Bartonella *infections in humans dogs and cats*

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Summary
Bartonellae are emerging vector-borne pathogens distributed worldwide that can cause various clinical symptoms in humans and animals, ranging from a mild flu-like illness to more severe manifestations such as endocarditis, myocarditis, arthritis, hepatitis, and arthralgia. Numerous mammalian species, including domestic animals such as dogs, cats, as well as humans, serve as reservoir hosts for various *Bartonella* species. The vectors play a central role in the transmission of these bacteria and pets and their ectoparasites can pose a serious risk of zoonoses. This paper reviews selected literature on important bartonellosis of dogs, cats, and humans with notes on transmission, vectors, pathogenesis, and diagnosis.

Infezioni da Bartonella *nell'uomo, nei cani e nei gatti*

Parole chiave
Bartonellosi,
Cani,
Gatti,
Vettori,
Zoonosi

Riassunto
Appartengono al genere *Bartonella* patogeni emergenti trasmessi da vettore che, distribuiti in tutto il mondo, possono indurre, in uomini e animali, una sintomatologia equiparabile ad una lieve influenza o manifestazioni più gravi come endocarditi, miocarditi, artriti, epatiti e artralgia. I vettori giocano un ruolo centrale nella trasmissione di questi batteri; uomini e mammiferi, inclusi cani e gatti, possono fungere da serbatoio per varie specie di *Bartonella* e gli ectoparassiti degli animali d'affezione possono essere vettori di agenti zoonosici. Questo articolo esamina la letteratura sulle più importanti bartonellosi del cane, del gatto e dell'uomo con note sulla trasmissione, sui vettori, sulla patogenesi e sulle diagnosi.

Introduction

Bartonella species are emerging vector-borne pathogens. Infections by these bacteria in humans and animals can cause various clinical symptoms. These range from a mild flu-like illness, to more severe manifestations such as endocarditis, myocarditis, arthritis, hepatitis, and arthralgia (Chomel *et al.* 2006, Boulouis *et al.* 2005). A total of 30 different species belong to the genus *Bartonella* (Cicuttin *et al.* 2014) and at least 13 species or subspecies are zoonotic (Perez *et al.* 2009). *Bartonella* species, which belong to the α-proteobacteria on the basis of their 16S rDNA sequences (Anderson 1997), are all closely related, and have over 98% homology in the sequences of their 16S rRNA genes as well as an evolutionary homology with members of the genus *Brucella* (Jacomo *et al.* 2002).

Bartonellae are haemotropic gram-negative bacteria that parasitize the erythrocytes and endothelial cells of mammalian hosts and are highly adapted to facilitate intracellular persistence (Breitschwerdt and Kordick 2000). Various arthropods act as vectors for these bacteria. These include sand flies, lice, ticks, and fleas (Jacomo *et al.* 2002, Chomel *et al.* 2009).

Natural hosts are humans, felids, canids, lagomorphs, and rodents, including a large number of rodent species that might be kept as pets (Breitschwerdt 2010, Chomel *et al.* 2012). Each *Bartonella* species appears to be highly adapted to 1 or few mammalian reservoir hosts. Infection in these hosts is characterised by long lasting intraerythrocytic bacteriemia. Among numerous other examples, *Bartonella henselae* has coevolved with cats, *Bartonella vinsonii* subsp. *berkhoffii* with canids, and *Bartonella bovis* with cattle (Breitschwerdt *et al.* 2010, Chomel *et al.* 2006). The incidental infection of a non-reservoir host does

not seem to lead to erythrocyte parasitism, but can cause various clinical manifestations, as in the case of the zoonotic *B. henselae* (Schulein *et al.* 2001).

Roaming animal populations can be a source of infection for domestic animals and humans. The method for managing stray animal populations in poor societies in particular needs to be improved (Seimenis and Tabbaa 2014). The global One Health paradigm proposes a much closer integration of human and veterinary medicine. It is essential that cross-species infectious agents are investigated in a collaborative approach by integrated teams of environmental, medical, and veterinary medical researchers (Breitschwerdt 2014, Seimenis 2008).

Vectors and transmission

An increasing number of arthropod vectors, including biting flies, fleas, keds, lice, sandflies, and ticks have been confirmed or suspected to be associated with the transmission of *Bartonella* spp. among animal populations. It must be stressed that there is an important difference between proven vector competence and potential vectors. Vector competence is based on experimental studies that demonstrate reliable transmission between the vector and the host. In most cases the detection of *Bartonella* spp. in an arthropod, as determined by culture and/or polymerase chain reaction (PCR), does not provide definitive proof of vector competence and merely represents the ingestion of Bartonella-infected blood from the bacteremic host (Billeter *et al.* 2008).

Natural *Bartonella* infections usually occur when the arthropod vector feeds on blood. *Bartonellae* may also be transmitted through arthropod faeces (Finkelstein *et al.* 2002). Table I summarizes the vectors for various *Bartonella* species (Billeter *et al.* 2008).

In Europe, fleas are particularly important in the transmission of *Bartonella* species from pets to humans because of their wide dissemination. The most widespread species is the cat flea *Ctenocephalides felis*, which is highly prevalent in both dogs and cats (Traversa *et al.* 2013). *Bartonellae* can be detected in fleas collected from hosts that were apparently uninfected. In some cases, species of *Bartonella* found in a host can be different from those found in its flea. This could result from fleas taking

Table I. *Vectors, known and suspected, for various* Bartonella *species (Billeter* et al. *2008).*

Confirmed vector	Suspected vector	*Bartonella* species
Lutzomyia verrucarum (sandfly)		*B. bacilliformis*
	Lutzomyia peruensis (sandfly)	*B. bacilliformis* and a novel *Bartonella* sp. resembling *B. grahamii* *B. quintana*
Pediculus humanushumanus (louse)		*B. quintana*
	Pediculus humanus capitis (louse)	*B. quintana*
	Rodent lice	A novel rodent *Bartonella* sp., resembling *B. henselae, B. tribocorum, B. phoceensis*, and *B. rattimassiliensis*
Ctenocephalides felis (cat flea)		*B. henselae*
	Ctenocephalides felis	*B. clarridgeiae, B. quintana,* and *B. koehlerae*
	Ctenocephalides canis (dog flea)	*B. henselae*
Ctenophthalmus nobilis nobilis (flea)		*B. grahamii* and *B. taylorii*
	Rodent fleas	Resembling *B. quintana, B. birtlesii*, resembling *B. clarridgeiae*, *B. elizabethae, B. koehlerae, B. doshiae, B. taylorii, B. tribocorum, B. vinsonii* subsp. *vinsonii*, *B. washoensis*, and novel *Bartonella* spp.
	Pulex spp. (human flea)	Resembling *B. vinsonii* subsp. *berkhoffii*, a novel *Bartonella* sp., and *B. quintana*
	Sternopsylla texanus (bat flea)	Novel *Bartonella* sp.
	Various mite species	Rodent *Bartonella* sp. Resembling *B. grahamii, B. doshiae*, and a potentially novel *Bartonella* sp.
	Lipoptena sp. (ked)	Resembling *B. schoenbuchensis, B. henselae, B.chomelii*, and a cervid strain of *Bartonella*
	Hippobosca equine (flies)	Resembling *B. schoenbuchensis, B. chomelii*, and a cervid strain of *Bartonella*
	Melophagus ovinus (flies)	Resembling *B. schoenbuchensis, B. chomelii*, and a cervid strain of *Bartonella*
	Haematobia sp. (biting flies)	*B. bovis*
	Stomoxys sp. (biting flies)	*B. henselae*

blood meals from multiple hosts and *Bartonella* persisting and replicating in the flea gut (Brinkerhoff *et al.* 2010, Gabriel *et al.* 2009).

Notes on human bartonellosis

Infectious diseases caused by *Bartonella* spp. have been described for more than 1000 years. Historically, infections with *B. bacilliformis* (which is endemic in South America) have been known since the dynasty of the Inca (Kaiser *et al.* 2011). *B. quintana* was detected in 4000-year-old human tissue originating from southeastern France (Drancourt *et al.* 2005) and in the mortal remains of soldiers of Napoleon's Grand Army in Vilnius, Lithuania (Kaiser *et al.* 2011).

Until 1990, the *Bartonella* species were responsible for causing only 2 diseases: Carrión disease, linked to *B. bacilliformis*, and Trench fever, which was attributable to *B. quintana* (Karem *et al.* 2000). *B. henselae* was first identified in 1990 by PCR and characterised as a new species in 1992 (Regnery *et al.* 1992). Many other *Bartonellae* have since been identified as causative agents of diseases in man and animals. The genomes of *B. henselae*, *B. quintana*, and *B. tribocorum* have been sequenced (Alsmark *et al.* 2004, Saenz *et al.* 2007) and diagnostic algorithms have been improved. Cat scratch disease (CSD) is the most common human infection caused by *Bartonella* species.

Humans are the only known reservoir hosts for *B. bacilliformis* and *B. quintana* (Bass 1997b).

Some studies have shown the ability of *Bartonellae* to survive in stored blood for more than 35 days with the potential for transfusion-associated infection (Lamas *et al.* 2008).

Table II shows the major Bartonellosis and their geographical distributions.

Cat scratch disease

Cat scratch disease (CSD) is caused by *B. henselae* and less frequently by *B. clarridgeiae*, *B. koehlerae*, *B. quintana*, and *B. doshiae* (Lamas *et al.* 2008). Its pathogens are transmitted by bites or scratches of infected cats. CSD is commonly diagnosed in children, but adults may also present the disease. CSD should be suspected in patients with regional unilateral lymphadenopathy, especially if there is a history of exposure to kittens or cats.

The clinical manifestation of *B. henselae* infection depends on the immune status of the patient. Usually, 3-10 days after a scratch or bite from an infected kitten or cat, immunocompetent hosts can develop a primary skin lesion that starts as a vesicle at the inoculation site. Regional ipsilateral inflammatory lymphadenopathy develops between 1 to 2 weeks later in 85%-90% of patients (Carithers 1985). Axillary, epitrochlear, neck, and jaw nodes are most frequently affected (Lamas *et al.* 2008, Ridder *et al.* 2002). Nodes may be tender with inflammatory signs (erythema, warmth) and suppurate in 13%-48% of cases (Carithers 1985). Infected lymph nodes

Table II. Bartonella *species associated and potentially associated with human disease and their distribution (Lamas* et al. *2008).*

Species	Diseases	Distribution
B. bacilliformis	Carrion disease	South America
B. rochalimaea	Bacteremia, fever, cutaneous lesions, and splenomegaly	Peru
B. quintana	Endocarditis, trench fever, BA*, CSD**, peliosis hepatis	South America Europe, USA, Africa
B. henselae	CSD, ocular manifestations, encephalopathy, aseptic meningitis, acute hemiplegia, dementia, acute psychiatric symptoms, fever, hepatosplenic abscesses, asymptomatic bacteremia, osteomyelitis, BA, peliosis hepatis, erythema nodosum, other skin lesions	South America, Europe, USA, Africa, Asia
B. elizabethae	Endocarditis	Europe, USA, Asia
B. clarridgeiae	CSD, sepsis, endocarditis	Europe, USA, Asia
B. clarridgeiae-like	Fever and splenomegaly	Peru
B. koehlerae	Endocarditis, CSD	USA
B. vinsonii subsp. *berkhoffii*	Endocarditis, arthralgia, myalgia, headache, fatigue	Europe, USA
B. washoensis	Fever and myocarditis	USA
B. tamiae	Fever	Thailand
B. grahamii	Neuroretinitis	Europe, Canada, Asia
B. doshiae	CSD	Europe
B. taylorii	Unknown	Europe
B. alsaticaa	Unknown	Europe
B. bovis	Unknown	Europe, Africa, North America

*BA = bacillary angiomatosis; ** CSD = cat scratch disease.

may form a pus-draining fistula through the skin (Kaiser *et al.* 2011). In some cases, CSD can lead to chronic ulcerative conjunctivitis and neuroretinitis, small foci of retinitis, and angiomatous lesions named Parinaud oculoglandular syndrome (POGS) (Biancardi and Curi 2013, Lamas *et al.* 2008). The onset of signs and symptoms can range from 1-4 weeks, depending on the syndrome presented, and may last several months (Carithers 1985). This disease is self-limiting. In a minority (5-20%) of *B. henselae*-infected immunocompetent patients, atypical manifestations of CSD (with or without lymphadenopathy) such as systemic infection with fever, hepatosplenomegaly, encephalitis, or osteomyelitis, can occur (Carithers 1985).

Because CSD is a self-limiting disease, its clinical relevance derives from the necessity to exclude other infectious or malignant processes (Klotz *et al.* 2011). Clinically, CSD is difficult to distinguish from lymphadenopathy caused by other microbial pathogens, such as atypical mycobacteria (Diederen 2007).

Immunocompromised patients infected with CSD can present multi-vasoproliferative lesions in the liver, spleen (visceral peliosis), or on the skin (bacillary angiomatosis) (Lamps *et al.* 2004, Jacomo *et al.* 2002).

Trench fever

B. quintana, the agent of Trench fever, caused large epidemics in Europe during World Wars I and II. The name 'trench fever' was chosen because the disease was first described in both Allied and German troops crowded into trenches during World War I (Raoult *et al.* 1999). The incidence of trench fever decreased after World War II; however, in the early 1990s, it was recognised as a major re-emerging infectious disease in urban homeless populations of developed countries who had poor living conditions characterised by extreme poverty, lack of hygiene and exposure to extremely low temperatures (Bonilla *et al.* 2009, Brouqui *et al.* 2005, Brouqui *et al.* 1999).

The human body louse (*Pediculus humanus humanus*) is the vector of *B. quintana*. The louse excretes *B. quintana* in its faeces during feeding. Faeces containing *B. quintana* are inoculated into the louse bite when the human scratches the bite site. *B. quintana* forms a biofilm-like structure in the louse faeces, which supports the prolonged survival of the bacteria within the faecal environment (Raoult *et al.* 1998). In a recent study, 33.3% of the body lice recovered from infested homeless individuals in California were PCR positive for *B. quintana*, underscoring the high prevalence of this potentially fatal bacterium in the human environment (Abromaitis *et al.* 2013).

Fleas may play a role as vectors of trench fever or other clinical manifestations that are caused by *B. quintana*. Cat fleas (*Ctenocephalides felis*) can acquire *B. quintana* by feeding and releasing viable organisms into their faeces. However, the biological role of *C. felis* in the transmission of *B. quintana* under natural conditions is yet to be defined (Kernif *et al.* 2014).

Moreover *B. quintana* has been detected in cat dental pulp, in a patient who owned a cat, and in treatment for chronic adenopathy (Rolain *et al.* 2003). These findings suggest that other possible vectors and transmission modes, similar to those of *B. henselae*, may exist (Badiaga *et al.* 2012).

Humans are the only confirmed reservoir host for *B. quintana*.

Carrion disease

Carrion disease, a biphasic disease, is caused by *B. bacilliformis*. The disease is endemic in some areas in the western side of the Cordillera of the Andes, affecting Ecuador, Colombia, and Peru, and has also been sporadically reported in Bolivia and Chile (Sanchez *et al.* 2012). The pathogen is transmitted by the bite of members of the genus *Lutzomyia*, including *L. verrucarum, L. peruensis*, and *L. pescei* (Sanchez *et al.* 2012).

Two well-established clinical phases have been described in this disease.

The first is the acute phase, the so-called Oroya Fever, in which *B. bacilliformis* infects the erythrocytes, causing severe anaemia and transient immunosuppression (Del Valle Mendoza *et al.* 2014). In the absence or delay of adequate treatment, up to 80% of patients may die during this phase (Schulein 2001). In immunodeficient patients, the response is predominantly vasculoproliferative (Lamas *et al.* 2008). Bacillary angiomatosis and bacillary peliosis have been reported most often in immunocompromised HIV-infected patients (Koehler *et al.* 1997). This is seen less frequently today, which is possibly due to the earlier detection of HIV serostatus and a reduced number of individuals with CD4 count below 50 lymphocyte cells/mm^3 (Lamas *et al.* 2008). The suppression of immune regulatory mechanisms may therefore play a role in the immunopathogenesis of *Bartonella* induced vasoproliferation (Beerlage *et al.* 2011).

The second, or chronic phase, which is also named Verruga Peruana or 'Peruvian warts', is characterised by the development of nodular dermal eruptions, themselves a result of vascular proliferation (Schulein 2001). Asymptomatic carriers have also been described in endemic areas (Del Valle Mendoza *et al.* 2014).

Cats

Cats can be infected by a wide variety of *Bartonellae* (Chomel *et al.* 1995a, Droz *et al.* 1999) and can also be co-infected with more than 1 *Bartonella* (Gurfield *et al.* 2001, Gurfield *et al.* 1997).

Cats are the natural reservoir of *B. henselae* and usually develop an asymptomatic intraerythrocytic bacteremia, which may persist for months or years (Kordick and Breitschwerdt 1995). The major competent vector is the cat flea, *C. felis* (Chomel *et al.* 1996). *B. henselae* or its DNA has also been detected in several other blood-feeding arthropods, such as ticks (*Dermacentor* spp., *Ixodes* spp.) (Tsai *et al.* 2011, Podsiadly *et al.* 2007) and biting flies (*Haematobia* spp., *Stomoxys* spp.) (Chung *et al.* 2004), however, no evidence of the role of these insects as competent vectors exists (Bouhsira *et al.* 2013).

The presence of *C. felis* fleas is essential for maintaining *B. henselae* infection within the cat population (Chomel 1996). Cats reported to have been infested with fleas during the preceding 6 months were more likely to be seropositive than cats without fleas (Chomel *et al.* 1995a). *B. henselae* transmission did not occur when infected cats lived together with uninfected cats in a flea-free environment. Transmission consequently does not occur through bites, scratches (in the absence of fleas), grooming, or sharing litter boxes and food dishes (Pennisi *et al.* 2013).

Cats naturally infected with *Bartonella* species usually do not show clinical signs. Both experimental and natural infection studies have tried to establish an association between clinical signs and infection, but a link has not been unequivocally proven (Pennisi *et al.* 2013).

In a recent study (Kernif *et al.* 2014), *B. quintana* was detected in cat fleas (*C. felis*) and was localised in the flea gastrointestinal gut by specific immunohistochemistry.

Stray cats present higher prevalence than pet cats (Boulouis *et al.* 2005). *B. henselae* infection appears to be more common in young cats, and infection decreases with the length of cat ownership (Gurfield 2001).

Temperature and relative humidity are the 2 most essential factors for the successful reproduction, development, and survival of fleas (Dryden *et al.* 1994). The seroprevalence of *B. henselae* is higher in the pet cat population in warm, humid climates than in cold, dry climates because *C. felis* fleas are more common in warmer climates (Chomel *et al.* 1995b) and cats have more fleas during the summer and autumn months than in the other 2 seasons (Farkas 2009). In addition, during the summer cats spend most of their time outside the house, whereas during autumn, they stay indoors.

The link between seasons and CSD incidence has been described in the United States (US) (Jackson *et al.* 1993), in Japan (Tsukahara *et al.* 2002), and in France (Sanguinetti-Morelli *et al.* 2011).

The United States is a large country with diverse climates. Analysis of three US national databases indicated that most CSD cases have occurred during September-January, with peaks in November and December (Jackson *et al.* 1993).

In Japan, 64% of CSD cases occurred during September-December and peaked in November.

In France, the CSD increased incidence in autumn, with peaks in December, and decreased in spring (Sanguinetti-Morelli *et al.* 2011).

Feline sexual activity also may influence the seasonality of CSD. In the Northern Hemisphere, cat reproduction increases during spring and summer months, and kittens stay with their mothers until they are 12-16 weeks of age (Sanguinetti-Morelli *et al.* 2011).

Bartonella laboratory testing is required for feline blood donors, for pet cats belonging to immunosuppressed persons, or when a human *Bartonella*-related disease is diagnosed in a cat's home (Pennisi *et al.* 2013).

Dogs

Bartonella spp. are considered important emerging pathogens in dogs worldwide (Breitschwerdt *et al.* 2010).

Canids and dogs can be infected by a wide variety of *Bartonella* species.

Among the species known to infect humans, nine species have been documented in dogs through culture isolation or DNA-based methods: *B. clarridgeiae*, *B. elizabethae*, *B. henselae*, *B. koehlerae*, *B. quintana*, *B. rochalimae*, *B. vinsonii* subsp. *berkhoffii* (hereafter *B. v. berkhoffii*), *B. volans* (including *volans*-like), and *B. washoensis* (Chomel and Kasten 2010, Chomel 2003, Diniz *et al.* 2013, Henn *et al.* 2009).

Domestic dogs may represent excellent epidemiological sentinels for *Bartonella* sp. infection in humans. This is due to several factors: exposure to the same household and recreational environments as humans, potential parasitism by the same vectors, as well as because of the wide diversity of *Bartonella* species identified (Bai *et al.* 2010, Diniz *et al.* 2013).

Canids have been reported as the main reservoirs for *B. v. berkhoffii*, likely for *B. rochalimae*, and candidate for *B. merieuxii* (Breitschwerdt *et al.* 2010a, Chomel *et al.* 2012, Chomel *et al.* 2014).

In dogs, *B. v. berkhoffii* has been identified as an important cause of endocarditis, cardiac arrhythmias,

myocarditis, granulomatous rhinitis, anterior uveitis, and chorioretinitis, whereas *B. henselae* has been implicated in peliosis hepatis, generalised pyogranulomatous lymphadenitis, panniculitis, endocarditis, polyarthritis, and idiopathic effusions (Breitschwerdt *et al.* 2010b, Breitschwerd *et al.* 2004, Fenimore *et al.* 2011). There is a growing body of evidence for the involvement of various *Bartonella* species in culture-negative infective canine endocarditis (Macdonald 2010).

Reasons for the variety of clinical manifestations of *Bartonella* infection in dogs reflect genetic or acquired differences in the host immune response, differences in virulence among *Bartonella* spp. and strains, and the impact of sequential or co-infection with other vector borne pathogens on disease expression (Balakrishnan *et al.* 2013).

Pathogenesis

The correlation between immune status and the development of disease manifestations may implicate an important immunopathogenic role for *Bartonellae* (Bass *et al.* 1997a, Koehleret *et al.* 2003). In humans, the opportunistic infection of immunocompromised individuals, particularly those affected by AIDS-related diseases, can result in serious systemic involvement including: bacillary angiomatosis, peliosis hepatis, endocarditis, and potentially dementia, while relatively uncommon systemic involvement has also been reported in immunocompetent individuals (Pappalardo 2000).

Once an animal is infected by a bite, scratch, or arthropod transmission, *Bartonella* species localise into erythrocytes and endothelial cells, which facilitates a potentially unique strategy for bacterial persistence within the blood stream of reservoir or non-reservoir species (Breitschwerdt 2008, Kordick *et al.* 1995, Rolain 2002). Bacteria invade and replicate intracellularly in a membrane-bound compartment until a critical density is reached. Thereafter, the number of intracellular bacteria remains static for the remaining lifespan of the infected erythrocytes that are indistinguishable from uninfected erythrocytes (Chomel *et al.* 2009). The non-hemolytic intracellular colonisation of erythrocytes and localisation within endothelial cells preserve *Bartonella* organisms for efficient vector transmission, protect *Bartonella* from the host immune response, facilitate widespread vascular dispersion throughout the tissues of the body, and potentially contribute to decreased antimicrobial efficacy (Breitschwerdt 2010a, Breitschwerdt 2008, Dehio 2001, Rolain *et al.* 2001, Rolain *et al.* 2003). A relapsing bacteremia can periodically occur. The establishment of a chronic intra-erythrocytic bacteremia takes place exclusively in the mammalian reservoir hosts (Chomel 2009). For some *Bartonellae*, like *B. tribocorum* and *B. quintana*, episodes of synchronous release of bacteria follow at intervals of approximately five days, probably as a result of the five-day infection cycle that is triggered by the re-infection of the primary niche by bacteria released at the end of each cycle. The exception to this rule is *B. bacilliformis*, which triggers massive haemolysis of colonised human erythrocytes, giving rise to an often fatal haemolytic anemia (Chomel *et al.* 2009).

Bartonella infection in animals, as in humans, can result in the production of substantial levels of a specific antibody. These antibodies, however, do not appear to provide protection following primary exposure to the organism. The humoral immune response may effectively eliminate extracellular or epicellular organisms, however, antibodies, which are unable to penetrate cells, would have no protective effect on intracellular *Bartonella* (Pappalardo 2000). Instead, antibodies might neutralise bacteria that are released from the primary niche and thereby abrogate the infection of additional erythrocytes as well as prevent re-infection of the primary niche (Chomel *et al.* 2009).

In vitro infection of human CD34 +progenitor cells with *B. henselae* suggests that these bacteria are capable of infecting bone marrow progenitor cells, which may contribute to ongoing erythrocytic infection (Mandle *et al.* 2005).

Isolation and diagnosis

Laboratory methods for the diagnosis of *Bartonella* infections include isolation of the organisms by culture, serological assays and molecular detection of *Bartonella* DNA in affected tissue (Diederen *et al.* 2007, Sander *et al.* 2001).

Bartonella species grow on axenic medium at 37°C, with 5% carbon dioxide, but can also be grown in broth with foetal bovine serum and in tissue culture (La Scola *et al.* 1999). Growth in axenic medium is hemin dependent (Wong *et al.* 1995), and agar should be enriched with rabbit and horse blood, which provides better growth than sheep blood. All *Bartonella* species grow slowly on blood agar, with primary isolates typically appearing after 12-14 days, but sometimes require 45 days to be visible (Diederen *et al.* 2007). All diagnostic tests have limitations. Both, serology and direct PCR from blood samples lack sensitivity in some patients, and the documentation of bacteremia in a patient in which the organism is not consistently present within erythrocytes also remains problematic (Breitschwerdt 2010a). Serology is limited by the deficiency of an antibody response. Evaluation of serological tests in some studies reported various sensitivities and specificities, depending on the study population, materials used,

and techniques (Bergmans *et al.* 1997, Breitschwerdt 2007, Sander *et al.* 2001).

DNA sequencing for *Bartonella* species and strain identification assures 100% test specificity. Since the causative bacteria cannot be easily cultured, the diagnosis usually relies on epidemiological, clinical, and serological criteria (Guiyedi *et al.* 2013, Perez *et al.* 2011).

Conclusions

The significance of zoonoses and communicable diseases continues to grow. Two-thirds of emerging pathogens are of zoonotic origin (WHO 2012). Among these, *Bartonellae* are emerging vector-borne pathogens that appear to be distributed in mammals worldwide with highest prevalence in areas where conditions are most favourable for arthropod vectors. The important role of dogs, cats, and their ectoparasites in the transmission cycle of zoonotic *Bartonellae* suggests relevant implications for urban hygiene. Pets may represent excellent epidemiological sentinels for *Bartonella* infection in humans due to several factors: exposure to similar household and recreational environments of humans, potential parasitism by the same vectors, wide diversity of *Bartonella* species identified.

Because of their human-animal-environment aspects, *Bartonella* and bartonellosis represent an important case study in support of the One Health approach, which champions efficient prevention and a correct and timely diagnosis.

Wildlife, domestic animal, and human health professionals need to work collectively in the prevention of every aspect of bartonellosis, including patient education and professional training.

Only the One Health approach has the potential to reduce the health threat posed by *Bartonella* spp. infection.

Further research in risk factors is necessary to better understand the epidemiology of *Bartonellae*, as well as to develop guidelines for man-pet relationships and healthy associated lifestyles.

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