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Bacterial canine vector-borne zoonotic diseases in "One Health" concept

George Valiakos

Department of Microbiology and Parasitology, Faculty of Veterinary Medicine, University of Thessaly, Trikalon 224, Karditsa, Greece.
Corresponding author: George Valiakos, e-mail: georgevaliakos@gmail.com
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Abstract

Canine vector-borne diseases constitute a large group of diseases transmitted by arthropods with worldwide distribution. A wide range of bacterial, viral, and parasitic agents that are transmitted by vectors cause disease to dogs, many of which can also affect humans and thus have an important zoonotic potential. Bacterial agents that are transmitted by vectors have been considered less important than viral or parasitic agents and are not commonly discussed in companion animal practice. However, close contact between pet animals and people offers favorable conditions for transmission of these bacteria. Many of these diseases have become a focus of interest for scientists in recent years. Increase in reservoir abundance, climate change, changing habitat structure, socio-political changes, and imports of dogs for welfare reasons and trade as well as traveling are considered to be potential factors for the pathogens and vectors introduction into new areas. Apart from, the veterinary aspect of these diseases, domestic dogs could play a central epidemiological role in the transmission of bacterial agents to humans, acting as reservoirs and sentinels, a circumstance that requires a One Health approach. This review highlights the most important of these bacterial agents, presenting updated current knowledge with special reference to treatment approach and One Health aspect.

Keywords: bacteria, canine, One Health, vectors, zoonoses.

Introduction

In the "One Health" approach of dealing with infectious diseases, it is of the utmost importance to organize a multidisciplinary cooperation between veterinary and human medicine practitioners working together for promoting animal and human health. Regarding the potential role of pet animals, and especially the dog, in the One Health approach, it is probably the most underrated, in comparison to the role given to livestock and wild animals. In developed countries, pet ownership plays an important role in family life. In 2012, there were approximately 70 million pet dogs and 74.1 million pet cats in the U.S. [1]. The dogs and cats population exceeds 180 million in the European countries [2].

Canine vector-borne diseases comprise a large group of diseases transmitted by arthropods with worldwide distribution. A wide range of bacterial, viral, and protozoal agents are causing diseases to dogs, many of which can also affect humans and thus have a zoonotic potential [3]. Interesting examples of such infections are viral, e.g., *West Nile Fever*, and tick-borne encephalitis. Regarding parasitic diseases and One Health, there are various important examples that are discussed, e.g., visceral leishmaniasis caused by *Leishmania infantum* for which dogs are the major reservoir hosts [4]. On the other hand, bacterial agents are considered less important and are not discussed in companion animal practice in a similar extent. This review will try to highlight the most important of these bacterial agents as referred in Table-1, presenting updated current knowledge with special reference to treatment approach and One Health aspect.

Order *Rickettsiales*: Ehrlichiosis, Anaplasmosis, and Rickettsiosis

Taxonomy today classifies the order *Rickettsiales* into two families, the Anaplasmataceae (includes four genera: *Anaplasma*, *Ehrlichia*, *Neorickettsia*, and *Wolbachia*) and the Rickettsiaceae (includes two genera: *Rickettsia* and *Orientia*). Genera *Anaplasma*, *Ehrlichia,* and *Rickettsia* are the ones with pathogenic members of interest.

Ehrlichiosis

Canine Ehrlichiosis is caused by *Ehrlichia canis,* and to lesser extend *Ehrlichia chaffeensis* and *Ehrlichia ewiingi*. The agents are transmitted to the host through the ticks and target blood cells. The diseases are often named based on the infected cell type: *E. canis* infects monocytes, and the disease is called canine monocytic ehrlichiosis (CME) [5]. *E. ewiingi* infects primarily neutrophils and eosinophils, and the disease is called canine granulocytic ehrlichiosis and human granulocytic ehrlichiosis. *E. chaffeensis* infects monocytes and macrophages, causing human monocytic ehrlichiosis. Recently, it has been reported that *Ehrlichia ruminantium* and *Ehrlichia muris* are also able to cause disease in dogs and humans [6,7].

Table-1: Canine bacterial vector-borne zoonotic diseases. The bacterial agents of each disease are listed.

Disease	Species
Lyme disase	*B. burgdorferi sensu lato* complex
Tick-borne relapsing fever	*Borrelia* relapsing fever species
Bartonellosis	*Bartonella* spp. (mainly *B. henselae*)
Ehrlichiosis	*E. canis, E. chaffeensis, E. ewingii*
Anaplasmosis	*A. phagocytophilum, A. platys*
Rickettsiosis	*R. rickettsia, R. conorii, R. felis, R. typhi*
Q fever	*Coxiella burnetii*

B. burgdorferi sensu lato = Borrelia burgdorferi sensu lato, *E. canis = Ehrlichia canis*, *E. chaffeensis = Ehrlichia chaffeensis*, *E. ewingii = Ehrlichia ewingii*, *A. phagocytophilum = Anaplasma phagocytophilum*, *A. platys = Anaplasma platys*, *R. rickettsia = Rickettsia rickettsia*, *R. conorii = Rickettsia conorii*, *R. felis = Rickettsia felis*, *R. typhi = Rickettsia typhi*

The disease in humans

Ehrlichiosis in humans is considered a rare disease; however, recently, *E. canis* human infection was reported from Venezuela. Six patients were reported to be *E. canis* polymerase chain reaction (PCR)-positive during 2002 at the Central Hospital in Barquisimeto, Lara State, Venezuela. Patients had fever of 2-6 days of duration; five of them had headache and/or myalgia, malaise, nausea, vomiting, and diarrhea, rash, arthralgia, bone pain, and/or abdominal pain. It is important to note that three of them were dog owners and two of them worked in rural areas [8].

Human infections caused by *E. chaffeensis* are reported in the United States, most cases occurring from April through September. In Europe, infections have been confirmed by numerous seroepidemiological studies in Italy [9], Czech Republic [10], Portugal [11], Croatia [12], and Serbia [13]. *E. chaffeensis* causes a potentially severe disease in humans; fever, lethargy, headache, myalgia, reduced platelets and sodium levels and elevated liver enzymes characterize acute infections, resulting in moderate to severe illness. Mortality rates can be as high as 3% [14].

Disease caused by *Ehrlichia ewingii* has been reported in a few human cases, mainly immune-suppressed people, with febrile mild to moderate clinical signs [15]. Abnormal liver function tests, leukopenia, and thrombocytopenia were the reported findings.

The disease in dogs

CME is a globally distributed, potentially fatal tick-borne disease caused by *E. canis*, principally transmitted by nymphs and adults of *Rhipicephalus sanguineus sensu lato* [16]. CME is a disease causing multisystemic disorder that can be acute, subclinical, or chronic in dogs. Symptoms of this disease include fever, lethargy, anorexia, weight loss, bleeding disorders, and lymphadenomegaly. The clinicopathological findings include anemia, leukopenia, thrombocytopenia, hypoalbuminemia, and hyperglobulinemia [17]. Coinfections with other tick-borne pathogens may influence clinical signs and laboratory test findings, thereby complicating diagnosis. CME has a worldwide distribution including Europe, America, Asia, and Africa [18]. *E. canis* was reported in *Rhipicephalus turanicus, Dermacentor marginatus* (nymphs) naturally and in *Dermacentor variabilis* experimentally as well [19,20].

Canine infections of *E. chaffeensis* are subclinical or mild [21]. *E. chaffeensis* is transmitted by *Amblyomma americanum* ticks in America, while there have been no confirmed cases of *E. chaffeensis*-infected ticks and dogs in Europe [22].

The most important reservoir host of *E. ewingii* has not been determined, but both dogs and deer are considered prime candidates [23]. The most important vector of *E. ewingii* in the U.S. is *A. americanum* but it has also been detected in *D. variabilis* and *R. sanguineus* [21,24]. Granulocytic ehrlichiosis caused by *E. ewingii* is a more common in dogs and humans in the southern USA, where *A. americanum* populations are high and feed on both hosts [21]. *E. ewingii* has been found in other countries of the world as well [25,26] but not in Europe.

Treatment in dogs

Ehrlichia spp. (as well as *Anaplasma* spp.) infections are being treated with members of the tetracycline family and especially doxycycline [22]. For CME, the treatment of choice is based in daily administration of doxycycline for 1 month. This treatment will lead to a complete response in most clinical cases [27].

One Health

All forms of ehrlichioses were considered to only infect animals, a few decades ago. Today, *E. canis, E. chaffeensis,* and *E. ewingii* are all known to cause human ehrlichiosis. However, there is no evidence of tick-borne transmission of the pathogens from dogs to humans; thus, the dogs have not been established as a reservoir for human disease.

Anaplasmosis

The best-known *Anaplasma* species is *Anaplasma phagocytophilum* and *Anaplasma platys*. *A. phagocytophilum* infects granulocytes (neutrophils and eosinophils) of humans and dogs and the caused disease is therefore called human or canine granulocytic anaplasmosis [28]. *Anaplasma platys* infects platelets and causes canine cyclic thrombocytopenia (CCT) [29]. *Anaplasma* spp. had so far been reported in dogs and ticks in Europe and all over the world [30-32].

The disease in humans

Fever, lethargy, headache, myalgia, reduced platelets, and elevated liver function enzymes characterize *Ixodes* transmitted *A. phagocytophilum* infection. Morbidity rate is low (<1%) and usually in association with other opportunistic infections [33].

The ability of *A. platys* to infect humans has been questioned; however, recently, *A. platys* DNA was PCR amplified from blood samples collected from a veterinarian [34] and two women from Venezuela [35].

In the last case, it was proved that both patients were exposed to *R. sanguineus*, the presumed tick vector, and experienced chronic, nonspecific clinical signs like headaches and muscle pains.

The disease in dogs

Following tick transmission, dogs can remain infected with *A. phagocytophilum* and *A. platys,* for months to years, before the elimination of the infection from immunological or treatment response or the development of chronic debilitating disease manifestations [36,37].

Disease caused by infection with *A. phagocytophilum* in dogs is characterized by acute onset of fever, anorexia, depression, lameness, myalgia, and reduced platelets [38]. *Ixodes ricinus* is the common vector of *A. phagocytophilum* in dogs and widely spreads in most European countries [22,39], while in North America, *Ixodes scapularis* and *Ixodes pacificus* in dogs are considered the most important vectors. Rodents are considered the primary reservoir hosts, although various mammal species may play a supplementary role as a source of infected ticks [40].

A. platys has been diagnosed in dogs causing CCT, an infectious disease considered to be a worldwide dog health problem. The main clinically observable symptoms of this disease are depression, fever, and anorexia, but asymptomatic infections may occur [41]. *A. platys* had been detected more often in *R. sanguineus* which was presumed to be the potential vector of it [42]. Recently, *A. platys* was found in *R. turanicus* and *Dendrobates auratus*, as well [19,43]. Regarding the geographic distribution of *A. platys*, molecular detection of *A. platys* in dogs was reported in countries in different continents including America [44,45], Europe [46], Asia [47], Oceania [48], and Africa [31].

Treatment in dogs

Doxycycline for 2-3 weeks for treating *A. phagocytophilum* infections and for 8-10 days for *A. platys* infections at dosage similar to the ones used for *E. canis* treatment is considered to be effective. Rifampin and levofloxacin are also effective *in vitro* against *A. phagocytophilum,* while in young dogs, chloramphenicol has been proposed as an alternative [49].

One Health

Dogs are natural hosts for *A. platys* but are considered opportunistic hosts for other *Anaplasma* spp. [50,51]. Dogs may play an epidemiological role in human infections as hosts of infected ticks, and owners may be exposed to the pathogens while removing infected ticks from their companion animals. The prevention of anaplasmosis infections in dogs must be based on tick control.

Rickettsiosis

The genus *Rickettsia* includes various bacterial species causing human and/or canine disease, including those in the spotted fever group and in the typhus group.

The disease in humans

Rocky Mountain spotted fever (RMSF) is the most common rickettsial disease in America, caused by *Rickettsia rickettsii* which is transmitted by *R. sanguineus*, *Dermacentor andersoni*, *Dermacentor variablis,* and *Amblyomma cajennese*. In Brazil, this disease has been called Brazilian spotted fever (BSF) with *A. cajennese* S.L. implicated as the major species responsible for BSF, followed by *Amblyomma aureolatum* [52]. Fever, headache, petechial rash, hyponatremia, and thrombocytopenia are the prominent clinical findings of this disease [53].

Rickettsia parkeri is an emerging tick-borne rickettsiosis agent in the America. During 2012-2014, five cases of *R. parkeri* rickettsiosis were identified by a single urgent care practice in Georgia. Erythema, swelling at the site of bite as well as fever, lymphadenopathy without fever, myalgia, fatigue, and headache are the symptoms reported [54].

Mediterranean spotted fever (MSF) caused by *Rickettsia conorii*, which is transmitted by *R. sanguineus*, is of greatest concern in Europe, Africa, and Asia. *R. conorii* was first described in 1910 from human patients in Tunis [55]. The main vector for *R. conorii* is *R. sanguineus* while other Ixodidae ticks as *I. ricinus* [56] and *Dermacentor* spp. have been described for Europe, and *Haemaphysalis leachi* or *Amblyomma hebraeum* for other endemic regions out-side Europe [57]. *R. sanguineus* is known for its low host preference for humans but it is the only tick species recorded from patients with lethal *R. conorii* infections [58]. Before this case and an outbreak reported from Portugal [59], *R. conorii* infection was considered to be less severe than *R. rickettsii* infection in North America. Mortality rates were as high as 32% in Portugal while the mortality of RMSF is 20% for untreated and 5% for patients under antibiotic therapy [60].

Rickettsia massiliae was recently recognized serologically in two patients presenting spotted fever disease in Romania [61]. The pathogen was also molecularly recognized in samples from clinically suspected patients to have rickettsial infection, in Tunisia [62].

Rickettsia felis is the causative agent of flea-borne spotted fever (FBSF) rickettsiosis in humans. A dog owner couple from Dusseldorf, Germany was diagnosed with classical symptoms and *R. felis* was identified as the causative agent by PCR, in 2000, being the first human case report in Europe [63]. It seems that clinical findings depend on the region of infection and include fever in patients from the tropics or fever associated with cutaneous manifestations in patients from Europe or America. Recently, FBSF infection was attributed in nine patients' sera found reactive to *R. felis*, in Australia [64].

Rickettsia typhi is the causative agent of murine typhus (MT) [65]. This disease is widely distributed through the world being one of the most prevalent rickettsial infections, and endemic in many coastal areas. MT is usually acute and mild but could cause severe illness and even death in some cases. The percentage of organ-specific complications (pneumonia, hepatitis, meningoencephalitis, and renal failure) does not usually exceed 10%, and severe cases are only around 2-4%, while mortality of MT ranges from 0% to 1%.

The disease in dogs

Dogs are susceptible to infection and clinical cases of RMSF, sometimes fatal, have been described [66,67]. Dogs may serve as sentinels of risk for RMSF in humans due to their susceptibility to *R. rickettsii* and high rates of tick exposure [68]. Dogs have been characterized as human rickettsiosis sentinels in various Latin American countries, by sharing the same tick species infesting humans and dogs [69,70].

There are only limited reports on canine clinical infection with *R. conorii*, i.e., an acute febrile infection of a 3-year-old Yorkshire terrier in Italy [71]. *R. sanguineus* is the predominant vector for *R. conorii* in Europe and North Africa. Despite earlier reports, recent studies indicate the dog, and not *R. sanguineus,* as the reservoir [72], and recent studies demonstrated lethal effects of *R. conorii* infections in ticks.

Concurrent *R. felis* infections in a dog and its owners were recently reported in a study from Spain [73]. The dog was afebrile but symptomatic (fatigue, vomiting, and diarrhea). Owners reported they had been bitten by fleas and dog was parasitized by fleas. *R. felis* has been detected molecularly in *Ctenocephalides felis* in more than 40 countries worldwide [74]. It has also been identified in more than 20 different hematophagous species (fleas, mosquitoes, soft and hard ticks, and mites) worldwide [75]. This evidence highlights the fact that *R. felis* is capable of infecting multiple hosts and vectors, something not common for Rickettsiae; in most cases, Rickettsiae is restricted to one or two vectors. The cat flea has been thought to be the only arthropod associated with biological transmission of *R. felis* despite the fact that the pathogen has been detected in various arthropods [76]. Cat flea, despite its name, is the major flea identified in dogs as well [77]. The latest studies from Australia point toward the dog as a reservoir for *R. felis* [78]. From a total of 100 pound dog blood samples examined by PCR, nine of the pound dogs were positive for *R. felis* DNA suggesting that dogs may act as a reservoir host for *R. felis* and a potential source of human rickettsial infection.

In a recent study in Spain, serological and molecular evidence of exposure of dogs to *R. typhi* were reported [79]. Dogs can be infected with the cat flea *C. felis*, which is described as a vector of *R. typhi*, and thus play a role in human infection. It appears though that *R. typhi* does not produce disease in dogs like it does in humans.

Treatment in dogs

The drug of choice for treating RMSF in dogs, as in humans, is doxycycline with the recommended treatment duration being from 7 to 21 days depending on the dosage [80] regardless of the dog age. The treatment with doxycycline leads to quick subsidence of fever and complete recovery with no expected sequelae or relapses. In a case of *R. felis* infection in Spain [73], the dog received terramycine and it quickly recovered.

One Health

Most patients infected with *R. felis* had contact with dogs [73,81,82] and some with cats [81,83], without reporting a history of flea exposure. However, some patients did not recall contact with animals or outdoor activities [84]. A tick bite [84,85] and being bitten by insects, including mosquitoes [86], were also mentioned.

Even though it is accepted that dogs become rickettsiaemic once infected with *R. conorii*, it is still unknown if this infection is sufficient to infect feeding ticks. Dogs are probably not capable of transmitting *R. conorii* directly but can function as sentinels for the presence of MSF [87]. Various scenarios have been proposed regarding the role of dogs in MSF epidemiology. For ticks with high host specificity, such as *R. sanguineus,* the dog functions as the predominant host species. In this scenario, *R. conorii* gets established within the tick population with an increasing risk of human infection while occasionally infested with *R. sanguineus*. *R. massiliae* has been also recently detected in *R. sanguineus* collected from dogs in Algeria [88], thus being able to be as well established within the tick population. Dogs could function as sentinels for the infection to humans when tick species with low host specificity like *I. ricinus* are involved. Finally, humans can be exposed to ticks (damaged parts and tick blood) containing rickettsia, following grooming and contamination of the dog's coat.

Lyme disease

Lyme borreliosis is a tick-transmitted inflammatory disease induced by spirochetes. The disease is named after the town of Lyme in Connecticut, USA, where a group of children with an unusual arthritic condition was studied. The causal agent was identified by Willie Burgdorfer as a spirochetal bacterium and named after him as *Borrelia burgdorferi* [89].

The disease in humans

Lyme disease is a significant human disease in endemic areas: Approximately, 85,000 cases are being reported annually in Europe and 300,000 cases in the USA; it is the most common tick-borne disease in the

northern hemisphere. Lyme disease is multisystemic affecting many organs (heart, central nervous system, and joints) and resulting in a variety of symptoms (flu-like symptoms, fatigue, peripheral neuropathy, arthritis, and cognitive dysfunction). Early localized infection results in a characteristic erythema migrans rash, after which spirochaetes can disseminate to various organs.

The *B. burgdorferi sensu lato* complex currently comprises at least 19 genospecies [90], with the 20th and 21st member been proposed recently, *Borrelia chilensis* [91], and *Borrelia mayonii* [92]; 10 members have been isolated from human patients. However, only three are being considered important human pathogens, *B. burgdorferi sensu stricto* in the USA and Europe, *Borrelia afzelii* and *Borrelia garinii* in Europe and Asia [93,94]. *B. burgdorferi sensu stricto* is often associated with arthritis, *B. afzelii* with acrodermatitis chronicum atrophicans and *B. garinii* with neurological disorders. Potential pathogenic *Borrelia* species include *Borrelia bavariensis*, *Borrelia bissettii*, *Borrelia kurtenbachii*, *Borrelia spielmanii*, *Borrelia lusitaniae*, *Borrelia Valaisiana,* and *Borrelia mayonii* [90,92]. Hard-bodied ticks of the genus *Ixodes* may transfer disease-causing spirochetes from reservoir host mammals to humans.

The disease in dogs

Based on current information, pathogenicity in dogs has been demonstrated for *B. burgdorferi sensu stricto* [95,96]. However, there have been some single cases of dogs infected with *B. garinii* and *B. afzelii* [97]. Approximately, 5% of dogs develop clinical signs of Lyme disease when exposed to *B. burgdorferi*. Lyme borreliosis in dogs is divided into an early and a late stage. The most common clinical signs of early lyme disease are lameness, fever, anorexia, lethargy, arthralgia, lymphadenopathy, and generalized pain. During the early stage, the spirochetes are susceptible to antibiotics and treatment can be effective. If left untreated, the organisms can take residence in areas not accessible to immune response or antibiotics; neurological, renal, cardiac disease, and arthritis are potential clinical signs of the late-stage disease [98]. In an experimental infection of five dogs, only one dog exhibited lameness, the predominant clinical sign for canine Lyme disease while all five seroconverted [99].

Several studies have been performed to estimate the prevalence of the pathogen or the humoral immune response in dogs in various countries: In Poland, 98 blood samples from a veterinary clinic were examined by PCR; 16 samples were positive for *B. burgdorferi sensu stricto* [100]. A serological survey on healthy military dogs was performed by Pejchalova, Zakovska [101] in the Czech Republic. In total, 399 samples were examined and 26 dogs (6.5%) were found positive for antibodies against *B. burgdorferi sensu lato*. Regarding Western Europe, a seroprevalence of 11.6% was reported by Merino, Serrano [102] in Spain. In France, in a large serological survey including 919 dog samples, a seroprevalence of 1.09% for *B. burgdorferi* was reported by Pantchev, Schaper [103]. The largest European serological investigation on the prevalence of *B. burgdorferi* was performed in Germany by Krupka, Pantchev [104], using immunochromatographic rapid test. Serum samples of 3005 dogs of a randomly selected dog population were investigated, as well as 2876 samples from dogs with a case history, to define the presence of antibodies against *B. burdgorferi*. The prevalence in dogs with a case history was significantly higher (11.8%), than the randomly selected dog group (7.7%).

Treatment in dogs

Until nowadays, optimal treatment procedure of Lyme disease in dogs is unknown. Opinions vary greatly on how to treat dogs but also on whether or not treat seropositive asymptomatic dogs. The currently recommended antibiotic treatments of Lyme disease require daily oral administrations of doxycycline or amoxicillin for a minimum of 1 month, making non-compliance a concern. However, recently two injections of cefovecin 2 weeks apart were efficacious against *B. burgdorferi sensu stricto* infection as demonstrated by serological testing, PCR and histopathology results [105].

One Health

Infected dogs provide a way by which infected ticks are transferred into the domestic environment. During removal of ticks from a pet animal, tick salivary gland material may be exposed to wounds on the owner's hands. Dogs are often more exposed to ticks than humans are, and seropositive dogs are typically detected sooner and in higher numbers than human Lyme disease cases in emerging high-risk areas. Dogs may therefore be sentinels for early identification of high-risk areas, allowing prompt implementation of preventive measures to protect public health. Veterinarians can, therefore, play an important public health role in raising Lyme disease risk awareness [106].

Relapsing fever

Relapsing fever is an arthropod-borne infection spread by lice and ticks. It is caused by a second group of several *Borrelia* relapsing fever species.

The disease in humans

The disease is characterized by two or more episodes of high fever (usually >39°C), headache, myalgias, arthralgias, nausea, and vomiting [107]. Jaundice, hepatosplenomegaly and myocarditis may also occur in a later stage. The initial febrile episode has duration of 3-6 days and is followed by an afebrile period of 4-14 day, after which fever and symptoms recur, along with high spirochetemia. Subsequent relapses are usually less severe and can follow at 1- to 2-week intervals. Two main forms of this infection

exist: Louse-borne relapsing fever (LBRF) and tick-borne relapsing fever (TBRF).

LBRF is caused by *Borrelia recurrentis* and transmitted from human to human via the human body louse *Pediculus humanus humanus*, which is linked to areas of overcrowding, war, and destitution [108]. Several cases in refugees from the Horn of Africa have been recently diagnosed in European countries [109]. Animal companions do not play any role in its transmission.

On the other hand, TBRF is caused by 10 or more *Borrelia* species (e.g., *Borrelia hermsii, Borrelia turicatae*, *Borrelia parkeri, Borrelia dittoing, Borrelia crocidurae, Borrelia coriaceae*, *Borrelia duttoni*, *B. hermsii, Borrelia hispanica*, and *Borrelia persica*) commonly transmitted to humans through the bite of infected soft ticks of the genus *Ornithodoros*. *Ornithodoros* ticks can live for many years between blood meals, harbor spirochaetes for prolonged periods and can transmit the pathogen vertically to offspring. *Borrelia miyamotoi* is an exception to the rule, as it is transmitted by the same *I. ricinus-persulcatus* species complex which also transmits *B. burgdorferi sensu lato* [110]. TBRF is a disease less studied than Lyme disease but found throughout Middle East, Africa, Europe and North and South America.

The disease in dogs

Disease in domestic animals due to relapsing fever *Borreliae* was rarely described; borreliosis with two species of relapsing fever *Borreliae*, *B. turicatae*, and *B. hermsii* has been reported to cause disease in dogs in the U.S. [111,112]. Dogs with *B. turicatae* and *B. hermsii* infection were febrile, lethargic, anorectic, anemic and thrombocytopenic. *B. persica* infection with similar symptoms has recently been reported in a young spirochetemic puppy from Iran [113] as well as a series of dogs and cats in Israel [114].

Treatment in dogs

The common treatment for human TBRF is with doxycycline [115] although treatment with amoxicillin has also been recommended [116]. Doxycycline is also considered to be the drug of choice for post-exposure prevention [117]. Based on human treatment and prophylaxis recommendations, it is also sensible to recommend doxycycline as the antibiotic of choice for canine TBRF infection. The use of doxycycline in reported cases was proven to be efficient [114].

One Health

It is obvious that reports of relapsing fever borreliosis in dogs is rare, while at the same time genetic analyses have shown that these pathogens are identical to the ones causing the disease to humans. Hence, the infection and disease might be considered a zoonosis, however, the roles of animals or humans in the transmission cycle of the pathogen needs further investigation. Of special interest is *B. miyamotoi*, which has only recently been identified as a human pathogen causing relapsing fever and little is known about its local impact on human health; transmission by *Ixodes* species may further implicate companion animals in its natural cycle, for which little information is still available [118].

Bartonellosis

Bartonella spp. is Gram-negative bacteria belonging to the family Bartonellaceae and is vector transmitted. Invasion of erythrocytes is a characteristic feature of the pathogenicity of these bacteria. Important diseases caused by *Bartonella* species in humans are Carrion's disease, caused by *Bartonella bacilliformis*, trench fever, a louse-borne disease caused by *Bartonella quintana* and the cat-scratch disease (CSD) mainly caused by *Bartonella henselae* with the domestic cat as the natural reservoir. The number of *Bartonella* species identified as zoonotic pathogens has increased considerably over the last decades. Pets have been recognized as a notable reservoir of various *Bartonella* spp.

The disease in humans

Bartonellosis is considered one of the most important potential emerging human infections. Most known and common is "CSD;" it is caused by *B. henselae* acquired from an infected cat and transmitted between cats by *C. felis* [119]. However, up to 11 species or subspecies of *Bartonella* are responsible for a wide range of symptoms that can include pathological findings in multiple organ systems induced by chronic infection. Apart from CSD, other diseases are Carrion's disease (*B. bacilliformis*), endocarditis (*B. quintana* and *B. henselae*), trench fever (*B. quintana*), hepatic peliosis (*B. henselae*), and bacillary angiomatosis (*B. quintana* and *B. henselae*) [120].

The disease in dogs

Bartonella infections in dogs, as in humans, exhibit a wide range of clinical signs involving various organ systems. The major canine pathogen is the tick-transmitted *Bartonella vinsonii* subsp. *berkhoffii*. Other *Bartonella* species are also reported from dogs associated with various clinical symptoms [119].

Owing to the relatively recent recognition that dogs can be infected with *B. vinsonii subsp. berkhoffii*, *B. henselae*, and potentially other *Bartonella* spp., seroprevalence data to various *Bartonella* spp. remains somewhat limited. In Morocco, 36-42% seroprevalence was found in stray dogs, while the percentage drops to 4% in pet dogs [121]. A similar study conducted in Algiers showed seroprevalence against *B. henselae* at 32.4% and against *B. vinsonii* subsp. *berkhoffii* at 27% [122]. In Florida, *Bartonella* spp. DNA was amplified from 14 of 80 dog blood samples (17.5%) and from 9 of 80 pooled fleas (11.3%) [123]. In a recent study in Greece, eight out of 38 dogs with Canine Leishmaniasis (21.1%) dogs were infected with one or two *Bartonella* species [124]. The findings of these studies provide evidence to support the

hypothesis that flea-infested dogs may be a reservoir host for *Bartonella* spp., inducing risks of transmission to humans.

Treatment in dogs

Canine bartonellosis treatment is based on antibiotics capable of crossing lipid membranes and reaching high intracellular concentrations, as doxycycline, azithromycin, and enrofloxacin. Treatment for several weeks is necessary in many cases to completely eliminate infection. Optimal treatment protocol of bartonellosis remains a controversial issue because of various outcomes in case reports and the lack of clinical therapeutic trials. Prolonged antibiotic therapy appears necessary [119].

One Health

Nowadays, *Bartonella* spp. has dragged health scientists' attention due to investigations showing that these species may be associated with various human syndromes that were previously considered chronic idiopathic diseases. Veterinarians have an occupational exposure risk due to their frequency of exposure to animal bites and body fluids, arthropods and their feces [119]. One Health programs should explore the significance of these pathogens for animal and human health.

Q fever

Q fever is a zoonosis caused by *Coxiella burnetii*, a pathogen with a worldwide distribution and an extremely complex reservoir system. Humans, farm animals (cattle, sheep, and goats) as well as companion animals have been reported to be infected by this organism.

The disease in humans

Q fever is a zoonosis caused by *C. burnetii*, a small obligate intracellular gram-negative bacterium of the *Legionellales* order. This zoonotic agent that has tropism for monocyte and macrophage cells. Transmission to humans occurs through the inhalation of aerosols from contaminated soil and animal excrement, primarily parturient fluids. Drinking raw milk is also likely a factor in the transmission of *C. burnetii*. Q fever in humans can manifest in three distinct syndromes; acute Q fever which includes flu-like illness, pneumonia, and hepatitis, chronic Q fever with possible endocarditis and osteoarticular disease and the immunological form known as post-Q fever fatigue syndrome [125].

The disease in dogs

Dogs can potentially be infected by inhalation of *C. burnetii* propagules from close contact with parturient animals, tick bites, consumption of placentas, or milk from infected ruminants. Dogs consuming raw meat diets and are free to hunt and scavenge wildlife may also be exposed to *C. burnetii*. Clinical disease of dogs is rare, showing reproduction symptoms like abortions, stillbirths, or weak newborn puppies.

C. burnetii DNA was detected in 4 (7%) of 54 canine placentas collected in 2011 at 5 veterinary practices in Netherlands [126]. In Hungary, 1 sample in a total of 126 shepherd, hunting, and stray dogs was PCR-positive, while 20.3% of dogs seroconverted [20]. Based on molecular results, this pathogen was also identified in dogs from Japan [127] and Brazil [128].

Treatment in dogs

Coxiella infections are variably susceptible to a single agent therapy for 2 weeks to 1 month with macrolides, potentiated sulfonamides or fluoroquinolones. A therapeutic protocol based on a combination of doxycycline and fluoroquinolones with rifampicin is considered to be more effective [129].

One Health

Since the discovery of *C. burnetii*, ticks have been shown to harbor and transmit the organism between different mammalian species [130,131]. Asymptomatic *C. burnetii*-infected dogs may undergo a period of recrudescence during pregnancy and shed enormous concentrations of the organism into the environment during and after parturition, constituting a source of infection for humans [132]. There is a continuing increase of reports indicating that contact with infected dogs represents a risk factor for acquiring the infection [128,133,134]. In Canada, a dog-related outbreak of Q fever was reported [135]. Although arthropod-borne transmission of Q fever in humans is not considered to be significant, *C. burnetii* has been isolated from ticks collected from dogs [136], and as ticks shed high loads of bacteria in their feces and saliva, they may be another potential source of bacterial transmission.

Conclusion

In this review, the present knowledge of canine vector-borne bacterial zoonoses is summarized. It is more than obvious that we cannot easily quantify the risks attributed to companion dogs mainly because our knowledge of the zoonoses derives from case reports. Thus, it is obvious that large-scale case–control studies are necessary to identify human–dog interactions that pose a risk for human infection. It would also be very important to calculate population attributable fractions to understand the relative contribution of companion animals to the transmission of zoonoses that may also be acquired from sources other than pets.

As demonstrated, treatment protocols are based on the administration of standard antimicrobial agents, especially doxycycline. This creates concerns regarding the development of antimicrobial resistance. Especially regarding *Ehrlichia* spp. and *Anaplasma* spp., antibiotic selective forces in ticks and animals are minimal, but there should not be any complacency, and data regarding new isolates should be updated to have a clear image of current resistance patterns. It has

already been mentioned that bacterial agents are not commonly discussed in companion animal practice, and thus there is a lack of knowledge regarding prevalence, epidemiology and antimicrobial susceptibility of these pathogens in the relevant pet population. In Europe, a centrally coordinated network collecting epidemiological data from each country is required for the surveillance of these zoonoses in companion animals. This surveillance system should also be extended to stray dogs in countries with this issue, like Greece, Bulgaria, Romania, etc. Reporting for agents that are already reportable in humans could allow the identification of common geographical or temporal trends in humans and dogs, combining epidemiological, statistical, and Geographical Information System tools in data analysis.

Another key element for reducing the zoonotic risks associated with dogs is training and education. Certain zoonotic infections transmitted by household pets, such as Lyme disease, Q fever infections, may be underdiagnosed by practitioners. Insufficient diagnostic tools, lack of awareness and difficulty in veterinary and medical practitioners' communication about vector-borne zoonoses transmitted by companion animals are the main causes. Education of veterinarians and physicians should refer to these zoonoses, if possible through joint courses and seminars. Awareness about the zoonotic risks should also be extended to dog owners, who often do not perceive their animals as possible sources of infections, indirectly increasing the risk of exposure and infection.

Authors' Contributions

GV conducted the bibliography research and prepared the manuscript.

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None.

Competing Interests

The authors declare that they have no competing interests.

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