Special Article

Emerging *Bartonella* in Humans and Animals in Asia and Australia

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Bartonella species, belonging to the alpha 2 subgroup of Proteobacteria, have either been considered or established as potential human and mammal pathogens. Five novel species of Bartonella have been reported in Thailand and Australia. Recently, three strains of B. tamiae were isolated from febrile illness patients in Thailand, while B. australis was isolated from kangaroos, and B. coopersplainsensis, B. queenslandensis, and B. rattiaustraliensis were isolated from rats in Australia. The 17 novel Bartonella strains isolated from rodents in southern China that were identified using the partial citrate synthase gene (gltA) sequence displayed a similar genetic diversity, as compared to those obtained from rodents captured in northern Thailand. Herein, the authors review and discuss the few available reports on Bartonella infection in order to raise awareness of Bartonella infection transmitted from mammalian reservoirs to humans via arthropod ectoparasitic vectors such as fleas, ticks, and lice in Asia and Australia. The identification of Bartonella species on these continents was reported in eastern Asia (China, Japan, Korea, Russia, and Taiwan), south central Asia (Afghanistan, Bangladesh, India, and Nepal), southeast Asia (Indonesia, Philippines, Singapore, and Thailand), the Middle East (Israel and Jordan), and Australia. The rate of Bartonella infection was found to be high in arthropod ectoparasitic vectors, mammals, and febrile patients in these tropical zones.

Keyword: *Bartonella*

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The phylogenetic relationship of *Bartonella*, within the Rhizobiales in the alpha subdivision of Proteobacteria, was organized by merging the genera *Rochalimaea* and *Grahamella* with *Bartonella* into the family Bartonellaceae[1,2]. The Rhizobiales encompass plant-associated soil bacteria, such as *Agrobacterium tumefaciens* and *Sinorhizobium meliloti*, including facultative intracellular pathogens such as *Bartonella* and *Brucella*. Bacteria of the genus *Bartonella* are characterized by small gram-negative, fastidious, and pleomorphic aerobic coccobacillary or bacillary rods (0.3 μm x 1 μm). These bacteria are facultative intracellular bacteria that naturally circulate between mammalian and arthropod vectors. This genus is able to invade and replicate inside human erythrocytes and endothelial cells. However, *Bartonella* species are not true obligate intracellular parasites, since these bacteria can be grown *in vitro* on enriched blood-containing media with visible colonies appearing after 5 to 45 days.

Bartonelloses are usually sporadic and epidemic worldwide, occurring in humans, domestic and wild terrestrial animals, and marine animals[3,4] (Fig. 1). The transmission of *Bartonella* to humans via arthropods is common, although it may occur via mammals, such as in the case of *B. alsatica*, which was first isolated from wild rabbits[5], then later isolated from the heart valve of a patient with endocarditis[6] and from a patient with cat scratch disease (CSD)[7]. Pets and cattle represent a large reservoir of hosts of *Bartonella* species, particularly cats and dogs, which

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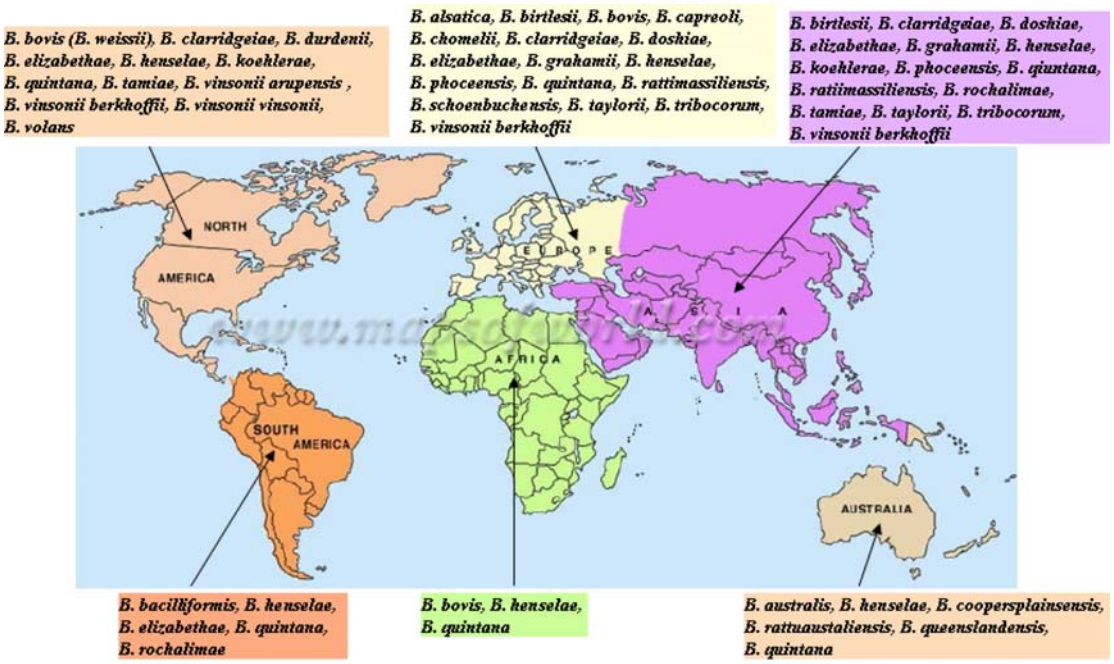

Fig. 1 Worldwide distribution of *Bartonella* species

are implied in human infection[8,9]. *B. henselae* and *B. koehlerae* have been isolated from owners' cats and dog, causing cat scratch disease in Asia. Endocarditis and fever were reported in humans in Israel[10], Japan[11-13], and Jordan[14], while one case of CSD was reported in Australia[15].

Along with an increased interest in the worldwide distribution of known bartonellae, La Scola et al described gene-sequencing-based criteria to increase the number of descriptions of novel members in the *Bartonella* genus in 2003[16]. Currently, the *Bartonella* database contains more than 30 named species and 3 subspecies (Fig. 2), after reclassification from the genera *Rochalimaea* and *Grahamella*.

The recognized *Bartonella* species, their reservoirs, vectors, and diseases in Asia and Australia are described in this review.

Bartonella species

Species of *Bartonella*, which are vector-borne pathogens, cause persistent and asymptomatic bacteremia in their natural hosts. There is substantial opportunity for uptake of these blood-borne bacteria by a variety of arthropod vectors that feed on animals and humans. Each species is highly adapted to the mammalian reservoir host in which the bacteria usually cause a long-lasting intraerythrocytic bacteremia[17].

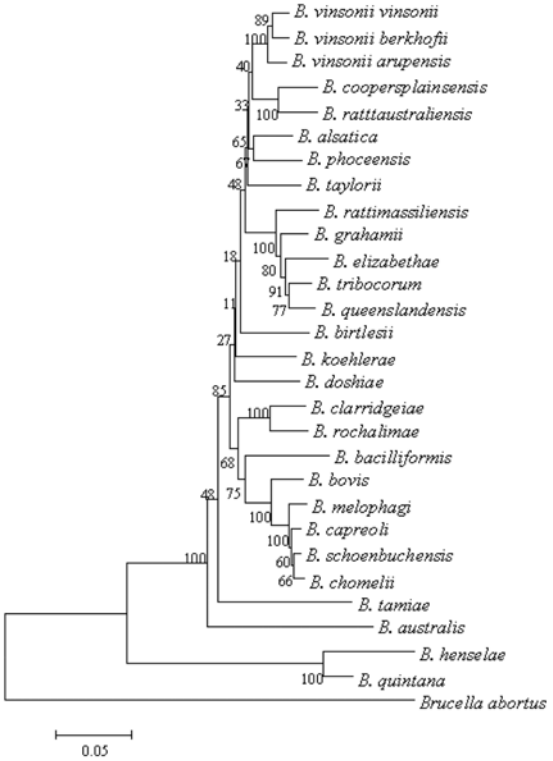

Fig. 2 Neighbor joining concatenated tree of *Bartonella* spp. based on *rpo*B, *glt*A, 16S rRNA and *fts*Z genes

Currently, there are more than 30 known *Bartonella* species that have been isolated from humans as well as wild and domestic animals, with a worldwide distribution (Table 1).

Bacteriology

The taxonomy of *Bartonella* is closely related to the genera *Brucella*, *Rhizobium*, and *Agrobacterium* and requires at least 7 days for growth on blood agar. The colonies are typically small (1-3 mm in diameter) and range from translucent to opaque in a white or cream color. The morphology may exhibit a dry to mucoid phase that depends on *in vitro* subsequent passage, and the variation may correlate with the antigenic phase variation described by Regnery and Tappero in 1995[18]. Biochemical tests are usually not conclusive for specific identification, since the bacteria are non-fermentative, unremarkable aerobes and the standard biochemical tests do not include hemin for *Bartonella* growth. The bacterial cells are described as delicate, pleomorphic, coccobacilli or as slightly curved rod-shaped bacilli that are gram-negative. The bacterial size is less than 3 □m in width, with most cells measuring 0.5 μm x 1.0 μm. There are two basic cell morphologies in *Bartonella* spp.: flagellated and non-flagellated cells[19,20]. The flagellae may serve as adhesins involved in erythrocyte invasion[21,22].

Genomics

The G + C content of *Bartonella* species is around 40 mol%, with values ranging from 38.5 mol% for *B. quintana*[23] to 41.1 mol% for *B. vinsonii*[24]. To date, four genome sequences of *Bartonella* species are available, *i.e.*, *B. quintana*, *B. bacilliformis*, *B. henselae*, and *B. tribocorum*. In addition, a cryptic plasmid called pBGR1 (size, 2 725 bp) was first isolated and identified from *B. grahamii* IBS376 by Seubert et al in 2003[25], and a plasmid termed pBT (size, 23 343 bp) from *B. tribocorum* CIP105476 was identified by Saenz et al in 2007[26]. Although the species definition in the *Bartonella* genus is based on polyphasic classification, which includes the determination of phenotypic characteristics and DNA-DNA homology, La Scola et al in 2003 proposed revised criteria for the species definition of *Bartonella* using partial *rpoB* and *gltA* sequencing[16].

Hosts

Table 1 presents the known species of *Bartonella* determined from a database review. *Bartonella* species are putative vector-transmitted, blood-borne, intracellular organisms. A vector preference for certain hosts could influence transmission, such as sandfly transmission for *B. bacilliformis*, louse transmission for *B. quintana*, flea transmission for *Bartonella* species, and transmission via ticks as recently indicated vectors for *Bartonella* species[27]. The host is a competent reservoir from which an arthropod vector can become infected and the bacteria can be transmitted to other susceptible hosts. Numerous *Bartonella* species infect a significant variety of domestic and wild mammalian hosts. Natural infections are highly prevalent and have mostly been characterized from rodent communities worldwide. With the exception of rodents, only one or a few mammalian species are permissive hosts for productive infection for any given *Bartonella* species. For instance, Yamato et al (2002) experimentally inoculated domestic cats with *B. koehlerae* and determined that all of the cats became bacteremic, indicating that domestic cats can readily become infected with *B. koehlerae*[28]. The results were supported in a study by Avidor et al in 2004, in which *B. koehlerae* was successfully isolated from a stray cat population and human endocarditis in Israel[10].

Natural hosts

Cats: Cats (pets and strays) are the main reservoir hosts for *B. henselae* infection. This pathogen is the predominant agent causing CSD in humans by cat biting or scratching. The transmission of *B. henselae* among cats most likely occurs via cat fleas (*Ctenocephalides felis*), although the cats remain healthy[29]. In Australia, Flexman et al (1995) succeeded in the isolation of *B. henselae* from the blood and fleas of a cat of a CSD patient with no previous history of bites or scratches[15]. In addition, Maruyama et al isolated *B. henselae* in 2004 from a Japanese patient that had a cat infested with fleas, and furthermore, *B. henselae* was isolated from these fleas[30]. Boulouis et al (2005) indicated that the prevalence of infection varied among strays or pets, with an increased ratio of infection from low in cold climates to high in warm and humid climates[31]. Domestic cats also serve as reservoirs for *B. clarridgeiae*, and co-infection with *B. clarridgeiae* and *B. henselae* has been demonstrated in Europe (France[32] and the Netherlands[33]), and Asia (Japan[34], Philippines[35], and Thailand[36]). *B. koehlerae* and *B. weissii* (now termed *B. bovis*) infections reported from domestic cats worldwide are rare. However, *B. koehlerae* was detected in cats in Israel by restriction fragment-length polymorphism of

Table 1. *Bartonella* species firstly isolated from mammals or humans

Bartonella species	First cultivation	Area	Vector	Reservoir	Human disease (s)
B. alsatica	Wild rabbit (*Oryctolagus cuniculus*)	Alsace, France		Rabbit	Endocarditis, lymphadenopathy
B. australis	Gray kangaroo (*Macropus giganteus*)	Queensland, Australia			
B. bacilliformis	Human		Sandfly	Human	Carrion's disease: Oroya fever and verruga peruana
B. birtlesii	Mouse (*Apodemus* spp.)	Bodensee, Germany		Rat	
B. bovis	Cow	Bissy, France		Cow	
B. capreoli	Roe deer (*Capreolus capreolus*)	Chize, France		Ruminant	
B. chomelii	Domestic cattle (*Bos taurus*)	Loire-Atlantique and Nord, France			
B. clarridgeiae	Cat		Cat flea	Cat	Cat scratch disease
B. coopersplainsensis	Mottle-tailed rat (*Rattus leucopus*)	Queensland, Australia			
B. doshiae	Woodland mammal (*Microtus agrestis*)	United Kingdom		Rat	
B. durdenii	Squirrel	United States			
B. elizabethae	Endocarditis patient	United States		Rat	Endocarditis, neuroretinitis
B. grahamii	Woodland mammal (*Clethrionomys glareolus*)	United Kingdom		Rat, insectivore	Neuroretinitis
B. henselae	Cat		Cat flea	Cat	Cat scratch disease, endocarditis, bacillary angiomatosis, bacillary peliosis, Parinaud's oculoglandular, neuroretinitis, osteomyelitis, arthropathy, bacteremia with fever
B. koehlerae	Domestic cat	California, United States		Cat	Endocarditis
B. melophagi					
B. peromysci	Mouse (*Peromyscus* spp.)			Mice	
B. phoceensis	Wild rat (*Rattus norvegicus*)	Marseille, France			
B. queenslandensis	Grassland melomys (*Melomys* spp.)	Queensland, Australia			
B. quintana	Human		Body louse	Human	Trench fever, endocarditis, bacillary angiomatosis
B. rattiaustraliensis	Tunney's rat (*Rattus tunneyi*)	Queensland, Australia			
B. rattimassiliensis	Rat (*Rattus norvegicus*)	Marseille, France			
B. rochalimae	Human	United States			Bacteremia, fever, splenomegaly
B. schoenbuchensis	Wild roe deer (*Capreolus capreolus*)	Germany	Deer ked	Ruminant	
B. silvicola	Bat				

Table 1. (Cont.)

Bartonella species	First cultivation	Area	Vector	Reservoir	Human disease (s)
B. talpae	Mole			Mole	
B. tamiae	Human	Khon Kaen, Thailand			Febrile illness
B. taylorii	Woodland mouse (*Apodemus* spp.)	United Kingdom		Rat	
B. tribocorum	Wild rat (*Rattus norvegicus*)	France			
B. vinsonii arupensis	Cattle rancher	United States	Ticks	Dog, rodent	Bacteremia with fever
B. vinsonii berkhoffii	Valvular endocarditis dog		Ticks	Dog	
B. vinsonii vinsonii	Vole (*Microtus pennsylvanicus*)		Vole ear mite	Vole	
B. volans	Squirrel	United States			
B. washoensis				Ground squirrel	Myocarditis
B. weissii	Domestic cat			Deer, elk, beef, cattle	

citrate synthase and riboflavin synthase genes[10]. High *B. quintana* antibody titers were reported by Baneth et al in 1996 from cats in Israel (39.5%) and by the IFA in North Carolina (40.4%)[37]. Furthermore, this agent was recently identified in a domestic cat tooth in Marseille, France, which suggests that cats may be an emerging source of *B. quintana* infection[38].

Dogs: The role of dogs as reservoir hosts of *Bartonella* spp. is less clear, as compared with cats. Domestic dogs are typically accidental hosts in non-tropical regions[9]. Epidemiological studies have demonstrated a higher prevalence of *B. vinsonii* subsp. *berkhoffii* antibodies in stray dogs in tropical areas, as compared to domestic dogs from northern latitudes. Baneth et al (1998) found that the sero-prevalence of *B. vinsonii* subsp. *berkhoffii*-infected dogs (10%) in Israel[39] was lower than that of domestic dogs from Thailand (38%)[40]. Conversely, a few dogs may infrequently be infected with *B. henselae*, *B. clarridgeiae*, *B. washoensis*, *B. elizabethae*, *B. quintana*, and *B. bovis*. Tsukahara et al (1998) and Tsujino et al (2004) reported *B. henselae* infection in dogs and puppies in Japan, respectively[11,13]. Therefore, cat scratch disease, which is primarily caused by *B. henselae*, may also result from the transmission of other *Bartonella* species from other animals, including dolphins or rabbits, as recently demonstrated for *B. alsatica*[7].

Humans: People become incidentally infected with *Bartonella* spp., as the organisms are normally found in the reservoir hosts. Three important species due to the major emerging infectious diseases in human are *B. bacilliformis*, the agent of Carrion's disease, *B. quintana*, the agent of trench fever, and *B. henselae*, the agent of cat scratch disease. Humans are the hosts and reservoirs of *B. bacilliformis* and *B. quintana*[8]. *B. bacilliformis* has a distribution only in South America[41], while *B. henselae* and *B. quintana* have a worldwide distribution. In Asia and Australia, *Bartonella* infections in humans mainly consisted of *B. henselae* and *B. quintana*, while *B. koehlerae* was reported from an endocarditis patient in Israel[10], and *B. tamiae* was first isolated from three patients with febrile illness in Thailand[42]. Diseases reported in Asia and Australia included endocarditis, CSD, prolonged fever, uveitis, and other less frequent manifestations (Table 2). On the other hand, 13 species or subspecies of *Bartonella* may cause human diseases worldwide, but the pathogenic role is largely uncharacterized for many species, such as *B. elizabethae*, *B. vinsonii* subsp. *arupensis*, *B. vinsonii* subsp. *berkhoffii*, *B. clarridgeiae*, *B. grahamii*, *B. washoensis, B. kohlerae*, *B. alsatica*, *B. rochalimae*, and the newly described *B. tamiae*[43].

Specific hosts

Rodents: Recent studies have indicated that numerous *Bartonella* species circulate in wild mammals. Rodent-associated *Bartonella* is generally a host-specific parasite, and several wild rodent-associated

Table 2. Identification of *Bartonella* species from human infection in Asia and Australia

Country	*Bartonella* spp.	Source	Sample	Diagnosis testing			Reference
				Serology	Culture	Molecular biology	
Australia	*B. henselae*	CSD patient	Blood leukocyte, serum, lymph node aspirate	IFA		16S rRNA	(15)
	B. quintana	Immunocompromised patient	Blood		Isolation	16S rRNA	(175)
	B. henselae	Atypical parinaud oculoglandular patient	Blood, tissue	IFA		PCR	(57)
	B. henselae	Parinaud's oculoglandular patient	Conjunctival scraping		Isolation	16S rRNA	(58)
	B. henselae	Neuroretinitis patient		IFA			(60)
	B. henselae	CSD with osteomyelitis	Vertebral column aspirate	Serologic test		PCR	(185)
	B. henselae	Endocarditis patient	Blood	Serologic test			(88)
	B. henselae	Humans; CSD and bacillary angiomatosis	Blood		Isolation	16S rRNA, *gltA*, *papA*, ITS-RFLP, AP-PCR, ERIC-PCR, IRS-PCR	(112)
	B. henselae	CSD patients	Lymph node		Isolation	*htrA*, *pap31*	(186)
	B. henselae	Endocarditis patient	Blood, aortic valve tissue	Serologic test		PCR	(89)
	B. quintana	Endocarditis patients	Aortic valve tissue		Isolation	ITS, MST	(85)
China	*Bartonella* spp.	Humans	Blood			ITS	(187)
	B. henselae	Healthy people		ELISA, IFA			(115)
India	*B. quintana*	Endocarditis	Blood	IFA, WB			(86)
Israel	*B. henselae*	CSD patients	Serum, pus, lymph node tissue	EIA	Isolation	16S rRNA, RFLP; *gltA*, *htrA*, dot blot hybridization	(169)
	B. henselae	CSD patient	Serum, pus	EIA		RFLP; *gltA*	(182)
	B. henselae	CSD patients	Serum, pus	EIA		16S rRNA, β-globulin, RFLP; *gltA*	(188)
	B. henselae	CSD patients	Serum, pus, lymph node	EIA	Isolation	RFLP; *gltA*	(189)
	B. henselae	Endocarditis patient	Serum, valve tissue	EIA		RFLP; *htrA*	(90)
	B. henselae	Endocarditis patients	Cardiac valve			RFLP; *gltA*, *ribC*	(10)
	B. koehlerae						
	B. quintana						
	B. henselae	CSD patients	Serum, lymph node tissue, pus	EIA	Isolation	PCR	(77)
Japan	*B. henselae*	CSD patients	Serum	IFA			(168)
	B. henselae	Child with fever, sore throat and lymphadenopathy	Serum	IFA			(11)
	B. henselae	FUO patients, patients with lymphadenopathy, pregnant woman	Serum	IFA			(56)

Table 2. (Cont.)

Country	*Bartonella* spp.	Source	Sample	Diagnosis testing			Reference
				Serology	Culture	Molecular biology	
Japan	*B. henselae*	Suspected CSD patients	Blood, serum	IFA		16S rRNA	(12)
	B. henselae	FUO patients	Serum	IFA			(110)
	B. henselae	Veterinary professionals	Serum	IP			(116)
	B. henselae	Hepatic granuloma patient					(114)
	B. henselae	Systemic juvenile rheumatoid arthritis	Blood, serum	IFA			(62)
	B. henselae	Suspected CSD patients, cardiovascular diseases, veterinary students	Serum	IFA			(91)
	B. henselae	Suspected CSD patients	Serum	IFA			(190)
	B. henselae	Uveitis patients Submacular exudate with serous		Serologic test			(106)
	B. henselae	Neuroretinitis	Serum, cerebrospinal fluid	Serologic test		PCR	(107)
	B. henselae	Ocular manifestation patients	Serum	Serologic test			(108)
	B. henselae	CSD patient	Lymph node, blood/serum	IFA	Isolation	ITS, 16S rRNA, PFGE	(30)
	B. henselae	Prolonged fever patients	Blood, serum, cerebrospinal fluid, biopsied material	IFA			(13)
	B. henselae	Suspected CSD patients	Serum	IFA			(78)
	B. henselae	Neuroretinitis	Serum	Serologic test			(109)
	B. quintana	Homeless people	Blood/serum	IFA	Isolation	ITS	(141)
	B. henselae	Uveitis patient	Vitreous aspirate	Serologic test	Isolation		(59)
	B. henselae	Prolonged fever without lymphadenopathy patients	Serum	IFA			(111)
	B. henselae	Osteomyelitis patient	Spinous	IFA		*htrA*	(61)
	B. henselae	Pyogenic splenic abscess infant	Serum	IFA			(113)
	B. henselae	Pericarditis patient	Serum	IFA			(92)
	B. quintana	Endocarditis patient	Blood		Isolation	16S rRNA	(87)
Jordan	*B. henselae, B. quintana*	Children from hospitals	Serum	IFA			(14)
Korea	*B. henselae*	CSD patient	Lymph node aspirate			*gltA*, *pap31*	(177)
Russia	*B. henselae* *B. quintana*	Humans	Serum	IFA			(117)
	B. henselae,	Human (after tick bites)	Blood cells			*groEL*	(191)

Table 2. (Cont.)

Country	*Bartonella* spp.	Source	Sample	Diagnosis testing			Reference
				Serology	Culture	Molecular biology	
Russia	*B. quintana*						
Taiwan	*B. henselae*	Veterinary professionals	Serum	IFA			(118)
	B. henselae	Patient scratched by dog		Serologic test			(192)
Thailand	*B. henselae*	Healthy blood donors	Serum	IFA			(119)
	B. tamiae	Febrile illness patients	Blood clot		Isolation	16S rRNA, *gltA*, *groEL*, ITS, *ftsZ*, *rpoB*	(42)
	B. henselae	Angiomatosis patient	Skin lesion		Isolation	16S rRNA	(63)

Bartonella species have been related to human diseases, including *B. elizabethae*, *B. grahamii*, *B. vinsonii* subsp. *Arupensis*, and *B. washoensis*. In contrast, the transmission route in rodents has not been determined. Previous studies have demonstrated that ectoparasites may be the main route of transmission for *Bartonella* infections in rodents[44,45]. Ellis et al (1999) found *Rattus norvegicus* and *R. rattus* from the United States and Portugal that carried *B. elizabethae* through following *B. grahamii* and other *Bartonella* species isolated from *Clethrionomys* species, *Mus musculus*, and *Rattus* species[46]. In addition, several *Bartonella* species identified from arthropods (Table 3) collected from rodents have been reported in Asia[47-53]. Different species of mice (*Apodemus* spp., *Mus* spp.), rodents (*Bandicota* spp., *Eothenomys* spp., *Rattus* spp.), shrews (*Crocidura* spp., *Sorex* spp.), and voles (*Microtus* spp., *Clethrionomys* spp.) act as primary vertebrate reservoirs of *Bartonella* species in Asia (Table 4).

Pathology

Bartonella species are zoonotic pathogens, and several species can cause infectious disease in humans. They are uniquely adapted to colonize in various hosts, including both vertebrate and invertebrate organisms. The bacteria can invade and multiply in several cell types, such as endothelial, epithelial, or red blood cells. Invasion in erythrocytes results in a long-lasting intraerythrocytic bacteremia and formation of vasoproliferative tumors. In addition to systemic disease, the infections may cause localized tissue manifestations. The most unusual feature of vascular tissue colonization induces angiogenesis, which is the pathological process of capillaries or vessels[54], and is observed during the convalescent phase of verruga peruana. Although the invasion process of *Bartonella* in endothelial cells is poorly understood, Brouqui and Raoult (1996) observed that *B. quintana* invaded endothelial cells *in vitro*. This present investigation determined the different steps that occur during invasion, which demonstrated the adherence of *B. quintana* to endothelial cells by phagocytosis and engulfment[55].

Bartonella spp. and pathogenesis in Asia and Australia

The vector-borne pathogens of *Bartonella* species are now considered as worldwide emerging diseases in humans. According to the data available regarding *Bartonella* species, *B. bacilliformis* infections have not been found in Asia or Australia. Only a few species of *Bartonella* causing human infections have been determined, including cases of *B. henselae*, *B. quintana*, three cases of *B. tamiae*, and one case of *B. koehlerae*, as shown in Table 2. The clinical manifestations include CSD, endocarditis, a few cases of atypical prolonged fever[13,42,56], parinaud oculoglandular[57,58], uveitis[59], neuroretinitis[60], osteomyelitis[61], rheumatoid arthritis[62], and angiomatosis[63].

The transmission routes of *Bartonella* spp. in mammals and humans occur via fleas, ticks, mites, and lice. *B. quintana* has been detected in human lice in Japan[64], Nepal[65], and Russia[66,67], while

Table 3. Identification of *Bartonella* species from arthropods in Asia and Australia

Country	*Bartonella* spp.	Source of sample collection			Diagnosis testing		Reference
		Sample	Reservoir	Area/method of collection	Culture	Molecular biology	
Afghanistan	*B. quintana, B. koehlerae, B. taylorii*	Fleas	*Meriones lybicus*			ITS	(51)
	B. elizabethae, B. dosihae	Fleas	*Rattus* spp.				
Australia	*B. henselae*	Fleas	Cat		Isolation	16S rRNA	(15)
China	*B. tribocorum*	*Xenopsylla cheopsis*	*Rattus tanezumi flavipectus*			*gltA*	(52)
	B. clarridgeiae	*Ctenophthalmus lushiensis*		Nests of voles			
	Bartonella spp.	*Haemaphysalis longicornis, Ixodes sinensis*	Wild hares	Pastures/ flagging		Nested PCR	(137)
Indonesia	*B. phoceensis*, *B. elizabethae, B. rattimassiliensis*	Fleas	Rodents, shrews			*gltA*	(50)
Japan	*B. quintana*	*Pediculus humanus*	Homeless people			18S rRNA	(64)
	B. henselae	Fleas	Cat		Isolation	16S rRNA, ITS	(30)
Korea	*B. doshiae, B. rattimassiliensis, B. tribocorum*	*Haemaphysalis* spp., *Ixodes* spp.	Wild rodents	Grassland, forest ground, vegetation/ flagging		16S rRNA	(49)
		Mesostigmatid mites	Wild rodents, insectivores				
Nepal	*B. quintana*	*Pediculus humanus capitis*, *P. humanus humanus*	Children			ITS	(65)
Russia	*B. quintana*	Body lice	Homeless people			PCR	(66)
	B. quintana	*Pediculus humanus corporis*	Homeless persons			*gltA*	(67)
	B. henselae	*Ixodes persulcatus*		Vegetation/ flagging		*groEL*	(68)
	Bartonella spp.	*Ixodes persulcatus,*		Vegetation/ flagging		*groEL*	(69)
		Dermacentor reticulatus		River valley and forest/ flagging			
Thailand	*B. henselae, B. clarridgeiae*	*Ctenocephalides felis*	Cats			ITS, *ftsZ*	(47)
	Bartonella spp.	*Nosopsylla fasciatus*	*Rattus surifer*				

B. koehlerae and *B. taylorii* were detected from fleas of gerbils (*Meriones lybicus*) in Afghanistan by Marie et al (2006)[51]. *B. henselae* and *B. clarridgeiae* were detected from fleas of cats in Australia[15], Japan[30], and Thailand[47]. Other *Bartonella* species, such as *B. elizabethae*, *B. doshiae*, *B. phoceensis*, *B. rattimassiliensis*, *B. tribocorum*, and *Bartonella* spp., were PCR amplified from fleas, ticks, and mites collected from rodents and wild hares in Afghanistan, China, Indonesia, Korea, and Thailand (Table 3). On the other hand, Morozova et al (2004) found *B. henselae* in ticks (*Ixodes persulcatus*) collected from vegetation by flagging[68], while Rar et al (2005) identified *Bartonella* spp. from ticks (*I. persulcatus* and *Dermacentor*

Table 4. Identification of *Bartonella* species from mammals in Asia and Australia

Country	*Bartonella* spp.	Source	Sample	Diagnosis testing			Reference
				Serology	Culture	Molecular biology	
Australia	*B. henselae*	Cat	leukocyte, lymph node aspirate		Isolation	16S rRNA	(15)
	B. henselae	Cats	Blood		Isolation	PCR	(193)
	Bartonella spp.	Endocarditis	Blood cats		Isolation		(194)
	B. henselae	Cats	Blood		Isolation	16S rRNA, *gltA*, *papA*, ITS-RFLP, AP-PCR, ERIC-PCR, IRS-PCR	(112)
	B. australis	*Macropus giganteus*	Blood		Isolation	16S rDNA, *gltA*, *rpoB*, *ftsZ*, ITS	(70)
	B. coopersplainsensis	*Rattus leucopus*	Blood		Isolation	16S rDNA, ITS, *ftsZ*, *rpoB*, *gltA*	Gundi et al, (Unpul.)
	B. rattiaustraliensis	*R. leucopus, R. tunneyi, R. conatus, Melomys* spp., *Uromys caudimaculatus*					
	B. queenslandensis	*R. leucopus, R. tunneyi, R. fuscipes, R. conatus, Melomys* spp.					
Bangladesh	*B. elizabethae*, *Bartonella* spp.	*Bandicota bengalensis*, *Rattus rattus*			Isolation	*gltA*	(195)
China	*B. elizabethae*	*Rattus* spp., *Apodemus* spp.	Blood		Isolation	*gltA*	(176)
	Bartonella spp.	*Rattus* spp., *Apodemus* spp., *Eothenomys* spp.					
	Bartonella spp.	*Mus pahari, Rattus norvegicus*, *R. tanezumi flavipectus*, *Eothenomys miletus*	Blood		Isolation	PCR	(196)
Indonesia	*B. henselae*, *B. clarridgeiae*	Cats	Blood		Isolation	RFLP; *gltA*	(183)
	B. henselae		Serum	IFA			
	B. phoceensis, *B. elizabethae, B. rattimassiliensis*	Rodents				*gltA*	(50)
Israel	*B. henselae, B. quintana*	Cats	Serum	IFA			(37)
	B. vinsonii berkhoffii	Dogs	Serum	IFA			(39)

Table 4. (Cont.)

Country	*Bartonella* spp.	Source	Sample	Diagnosis testing			Reference
				Serology	Culture	Molecular biology	
Israel	*B. koehlerae*	Cat	Blood			RFLP; *gltA*, *ribC*	(10)
Japan	*B. henselae*	Cats	Serum	IFA			(197)
	B. henselae	Cats	Blood		Isolation	RFLP; *gltA*	(181)
	B. henselae	Cats	Serum	IFA			(198)
	B. henselae	Puppy, dogs	Blood, serum, gingival, buccal membrane, oral swab, nail clipping	IFA		*htrA*, nested PCR	(11)
	B. henselae, *B. clarridgeiae*	Cats	Blood		Isolation	16S rRNA, PFGE, RFLP; *gltA*	(34)
	B. henselae	Cats	Blood, serum	IFA	Isolation	RFLP; *gltA*, PFGE	(184)
	B. henselae	Cats	Serum	IFA			(199)
	B. henselae	Cat, dog	Buccal swab			PCR	(13)
	B. grahamii	*Apodemus speciosus*, *A. argenteus*	Blood		Isolation	*rpoB*, *gltA*, RFLP; *rpoB*	(179)
	B. tribocorum or *B. elizabethae*	*A. speciosus*, *A. argenteus*, *Rattus rattus*					
	B. tribocorum or *B. rattimassiliensis*	*R. rattus*					
	B. rattimassiliensis	*R. rattus*					
	B. phoceensis	*R. rattus*					
	B. taylorii	*A. speciosus*, Clethrionomys fufocanus bedfordiae					
	Bartonella spp.	*A. speciosus*, *A. argenteus*					
Jordan	*B. henselae*	Cats	Blood		Isolation		(14)
Korea	*B. elizabethae*	*Apodemus agrarius*	Spleen			*gltA*	(200)
	B. henselae or *B. doshiae*, *B. birtlesii*, *B. elizabethae*	*Apodemus agrarius*, *Crocidura lasiura*, *Eothenomys regulus*	Spleen			23S rRNA, *groEL*	(49)
Philippines	*B. henselae*, *B. clarridgeiae*	Cats	Blood, serum	IFA, EIA	Isolation	RFLP; *gltA*, 16S rRNA	(35)
Russia	*B. grahamii*,	*Apodemus agrarius*, *A. peninsulae*	Spleen, liver			*gltA*	(178)

Table 4. (Cont.)

Country	*Bartonella* spp.	Source	Sample	Diagnosis testing			Reference
				Serology	Culture	Molecular biology	
Russia	*B. taylorii,*	*A. peninsulae, Clethrionomys rufocanus, Microtus fortis*					
	Bartonella spp.	*A. agrarius, A. peninsulae*					
	B. grahamii, B. taylorii	*Apodemus flavicollis, A. uralensis, Clethrionomys glareolus, Mus musculus, Microtus arvalis,Sorex araneus*	Blood		Isolation	RFLP; *gltA*, *ftsZ*, *ribC*, 16S rRNA	(180)
Singapore	*B. henselae*	Cats	Serum	IFA			(201)
Taiwan	*B. henselae, B. clarridgeiae*	Cats	Blood, serum	IFA	Isolation	ITS, 16S rRNA, RFLP; *gltA*	(118)
	B. elizabethae	*Rattus norvegicus*				PCR/RFLP, ITS, *gltA*, *ftsZ*, *rpoB*	(53)
	B. tribocorum						
	B. rochalimae						
Thailand	*B. henselae*	Cats	Serum	IFA			(202)
	B. henselae, B. clarridgeiae	Cats	Blood		Isolation	16S rRNA, RFLP; *gltA*	(36)
	B. vinsonii berkhoffii	Dogs	Serum	IFA			(40)
	B. grahamii, B. elizabethae	*Bandicota indica, Rattus losea, R. rattus*	Blood		Isolation	*gltA*	(48)
	Bartonella spp.	*B. indica*					

reticulatus) collected in river valleys, forests, and vegetation in western Siberia, Russia[69]. In addition, Li et al (2007) amplified *B. clarridgeaie* from fleas (*Ctenophthalmus lushuiensis*) collected from the nests of voles in China[52].

Table 4 shows the association of *Bartonella* species with mammals in Asia and Australia. *B. henselae*, *B. clarridgeiae*, *B. quintana*, *B. elizabethae*, *B. grahamii*, *B. tribocorum*, *B. taylorii*, *B. koehlerae*, *B. doshiae*, *B. birtlesii*, *B. phoceensis*, *B. vinsonii* subsp. *berkhoffii*, *B. coopersplainsensis*, *B. queenslandensis*, *B. rattiaustraliensis*, and a novel *Bartonella* spp. were detected from cats, dogs, and rodents, while *B. australis* was isolated from the Australian gray kangaroo (*Macropus giganteus*)[70]. Cats and dogs are closely related to humans, acting as reservoirs of *Bartonella* infection. Cats in Asia and Australia are mainly infected by *B. henselae*, and only a few have been indicated to carry *B. clarridgeiae*. Conversely, *B. quintana*[37] and *B. koehlerae*[10] have been reported in Israel. In the case of dogs, which were defined as reservoirs of *B. vinsonii* subsp. *berkhoffii* infection, Baneth et al (1998) and Suksawat et al (2001) reported antibody titers in dogs in Israel[39] and Thailand[40], respectively. Tsukahara et al (1998) and Tsujino et al (2004) identified *B. henselae* from domestic dogs in Japan[11,13]. In addition, rodents play an important role in *Bartonella* infection, since several species of *Bartonella* have been detected in rodents by isolation and/or molecular detection, as presented in Table 4.

Clinical manifestation

Bartonella species are now considered to be emerging pathogens. Of the 25 currently recognized species, *B. henselae*, *B. quintana*, *B. koehlerae*, and *B. tamiae* have been reported from patients or healthy persons in Asia and Australia. *Bartonella* pathogens are adapted to colonize within human hosts, notably by the adherence and invasion of red blood cells or by colonization of endothelial cells, which may result in the formation of vasoproliferative tumors after colonization. Only endothelial cells and erythrocytes are permissive to *Bartonella in vivo*. In addition to the organs that may host *Bartonella* infection, bone marrow, brain, penis, vulva, cervix, and muscles involved in bacillary angiomatosis may play roles as sanctuary sites or primary niches in *Bartonella* pathogenesis[71-75]. Moreover, Musso et al (2001) found *B. henselae* infection and proinflammation in murine macrophages *in vitro*[76].

Cat scratch disease: *B. henselae* is not only the predominant causative agent of CSD, but some strains of *B. clarridgeiae* and one case of *B. alsatica*[7] have also been associated with CSD in humans. The French physician Debr□ first described CSD in 1950 in patients suffering from inflamed lymph nodes following cat scratches. The clinical manifestations of CSD exhibit a wide spectrum from typical to atypical CSD in patients with mild to severe disease. Usually, CSD is not severe in healthy persons, but it can be problematic in immunocompromised patients. The typical manifestation exhibits skin lesions of granulomatous, swollen lymph nodes near the site of cat biting or scratching. Prolonged fever, sore throat, headache, anorexia, nausea, vomiting, and malaise are common clinical syndromes in patients, while atypical symptoms involving the eyes, liver, spleen, central nervous system, skin, bones, or other organs are less common. In complicated cases, patients may develop osteomyelitis, arthropathy, or arthralgia from knee, wrist, ankle, or elbow joints[15,77]. Neuroretinitis, encephalopathy, hepatosplenic granuloma, and Parinaud's oculoglandular syndrome have also been reported as atypical CSD. Although *B. clarridgeiae* can serve as a causative agent of CSD, Tsuneoka et al (2004) failed to detect *B. clarridgeiae* in Japanese patients with suspected CSD after sera were absorbed with *B. henselae* using IFA[78].

Endocarditis: *Bartonella* endocarditis has been recognized since the 1990s[24,79-82], with the first report involving an HIV-infected homosexual man[80]. The causative pathogens of *Bartonella* endocarditis include *B. quintana*, *B. henselae*, *B. elizabethae*, *B. vinsonii* subsp. *berkhoffii*, *B. koehlerae*, or *B. alsatica*. The incidence of *Bartonella* endocarditis in each country is unknown. However, Raoult et al (1996) diagnosed 22 new cases of *Bartonella* endocarditis and found that 3% of all cases were derived from France and Canada[82]. In addition to expanding the spectrum and known characteristics of *Bartonella* endocarditis, blood culture-negative endocarditis cases have been further reinforced[82-84]. Only a few reports of *Bartonella* endocarditis were identified in Asia and Australia, and this pathogen was found primarily in India, Japan, and Australia. *B. quintana*[85-87] and *B. henselae*[88-90] have been frequently identified, while one case due to *B. koehlerae* infection was reported by Avidor et al (2004)[10]. In addition to heart diseases due to *B. henselae*, 3.1% of Japanese patients with cardiovascular diseases[91] and one pediatric case was associated with pneumonia, pleural effusion. Pericarditis following CSD[92] was also suspected by serological investigation.

Eye diseases: A spectrum of eye diseases has been associated with the *Bartonella* species since 1889. The history of *Bartonella*-related eye diseases began with a report by Henri Parinaud of the first clinical description of ocular bartonellosis[93]. Infections of Parinaud oculoglandular syndrome, which is the most common ocular manifestation due to *B. henselae*[94-102], have been recognized with increasing frequency. Parinaud oculoglandular patients typically have a unilateral eye redness, foreign body sensation, and epiphora, while mild cases present lid swelling[103]. Parinaud oculoglandular syndrome may result from *B. quintana*[104] and *B. grahamii*[105] with inflammation and neuroretinitis, respectively. In addition to the pathogen of *B. henselae* that results in eye diseases in Asia and Australia, Parinaud oculoglandular syndrome, neuroretinitis, and uveitis have been reported in Japan since 1997[59,106-109].

Miscellaneous clinical presentations: *B. henselae* can cause uncommon manifestations in humans, such as encephalopathy, encephalitis, radiculitis, myelitis, thrombocytopenic purpura, osteomyelitis, and hepatosplenic disease[99,103]. In Asian and Australian countries, *B. henselae* has rarely been associated with osteomyelitis[62], and systemic juvenile rheumatoid arthritis[61] has been diagnosed in Japanese patients. *B. henselae* has been reported in prolonged fever[13,56,110,111], bacillary angiomatosis[63,112], pyogenic splenic abscess[113], and giant hepatic granuloma[114], while the newly described *B. tamiae*

has been isolated from febrile illness patients in Thailand[42]. In contrast, healthy persons or veterinary professionals (cat care) can be infected with *B. henselae* or *B. quintana* without symptoms, as previously reported in China[115], Japan[91,116], Russia[117], Taiwan[118] and Thailand[119].

Reservoir hosts

Zoonotic infections caused by *Bartonella* species, which are associated with rural areas, are increasingly emerging and being recognized in urban environments. Usually *Bartonella* species associate between the spectrum of natural or incidental hosts and the vector most likely due to the geographic distribution of the organisms. This genus has been identified or isolated worldwide in a wide range of mammalian species, including cats, dogs, rabbits, rodents, and cattle.

Humans and animals: The main reservoirs of *B. bacilliformis* and *B. quintana* are humans. Other *Bartonella* species, such as *B. henselae*, *B. clarridgeiae*, *B. koehlerae*, *B. alsatica*, *B. vinsonii* subsp. *arupensis*, *B. vinsonii* subsp. *berkhoffii*, and *B. grahamii*, are implicated as human pathogens and zoonoses. People usually become incidentally infected with *Bartonella* species.

Numerous mammals act as reservoir hosts of *Bartonella* infection. Species of *Bartonella* were first isolated from small rodents, such as *B. birtlesii* isolated from German *Apodemus* spp.[120]; *B. coopersplainsensis*, *B. queenslandensis*, and *B. rattiaustraliensis* isolated from Australian *Rattus* spp. (Gundi et al, unpubl); *B. doshiae*, *B. grahamii*, and *B. taylorii* isolated from *Microtus agrestis*, *Clethrionomys glareolus*, and *Apodemus* spp. in the United Kingdom[2] and *B. tribocorum*, *B. phoceensis*, and *B. rattimassiliensis* isolated from French *R. norvegicus*[121,122]. In addition, *B. bovis*, *B. capreoli*, *B. chomelii*, and *B. schoenbuchensis* were isolated from European ruminants[123-125] and rare herbivore mammals. Wild rabbits (*Oryctolagus cuniculus*) and gray kangaroos (*Macropus giganteus*) were related to *B. alsatica*[5] and *B. australis*[70] infections, respectively.

Vectors: Many *Bartonella* species are vector-borne diseases. The cycle contains a reservoir with chronic intraerythrocytic bacteremia and vector-transmitted parasites from the reservoir hosts to new susceptible hosts, natural reservoirs, new competent reservoirs, or incidental hosts[8]. The ectoparasites involved in *Bartonella* transmission are sandflies, lice, fleas, mites, and ticks. The sandfly, particularly *Lutzomyia verrucarum*, is the vector of *B. bacilliformis*, whereas *L. peruensis* has been suspected to transmit a *Bartonella* spp. resembling *B. grahamii*[126]. In addition, various kinds of fleas, such as *Ctenocephalides felis* (cat flea), *C. canis* (dog flea), *Ctenophthalmus* spp., *Leptopsylla segnis*, *Nosopsyllus fasciatus*, *Xenopsylla cheopis* (rodents' flea), *Sternopsylla texanus* (bat flea), *Orchopeas howardi* (flying squirrel flea) and *Pulex imitans* (human flea), have been associated with *Bartonella* transmission in mammals[44,47,52,127-131]. Moreover, Flexman et al (1995) and Maruyama et al (2004) have isolated *B. henselae* from fleas collected from cats in both Australia[15] and Japan[30]. To better understand other potential or suspected vectors due to *Bartonella* transmission, various arthropods have been studied. *B. schoenbuchensis* and *B. henselae* were identified from deer keds (*Lipoptena mazamae*) collected from white-tailed deer in the USA[132]. Furthermore, ticks (*Amblyomma americanum*, *Carios kelleyi*, *Dermacentor* spp., *Haemaphysalis* spp., *Ixodes* spp., and *Rhipicephalus sanguineus*) and mites also harbor *Bartonella* spp[133-136]. Interestingly, vectors collected from the nests of voles and flagging at pastures, forests, and vegetation due to reservoir habitats have been found to be infected with *Bartonella* in China[52,137], Korea[49], and Russia[68,69]. As for many vector-borne bartonellosis infections with regard to arthropods, vector competence and vector potential are necessary to reduce infection prevalence in the principal host.

Epidemiology

Bartonella species are worldwide zoonosis agents that cause diseases in mammals, including humans as well as rodents, canines, felids, humans, insectivores, herbivores, and even sea animals[3,4]. Although the epidemiology of bartonella infections remains poorly understood, the chronically infected host may serve as a reservoir and the pathogen is usually transmitted and enhanced by persistent infection of arthropod vectors[138].

B. quintana: Trench fever, a mild 5-day relapsing fever, is caused by exposure to infected human body lice (*Pediculus humanus*) through the feces. *B. quintana* shed in the feces of lice can infect humans through the open skin around bites or scratches. This pathogen was a leading cause of infectious morbidity among soldiers during World War I and recurred in eastern Europe during World War II[139]. Recently, *B. quintana* has re-emerged worldwide, resulting in several clinical syndromes, including

bacillary angiomatosis, bacillary peliosis, endocarditis, and prolonged bacteremia. The major risk factors for *B. quintana* infections are homelessness, chronic alcoholism, immunocompromise, and human immunodeficiency virus infection (HIV). Brouqui et al (2005) reported that 7.5% of 930 homeless people from France, eastern Europe, and northern Africa were infected with *B. quintana*[140]. Among the Japanese homeless population, urban trench fever was also suggested as an endemic disease[141].

B. henselae: CSD caused by *B. henselae* is mainly characterized by a benign regional lymphadenopathy after scratching or biting by an infected cat. Complications may develop, such as Parinaud's oculoglandular syndrome, encephalitis, endocarditis, hemolytic anemia, hepatosplenomegaly, glomerulonephritis, pneumonia, relapsing bacteremia, and osteomyelitis[31,142]. In contrast, *B. henselae* was first isolated from an AIDS patient with low CD4 counts[143], while Dolan et al (1993) isolated this pathogen from a patient with CSD lymphadenitis[144]. *B. henselae* is distributed worldwide, including South America, Europe, North America, Africa, Asia, and Australia.

***B. bacilliformis*:** Carrion's disease (acute Oroya fever and chronic verruga peruana), caused by *B. bacilliformis*, was first described in 1905 within erythrocytes[43]. The pathogen is transmitted by the sandfly (*Lutzomyia verrucarum*) and is distributed in South America, particularly in endemic areas of Peru, Ecuador, and Columbia[145-148]. In Peru, the epidemiology has changed over the last decade[41]. Recently, outbreaks of Carrions's disease have been described in new endemic areas of Peru[146,149] and have affected younger people with a higher mortality rate, as compared to older patients[41].

B. elizabethae: Endocarditis due to *B. elizabethae*[24] has been found in the USA. Among rodents, bacteria are transmitted by fleas of rats (*Rattus* spp. and *Mus* spp.) and wild rodents [43]. Additionally, this *Bartonella* species has been isolated from urban rats in various parts of the world. Homeless people or intravenous drug users may be exposed to rodent-borne *B. elizabethae*[150-152]. Exposure can also occur through the outdoor activity of orienteers[153] in both the USA and Sweden. *B. elizabethae* has been reported in patients with neuroretinitis[154], among clinic patients[155] and healthy blood donors[156,157].

Other Bartonella spp.: Other *Bartonella* spp. causing rare cases in humans include: *B. clarridgeiae*, *B. koehlerae*, *B. vinsonii* subsp. *arupensis*, *B. vinsonii* subsp. *berkhoffii*, *B. alsatica*, *B. grahamii*, and *B. washoensis*. These agents can cause CSD, endocarditis, neuroretinitis, sepsis, and arthralgia/myalgia/headache/fatigue. Recently, *B. alsatica* was first isolated from rabbits[5], was then isolated from a heart valve of a patient with endocarditis[6], and was later isolated in a patient with cat scratch disease in France[7]. Conversely, *B. tamiae* was isolated from Thai patients[42] and detected in *Amblyomma americanum* ticks in the USA[136], while *B. rochalimae* isolated from a woman with fever, bacteremia, and splenomegaly in Peru[158] was also currently identified in *Rattus norvegicus* from Taiwan[53]. Based on this review, it can be determined that several *Bartonella* spp. can cause emerging diseases in humans, as the reservoir hosts or arthropods are closely associated to human life.

Diagnosis

The diagnosis of CSD has been performed using five criteria: the presence of cutaneous inoculation sites, chronic lymphadenopathy, cat contact (scratches or bites), a granuloma observed in histologic examination of lymph node tissue biopsies, or a positive skin test[159]. In addition to the Duke criteria of infective endocarditis due to *B. quintana*, serologic tests or PCR-based testing for culture-negative endocarditis may be suitable for inclusion in major criteria[160].

Culture: Suitable methods that are widely used for *Bartonella* isolation include either direct plating on solid blood agar[143], or cocultivation in cell cultures[161-163]. *Bartonella* can be grown on blood-enriched agar in a humid, 5% CO_2 atmosphere at 34-37°C. The primary isolation may require incubation times that exceed 3-4 weeks to visualize the colonies. Lysis centrifugation and frozen techniques can enhance the recovery of *Bartonella* from blood[164]. Cell culture methods allow for a rapid *in vitro* growth of bartonellae in endothelial cells, L929, and HeLa cells[162,163,165]. Furthermore, a combination of both methods may be useful for the recovery of *Bartonella* spp[163]. Recently, Cadenas et al (2007) developed an insect-based liquid culture media (*Bartonella* alpha-Proteobacteria growth medium, BAPGM) for culture of the fastidious and slow-growing *Bartonella*[166]. Moreover, Riess et al (2008) described an easy-to-prepare liquid medium, which uses Schneider's medium, fetal calf serum, and sucrose and allows for fast and reliable growth of several *Bartonella* spp[167]. Interestingly, this medium does not contain hemin, which was considered essential for the growth of *Bartonella* species.

Serology: Currently, there are two available serologic methods for the diagnosis of *Bartonella* infections, enzyme-linked immunoassay (ELISA or EIA) and indirect fluorescent assay (IFA). Both methods use body fluids, such as serum, plasma, or cerebrospinal fluid, for the detection of antibodies. Although, serologic testing cannot use to distinguish the species of *Bartonella*, patients with CSD, endocarditis, and prolonged fever caused by *B. henselae*, including healthy persons are usually diagnosed via IFA or EIA[8,13,15,61,77,90,110,115,168-170]. An IgG antibody titer $\geq$ 1:64 is considered as positive for *B. henselae* infections, such as CSD, whereas *Bartonella*-associated endocarditis in humans and animals exhibits higher IFA antibody titers > 1:800[8,31,170]. In addition to other serologic testing, immunoperoxidase (IP) tests have been performed for seroprevalence of *B. henselae* among veterinary professionals in Japan[116]. Western blot analysis is useful for the diagnosis of endocarditis[171]. Balakristhnan et al (2008) have used western blot techniques to identify *B. quintana* as an agent of endocarditis in India[86]. Conversely, physicians must carefully observe both acute and convalescent antibody titers of patients to diagnose *Bartonella* infections when using serologic methods.

Molecular-based detection: Molecular techniques. such as polymerase chain reaction (PCR), have been widely used for the diagnosis of *Bartonella* infection. The first specific primers were designed by Relman et al (1990) to amplify the conserved regions of the 16S rRNA gene from formalin-fixed tissue obtained from the skin lesions of bacillary angiomatosis patients[172]. Furthermore, the strategies of PCR have improved the identification of genus-specific or species-specific *Bartonella* strains. During 2003 to 2006, Rolain et al successfully developed a real-time PCR-based method for the detection of CSD from lymph node biopsy specimens by using specific primers and probes for ITS and *pap31* genes, which encode a major protein associated with a phage, to differentiate *B. henselae* from *Bartonella* spp. infections[22,173,174]. Currently, devised targets of *Bartonella* identification from the 16S rRNA gene[15,34,35,63,87,175], 18S rRNA gene[64], 23S rRNA gene[49], citrate synthase gene (*gltA*)[50,52,176-178], cell division gene (*ftsZ*)[47,70], heat shock protein genes (*htrA*)[11,61,169], *groEL*[42,68,69], RNA polymerase beta-subunit gene (*rpoB*)[70,179], and 16S-23S rRNA intergenic spacer (ITS)[51,85,141] have been developed to allow for the identification of *Bartonella* spp. at the species level by sequencing amplicons. In addition to the RFLP technique, PCR fragments of 16S rRNA[35,180], ITS[53,112], *gltA*[118,169,181-184], *htrA*[90], riboflavin synthase gene (*ribC*)[10,180], *rpoB*[53,179], or *ftsZ*[53,180] have been produced for the identification of *Bartonella* species by restriction endonuclease digestion.

Conclusion

Bartonellae have a worldwide distribution in nature, and natural reservoirs or incidental hosts usually transmit etiologic organisms via arthropod vectors (*e.g.* cat fleas, dog fleas, rodent fleas, human lice, ticks, etc). This review included descriptions of four species of *Bartonella*; *B. henselae*, *B. quintana*, *B. koehlerae*, and the newly described *B. tamiae* in Asian and Australian patients. Frequently, *B. henselae* includes symptomatic and asymptomatic syndromes, such as CSD, endocarditis, bacillary angiomatosis, uveitis/neuroretinitis/Parinaud's oculoglandular syndrome, prolonged fever, and rare cases of rheumatoid arthritis and osteomyelitis. The manifestations of *Bartonella* infections have not only been recognized among immunocompromised and homeless people, but have also been found in healthy individuals and veterinary professionals. In addition to reservoirs, rodents usually harbor various species of *Bartonella*, including *B. rochalimae*, which cause disease in humans, while cats and dogs act as reservoirs of *B. henselae*, *B. clarridgeiae*, and *B. vinsonii* subsp. *berkhoffii*. Furthermore, arthropods that live in areas of animal reservoirs are of concern for *Bartonella* infections, as determined in this review.

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การติดเชื้อบาร์โทเนลลา: โรคติดเชื้ออุบัติใหม่ในคนและสัตว์ในภูมิภาคเอเชียและออสเตรเลีย

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เชื้อบาร์โทเนลลา (Bartonella spp.) เป็นแบคทีเรียกลุ่มหนึ่งในอัลฟา-2-โปรทีโอแบคทีเรีย (alpha2 subgroup of Proteobacteria) เป็นเชื้อแบคทีเรียซึ่งติดเชื้อได้ทั้งในคนและสัตว์เลี้ยงลูกด้วยนม เพิ่งมีรายงานพบเชื้อบาร์โทเนลลาสายพันธุ์ใหม่จำนวน 5 สายพันธุ์ในประเทศไทยและออสเตรเลียได้แก่ B. tamiae จำนวน 3 สายพันธุ์จากผู้ป่วยไข้ไม่ทราบสาเหตุในประเทศไทย B. australis จากจิงโจ้ B. coopersplainsensis, B. queenslandensis และ B. rattiaustraliensis จากหนูที่ประเทศออสเตรเลีย นอกจากนั้นมีรายงานผลการศึกษา ลำดับเบสของจีน citrate synthase gene A (gltA) ของเชื้อบาร์โทเนลลาจำนวน 17 สายพันธุ์ซึ่งแยกเชื้อได้จาก สัตว์ฟันแทะทางตอนใต้ของประเทศจีน พบความหลากหลายทางพันธุกรรมเช่นเดียวกับเชื้อที่พบในสัตว์ฟันแทะในประเทศไทย ดังนั้นเพื่อให้ทราบถึงสถานการณ์ และนึกถึงการวินิจฉัยการติดเชื้อชนิดนี้ในคนและสัตว์ ซึ่งอาจติดเชื้อจากสัตว์เลี้ยงลูกด้วยนมโดยมีแมลงต่าง ๆ เป็นพาหะ ผู้นิพนธ์จึงได้ทบทวนวารสารเกี่ยวกับการติดเชื้อ นี้ในภูมิภาคเอเชียและออสเตรเลีย พบว่ามีรายงานการแยกเชื้อบาร์โทเนลลาจากประเทศต่าง ๆ ในภูมิภาค เอเชียตะวันออก ได้แก่ จีน ญี่ปุ่น เกาหลี รัสเซีย ไต้หวัน จากภูมิภาคเอเชียใต้ ได้แก่ อัฟกานิสถาน บังคลาเทศ อินเดีย เนปาล จากภูมิภาคเอเชียอาคเนย์ ได้แก่ อินโดนีเซีย ฟิลิปปินส์ สิงคโปร์ ไทย จากภูมิภาคเอเชียตะวันออกกลาง ได้แก่ อิสราเอล จอร์แดน และจากประเทศออสเตรเลีย โดยรายงานเหล่านี้พบการติดเชื้อบาร์โทเนลลาได้บ่อยในแมลงชนิดต่าง ๆ ที่เป็นพาหะ สัตว์เลี้ยงลูกด้วยนมและผู้ป่วยไข้ไม่ทราบสาเหตุในภูมิภาคดังกล่าว