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Lyme disease: review and update of a potentially emerging zoonosis in South America

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Lyme disease in South America: review and update

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Abstract
Lyme disease is a multisystemic inflammatory disease caused by spirochetes belonging to the geno-specific complex *Borrelia burgdorferi sensu lato* (*Bbsl*). It is transmitted to humans through ticks of the genus *Ixodes*, being *Ixodes scapularis* responsible for the transmission in most of the cases reported worldwide. Manifests with cutaneous, cardiac, neurological, and articular manifestations, with the cutaneous condition known as chronic migratory erythema being the most important antecedent for the clinical diagnosis of the disease, confirming it with complementary tests such as ELISA, Western blot and PCR. This information will be crucial to initiate appropriate treatment for each phase of the disease. Although, this disease is observed mainly in North America and Europe, recently new strains of *Bbsl*, or related species, have been described in Brazil, Uruguay and Chile. Still, in order to determine the distribution of this species in South America, it is necessary to conduct genetic and microbiological studies not only to clinical cases but also vectors and possible reservoirs, in order to obtain useful information for the epidemiological and clinical management of the disease.

Key words: zoonoses, *Ixodes*, Lyme disease, *Borrelia burgdorferi*

Enfermedad de Lyme: revisión y actualización de una potencial zoonosis emergente en Sudamérica

Resumen. La enfermedad de Lyme es una enfermedad inflamatoria multisistémica causada por espiroquetas pertenecientes al complejo genoespecífico *Borrelia burgdorferi sensu lato* (*Bbsl*). Se transmite al ser humano a través de garrapatas del género *Ixodes*, siendo *Ixodes scapularis* la responsable de la transmisión en la mayoría de los casos reportados a nivel mundial. Cursa con manifestaciones cutáneas, cardiacas, neurológicas y articulares, siendo la afección cutánea denominada eritema migratorio crónico el antecedente más importante para el diagnóstico clínico de la enfermedad y para confirmar el diagnóstico los exámenes complementarios utilizados son ELISA, Western blot y PCR. Esta información será fundamental para comenzar con el tratamiento que corresponda a cada fase de la enfermedad. A pesar de que es una enfermedad observada principalmente en norte América y en Europa, recientemente se han descrito nuevas cepas de *Bbsl* o nuevas especies relacionadas en Brasil, Uruguay y Chile. Para poder determinar la distribución de esta especie en Sudamérica, es necesario realizar estudios genéticos y microbiológicos no solo a los casos clínicos, sino también considerar a vectores y posibles reservorios, de tal manera de obtener información útil para el manejo epidemiológico y clínico de la enfermedad.

Palabras clave: zoonosis, *Ixodes*, enfermedad de Lyme, *Borrelia burgdorferi.*

INTRODUCTION

Increased human–animal interfaces impose threats on human life by creating scope for the emergence and resurgence of many infectious diseases (Debnath et al. 2021). Furthermore, alterations in ecosystem conditions promote the appearance or dispersion of new infectious agents, altering the previous balance achieved, favoring untimely proliferation (Monsalve et al. 2009).

Lyme disease was described in 1975, at Lyme town, in the state of Connecticut, United States of America, by reason of an outbreak in local children, which in the first

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instance it was attributed to juvenile *Rheumatoid Arthritis* (Portillo et al. 2014, Applegren and Kraus 2017). However, the presence of this disease in human history dates back to way long before this episode (Soares et al. 2000).

Today, Lyme disease it is known as "the latest great mimic", in consequence to the fact of the broad clinical spectrum that can provoke, except in the case of erythema migrans, which is a pathognomonic sign of the disease. The rest of the clinical manifestations must be confirmed by microbiological and molecular test to have a definitive diagnosis (Vásquez et al. 2015).

Lyme borreliosis or Lyme disease it is a worldwide distributed zoonosis, produced by spirochetes of the complex *Borrelia burgdorferi sensu lato* (*Bbsl*), transmitted by a tick bite of *Ixodes* genus, previously infected from wildlife reservoirs (Applegren and Kraus 2017). This disease is the leading infectious pathology transmitted by vectors in North America and Europe (Summers et al. 2005), with a rising incidence in the past years (Coipan et al. 2013), where it has been observed an evident increase of cases in the United States of America, from 10.000 cases in the year 1991 to more than 25.000 cases in 2014. It has been estimated 200.000 European cases per year, with a high incidence in southern Scandinavia, and in central and eastern Europe (Espí et al. 2016, Lou and Wu 2017). In South America, the recognition and the appearance of disease transmitted by ticks has increased because of the awareness of Lyme disease (Robles et al. 2018). Spirochetes have been detected in blood samples of Brazilians patients with similar clinical signs of Lyme borreliosis, and in patients with erythema migrans (EM). A study made with patients with different skin issues (distinct of Lyme disease) in Brazil, revealed that a 7% of them were ELISA positive, and more than 50% of these patients had a positive Western blot. Between 1992 and 1999, there were six notified cases with Lyme borreliosis, with ME, ELISA serology positive and spirochetes direct detection (Robles et al. 2018), also in Chile in 2018 there was an imported case of Lyme disease (Vásquez et al. 2015).

The purpose of this document is to contribute with updated information with a relevant background of this disease, such as etiological agent, biological cycle, clinical signs, treatment and prevention.

History

Lyme disease was first described in 1975 by the rheumatologist Allen Sterre in consequence of an epidemic outbreak of oligoarthritis at Old Lyme town at Connecticut (Summers et al. 2005, Portillo et al. 2014). Later that year, the entomologist William Burgdorfer suspected, in the first instance, spirochetes where responsible for causing the illness (Burgdorfer 1984).

Since 1990 it started to establish the different clinical presentations of the disease in other continents, beginning with *B. garinni* as responsible for neurological signs in European and Japanese patients (Baranton et al. 1992). Subsequently, in Europe, Rusia and Japan, patients with chronic atrophic acrodermatitis were attributed to *B. afzelii* (Canica et al. 1993). Afterwards, in 1993 was discovered *B. japonica*, which is considered with a low pathogenicity for humans (Kawabata et al. 1993). This strain was labelled as B31, which was the first species described as *B. burgdorferi* sensu stricto (ss), responsible of joint pathologies related in North America and to the other species from the group complex of *Bbsl* (Soares et al. 2000).

Etiology

Spirochetes of the genus *Borrelia* are a causal agent of Lyme disease (Biesiada et al. 2012). Specifically, the genospecies of the complex *B. burgdorferi sensu lato* (Johnson et al. 1984, Portillo et al. 2014), which includes multiple genospecies and it has been described 17 of them worldwide; *B. burgdorferi sensu stricto*, *B. garinii*, *B. afzelli, B. japónica, B. tanukii, B. turdi, B. valaisiana, B. lusitaniae, B. sinica, B. bissettiae, B. californiensis, B. carolinensis, B. spielmanii, B. yangtze, B. americana*, *B. bavariensis*, *B. kurtenbachii*; and there are four more waiting for its confirmation; *B. chilensis* (Ivanova et al. 2014), *B. andersonii, B. finlandensis* and *B. mayonii* (Steere et al. 2004, Cutler et al. 2017). From de previously mentioned, at least it has been demonstrated that five of them are pathogenic to humans, which are; *B. afzelii*, *B. garinii*, *B. burgdoferi* sensu stricto, *B. spielmanii* and *B. bavariensis* (Wormser et al. 2006, Biesiada et al. 2012, Vásquez et al. 2015).

B. burgdorferi is an intriguing and unique bacterium. It is most notorious for being the primary causative agent of Lyme disease in North America (Burgdorfer et al. 1982). Unlike other gram negatives, *B. burgdorferi* has a lipopolysaccharide absence and possess abundant superficial lipoproteins (Motaleb et al. 2000, García et al. 2014). Concerning the *Borrelia* chromosome, it is known that it is relatively small (Agüero et al. 2005, Schutzer et al. 2011), and it does not possess cellular biosynthesis genes, this is why *B. burgdoferi sensu lato* has a limited metabolic capacity (Coipan et al. 2013, García et al. 2014), what explains why is an obligated parasite, which needs a complex ambient with enough conditions for its survival (Marques 2008, Biesiada et al. 2012). The *B. burgdorferi* genome has, at least, 123 genes that encode for lipoproteins for his environment adaption (Baranon et al. 1992, Derdáková and Lenzáková 2005, Schutzer et al. 2011). A and C external superficial proteins (OspA and OpsC) have been well described by their immunogenic role in the spirochete survival in different hosts and the transmission of it through tick bites, allowing it to adapt to the body temperature of the host (Kawabata et al. 1993, Schutzer et al. 2011, Medlock et al. 2013).

Pathogeny and Epidemiology

Through a tick bite of the genus *Ixodes* the *B. burgdorferi* is transmitted to humans, which got infected previously by absorbing blood from a contaminated mammal with the spirochete (Barbour et al. 1983, Lo Re et al. 2004, Applegren et al. 2017). When the tick sucks the blood, the *Borrelia* which is parasitizing the digestive tube and saliva penetrates by micro-wounds to the host previously caused, extrinsically migrating through the skin, inflicting EM lesion (Márquez-Jiménez et al. 2005, Olmo

et al. 2014). After reaching the local lymphatic system, from where they enter the bloodstream, bacteraemia starts after a few hours later, showing a particular tropism to the nervous system (Neuroborreliosis), joints (Lyme arthritis) and heart (Lyme carditis) (Wormser et al. 2006, Jahfari et al. 2017, Patel et al. 2017).

Lyme disease vectors belong to the Ixodida order, Ixodidae family (hard ticks) and *Ixodes* and *Amplyomma* genus (Barbour et al. 1983, Burgdorfer 1984, Márquez-Jiménez et al. 2005, De la Fuente et al. 2008). *Borrelia* spirochete has also been isolated from mosquitos, fleas and flies, but it was established that these insects do not have a role in the disease in humans (Biesiada et al. 2012). The distribution of the *Ixodes* genus is global, and the main responsible of Lyme disease at the east and centre of North America is *I. scapularis; I. ricinus* in Europe and *I. persulcatus* in Asia (Urioste et al. 1994, Lo Re et al. 2004, De la Fuente et al. 2008, Olmo et al. 2014). Other tick species which might be involved in the *Bb*ls transmission is the neotropical tick *I. pararicinus*, distributed in South America in Argentina, Colombia and Uruguay. But also, it is possible to establish in Bolivia, Brasil, Chile and Peru (Robles et al. 2018). Small mammals play an essential role in the transmission and maintenance cycles of *Borrelia* spirochetes. In Chile, recent studies have characterized novel *Borrelia* genotypes in ticks collected from small mammals, a fact that suggests that these vertebrates are hosts for spirochetes from this genus (Thomas 2020). The biological cycle of theses ticks is completed in two years. During this time, they pass through four development stages: egg, six-legged larva, eight-legged nymph and dimorphic eight-legged adult, being the three last stages where they need to feed blood from vertebrates (De la Fuente et al. 2008, Olmo et al. 2014). From the before mentioned, the nymph stage is the most dangerous for humans, for two reasons; first of all, nymphs are small and hard to detect and, the second reason they are more active in summer, coinciding with the highest peak of outdoor activities (Barbour et al. 1983, Burgdorfer 1984, Lo Re et al. 2004). Even if adult ticks have a significant risk to be infected, they are easily detected by their bigger size (García et al. 2014). Accordingly, the most hazardous seasons are Spring at not humid zones, and Summer in humid regions, giving to the nymph a perfect temperature and humidity for their development, being the principal vector of the infection (Olmo et al. 2014).

The most common *Borrelia* that causes the disease in North America is *B. burgdorferi sensu lato, B. garinii* in Europe and *B. afzelii* in Asia (Biesiada et al. 2012, Olmo et al. 2014). In the United States of America, the wild cycle of the spirochete is enzoonotic, the white-footed mouse, *Peromyscus leucopus* (Rafinesque), is a reservoir for the Lyme disease spirochete *Borrelia burgdorferi* sensu stricto (Parise et al. 2020). Besides, *I. scapularis* larvae and nymphs can also feed on birds, such as the common Blackbird (*Turdus merula*) and American robin (*T. migratorius*), while adult ticks prefer other big mammals like cows (*Bos taurus*), and dogs (*Canis lupus familiaris*) (Soares et al. 2000, Little et al. 2010, Smith et al. 2012). Birds are capable of transporting pathogen agents and parasites through their migration routes (Tuemmers et al. 2011). Another critical point is global warming because climate influences in bird migration routes, and being able to be a vehicle for infected ticks; these can be distributed in a different territory and establish in a new genospecies of *B. burgdorferi sensu strict*, which would be an advantage for new vectors and host (Medlock et al. 2013). From 1996 to 2022, cases of Lyme disease in the United States are identified by the United States Centres for Disease Control and Prevention, which have been grouped in the following graph (Figure 1) (CDC, 2024).

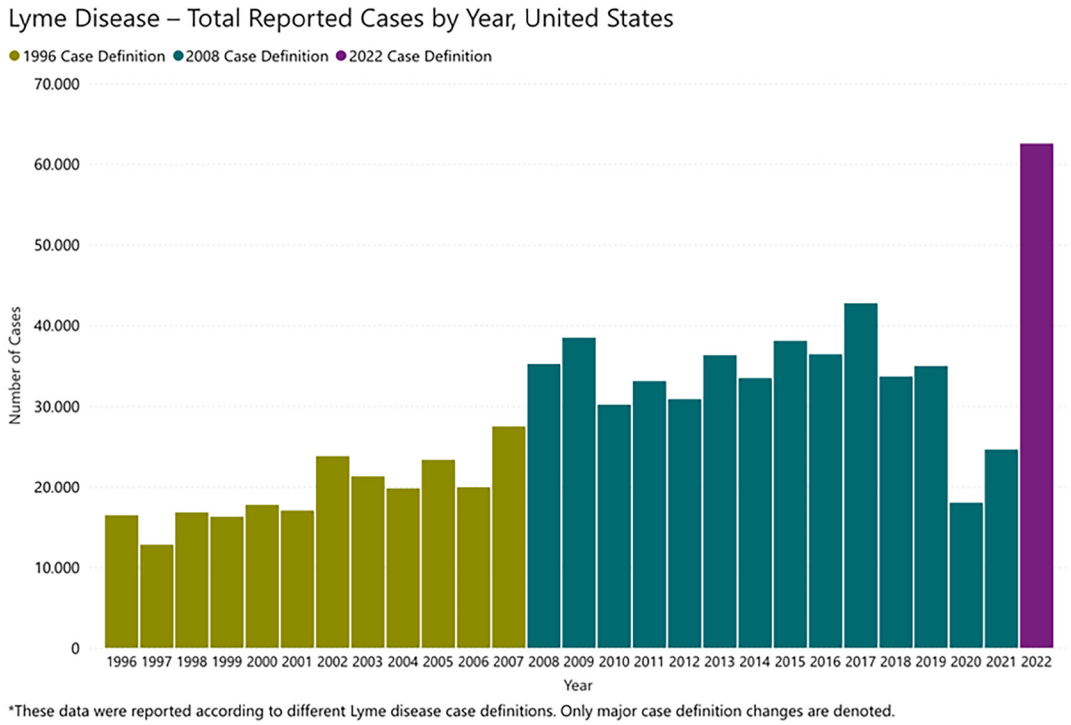

Figure 1. Total reported cases of Lyme disease (Taken from, CDC 2024).

In endemic areas, Lyme borreliosis has been described in domestic animals such as horses (Hahn et al. 1996, Divers 2013, Lou and Wu 2017), cows (Burgess 1988), dogs and cats (Krupka and Straubinger 2010). Herrera et al. (2012), reported that only a 10% of seropositive horses manifested clinical signs, the most frequent ones were claudication, uveitis and lethargy; in cows, the preeminent signs, not having records of seropositive cases, were lameness, fever and depression; and finally, cats (*Felis catus*) were described as the most resistant species to the infection, only recording lameness that remitted with antibiotics treatment, such as amoxicillin.

In South America, Lyme disease has been reported in countries like Brazil, Peru, Bolivia, Uruguay and Chile. A study completed in Brazil evaluated patients with different skin disorders (others than Lyme disease) and 7% of them were ELISA positive to *B. burgdorferi*, and more than 50% were Western-plot positive (Robles et al. 2018). In 1991, the first case reported in Peru was from retrospective serological research of farmers, identifying 2% of the samples positive for antibodies against *B. burgdorferi* (Need and Escamilla 1991). Afterwards, between 1991 and 1992, there were 6 cases notified, with EM, positive ELISA serology with EM and direct detections of spirochetes (Robles et al. 2018). Another study performed in Pirua and Amazon detected antibodies against 10% of a total of 232 samples taken from farmers (Cervantes 2018). It was reported of healthy farmers of Tarija, Bolivia, a minor seroprevalence (3%) (Cervantes 2018). It is vital to highlight that these studies also detected the presence of tick of the genus *Ixodes*, *Amblyomma*, *Phiphicephalus*, *Anocentor* and *Boophilusen* Piura and Amazon, in Bolivia ticks were from the *Dermacentor* genus. A slightly higher figure was seen in a Colombian rural population (4.6%), additionally in Chile was reported an imported case of Lyme disease in 2018 (Villagra et al. 2018).

During 2022 (Mancilla et al. 2022) developed a study that aimed to determine the presence of borrelias in wild mammals in the department of Caldeas, Colombia. The results represent the first molecular evidence of *B. burgdorferi sensu stricto* in South America.

Clinical signs

The clinical aspects of Lyme disease are extensive, affecting multiple organs and systems (Urioste et al. 1994), is very common to find symptoms in skin, joints, heart, and nervous system where it can derive in meningitis, cranial neuropathy and peripheral radiculopathy (Barbour et al. 1983, Wormser et al. 2006). Lyme disease, for clinical purpose, is divided into three stages: early localized disease, early disseminated Lyme and late disseminated Lyme disease. There is a chronic presentation called post-Lyme syndrome (García et al. 2014).

Stage I: Early Localized Disease. It starts at the moment the spirochete is inoculated into the host through the tick bite, which it takes 48 hours approximately. Afterwards, the classic and pathognomonic sign erythema migrans appears at the bite site (Müllegger and Glatz 2008, García et al. 2014, Sunder and Bernard 2015). It usually presents with flu-like symptoms: cough, rhinitis, sinusitis, odynophagia, headache and regional lymphadenopathy (Villagra and Martínez 2018).

The erythema migrans sign is characteristic, which is considered at the definitive diagnosis of Lyme borreliosis (Jahfari et al. 2017). However, it has to be considered differential diagnoses, among them, are Granuloma annulare, fixed pigmented erythema, Morphea, Erysipelas, cellulitis, ringworm and contact dermatitis (Marques 2008, García et al. 2014).

Stage II: Early Disseminated Lyme. The blood dissemination is the second phase of the infection (Sunders and Bernard 2015). The distinctive characteristic of this stage is the systemic affection; the spirochetes spread to the skeletal-muscle system (60%), skin (20-25%), central nervous system (10%) and heart (5%). Patients also present constitutional symptoms: fever, headache, slight stiff neck, general skeletal-muscle pain, arthralgias, and general condition (García et al. 2014).

Stage III: Late Disseminated Lyme Disease. The most frequent signs at this point are rheumatologic. The patient has asymmetric inflammatory arthritis, affecting one or a few joints, called Lyme arthritis (Vásquez et al. 2015). In this stage, the disease can also manifest neuroborreliosis, affecting the peripheric (PNS) and central nervous system (CNS) (Fernández 2012).

Post-Lyme Syndrome or chronic infection: Unspecific symptoms are seen in this stage, such as headaches, fatigue and arthralgias, that can persist months after treatment (Marques 2008, Olmo et al. 2014). However, there is a Lyme disease syndrome, where a sub-group of people suffer persistent signs for six months or more, known as Chronic Lyme disease (Crowder et al. 2014). Approximately 10% of patients experience prolonged symptoms (asthenia, diffuse pain, cognitive problems, etc.), after Lyme disease (DeLong et al. 2019).

Diagnosis

Lyme disease is easy to diagnose if there is a history of tick bites, if you are in an endemic area and the characteristic sign called EM. Otherwise, this pathology can be confused with other diseases, such as fibromyalgia, chronic fatigue syndrome or multiple sclerosis. That is why it is essential to perform a molecular and microbiological test to confirm (Müllegger and Glatz 2008, Olmo et al. 2014).

There are two tests used for diagnostic confirmation: Enzyme-Linked ImmunoSorbent Assay (ELISA) and Western Blot. When there is a suspicious patient, the first tests made is the ELISA test, then to confirm it is done the Western Blot test (Norman et al. 1996, Biesiada et al. 2012). But because it takes some people weeks to produce enough antibodies against the spirochetes, there are cases of false negatives (Müllegger and Glatz 2008, Sunder and Bernard 2015). The Polymerase Chain Reaction (PCR) is a direct diagnosis method, detecting the bacteria genome, by a cutaneous biopsy of the EM, with a 60-70% of sensitivity, while a 76% in chronic atrophic acrodermatitis. The sensitivity in the synovial liquid is 60-82%. In cerebrospinal fluid, the sensitivity is notoriously lower (40%), and only 15% in plasma (Sunder and Bernard 2015).

The lack of sensitive and specific diagnostic tests makes the management of Lyme disease challenging (Bahadori et al. 2023).

Treatment

ß-lactams belonging to the penicillin class of antimicrobial agents, such as penicillin, amoxicillin, and III generation cephalosporins such as ceftriaxone, have been shown to be highly active against B. burgdorferi s.l. in vitro. They are also clinically efficacious and, thus, regarded as agents of choice when it comes to the treatment of LB (Hunfeld et al, 2023).

Depending on the stage of the disease and clinical signs, as the type and physiological state of the patient, it is decided what medication is used in each case (Müllegger and Glatz 2008, Krupka and Straubinger 2010).

Prevention

The best way to prevent a *B. burgdorferi s.s.* infection is to avoid tick-infested areas. However, if you need to be exposed due to walking, sports, or work, it is recommended to continually inspect the skin, wear long-sleeve shirts tucked into pants, and ideally tuck the pants into socks (Wormser et al. 2006). This allows time to locate any ticks. If a tick is attached to the skin, it should be removed entirely as soon as possible with fine tweezers, before it transmits the spirochete (Krupka and Straubinger 2010).

The Latin American context

Epidemiology of Lyme disease is still emerging and varies across different countries due to ecological, climatic, and geographical factors. Different species of *Ixodes* ticks are found in various regions of Latin America. While *I. scapularis* is absent, species such as *I. parariciunus* (Figure 3 B), *I. loricatus* (Figure 2), and *I. aragaoi* (Figure 3 A) have been considered potential tick vectors for *B. burgdorferi* in countries like Argentina and Brazil (Lucca 2024).

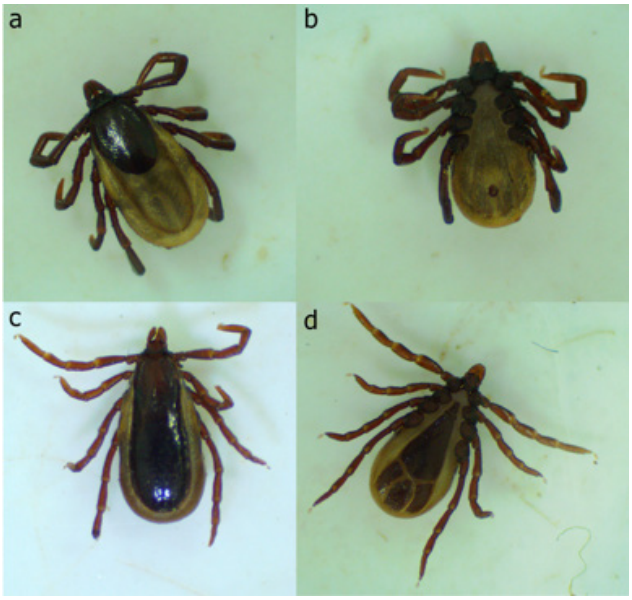

Figure 2. *Ixodes loricatus* adults collected on *Didelphis aurita* opossums (Bezerra-Santos 2021).

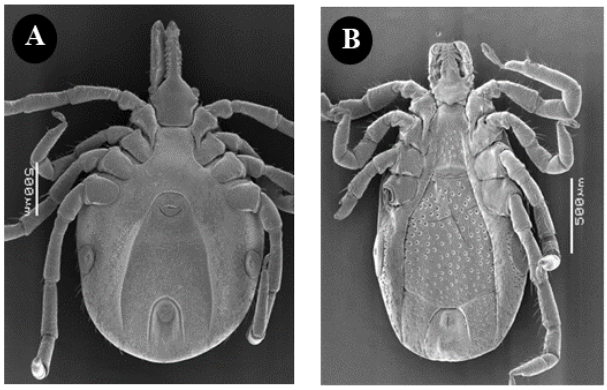

Figure 3. A: Ventral view of males of *Ixodes aragaoi.* B: Ventral view of female of *Ixodes parariciunus* (Saracho-Bottero 2020).

In Argentina, several tick species have been identified, and their potential involvement in the transmission of *B. burgdorferi* has been a topic of investigation. In Argentina, the tick species that could transmit this disease include: *I. scapularis, I. pacificus, I. ricinus complex, I. parariciunus, I. loricatus, I. aragaoi, A. cajennense* and *Rhipicephalus sanguineus* (Lucca 2024). In Uruguay, there are four *Ixodes* species currently identified: *I. auritulus*, *I. longiscutatus, I. loricatus* and *I. aragaoi* (Nava et al. 2017).

In the southern cone of South America different haplotypes of *Bbsl* have been detected in *Ixodes* spp. from Argentina, southern Brazil, Chile, and Uruguay (Carvalho 2019). In Chile, Argentina and Brazil, *Bbsl* have been detected infecting *Ixodes* species that are not members of the *I. ricinus* complex. In Chile, *B. chilensis* was described in association with *I. stilesi* and *Borrelia* sp. (Carvalho 2019).

In studies conducted in Argentina and Latin America, it becomes evident that there are high probabilities of Lyme disease being present in this region. Furthermore, birds may play a role in distributing or disseminating this microorganism, transcending geographical barriers and distances, potentially contributing to the emergence of Lyme disease and other borrelioses in various countries (Lucca 2024). In the same line of the importance of the birds 'role, Carvalho in 2019 aimed his study to determine the presence of *Bbsl* in *I. auritulus* ticks collected from birds and vegetation in two localities of southeastern Uruguay, in which she found 306 specimens of *I. auritulus* from 392 passerine birds sampled. In the case of ticks, humans are always accidental hosts (Sala 2016). Ticks are particularly interesting organisms because of the evolution of their host range and of the consequences in the epidemiological spread of disease. The infection of ticks originates from animals which act as reservoirs (Sala 2016).

In 2017, an article was published on the identification and classification of ticks present in the wildlife of southern Chile, specifically in the pudu deer, with the aim of identifying two species of *Ixodes* and their relationship with borrelial bacteria. This study showed that a total of 179 ticks were collected from 36 of the 66 examined deer. Two *Ixodes* species were identified based on morphological features and confirmed with molecular data: *I. stilesi* (n = 167) and *I. taglei* (n = 12). The prevalence of *I. stilesi* on the deer was 47% (31/66, C.I. = 34.6 - 59.7%) whereas for *I. taglei* it was 7.6% (5/66, C.I. = 2.5 - 16.8%). No animal

carried both tick species (Verdugo, 2017), While in northern Chile, Thomas (2020) aimed his study to determine the presence of Borrelia DNA in small mammals that inhabit northern Chile. In winter of 2018, 58 small mammals were captured in five localities. Blood samples were collected from rodents and DNA was extracted to determine the presence of *Borrelia* DNA by PCR targeting the flaB gene and rrs–rrlA intergenic spacer (IGS). From three individuals (5%), belonging to two rodent species of Cricetidae family (*Phyllotis xanthopygus* and *Oligoryzomys longicaudatus*), were retrieved three flaB and two IGS *Borrelia* genotypes. Their results showed that rodents may play a role as reservoirs for borrelial spirochetes in Chile.

CONCLUSIONS

As new investigations of Lyme disease progress, new competent host-reservoirs for the spirochete have been described, indicating its adaptability to new geographic zones, such as South America. This region harbors possible vectors and members of the *B. burgdorferi sensu lato* genospecies complex, such as *B. chilensis*. Although *B. chilensis* is not considered pathogenic for humans, it opens new research hypotheses regarding the presence of autochthonous strains in South America. The articles in this review highlight the need for more studies involving arthropods and vertebrates to understand the current status of *Borrelia* spp. circulation in South American countries. Finally, it is important for health professionals and veterinarians to recognize the clinical signs in humans and animals that could lead to a Lyme disease diagnosis, thereby reducing the risk of contracting this zoonosis.

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