cdc.gov/ticks/removing_a_tick.html

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