Review article

Factors associated with the rapid emergence of zoonotic *Bartonella* infections

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Abstract – Within the last 15 years, several bacteria of the genus *Bartonella* were recognized as zoonotic agents in humans and isolated from various mammalian reservoirs. Based on either isolation of the bacterium or PCR testing, eight *Bartonella* species or subspecies have been recognized as zoonotic agents, including *B. henselae*, *B. elizabethae*, *B. grahamii*, *B. vinsonii* subsp. *arupensis*, *B. vinsonii* subsp. *berkhoffii*, *B. grahamii*, *B. washoensis* and more recently *B. koehlerae*. The present manuscript reviews the factors associated with the emergence of these zoonotic pathogens, including better diagnostic tools and methods to identify these fastidious bacteria, host immunosuppression (caused by infectious agents, cancer, aging or induced by immunosuppressive drugs), the interaction of co-infection by several infectious agents that may enhanced the pathogenecity of these bacteria, increased outdoor activity leading to exposure to wildlife reservoirs or vectors, poverty and low income associated with infestation by various ectoparasites, such as body lice and finally the dispersal of *Bartonellae* around the world. Furthermore, a description of the main epidemiological and clinical features of zoonotic *Bartonellae* is given. Finally, the main means for diagnosis, treatment and prevention of these diseases are presented.

***Bartonella* spp. / emerging zoonoses / cat / dog / rodents**

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1. INTRODUCTION

Within the last 15 years, several new bacteria of the genus *Bartonella* were recognized as emerging zoonotic agents in humans and isolated from several mammalian reservoirs. If cat scratch disease (CSD) was a well known zoonosis in search of an etiological agent, the recognition of *Bartonella henselae* as its main etiological agent lead to the recognition of several different clinical syndromes caused by this bacterium in humans and in carnivores. In fact, the recognition of *B. henselae* as the agent of CSD was indirectly the result of the identification of a new bacterium causing a new zoonosis called bacillary angiomatosis in immunocompromised individuals, mainly AIDS patients [191, 193]. Furthermore, several rodent-borne *Bartonella* emerged as zoonotic agents in both humans and dogs [52].

Bartonella spp. are fastidious hemotropic Gram-negative organisms that have been recently identified in a wide range of domestic and wild mammals [25]. Based on either isolation of the bacterium or PCR testing, eight *Bartonella* species or subspecies have been recognized as zoonotic agents, including *B. henselae*, *B. elizabethae*, *B. grahamii*,

B. vinsonii subsp. *arupensis*, *B. vinsonii* subsp. *berkhoffii*, *B. grahamii*, *B. washoensis* [52] and more recently *B. koehlerae* [8]. At present, *B. clarridgeiae* is only considered as a possible zoonotic agent based on serological evidence in infected humans [136, 159, 205]. *Bartonella* species are usually vector-borne and the vector varies with the *Bartonella* species involved (i.e. sandflies for *B. bacilliformis* or human body lice for *B. quintana*) [52]. Although cat scratch disease (CSD) was described in France more than 50 years ago by Debré et al. [63], it is only in the last decade that *Bartonella henselae* was recognized as its etiological agent [69, 191, 235]. Cats represent the main reservoir of this bacterium, which is transmitted from cat to cat via the cat flea (*Ctenocephalides felis*) [46, 128]. Since the isolation of *B. henselae* from domestic cats in 1992, several new *Bartonella* species or subspecies have been identified in domestic and wild carnivores [52]. Similarly, new species of *Bartonella* have been identified in wild rodents and domestic and wild ruminants, with an increasing number of reports of human and canine infections caused by some of these rodent-borne *Bartonella* species.

2. FACTORS OF EMERGENCE OF ZOONOTIC *BARTONELLAE*

Several factors have lead to the emergence of *Bartonellae* as agents of zoonotic infections, which include:

2.1. Advanced diagnostic tools and methods

Among these, the development of molecular biology tools, especially the use of the polymerase chain reaction (PCR), improved the identification of these fastidious bacteria. Most human cases are now diagnosed based on PCR testing of tissue biopsies or serology using specific antigens, as isolation from the blood is quite uncommon from most cases [115]. Similarly, isolation of *Bartonella* from dogs is quite rare and most cases have been identified based on PCR of tissue samples, such as cardiac valves and liver biopsies [52].

2.2. Weakening of the host immune system associated with the emergence of immunocompromising diseases, organ transplant and cancer therapy

The first isolation of *B. henselae* was performed from the bloodstream of an AIDS patient presenting with very low CD4 counts [191], as severely immunocompromised people can be bacteremic for several weeks when suffering from bacillary angiomatosis [127]. Cases of bacillary angiomatosis were then associated with this bacterium when such patients had been exposed to a domestic cat (usually being scratched) [129]. Recently, a high rate of *Bartonella henselae* infection in HIV-positive outpatients in Johannesburg, South Africa was reported with almost 10% of the 188 patients being *Bartonella* bacteremic, as determined by nested polymerase chain reaction [87].

2.3. Co-infection by several infectious agents

Severe clinical forms of *B. henselae* infections have been reported in patients co-infected with other infectious organisms, such as *Borrelia* [78, 185], HIV [130] or Esptein-Barr virus [209]. In dogs, all *Bartonella* endocarditis cases reported in a study from northern California were seropositive for *A. phagocytophilum*, suggesting that co-infection by these two vector-borne agents could lead to this severe pathology [154]. Similarly, in the eastern USA and in Thailand, co-infection of dogs with several tick-borne pathogens, including *Bartonella* has been documented [27, 138, 181, 215, 220].

2.4. Increased outdoor activity, poverty and low income

Human exposure to some rodent-borne *Bartonellae*, especially *B. elizabethae* has been associated with exposure to rats among homeless people or intravenous drug users in urban areas of the USA [42, 56, 57, 77] or to outdoor activity in northern Europe, especially in orienteers in Sweden [155, 229]. Exposure to ticks has also been suggested for human infections [78, 152, 235]. Additionally, it was demonstrated that for dogs, living in a rural environment and being heavily exposed to ticks and fleas were risk factors associated with *Bartonella* infection [181]. In northern California, herding dogs were more likely to be *Bartonella* seropositive and toy dogs less likely to be seropositive than other breeds of dogs [107].

2.5. Dispersal of *Bartonellae* around the world

Ellis et al. [77] and Childs et al. [42] have both stated that: "accumulating data suggest an Old World origin for a group of bacteria that include *B. elizabethae*, a human pathogen first identified from the New World. The potential public health significance of these newly described organisms is undefined, but of international interest as their vertebrate reservoir has been introduced

throughout the world". Similarly, the distribution in various parts of the world of different genotypes/phenotypes of *B. henselae* by human's migrating with their pet cats may have occurred in the last few centuries. A recent report of the presence of *B. henselae* DNA in the teeth of cats buried in France between the XIIIth and XVIth Centuries indicated the presence of mainly genotype Houston I whereas in present times genotype Marseille is highly predominant in cats in that country [142]. It is also interesting to note that some reports [16, 68] have emphasized that *B. henselae* genotype Houston was more commonly identified in human cases of CSD whereas genotype Marseille was predominantly isolated within the respective cat populations.

3. BACTERIOLOGICAL FEATURES

Bartonellaceae are small gram-negative rods. Until recently, the genus *Bartonella* consisted of only one species, *B. bacilliformis.* The genus now combines all the species of the three genera *Bartonella, Rochalimaea*, and *Grahamella* into the family Bartonellaceae and the genus *Bartonella*; the family Bartonellaceae has also been removed from the order *Rickettsiales* [21, 30]. They are members of the alpha-2 subgroup of the alpha-proteobacteria. Most of these bacteria are erythrocyte-adherent bacilli. The present family consists of more than 20 species or subspecies, of which at least eight are human pathogens [52].

Bartonellaceae are fastidious, aerobic, short, pleomorphic gram-negative coccobacillary or bacillary rods ($0.6\,\mu m \times 1.0\,\mu m$) that take from 5 to 15 days and up to 45 days on primary culture to form visible colonies on enriched blood-containing media, as they are highly hemin-dependent [44]. In infected tissues, Warthin-Starry silver impregnation stain reveals small bacilli, which tend to appear as clumps of tightly compacted organisms. Similarly, small organisms can be identified in red blood cells by May-Grünwald Giemsa coloration. *Bartonellae* have a close evolutionary homology with members of the genera *Brucella*, *Agrobacterium* and *Rhizobium*. Bartonellaceae have the ability to infect red blood cells and to cause prolonged intraerythrocytic bacteremia in their specific mammalian reservoir host [64]. Such an infection has been well described in an experimental model of infection of rats with *B. tribocorum* [207]. Furthermore, these bacteria are unique among all known bacterial pathogens in their ability to cause vasoproliferative lesions through their ability to invade endothelial cells and trigger proliferation and migration of these cells [64].

Traditionally, *Bartonella* are cultivated in semisolid nutrient agar containing fresh rabbit blood (or sheep or horse blood) at 35 °C (except for *B. bacilliformis*, which grows best at 28 °C) in 5% CO_2. On primary isolation, some *Bartonella*, such as *B. henselae, B. clarridgeiae, B. vinsonii*, or *B. elizabethae* have colonies with a white, rough, dry, raised appearance and pit the medium. They are hard to break up or transfer. Because of the slow growth of these bacteria, standard biochemical methods for identification may not be applicable. The *Bartonella* are catalase, oxidase, urease and nitrate reductase negative [25]. Measurement of preformed enzymes and standard testing has revealed differences between *Bartonella* species. Most species are biochemically inert except for the production of peptidases [25].

Molecular genetic methods such as restriction fragment length polymorphism (RFLP) of genes encoding citrate synthase, 16S rRNA or 16S–23S rRNA spacer region, and more recently analysis based on polymerase chain reaction (PCR) of random, repetitive extragenic palindromic sequences have been used to distinguish strains and species of *Bartonella.* RFLP or sequence analysis of 16S rRNA, citrate synthase genes after PCR amplification both directly from specimens or pure cultures have been largely used for detecting and characterizing *Bartonella*. More recently, identification has also been performed with the amplification of the 16S-23S rRNA intergenic

spacer region (ITS) [201] or protein-coding genes. The genes the more widely used are those coding for the citrate synthase (*gltA*), the heat shock protein (*groEL*), the riboflavine (*ribC*), the RNA polymerase beta subunit (*rpoB*), a cell division protein (*ftsZ*) and a 17 kDa antigen [145].

4. EPIDEMIOLOGICAL FEATURES

4.1. Zoonotic *Bartonellae* with a feline or canine reservoir

Cat scratch disease is certainly the most common *Bartonella* zoonosis worldwide. Human cases have been reported from several continents, including North America, Europe, Australia, and from most countries where investigators looked for such an infection [25, 52]. It has been estimated that more than 22 000 human cases occurred in the USA in 1992, with an estimated incidence of disease in ambulatory patients of 9.3 per 100 000 persons per year [113]. In the Netherlands, the estimated number of CSD was 2 000 cases per year or 12.5 cases/ 100 000 persons [17]. Therefore, such observations suggest that worldwide several thousand cases of CSD may occur every year in many countries. Overall, CSD is more likely to occur in children and young adults [35]. Transmission from cat to human mainly occurs directly by a cat scratch and possibly via a cat bite [35] or possibly by a flea or a tick bite [152, 197, 235]. However, it is now suggested that flea bites are an unlikely mode of infection and that flea feces may be the only infecting material that could be inoculated by a cat scratch [83, 84]. *B. henselae* DNA was recently detected in a biting fly, raising concern about the role of these biting insects as *Bartonella* vector [54]. In immunocompromised individuals, bacillary angiomatosis and bacillary peliosis caused by *B. henselae* are usually associated with exposure to cats and cat fleas [127, 129]. However, bacillary peliosis was a clinical feature seen only in patients infected with *B. henselae* [129]. Different *Bartonella* species, but more frequently *B. henselae* and

B. quintana, can cause human endocarditis [31]. An estimated 3% of all cases of human endocarditis have been attributed to *Bartonella* infection [189]. However, only *B. henselae* is considered to be zoonotic among these two *Bartonella* species. In Sweden, the emergence of orienteering (countryside running based on navigational acuity using map and compass-reading skills) was marked between 1979 and 1992 by an elevated rate of sudden unexpected cardiac deaths in top-ranked competitors [229]. Four of these deaths were likely caused by *B. henselae* and *B. quintana*, as DNA was detected in the cardiac tissue of 4 of the 5 cases tested and in the lung of the fifth case, whereas no *Bartonella* DNA was detected in six control hearts.

In humans, *B. clarridgeiae* antibodies have been reported in a suspect case of CSD and in a patient with a chest-wall abscess [136, 159]. Furthermore, anti-flagella (FlaA) specific antibodies against *B. clarridgeiae* were detected in 3.9% of 724 patients with lymphadenopathy [205]. However, significant cross-reactivity between *B. henselae* and *B. clarridgeiae* was noted in a recent study from Japan [219]. These serological investigations suggest that *B. clarridgeiae* may be a minor causative agent of CSD.

More recently, the first human case of endocarditis associated with *B. koehlerae*, was reported from Israel [8]. Furthermore, these authors were able to isolate *B. koehlerae* from a bacteremic stray cat from that country.

Domestic cats are the main reservoir for *B. henselae*, *B. clarridgeiae* and *B. koehlerae* [45, 128, 192]. Sero-epidemiological and bacteriological studies have demonstrated the worldwide distribution of *B. henselae* infection in domestic cats. *B. henselae* antibody prevalence varies from 5% to 80%, and bacteremia prevalence ranges from a few percent to more than half of the population tested, according to the geographical location and the cat status (pet or stray). Data of surveys concerning cat populations are summarized in Tables I, II, III for

Table I. Surveys of *Bartonella* spp. infections (bacteremia or antibodies) in domestic cats in France, Germany and the Netherlands.

Country (location)	Survey	Cat population	Bartonella	Prevalence positive/total (%)	Reference
France (Paris)	B	Pets	B.spp.	72/436 (**16.5**)	[100]
			B.h.	H: 11/72 (**15.3**)	
				M: 36/72 (**50**)	
				H + M: 2/72 (**2.8**)	
			B.c.	15/72 (**20.8**)	
			B.h. + B.c.	8/72 (**2**)	
	S	Pets	B.h. + B.c.	179/436 (**41.1**)	
France (Lyon)	B	Pets	B.spp.	8/99 (**8.1**)	[199]
			B.h.	H: 6/8 (**75**)	
				M: 0/8 (**0**)	
			B.c.	2/8 (**25**)	
France (Nancy)	B	Strays	B.spp.	50/94 (**53**)	[106]
			B.h.	H: 17/50 (**34**)	
				M: 18/50 (**36**)	
			B.c.	15/50 (**30**)	
France (Marseille?)	B	Strays	B.spp.	38/61 (**62.3**)	[143]
			B.h.	H: 15/38 (**39.5**)	
				M: 7/38 (**18.4**)	
			B.c.	16/38 (**42.1**)	
Germany	S	Pets	B.h.	107/713 (**15**)	[103]
Germany (Freiburg)	B	Pets	B.h.	13/100 (**13**)	[203]
Germany (Berlin)	B	Pets/Strays	B.h.	20/193 (**10.4**)	[7]
				Pets: 1/97 (**1**)	
				Stray: 19/96 (**18.7**)	
				H: 1/20 (**5**)	
				M: 18/20 (**90**)	
			B.c.	1/20 (a stray cat) (**5**)	
The Netherlands	B	Shelter	B.h.	25/113 (**22**)	[17]
				H: 6/25 (**24**)	
				M: 10/25 (**40**)	
			B.h./B.c.	5/25 (**20**)	
			B.c.	4/25 (**16**)	
	S	Shelter/Pets	B.h.	Not given (**35–60**)	
				Pets: 28/50 (**56**)	
				Shelter: 56/113 (**50**)	

S: seroprevalence, B: bacteremia prevalence, B.h.: *Bartonella henselae*, B.c.: *Bartonella clarridgeiae*, B.spp.: *Bartonella* species, H: type I (Houston I), M: type II (Marseille).

Table II. Surveys of *Bartonella* spp. infections (bacteremia or antibodies) in domestic cats in northern and central Europe.

Country	Survey	Cat population	Bartonella	Prevalence positive/total (**%**)	Reference
Austria	S	Pets	B.h.	32/96 (**33.3**)	[3]
Czech Republic	B	Pets/Shelter/Stray	B.h.	5/61 (**8**) M: 5/5 (**100**) Pets: 0/34 (**0**) Shelter: 1/21 (**5**) Stray: 4/6 (**66.6**)	[170]
Denmark	B	Pets/Shelter	B.h.	21/93 (**22.6**) H: 1/21 (**5**) M: 20/21 (**95**) Pets: 8/44 (**18.2**) Shelter: 13/49 (**26.5**)	[49]
	S	Pets/Shelter	B.h.	42/92 (**45.6**)	
Denmark (North Zealand)	B	Strays	B.h.	11/25 (**44**) M: 11/11 (**100**)	[75]
Norway	B	Pets	B.spp.	0/100 (**0**)	[15]
	S	Pets	B.h. (EIA)	1/100 (**1**)	
			B.h. (IFA)	0/100 (**0**)	
Poland	S	Shelters	B.h.	31/36 (**86**)	[184]
Sweden	S	Pets	B.h.	3/292 (**1**)	[108]
Sweden (Stockholm and southern Sweden)	B	Pets	B.h.	2/91 (**2.2**) M: 2/2 (**100**)	[76]
Switzerland	S	Pets	B.h.	60/728 (**8.3**)	[92]
United Kingdom (Bristol and Southwest UK)	B	Pets	B.h.	34/360 (**9.4**) H: 2/34 (**6**) M: 30/34 (**88**) H + M: 2/34 (**6**)	[22]
United Kingdom	S	Pets	B.h.	28/69 (**40.6**)	[13]
	S	Feral	B.h.	33/79 (**41.8**)	
United Kingdom	B	Pets	B.h.	40/351 (**11.4**)	[147]

S: seroprevalence, B: bacteremia prevalence, B.h.: *Bartonella henselae*, B.c.: *Bartonella clarridgeiae*, B.spp.: *Bartonella* species, EIA: ELISA, IFA: immunofluorescence, H: type I (Houston I), M: type II (Marseille).

Table III. Surveys of *Bartonella* spp. infections (bacteremia or antibodies) in domestic cats in Italy and Portugal.

Country	Survey	Cat population	Bartonella	Prevalence positive/total (**%**)	Reference
Italy (Lombardia) (3 urban, 3 rural areas)	B	Stray	B.spp. B.h.	140/769 (**18**) H: 27/131 (**20.6**) M: 80/131 (**61.1**) H + M: 24/131 (**18**)	[81]
	S	Stray	B.h.	207/540 (**38**)	
Italy (northern)	B	Stray	B.h.	361/1585 (**23**) Not given (**26**) Not given (**52**)	[82]
			B.c.	Not given (**5**)	
	S	Stray	B.h.	553/1416 (**39**)	
Italy (Tuscany)	B	Pets/catteries	B.spp.	0/28 (**0**)	[73]
	S	Pets/catteries	B.h.	98/427 (**23**)	
Italy (Reggio Emilia)	B	Pets	B.h.	24/248 (**9.7**)	[33]
Portugal	S	Pets	B.h.	1/14 (**6.7**)	[41]

S: seroprevalence, B: bacteremia prevalence, B.h.: *Bartonella henselae*, B.c.: *Bartonella clarridgeiae*, B.spp.: *Bartonella* species, H: type I (Houston I), M: type II (Marseille).

Europe, Table IV for Asia and Oceania, Table V for the Americas and Table VI for Africa and the Middle East. Cats are usually bacteremic for several weeks, based on experimental infections; but some cats can be bacteremic for more than a year, as shown in natural settings [132, 133] or experimentally [1, 131, 135, 137]. However, prevalence and level (number of colony forming units per millilitre of blood) of bacteremia are usually higher in young cats (< 1 year) than in adult cats [45]. Two main genotypes/serotypes of *B. henselae* have been described [16, 70, 144], and major regional variations in the respective prevalence of *B. henselae* type I (Houston) and type II (Marseille) have been reported in domestic cat populations (Tabs. I–VI). Co-infection of cats with these two genotypes has also been reported [17, 99]. Transmission of infection among cats requires the presence of fleas [46]. However, it is strongly suggested that infection among cats is occurring through inoculation of flea feces rather than flea bites [83, 84]. *Bartonella clarridgeiae* is unevenly distributed in cat populations worldwide, with a prevalence of 30% to 36% of all *Bartonella* isolates in some studies (France, the Netherlands or Philippines) to no more than 10% in the southeastern USA and Japan or Taiwan and lack of isolation in several studies in Europe, Australia and North America [52, 95]. *Bartonella koehlerae* has been isolated only from two cats in California, one cat in France and recently in one cat in Israel [8, 72, 196]. Furthermore, *Bartonella* infection has been reported in wild felids, such as pumas and bobcats in the New World [53].

Bartonella vinsonii subsp. *berkhoffii* was identified in a human case of endocarditis

Table IV. Surveys on *Bartonella* spp. infections (bacteremia or antibodies) in domestic cats in Asia and Oceania.

Country	Survey	Cat Population	Bartonella	Prevalence positive/total (%)	Reference
Australia (Sydney)	B	Pets/Feral	B.h.	27/77 (**35**) Pets: 3/18 (**16**) Feral: 24/59 (**40**)	[24]
Australia (Melbourne)	B	Pets	B.h.	45/342 (**13.2**)	[174]
New Zealand (Auckland)	B	Pets	B.h.	8/48 (17)	[117]
Japan	S	Pets	B.h.	30/199 (**15.1**)	[221]
Japan (Kanagawa, Saitama Prefectures)	S	Pets	B.h.	43/471 (**9.1**)	[165]
Japan	S	Pets	B.h.	128/1447 (**8.8**)	[168]
Japan	B	Pets/Pound	B.h.	3/33 (**9.1**)	[164]
Japan	B	Pets	B.spp. B.h.	50/690 (**7.2**) H: 43/45 (**95.5**) M: 1/45 (**2.2**)	[166]
			B.c.	4/50 (**8**)	
			B.c. + B.h.	1/50 (**2**)	
Indonesia (Jakarta)	B	Stray	B.h.	6/14 (**43**)	[163]
			B.c.	3/14 (**21**)	
	S	Stray	B.h.	40/74 (**54**)	
Philippines (Manilla)	B	Stray	B.spp. B.h.	19/31 (**61**) H: 13/19 (**68.4**)	[47]
			B.c.	2/19 (**10.5**)	
			B.h. + B.c.	4/19 (**21**)	
	S	Stray	B.h.	73/107 (**68**)	
			B.c.	70/107 (**65**)	
Singapore	S	Stray	B.h.	38/80 (**47.5**)	[173]
Thailand	B	Pets/Stray	B.spp.	76/275 (**27.6**)	[167]
			B.h.	63/76 (**83**)	
			B.c.	9/76 (**11.8**)	
			B.h. + B.c.	4/76 (**5.3**)	
			B.h.	H: 48/67 (**71.6**) M: 13/67 (**19.4**)	

S: seroprevalence, B: Bacteremia prevalence, B.h.: *Bartonella henselae*, B.c.: *Bartonella clarridgeiae*, B.spp.: *Bartonella* species, H: type I (Houston I), M: type II (Marseille).

Table V. Surveys on *Bartonella* spp. infections (bacteremia or antibodies) in domestic cats in the Americas.

Country	Survey	Cat population	Bartonella	Prevalence positive/total (**%**)	Reference
Brazil	S	Pets?	B.h.	Not given (**46**)	cited in [224]
Chile (Valdivia)	S	Pets	B.h.	54/76 (**71**)	[236]
			B.c.	Not given (**18.6**)	
Canada	S	Pets	B.h.	43/242 (**17.8**)	[149]
USA/Canada	S	Pets	B.h.	175/628 (**27.9**)	[116]
USA	S	Pets/Shelter	B.h.	370/1314 (**28.2**)	[41]
USA (Baltimore)	S	Stray/Vet. Hosp.	B.h.	77/592 (**13**)	[40]
USA (North Carolina)	S	Pets	B.h.	46/114 (**40.4**)	[12]
USA (Florida)	S	Feral/Stray	B.h.	186/553 (**33.6**)	[153]
USA (North Carolina)	S	Feral	B.h.	93/100 (**93**)	[176]
	S	Pets	B.h	57/76 (**75**)	
USA (California)	B	Pets/Stray	B.h.	81/205 (**39.5**) Pets: 24/112 (**21.4**) Stray: 57/93 (**61.3**)	[45]
	S	Pets/Stray	B.h.	165/205 (**81**)	
USA	B	Pets	B.h.	65/271 (**24**) H: 14/49 (**28.6**) M: 32/49 (**65.3**) H + M: 3/49 (**6.1**)	[98]
			B.c.	(**0**)	
	S	Pets	B.h.	138/271 (**51**)	

S: seroprevalence, B: Bacteremia prevalence, B.h.: *Bartonella henselae*, B.c.: *Bartonella clarridgeiae*, B.spp.: *Bartonella* species, H: type I (Houston I), M: type II (Marseille).

Table VI. Serosurveys on *Bartonella* spp. infection in domestic cats in Africa and the Middle East.

Country	Survey	Cat population	Bartonella	Prevalence positive/total (**%**)	Reference
Egypt	S	Pets	B.h.	5/42 (**12**)	[41]
Israel	S	Pets	B.h.	45/114 (**39.5**)	[12]
Israel	B	Stray	B.h.	40/48 (**83**)	[8]
			B.c.	7/48 (**15**)	
			B.k.	1/48 (**2**)	
Jordan	S	Pets	B.h.	55/153 (**36**) true prevalence (**32**)	[4]
South Africa	S	Shelter	B.h.	11/52 (**21**)	[120]
	B	Pets	B.h.	1/31 (**3.2**) (H: 1/1)	[187]
Zimbabwe	S	Pets/Shelter	B.h.	28/119 (**24**)	[120]
	B	Pets	B.h.	2/25 (**8**)	[121]

S: seroprevalence, B: Bacteremia prevalence, B.h.: *Bartonella henselae*, B.c.: *Bartonella clarridgeiae*, B.k.: *Bartonella koehlerae*, B.spp.: *Bartonella* species, H: type I (Houston I), M: type II (Marseille).

[200]. This subspecies appears to be the most common *Bartonella* species/subspecies causing endocarditis in dogs [25]; however, other *Bartonella* species, including *B. clarridgeiae*, *B. washoensis* have been identified in canine endocarditis cases [48, 50, 154]. Overall, the prevalence of *B. vinsonii* subsp. *berkhoffii* antibodies in pet dogs is quite low (< 5%) [107, 181, 212], but can be higher in specific populations [11, 111] and in free-roaming dogs in the tropics ranging from 19% (5/26) for dogs from French Guyana and Martinique to 65% (33/51) for native dogs from Sudan[1]. In the western USA, coyotes (*Canis latrans*) constitute a major reservoir for *Bartonella vinsonii* subsp. *berkhoffii* [37, 38]. Limited data is available about the seroprevalence of *B. henselae* in dogs [13, 65, 107] which was found to also be quite low. However, a recent study reported higher prevalence of *B. henselae* antibodies in healthy (10.1%) and sick (27.2%) dogs from the southeastern USA [212].

4.2. Rodent-borne zoonotic *Bartonellae*

At present, only a limited number of human infections caused by rodent-borne *Bartonella* species or subspecies have been described in the scientific literature. There are still many unknown risk factors associated with such infections (i.e. mode of

[1] Davoust B., Drancourt M., Boni M., et al., Survey of seroprevalence of *Bartonella vinsonii*, *Ehrlichia canis* and *Coxiella burnetii* in dogs in southeast France, French Guyana, Martinique, Senegal, Ivory Coast and Sudan, EUWOG-ASR Joint Meeting, Marseille, France, 14–16 June 1999, Abstract 232B.

infection, vector involved, source of infection). Among the rodent-borne *Bartonellae*, *B. elizabethae* infection seems to be quite prevalent in intravenous (IV) drug users and homeless people in various parts of the USA and also in Sweden [56, 57, 156], based on serological studies. In IV drug users, *B. elizabethae* seroprevalence ranged from 33% in Baltimore [56] to 39% in Stockholm [156] and 46% in New York [57]. In homeless people from Los Angeles, California, the seroprevalence was 12.5% [210]. Furthermore, 31% of 1 136 Swedish orienteers were seropositive for *B. elizabethae* [155]. Infections caused by *B. elizabethae* in humans have been associated with endocarditis and neuroretinitis [60, 177]. However, such studies based only on serological data need to be confirmed by identification of this pathogen either by PCR methods or isolation. Rats (*Rattus norvegicus*) constitute the main reservoir of *B. elizabethae* [42, 77]. This *Bartonella* species has been isolated from urban rats from various parts of the world, including the USA (Louisiana, Maryland), Portugal and Peru [19, 77]. In China, Yunnan rats are infected with a large number of *Bartonella* strains that are genetically related to *B. elizabethae* [234]. In Thailand, a number of the *Bartonella* isolates from Thai rodents are closely related to *B. grahamii* and *B. elizabethae*, two species that have been associated with human illness [36].

Bartonella grahamii has been mainly isolated from bank voles (*Clethrionomys glareolus*) in the United Kingdom [20] and Poland [10] and from yellow-necked mice (*Apodemus flavicollis*) in Sweden [110], but has also been isolated from rats in the USA and a domestic mouse captured in California [77]. The rodent flea *Ctenophthalmus nobilis* was recently shown to be a competent vector of at least two *Bartonella* species, *B. grahamii*, which has previously been associated with human ocular infection (neuroretinitis and retinal artery occlusion) [123, 208], and *B. taylorii* [23]. White-footed mice (*Peromyscus leucopus*) are the reservoir of *B. vinsonii* subspecies *arupensis*, which has been isolated from 5% of 81 mice tested from Minnesota and Wisconsin and associated with one human infection (fever, bacteremia, neurological symptoms) [109, 228]. California ground squirrels (*Spermophilus beecheyi*) are the main reservoir of *B. washoensis*, which has been identified in a human case of myocarditis [139] and in a case of endocarditis in a dog [50]. Finally, isolation of *B. henselae* type Houston I from three long-tailed field mice (*Apodemus sylvaticus*) was very recently reported [75] and raises an interesting question about the possibility of natural infection of wild rodents with *B. henselae*. Further studies will be required to determine if rodents could be another natural reservoir of this bacterium beside its feline reservoir.

The epidemiological importance of rodent-borne *Bartonella* spp. as a cause of disease in animals and man is emerging, as suggested for a novel rodent *Bartonella*-associated febrile illness in the rural southwestern USA, based on serological evidence[2]. A few patients had high antibody titers against a strain of *Bartonella* isolated from a white-throated wood rat (*Neotoma albigula*). Many new *Bartonella* species have been identified in South East Asia [36, 234] and some of them could be a source of human infection (Kosoy M., personal communication).

5. CLINICAL FEATURES

5.1. Humans

Classical Cat Scratch Disease: CSD caused by *B. henselae* is mainly characterized by a benign regional lympadenopathy [35, 43, 63, 157]. Usually after a cat scratch, a papule and then a pustule develops within

[2] Kosoy M., Ying B., Koster F., Gage K., Ecological and epidemiological implications of high genetic and antigenic diversity of rodent-borne *Bartonella* strains in the US West, American Society for Rickettsiology – *Bartonella* as an emerging pathogen group. 2001 joint conference, Big Sky, Montana, USA, 18–22 August 2001, Abstract 108.

Table VII. Miscellanous manifestations of *Bartonella henselae* infection in humans.

Clinical manifestations	References
Tumoral and Pseudotumoral manifestations of CSD	
Mimicking breast tumor, breast mass	[93, 160]
Granulomatous hepatitis and necrotizing splenitis	[150]
Simulating lymphoma	[90, 183, 231]
Gammopathy	[140]
Simulating rhabdomyosarcoma	[161]
Mimicking parotid malignancy	[122]
Pseudotumoral presentation	[74]
Simulating a malignant process of the chest wall	[172]
Peripheral lymphadenopathy	[14]
Myelodysplastic syndrome	[225]
Joint and/or bone localisation	
Arthritis, arthralgy	[5, 105]
Osteomyelitis	[148]
Skin localisation	
Skin nodules, cutaneous vasculitis	[206]
Erythema nodosum, granuloma annulare	[211]
Petechial, papular and vasculitic skin lesions,	[225]
Unusual eruption	[146]
Paronychia	[202]
Miscellaneous	
Endocarditis	[31, 70, 85, 101, 189, 223]
Henoch-Schonlein purpura	[9]
Purpura with leukocytoclasic vasculitis	[206]
Glomerulonephritis	[223]
Periodontitis	[55]

7 to 12 days at the inoculation site [35, 115, 157]. A regional lymphadenopathy (usually involving a single lymph node) develops one to three weeks after the inoculation and can persist a few weeks to several months [35]. Abscessed lymph nodes are reported occasionally in 12% [35] up to 48% of the cases [62]. Low-grade fever, malaise and aching are often reported; and in some instances, headache, anorexia and splenomegaly can occur. The various clinical manifestations of *B. henselae* infection are summarized in Table VII.

Atypical CSD: From 5% to 9% of CSD cases may develop atypical manifestations, including Parinaud's oculoglandular syndrome, encephalitis, endocarditis, hemolytic anemia, hepatosplenomegaly, glomerulonephritis, pneumonia, relapsing bacteremia, and osteomyelitis [157]. Cat scratch disease encephalopathy (CSDE), possibly associated with an immune-mediated response to *B. henselae* infection, is one of the most severe complications of CSD [175]. Patients with CSDE usually completely recover within one year without any sequelae. However,

Table VIII. Neurologic manifestations of *Bartonella henselae* infection in humans.

Clinical signs	References
Epilepsia partialis continua	[188]
Encephalopathy	[102, 162, 175]
Status epilepticus	[6, 79, 102]
Peripheral facial nerve paralysis	[227]
Coma	[102]
Fatal meningitis and encephalitis	[89, 162]
Meningoencephalitis	[216]
Meningitis	[230]
Hemiplegia	[195]

one case of fatal meningitis and encephalitis was reported in a 4-year-old child [89].

An expanding clinical spectrum associated with *B. henselae* infection: *B. henselae* has been identified as a frequent cause of prolonged fever and fever of unknown origin in children [114, 217, 218].

Besides a wider spectrum of neurological symptoms (Tab. VIII), many ocular lesions have also been associated with *Bartonella* infection, such as uveitis, focal retinal phlebitis, neuroretinitis, retinal and optical nerve neovascularization, retinal artery and vein occlusion (Tab. IX). It is important to indicate that most of these observations have mainly been based on the presence of *Bartonella* antibodies or a proven seroconversion rather than by isolation or positive PCR.

Tumoral and pseudo-tumoral lesions have also been reported, such as lesions mimicking breast tumor or rhabdomyosarcoma, lymphoma and gammopathy, as well as granulomatous hepatitis and necrotizing splenitis (Tab. VII). Rheumatic manifestations (arthralgia, arthritis) of *Bartonella* infection have been described both in children and adults (Tab. VII), as well as erythema nodosum [35, 211], leukocytoclastic vasculitis [104], fever of unknown origin with myalgia [114] and arthralgia [5, 35, 105]. Cases of osteomyelitis have also been described [148]. A causative role for *B. henselae* in Henoch-Schonlein purpura (HSP) was suggested based on serological evidence, as 12 (67%) of 18 HSP patients were seropositive versus only 8 (14%) of 57 controls [9]. HSP is an immune-mediated vasculitis that is characterized by excessive IgA production and frequently associated with thrombocytopenia. Monoclonal and biclonal

Table IX. Ocular manifestations of *Bartonella* spp. infection in humans.

Clinical signs	References
Uveitis	[71, 179]
Multifocal retinitis, neuroretinitis/stellate neuroretinitis (Leber's neuroretinitis) macular star/neovascularization	[18, 58, 59, 126, 169, 179, 180]
Parinaud's oculoglandular syndrome	[58, 80]
Retinal artery and vein occlusion, neovascular glaucoma, severe vision loss.	[94]
Optic disk edema with peripapillary serous retinal detachment	[226]
Peripapillary angioma,	[94]
Retinochoroidal exsudate, retinal phlebitis	[67]
Disciform keratitis	[88]
Retinal and optic nerve neovascularization	[169]
Focal retinochoroiditis, unifocal helioid choroiditis	[58, 186]
Posterior segment involvement	[125]

gammopathy in two patients infected with *Bartonella henselae* has also been described [140]. *Bartonella* have also been suggested as a cause of granulum annulare [211] and glomerulonephritis associated with negative culture endocarditis [223]. The first case of spontaneous splenic rupture caused by infection with *B. henselae* was recently reported, leading to massive hemoperitoneum [61]. Lesion of the spleen is common in disseminated infection with *B. henselae* [213], but massive spontaneous hemoperitoneum was only reported in association with hepatic bacillary peliosis in an HIV-infected patient [151].

Bartonella spp. were first described as a cause of human endocarditis in three separate reports in 1993, one caused by *B. quintana* in an immunocompromised individual [214], one caused by *B. elizabethae* in an immunocompetent patient [60] and the third caused by *B.* (*Rochalimaea*) *henselae* [101]. *Bartonella* species, mainly *B. quintana* and *B. henselae*, account for approximately 3% of human endocarditis cases, with more than 100 human cases reported in the international literature since 1993 [85, 189, 190]. In most human cases of *Bartonella* endocarditis, the vegetative lesions are preferentially located on the aortic valve [189] and most patients have high antibody titers [86]. Furthermore, most cases of *B. henselae* endocarditis are culture negative but positive by DNA amplification [85]. *Bartonella henselae* and *B. quintana* DNA were also detected in the cardiac tissue of four young Swedish orienteers who died of unexpected sudden cardiac death [229].

In immunocompromised individuals, bacillary angiomatosis (BA) is one of the most common clinical manifestations of *Bartonella* infections [127]. The presence of chronic vascular proliferative lesions is observed. HIV infected patients with CD4$^+$ cell counts of less than 50/mm^3 are more likely to develop BA lesions. Histopathologically, cutaneous BA is characterized by a tumor-like growth pattern with proliferation of capillaries having protuberant epitheloid

endothelial cells [127, 193]. In transplant patients, various clinical manifestations or pathological lesions have been reported, such as pulmonary nodules [34] or sternal abscess [32], disseminated infection with granulomatous hepatitis [112], acute organ rejection [66], bacillary peliosis [2] and bacillary angiomatosis [118]. A case of hemophagocytic syndrome in a transplant patient was recently associated with *B. henselae* infection [119]. Hemophagocytic syndrome (HPS) combines febrile hepatosplenomegaly, pancytopenia, hypofibrinemia, and liver dysfunction.

5.2. Cats

Cats usually appear to be healthy carriers of *B. henselae*, as limited pathology has been associated with natural infection. However, due to the high prevalence of infection in cat populations, it has been difficult to attribute specific clinical signs to cats naturally infected with *B. henselae* [43, 45]. Based on serological results, naturally infected cats were more likely to have lymphadenitis and gingivitis, especially those co-infected with the feline immunodeficiency virus [222]. Such an association was also demonstrated between *B. henselae* seropositivity and presence of stomatitis or urological diseases [92]. *Bartonella henselae* has been implicated as a potential cause of anterior uveitis in cats [141] and a PCR confirmed case of *B. henselae* endocarditis was described in a cat from California [51].

In experimental conditions, cats infected with *B. henselae* (mainly type II, feline isolates) have developed various clinical signs [96, 137, 178]. The most commonly reported sign is fever, which usually does not last for more than a week [95]. Local inflammation (erythema, swelling) at the site of inoculation and localized or generalized lymphadenopathy have also been observed. Some other signs include lethargy and anorexia. Some cats also developed mild neurological signs, such as nystagmus, tremors, focal motor seizures, and behavior changes [95]. Reproductive disorders (stillbirths, lack of

pregnancy or pregnancy only after repeated breedings) were reported in experimentally infected queens [97]. Variation in pathogenicity of strains has been suggested for differences in clinical signs observed in experimental conditions [178].

5.3. Dogs

The first isolation of *Bartonella* from a dog occurred in a case of endocarditis in 1993 [26, 134]. Since then, *Bartonella vinsonii* subsp. *berkhoffii* has been identified as an important cause of canine endocarditis [26, 28], and was determined as the cause of one human endocarditis case [200]. As in humans, the clinical spectrum of *Bartonella* infection in dogs is expanding, as it is now associated with cardiac arrhythmias, endocarditis and myocarditis [28], as well as granulomatous lymphadenitis and granulomatous rhinitis [182]. In both humans and dogs, *Bartonella* associated cases of endocarditis usually involve the aortic valve and are characterized by massive vegetative lesions [154]. At one veterinary teaching hospital, *Bartonella* infection was implicated in almost one third of the endocarditis cases diagnosed over a two-year period [154]. Based upon serological evidence, infection with *B. vinsonii* subsp. *berkhoffii* may also cause immune-mediated hemolytic anemia, neutrophilic or granulomatous meningo encephalitis, neutrophilic polyarthritis, cutaneous vasculitis, and uveitis in dogs [29]. A case-control study of clinical diagnosis associated with dogs seropositive for *Bartonella* spp. suggests an association with lameness, arthritis-related lameness, splenomegaly and nasal discharge/epistaxis [107]. However, *B. vinsonii* subsp. *berkhoffii* has also been isolated from clinically healthy dogs, which may be long-term carriers of the bacterium [132]. Dogs can be infected by several other zoonotic *Bartonella* species, including *B. clarridgeiae* isolated from the blood of a dog with endocarditis [48] and detected by PCR in a dog with hepatic lymphocytic hepatitis [91]. *B. henselae* DNA has been detected in a dog

with peliosis hepatis [124] and more recently in a dog with granulomatous hepatopathy [91]. *Bartonella henselae* DNA was amplified from the blood of three dogs with various clinical entities [171]. *Bartonella elizabethae* DNA was also detected in the blood of a sick dog [171]. Finally, *B. washoensis*, a rodent borne zoonotic *Bartonella*, was isolated from a dog suffering from mitral endocarditis [50].

6. DIAGNOSIS

6.1. Clinical diagnosis

In humans, clinical diagnosis of cat scratch disease is based on detection of an enlarged lymph node and possibly the presence of a small vesicle or granuloma at the inoculation site. However, clinical diagnosis of atypical forms of CSD and other emerging syndromes associated with *B. henselae* infection or other zoonotic *Bartonella* species is not easy and requires laboratory diagnostic means. In culture negative cases, using classical isolation media, the presence of epidemiological factors such a cat scratch or bite, owning a cat, possible contact with rodent, with fleas, ticks or other blood sucking arthropods may suggest such an etiology and should lead to *Bartonella* specific testing (serology, culture or PCR).

In dogs and cats, clinical diagnosis is usually not easy, as the clinical spectrum of *Bartonella* infection is not fully elucidated. *Bartonella* infection should be suspected in dogs with endocarditis, especially if affecting the aortic valve [154]. It also should be suspected in dogs with prolonged or intermittent fever, lethargy, unexplained lameness, or unexplained granulomatous disease. Similarly, veterinarians should consider performing a diagnostic test for *Bartonella* infection in sick dogs, when there is clinical or epidemiological suspicion of tick exposure. Thrombocytopenia, anemia, neutrophilic leukocytosis, and eosinophilia are the most commonly detected hematologic abnormalities in dogs seropositive for *B. vinsonii*

subsp. *berkhoffii* [29]. In all cases, suspicion of *Bartonella* infection is mainly established through serological testing, which provides evidence of *Bartonella* exposure [113, 115].

6.2. Serologic testing

In humans, serologic testing (mainly IFA testing) is the reference test for diagnosis of cat scratch disease [86, 115]. An IgG anti-*B. henselae* antibody titer ≥ 1:64 is considered as positive for infection when patients are tested at least two to three weeks after a suspected infection. *Bartonella*-associated endocarditis in humans and animals is usually associated with much higher IFA antibody titers (> 1:800) [86, 115]. Commercially prepared IFA slides for *B. henselae* and *B. quintana* antigens are available. Zangwill et al. [235] estimated the sensitivity and specificity of a *B. henselae*-based IFA to be 84% and 96%, respectively. A study comparing two commercially available IFA tests reported that the tests for IgG antibodies to *B. henselae* had higher sensitivities (100% and 85%, respectively) than specificities (70% and 73%, respectively), although this may have been the result of previous exposure to *B. henselae* among the healthy controls designated as the non-infected group [204]. Furthermore, a limiting diagnostic factor in humans is the lack of commercial tests for most rodent-borne zoonotic *Bartonella* species.

In cats, serologic testing is of limited diagnostic value, as many cats (especially stray cats) are likely to be seropositive against *B. henselae* [45]. Testing is indicated in kittens or recently adopted cats, because seronegative cats are more likely not to be bacteremic. Similarly, persons who may have immunocompromising conditions should require that an IFA test detecting antibodies against *B. henselae* be performed on cats prior to adoption. However, bacteremia in seronegative cats has been reported in a few instances and the antibodies usually cross-react with several *Bartonella* antigens [52]. As shown in one

of our studies, serological screening for *Bartonella* antibodies may not be useful for the identification of bacteremic cats (positive predicite value = 46.4%), but the lack of antibodies to *B. henselae* was highly predictive of the absence of bacteremia (negative predicite value = 89.7%) [45]. Because of these limitations for serologic testing, bacterial isolation or PCR assay are necessary to identify the infecting *Bartonella* spp.

In dogs, as for humans, diagnosis of *Bartonella* infection is largely based on the presence of specific antibodies. Testing for various antigens seems to be appropriate, including *B. vinsonii berkhoffii* and *B. henselae* [107, 212].

No formal test evaluation studies have been undertaken to estimate the sensitivities and specificities of the serological tests commonly used for the diagnosis of *Bartonella* infection in cats and dogs. One study investigating the seroprevalence of *B. henselae* and *B. quintana* among pet cats in Jordan did provide estimates of sensitivity and specificity for the IFA used in the study [4]. That author reported that the sensitivities of the *B. henselae* IgG and *B. quintana* IgG IFA tests were 99% and 88%, respectively, while the specificities were 94% and 90%, respectively. These results will have to be validated, however, as it is unclear how infection status of cats was determined and whether they were representative of a population of naturally infected cats.

6.3. Bacterial isolation or PCR assay

Isolation of *Bartonella* spp. from cats or from humans with bacillary angiomatosis (for whom serologic testing may not be useful, because patients often do not mount detectable antibodies) is much easier than isolation of those organisms from other animal species or non-immunocompromised individuals. A positive blood culture or culture of other tissue is the most reliable test for definitive diagnosis of active *Bartonella* infection [95]. However, in cats, multiple blood cultures may be necessary because of

the relapsing nature of feline *Bartonella* bacteremia [137]. In humans with cat scratch disease or dogs with *Bartonella* infection, isolation of these bacteria is rarely successful. Isolation of *Bartonella* from blood samples is performed usually by using either pediatric lysis-centrifugation tubes or more commonly plastic tubes containing EDTA. The use of plastic EDTA tubes has the advantage to prevent breakage of the blood tube when subjected to low temperature freezing and avoid the risk of sample contamination during transfer from glass to plastic tubes prior to freezing. Anticoagulated blood is plated (usually after freezing to induce RBC lysis) onto fresh rabbit blood agar and incubated for at least four weeks at 35 °C with an atmosphere containing 5% carbon dioxide. Identification of the isolate is performed using molecular techniques, such as PCR or partial sequencing of selected genes.

Compared with bacteriologic culture, extraction of DNA from tissue samples and PCR testing has been more successful as a method of diagnosis of *Bartonella* infection in humans and dogs [115, 127, 154, 191]. Frozen tissue samples or fresh biopsy specimens can be easily tested. Polymerase chain reaction assay of paraffin-embedded tissues is more cumbersome, but possible. Testing should be performed by laboratory personnals who are familiar with processing these fastidious organisms; laboratories should be contacted for specific instructions for sample collection and submission.

7. TREATMENT

In humans, infected with *B. henselae*, treatment is different for immunocompetent patients having classical symptoms of cat scratch disease than for immunocompromised patients with angiomatous proliferative diseases [127]. For immunocompetent patients, numerous antimicrobial agents have been advocated for the treatment of typical CSD. However, in most instances, antibiotics do not appear to shorten or improve the course of the infection [198].

In human cases of *Bartonella* endocarditis, effective antibiotic therapy should include an aminoglycoside prescribed for a minimum of two weeks [190]. In immunocompromised patients with bacillary angiomatosis or bacillary peliosis, the effectiveness of treatments with various antimicrobial substances has been evaluated [127]. Overall, tetracyclines, erythromycin, rifampin, azithromycin, doxycycline or a combination of these antibiotics are effective and should be administered in these patients for at least six weeks and be continued for 4 to 6 months in those who have relapses [158, 198].

In cats, antimicrobial agents are not commonly used or recommended for treatment or prevention of *B. henselae*, as antibiotic treatments tested to date may reduce the level of bacteremia but do not clear the cats from their infection [135, 194]. Additionally, the minimal effectiveness of these antimicrobial agents could be explained by the fact that *Bartonella* species are intracellular organisms.

In dogs, no study has been performed to determine the efficacy of antibiotics for treatment of *Bartonella* infection. However, it is likely that antibiotics such as doxycycline (10 mg/kg/day) or tetracycline could reduce the level of bacteremia during chronic infections, but should be administered for prolonged periods of time (4–6 weeks). Fluoroquinolones alone or in combination with amoxicillin have also elicited a positive therapeutic response in dogs [29], as repeated *B. vinsonii* subsp. *berkhoffii* antibody titers became negative after treatment. However, antibiotic therapy may not be very effective when the lesions of endocarditis are already well established.

8. PREVENTION

Domestic cats represent the main reservoir for *B. henselae* and cat ownership is now surpassing dog ownership in many industrialized countries [52]. Selecting an appropriate pet cat is important to avoid such a

risk. In most instances, seronegative cats are more likely not to be bacteremic and to be safe for ownership [52]. Conversely, young kittens, especially impounded kittens and flea-infested kittens, are more likely to be bacteremic [45, 128]. It has also been shown that multiple cat ownership was associated with an increased risk for *Bartonella* infection [100]. Therefore, potential pet cat owners, especially if they are immunocompromised, should seek a cat raised in a "clean", flea-controlled environment. In case of adoption, especially when the cat origin is not well defined, it is recommended that serological testing be performed. Only seronegative cats should be adopted when immunocompromised individuals may be exposed to the adopted cat. Flea control is also one of the major control measures to prevent cat infection and its spread from cat to cat and potentially the spread from cats to humans [43]. Overall, effective means of preventing *B. henselae* infection are common sense, hygiene, and, possibly, modification of behavior of the cat owners themselves. Wash hands after handling pets, and clean any cuts, bites or scratches promptly with soap and water. Development of a feline vaccine to prevent the spread of infection in cat populations and reduce human risk of infection is being considered. However, the wide diversity of *Bartonella* isolates even within the same genotype has been of concern for development of an effective feline vaccine. The lack of cross-protectivity between *B. henselae* genotype Marseille and *B. henselae* genotype Houston I was demonstrated a few years ago [232]. Nevertheless, a more recent study was able to demonstrate an unidirectional protective effect using a *B. henselae* Houston I strain against a *B. henselae* Marseille strain challenge [233].

Canine *Bartonella* infections are also likely to be vector-borne and ticks have been suggested as possible vectors of *B. vinsonii* subsp. *berkhoffii* [27, 39, 181]. Therefore, prevention of tick infestation should be one of the main control measures that are employed in the clinical setting. Use of tick repellents and cleaning of the dog after a walk in high-risk terrain should be done systematically to prevent not only *Bartonella,* but also other tick-borne infections. Flea control measures are also important, as dogs may become infected with *B. henselae* [212], possibly when exposed to cat fleas, which are known to transmit the infection among cats.

9. CONCLUSION

Beside cat scratch disease, a well-known zoonosis for which the etiological agent was finally identified at the end of the XXth Century, several new zoonotic *Bartonella* infections have recently been recognized. Most of these zoonotic pathogens have a rodent reservoir and it is likely that new rodent-borne *Bartonella* species will be identified in the near future, some of which will likely be zoonotic. Most *Bartonella* species are vector borne and such vectors still need to be identified for several emerging zoonotic *Bartonella* species. Finally, the clinical spectrum of *Bartonella* infections in both humans and dogs has greatly widened since better tools for identification of these bacteria became available.

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