

Human Bartonellosis: an underappreciated public health problem?

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Abstract

Bartonella spp. bacteria can be found around the globe and are the causative agents of multiple human diseases. The most well-known infection is called cat-scratch disease, which causes mild lymphadenopathy and fever. As our knowledge of these bacteria grows, new presentations of disease have been recognized with serious manifestations. Not only has more severe disease been associated with these bacteria, but *Bartonella* species have also been discovered in a wide range of mammals and the pathogens' DNA can be found in multiple vectors. This review will focus on some common mammalian reservoirs as well as the suspected vectors in relation to disease transmission and prevalence. Understanding the complex interactions between these bacteria, their vectors, and reservoirs as well as the breadth of infection by *Bartonella* around the world will help to assess the impact of Bartonellosis on public health.

Over 30 *Bartonella spp.* have been found to cause human disease¹. These fastidious, gram-negative bacteria cause the clinically complex disease known as bartonellosis. Infections cause a variety of signs and symptoms, from mild flu-like to more severe^{2,3}. Historically, the most common causative agents for human disease have been *Bartonella henselae*, *Bartonella quintana*, and *Bartonella bacilliformis*. However, more recent information ties many *Bartonella* species to emerging disease (Table 1)¹⁻⁵.

Bartonellosis is characterized by a prolonged intraerythrocytic bacteremia with a diverse array of reservoirs hosts¹. Natural hosts of *Bartonella spp* include humans, cats, dogs, rabbits, rodents, horses, cattle, and other wild animals^{2,3,5}. The severity of clinical manifestations correlates with the immune status of the patient. This allows *Bartonella spp* to persist in the blood of hosts as a chronic infection and accounts for the range of clinical manifestations (Figure 1)¹. Known diseases caused by *Bartonella* infections include: Carrion's disease, cat-scratch disease, chronic lymphadenopathy, trench fever, chronic bacteraemia, culture-negative endocarditis, bacillary angiomatosis, and bacillary peliosis^{1,4-6}. Recently, *Bartonella* infections have been linked to more severe manifestations such as hallucinations, weight loss, muscle fatigue, partial paralysis and other neurological manifestations^{7,8}. A few case studies have also documented *Bartonella* in tumors, particularly those of mammary tissue⁹⁻¹¹. The potential involvement of this pathogen in breast tumorigenesis is both disconcerting and warrants significantly more research. *Bartonella spp.* are zoonotic pathogens transmitted from mammals to humans through a variety of insect vectors including the sand fly, cat flea, and human body louse^{2,5}. New evidence suggests that ticks, red ants, and spiders can also transmit *Bartonella*¹²⁻¹⁵. The diversity of newly discovered *Bartonella* species, the large number and ecologically diverse animal reservoir hosts, and the large spectrum of arthropod vectors that can transmit these bacteria among animals and humans are major causes for public health concern.

Table 1. Known *Bartonella* Species, their Hosts and Vectors

Table has been adapted from Breitschwerdt, 2017¹

Bartonella Species	Host (s)	Vector(s)
<i>B. henselae</i>	Cat, human, dogs, horses	Fleas, lice, ticks, spiders
<i>B. quintana</i>	Humans, cats, dogs	Human body lice, fleas
<i>B. bacilliformis</i>	Humans	Sandflies, fleas
<i>B. koehlerae</i>	Cats, dogs, humans	Fleas, ticks
<i>B. vinsonii ssp berkhoffi</i>	Dogs, horses, foxes, humans	Fleas, ticks
<i>B. bovis</i>	Cattle, cats, dogs, human	Biting flies, ticks
<i>B. clarridgeiae</i>	Cats, dogs	Fleas, ticks
<i>B. rattimassiliensis</i>	Rats	Fleas
<i>B. tamiae</i>	Rats, humans	Fleas, mites
<i>B. tribocorum</i>	Rats	Fleas
<i>B. rousetii</i>	Bats	Bat flies,
<i>B. schoenbuchensis</i>	Cattle	Biting flies, ticks
<i>B. chomelii</i>	cattle	Biting flies, ticks
<i>B. doshiae</i>	Rats, humans	Fleas
<i>B. grahamii</i>	Mice, humans	Fleas, ticks
<i>B. birtlesii</i>	Mice	Fleas, ticks
<i>B. mayotimonensis</i>	Bats, humans	Bat flies, fleas, ticks
<i>B. elizabethae</i>	Rats, humans, dogs	Fleas
<i>B. washoensis</i>	Dogs, humans	Fleas, ticks
<i>B. rochalimae</i>	Dogs, humans	Sandflies, fleas, ticks
<i>B. vinsonii ssp arupensis</i>	Dogs, humans	Fleas, ticks
<i>B. melophagi</i>	Sheep, humans	Sheep keds

1. B., B. E., Bartonellosis, One Health and all creatures great and small. *Veterinary Dermatology* **2017**, 28 (1), 96-e21.

I. Bartonella in domestic animals and the potential for transmission

Cats:

Cats become infected with many different species of *Bartonella*, yet the symptoms of these infections widely vary. In 1995, evidence established that cats were the main reservoir for *Bartonella henselae*, the causative agent of cat-scratch disease¹⁶. Cat-scratch disease is a self-limiting but long-lasting swelling of the draining lymph nodes from the site of infection. Patients

present with regional lymphadenitis about 3-10 days after the cat scratch, and the papule will last anywhere from a few days to 2-3 weeks ¹.

Cats have also been discovered as reservoirs for other *Bartonella* species such as *B. clarridgeiae*, and *B. koehlerae* ^{6, 17, 18}. *B. clarridgeiae* and *B. koehlerae* are both causative agents of cat-scratch disease, but to a lesser extent than *B. henselae*. Of significance, *B. koehlerae* has been associated with more serious disease ^{1, 18} including endocarditis and neuropathy ^{15, 19}. *Bartonella* endocarditis typically appears in patients with pre-existing heart valve diseases and results in blood-culture-negative endocarditis ¹⁹. Neurological disease has been reported in multiple case studies ^{7, 15, 20}. In one case study, a woman was experiencing depression, anxiety, mood swings, severe headaches and hallucinations. Once diagnosed with Bartonellosis through an immunofluorescent antibody detection assay, the patient was treated with antibiotics and her neurological symptoms ceased ⁷.

Cats infected with *Bartonella* usually have asymptomatic bacteremia that can last for many months. Transmission to humans occurs through the cat flea *Ctenocephalides felis*, and directly from a cat scratch ^{3, 6}. There has been some debate on whether the bacteria can be transmitted from a cat's bite. In a case report from 2006, a woman was bitten by a cat and identical *Bartonella quintana* DNA was isolated from both the woman and the cat that bit her; however, the woman admitted to daily exposure to biting flies and mosquitoes, with occasional exposure to ticks and fleas, as well as having been bitten by a dog earlier that day, so the source of the bacteria remained difficult to determine ²¹. Transmission between cats through *C. felis* has been shown experimentally ²². Some new evidence also indicates that ticks can transmit *B. henselae*. In this case, *Ixodes ricinus* ticks removed from a cat that had anti-*B. henselae* IgG antibodies also tested positive by PCR for *B. henselae* DNA ²³.

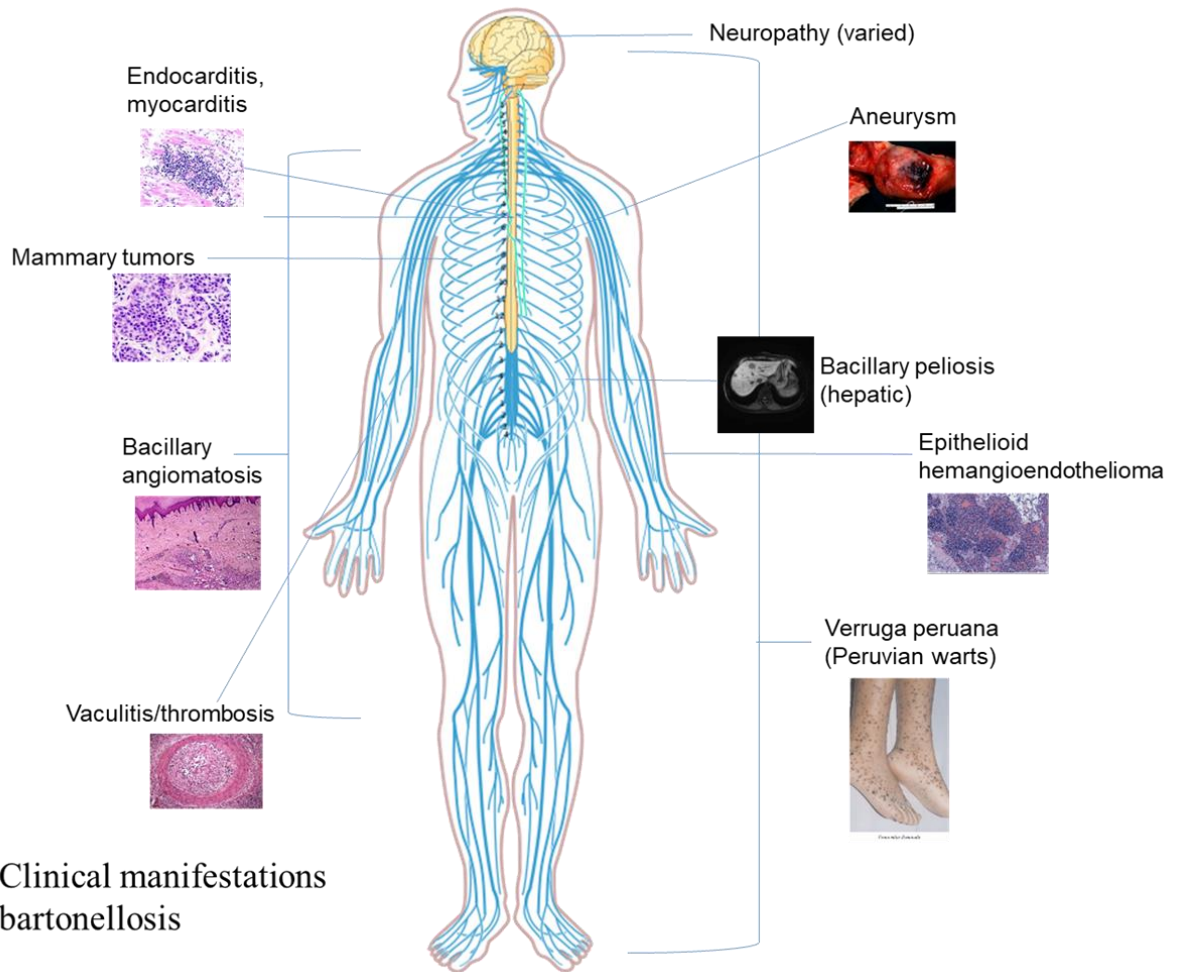


Figure 1. Clinical manifestations of human bartonellosis

Dogs:

Dogs have been infected with *B. henselae*, *B. vinsonii subsp.berkhoffii*, *B. koehlerae*, *B. clarridgeiae*, *B. elizabethae*, *B. washoensis*, *B. quintana*, and *B. rochalimae*²⁴⁻²⁶. Due to the symptomology of infected dogs, it is hypothesized that dogs are more likely accidental hosts of *Bartonella*. Infections with these pathogens result in endocarditis, myocarditis and granulomatous disease in dogs, similar to disease caused in humans²⁷.

Although a majority of these infections are thought to be accidental, dogs are most likely the reservoir of a few species of *Bartonella* including *B. vinsonii subsp. berkhoffii* and *B. vinsonii subsp. arupensis*¹. *Bartonella* has been isolated from stray and domestic dogs in Chile, Sri Lanka, Brazil, and Columbia with asymptomatic dogs exhibiting high infection rates with *B. henselae* and *B. vinsonii subsp. berkhoffii*²⁴⁻²⁶.

Transmission of *Bartonella* between dogs is through vectors such as fleas²⁶. Not much evidence exists to support direct transmission from dogs to humans. However, a case in which a veterinarian and his daughter were infected with *B. vinsonii subsp. berkhoffii* along with their

dog was documented²⁰. The father and daughter were experiencing neurological symptoms and weight loss, and once antibiotics were administered, the symptoms ceased²⁰. Although there is no direct evidence dogs can transmit *Bartonella* to humans, *B. henselae*, *B. bovis*, *B. quintana*, and *B. vinsonii subsp. berkhoffii* DNA has been isolated through PCR in dog saliva²⁸. Although *Bartonella* DNA has been detected in saliva, more evidence is needed to substantiate the notion of direct transmission from dogs to humans. The most likely mode of transmission is through a vector such as fleas or lice, which are known to transmit different *Bartonella* species.

Other domestic animals:

In 2007, a novel study found that two horses were infected with *B. henselae*²⁹. Since then, *Bartonella* infection has been investigated through experimental infection and naturally-occurring infection in horses^{30,31}. *B. henselae*-infected horses develop acute bacteremia with no long-term effects and *B. bovis*-infected horses mostly are unaffected (1 horse had acute bacteremia)³⁰. Subsequent to these studies, healthy and sick horses have been investigated for the presence of other *Bartonella* spp. Of note, *B. henselae*, *B. vinsonii subsp. berkhoffii*, and novel *Bartonella* have been identified in horses by utilizing enrichment culture developed by the Breitschwerdt lab³¹. Transmission may be occurring through biting flies, ticks, and lice³¹. Since the listed *Bartonella* spp. found in horses cause disease in humans, horses may prove an important reservoir for these bacteria and aid in the spread of infection through arthropod vectors.

Cattle are reservoirs of *B. bovis*, *B. schoenbuchensis*, and *B. chomelii*³²⁻³⁵. None of the aforementioned *Bartonella* sp. have been identified as human pathogens. , Transmission between cattle occurs through many different vectors. In one study, *B. henselae* was identified in 12% of cows from Israel³⁶. Although there is no evidence that direct transmission is occurring, the potential exists for these reservoirs to transmit other *Bartonella* spp. in the future.

Sheep and sheep keds are a reservoir of *B. melophagi*³⁷. *B. melophagi* can only be found in domestic sheep species and does cause disease in humans^{37,38}. It has been isolated from two patients, each having nonspecific abnormalities, including difficulty sleeping, muscle weakness, joint pain, and facial tremors³⁸. Acute infection has been followed by reoccurring symptoms for up to 2 years after infection³⁸. Although the strain has not been identified in many people, those working closely with animals such as horses, cattle, and sheep should be aware of bartonellosis and the associated symptoms.

II. Vectors for Bartonella species

Numerous different vectors transmit *Bartonella* species. These include fleas, keds, lice, sand flies, and potentially ticks, mites, and spiders⁵. In the following section, evidence of transmission will be discussed as well as prevalence of these vectors in the wild.

A. Fleas and Lice

In 1996, it was determined that the cat flea, *Ctenocephalides felis*, was responsible for the transmission of *Bartonella henselae* between cats²². Fleas were removed from bacteremic cats and placed on specific-pathogen free kittens, which all became bacteremic 2 weeks after flea placement, except one that became bacteremic 6 weeks after placement²². To demonstrate that transmission did not occur directly between cats, infected cats were caged with specific-pathogen free kittens for 21 days, and the specific-pathogen free kittens did not develop bacteremia despite playing (biting and scratching) occurring between the cats²². *C. felis* has been implicated in the transmission of other *Bartonella* species such as *B. quintana*, *B. clarridgeiae*, and *B. koehlerae*³⁹⁻⁴¹. *B. quintana* was also culturable from flea feces, implicating this vector in the transmission of trench fever, although the fleas were fed on infected blood, not representing a natural infection³⁹.

Other flea species have also been associated with *Bartonella* transmission, in particular, rat fleas. *Xenopsylla sp.* fleas collected from Palestine, Rwanda, Thailand, and in the US (California), are known to be infected with differing *Bartonella* species⁴¹⁻⁴⁴. Other fleas such as *Leptopsylla taschenbergi*, a flea associated with micromammals, have been collected from the wild and are infected with *Bartonella* species as well⁴⁵. Links between rats and *Bartonella* are important to observe; as humans colonize more discrete areas of the world, the emergence of vector-borne disease increases due to our arrival into the life cycle of these pathogens.

Lice have been documented as transmitting *Bartonella quintana* since the 1920s, after World War I⁴⁶. Many soldiers contracted trench fever in World War I and in World War II as well. The disease is found in unsanitary environments, where bathing infrequency allows body lice to serve as vectors. A reemergence of trench fever has been documented in homeless populations around the world in countries such as Colombia, Algeria, France, and in cities of the United States such as Washington D.C., San Francisco, and Seattle⁴⁷⁻⁵². The disease is mostly associated with body lice. Green-fluorescent protein-expressing *B. quintana* as an experimental system were found to replicate in the louse gut and viable bacteria were also found in the feces of *Pediculus humanus* after the lice fed on an infected rabbit⁵³. The role of head lice in transmitting *B. quintana* is less well understood. In Africa, head and body lice were collected from 37 mono-infested individuals. The findings showed that 48 of 143 body lice and only 6 of 31 head lice harbored *B. quintana*⁵⁴. One report showed that head lice could be experimentally infected and *B. quintana* was found in the feces, but there was a higher amount of viable *B. quintana* in body lice than in head lice⁵⁵. Most humans become infected with *B. quintana* due to louse feces, so the smaller frequency of infection caused by head lice makes sense, with fewer viable bacteria present in head lice feces. While fleas and lice are well-established vectors for transmitting different strains of *Bartonella*, increasing evidence links many other vectors to *Bartonella spp.*

B. Arachnids (spiders and ticks)

Over the last 10 years, the topic of ticks transmitting *Bartonella* species has been widely debated. Evidence exists to support the transmission of *Bartonella* through many different species of ticks. *Ixodid* ticks, also known as hard ticks, appear to be the main type of tick associated with these bacteria. Tick cell lines have been used to show that *Bartonella* can replicate and survive within *Amblyoma americanum*, *Rhipicephalus sanguineus*, and *Ixodes scapularis* cells⁵⁶. In California, questing ticks of *Ixodes pacificus*, *Dermacentor occidentalis*, and *Dermacentor variabilis* were collected when in adult and nymphal stages and tested for *Bartonella* by PCR for the citrate synthase gene.⁵⁷ All types of ticks were found to contain *Bartonella* DNA, although in varying percentages and locations. These data alone do not prove that ticks can transmit *Bartonella* spp. Bacteria; however, the results do show *Bartonella* DNA occurring naturally in these wild ticks. In Palestine, *Hyalomma* spp., *Haemaphysalis* spp., and *Rhipicephalus* spp. ticks were collected from domestic animals and tested by PCR for the *Bartonella* intergenic transcribed spacer (ITS) region⁵⁸. These ticks were infected with 4 strains of *Bartonella*: *B. rochalimae*, *B. chomelii*, *B. bovis*, and *B. koehlerae*⁵⁸. While this study tested a collection of ticks found on domestic animals, the results suggest that individuals in close contact with these animals should be aware of the potential for transmission through tick bites.

In a sampling of ticks (*Ixodes scapularis* and *Dermacentor variabilis*) and rodents (*Peromyscus leucopus*) from southern Indiana, the midgut contents of the tick species and rodent blood were analyzed by 16S sequencing. *Bartonella* was present in a moderate percentage (26% in *Dv* and 36% in *Is*) of larvae and nymphs of both tick species, even those scored as unengorged, but was present in the majority (98.5%) of the rodents tested⁵⁹. *Ixodes ricinus* has been a focus of studies that support tick transmission of *Bartonella* spp. in Europe. This is because *I. ricinus* is an important vector for tick-borne disease in Europe⁶⁰. *I. ricinus* have been collected in larval, nymphal, and adult stages in Austria⁶¹. The analyses revealed that 2.1% of all ticks were infected with *Bartonella* spp., with the highest rate in ticks derived from Vienna (with a 7.5% infection rate) and that adult ticks had a higher prevalence than other stages⁶¹. *B. henselae*, *B. doshiae*, and *B. grahamii* DNA was amplified and this was the first study to find *Bartonella*-infected ticks in Austria⁶¹. *B. henselae* DNA has also been isolated from *I. ricinus* removed from an infected cat. However, whether the cat gave the tick *Bartonella* or vice versa cannot be established, so the vector competence of these ticks for transmission cannot be determined⁶². A lab in France has studied the relationship between *I. ricinus* and *Bartonella* transmission. One study focused on the ability of ticks to maintain infection from one life stage to the next, and tested vertical transmission from adults to eggs. The authors used *B. henselae* and found that transstadial transmission was possible and that transovarial transmission was not likely⁶³. The researchers also supplied evidence to support vector competency of *I. ricinus* by amplifying *B. henselae* DNA from the salivary glands of infected ticks and amplifying DNA from blood 72 hours after infected ticks fed through an artificial system⁶³. Although the evidence strongly suggests the ability of ticks to transmit these bacteria, the system employed artificial means for

feeding, so one major critique has been that it is not representative of a natural blood meal from a host. To address this issue, another experiment was performed to assess vector competency of *I. ricinus* to transmit *Bartonella birtlesii*⁶⁴. Mice were infected with *B. birtlesii* through intravenous injection via tail vein, and once mice were infected, naïve ticks were fed on the mice and kept for 3 months to molt. Nymphal ticks were shown to transmit *B. birtlesii* to naïve mice, and adult ticks were shown to infect blood through a feeder method⁶⁴. *B. birtlesii* was identified in the blood of the recipient mice through PCR and immunofluorescence⁶⁴. This evidence strongly supports transmission of these bacteria by ticks. However, the limitation is that this only supports *I. ricinus*' ability to transmit a very specific strain of *Bartonella*, *B. birtlesii*, which is not linked to human disease. Concerns such as these related to vector competence and transmission can only be quelled by repeated studies utilizing multiple strains of *Bartonella* and differing tick species.

An interesting case study provided evidence of spiders transmitting *Bartonella*. A mother and two sons suffered from neurological symptoms following bites suspected from woodlouse hunter spiders¹⁵. *Bartonella henselae* DNA was amplified from the blood of the family as well as from a woodlouse and a woodlouse hunter spider near the family's home¹⁵. It cannot be determined if the family contracted the bacteria from the woodlouse, woodlouse hunter spider, or if the lice and spiders contracted the bacteria from the family. This case study points to the importance for diagnosticians to test for bacterial infections after suspected arachnid bites. It also emphasizes the lack of knowledge on the possible vectors that transmit *Bartonella* as well as the range of manifestations by infection with *Bartonella*.

III. *Bartonella* in the wild (reservoirs)

Rodents

Rats have been closely associated with human zoonotic diseases. Urban communities provide excellent niches for rat survival, with access to many resources through contact with humans⁶⁵. Rats have links to zoonotic infections such as plague and have vectors associated with this disease, mainly *Xenopsylla cheopis*, the oriental rat flea⁶⁶. However, rats can be infested with many ectoparasites such as lice, fleas, mites, and ticks, implicating them in transmission cycles of many diseases. These links have led researchers to investigate rodents and their common ectoparasites in the transmission of *Bartonella* spp.

Bartonella elizabethae complex *sensu lato* is closely associated with different rat species⁶⁷. Phylogeographic analysis utilizing and comparing the citrate synthase gene of *Bartonella* to rats and other rodents found that *Bartonella* originated in Southeast Asia and dispersal of the bacteria was due to rats and other rodents⁶⁷. *Bartonella elizabethae* has been identified as an agent in culture negative endocarditis in humans since 1993⁶⁸.

In Thailand, several studies have been performed on the persistence of *Bartonella* infection in rats, in their ectoparasites, and in humans by testing serum samples. In 2004, a survey of wild

rodents showed an 8.7% infection rate and the researchers identified a novel *Bartonella* species with close relation to *B. elizabethae*⁶⁹. In 2015, another group identified *Bartonella* DNA in 17% of rodents, with a high prevalence in *Badicota spp.* and *Rattus spp* rats⁴³. In the latter study, ectoparasites from the rats were also collected and the results showed that 57.1% lice and 25.8% of collected fleas possessed *Bartonella* DNA ; a lower prevalence was found in ticks(3.5%), and mites, (1.7%)⁴³. It was also noted that rats in areas of high ectoparasite numbers had a higher prevalence of *Bartonella* infection rates. This is important to distinguish because the route of transmission from rats to humans is poorly understood in *Bartonella* infections, but likely is due to a vector.

A serological survey in Thailand found 20 out of 261 human samples contained *Bartonella* DNA⁷⁰. After amplification of the citrate synthase gene, two patients were identified as actively infected with *B. henselae*⁷⁰. The remaining patients were infected with *Bartonella* containing unique sequences, with close relation to *B. elizabethae*, *B. tribocorum*, *B. rattimassiliensis*, *B. vinsonii subsp. arupensis*, and *B. tamiae*⁷⁰. *Bartonella tamiae* was first sequenced from humans exhibiting cat-scratch disease-like illness and has since been sequenced from chiggers removed from rats and directly from rats^{71, 72}.

Other areas of the world have surveyed rodent populations for the presence of *Bartonella spp.* bacteria. In the country of Georgia, a woman developed lymphadenopathy and fever due to a *Bartonella* species related to *B. tribocorum* and *B. elizabethae*⁷³. When the local rodent population was surveyed, 41.2% were found to harbor *Bartonella* DNA and 37.2% were positive by culture⁷⁴. In Kenya, a staggering 60% of *Rattus spp.* rats in urban populations had *Bartonella*, whereas only 13% rats in a rural location had *Bartonella*⁷⁵. All the data implicate rodents in the transmission cycle of *Bartonella* to humans, with rats in particular. However much much regarding means of transmission from rodents to humans remains unknown. The relationship of rodents and the transmission of *Bartonella* should be studied closer and more thoroughly with controlled experiments to determine the exact routes of transmission between rodents, transmission between rodents and their vectors, as well as rodents to humans to determine risk of *Bartonella* infections to humans.

Bats

Bats are common mammals that have a large geographic distribution, with links to emerging pathogens⁷⁶. Specifically, their link to viral pathogens is understood, but their link to emerging bacterial pathogens is less well characterized⁷⁷. *Bartonella mayotimonensis*, which caused culture-negative endocarditis in a male patient, has been linked to bats^{78, 79}. Since this occurrence, more studies have been conducted to investigate the relationship between bats and *Bartonella spp.*

Bartonella isolated from bats in Georgia were sequenced and analyses of homology identified strains related to those isolated from dogs in Thailand and a relationship to strains isolated from

humans in Poland⁷⁷. Ectoparasites, such as ticks and bat flies, are thought to serve as a primary route of transmission between bats⁷⁷. *Bartonella* has also been isolated from bats in France, Spain, Brazil, Argentina, Thailand, Romania, Hungary, and Africa^{76, 80-84}.

Bat flies, in particular, are implicated as the most likely vector transmitting *Bartonella* between bats. However, studies have shown that although bat flies do test positive for *Bartonella* DNA, the strains typically differ from those isolated from bat host populations⁸⁵. The genetic diversity of bat flies and the *Bartonella* sp. isolated from these ectoparasites supports shared evolution and suggests that horizontal transmission may be occurring⁸⁴.

One interesting study determined a link between bats and humans. Twice a year an African population goes into a bat cave to collect bats for consumption⁷⁶. Bats and bat flies were collected and sequenced for *Bartonella* prevalence and human populations in the surrounding area were also surveyed for *Bartonella* infections. A novel species, named *Bartonella rousetti*, was isolated from bats and bat flies. In addition, 8 out of 204 persons surveyed were seroreactive to *B. rousetti*⁷⁶. This study implicates bats as an important reservoir for human *Bartonella* infections, although the direct link to human disease is unclear.

IV. Bartonella as a possible co-infection of the Lyme Borrelia-transmitting (deer) ticks

Over the last 10 years, there has been more supportive evidence gathered to support co-infection with *Bartonella* and *Borrelia burgdorferi*. Most evidence has occurred through collection of questing ticks, but serological surveys have also been conducted in Europe to estimate the incidence of human co-infection. Although it is difficult to determine whether these co-infections occurred upon one tick bite or over the course of multiple tick bites, one thing is clear; co-infection with these pathogens leads to difficulty clearing either infection and antibiotic treatment should differ for individuals infected with multiple pathogens.

In 2006, a study conducted in New Jersey found that out of 168 questing *Ixodes scapularis* ticks collected, 6.55% were infected with *Bartonella henselae* and 1.19% were co-infected with *B. henselae* and *Borrelia burgdorferi*⁸⁶. Interestingly, there were 3 reported cases of individuals co-infected with *B. henselae* and *B. burgdorferi* in New Jersey in 2001⁸⁷. *I. scapularis* ticks were obtained from one of the patient's household and tested positive for *B. henselae* and *Borrelia burgdorferi* DNA using PCR⁸⁷. These patients all had neuroborreliosis and after treatment with antibiotics, their symptoms did not improve. However, once diagnosed as co-infected and placed on a more potent antibiotic regimen, symptoms improved⁸⁷. There is no direct evidence that the patients described acquired the infections simultaneously. Nevertheless, patients treated for Lyme disease should be examined for existing co-infections prior to antibiotic therapy. Initial discovery of co-infection could lead to improved patient outcome.

In Europe, *I. ricinus* ticks transmit many diseases. Studies have been conducted whereby questing ticks were collected and serological data was analyzed in regions to determine risk for

co-infections with *Borrelia*. In France in 2011, a survey showed that with a 32% *I. ricinus* rate of infection with *B. burgdorferi*, only about 0.1% demonstrated co-infection with *Bartonella*, which was identified to be *B. birtlesii*⁸⁸. In other parts of Europe, such as Germany, as much as 6.9% of the *I. ricinus* ticks were found to be infected with *Bartonella* and 25% of those ticks were co-infected with *Borrelia burgdorferi*⁸⁹. A survey in Poland, on the other hand, found roughly 1.6% of *I. ricinus* ticks collected to be co-infected with *Bartonella henselae* and *Borrelia burgdorferi*⁹⁰. Although the ticks collected seem to have small percentages of co-infection, serological studies performed in Poland appear to support the hypothesis of this co-infection model. Sera obtained from foresters, farmers, and healthy control patients found that 23.1% of foresters, 27.7% of farmers, and 37.5% of control groups had antibodies to *Bartonella*⁹¹. Co-infection risk was directly linked to occupational exposure, where 9.2% of forestry workers and 7.7% of farmers were co-infected with *Bartonella* and *B. burgdorferi*⁹¹. Most recently, a serological analysis of more than 400 Lyme patient samples revealed that most patients possess antibodies to multiple tick-transmitted pathogens⁹². Depending on the Lyme disease patient category, between 15-33% were also seropositive for *Bartonella henselae*. These data support the possibility of co-infection through a vector such as ticks. However, the occurrence of infection could have been either simultaneous or consecutive.

In summary, the prevalence of *Bartonella* appears to be very broad, as these pathogens can utilize multiple vectors and infect a diverse range of hosts. Given the complex clinical manifestations and difficulty in effective treatment, the impact of these bacteria on human health may be more significant than is currently appreciated. These factors warrant further research on *Bartonella* prevalence, risks for infection and pathobiology in mammalian hosts.

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