Review

# Managing canine vector-borne diseases of zoonotic concern: part one

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**Canine vector-borne diseases (CVBDs) comprise a group of globally distributed and rapidly spreading illnesses that are caused by a range of pathogens transmitted by arthropods including ticks, fleas, mosquitoes and phlebotomine sandflies. In addition to their veterinary importance, some CVBD-causing pathogens are of major zoonotic concern. Recent studies using sophisticated and advanced methodologies and technologies have provided new insights into the epidemiology of many CVBDs. This review is the first of two articles and focuses on the zoonotic relevance of CVBDs, the significance of co-infection and the role of infected but clinically healthy dogs in spreading different pathogens among human and canine populations.**

## Zoonotic relevance of canine vector-borne diseases

Parasitic arthropods (e.g. ticks, fleas, mosquitoes and phlebotomine sandflies) are efficient vectors of a large number of bacteria, viruses, protozoa and helminths affecting livestock, pets and humans worldwide. Globally, vector-borne diseases impact human and animal health and the global economy, representing approximately 17% of the burden of all infectious diseases and causing millions of dollars in losses to the livestock industry annually [1]. In recent years, there has been increasing concern about the global spread of parasitic arthropods and the pathogens they transmit across the planet, which has been influenced by environmental and climatic changes, enhanced international commerce, increased and more rapid global transport, human and animal population dynamics, and emerging drug resistance among both vectors and pathogens [2].

The explosion of the canine population, the social role that dogs have in developed countries (e.g. as therapy dogs for people with mental disorders or as assistants for people with disabilities [3]) and their increasingly close relationship with humans in both urban and rural areas pose new concerns for human public health. Dogs are competent reservoir hosts of several zoonotic agents and can serve as a readily available source of nutrition for many blood-feeding arthropods (Table 1). Therefore, the growing medical interest in canine vector-borne diseases (CVBDs) is directly related to animal welfare and public health.

The distribution of many CVBDs has been affected by the (re)introduction of 'novel' vector species in areas that were previously free from them, such as *Aedes albopictus* in Europe [4], and the (re)emergence of vector-borne pathogens – including *Dirofilaria immitis*, *Ehrlichia canis* and *Hepatozoon americanum* in North America [5]; *Anaplasma platys* (formerly *Ehrlichia platys*) in Australia [6]; and *Leishmania infantum* in North America [7] and northern Europe [8]. Furthermore, a number of micro- and macroclimatic and other environmental conditions might favor the spread of vectors into new geographical areas, impacting the prevalence of infection by different pathogens in both vector and host populations [9,10]. Thus, climate change and global warming, through their effect on local climate conditions, have been examined as causes for temporal and spatial distribution of some tick-borne diseases, including rickettsioses and canine babesiosis [9,11]. The spread of some CVBDs has increased the risk of (re)emergence of certain metazoonotic diseases (see Glossary), which are driven by a number of biological and ecological factors. These diseases are also regulated by interactions among pathogens, vectors and the competence of the host immune system at both the individual and the population level. Our understanding of the complex interactions involved in the epidemiology of CVBDs is, in many cases, fragmentary because of the limited amount of data

### Glossary

**Co-infection**: the simultaneous infection of a vertebrate or an arthropod host by more than one CVBD-causing pathogen. Co-infection is an event mainly linked to high vector-population density and pathogen circulation within an animal population.
**Metazoonosis**: an infection caused by a pathogen (e.g. some *Leishmania* spp.) that can be transmitted from dogs to humans via an arthropod vector.
**Non-clinical animals (or clinically healthy animals or healthy infected dogs)**: animals infected by one or more CVBD-causing pathogens that, in contrast to clinical animals, do not exhibit apparent clinical signs and hematological or biochemical abnormalities. The classification of these animals is based upon both their history and physical examination.
**Occult infection**: an infection of dogs that does not display detectable abnormalities at the physical examination but might present hematological alterations consistent with a chronic, 'hidden' infection. This infection is not detectable by usual diagnostic methods and might be recognized by secondary clinical manifestations at first.
**Prepatent period**: the interval between infection of an individual by a vector-borne pathogen and the first ability to detect a diagnostic stage of the organism from the vertebrate host.
**Incubation period**: the interval between infection of an individual by a vector-borne pathogen and the appearance of first clinical signs or laboratorial alterations related to the infection.

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**Table 1. Canine vector-borne pathogens of major zoonotic concern**

| Pathogen | Disease | Vectors | Geographical distribution | Zoonotic relevance | Refs |
|---|---|---|---|---|---|
| *Leishmania amazonensis* | Visceral leishmaniasis[a] | Phlebotomine sandflies (Psychodidae) | South America | High | [58] |
| *L. infantum* | Visceral leishmaniasis | Phlebotomine sandflies (Psychodidae) | Africa; North, Central and South America; Asia; and Europe | High | [15] |
| *L. braziliensis* | Mucocutaneous leishmaniasis | Phlebotomine sandflies (Psychodidae) | North, Central and South America | High | [59] |
| *L. colombiensis* | Visceral leishmaniasis[b] | Phlebotomine sandflies (Psychodidae) | Central and South America | High | [60] |
| *L. major* | Localized cutaneous leishmaniasis | Phlebotomine sandflies (Psychodidae) | Africa and Asia | High | [61] |
| *L. peruviana* | Localized cutaneous leishmaniasis | Phlebotomine sandflies (Psychodidae) | Peruvian Andes | High | [62] |
| *L. tropica* | Cutaneous leishmaniasis | Phlebotomine sandflies (Psychodidae) | Africa, Asia and Europe | High | [63] |
| *Trypanosoma cruzi* | Trypanosomiasis (Chagas disease) | Triatomine bugs (Reduviidae) | North, Central and South America | High | [64] |
| *Babesia canis canis* | Babesiosis | Ticks (Ixodidae) | Europe | Low?[c] | [65] |
| *B. canis vogeli* | Babesiosis | Ticks (Ixodidae) | Worldwide | Low? | [65] |
| *B. canis rossi* | Babesiosis | Ticks (Ixodidae) | Africa | Low? | [65] |
| *B. gibsoni* | Babesiosis | Ticks (Ixodidae) | Worldwide | Low | [65] |
| *Anaplasma phagocytophilum* | Granulocytic anaplasmosis | Ticks (Ixodidae) | Worldwide | High | [5] |
| *A. platys* | Cyclic thrombocytopenia | Ticks (Ixodidae)? | Worldwide | Low? | [66] |
| *Ehrlichia canis* | Monocytic ehrlichiosis | Ticks (Ixodidae) | Worldwide | High | [67] |
| *E. chaffeensis* | Monocytic ehrlichiosis | Ticks (Ixodidae) | Worldwide | High | [37] |
| *E. ewingii* | Granulocytic ehrlichiosis | Ticks (Ixodidae) | North America | High | [37] |
| *Bartonella henselae* | Cat scratch disease | Fleas (Pulicidae) and ticks (Ixodidae)? | Worldwide | High | [41] |
| *B. vinsonii* subsp. *berkhoffii* | Bartonellosis | Ticks (Ixodidae)? | Worldwide | High | [41] |
| *Borrelia burgdorferi* | Lyme disease | Ticks (Ixodidae) | Worldwide | High | [37] |
| *Rickettsia rickettsii* | Rocky Mountain spotted fever | Ticks (Ixodidae) | North, Central and South America | High | [68] |
| *Rickettsia conorii* | Mediterranean spotted fever | Ticks (Ixodidae) | Mediterranean countries, Africa, Southwest Asia and India | High | [69] |
| *Dirofilaria immitis* | Dirofilariasis | Mosquitoes (Culicidae) | Worldwide | High | [5] |
| *D. repens* | Dirofilariasis | Mosquitoes (Culicidae) | Africa, Asia and Europe | High | [5] |
| *Dipylidium caninum* | Intestinal helminthiasis | Fleas (Pulicidae) and lice (Boopidae and Trichodectidae) | Worldwide | Low | [5] |
| *Thelazia callipaeda* | Ocular infection | Flies (Drosophilidae) | Asia and Europe | Moderate | [70] |

[a] *L. amazonensis* causes cutaneous leishmaniasis in humans in South America but has been detected recently in two Brazilian dogs showing clinical signs indicative of visceral leishmaniasis [58].
[b] *L. colombiensis* causes cutaneous leishmaniasis in humans in South America but has been isolated from a dog with visceral leishmaniasis in Venezuela [60].
[c] A '?' indicates that data are uncertain, both when referring to zoonotic relevance and when referring to vectors.

on many aspects related to these diseases in endemic areas and the lack of funding for research on animal reservoir and vector interactions. This review focuses on the zoonotic relevance of CVBDs, the role of infected but healthy dogs in spreading different pathogens among human and canine populations and the significance of co-infection.

## Two worlds, different priorities...

The increasing risk of vector-borne disease transmission worldwide has been attributed to several factors, including anthropogenic pressure on the environment (e.g. deforestation, irrigation, changes in land use and rapid urbanization [12]) and the changing dynamics of human, dog and vector populations. Indeed, these factors have impacted the biology and ecology of arthropod vectors in terms of reproduction rates, longevity, food consumption, and the period that is necessary for development and subsequent transmission of certain pathogens [2]. As a consequence, the risk of exposure of dogs and humans to the same vector-borne pathogens has increased notably in many parts of the world [13].

The burden of vector-borne diseases in a given country might be influenced by a number of factors, including socioeconomic status (e.g. income levels, education levels and health-related behaviors), the scope and efficiency of the veterinary medical infrastructure, and the extent to which veterinary and human public health services are interrelated [14]. This means that developed and developing countries could have substantially different priorities in terms of management of CVBDs.

In developed countries, dog care and welfare are maintained at high standards. At the same time, the number of dogs traveling with their owners and the importation and relocation of infected animals from an endemic to a non-endemic area (e.g. from southern European countries to northern European countries) has increased considerably [15], ultimately leading to a higher risk of the introduction of exotic CVBDs. This is the case for canine leishmaniasis, which has been considered as an emerging travel-associated disease in central Europe for a long time; in addition, autochthonous foci of *Leishmania* parasites have been recorded recently [16]. Furthermore, the relocation of dogs

infected by *D. immitis* from the areas stricken by Hurricane Katrina (e.g. New Orleans and Louisiana) resulted in the introduction of this filarid into other non-endemic areas of the United States[*]. In the same way, the existence of public kennels for stray dogs, regardless of their health condition, in areas where CVBDs are endemic (e.g. Italy and Spain) contributes to the maintenance of the endemicity of many diseases, such as leishmaniasis and ehrlichiosis, in suburban and urban areas [17,18].

Vector-borne diseases affecting humans (e.g. malaria, leishmaniasis, lymphatic filariasis and dengue fever), along with those affecting livestock health and production, constitute a high-priority issue for public health and veterinary services in developing countries [19]. As a result, CVBDs remain a considerably lower priority, despite the high number of stray dogs and the high risk of zoonotic transmission by arthropod vectors living in the same microenvironments. Nonetheless, poor socioeconomic conditions and low education standards constitute potential risk factors in the spread of zoonotic CVBDs such as leishmaniasis, particularly in the presence of high-density vector populations [20]. Moreover, the association between human immunodeficiency virus (HIV) or other immune-suppressive conditions and visceral leishmaniasis caused by *L. infantum* (syn. *Leishmania chagasi*) or *Leishmania donovani* represents an emerging problem for people living in rural and suburban areas, mainly in Latin America and Africa [21]. In contrast, in countries with higher health standards, visceral leishmaniasis is most frequently associated with immunological disorders (e.g. HIV), neoplasias, organ transplantation or use of immunosuppressive drugs (e.g. corticosteroids) [22].

In developing and many developed countries, data on the distribution of arthropods and CVBDs are often scant, anecdotal and outdated, probably as a result of poorly developed veterinary diagnostic services and a lack of surveillance at local or regional levels [23]. As a consequence, the development of new and ultimately endemic foci of CVBDs in non-endemic areas could occur in the absence of efficient veterinary and public health surveillance networks, possibly resulting in a rapid spread of the infection within human and animal populations [24]. Thus, the approaches for managing CVBDs of zoonotic relevance in developed and developing nations might vary by necessity. In developed countries, priorities for controlling CVBDs include an effective, sustainable and environmentally sensitive approach to disease control, whereas in the poorest socioeconomic contexts, they include a practical approach that is driven by economic and public health interests. As an example of conflicting interests, the choice between culling [25] and treatment of *Leishmania*-infected dogs might be a matter of ethical and human issues versus cost-effective control strategies. In endemic areas, the network of biological and ecological factors involved in pathogen–vector–host interactions, coupled with immunological aberrations in receptive hosts, might result in a complex clinical and epidemiological scenario. In this complex context, the role of non-clinical, persistently infected dogs and the importance of co-infections by multiple pathogens remain two issues to be further addressed.

## Infected or diseased: the role of clinically healthy animals

The persistence of intracellular parasite burden and the development of clinical disease often depends on the balance between the cellular and humoral immune responses (orchestrated by the Th1/Th2 cytokine profile expression [26,27]), which could result in a complex epidemiological picture with a diverse range of clinical manifestations (from self-curing lesions to life-threatening visceral disease) in endemic areas. Certain organisms (e.g. *L. infantum*, *E. canis, Bartonella vinsonii* subsp. *berkhoffii*, and *Babesia canis vogeli*) might be associated with long-term non-clinical or occult infections, whereas some bacterial and viral infections can be acutely fatal or induce an immune response that ultimately limits the time for pathogen circulation in the peripheral blood.

Based upon the long evolutionary interactions between various vector-borne bacteria, protozoa and viruses and mammalian hosts, persistent non-clinical or occult infection should be considered the rule and disease development the exception. However, establishing that a healthy dog is infected by one or more vector-borne pathogens can be diagnostically challenging because of the variable prepatent periods. In general terms, healthy infected dogs are those without apparent clinical signs or hematological or biochemical abnormalities (e.g. anemia, thrombocytopenia and hyperproteinenia). In the case of canine leishmaniasis, it has been proposed that healthy infected dogs are those that are considered non-ill by their owners and, thus, have a lower chance of being tested and diagnosed as infected by veterinarians[‡]. In *Leishmania*-endemic areas, the percentage of healthy infected dogs, as estimated by PCR (e.g. approximately 62% in Greece [28]) and serology (e.g. 85% in Northeast Brazil [29]), is much higher than the respective prevalence of sick ones. It has also been demonstrated that phlebotomine sandflies feeding on healthy infected dogs can become infected by *L. infantum* [30]. Thus, healthy dogs could serve as reservoirs for the transmission of *L. infantum* to receptive animals and humans, mainly in the presence of high-density vector populations and lack of control measures [31]. In some regions, there is a close relationship between the presence of *L.-infantum*-infected dogs (regardless of their health status) and seropositivity in humans [32]. Similarly, during the chronic phase of canine monocytic ehrlichiosis caused by *E. canis*, dogs might seem healthy with no or only minor hematological abnormalities but still act as efficient carriers of the bacteria [33]. However, unlike *Leishmania* spp., *E. canis* can only be transmitted to a receptive host by a tick that engorged during the acute phase of disease, but it can be transmitted for at least 155 days after the detachment [34]. Consequently, a clear definition of the concepts of therapeutic- or self-induced recovery, occult infection, non-clinical animals and disease causation are key concepts for

[*] Bowman, D.D. (2007) Spread of companion animal vector-borne parasitic disease in the US and Europe: concerns relative to travel, national disasters, shelter-source animals and wildlife. Proceedings of the 2nd Canine Vector-Borne Disease (CVBD) Symposium, pp 16–23.

[‡] Capelli, G. (2007) Asymptomatic and symptomatic dogs in endemic areas, their role in the epidemiology of CanL. Proceedings of the 2nd Canine Vector-Borne Disease (CVBD) Symposium, pp 58–63.

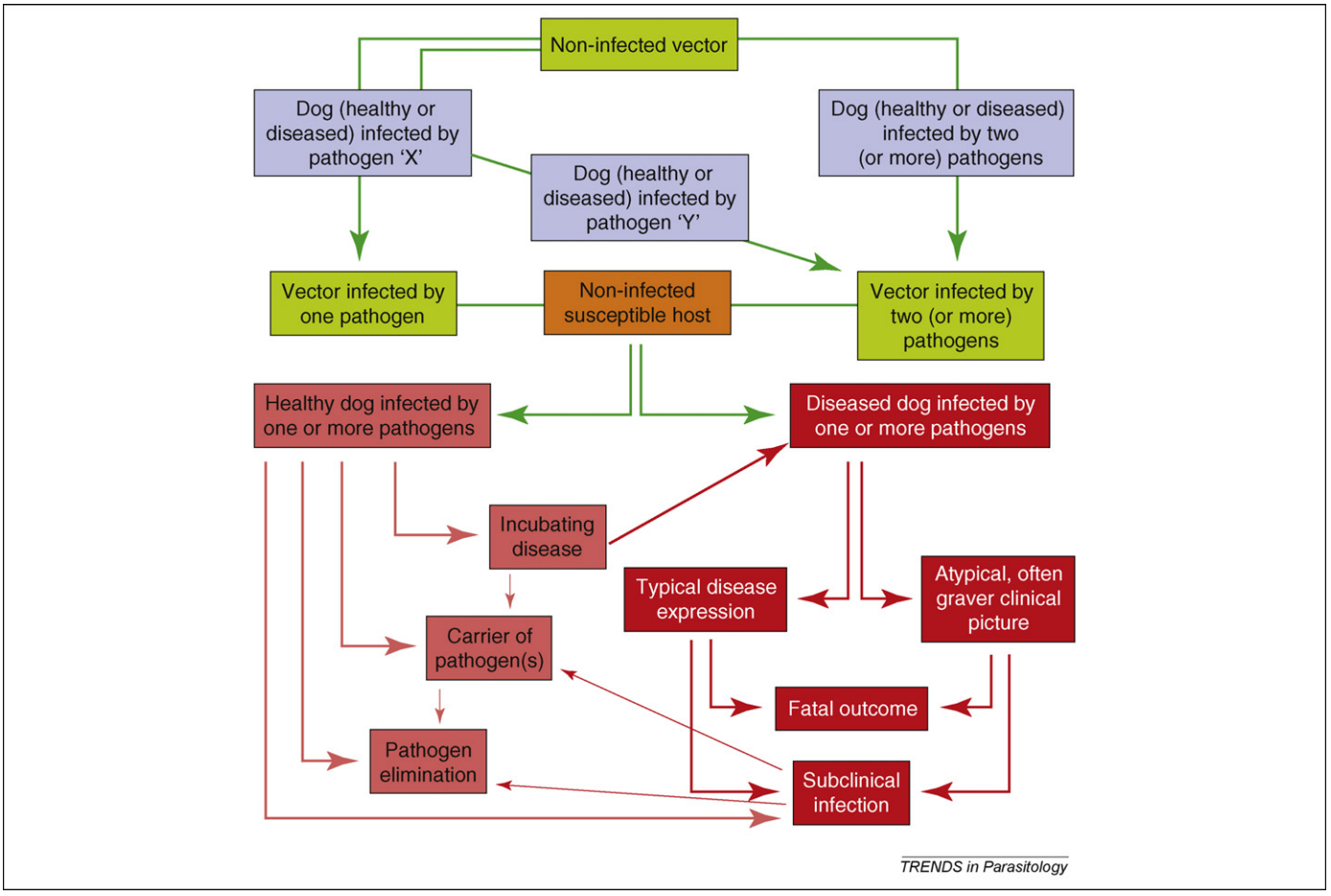


**Figure 1**. Flowchart showing different outcomes for uninfected and infected vectors and dogs. This flowchart illustrates the different infection situations occurring in endemic areas. A susceptible dog can become infected by different vector-borne pathogens simultaneously (i.e. when the dog is exposed to a vector that is co-infected by two or more pathogens) or at distinct periods of time (i.e. when the dog is exposed to different vectors infected by different pathogens at distinct periods of time).

clinical and epidemiological studies, as well as investigations addressing the zoonotic potential, diagnosis, therapy and control of CVBDs.

## Significance of co-infection

In areas where CVBDs are endemic, co-infection is a frequent event in dogs, particularly those living in an environment in which the vector population density is high. Depending upon the presence and abundance of arthropod vectors, dogs can be infected simultaneously or sequentially with a large number of vector-borne pathogens such as *B. canis vogeli*, *Hepatozoon canis*, *E. canis*, *A. platys*, *Anaplasma phagocytophilum*, *B. vinsonii* subsp. *berkhoffii*, *Bartonella henselae*, *Borrelia burgdorferi*, *L. infantum*, *Dirofilaria repens* and *D. immitis*. Importantly, some arthropods are competent vectors of more than one pathogen. Dogs might thus be exposed to vectors infected with single pathogens at different points in time or to vectors concurrently infected with multiple pathogens, favoring the occurrence of co-infections (Figure 1). Naïve ticks can become co-infected with two or more pathogens after a single bloodmeal from a co-infected host or by feeding on different hosts at different life stages [35]. In both cases, the role of various reservoir hosts (e.g. rodents, dogs and deer), which might eventually be simultaneously infected by multiple pathogens, is of paramount importance in maintaining the enzootic cycle. In Europe, for example, *Ixodes ricinus* ticks have been found to be naturally co-infected by *B. burgdorferi sensu lato* genogroup and either *A. phagocytophilum* or *Babesia microti*, as well by all three pathogens [35]. Co-infections depend not only on the circulation of pathogens and the presence of competent vectors and reservoirs but also on complex interactions between pathogens in definitive and intermediate hosts. For instance, dual infection with *B. burgdorferi* and *A. phagocytophilum* in experimentally infected mice increased bacterial burden and pathogen transmission to *Ixodes* ticks that were allowed to feed on them [36]. In dogs, simultaneous or sequential infection with *B. burgdorferi* and *A. phagocytophilum* might be more likely to induce disease than single infections with either organism alone [37].

In a co-infected animal, the complex intracellular pathways that are routinely manipulated by different pathogens to facilitate their escape from the host immune system further complicate the pathophysiology of disease, making the incubation period, clinical outcome and prognosis unpredictable for individual patients. It has been suggested that *L. infantum* has a prominent role as a predisposing factor for infection by other pathogens [26]. Co-infections with *E. canis* and *L. infantum* are frequently detected in the Mediterranean region [38]. There is evidence that cellular and humoral immune responses are downregulated during canine leishmaniasis, possibly

contributing to reactivation of disease in subclinical *E. canis* carriers and/or in failure of diagnosis [26]. In addition, *E. canis* infection downregulates canine major histocompatibility complex class II receptors [39], which could potentiate clinical progression of canine leishmaniasis. Furthermore, co-infection by *E. canis* and *L. infantum* might also be involved in reducing platelet aggregation response and increasing activated partial thromboplastin time, when co-infected dogs are compared to dogs infected by each pathogen alone [40].

The role of *B. vinsonii* subsp. *berkhoffii* as a disease agent in dogs and humans has been investigated under field and laboratory conditions [41]. Experimentally, *B. vinsonii* subsp. *berkhoffii* induces an immunosuppressive condition in dogs (i.e. $CD8^+$ lymphocytopenia, impaired monocytic phagocytosis and altered antigen presentation to T-helper cells) and, thus, its role in co-infections is probably more relevant than is currently recognized [42]. For example, co-infection with *Bartonella* spp. and *E. canis* might predispose dogs to epistaxis (a clinical sign classically attributed to *E. canis* and *L. infantum*) and could cause persistent epistaxis in dogs after therapeutic elimination of *E. canis* owing to failure of doxycycline to eliminate *B. vinsonii* subsp. *berkhoffii* [43]. Analogously, in areas where only one pathogen (e.g. *L. infantum*) predominates, the correct diagnosis of epistaxis by *B. vinsonii* subsp. *berkhoffii* might be extremely challenging [44].

A major question that deserves more attention is whether, in comparision with single infections, co-infections with two or more vector-borne pathogens induce synergistic and more clinically relevant immunosuppression in dogs [37]. Clearly, interactions occurring among different combinations of vector-borne pathogens and their effects on the host immune system should be further investigated. Ideally, these studies should be performed using competent vectors for transmission to obtain results as close as possible to reality. In addition, studies to determine whether persistent occult infection with one organism influences the acquisition and subsequent transmission of other pathogens are needed.

## Concluding remarks and future directions

In the past decades, advances in basic knowledge on several aspects of CVBDs have consistently increased by virtue of molecular technologies (e.g. real-time PCR and nucleotide sequencing), mathematical models, remote-sensing and geographical information systems and, also, increased research interest [45]. However, many relevant aspects of the pathogen–vector–host interface are still poorly understood. For example, studies have demonstrated that antigens present in the saliva of phlebotomine sandflies modulate the host immune system, enhancing *Leishmania* infectivity or eliciting a protective host immune response against the protozoa [46]. A recent study, using killed *Leishmania* organisms in sandfly saliva extract plus a saponin adjuvant, demonstrated the potential of this strategy for canine vaccination [47]. Basic knowledge on the immunomodulatory effects of molecules present in arthropod saliva has accelerated the research towards the development of vaccines against different arthropods, including phlebotomine sandflies, mosquitoes and ticks (for a review, see Ref. [45]).

For almost all CVBD-related pathogens, information regarding the biochemical composition of arthropod antigens, principal developmental stages involved in transmission and factors that influence transmission rates

**Box 1. *Rhipicephalus sanguineus*: spreading and vector competence**

*Rhipicephalus sanguineus*, commonly known as the kennel tick or brown dog tick, is an example of 'parasite globalization' owning to its ubiquitous distribution, which has clearly been facilitated by the dog, its primary host. Its biological life cycle, off-host ecology, feeding behavior, adaptability to different environmental conditions and competence to transmit many pathogens make *R. sanguineus* one of the most important vectors of pathogens of medical and veterinary significance [55]. *R. sanguineus* is a three-host tick species chiefly associated with dogs (Figure I) but can eventually parasitize other hosts, including humans [56]. Brown dog ticks are found wherever dogs are in the world, although they are more abundant in regions with warm climates throughout the tropics and subtropics, where they might complete two or more life cycles each year [55]. This tick infests dogs in both urban and rural areas and is adapted to survive in both indoor and outdoor environments [55]. Ticks generally identified as *R. sanguineus* belong to a group of ten or so closely related species, the taxonomy of which is controversial [55]. *R. sanguineus* ticks are vectors of a wide range of pathogens, including *Rickettsia conorii*, *R. rickettsii*, *E. canis*, *H. canis*, *B. canis vogeli* and *B. gibsoni* (for a review, see Ref. [55]). The widespread distribution of *R. sanguineus* in many tropical, subtropical and temperate areas of the world and its eminent risk of introduction into new areas could cause changes in the tick-borne pathogen distribution, which will ultimately favor the spread of CVBDs into new ecological niches. For example, *R. sanguineus* is the most common ectoparasite infesting dogs in the Mediterranean region and South America, where canine leishmaniasis is endemic. Studies indicate that *R. sanguineus* experimentally infected with *L. infantum* can transmit the infection to hamsters orally or peritoneally when inoculated with tick macerates [57]. However, further basic research is needed to demonstrate the life cycle of *L. infantum* within the tick and its ability of transmitting the infection to a naïve dog during blood feeding. Such a method of *Leishmania* transmission could explain the low density (or even absence) of primary vectors in some regions of South America, where canine leishmaniasis is highly endemic.

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**Figure I**. Example of *R. sanguineus* infestation. Stray dog living in an urban area presenting with a massive infestation of *R. sanguineus* ticks (both immature and adult).

are scant and mainly limited to laboratory reports on ticks [34]. For instance, the period between the bite of an arthropod vector and the transmission can vary. The transmission might occur soon after the bite of the arthropod (e.g. transmission of *Leishmania* spp. and *D. immitis* by phlebotomine sandflies and mosquitoes, respectively) or require a pre-activation period that might last for hours (e.g. transmission of *B. burgdorferi* and *Rickettsia rickettsii* by ticks [34,48]). However, pathogen-transmission times under field conditions might be affected by unpredictable events, such as the physiological status of ticks (e.g. interrupting *Ixodes scapularis* bloodmeal could shorten the transmission time of *B. burgdorferi* into a new receptive host), the co-feeding of many ticks at the same time and site (favoring intrastadial transmission), interrupted tick feeding by certain tick species (e.g. *Rhipicephalus sanguineus* [49]), pathogen load, and the host immune response [50]. The vectorial role of tick immature stages and the significance of alternative modes of transmission (e.g. by arthropod feces or by ingestion of infected arthropods) also deserve to be investigated to correctly evaluate the efficacy of the acaricidal or repellent effect of active compounds used in the control of CVBDs.

Alternative modes of transmission need to be better investigated, particularly in non-endemic areas where competent vectors are often absent. This is the case for canine leishmaniasis in the United States, where blood transfusion and vertical transmission have been suggested as alternative modes of transmission in the absence of suitable phlebotomine sandfly vectors [51,52]. Transmission of *Babesia gibsoni* via dog bites is another example of an alternative mode of transmission because recipient dogs can develop life-threatening immune-mediated hemolytic anemia without exposure to the classical tick vector [53]. Perhaps the aforementioned ways of transmission should be considered of low epidemiological significance; however, they could be relevant for individual canine patients and for the first introduction of a pathogen in an area previously free from this pathogen where alternative vectors could be present (e.g. *R. sanguineus*) (Box 1). The spectrum of potential vectors should be better investigated where cases of CVBDs have been diagnosed, despite an apparent absence of competent vectors.

A scant number of genetic studies have investigated the degree of resistance or susceptibility of specific dog breeds to different CVBD-related pathogens. Genetic studies on dogs affected by *L. infantum* demonstrated that Ibizan hounds were resistant to canine leishmaniasis because they quickly develop a strong cellular immune response [15]. Conversely, other breeds (e.g. boxers) were susceptible because of a nucleotidic mutation in the promoter region of the *Slc11a1* gene that results in downregulation of *Leishmania*-infected macrophage function [15]. In Hungary, it has been suggested that some dog breeds (e.g. German shepherd and Komondor) are more susceptible to *B. canis* infection [54]. However, little is known of the possible genetic factors driving susceptibility or resistance to *B. canis* infection in different dog breeds.

If addressed, the issues discussed above could contribute to increasing the reliability of sophisticated predictive models and diagnostic tools now available for controlling CVBDs [45]. Nonetheless, the generation of new basic knowledge to decipher the complex interactions between vectors, pathogens, hosts and the environment is essential to provide new insights into the management of CVBDs and overcome potential barriers linked to the lack of infrastructure of public health and veterinary services, particularly in developing nations.

## References

1 World Health Organization Report (2004) *Changing history*. World Health Organization, (Geneva, Switzerland)
2 Knols, B.G.J. and Takken, W. (2007) Alarm bells ringing: more of the same, and new and novel diseases and pests. In *Emerging Pests and Vector-Borne Diseases in Europe* (Takken, W. and Knols, B.G.J., eds), pp. 13–19, Wageningen Academic Publishers
3 Ormerod, E.J. *et al.* (2005) Therapeutic applications of the human-companion animal bond. *Vet. Rec.* 157, 689–691
4 Scholte, E.J. and Schaffner, F. (2007) Waiting for the tiger: establishment and spread of the Aedes albopictus mosquito in Europe. In *Emerging Pests and Vector-Borne Diseases in Europe* (Takken, W. and Knols, B.G.J., eds), pp. 241–260, Wageningen Academic Publishers
5 Shaw, S.E. and Day, M.J., eds (2005) *Arthropod-borne infectious diseases of the dog and cat*, Manson Publishing
6 Brown, G.K. *et al.* (2005) Molecular detection of *Anaplasma platys* in lice collected from dogs in Australia. *Aust. Vet. J.* 83, 101–102
7 Duprey, Z.H. *et al.* (2006) Canine visceral leishmaniasis, United States and Canada, 2000-2003. *Emerg. Infect. Dis* 12, 440–446
8 Naucke, T.J. and Schmitt, C. (2004) Is leishmaniasis becoming endemic in Germany? *Int. J. Med. Microbiol.* 293, 179–181
9 Leschnik, M. *et al.* (2008) Seasonal occurrence of canine babesiosis is influenced by local climate conditions. *Int. J. Med. Microbiol.* 298, 243–248
10 Maroli, M. *et al.* (2008) The northward spread of leishmaniasis in Italy: evidence from retrospective and ongoing studies on the canine reservoir and phlebotomine vectors. *Trop. Med. Int. Health* 13, 256–264
11 Parola, P. *et al.* (2008) Warmer weather linked to tick attack and emergence of severe rickettsioses. *PLoS Negl. Trop. Dis.* 2, e338
12 Haines, A. *et al.* (2006) Climate change and human health: impacts, vulnerability, and mitigation. *Lancet* 367, 2101–2109
13 Pherez, F.M. (2007) Factors affecting the emergence and prevalence of vector borne infections (VBI) and the role of vertical transmission (VT). *J. Vector Borne Dis.* 44, 157–163
14 Khasnis, A.A. and Nettleman, M.D. (2005) Global warming and infectious disease. *Arch. Med. Res.* 36, 689–696
15 Baneth, G. *et al.* (2008) Canine leishmaniosis – new concepts and insights on an expanding zoonosis: part one. *Trends Parasitol.* 24, 324–330
16 Naucke, T.J. *et al.* (2008) Sandflies and leishmaniasis in Germany. *Parasitol. Res.* 103, 65–68
17 Otranto, D. *et al.* (2007) Efficacy of a combination of 10% imidacloprid/50% permethrin for the prevention of leishmaniasis in kennelled dogs in an endemic area. *Vet. Parasitol.* 144, 270–278
18 Otranto, D. *et al.* (2008) Application of 10% imidacloprid/50% permethrin to prevent *Ehrlichia canis* exposure in dogs under natural conditions. *Vet. Parasitol.* 153, 320–328
19 Irwin, P.J. and Jefferies, R. (2004) Arthropod-transmitted diseases of companion animals in Southeast Asia. *Trends Parasitol.* 1, 27–34
20 Werneck, G.L. *et al.* (2007) Multilevel modelling of the incidence of visceral leishmaniasis in Teresina, Brazil. *Epidemiol. Infect* 135, 195–201
21 Dujardin, J.C. (2006) Risk factors in the spread of leishmaniases: towards integrated monitoring? *Trends Parasitol.* 22, 4–6
22 Basset, D. *et al.* (2005) Visceral leishmaniasis in organ transplant recipients: 11 new cases and a review of the literature. *Microbes Infect.* 7, 1370–1375
23 Dantas-Torres, F. (2008) Canine vector-borne diseases in Brazil. *Parasit. Vectors* 1, 25
24 Enserink, M. (2007) Tropical disease follows mosquitoes to Europe. *Science* 317, 1485

25 Nunes, C.M. *et al.* (2008) Dog culling and replacement in an area endemic for visceral leishmaniasis in Brazil. *Vet. Parasitol.* 153, 19–23
26 Barbieri, C.L. (2006) Immunology of canine leishmaniasis. *Parasite Immunol.* 28, 329–337
27 Belkaid, Y. *et al.* (2006) Parasites and immunoregulatory T cells. *Curr. Opin. Immunol.* 18, 406–412
28 Leontides, L.S. *et al.* (2002) A cross-sectional study of *Leishmania* spp. infection in clinically healthy dogs with polymerase chain reaction and serology in Greece. *Vet. Parasitol.* 109, 19–27
29 Dantas-Torres, F. *et al.* (2006) Seroepidemiological survey on canine leishmaniasis among dogs from an urban area of Brazil. *Vet. Parasitol.* 140, 54–60
30 Michalsky, E.M. *et al.* (2007) Infectivity of seropositive dogs, showing different clinical forms of leishmaniasis, to *Lutzomyia longipalpis* phlebotomine sand flies. *Vet. Parasitol.* 147, 67–76
31 Margonari, C. *et al.* (2006) Epidemiology of visceral leishmaniasis through spatial analysis, in Belo Horizonte municipality, state of Minas Gerais, Brazil. *Mem. Inst. Oswaldo Cruz* 101, 31–38
32 Gavgani, A.S. *et al.* (2002) Domestic dog ownership in Iran is a risk factor for human infection with *Leishmania infantum*. *Am. J. Trop. Med. Hyg.* 67, 511–515
33 Schaefer, J.J. *et al.* (2007) Tick acquisition of *Ehrlichia canis* from dogs treated with doxycycline hyclate. *Antimicrob. Agents Chemother.* 51, 3394–3396
34 Kidd, L. and Breitschwerdt, E.B. (2003) Transmission times and prevention of tick-borne diseases in dogs. *Compend. Contin. Educ. Pract. Vet.* 10, 742–751
35 Swanson, S.J. *et al.* (2006) Coinfections acquired from *Ixodes* ticks. *Clin. Microbiol. Rev.* 19, 708–727
36 Thomas, V. *et al.* (2001) Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. *Infect. Immun.* 69, 3359–3371
37 Beall, M.J. *et al.* (2008) Serological and molecular prevalence of *Borrelia burgdorferi, Anaplasma phagocytophilum*, and *Ehrlichia* species in dogs from Minnesota. *Vector Borne Zoonotic Dis.* 8, 455–464
38 Trotz-Williams, L.A. and Trees, A.J. (2003) Systematic review of the distribution of the major vector-borne parasitic infections in dogs and cats in Europe. *Vet. Rec.* 152, 97–105
39 Harrus, S. *et al.* (2003) Down-regulation of MHC class II receptors of DH82 cells, following infection with *Ehrlichia canis*. *Vet. Immunol. Immunopathol.* 96, 239–243
40 Cortese, L. *et al.* (2006) Platelet aggregation and haemostatic response in dogs naturally coinfected by *Leishmania infantum* and *Ehrlichia canis*. *J. Vet. Med. A* 53, 546–548
41 Chomel, B.B. *et al.* (2006) *Bartonella* spp. in pets and effect on human health. *Emerg. Infect. Dis.* 12, 389–394
42 Pappalardo, B.L. *et al.* (2001) Immunopathology of *Bartonella vinsonii* (*berkhoffii*) in experimentally infected dogs. *Vet. Immunol. Immunopathol.* 83, 125–147
43 Breitschwerdt, E.B. *et al.* (2005) *Bartonella* species as a potential cause of epistaxis in dogs. *J. Clin. Microbiol.* 43, 2529–2533
44 Petanides, T.A. *et al.* (2008) Factors associated with the occurrence of epistaxis in natural canine leishmaniasis (*Leishmania infantum*). *J. Vet. Intern. Med.* 22, 866–872
45 Otranto, D. and Wall, R. (2008) New strategies for the control of arthropod vectors of disease in dogs and cats. *Med. Vet. Entomol.* 22, 291–302
46 Oliveira, F. *et al.* (2008) Immunity to distinct sand fly salivary proteins primes the anti-*Leishmania* immune response towards protection or exacerbation of disease. *PLoS Negl. Trop. Dis.* 2, e226
47 Giunchetti, R.C. *et al.* (2008) A killed *Leishmania* vaccine with sand fly saliva extract and saponin adjuvant displays immunogenicity in dogs. *Vaccine* 26, 623–638
48 Dantas-Torres, F. (2007) Rocky Mountain spotted fever. *Lancet Infect. Dis.* 7, 724–732
49 Little, S.E. *et al.* (2007) Movement of *Rhipicephalus sanguineus*. *Vet. Parasitol.* 150, 139–145
50 Wikel, S.K. (1999) Tick modulation of host immunity: an important factor in pathogen transmission. *Int. J. Parasitol.* 29, 851–859
51 Rosypal, A.C. *et al.* (2005) Transplacental transmission of a North American isolate of *Leishmania infantum* in an experimentally infected beagle. *J. Parasitol.* 91, 970–972
52 Freitas, E. *et al.* (2006) Transmission of *Leishmania infantum* via blood transfusion in dogs: potential for infection and importance of clinical factors. *Vet. Parasitol.* 137, 159–167
53 Birkenheuer, A.J. *et al.* (2005) Distribution of babesiosis among dogs in the United States and association with dog bites: 150 cases (2000-2003). *J. Am. Vet. Med. Assoc.* 227, 942–947
54 Hornok, S. *et al.* (2006) Seroprevalence of canine babesiosis in Hungary suggesting breed predisposition. *Parasitol. Res.* 99, 638–642
55 Dantas-Torres, F. (2008) The brown dog tick, *Rhipicephalus sanguineus* (Latreille, 1806) (Acari: Ixodidae): from taxonomy to control. *Vet. Parasitol* 152, 173–185
56 Dantas-Torres, F. *et al.* (2006) *Rhipicephalus sanguineus* (Acari: Ixodidae), the brown dog tick, parasitizing humans in Brazil. *Rev. Soc. Bras. Med. Trop.* 39, 64–67
57 Coutinho, M.T. *et al.* (2005) Participation of *Rhipicephalus sanguineus* (Acari: Ixodidae) in the epidemiology of canine visceral leishmaniasis. *Vet. Parasitol.* 128, 149–155
58 Tolezano, J.E. *et al.* (2007) The first records of *Leishmania* (*Leishmania*) *amazonensis* in dogs (*Canis familiaris*) diagnosed clinically as having canine visceral leishmaniasis from Araçatuba County, São Paulo State, Brazil. *Vet. Parasitol* 149, 280–284
59 Pirmez, C. *et al.* (1988) Experimental canine mucocutaneous leishmaniasis (*Leishmania braziliensis braziliensis*). *Mem. Inst. Oswaldo Cruz* 83, 145–151
60 Delgado, O. *et al.* (1993) Leishmania colombiensis in Venezuela. *Am. J. Trop. Med. Hyg.* 48, 145–147
61 Morsy, T.A. *et al.* (1987) Natural infections of *Leishmania major* in domestic dogs from Alexandria. *Egypt. Am. J. Trop. Med. Hyg.* 37, 49–52
62 Llanos-Cuentas, E.A. *et al.* (1999) Natural infections of *Leishmania peruviana* in animals in the Peruvian Andes. *Trans. R. Soc. Trop. Med. Hyg.* 93, 15–20
63 Dereure, J. *et al.* (1991) *Leishmania tropica* in Morocco: infection in dogs. *Trans. R. Soc. Trop. Med. Hyg.* 85, 595
64 Machado, E.M. *et al.* (2001) A study of experimental reinfection by *Trypanosoma cruzi* in dogs. *Am. J. Trop. Med. Hyg.* 65, 958–965
65 Uilenberg, G. (2006) *Babesia* – a historical overview. *Vet. Parasitol.* 138, 3–10
66 Eddlestone, S.M. *et al.* (2007) PCR detection of *Anaplasma platys* in blood and tissue of dogs during acute phase of experimental infection. *Exp. Parasitol.* 115, 205–210
67 Harrus, S. *et al.* (1999) Recent advance in determining the pathogenesis of canine monocytic ehrlichiosis. *J. Clin. Microbiol.* 37, 2745–2749
68 Breitschwerdt, E.B. *et al.* (1988) Clinical, hematologic, and humoral immune response in female dogs inoculated with *Rickettsia rickettsii* and *Rickettsia montana*. *Am. J. Vet. Res.* 49, 70–76
69 Rovery, C. *et al.* (2008) Questions on Mediterranean spotted fever a century after its discovery. *Emerg. Infect. Dis.* 14, 1360–1367
70 Otranto, D. and Dutto, M. (2008) Human thelaziasis. *Europe. Emerg. Infect. Dis.* 14, 647–649