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Bartonella spp. - a chance to establish One Health concepts in veterinary and human medicine

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Abstract

Infectious diseases remain a remarkable health threat for humans and animals. In the past, the epidemiology, etiology and pathology of infectious agents affecting humans and animals have mostly been investigated in separate studies. However, it is evident, that combined approaches are needed to understand geographical distribution, transmission and infection biology of "zoonotic agents". The genus *Bartonella* represents a congenial example of the synergistic benefits that can arise from such combined approaches: *Bartonella* spp. infect a broad variety of animals, are linked with a constantly increasing number of human diseases and are transmitted via arthropod vectors. As a result, the genus *Bartonella* is predestined to play a pivotal role in establishing a One Health concept combining veterinary and human medicine.

Keywords: Ticks, Fleas, Lice, Cats, Dogs, Humans, Infection, Transmission, Zoonosis

Background

The threat of infectious diseases to mankind has never been greater than today. For the first time, political leaders of the 41st "G7 summit" in Schloss Elmau/Germany on June 7–8, 2015, set the topic "global health" (including infectious diseases) as one of the key issues on their agenda. In the past, health issues played only a minor part in such international economic summits. However, governments have now realized that public health is an essential prerequisite for education, working capacity and therefore the economic prosperity of societies.

In this regard, it is important to recognize that human health and animal health are closely linked. An estimated 75 % of emerging infectious diseases are zoonotic and 28 % vector-borne [1]. Global warming represents an additional factor promoting the spread of these diseases as the geographic range of some vectors and reservoir hosts expands in response to a changing climate [2].

To respond to these challenges, the One Health concept aims to establish interdisciplinary collaborations between medical, veterinary and environmental researchers as well as public health officials for the early detection of health hazards affecting both humans and animals and to fight them on multiple levels. The genus *Bartonella* represents a prototypical example for zoonotic pathogens as *Bartonella* species are infectious agents for humans and animals. High pathogen prevalence and severe courses of infection raise the importance to investigate possible routes of transmission and to combat infections.

The genus *Bartonella*: a diverse and expanding group of bacteria

The bacterial genus of *Bartonella* is comprised of Gram-negative, slow growing and facultative intracellular pathogens that infect mainly mammalian hosts and are often transferred via blood sucking arthropod vectors. *Bartonella* infections of humans and animals are often characterized by an intraerythrocytic bacteremia. At least 20 species are known to cause host-specific intraerythrocytic infections in their specific mammalian reservoir hosts, including the human-specific pathogens *Bartonella quintana* and *Bartonella bacilliformis*, the agents of trench fever and Oroya fever, respectively. A secondary tissue phase can be associated with development

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of vasculoproliferative lesions, e.g. bacillary angiomatosis (*Bartonella henselae, B. quintana*) or verruga peruana (*B. bacilliformis*) and may play a role in various other dermal conditions [3–7].

Molecular epidemiology techniques have revealed a remarkable diversity within the genus *Bartonella*. A wide variety of *Bartonella* spp. specialized to various mammalian hosts and transferred by specific arthropod vectors have been identified over the years and the prevalence of infection appears to be widespread across species and geographic regions. At least 13 species of *Bartonella* have been identified as pathogenic to humans with three species responsible for most of the clinically relevant infections in humans: *B. bacilliformis*, *B. quintana* and *B. henselae* [6].

Bartonella spp. infections are often chronic or asymptomatic in their reservoir hosts. Bacteria have been shown to infect erythrocytes, endothelial cells, macrophages and even human stem cells [8–17]. The infection of erythroctyes is host-specific and mediated by the so-called "Trw"-type 4 secretion system which facilitates host-restricted adhesion to erythrocytes [18]. Localized tissue manifestations may occur in reservoir and incidental hosts and the growth of bacteria in vascular tissue can lead to angioproliferative tumors and inflammation [5, 6, 12, 19]. The ability of *Bartonella* spp. to persist within immunoprivileged intracellular habitats is probably a key factor contributing to the establishment of chronic infections; however, the cyclic release of bacteria to the blood stream or the hemolytic activity of some species can also result in dramatic illnesses such as trench fever or Oroya fever, respectively [20]. The presence of *Bartonella* spp. in the blood stream of infected hosts or within the erythrocytes also facilitates their transfer via ingestion along with the blood meal of arthropod vectors [5, 21].

Bartonella spp. infections in animals

Cat infections

Cats are the main reservoir host for the species *B. henselae, B. clarridgeiae* (both of which can cause cat scratch disease) and *B. koehlerae* (a causative agent of endocarditis in humans) [22–24]. Infected cats are often clinically asymptomatic although they suffer from relapsing bacteremia over long periods of time [25]. Co-infections with more than one *Bartonella* species are not uncommon [26–29].

Transmission of *Bartonella* spp. among cats occurs via arthropod vectors, predominantly fleas. Uninfected cats kept together with infected cats in a specific ectoparasite-free environment do not become seropositive emphasizing the importance of arthropod vectors in the transmission of disease. Furthermore, the transmission via arthropod vectors appears to be essential as no direct transmission of *B. henselae* from cat to cat has been documented experimentally and flea-prevention measures have been shown to be effective in preventing pathogen transmission [30–35]. Prevalence of infection is highest in warm, moist areas with a higher ectoparasite burden (0 % in Norway *versus* 68 % in the Phillipines) [8, 22, 30, 36–38]. Up to 50 % of all cats (stray and pet) living in regions where fleas are endemic, harbor bacteremic *Bartonella* infections [26, 28]. Usually, cats are bacteremic for weeks or months but even longer infection intervals are possible. Young cats are more likely to be bacteremic than old cats and stray cats more than pet cats [8, 22, 23]. Cats were tested in several regions of Spain, for *B. henselae* seroreactivity and 50 % were shown to be positive. It is known, however, that serum antibodies have a limited value for the detection of active infections. In the same study, DNA of *Bartonella* spp. was detected in 4.4 % of the examined cat fleas [39]. *Bartonella* spp. have also been isolated from cat blood in various other locations throughout the world (e.g. from San Francisco/USA, North Carolina/USA, Hawaii/USA, Japan, Sydney, New Zealand, the Netherlands, France, Indonesia and Germany) [26, 28, 40–49].

Those *Bartonella* strains which have been isolated from healthy cats were usually not of the same genetic background as those strains detected from infected humans. Some of the feline strains were never found on patients and therefore might be less pathogenic for humans [50, 51].

Although healthy cats can be infected with *B. henselae* and *B. clarridgeiae* for months or even years, there is evidence that cats may also suffer from the persistent infection [26]. Especially infections with *Bartonella* spp. that are not believed to be specifically adapted to the cat as reservoir host (e.g. *Bartonella vinsonii* subsp. *berkhoffii*) can result in more serious clinical symptoms, e.g. osteomyelitis [30, 31, 52]. Several seroepidemiological studies indicated a correlation between seroreactivity and stomatitis, kidney- and urinary tract-diseases and uveitis [26, 53–55]. Another survey found that stomatitis is associated with the detection of *Bartonella* spp. but not with seroreactivity and revealed no association with uveitis, neurological symptoms and chronic kidney diseases; however, a weak association between seroreactivity and idiopathic feline lower urinary tract disease was detected [56]. Cats experimentally infected with *B. henselae* or *B. clarridgeiae* were found to suffer from fever, eosinophilia, lymphadenomegaly and anemia. Perinatal transmission was not described but reproductive disorders were observed. Furthermore, some cats suffered from transient neurological disorders, endocarditis and focal myocarditis [26, 57–62].

Isolation of *Bartonella* spp. has been possible from cats whose owners suffered from cat scratch disease and

bacillary angiomatosis and *B. clarridgeiae* was isolated from a kitten that had caused cat scratch disease in a veterinarian [25, 26, 40, 63]. *Bartonella quintana* was found in the mouth of a domestic cat and there are reported cases of humans suffering from *B. quintana* infections where no louse infestation was verifiable but contact with cats was reported [30, 64]. In one case *B. qintana* was detected in a woman and two cats, one of which had bitten the woman previously providing further evidence for the incidental zoonotic transmission of *Bartonella* between animals and humans [65]. Antimicrobial treatment for pathogen eradication in cats is not broadly recommended; therefore, ectoparasite-control (e.g. collars containing acaricides) is crucial as the main instrument to lower the *Bartonella* prevalence in cats and therefore reduces the risk of pathogen-transmission to humans [30, 35].

Dog infections

Dogs represent an incidental host for *Bartonella* and two species are known to cause clinically apparent infections: *B. vinsonii* subsp. *berkhoffii*, causing endocarditis, arrhythmias, myocarditis, granulomatous lymphadenitis and granulomatous rhinitis, and *B. henselae* causing peliosis hepatis [66–71]. In a study from the United States surveying *Bartonella* bacteremia in dogs, *B. henselae* was found in 30 of 61 infected dogs [72]; however, there are also rare cases in which other *Bartonella* spp. have caused disease in dogs: *B. clarridgeiae*, *B. washoensis* and *B. quintana* were isolated from dogs suffering from endocarditis [8, 22, 23]. To date, all *Bartonella* spp. identified in sick dogs are also known as pathogenic or potentially pathogenic infectious agents for humans and this observation led to the suggestion that dogs might act as useful sentinel species and important comparative models for human infections [22, 73].

Domestic dogs are generally incidental hosts for *B. henselae* with a reported seroprevalence of ~10 % in healthy dogs in the United States and ~27 % in sick dogs [30, 74]. Similar to cat epidemiology, seroprevalence increases in warmer regions [30]. *Bartonella henselae*, *B. quintana*, *B. vinsonii* subsp. *berkhoffii* and *B. bovis* have been detected in mouth swabs from dogs and there is some evidence that dogs may be able to transmit *B. henselae* to humans via bites [22, 30, 37, 75]. Because of the prolonged bacteremia of *B. vinsonii* subsp. *berkoffii* in dogs, they are suspected to represent the reservoir host of these bacteria and seroreactivity of dogs against *B. vinsonii* subsp. *berkoffii* is found worldwide [22, 26, 32]. In Gabon, *B. clarridgeiae* was also isolated from ~2 % of the examined dogs indicating that these animals may represent a potential reservoir host for *Bartonella* spp. in Africa [76].

Serological surveys suggest that *B. vinsonii* subsp. *berkhoffii* may also cause immuno-mediated hemolytic anemia, neutrophil or granulomatous meningoencephalitis, neutrophil polyarthritis and uveitis in dogs [8, 22]. *Bartonella vinsonii* subsp. *berkhoffii* can cause endocarditis, especially in large breed dogs with a predisposition for aortic valve involvement. Intermittent lameness and fever of unknown origin can occur several months before endocarditis. Myocarditis without an associated endocarditis is also possible and may result in arrhythmias, syncope or sudden death [26, 67]. To detect *Bartonella* spp. as the causative agent of infectious endocarditis in dogs, diagnostic PCRs should be performed from blood or heart valve specimen as blood cultures often remain negative [77, 78]. High antibody-titers and characteristic lesions in echocardiography are also suspicious for *Bartonella* endocarditis. In most cases, *Bartonella* infect the aortic valve causing aortic insufficiency leading to severe chronic heart failure and arrhythmias [66–68, 77, 79, 80].

Infections of other mammals

There are many publications describing *Bartonella* infections of numerous mammals and even reptiles. For instance, *Bartonella* spp. have been detected in a wide variety of wild and domestic animals throughout the world including, e.g. mountain lions, bobcats, coyotes, grey foxes, elks, mule deer, cougars, rabbits, several rodent species, cattle, belugas, bats and porpoises. However, it is unclear which diseases if any are associated with such infections and if these animals play a role as potential reservoir hosts. [26, 30, 81–92].

Bartonella spp. infections of humans

The first human pathogenic *Bartonella* species to be identified in the early 1900s was *B. bacilliformis*. This human-specific bacterium causes a biphasic disease characterised by a primary hemolytic fever ("Oroya fever") with high mortality (up to 90 %), followed by a chronic vasculoproliferative tissue phase ("verruga peruana"). Pathogens are transmitted by the sand fly (*Lutzomyia verrucarum*). The human body louse (*Pediculus humanus humanus*) transmits *B. quintana*, a second human pathogenic *Bartonella* species which emerged as a major agent of disease causing debilitating cyclic fever ("trench fever") during World War I. Today, trench fever occurs mainly in the homeless population or among drug addicts. Endocarditis, generalized lymphadenopathy and bacillary angiomatosis are symptoms of *B. quintana* infections in immunocompromised people [93–100].

Of the three most significant human pathogenic *Bartonella* species *B. henselae* is the most common symptomatic infection causing agent identified in the modern clinical setting. *Bartonella henselae* infection is the cause of multiple clinical entities in humans and infections result in differential disease outcomes often depending on the immune status of the patient. Humans become infected

via the scratches or bites of infected cats contaminated with infected flea feces or are directly contaminated with infected blood. Dogs are also suspected to be an additional reservoir for *B. henselae* transmission to humans [41]. In immunocompetent patients, infections normally cause cat scratch disease which is often self-limiting with no need for antibiotic treatment. Typically, two to three weeks after infection, a unilateral lymphadenitis in the draining region of the lymph node near the site of inoculation can be observed. In ~10 % of the cases, the lymph node forms a fistula where pus is draining. Other symptoms include chronic lymph node swelling, fever, headache, skin and mucosal lesions near the inoculation site and splenomegaly. "Blood-culture negative"-endocarditis, oculoglandular involvement ("Parinaud's syndrome"), encephalopathy, neuroretinitis and osteomyelitis are described as complications of infection [101]. Recurring or systemic infections can be treated with macrolides. In immunocompromised hosts, chronic infections can occur, leading to angioproliferative diseases like bacillary angiomatosis and peliosis hepatis which can be fatal if not treated [6, 19].

Several *Bartonella* spp. have been reported as cause of fever of unknown origin and culture-negative endocarditis in humans and animals [102–105]. In humans, endocarditis caused by *B. henselae*, *B. quintana*, *B. elizabethae*, *B. vinsonii* subsp. *berkhoffii*, *B. vinsonii* subsp. *arupensis*, *B. koehlerae*, *B. alsatica*, *B. washoensis* and Candidatus *B. mayotimonensis* have been reported [24, 106–114]; however, human endocarditis cases are most often associated with *B. henselae* and *B. quintana* [79, 80, 115]. In most cases, high anti-*Bartonella*-IgG antibody-titers can be detected [102, 116].

Co-infections with more than one *Bartonella* spp. (even in immunocompetent patients) [117–119] and with other zoonotic bacterial species have been reported. Co-infections with *Borrelia burgdorferi* (*sensu lato*) and *B. henselae* were described in patients with atypical neuroborreliosis [120–122]. Furthermore, surveys showed the occurrence of co-infections with *B. henselae* in people suffering from persistent symptoms after borreliosis treatment where ticks might have been the source of infection [121]. The transmission of multiple pathogens via co-infected vectors might contribute to atypical disease progression and should be considered for the diagnosis of tick-borne diseases [121, 123, 124]. However, it must be stated that the occurrence of chronic, atypical tick-borne co-infections in patients with chronic, nonspecific illnesses is highly controversially discussed. As reviewed by Lantos & Wormser, in most reported cases of *Bartonella* and *Borrelia* co-infections, laboratory diagnostics were not properly performed [125].

Different population groups are exposed to animals and arthropod vectors in variable dimensions. In particular, veterinarians, veterinary technicians or zookeepers might be at increased risk of infection with *Bartonella* spp. [119, 126]. For example, one case of *B. vinsonii* subsp. *berkhoffii*, transmission to a veterinarian was likely caused by a needle puncture injury [127]. *Bartonella* infections have even been suspected to have been a contributing factor in the death of two veterinarians in 2013 [128]. In an epidemiological study, *Bartonella* DNA was also detected in the blood of 28 % of veterinary workers whereas no *Bartonella* was detected in control subjects [126]. The prevalence of *Bartonella* infections has also been found to be elevated in other risk groups. In a recent study in Germany *B. henselae* IgG antibodies were found in ~45 % of forestry workers which may be due to a higher contact with arthropods which is inevitable during forest work [129]. From a One Health perspective, the identification of possible vectors and means of *Bartonella* transmission is crucial to reduce occupational hazards in certain risk groups and prevent such cases of *Bartonella* transmission in future.

Blood transfusion has also been identified as a risk factor for the transmission of *Bartonella* infections. The transmission of infection via blood transfusion was first shown 20 years ago in cats [58] and a very recent study from Brazil has also indicated a ~3 % prevalence of *Bartonella* spp. in asymptomatic human blood donors. Remarkably, the results of this study found that professionals with animal contact were seven times more likely to harbor *Bartonella* than other blood donors and individuals with cat contact or a history of tick bite were three to four times more likely to be infected with *Bartonella* spp. [130]. Considering that patients receiving blood transfusions are already in a state of weakened health, screening of blood donors for *Bartonella* infections, especially in certain risk groups should be considered to prevent transmission of infection.

Vector transmission of *Bartonella* spp.

The transmission cycle of bartonellosis is typical for vector-borne diseases. Typically, infections are characterized by persistent intraerythrocytic bacteremia within the reservoir host. Infected blood is ingested by the blood sucking arthropod vector and subsequently transmitted to a further reservoir or incidental host. To date, vector-competence of several arthropods has been proven for *Bartonella* spp. transmission and additional vectors competencies are suspected in many more.

Flea transmission of *Bartonella* spp.

The cat flea (*Ctenocephalides felis*) represents the main vector for *B. henselae* infection among cats. Its vector-competence for *B. henselae* transmission is experimentally proven and its presence is essential for the maintenance of *B. henselae* infection within the cat population. The

contamination of the flea-feeding wound, or other wounds such as scratches or bites with contaminated flea feces has been identified as an important transmission route among hosts including cats and humans [30, 33, 96, 131–133]. Bacteria are replicating in the flea's intestine and are secreted with the feces over the life-span of the flea (~12 days). The excreted flea feces contain *B. henselae* within 24 h of a blood meal [134].

Further supporting the importance of the flea as a vector of *B. henselae* transmission, epidemiological studies have shown an increased risk of *B. henselae* infection in cats suffering from flea infestation and the use of flea-prevention collars has also been shown to be effective in preventing the transmission of *B. henselae* infection from cat to cat [35]. Once infected, *B. henselae* bacteremia in cats can last for weeks, months or even longer than one year supporting further vector-transmission [22, 23, 29, 39, 132, 135, 136]. In addition to *B. henselae*, cats are susceptible to infections with *B. quintana*, *B. koehlerae*, *B. clarridgeiae*, *B. vinsonii* subsp. *berkhoffii* and *B. bovis* which have also been detected in cat fleas. With the exception of *B. bovis*, these species can also be pathogenic to humans [6, 30, 52, 137]. Flea control is highly recommended in endemic areas to reduce the pathogen exposition of cats and humans [39].

In addition to the cat flea various other flea species may also play important roles in *Bartonella* transmission. *Bartonella* spp. were detected in several flea species collected from bats and different rodents [30, 96, 138–144]. Vector-competence, however, has not been confirmed experimentally for these species.

Louse transmission of *Bartonella* spp.

The human body louse (*Pediculus humanus humanus*) represents the vector of human to human-transmission of *B. quintana*. Environmental factors supporting louse infestation such as unhygienic living conditions lead to an increased risk of infection. In the past, infections with *B. quintana* were a severe medical problem in the trenches and in prisoners of war camps of World War I from which the name "trench fever" arises. Today, mostly homeless people or drug addicts are affected resulting in the term "urban trench fever" [99, 145]. The vector becomes infected when adult lice feed on bacteremic hosts. *Bartonella quintana* reaches the louse gut and can infect humans when bite sites or other wounds are contaminated with infected louse feces [30, 64, 65, 96, 97, 146]. *Bartonella* spp. have also been detected from several other louse species (e.g. *Neohaematopinus sciuri*, *Hoplopleura sciuricola, Pediculus humanus capitis* and others) which may also serve as vectors [96, 139, 147, 148].

Sand fly transmission of *Bartonella* spp.

The sand fly (*Lutzomyia verrucarum*) transmits *B. bacilliformis* from humans to humans and its vector-competence has been proven experimentally [96, 98, 149–151]. The occurrence of the disease is strictly limited to the Peruvian Andes where the vector is endemic. However, it should be considered that climate change may extend the distribution area of this vector and thereby increase the spread of *B. bacilliformis*.

Tick transmission of *Bartonella* spp.

Ticks are known to act as vectors for many different bacterial, protozoan and viral pathogens. Hard ticks (e.g. *Ixodes* spp., *Dermacentor* spp.) usually feed three times during their life-cycle and can possibly be infected with different pathogens during every blood meal. Hosts can be bitten by ticks several times during their lifetime presenting multiple opportunities for pathogen transmission [152–154]. Several studies have detected the presence of *Bartonella* spp. in various tick species from around the world [26, 84, 93, 120, 121, 123, 138, 152, 155–168]. The prevalence of *Bartonella* DNA in hard ticks in Europe has been shown to be as high as 40 % [158]. In a recent study conducted in Finland, ticks were found to contain no detectable *Bartonella* DNA whereas DNA of *Borrelia* spp. was found frequently at ~ 19 % [169]. On the other hand, *Bartonella* DNA was detected in ~2 % of ticks collected in a recent study from Austria [170]. Figure 1 displays the percentage of ticks found to harbor *Bartonella* in different studies. Overall, in ~15 % of ticks studied *Bartonella* DNA was detectable.

Vector competence has been demonstrated experimentally by the use of artificial tick-feeding procedures for *B. henselae* [171] and a murine *B. birtlesii* infection model [172]; however, vector competence of naturally infected ticks has still not been confirmed.

Bartonella DNA has been detected in hard ticks removed from dogs. However, as DNA was detectable in only some but not all ticks removed from one particular dog, the infection of the tick may have been acquired from another source previously [173]. Furthermore, several studies indicate co-transmission of *Bartonella* with other tick-borne pathogens (e.g. *Ehrlichia, Babesia*) in dogs [66, 174–178]. In a study surveying dogs with endocarditis from California, all dogs that were infected with *Bartonella* were also seroreactive to *Anaplasma phagocytophilum,* another tick-borne pathogen [77].

In two cases, *B. henselae* DNA was detected in ticks collected from the home of patients which suffered from Lyme disease and which did not respond to a *Borrelia*-specific antibiotic therapy. In another study, *Bartonella* DNA was detectable in human blood after tick bites and recently, *B. henselae* and three other animal-associated

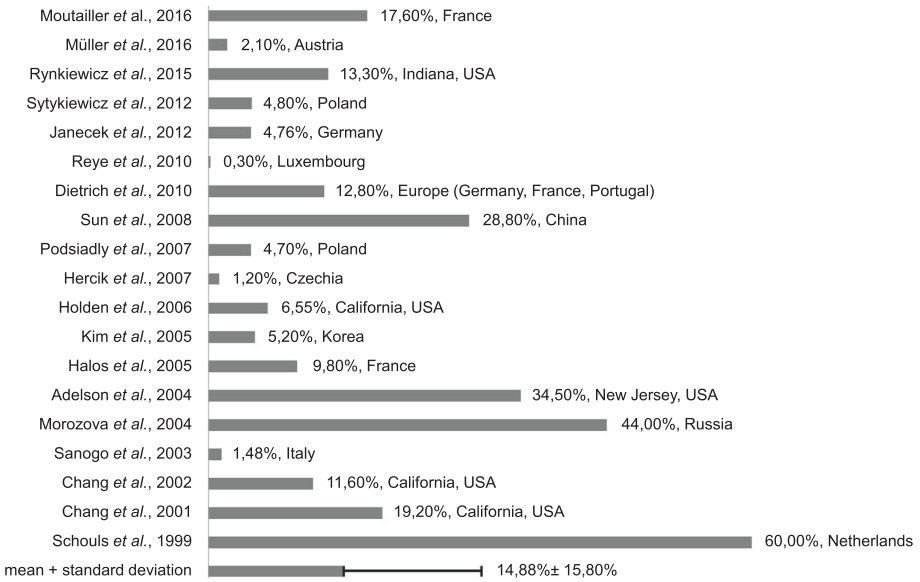

Fig. 1 Percentage of ticks found to harbor *Bartonella* spp. DNA (literature review). Presence of *Bartonella* spp. was determined via molecular techniques. Overall, *Bartonella* spp. were found in ~14.88 ± 15.80 % of ticks. Countries in which ticks were collected are depicted within the diagram

Bartonella species (*B. doshiae, B. schoenbuchensis* and *B. tribocorum*) were isolated from patients suffering from undifferentiated chronic illness and who had reported tick bites [121, 179, 180].

Several case reports of *B. henselae* infections of humans have been published where no or very limited cat contact was reported, limiting the possibility of transmission via cats or cat fleas. Authors concluded that transmission via arthropod vectors (e.g. ticks) may provide an alternative explanation [96, 181].

The most important reservoir hosts for tick-borne pathogens are small rodents as they are the preferred hosts of tick larvae and nymphs. Several *Bartonella* spp. have been detected in these small mammals further supporting the possibility that ticks may represent a vector for *Bartonella* transmission [84, 87, 152–154, 162, 182, 183]. *Bartonella* spp. have also been isolated from cattle and mule deer in North America. As ruminants are rarely infested with fleas, ticks seem to be more likely to transmit these pathogens to these animals [81].

Nevertheless, it must be mentioned that the transmission of *Bartonella* spp. via ticks to humans and animals is still controversially discussed. Clearly, *Bartonella* DNA which was found in several tick species in multiple studies does not prove the presence of viable bacteria. Therefore, some researchers doubt heavily that *Bartonella* spp. are transmitted by ticks [125, 184]. Furthermore, concerns about the relevance of experimental tick transmission studies performed with an artificial feeding system [171] have been raised [184]: the amount of colony forming units in the blood was criticized to be much higher than it would be in natural infected bacteremic cats and the *B. henselae* strain that was used is not representative for *Bartonella* strains found in nature [184]. Building on these points, the authors conclude that neither of these studies demonstrated transmission of *Bartonella* spp. from ticks to mammalian hosts [125]. At least for *B. birtlesii*, tick transmission was proven in a murine infection model [172] whereas a *bona fide* tick transmission of *B. henselae* has not been demonstrated so far.

The role of other arthropods in the transmission of *Bartonella* spp.

Bartonella species have been found in biting flies collected from cattle in California: *B. bovis* was detected in a horn fly (*Haematobia* spp.) and *B. henselae* was found in a stable fly (*Stomoxy* spp.) [185]. Several studies found *Bartonella* spp. in mites collected from rodents and bats from Korea, Egypt and Costa Rica [96, 162, 186]. Deer keds (*Lipoptena mazamae* and *Lipoptena cervi*) were shown to be infected with *B. henselae* and *B. schoenbuchensis* [30, 187–189]. *Lipoptena* species usually feed on deer but were also found on horses, cattle and humans. *Bartonella schoenbuchensis* was detected in *Lipoptena cervi* from a deer (*Capreolus capreolus*) in Germany and is suspected to be the causative agent of deer ked dermatitis in humans [190]. *Bartonella* was also found in several other species of the family *Hippoboscidae* indicating that they may play a role in the transmission of these bacteria [96, 191]. However, no experimental transmission studies with these species have been performed nor do any data exist on the transmission of *B. schoenbuchensis* by *Lipoptena* spp. to humans.

The need for scientific One Health approaches in *Bartonella* research

When discussing transmission of *Bartonella* spp. from animals to humans, e.g. via arthropod vectors, a more integrative approach elucidating *Bartonella* prevalence in vectors as well as the infection status of animals and humans would clearly help to increase understanding of *Bartonella* infection dynamics, infection risk and prevent speculative and non-evidence-based conclusions. Such an approach might, for instance, include the investigation of the prevalence of *Bartonella* DNA or (even more reliable) of viable *Bartonella* species in feeding ticks, combined with parallel detection of these pathogens via direct detection or seroprevalence in animals (e.g. pets) and humans (e.g. pet owners). Figure 2 shows this concept of such a One Health approach.

For instance, a coordinated set of data might include (i) the pathogen-DNA status of questing ticks (with bacterial, e.g. *Bartonella* 16S-rDNA sequences; analyzed by conventional PCRs or metagenomics analysis), (ii) the direct detection of these pathogen(s) or detection of pathogen-specific (e.g. *Bartonella*) antibodies in animals (arguing for infection of the pet), and (iii) the direct detection of these pathogen(s) if feasible or the determination of the respective pathogen-specific antibodies in humans (e.g. pet owner) in parallel (arguing for a previous or present infection).

First incidental results from a clinical case revealed interesting findings: In a female, adult, half-engorged *I. ricinus* tick (black forest, Germany) which was feeding for ~1–2 days on a cat, *Bartonella*-DNA was detected via nested-PCR. Sequence analysis revealed most likely the presence of *B. henselae* 16S-rDNA (99 % sequence homology). For medical reasons, a serum sample from the cat was taken (because of unspecific illness). Immunofluorescence testing revealed cat antibody titers of 1:640 whereas no specific *B. henselae*-antibodies were detected in the pet owner. This setting might be interpreted as follows: The questing *I. ricinus* tick was probably ingesting *B. henselae*-containing cat blood as anti-*B. henselae* IgG antibodies were detectable. The pet owner, however, had no serological evidence for having been exposed to *B. henselae*. As a further option, a chronic *B. henselae* infection of the cat might additionally be confirmed (e.g. via PCR-analysis of peripheral blood). The application of such One Health approaches in prospective scientific studies would be useful to assess the real risk of transmission of *Bartonella* spp. from pets to pet owners and to clarify the role of ticks in this process.

Conclusions

The cumulative data collected in many studies and conducted in several countries throughout the world indicate that infections with *Bartonella* spp. might represent an underappreciated danger for human and animal health. A great deal more research is needed to specify arthropod vectors and characteristics of diseases caused by *Bartonella* species. To date, strict

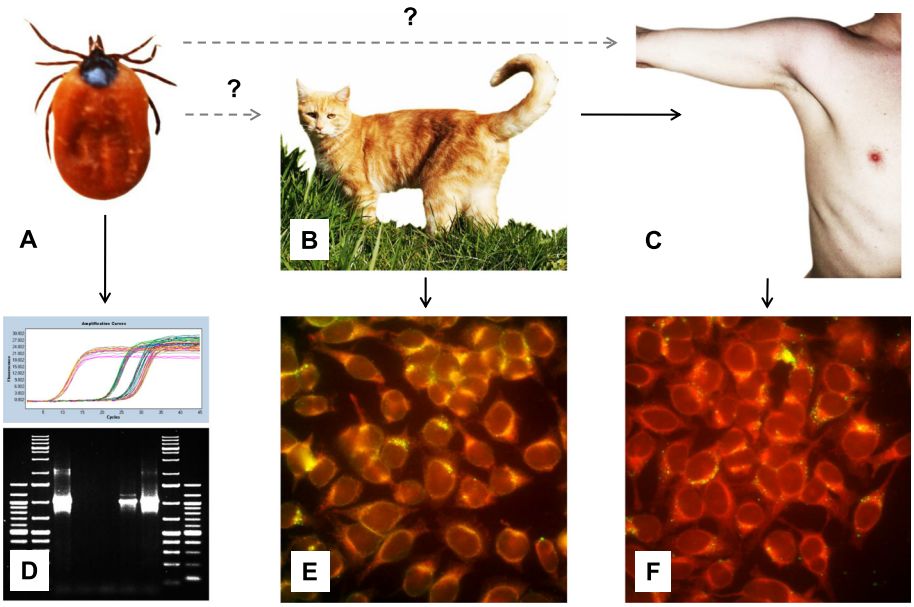

Fig. 2 One Health concept for detecting of *Bartonella* infections in humans and domestic animals. Fleas transmit *B. henselae* to cats. Transmission of *B. henselae* by ticks, e.g. *Ixodes ricinus* **a** to cats **b** or humans **c** is assumed but controversially discussed. *Bartonella* DNA can be detected in ticks via real-time PCR or conventional PCR **d**. Finally, *B. henselae* infections of cats and humans can be diagnosed by indirect immunofluorescence analysis (anti-B. henselae-IgG: green, **e**, **f**)

ectoparasite-control is highly recommended to lower the risk of *Bartonella* infection from arthropod vectors to domestic animals and pets, thereby preventing pathogen transmission from animals to human owners. Overall, these results demonstrate that reliable data about vector transmission of *Bartonella* spp. from animals to humans can only be generated through the application of scientific One Health approaches which take into account the epidemiological factors and interactions of humans, animals and their environments as an integrated system.

Abbreviations
DNA: deoxyribonucleic acid; PCR: polymerase chain reaction.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
YR: performing experiments, analysis of literature, manuscript writing. FOR: analysis of literature, manuscript writing. VK: analysis of literature, manuscript writing. All authors read and approved the final version of the manuscript.

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