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Evaluation of the available animal models for *Bartonella* infections

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ABSTRACT

The diseases caused by the *Bartonella* genus of bacteria are clinically diverse, and can be challenging to cure. The study of bartonellosis has been hampered by the lack of a suitable animal model. Preclinical studies for novel therapeutics and a competent host for vector transmission studies are needed to fill critical knowledge gaps. The studies included here are a representation of in vivo *Bartonella* research and the corresponding challenges. This review examines the current state of available animal models by assessing the success of various model species and strains in *Bartonella* infection. With a focus on the strengths and weaknesses of current animal models, the importance of these models for improvement of human health and veterinary care is emphasized.

1. Introduction

Bartonellosis is a class of infections by the bacteria in the *Bartonella* genus. Infections with these bacteria are perceived as rare, making it difficult to study the effect of these infections on the human host. *Bartonella* is a genus of vector-borne, gram-negative bacteria that can be transmitted by sandflies, lice, fleas, and possibly ticks [1]. In addition, direct transmission from cats is well documented [2]. The bacteria are present in the saliva and/or feces of the vector. After the host has been bitten by the vector, the bacteria are either injected into the host by way of the saliva or introduced to the lower layers of dermal tissue by scratching infected feces into the bite site. Once the bacteria enter the bloodstream, they infect erythrocytes and travel throughout the host body. The primary niche for this genus of bacteria has not yet been identified and very well may be species or host specific. Infection with differing species can have a large impact on the pathology, diagnosis, treatment, and prognosis of a patient.

The family of diseases characterized as bartonellosis is diverse and not well-understood. As with Lyme disease, which is also vector-borne, many of the associated symptoms are non-specific and the severity of clinical presentation varies widely. This complicates the diagnosis of bartonellosis and results in only the severely ill, who are unable to clear the infection by themselves or with minimal medical intervention, being formally diagnosed. An extremely important consideration is the effectiveness of antimicrobial treatments for *Bartonella* infections. The multiple species of *Bartonella* exhibit variability in antibiotic susceptibility, and treatment is often determined by clinical manifestation rather than the infecting species [3]. Indeed, there is currently no single treatment that is effective for all *Bartonella*-associated diseases [4]. A reliable preclinical animal model for the testing of existing and novel therapeutics will propel this field forward. The purpose of this review is to evaluate the most commonly used animal models in *Bartonella* disease research, the work that has been done to develop these models, and what is lacking in the *Bartonella* field.

2. Human bartonellosis

A variety of disease manifestations are commonly seen in the clinical setting. A brief description of some of these manifestations is included in this section. When considering the diagnosis of bartonellosis, it is important to consider that complicated pathologies can correlate with any of multiple *Bartonella* species. Table 1 compares the most frequently identified clinical findings with which *Bartonella* species they have been associated.

3. Carrion's disease

Carrion's disease is a severe form of bartonellosis caused by *Bartonella bacilliformis*. This pathogen and its associated diseases are localized to the Andes Mountain ranges in South America. Carrion's disease can be classified into two separate disease states: the acute hemolytic phase also known as Oroya fever, with a mortality rate of 44–88%, and a cutaneous manifestation known as verruga peruana. However, with proper diagnosis and treatment, the mortality rate drops significantly [33].The clinical presentation of Carrion's disease is established and quite different from the presentation of other forms of bartonellosis. For

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Table 1
Human disease manifestations and associated *Bartonella* spp. disease.

Disease	Bartonella spp.	ref
Cat scratch disease	*B. henselae, B. quintana, B. clarridgeiae*	[5–8]
Carrion's disease Verruga peruana	*B. bacilliformis*	[9]
Trench Fever	*B. quintana*	[10]
Bacillary angiomatosis	*B. henselae, B. quintana*	[11]
Bacteremia	*B. henselae, B. quintana, B. clarridgeiae, B. elizabethae, B. bacilliformis*	[12–15]
Fever of Unknown Origin	*B. henselae, B. quintana, B. rochalimae B. tamiae, B. rattimassiliensis, B. elizabethae, B. tribocorum*	[16–19]
Blood-culture negative endocarditis	*B. quintana, B. henselae, B. alsatica, B. koehlerae, B. vinsonii* subsp. *arupensis, B. vinsonii* subsp. *berkhoffi, B. elizabethae, B. mayotimonensis*	[15,20–25]
Ocular	*B. henselae, B. grahamii, B. elizabethae*	[26–28]
Neurological	*B. henselae, B. quintana, B. vinsonii subsp. berkhoffi, B. koehlerae, rare rodent species of Bartonella*	[29–32]

these reasons, *B. bacilliformis* is not discussed in this review. For more information in Carrion's disease or *B. bacilliformis* please refer to Garcia-Quintanilla's "Carrion's disease: more than a neglected disease" review [9].

4. Cat scratch disease

Globally, most *Bartonella* infections are associated with *Bartonella henselae*. This species of *Bartonella* is transmitted to cats by cat fleas (*Ctenocephalides felis*) and is the causative agent of cat scratch disease (CSD) in humans. Transmission to humans occurs by bites or scratches of infected cats [34]. Reported symptoms include low grade fever, swollen lymph nodes, and a papule at the scratch site. In a healthy, immunocompetent patient, these symptoms typically subside on their own, without treatment or with minimal care [35]. However, in immunocompromised patients, these signs can progress into more severe manifestations such as endocarditis, encephalitis, bacillary angiomatosis, or neuroretinitis.

5. Trench fever

Another commonly recognized form of bartonellosis is trench fever, historically caused by *Bartonella quintana*-infected human body lice (*Pediculus humanus corporis*). Today, trench fever is seen among the homeless populations in multiple metropolitan areas [36]. In addition to the high fever associated with this disease, symptoms include severe headaches, eye pain, and intense muscle pain in the legs. The most distinguishing feature of this illness is the high fever which lasts for many days before subsiding and returning approximately a week after. This cyclic pattern can be repeated many times, leading to an extended disease course.

6. Endocarditis

Patients that present with infectious endocarditis often have a history of valve replacements, heart transplants, or otherwise compromised cardiac tissue [37]. Bartonellosis endocarditis is often difficult to diagnose and relies on blood and valve biopsy cultures. However, due to the fastidious nature of *Bartonella* spp., the samples are often returned as "blood culture negative endocarditis" or BCNE. Patient outcomes are heavily dependent on timely treatment. The formation of a bacterial biofilm is a likely cause of *Bartonella*-induced endocarditis, typically associated with *B. quintana* and *B. henselae,* but also others (Table 1). It is imperative that *Bartonella* infections are diagnosed prior to biofilm formation and subsequent endocarditis so that the infection can be properly treated and eradicated.

7. Bacillary angiomatosis and bacillary peliosis

Bacillary angiomatosis and peliosis describe abnormal growth of blood vessels near the skin or internal organs, respectively, which can continue to grow uncontrollably like tumors [38,39]. Bacillary peliosis is often found in blood-containing organs such as the liver and spleen [40]. This form of angiomatosis is typically found on the kidneys. When *Bartonella* infection (Table 1) is the etiological cause of the bacillary angiomatosis or peliosis, the bacteria can often be identified in the biopsies of the vascular tumors [41–43].

8. Importance of animal models

The various forms of bartonellosis are identified primarily in immunocompromised individuals. The subtle progression of the disease is not well understood, particularly when the disease becomes self-limiting or becomes latent in the vertebrate host. Evidence from many other vector-borne pathogens indicate that early diagnosis and treatment leads to better outcomes [44]. Relevant, accurate, and applicable animal models are necessary for understanding the early stages of this disease; only then will we have the tools necessary for drug development and prevention strategies. The inability to monitor the disease states of naturally occurring *Bartonella* infections highlights the need for the development of a proper animal model.

A complicating factor in monitoring disease states of vector-borne pathogens is the concept of reservoirs and hosts. Typically, a reservoir can remain infected with minimal to no clinical or pathological findings. The pathogen uses the reservoir host to multiply and spread to potential vectors [45]. This differs from a susceptible host, which shows signs of infection according to disease pathology. Some of the most common reservoirs for *Bartonella* species include cats, wild mice, dogs, rats, and macaques [46,47]. *Bartonella* has been identified in several other animals, but it is unknown if these animals serve as susceptible hosts or reservoirs. These include foxes, horses, bats, and deer.

A common example of this reservoir/host/vector/pathogen relationship is *Borrelia burgdorferi*. It is well documented that the white-footed mouse or other reservoir host is necessary for pathogen acquisition to the ticks [48]. These mice can be chronically infected without exhibiting the signs commonly associated with long-term Lyme disease such as facial palsy, arthritis, endocarditis, or inflammation of the brain and spinal cord [49,50]. In the case of *B. henselae*, cats do occasionally develop signs such as endocarditis, neuroretinitis, bacillary angiomatosis, and/or pyrexia, complicating the division of host and reservoir [51].

The development of an animal model is complicated by the host specificity of each pathogen and the ability for many of the host species to act as reservoirs. While the bare minimum requirement for an animal model would be successful infection, disease models would include pathologies commonly seen in human and animal patients. Infection models have been developed using rodents such as mice and rats. These models become bacteremic for acute and/or chronic infections but much like natural reservoirs, do not show clinical signs or clinical signs have not been assessed. The studies presented here aimed to identify disease models by examining infection rate, clinical signs, and/or histological changes. This review does not focus on the use of animal models for studying *Bartonella* biology in natural hosts [52,53].

It is unknown if animals tested in field studies have any disease pathology. The recurrent nature of *Bartonella* complicates field sampling as infected animals may be in a dormant stage of the disease [54]. Blood samples taken from captured animals or ectoparasites removed from the animals and can be tested [54], but these tests are only able to identify potential bacteremia in the animal, which may not be sustained [54]. Even when animals do show bacteremia, without extensive internal organ tissue biopsies, there is no way to determine if the animal is

exhibiting any symptoms or microscopic pathology. There is little to no survey data regarding the health of the animal, and tissue tropism is unknown because biopsies are not taken. These factors make it difficult to determine the exact reservoir hosts for these pathogens.

There has been some success in the development of an infected model defined by bacteremia (Tables 2 and 3). However, the correlation of using mice, a reservoir host, as a model for a rodent-associated *Bartonella* presents a challenge. Although rodent-associated *Bartonella* species have been identified in human cases, many of these species are also associated with domestic animals such as dogs and cats [51,55].

The studies presented here represent a thorough survey of the published experimental data regarding *Bartonella* infections. Table 2 summarizes the collection of mouse data by comparing strain of mouse used, species of *Bartonella* utilized, and the associated findings. This table also helps to highlight the variety of methods used to determine infection. While many of the studies presented here claim a successful animal model, the benchmarks for success vary widely. It is also important to note that customary publishing practices of presenting only positive data skew the literature. A compilation of studies that did not produce successful animal models could lead to more insights regarding *Bartonella* infection.

9. Description of animal models

Animals used for modeling range from small rodents to non-human primates, with each species having the ability to mimic some aspect of human disease. In the case of *Bartonella,* a well-established animal model has not been developed for human-specific strains. Many factors play a role in the difficulty in developing this model. *Bartonella* species are very host-specific when it comes to infection. Even when one species has developed the ability to infect more than one host species, the range is limited and often evolutionarily related. Fig. 1 gives an overview of animals that have commonly been used and the associated bacterial species. Here we describe experimental *Bartonella* infections in many mouse strains and other potential hosts and assess their suitability as an animal model.

Table 2
Description of various Bartonella spp. in mouse strains and the reported results.

Mouse Strain	Bartonella spp	Inoculation route (dose if available	Methodology	Results (# bacteremic mice, length of bacteremia, PCR positives w/ or w/out tissue identification)	Clinical Findings
Swiss Webster	*B. elizabethae*	SC (10^1–10^6 CFU) [56]	Blood culture	1/6 at 10^6 [56] 1/6 at 10^5 [56]	Clinical signs not assessed
	B. tamiae	SC (10^6–10^7) [57]	PCR Pathology	3/12 [57]	Multiple findings in the skin, liver, kidney, heart, and spleen [57]
	B. birtlesii	IV (3×10^5CFU) [58]	Cell culture	9 weeks [58]	Clinical signs not assessed
BALB/c	*B. elizabethae*	SC (10^1–10^6 CFU) [56] IV (3×10^5–10^7) [58]	Blood culture	1/6 at 10^6 [56]	Clinical signs not assessed
	B. birtlesii	SC (3.4–10^7) [58] ID (9×10^5) [58] PO (4×10^3-3×10^8) [58] IV (5×10^7 CFU) [59]	Blood culture [58] Blood and biopsy culture [59]	5 weeks [58] Bacteremia - 40 days [59] Culture positive blood, spleen, and liver [59]	Clinical signs not assessed
	B. henselae	Blood transfusion [60] IP 10^4 CFU [60,61]	Nested PCR [60] Nested PCR [61]	IP 2/4 Liver & Spleen [60] Transfusion 2/4 Spleen [60] 2/4 at 4 days [61] 4/4 at 21 days [61]	Positive Skin biopsy at day 4 (confocal) [61]
C57Bl/6	*B. elizabethae*	SC (10^1–10^6 CFU) [56] IV (3×10^5 CFU) [58]	Blood culture	2/6 at 10^6 [56]	Clinical signs not assessed
	B. birtlesii	SC (5×10^3–1.4×10^7 CFU) [58] SC (3.4-800 CFU) [58]	Blood culture	IV 4 weeks [58] SC +30 days [58]	Clinical signs not assessed
OF1	*B. birtlesii*	IV (5×10^8 CFU) [62] Tick-feeding [62]	PCR of blood and/or blood/biopsy culture	3/3 gDNA in cultures of blood and livers [62]	Clinical signs not assessed
CD1	*B. tribocorum*	SC (10, 100, 1000 CFU) [63]	Blood culture	21/36 [63]	Clinical signs not assessed
Immuno-compromised	*B. birtlesii*	SC (6×10^5 CFU) [58] 0.12–0.4 OD_{600}* [64]	Cell culture [58] Blood culture [64] Pathology [64]	All mice up to 40 days [58] 2 months [64]	"Obvious and striking liver pathology" [64]
	B. henselae	IP (10^3 CFU) [65] IP (2×10^8 CFU) [66]	Nested PCR [65] PCR [66] Pathology [66]	4/4 All livers and one spleen [65] All infected livers [66]	*B. henselae* can infect sickle-disease RBCs [65] More infected hepatic cells in immune-compromised mice [66] Changes in cytokine and immune cell concentrations [66]
	B. taylorii	0.12–0.4 OD_{600}* [64]	Blood culture [64] qPCR [64] Pathology [64]	2 months by culture [64] +120 days by qPCR [64]	"Obvious & striking liver pathology" [64] Enlarged Spleens, granulomatous nephritis, splenomegaly [64]
	B. grahamii	0.12–0.4 OD_{600}* [64]	Blood culture [64]	2 months [64]	Clinical signs not assessed

ID – intradermal, IV – intravenous, SC – subcutaneous, IP - intraperitoneal injection routes.
* 1 $OD_{600} = 8 \times 10^9$ genome equivalents(1).

Table 3
Experimental infections of various animal models for Bartonellosis.

Animal Model	*Bartonella* species	Inoculation route (dose if available)	Successfully infected animals (culture/PCR)	Clinical Findings
Mice	Strain-dependent, see Table 2 for more details			
Cats				
	B. henselae [67]	ID (8×10^2 CFU, 1×10^6 CFU) IV (5×10^1 CFU, 2×10^5 CFU)	ID (8/8), IV (2/16)	Bacteremia, no clinical abnormalities
	B. henselae, multiple strains [68]	ID (6.6×10^6 CFU/ml to 9.6×10^7 CFU/ml)	12/12	Bacteremia, fever in 6/6 cats infected with feline strain
	B. henselae [69]	Donor blood (IM and IV) and urine (IM)	Donor blood (12/18) urine (0/6)	Fever (6/18), lymphadenopathy (8/18), neurological issues (2/18)
	B. henselae, *B. clarridgeiae* [70]	Donor blood (IV)	18/18 (multiple inoculations if negative)	Multiple histopathological findings in all animals, single cat with CNS abnormalities
	B. henselae [71]	Infected fleas ID (5×10^6 CFU) close contact	Fleas (5/5) ID (5/5) close contact (0/2)	Bacteremia, no clinical abnormalities
	B. vinsonii, *B. rochalimae,* *B. bovis,* *B. quintana* [72]	ID (2.84×10^6 CFU/ml to 3.6×10^9 CFU/ml) IV (2×10^4 CFU/ml)	3/33 total	Only 3 bacteremic cats, authors report multiple animals seroconverted. No clinical signs.
Dogs				
	B. koehlerae, *B. henselae,* *B. vinsonii* [73]	SC (5×10^4 $TCID_{50}$ *B. henselae*) (3×10^4 $TCID_{50}$ *B. vinsonii*)	2/2 (*B. henselae* and *B. koehlerae*)	Only 1 tissue in each animal was positive post necropsy, no clinical signs of infection
	B. henselae, *B. v. berkhoffi,* *B. rochalimae* [74]	ID (2.4×10^6–1.1×10^9 CFU/ml *B. henselae*) (7.6×10^7–2.4×10^9 CFU/ml *B. v. berkhoffi*) (9.2×10^6 CFU/ml *B. rochalimae*)	0/6 bacteremia, but 6/6 seroconverted (*B. henselae*), 3/4 (*B. v. berkhoffi*), 2/2 (*B. rochalimae*)	Swelling (*B. v. berkhoffi*, *B. rochalimae*) or necrotic lesions (*B. henselae*) at inoculation site
Non-Human Primates				
	B. quintana [75]	IV (lice intestine broth, unknown dose)	7/7 Rhesus macaques	3/7 animals had fever
	B. quintana [76]	IV (unknown dose)	4/4 Rhesus macaques	Bacteremia, no clinical abnormalities
	B. quintana [77]	ID (6.6×10^7 CFU/ml)	Single Rhesus macaque	Bacteremia, no clinical abnormalities
	B. bacilliformis [78]	ID (9.5×10^7 CFU/ml) IV (1.1×10^6 CFU/ml)	6/6 Owl monkeys (*Aotus nancymaae*)	Parasitemia via Giemsa staining of blood, lesions at ID sites of infection

ID – intradermal, IV – intravenous, SC – subcutaneous injection routes.

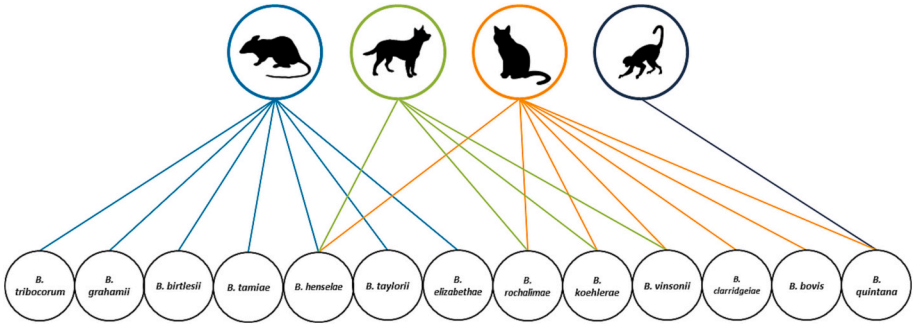

Fig. 1. For each host shown, the associated Bartonella species used for experimental infection is linked. Some have been tested in multiple hosts.

10. Mice

10.1. Swiss Webster

Swiss Webster (SW) is an outbred strain of mice commonly used in toxicology, cancer research, and general research. This strain of mice often becomes bacteremic with rodent-associated *Bartonella* spp. In one study, SW mice infected with *B. birtlesii* were bacteremic, according to blood cultures, for up to 9 weeks [58]. A study of SW mice infected with *B. elizabethae* had less success in that only 2 of the 36 mice inoculated became bacteremic [56]. This is contrary to SW mice that were inoculated with three isolates of *B. tamiae*, in which all 12 mice developed a thickened and tough skin at the inoculation site that resolved by week 4 post-infection. The mice also developed subcutaneous masses on the lateral thorax and inguinal lymph node enlargement, some of which persisted until the end of the study at 6 weeks. PCR analysis of the masses showed *B. tamiae* DNA was present in mice inoculated with each isolate [57]. Histopathology of biopsies taken during necropsy show extensive immunological changes. Granulomas were noted on the liver, lymph nodes, and kidneys. Pyrogranulomas were found in the lymph nodes and spleen. Additional histological findings included necrotizing dermatitis and myocarditis with granulomas in the right and left atria [57].

10.2. OF1

The OF1 mouse is an outbred strain commonly used in toxicology, teratology, pharmacology, and physiology. They are known for their rapid growth and high breeding success. OF1 mice were used in one study to examine the transmission potential of *B. birtlesii* by *Ixodes ricinus* ticks. A single mouse was infected by intravenous injection and was positive when tested for *B. birtlesii* for at least 2.5 weeks with semi-nested PCR. The mouse continued to be used as a bacteremic source of blood for the ticks. Of note, *I. ricinus* ticks were able to acquire the bacteria from the mice and transmit it back into naïve mice [62]. The combination of these data suggests that *B. birtlesii* can infect OF1 mice, yet higher numbers are needed to be certain.

10.3. BALB/c

This mouse strain is considered a multipurpose model and is used for hybridoma development, monoclonal antibody production, and infectious disease research, including multiple *Bartonella* infection studies. A comparison of injection methods showed that BALB/c mice were more bacteremic when subcutaneously injected with *B. birtlesii* compared to intravenous injection, and bacteremia persisted for 5 weeks post-injection [58]. Intradermal injection resulted in a quicker emergence of bacteremia, although the infection was cleared quicker and bacteremia was lower than in mice infected by the subcutaneous route. Another study of BALB/c mice, this time infected with *B. henselae* by intraperitoneal injection, showed the presence of *Bartonella* DNA in the spleen, liver, and skin as soon as 4 days post-injection. Blood samples taken from the mice at days 4 and 21 showed *Bartonella* DNA was present in all of the 21 day samples [61]. This study highlights the need for extended experiments to fully understand the complexities of *Bartonella* infections. In this strain of mice, *B. elizabethae* was able to infect 1 out of 6 mice within one week. This infection lasted 7 weeks as measured by blood culture [56]. Another study looked at infections of *B. henselae* by intraperitoneal injection and by blood transfusion. The study showed that 2 of 4 animals had *Bartonella* DNA in their spleens and one had *Bartonella* DNA in the liver. Blood from infected mice was transfused into naïve mice, of which 2 out of 4 mice had *Bartonella* DNA detected in their spleen. Interestingly, despite infectious blood being transfused, the blood collected from all recipient animals was negative by PCR [60]. Another study result showed that infection with *B. henselae* resulted in bacterial colonization of the liver three days after infection. *Bartonella* DNA was detectable from the blood and liver at 3- and 7-days post-infection, and at 3-, 7-, and 14-days post-infection in the spleen. IgM was detectable in the plasma of infected mice after 3 and 7 days but undetectable by 14-days post-infection [79]. Infection with *B. birtlesii* resulted in mice becoming bacteremic on average 8 days after infection and peaking on 14-days post-infection. These mice were no longer bacteremic at 10 weeks, and none of the mice relapsed in the following 4 weeks [80]. Another BALB/c mouse study aimed to evaluate the different routes of inoculation of *B. henselae* regarding the generation of immune responses. When mice were inoculated by intraperitoneal (IP) injection, the liver and mesenteric lymph nodes were positive as early as 6-h post-injection and the spleen, liver, and kidney were positive up to 7 days, according to PCR. *Bartonella* DNA was not amplified in whole blood samples of these mice. None of the inoculation routes at standard doses were able to produce bacterial colonies with culture. However, at high doses, IP-injected mice did have bacteria present in the tissues within 24 h, despite all blood cultures remaining negative [81].

10.4. C57BL/6

C57BL/6 mice are one of the most used strains in biomedical research. This breed of mouse is particularly useful due to its permissive background for transgenic/knockout model development and genetic homogeneity. In *Bartonella* research, C57BL/6 mice have been infected with *B. elizabethae* and *B. birtlesii*. When inoculated with *B. elizabethae*, 2 out of 6 mice became bacteremic at 2- and 3-weeks post-infection and remained bacteremic for 7–8 weeks. No illness was observed and no samples were collected for histopathology [56]. Conversely, *B. birtlesii* inoculation led to high levels of bacteremia after just 1 week but also cleared as quickly as 5 weeks post-injection. It is important to note that the total number of infected mice was not reported in this study and samples were not taken for pathology [58]. This strain of mouse has been used to develop mutant strains that are deficient in IL-10, CD4, and CD8. In one study, IL-10-deficient mice did not become infected with *B. birtlesii*. When compared to controls, CD8-deficient mice had no change in bacteremia while bacteremia in CD4-deficient mice indicated an increase in length and quantity of bacterial burden. When both CD4 and CD8 were knocked out, the bacteremia was intermediate to the two single knock outs, indicating that the infection is partially controlled by helper T cell responses [58]. This comprehensive analysis of mouse models compared mouse strain, route, and dose of *B. birtlesii* for the duration of bacteremia. The study found that the mice became bacteremic early with intradermal inoculation, but longer-lasting bacteremia was induced with subcutaneous (SC) or intravenous routes. Another study showed that SC injection of 10^8 CFUs of *B. henselae* and *B. grahamii* were required to induce transient local inflammation [82]. Lymphadenopathy was observed in mice infected with either strain but was more pronounced with *B. henselae*. Lymph nodes from 5 out of 6 mice infected with *B. henselae* contained culturable bacteria at day 1, but by day 20 had become sterile. However, in 5 out of 15 of the mice tested, DNA could still be found at day 21 in the lymph nodes and spleen. Researchers stated that mice infected with *B. grahamii* showed similar results. Despite the lymphadenopathy and cultivatable bacteria in the lymph nodes and spleens, no live bacteria or DNA were found in the liver, heart, or blood up to 21 days [82]. Another study showed that the liver and spleen are capable of clearing culturable bacteria within 6 days and can only be found in a few brain and blood samples before 6 h [83]. Despite the quick clearance of the bacteria, *B. henselae* DNA was found in all livers tested at 3 months post-infection. Histopathology of the livers at 3 days, 2 weeks, 4 weeks, and 3 months showed the progression of pathology. At 3 days post-infection, the tissues had few small aggregates of lymphocytes and monocytes. After 2 weeks post-infection, the granulomatous lesions became more obvious and consisted of lymphocytes, monocytes, and epithelioid cells. At week 4, the inflammatory lesions were greatly reduced and by month 3, the tissues were devoid of inflammatory lesions [83]. These studies differ from Arvand et al. [84] who found cultivatable bacteria up to 3 days post-infection from liver and up to 6 days post-infection from the spleens. *Bartonella* DNA could be amplified from the livers of infected mice up to 12 weeks post-infection. The infected livers did have mononuclear cell infiltrates at 2 weeks post-infection and these lesions expanded in size and number up to 12 weeks post-infection. The mice in this study seroconverted at 2 weeks post-infection which continued until 12 weeks post-infection. At the end of the study at 20 weeks, serology and pathology had returned to normal levels [84].

10.5. CD1

CD1 mice are an outbred strain which makes them genetically diverse, like Swiss-webster mice. Despite their popular use, only one study was identified in which CD1 mice were inoculated with two strains of *B. tribocorum* isolated from two different species of mouse. Both strains had success infecting these mice with 67% (12/18) and 61% (11/18) efficiency. Of the 23 mice, some of them had relapsing bacteremia and 8/30 (26.7%) still had bacteremia at the end of the 27-week study [63].

10.6. SCID

SCID (severe combined immunodeficiency disease) mice have a

genetic mutation that affects B and T lymphocyte maturation. The beige mutation results in defective natural killer cells. Because of these mutations, SCID and SCID/beige mice are ideal models for studying the immune system, pathogenicity of microbes, and tumor growth. In the cases of *Bartonella,* exposure to the pathogen does not always lead to pathology in the host, so the lack of an intact immune system in these species allows the *Bartonella* to invade host cells more readily. Since atypical bartonellosis presents in immunocompromised patients more often, the use of immunocompromised mice may better mimic the disease process in humans. An experimental infection of SCID and SCID/beige mice with *B. taylorii, B. birtlesii, B. doshiae*, and *B. grahamii* showed that the bacteria can persist in the bloodstream for up to 2 months [64]. SCID mice had low levels of *B. taylorii*, but high levels of bacteremia were found in SCID/beige mice infected with *B. taylorii, B. grahamii*, and *B. birtlesii*. The difference in bacteremia between SCID and SCID/beige indicates that natural killer cells are partially responsible for clearance of the bacteria. SCID/beige mice infected with *B. taylorii* showed extensive levels of pathology in the liver, kidneys, and spleen. Other studies utilized SCID mice infected with *B. henselae* and noted pathologies in the liver of infected animals with no notable differences in the spleens or aorta of these animals [85].

10.7. AHNAK knockout

At least one study has used AHNAK knockout mice to study the effects of *B. henselae* infection. This mutant mouse strain no longer produces the Neuroblast Differentiation-Associated Protein, a large structural scaffold protein. This protein has multiple roles in the cell but primarily functions as a component of calcium signaling during CD4+ T cell activation. Although the researchers were able to identify *B. henselae* DNA in both the wild-type and mutant mice, closer histopathological analysis showed that only a few cells were infected in the liver of wild-type mice, but significantly more cells were infected in the knockout mice. After day 18, granulomatous mononuclear cells were identified in the liver of both the wild-type and knockout mice, with significantly more in the knockout group. Like SCID mice, the lack of T cell activation results in a more severe form of the disease [66].

11. Cats

Cats are an outbred animal model often used to research genetic and neurological conditions, as well as a naturally-occurring AIDS model from Feline Immunodeficiency Virus (FIV) [86]. Like mice, cats are a natural reservoir and host for some *Bartonella* species, predominantly *B. henselae*. Survey data has also determined that *B. clarridgeiae* and *B. koehlerae* can use felines as a reservoir [51,67,87–89]. Cats infected with *Bartonella* can have asymptomatic intraerythrocytic bacteremia that can last for months or years [90]. The percentage of bacteremic cats in households of patients with Cat Scratch Disease (CSD) is significantly higher than in domestic environments where CSD is not present [91].

Even though they lack clinical signs, infection rates in cats are high and relapsing bacteremia can be identified using common laboratory techniques such as PCR, blood culture, or immunoblot. Experimental infection of cats with *B. henselae* indicated that intradermal injection led to higher bacteria counts when compared to intravenous injection [67]. In a comparison of bacteremia duration between three *Bartonella* species including *B. koehlerae*, *B. henselae*, and *B. clarridgeiae*, *B. henselae* remained in the blood for 37–77 days, while *B. koehlerae* was evident by bacteremia for 70–78 days with no sign of relapsing bacteremia in either. However, when felines were infected with *B. clarridgeiae,* they were bacteremic for 263–363 days, including relapses. IgG and IgM antibodies were detected as early as 15 days post infection and persisted past 200 days (the full length of the study) [68].

Clinical disease in cats has been documented by Kordick, et al. [69] after intramuscular or intravenous injection of donor blood infected with *B. henselae*. After infection, some cats became febrile, but only 2 out of 14 animals exhibited clinical signs. This appears consistent with what is observed in the clinical setting [69]. A later study utilized blood from *B. henselae* or *B. clarridgeiae*-infected donor cats for intravenously inoculation. These cats exhibited acute anemia and fever, as well as intermittent bacteremia, but infection was not accompanied by clinical signs. One cat did experience focal motor seizures, nystagmus, and intermittent rigidity in the first 4 months. Out of the 18 cats in the experiment, 9 tested positive by either PCR or serology. At necropsy, many of the cats displayed histopathology of the lymph nodes, spleen, kidneys, heart, and eyes. *Bartonella* DNA was identified in the brain, lymph nodes, lung, left ventricle, liver, and kidney [70].

Horizontal and vertical transmission of *B. henselae* between cats has rarely been studied but has not been successful. In a preliminary study focusing on both naturally and experimentally infected cats, Abbot et al. described the lack of direct cat-cat transmission [67]. One study aimed to determine the ability of *B. henselae* to infect newborn cats by infecting the pregnant queens in mid- to late-pregnancy. All the queens became bacteremic within 2 weeks and were bacteremic at the time of delivery. Of the five pregnancies, three resulted in live births. Kittens born to these three queens were not bacteremic by qPCR or culture. Interestingly, kittens from each litter exhibited markedly different antibody responses including transient colostral antibodies, extended seropositivity, and no maternal IgG antibodies [68].

Additional *Bartonella* spp. were tested to determine their ability to infect cats [68]. *B. vinsonii, B. rochalimae, B. bovis,* and *B. quintana* were intradermally injected into cats aged 6–18 months (1/15 cat was inoculated by IV, 1/15 cat was age 3 yrs). Bacteremia was measured in only 3 out of 4 *B. rochalimae*-infected animals, and one of these animals displayed evidence of recurrent bacteremia. Although many of the cats never exhibited bacteremia, many of them seroconverted. Time elapsed between injection and seroconversion differed for each species. *B. vinsonii*-infected cats had measurable antibodies 3–4 weeks after injection, while *B. rochalimae*-infected cats became serologically positive by 14 days post injection. The cats inoculated with the feline strain of *B. bovis* mounted a rapid response with 5 of 6 cats seroconverting in the first 7–10 days while the bovine *B. bovis* strain seroconversion took 2–3 weeks. Interestingly, cats infected with either of two strains of *B. quintana* showed opposite effects. Cats infected with the human strain of *B. quintana* seroconverted in 2–3 weeks and remained positive through the end of the experiment. Conversely, cats injected with the feline strain of *B. quintana* did not show any signs of a serological response [72].

12. Dogs

Clinical signs of *Bartonella*-infected dogs include endocarditis, myocarditis, vasculitis, and granulomatous disease [92,93]. In one study, two golden retrievers that had naturally been infected with *B. koehlerae* were experimentally infected with *B. vinsonii berkhoffi* or *B. henselae. B. koehlerae* was identified by PCR and culture prior to experimental infection, but no *Bartonella* DNA was identified after. Both dogs became seropositive to their respective bacteria between weeks 2–4, and cultures from one animal had *B. henselae* in the bone marrow and *B. koehlerae* in the lungs. The dog infected with *B. vinsonii berkhoffii* did generate an antibody response but none of the tissues collected for analysis grew *Bartonella* in culture. There were, however, significant pathological findings. Gross lesions were seen in the to the lungs and pleura, adrenal cortex, salivary gland and trigeminal ganglion [73]. This study reveals that infection of dogs with these strains of *Bartonella* can lead to multiorgan pathology.

B. henselae and *B. vinsonii* infections were repeated in another study using beagles, which also included *B. rochalimae*. In this study, *B. henselae* caused severe and necrotic lesions at the site of inoculation which persisted for 10–20 days. All the *B. henselae*-infected dogs did seroconvert within 2 weeks of inoculation, although none of the dogs became bacteremic. For the animals infected with the other *Bartonella*

species, there were no clinical or physical abnormalities except mild inflammation at the injection site. Dogs inoculated with *B. vinsonii berkhoffi* had a persistent bacteremia that lasted for 60- and 70-days post-inoculation. Antibody titers were low but measurable in these dogs for up to 90 days. In the case of *B. rochalimae,* the dogs became bacteremic at days 19 and 24 post-inoculation although the bacteremia only lasted 2–2.5 weeks [74].

13. Non-human primates (NHP)

Several screening studies in animal-care facilities have found that non-human primates (NHPs) harbor *Bartonella quintana* without any clinical signs, indicating they are a natural reservoir for the bacteria. Few experimental studies have been conducted to examine *Bartonella* infection in non-human primates. The first documented study, performed in 1953 by Mooser and Weyer, used the contents of *B. quintana*-infected lice (*Pediculus spp*) intestines to intravenously infect 7 rhesus macaques [75]. Infection was confirmed when uninfected lice were allowed to feed on the animals and subsequent microscopic examination of louse hemolymph produced *Bartonella*-positive slides. The macaques were bacteremic for approximately 100 days, after which uninfected lice did not become positive. The animals did not show clinical signs of infection throughout the study, although the authors did note a transient rise in body temperature in 3 out of 7 animals. A later study found that *B. quintana* isolated from rhesus macaques during surveillance was able to be cultured and intravenously injected into 4 non-infected animals [76]. All animals displayed intermittent, transient bacteremia throughout the next 100 days after infection, and none of the animals displayed clinical signs of disease. In both studies, the exact inoculation dose was unknown. A macaque model of infection for *B. quintana* has been described for bacteremia, with published data from one representative animal [77]. This animal was infected with 6.6×10^7 CFU of *B. quintana* via the intradermal route and subsequently displayed intermittent levels of bacteremia over 100 days, but no clinical signs of disease.

In addition to the studies using *Bartonella quintana*, one publication describes the susceptibility of owl monkeys to *Bartonella bacilliformis* infection [78]. Animals were infected with 1.1×10^6 CFU intravenously ($n = 3$) or 9.5×10^7 CFU intradermally (n = 3). In the intradermal-inoculated group, one animal presented with fever and skin lesions. Two out of 3 animals in each group presented with bacteremia as measured through Giemsa staining. However, PCR and blood culture tests were negative in both groups. This study demonstrated that a species of new world non-human primate could become infected and present mild disease with a different *Bartonella* strain.

A compilation of the studies conducted in cats, dogs and primates is presented in Table 3. An important limitation to the studies in rodents, dogs and cats is the detection of Bartonella DNA exclusively as evidence for infection. Ideally, cultures would be used to validate a productive infection, because DNA could be detected from environmental contamination. A recent study indicated that blood supplementation could enrich the culture and increase the chances of live bacteria acquisition [94].

14. Conclusion

The data presented in this review stands as an indicator of the convoluted and complex nature of animal models for bartonellosis research. An ideal animal model for bartonellosis would accurately represent human clinical presentation and have measurable changes in pathology and bacteremia. Without a normalized set of clinical signs or symptoms, identifying a suitable pathological model is difficult. Where dogs may exhibit pathology, cats typically only exhibit bacteremia. Only certain combinations of *Bartonella* species and mouse strains lead to persistence and rarely, pathology. This is likely due to the utilization of multiple reservoir hosts by the ubiquitous *Bartonella* genus of bacteria.

None of the models presented here meet all criteria for an accurate, measurable, and pathological model. Selection criteria should be heavily dependent on experimental needs. For example, although Swiss Webster strain mice display pathological signs in many tissues, the low measurable infection rate limits it's use in antibiotic treatment studies. However, this same strain of mouse may be useful when studying disease progress or severity. Using non-traditional models such as cats and dogs may be of use in some *Bartonella* studies. Cats display extended bacteremia states as seen in some human cases of bartonellosis, indicating they could be a good model for chronic infections with serological findings (Table 3).

In lieu of a pathological model, infectious models serve as the primary data source for therapeutic drug testing. Without primary research examining the changing pathologies from multiple strains and mutations of *Bartonella* spp., treatments cannot be broadly targeted. As co-infections between *Bartonella* and other vector-borne pathogens, such as *B. burgdorferi*, emerge as a factor in disease progression, the need for a versatile pathological model becomes more apparent. Despite the difficult circumstances presented here, it is the aim of these authors and many others in the field of *Bartonella* to identify the best model for the research purpose.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Data availability

No data was used for the research described in the article.

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References

[1] S.A. Billeter, et al., Detection of two Bartonella tamiae-like sequences in Amblyomma americanum (Acari: Ixodidae) using 16S-23S intergenic spacer region-specific primers, J. Med. Entomol. 45 (2008) 176–179.
[2] Y. Regier, F. Órourke, V.A.J. Kempf, Bartonella spp. - A chance to establish One Health concepts in veterinary and human medicine, in: Parasites and Vectors, 2016, pp. 1–12. Parasites & Vectors.
[3] G. Prutsky, et al., Treatment outcomes of human bartonellosis: a systematic review and meta-analysis, Int. J. Infect. Dis. 17 (2013) e811–e819.
[4] E. Angelakis, D. Raoult, Pathogenicity and treatment of Bartonella infections, Int. J. Antimicrob. Agents 44 (1) (2014) 16–25.
[5] D.W. McCormick, et al., Bartonella spp infections identified by molecular methods US, Emerg. Infect. Dis. 29 (3) (2023) 467–476.
[6] A. Sander, et al., Characterization of Bartonella clarridgeiae Flagellin (FlaA) and detection of Antiflagellin antibodies in patients with lymphadenopathy, J. Clin. Microbiol. 38 (8) (2000) 2943–2948.
[7] J.-M. Rolain, et al., Lymph node biopsy Speciments and diagnosis of cat scratch disease, Emerg. Infect. Dis. 12 (9) (2006) 1338–1344.
[8] R.C. Jerris, R.L. Regnery, Will the real agent of cat-scratch disease please stand up? Annu. Rev. Microbiol. 50 (1996) 707–725.
[9] M. Garcia-Quintanilla, et al., Carrion's disease: more than a neglected disease, Parasit. Vectors 12 (1) (2019) 141.
[10] G.M. Anstead, The centenary of the discovery of trench fever, an emerging infectious disease of World War 1, Lancet Infect. Dis. 16 (8) (2016) e164–e172.
[11] R.L. Regnery, J. Tappero, Unraveling mysteries associated with cat-scratch disease, bacillary angiomatosis, and related syndromes, Emerg. Infect. Dis. 1 (1) (1995) 16–21.
[12] M.R. Drummond, et al., Comparison of molecular methods for Bartonella henselae detection in blood donors, PLoS Negl. Trop. Dis. 17 (6) (2023), e0011336.

[13] B.H. Mai, et al., Five millennia of Bartonella quintana bacteraemia, PLoS One 15 (11) (2020), e0239526.
[14] J. del Valle Mendoza, et al., Diagnosis of Carrion's disease by direct blood PCR in thin blood smear negative samples, PLoS One 9 (3) (2014), e92283.
[15] J.S. Daly, et al., Rochalimaea elizabethae sp. nov. isolated from a patient with endocarditis, J. Clin. Microbiol. 31 (4) (1993) 872–881.
[16] M. Tsukahara, et al., Bartonella henselae infection as a cause of fever of unknown origin, J. Clin. Microbiol. 38 (5) (2000) 1990–1991.
[17] M.E. Eremeeva, et al., Bacteremia, fever, and splenomegaly caused by a newly recognized Bartonella species, N. Engl. J. Med. 356 (23) (2007) 2381–2387.
[18] M. Kosoy, et al., Bartonella tamiae sp. nov., a newly recognized pathogen isolated from three human patients from Thailand, J. Clin. Microbiol. 46 (2) (2008) 772–775.
[19] M. Kosoy, et al., Identification of Bartonella infections in febrile human patients from Thailand and their potential animal reservoirs, Am. J. Trop. Med. Hyg. 82 (6) (2010) 1140–1145.
[20] D. Raoult, et al., First isolation of Bartonella alsatica from a valve of a patient with endocarditis, J. Clin. Microbiol. 44 (1) (2006) 278–279.
[21] U. Okaro, et al., Bartonella species, an emerging cause of blood-culture-negative endocarditis, Clin. Microbiol. Rev. 30 (3) (2017) 709–746.
[22] B. Avidor, et al., Bartonella koehlerae, a new cat-associated agent of culture-negative human endocarditis, J. Clin. Microbiol. 42 (8) (2004) 3462–3468.
[23] E.Y. Lin, et al., Candidatus Bartonella mayotimonensis and endocarditis, Emerg. Infect. Dis. 16 (3) (2010) 500–503.
[24] L. Olarte, et al., Bartonella vinsonii endocarditis in an adolescent with congenital heart disease, Pediatr. Infect. Dis. J. 31 (5) (2012) 531–534.
[25] V. Roux, et al., Bartonella vinsonii subsp. berkhoffii as an agent of afebrile blood culture-negative endocarditis in a human, J. Clin. Microbiol. 38 (4) (2000) 1698–1700.
[26] A. Acar, et al., A case series of cat-scratch disease with ocular manifestations: clinical findings and treatment approach, Turk. J. Ophthalmol. 53 (4) (2023) 226–233.
[27] F.T. Kerkhoff, et al., Demonstration of Bartonella grahamii DNA in ocular fluids of a patient with Neuroretinitis, J. Clin. Microbiol. 37 (12) (1999) 4034–4038.
[28] H.S. O'Halloran, et al., Leber's neuroretinitis in a patient with serologic evidence of Bartonella elizabethae, Retina 18 (3) (1998) 276–278.
[29] J.H. Parrott, et al., Central nervous system infection associated with Bartonella quintana - a report of two cases, Pediatrics 100 (1997) 403–408.
[30] M. Nakamura, et al., Cat scratch disease-associated encephalitis followed by parkinsonism, Intern. Med. 61 (20) (2022) 3115–3120.
[31] E.B. Breitschwerdt, et al., Bartonella sp. bacteremia in patients with neurological and neurocognitive dysfunction, J. Clin. Microbiol. 46 (9) (2008) 2856–2861.
[32] R.G. Maggi, et al., Bartonella spp. bacteremia and rheumatic symptoms in patients from Lyme disease-endemic region, Emerg. Infect. Dis. 18 (5) (2012) 783–791.
[33] M. Kosek, et al., Natural history of infection with Bartonella bacilliformis in a nonendemic population, J. Infect. Dis. 182 (2000) 865–872.
[34] B.B. Chomel, R.W. Kasten, Bartonellosis, an increasingly recognized zoonosis, J. Appl. Microbiol. 109 (3) (2010) 743–750.
[35] Prevention, C.D.C. *Bartonella henselae infection or cat scratch disease (CSD)*. Bartonella Infection January 10, 2022 [cited 2022 July 20, 2022].
[36] M.E. Ohl, D.H. Spach, Bartonella quintana and Urban Trench Fever, Clin. Infect. Dis. 31 (1) (2000) 131–135.
[37] R. Ghashghaei, et al., Bartonella endocarditis, J. Cardiol. Cases 13 (1) (2016) 1–3.
[38] S. Akram, , et al.Bacillary Angiomatosis, StatPearls., Treasure Island, StatPearls Publishing, FL, 2021.
[39] S. Claasens, et al., Bacillary angiomatosis presenting with polymorphic skin lesions, IDCases 6 (2016) 77–78.
[40] S. Alkan, J.M. Orenstein, Bacillary peliosis hepatis, N. Engl. J. Med. 324 (21) (1991) 1513–1514.
[41] J. Corral, et al., First report of bacillary Angiomatosis by Bartonella elizabethae in an HIV-positive patient, Am. J. Dermatopathol. 41 (2019) 750–753.
[42] J.F. Schwensen, R.H. Nielsen, M. Helleberg, Bacillary angiomatosis in a solid organ transplant recipient, IDCases (2019) 18.
[43] B.M. Mitchell, R.L. Font, Molecular detection of Bartonella henselae for the diagnosis of cat scratch disease and bacillary Angiomatosis of the conjunctiva, Cornea 30 (7) (2011) 807–814.
[44] Organization;, W.H, Report of an Informal Expert Consultation SEARO, New Delhi, 7–8 April 2014, WHO Regional Office for South-East Asia, 2014.
[45] M. Québatte, C. Dehio, Bartonella gene transfer agent: Evolution, function, and proposed role in host adaptation, in: Cellular Microbiology, 2019, pp. 1–9.
[46] M. Kosoy, I. Goodrich, Comparative ecology of Bartonella and Brucella infections in wild carnivores, in: Frontiers in Veterinary Science, 2019, pp. 1–32.
[47] F. Iannino, et al., Bartonella infections in humans dogs and cats, Vet. Ital. 54 (1) (2018) 63–72.
[48] J. Couret, S. Schofield, S. Narasimhan, The environment, the tick, and the pathogen - it is an ensemble, Front. Cell. Infect. Microbiol. 12 (2022) 1049646.
[49] E.M. Bosler, et al., Prevalence of the lyme disease spirochete in populations of white-tailed deer and white-footed mice, Yale J. Biol. Med. 57 (4) (1984) 651–659.
[50] L.A. Magnarelli, J.F. Anderson, W.A. Chappell, Geographic distributions of humans, raccoons, and white-footed mice with antibodies to Lyme disease spirochetes in Connecticut, Yale J. Biol. Med. 57 (1984) 619–626.
[51] A. Alvarez-Fernandez, E.B. Breitschwerdt, L. Solano-Gallego, Bartonella infections in cats and dogs including zoonotic aspects, Parasit. Vectors 11 (2018) 624.
[52] R. Heller, et al., Bartonella tribocorum sp. nov., a new Bartonella species isolated from the blood of wild rats, Int. J. Syst. Bacteriol. 48 (1998) 1333–1339.
[53] R. Schulein, C. Dehio, The VirB/VirD4 type IV secretion system of Bartonella is essential for establishing intraerythrocytic infection, Mol. Microbiol. 46 (4) (2002) 1053–1067.
[54] R. Gutierrez, et al., Bartonella infection in rodents and their flea ectoparasites: an overview, Vector Borne Zoonotic Dis. 15 (1) (2015) 27–39.
[55] M. Krugel, et al., Emerging rodent-associated Bartonella: a threat for human health? Parasit. Vectors 15 (113) (2022).
[56] L. Colton, H. Kabeya, M. Kosoy, Experimental infection of three laboratory mouse stocks with a shrew origin Bartonella elizabethae strain: an evaluation of bacterial host switching potential, Infect. Ecol. Epidemiol. 2 (1) (2012).
[57] L. Colton, et al., Human isolates of Bartonella tamiae induce pathology in experimentally inoculated immunocompetent mice, BMC Infect. Dis. 10 (229) (2010).
[58] G. Marignac, et al., Murine model for Bartonella birtlesii infection: new aspects, Comp. Immunol. Microbiol. Infect. Dis. 33 (2010) 95–107.
[59] H.K. Deng, et al., Role of the spleen in Bartonella spp. infection, FEMS Immunol. Med. Microbiol. 64 (2012) 143–145.
[60] M.N. da Silva, et al., Bartonella henselae transmission by blood transfusion in mice, Transfusion 56 (6 Pt 2) (2016) 1556–1559.
[61] M.N. da Silva, et al., Acute and late Bartonella henselae murine model infection, Vector-Borne Zoonotic Dis. 17 (3) (2017) 206–208.
[62] C. Reis, et al., Vector competence of the tick Ixodes ricinus for transmission of Bartonella birtlesii, PLoS Negl. Trop. Dis. 5 (5) (2011), e1186.
[63] L. Colton, M. Kosoy, Experimental infection of laboratory mice with two Bartonella tribocorum strains from wild Mus species: a homologous host-bacteria model system at the genus level, Parasitology 140 (2013) 61–68.
[64] L. Chiaraviglio, et al., An immunocompromised murine model of chronic Bartonella infection, Am. J. Pathol. 176 (6) (2010) 2753–2763.
[65] A.R. de Almeida, et al., Bartonella henselae infection in sickle cell disease mice is associated with hyperalgesia, Vector-Borne Zoonotic Dis. 19 (2) (2019) 102–105.
[66] E.W. Choi, et al., Ahnak-knockout mice show susceptibility to Bartonella henselae infection because of CD4+ T cell inactivation and decreased cytokine secretion, BMB Rep. 52 (4) (2019) 289–294.
[67] R.C. Abbott, et al., Experimental and natural infection with Bartonella henselae in domestic cats, Comp. Immunol. Microbiol. Infect. Dis. 20 (1997) 41–51.
[68] K. Yamamoto, et al., Experimental infection of specific pathogen free (SPF) cats with two different strains of Bartonella henselae type I: a comparative study, Vet. Res. 33 (2002) 669–684.
[69] D.L. Kordick, E.B. Breitschwerdt, Relapsing bacteremia after blood transmission of Bartonella henselae to cats, Am. J. Vet. Res. 58 (5) (1997) 492–497.
[70] D.L. Kordick, et al., Clinical and pathologic evaluation of chronic Bartonella henselae or Bartonella clarridgeiae infection in cats, J. Clin. Microbiol. 37 (5) (1999) 1536–1547.
[71] B.B. Chomel, et al., Experimental transmission of Bartonella henselae by the cat flea, J. Clin. Microbiol. 34 (8) (1996) 1952–1956.
[72] B.B. Chomel, et al., Experimental infection of cats with Afipia felis and various Bartonella species or subspecies, Vet. Microbiol. 172 (2014) 505–510.
[73] N. Balakrishnan, et al., Experimental infection of dogs with Bartonella henselae and Bartonella vinsonii subsp. berkhoffii, Vet. Immunol. Immunopathol. 156 (2013) 153–158.
[74] B.B. Chomel, et al., Experimental infection of dogs with various Bartonella species or subspecies isolated from their natural reservoir, Vet. Microbiol. 168 (2014) 169–176.
[75] H. Mooser, F. Weyer, Experimental infection of Macacus rhesus with Rickettsia quintana (trench fever), Proc. Soc. Exp. Biol. Med. 83 (1953) 699–701.
[76] H. Li, et al., Transmission and Maintenance Cycle of Bartonella quintana among Rhesus Macaques, China, Emerg. Infect. Dis. 19 (2) (2013) 297–300.
[77] P. Zhang, et al., A family of variably expressed outer-membrane proteins (Vomp) mediates adhesion and autoaggregation in Bartonella quintana, PNAS 101 (2004) 1363–13635.
[78] D.E. Bentzel, et al., Susceptibility of owl monkeys (Aotus nancymaae) to experimental infection with Bartonella bacilliformis, Comp. Med. 58 (2008) 76–80.
[79] H. Kabeya, et al., Immune responses of immunocompetent and immunocompromised mice experimentally infected with Bartonella henselae, J. Vet. Med. Sci. 65 (4) (2003) 479–484.
[80] H.J. Boulouis, et al., Kinetics of Bartonella birtlesii infection in experimentally infected mice and pathogenic effect on reproductive functions, Infect. Immun. 69 (9) (2001) 5313–5317.
[81] K.L. Karem, et al., Characterization of Bartonella henselae-specific immunity in BALB/c mice, Immunology 97 (1999) 352–358.
[82] S. Kunz, et al., Lymphadenopathy in a novel mouse model of Bartonella-induced cat scratch disease results from lymphocyte immigration and proliferation and is regulated by interferon-α/β, Am. J. Pathol. 172 (4) (2008) 1005–1018.
[83] T. Regnath, et al., Murine model of Bartonella henselae infection in the immunocompetent host, Infect. Immun. 66 (11) (1998) 5534–5536.
[84] M. Arvand, et al., Bartonella henselae-specific cell-mediated immune responses display a predominantly Th1 phenotype in experimentally infected C57BL/6 mice, Infect. Immun. 69 (10) (2001) 6427–6433.
[85] C. Pagliuca, et al., Novel approach for evaluation of Bacteroides fragilis protective role against Bartonella henselae liver damage in immunocompromised murine model, Front. Microbiol. 7 (2016).
[86] B. Griffin, H.J. Baker, Domestic cats as laboratory animals, Lab. Anim. Med. 7 (2002) 50015–50016.
[87] S. Droz, et al., Bartonella koehlerae sp. nov., isolated from cats, J. Clin. Microbiol. 37 (1999) 1117–1122.

[88] A.N. Gurfield, et al., Coinfection with Bartonella clarridgeiae and Bartonella henselae and with different Bartonella henselae strains in domestic cats, J. Clin. Microbiol. 35 (1997) 2120–2123.
[89] A.M. Margileth, D.F. Baehren, Chest-wall abscess due to cat-scratch disease (CSD) in an adult with antibodies to Bartonella clarridgeiae: case report and review of the thoracopulmonary manifestion of CSD, Clin. Infect. Dis. 27 (1998) 353–357.
[90] E. Breitschwerdt, Bartonellosis, one health and all creatures great and small, Vet. Dermatol. 28 (2017) 96–e21.
[91] D.L. Kordick, et al., Prolonged Bartonella bacteremia in cats associated with cat-scratch disease patients, J. Clin. Microbiol. 33 (1995) 3245–3251.
[92] P.P.V.P. Diniz, et al., Infection of domestic dogs in Peru by zoonotic Bartonella species: a cross-sectional prevalence study of 219 asymptomatic dogs, PLoS Negl. Trop. Dis. 7 (9) (2013), e2393.
[93] E.C. Brenner, et al., Bartonella infection in urban and rural dogs from the tropics: Brazil, Colombia, Sri Lanka and Vietnam, Epidemiol. Infect. 141 (1) (2013) 54–61.
[94] C. Liedig, et al., Blood supplementation enhances Bartonella henselae growth and molecular detection of bacterial DNA in liquid culture, Microbiol. Spectrum 11 (3) (2023).