Neglected vector-borne zoonoses in Europe: Into the wild

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Abstract

Wild vertebrates are involved in the transmission cycles of numerous pathogens. Additionally, they can affect the abundance of arthropod vectors. Urbanization, landscape and climate changes, and the adaptation of vectors and wildlife to human habitats represent complex and evolving scenarios, which affect the interface of vector, wildlife and human populations, frequently with a consequent increase in zoonotic risk. While considerable attention has focused on these interrelations with regard to certain major vector-borne pathogens such as *Borrelia burgdorferi* s.l. and tick-borne encephalitis virus, information regarding many other zoonotic pathogens is more dispersed. In this review, we discuss the possible role of wildlife in the maintenance and spread of some of these neglected zoonoses in Europe. We present case studies on the role of rodents in the cycles of *Bartonella* spp., of wild ungulates in the cycle of *Babesia* spp., and of various wildlife species in the life cycle of *Leishmania infantum*, *Anaplasma phagocytophilum* and *Rickettsia* spp.

These examples highlight the usefulness of surveillance strategies focused on neglected zoonotic agents in wildlife as a source of valuable information for health professionals, nature managers and (local) decision-makers. These benefits could be further enhanced by increased collaboration between researchers and stakeholders across Europe and a more harmonised and coordinated approach for data collection.

Key words: wildlife, zoonoses, arthropod vectors, surveillance

1. Introduction

Wildlife has long been recognized to have a major role in the transmission and maintenance of zoonotic agents, as most emerging infectious diseases are of wildlife origin (Jones et al., 2008). However, knowledge of the pathogens that naturally occur in wild animals and their potential to spread to humans and domestic animals is still scarce (Thompson, 2013). This is particularly true for microorganisms transmitted by vectors, which have multi-component transmission cycles affected by the ecology as well as the dynamics and life cycles of both vectors and pathogens (Hollingsworth et al., 2015). Such transmission systems often include diverse wild vertebrate hosts, which can serve as reservoirs or amplification hosts for pathogens, as well as a food source for the hematophagous arthropods themselves.

Wildlife disease monitoring for emerging as well as for certain autochthonous, but neglected vector-borne diseases (VBD), is an essential component of surveillance systems, not only for public health, but also for veterinary and ecological health (Evensen, 2008; Braks et al., 2014). While the need for such wildlife disease monitoring programmes is internationally recognised (http://www.glews.net) as the emergence of infectious diseases of wildlife origin is frequently of global concern (Jones et al., 2008; Keesing et al., 2010; Olival et al., 2017), their surveillance, control and prevention chiefly require local actions. Work on the ground and allocation of resources is usually focused on local priorities and interests and subject to short-term planning. Any potential international surveillance programmes are further hampered by inconsistencies in case acquisition (capture and handling of animals), sampling strategies, diagnostics and data interpretation, and inadequate wildlife surveillance infrastructures (Stallknecht, 2007). Here we present the current state of knowledge of the role of wildlife in the emergence and ecology of a number of neglected vector-borne zoonoses in Europe. We hope that this critical review will help to promote future international collaborations focused on the detection, prevention and control of VBD in wildlife.

2. Wildlife population dynamics and their effects on vector abundance

The restoration of natural habitats under the European Union programme for protected areas (Natura 2000;http://ec.europa.eu/environment/nature/), aimed at establishing a connected network of natural habitats, as well as the legal protection and reintroduction of many wildlife species, and certain land use changes (Milner et al., 2006), are expected not only to benefit various wildlife species, but may also boost vector populations and allow them to spread and establish in new areas.

A much-cited example of how wildlife populations affect the abundance of vectors, is that of deer and *Ixodes ricinus* ticks. The last couple of decades have seen a dramatic increase in the abundance and geographic distribution of various deer species, particularly roe, red and fallow deer (Milner et al., 2006; Burbaitė and Csányi, 2009, 2010). While immature stages may feed on a variety of wildlife hosts, including small rodents, insectivores and birds (Hofmeester et al., 2016), several studies have documented high infestation levels of deer with all developmental stages of ticks (Kiffner et al., 2010; Qviller et al., 2013). Deer species are thus considered the main determinants of tick abundance (Mihalca and Sandor, 2013). In fact, some investigations have reported a direct correlation between deer and tick numbers (Gilbert et al., 2012; Qviller et al., 2013). Others have found that once a deer population has reached a threshold level, the number of deer does not significantly affect tick density, indicating that spread rather than abundance is the main driver for boosting tick populations (Hofmeester et al., 2017). It is important, however, to differentiate between the overall abundance of ticks in a habitat and the expected number of ticks questing at any point in time. According to Dobson and Randolph (2011), the former is boosted by greater host abundance (particularly in areas recently colonized by deer), while the latter is expected to decline in areas with high deer densities, as unfed ticks quickly find a new host and spend less time questing. It is also necessary to stress that the specific level of tick infestation on hosts is dependent on the host's feeding and roaming behaviour. For example, moose (*Alces alces*), which mainly feed

from branches on trees, harbour fewer ticks on their heads and ears than red and roe deer (Handeland et al., 2013); the latter two species are mainly ground feeders with ample opportunity to encounter all life stages of *I. ricinus*. In addition, deer represent important vehicles for tick distribution over long distances (Vor et al., 2010).

For other vectors populations, the effects of wildlife host dynamics have been less intensively studied. For example, sand flies are vectors of *Leishmania infantum*, phleboviruses and other pathogens in southern Europe, but there is a limited understanding of their spatial distribution of and relationship with wild host abundance. In particular, information is lacking on sandfly breeding sites, and trapping is mainly aimed at the adult stages (Feliciangeli, 2004). Adult female sand flies, which are the only developmental stage able to transmit pathogens as they require a blood meal to develop the eggs, may feed on a wide variety of wild mammal and bird species (Bongiorno et al., 2003; Millán et al., 2014). In rural areas, sand flies congregate in buildings housing domestic animals, such as sheep sheds, bird houses and dog kennels (Dantas-Torres et al., 2014; Risueño et al., 2017). However, they are also found in natural and abandoned habitats such as rabbit burrows, caves and old ruined buildings, where they rely on wildlife for food. The ability of wildlife to increase and sustain enormous sand fly populations is demonstrated in the ongoing outbreak of human leishmaniosis in Fuenlabrada, Madrid, which is associated with an explosion in the population of hares (*Lepus granatensis*) in green areas integrated into a new housing development built on agricultural land (Molina et al., 2012; Carrillo et al., 2013).

While there are several studies on the role of wildlife on flea dynamics in North America, mostly focused on the ecology of the plague, such research is scarce in Europe. One survey reported that 70% of all flea species are found on rodents (Medvedev, 2002). For example, fleas in the Palaearctic region preferentially parasitize voles, gerbils and hamsters (Medvedev and Krasnov, 2006), and to a lesser extent other wildlife hosts such as hares and carnivores (mainly foxes) (Foley et al., 2017). Moreover, flea abundance positively correlates with host density in many flea-host

associations (reviewed by Krasnov, 2008). On the other hand, more diverse host communities could lead to a decrease in flea prevalence. Krasnov (2008) divided fleas into three main categories: (i) fleas of poultry, livestock and pets; (ii) fleas of commensal birds and mammals (sparrows, pigeons, house martins, rats and mice); and (iii) fleas of wild birds and mammals. While the first two groupings show a relatively uniform flea species composition, species in the third category have a much more diverse pattern, depending on the specific wildlife composition in the region and its flea fauna.

All of these examples show that a rise in the number of certain wildlife hosts can increase the abundance and distribution of vectors. In some cases this situation results directly in an increase in VBD, as shown in the example of sand flies and hares in Spain. Many wildlife host/vector/pathogen relationships, however, are more complex, particularly if the wildlife host is not a competent pathogen reservoir and the vector is a generalist. In this case, a boost in wildlife host population can have a 'dilution' effect, i.e. it can reduce the pathogen prevalence in the vectors (Dudek, 2014). It has also been postulated that reduced biodiversity may favour transmission of vector-borne pathogens because many severely degraded environments of low biodiversity still abound in rodents (Dudek, 2014), many of which are competent reservoirs for a multitude of disease agents. Consequently, the declining biodiversity currently experienced in many habitats all over the world may be advantageous to certain pathogens and their vectors, potentially increasing the risk of pathogen exposure (Daszak et al., 2007). However, it should also be borne in mind that there are natural habitats of low biodiversity, such as bogland or tundra, which do not necessarily represent high risk VBD areas. Care must be taken therefore when extrapolating from the wildlife transmission dynamics of one pathogen to another.

3. Urbanization of wildlife and vectors

Green spaces and corridors in cities and (sub)urban areas not only improve human well-being (Hansen and Pauleit, 2014) but can also help to mitigate the negative effects of heat waves, air pollution, flooding and possible other health risks (IPCC, 2013). In addition, they can contribute to conservation strategies for wildlife and biodiversity. For example, forty-eight different mammal species, from bats to wild boars, have been recorded in Budapest (Tóth-Ronkay et al., 2015). Some mammal species, such as hedgehogs and squirrels, can reach higher densities in (sub)urban habitats than rural environments (Reeve, 1994; Tóth-Ronkay et al., 2015).

On the other hand, the trend in increasing urban green spaces and spatial expansion of urbanized areas into agricultural and nature habitats also increases the dispersal and abundance of vectors into urban areas and their contact with humans (Maetzel et al., 2005; Gassner et al., 2016; Paul et al., 2016;Vourc'h et al., 2016). As a matter of fact, *I. ricinus* (and to a lesser extent other tick species) are found in city parks, urban forests, private gardens and other green spaces in and around cities across Europe (Schorn et al., 2011; Buczek et al., 2014; Hornok et al., 2014; Mancini et al., 2014; Venclíková et al., 2014; Nelson et al., 2015; Starostzik, 2015; Szekeres et al., 2016). Although tick densities in these areas are generally low, the risk of acquiring a tick bite can be substantial, because of the relatively high exposure rates of humans. In fact, a Dutch survey found that approximately 30% of tick bites were acquired in gardens (Mulder et al., 2013). While the ecological and environmental requirements for the establishment and maintenance of *I. ricinus* in its natural habitats are well known (Randolph, 2004; Medlock et al., 2013), our understanding of the tick's enzootic cycle in urban green spaces is very limited. For example, it is conceivable that shade from buildings, ornamental trees, shrubs and hedges provide protection from desiccation in urban settings. This could be critical for *I. ricinus* which does not survive for long at humidities below 80% (Randolph and Storey, 1999). On the other hand, where the density of feeding or propagation hosts is too low to sustain a complete enzootic cycle, tick presence may depend on the continuous

introduction from forest areas, particularly via birds (Hasle, 2013). It is possible that in urban settings medium-sized mammals, such as hedgehogs, squirrels, and (stone) martens replace deer as the main 'propagation hosts' (Gern et al., 1991, 1997; Labuda and Randolph, 1999).

With regard to sand flies, human residential environments can also provide suitable conditions for all stages of their life cycle, which takes around 30-45 days depending on environmental temperature and sand fly species (Killick-Kendrick, 1999; Alexander, 2000; Volf and Volfova, 2011). While most species are predominantly exophagic and exophilic (i.e. feeding and egg development occur outdoors), adults take cover in houses, cellars and animal buildings, when they are inactive during the day. Moreover, gardens and other periurban habitats provide ideal breeding sites with organic matter for the larvae to feed on, and shelter from sunlight and desiccation. Foxes, which are one of the most common urbanised mammal species in Europe and highly susceptible to *L. infantum* infection, have long been considered a potential source of introducing *Leishmania* from sylvatic to domestic environments (Ashford and Bettini, 1987). However, more recent PCR-based studies have shown that *L. infantum* is also endemic in many other wildlife species such as mustelids, felines, rodents and lagomorphs that live in close proximity to humans and dogs (Del Río et al., 2014; Millán et al., 2014). Moreover, domestic and sylvatic *L. infantum* cycles are bidirectional. For example, the ITS-LOMBARDI *L. infantum* strain -recently isolated from hares in the Fuenlabrada outbreak-was first identified in a human cutaneous leishmaniosis case in 1987, and has probably been circulating in this area for some time (Chicharro, et al., 2013; Martín-Martín et al., 2015).

Urbanization has also important effects on mosquito vectors, with some species particularly being favoured by anthropogenic environmental changes. For example, several *Anopheles, Culex* and *Aedes* spp. easily find suitable habitats in urban areas, not least because of numerous artificial breeding sites created by humans (e.g. water deposits, swimming pools, gardens) (Ferraguti et al., 2016) and milder temperatures in winter (LaDeau et al., 2015). In fact, studies on the invasive

mosquito species *Aedes albopictus* have shown that this parasite survives better in anthropized environments than in its natural habitats (Li et al., 2014; Roche et al., 2015). In anthropically altered areas, frequency of human bites may thus be increased, with higher rates of transmission of mosquito-borne pathogens (LaDeau et al., 2015). More suitable climatic conditions for the vectors, and the presence of competent wild birds, also in urban areas, are implicated in the expanding incidence of West Nile Virus infections in Europe (Semenza et al., 2016).

While fleas usually gain access to human habitations via pets and periurban rodents, modern living conditions, particularly central heating, may help to create microclimate conditions suitable for the development of pre-imago stages throughout the year (Krasnov, 2008).

4. Examples of neglected zoonotic pathogens and their wildlife reservoirs

'Neglected' pathogens are pathogens characterized by a low level of public awareness, and research focus and/or funding. Some pathogens may be neglected only in certain geographical areas or certain hosts. Our review focuses on zoonotic pathogen-wildlife host systems that have received limited attention in the published literature and for which important knowledge gaps remain. Table 1 provides an overview of these pathogens, their known and suspected vectors and wildlife reservoirs.

4.1. Rodents and flea-transmitted *Bartonella* spp.

The genus *Bartonella* comprises several species that infect a large number of vertebrates, parasitizing erythrocytes and causing a persistent bacteraemia (Maggi et al., 2012). The main transmission route is via the faeces of ectoparasites (such as fleas and other hematophagous arthropods), which can enter the body through superficial scratches on the skin (Buffet et al., 2013).As a result of improved diagnostic techniques, the reported incidence of zoonotic *Bartonella*

infections has been increasing over the last number of years (Edouard et al., 2015), particularly in people living under poor hygienic conditions and/or suffering from immunodeficiency (Mosepele et al., 2012).

Contact with wild rodents is likely to be a risk factor for infection, since these animals are the preferential reservoir hosts of several *Bartonella* species in nature. *B. elizabethae*, associated with the black rat and Oriental rat fleas (*Xenopsylla cheopis*), and *B.grahamii*, associated with wild mice and voles and transmitted by rodent fleas, are recognized as zoonotic pathogens (Chomel and Kasten, 2010). Moreover, the pathogenic *B. quintana* and *B. koehlerae* have been detected in rodent fleas (Mariè et al., 2006), and several studies have reported rodent infections with as yet unknown genotypes (Silaghi et al., 2016).

While fleas are suspected to be the main vectors of *Bartonella* in wild rodent populations (Billeter et al., 2008), few flea species have been unequivocally shown to be competent vectors of *Bartonella* spp. A notable exception is *Ctenophthalmus nobilis*, a common parasite of small mammals in Western Europe and competent vector of *B.grahamii* and *B.taylorii* (Bown et al., 2004). The situation is further complicated by the fact that fleas only show host preference but no clear host specificity (Silaghi et al., 2016). The role of other arthropods as potential *Bartonella* vectors and reservoirs also remains to be elucidated. Reis et al. (2011) experimentally demonstrated the vector competence of *I. ricinus* for *B. birtlesii*. Moreover, certain *Bartonella* spp., including the rodent-associated *B. doshiae* and *B. tribocorum*, have recently been isolated from blood samples of human patients with nonspecific chronic symptoms and history of tick-bite. However, so far it has not been possible to establish a causal link between *Bartonella* spp., clinical signs, and tick bite (Vayssier-Taussatet al., 2016).

In Europe, *Bartonella* prevalence rates of between 14 and 85% have been reported from various species of rats, squirrels, voles and mice (Ellis et al., 1999*;* Bown et al., 2002, 2004; Telfer et al., 2007a, 2007b; Buffet et al., 2013; Kraljik et al., 2015; Silaghi et al., 2016). According to these

studies, infection prevalence was affected by the level of infestation with the relevant vector, the rodents' resistance to infection, their population density, contact rates, and certain behaviours that could facilitate transmission by non-vectorial routes. Moreover, seasonal fluctuations in prevalence rates may be linked to seasonal activity patterns of various flea vectors, while the length of infection is dependent on the specific *Bartonella* species present (Telfer et al., 2007a, 2007b).

As this brief overview shows, many aspects of the complex interactions between zoonotic *Bartonella* spp., their wildlife hosts and arthropod vectors are yet to be determined. *Bartonella* diversity in rodents is particularly challenging, since co-infections with different species or variants in rodent hosts and vectors (particularly in fleas) are very common (Gutiérrez et al., 2015), which may also have consequences on the transmission dynamics and clinical disease in humans.

4.2. Rodents and other wildlife as reservoirs of *Leishmania infantum*

Leishmania infantum is a protozoan transmitted by *Phlebotomus* spp. sand flies, causing life threatening zoonotic visceral Leishmaniosis (VL).In southern Europe, VL affects hundreds of people every year and is considered the most important disease of dogs (Moreno and Alvar, 2004; Ready, 2010; Gradoni, 2013). Many wildlife species can be infected by *L. infantum* but, in contrast to dogs and humans, disease is rarely reported and parasite burdens are often comparatively low(reviewed by Ashford and Bettini, 1987; Ashford, 1996; Quinnell and Courtenay, 2009; Antoniou et al., 2013; Del Río et al., 2014; Millán et al., 2014; Roque and Jansen, 2014). Given the large number of potential reservoirs that share habitats with *Leishmania* spp., it is difficult to determine which of them can serve as the primary reservoir of infection, capable of maintaining parasite endemicity indefinitely in the absence of a human or canine host. Moreover, even within specific host species, there are likely individual differences with regard to susceptibility to infection and infectiousness, depending on the parasite strain and host intrinsic and external factors (Roque and Jansen, 2014). The best approach to assess the reservoir status is to demonstrate host

susceptibility to infection and ability to transmit the parasite to the vector by performing xenodiagnostic experiments. However, hosts able to meet these criteria may still not have primary reservoir capacity, in which case they are considered secondary reservoir hosts (Quinnell and Courtenay, 2009).

With the exception of hares (*Lepus granatensis*), no wildlife species has so far been associated with leishmaniosis outbreaks in Europe. Xenodiagnostic experiments have confirmed that hares, rabbits (*Oryctolagus cuniculus*), black rats (*Rattus rattus*) and the American crab-eating fox (*Cerdocyon thous*) can transmit *L. infantum* to sand flies (Quinnell and Courtenay, 2009; Jiménez et al., 2014). Moreover, it is likely that infected red foxes (*Vulpes vulpes*) and other canids in Europe are also able to transmit these parasites to sand flies (Ashford and Bettini, 1987). The reservoir role of other sylvatic species known to be susceptible to *L. infantum* infection, including felines, mustelids, insectivores, and chiroptera, remains to be determined (Millán et al., 2014).

Murine (*Mus musculus*) and hamster (*Mesocricetus auratus*) laboratory models have been extensively used to investigate the clinical and immunological features of *Leishmania* infections, and the latter species is highly susceptible to visceralising *L. infantum* infection (Loría-Cervera and Andrade-Narváez, 2014; Moreira et al., 2016). Similarly in the wild, the potential epidemiological role of rodents in the *L. infantum* transmission cycle has attracted attention for a long time. In early experiments in France, Rioux et al. (1968), using non-molecular methods, failed to detect *L. infantum* in over 250 wild rodents including mice (*Apodemus* spp.), dormice (*Glis glis* and *Elyonis quercinus*) and rats (*Rattus* spp.). They were, however, able to infect these species with the parasite experimentally, noting differences in susceptibility. At the time, *L. infantum* strains had been isolated from black rats in Italy, showing identical isoenzymatic patterns to those from humans. Sand flies became infected with the strain after feeding on rats only when the rats were inoculated with high parasite doses or when immunosuppressed with a hydrocortisone treatment, leading to the conclusion that black rats are naturally resistant to *L. infantum* infection (reviewed by Ashford and

Bettini, 1987). Several epidemiological studies have since demonstrated the presence of *L. infantum* DNA and specific antibodies in naturally infected rodents in Europe (Quinnell and Courtenay, 2009; Millán et al., 2014). Infected rodents in these studies originated from areas where dogs and other wild carnivore primary hosts were also present, so that the rodents' epidemiological role in *L. infantum* transmission could not be confirmed. More recently, *L. infantum* DNA was detected in spleen samples from 11 out of 71 black rats from the Mediterranean island of Montecristo, a natural reserve where dogs are absent, suggesting that they may act as an alternative primary reservoir host (Zanet et al., 2014).

In summary, *L. infantum* has a remarkable ability to infect domestic and wild mammals, though clinical cases in wild animals are rarely observed. Little is known about the role of wildlife species as potential reservoirs or the degree of interaction between domestic and sylvatic *L. infantum* life cycles. However, there is strong evidence that anthropogenic disturbance of the vector and wildlife natural environment can lead to infection build-up and spill-over leading to epidemics in susceptible humans.

4.3. Wildlife species with a role in zoonotic anaplasmosis

The zoonotic obligate intracellular bacterium *Anaplasma phagocytophilum* occurs worldwide in the Northern Hemisphere and is transmitted between different species of vertebrates by the bite of ticks. In Europe the only known vector is *I. ricinus* (Jahfari et al., 2014; Stuen et al., 2013a). *Anaplasma phagocytophilum* causes granulocytic anaplasmosis in domestic ruminants, horses, dogs, cats, other mammalian species as well as in humans (Stuen et al., 2013a). Even though granulocytic anaplasmosis is generally seen as a mild and self-limiting disease, hospitalization and need for intensive care has been reported from isolated human cases (Dumler, 2012).

Although the pathogen has been detected in many vertebrates, including birds, deer, rodents and insectivores, it is unknown which species actually contribute as reservoir hosts in a significant way to the complex transmission cycle.

For example, few studies to date have focused on the role of ornithophilic hard-ticks in the eco-epidemiology of *A. phagocytophilum*. There is some evidence that blackbirds (*Turdus merula*) may be a reservoir host. For one, it is a common avian host of immature *I. ricinus*, mainly due to its ground-feeding behaviour (Hasle, 2013). For another, it is the most frequently reported bird in Europe to be infected with *A. phagocytophilum* and the most common species to carry infected ticks, including larval stages. A potential reservoir role for other bird species was also suggested by the higher prevalence in ticks collected from avian hosts, compared to those questing in the same habitat in Switzerland (Lommano et al., 2014). However, Jahfari et al. (2014) showed that the *A. phagocytophilum* 'ecotype' which was associated with avian hosts was absent in samples from all other hosts, indicating that it may be restricted to bird-ornithophilic tick systems. With regard to ecotypes that circulate in wild mammals and humans, it appears that birds are not an important source of infection and that their epidemiological role in zoonotic infections may be marginal.

Among mammalian wildlife species, roe deer and red deer are well-documented hosts of *A. phagocytophilum* with high prevalence rates reported (Petrovec et al., 2002; Michalik et al., 2009; Silaghi et al., 2011; Mysterud et al., 2013; Overzier et al., 2013; Stuen et al., 2013a, 2013b). They are thought to significantly contribute to the spread of the organism by providing a persistent pathogen reservoir, in addition to serving as vehicles for infected and uninfected ticks. However, whether deer are significant contributors to human granulocytic anaplasmosis in Europe is doubtful, because clinical cases are only rarely reported (Stuen et al., 2013a).

While rodents are often suspected to serve as reservoir for *A. phagocytophilum*, their infection rates are actually quite low in Europe (Liz et al., 2000; Bown et al., 2003; Hulínská et al., 2004; Blaňarová et al., 2014; Kallio et al., 2014). In fact, several studies reported a complete absence of

infection in all rodent species screened (Silaghi et al., 2012a; Blaňarová et al., 2014; Svitálková et al., 2015). Moreover, a xenodiagnostic study concluded that *Apodemus* spp. and *M. glareolus* were not competent reservoirs for *A. phagocytophilum* (Burri et al., 2014). Some authors consider them accidental hosts (Obiegala et al., 2014), while others suggest that they may act as hosts only for certain *A. phagocytophilum* variants (Blaňarová et al., 2014). On the other hand, certain insectivore species showed significantly higher prevalence rates (Liz et al., 2000; Barandika et al., 2007;Bown et al., 2011; Silaghi et al., 2012a; Földvári et al., 2014).

Several so-called 'niche cycle' have been suggested for *A. phagocytophilum*. These are defined by a competent reservoir host and at least two tick species, with at least two developmental stages each. One of these two tick species must be endophilic and specific for the reservoir host in question, and the other one exophilic, with a broad host range. It is hypothesised that established niche cycles are sufficient to maintain a stable and constant endemic cycle of certain genetic variants of *A. phagocytophilum* in a given geographic area. Such a niche cycle has been proposed for hedgehogs, which are frequently infested with all three life stages of *I.ricinus* as well as the hedgehog tick, *Ixodes hexagonus* (Földvári et al., 2011; Pfäffle et al., 2011; Dumitrache et al., 2013; Dziemian et al., 2015). Other insectivore species, such as the common shrew, also fulfil the criteria for a niche cycle, as they are frequently infected with *A. phagocytophilum* in addition to numerous larvae and nymphs of *I. ricinus* and *I. trianguliceps* (nidicolous tick) (Bown et al., 2011). Moreover, niche cycles have been proposed for certain rodent *species (M. glareolus, A. flavicollis,* and *A. agrarius*) and *I. ricinus/I. trianguliceps,* chiefly involving *A. phagocytophilum* genotypes that do not have zoonotic significance (Blaňarová et al., 2014).

It is clear that significant knowledge gaps remain regarding the specific host associations of zoonotic *A. phagocytophilum* genotypes and the vector competence of various tick species. Without this information, endemic cycles of zoonotic anaplasmosis in nature will remain obscure.

4.4 Wildlife species and *Rickettsia* spp.

Rickettsiae are obligate intracellular bacteria, which can be separated in two main groups: the typhus (TG) and spotted fever group (SFG). Although effective treatments exist for many *Rickettsia* species, some are still associated with severe, sometimes fatal disease. It is the case of *R. conorii*, the most pathogenic tick-borne rickettsia in Europe and causative agent of Mediterranean spotted fever (MSF)(Portillo et al., 2015). Two strains, *R. conorii* Malish and Israeli tick typhus strain, are associated with human and canine disease (De Sousa et al., 2008; Alexandre et al., 2011;Solano-Gallego et al., 2015). The 'kennel tick' or 'brown dog tick', *Rhipicephalus sanguineus*, transmits both strains. Although this tick has a close evolutionary relationship with domestic dogs and feeds primarily on them, it can survive in a wide range of ecological niches and parasitize many wild and domestic species (Gray et al., 2013).

Serosurveys indicate that wild carnivores are frequently exposed to rickettsiae (Marquez and Millán, 2009; Lledó et al., 2016; Millán et al., 2016). However, as rickettsial DNA has never been detected in blood or tissue samples collected from wild carnivores (including genets, red foxes, martens and badgers) (Márquez and Millán, 2009; Torina et al., 2013;Millán et al., 2016),it is thought that these animals have a negligible role in the transmission (Millán et al., 2016).

In contrast, there is evidence that wild rabbits (*O.cuniculus*) and hares (*Lepus europaeus* and *L. granatensis*) have a role as reservoir hosts for *R. conorii* and also in the circulation of other *Rickettsia* species (Le Gac, 1966; Ruiz-Beltrán et al., 1992; Rovery et al., 2008), such as *R. slovaca* (Rehácek et al., 1978). In Italy, antibodies against *R. conorii* and *R. slovaca* were detected in wild rabbits, and inoculation of guinea pigs with homogenates of *Rhipicephalus pusillus* ticks isolated from these rabbits resulted in a seroconversion to *R. conorii* (Ciceroni et al., 1988). However, due to cross-reactivity of antibodies within the SFG, these experiments do not unequivocally confirm the role of *Rh. pusillus* as a vector of *R. conorii*. To date, there is no further evidence that this tick species, which is a common ectoparasite of wild rabbits in the Mediterranean region, serves as a

vector for *R. conorii,* although it is known to transmit *R. sibirica mongolotimonae* in Portugal, Spain, and France (De Sousa et al.,2006; Toledo et al., 2009; Parola et al., 2013).

Small mammals, particularly mice and voles, have also been considered important in the natural transmission cycle of certain SFG *Rickettsia* species including *R. slovaca, R. felis* and *R. helvetica* (Rehácek et al., 1976,1992; Schex et al., 2011;Martello et al., 2013).In contrast, other authors failed to identify *R. monacensis* and *R. helvetica* in the blood of *Apodemus* spp., *M. glareolus* and xenodiagnostic ticks, although attached *I. ricinus* tested positive, and suggested that these rodents are not reservoirs for SFG species (Burri et al., 2014;Biernat et al., 2016).

More recently, studies have shown that lizards may have a more prominent role as reservoirs than previously thought. In fact, systemic infection by *R. helvetica* was detected in lizards captured in Portugal and Italy (De Sousa et al., 2012; Tomassone et al., 2017).

In conclusion, a better understanding of the eco-epidemiology of rickettsial disease in specific geographic regions may help to reduce and even prevent outbreaks. For example, an imbalance in the rodent population in Porto Santo Island, Madeira, Portugal, lead to increased incidence of human cases of murine typhus, a disease caused by *R. typhi* and transmitted by the rat flea; weather conditions and human interventions were shown to cause such imbalance (Bacellar et al., 1998). The factors that affect the abundance, distribution and density of wild reservoir hosts and vectors, which can conspire to reduce or increase rickettsial infection rates, deserve detailed investigations.

4.4. Wild ungulates and *Babesia* spp.

It is thought that the main - if not the only - vector for human babesiosis in Europe is *I. ricinus* (Gray et al., 2010). In contrast to the relatively high incidence of human babesiosis in the USA, the number of cases in Europe has remained extremely low. To date, less than 50 cases have been reported (Hildebrandt et al., 2013; González et al., 2015; Mørch et al., 2015). These include about 40 cases attributed to the cattle parasite *Babesia divergens,* three to *B. venatorum* (formerly 'EU1-

3') and just two autochthonous case attributed to *B. microti* (Hildebrandt et al., 2007; Arsuaga et al., 2016). Infections with *B. divergens* are mostly confined to asplenic patients, where they are characterized by septic fever, severe anaemia, haemoglobinuria and jaundice due to widespread haemolysis. By comparison, infections with the other two *Babesia* spp. appear to be less severe although all four reported cases also occurred in asplenic or immunocompromised patients (Herwaldt et al., 2003; Häselbarth et al., 2007; Gray et al., 2010). In contrast to this very low clinical incidence, significant seroprevalence rates have been recorded in many parts of Europe, particularly among people with a high risk of occupational exposure such as foresters, hunters, farmers and veterinarians, or those with a history of tick-bite and/or tick-borne disease (Gorenflot et al., 1998; Foppa et al., 2002; Hunfeld et al., 2002; Gabrielli et al., 2014; Żukiewicz-Sobczak et al., 2014; Lempereur et al., 2015), indicating that human infection with *Babesia* spp. is not such a rare event, but that immunocompetent individuals may be largely resistant to disease. Alternatively, it is also conceivable that many of the *Babesia* species/subspecies carried by *I. ricinus* in Europe are not infectious to humans although they may cause seroconversion.

A large number of epidemiological surveys have screened deer blood or spleen for the presence of *Babesia* spp. using PCR protocols targeting the 18S rRNA gene. Sequence analysis revealed a bewildering array of strains and/or species many of which were described as '*B. divergens*-like'. However, detailed investigation of several human, bovine and deer isolates indicated that only isolates that were over 99.9% identical with the *B. divergens* reference sequence (U16370, a cattle isolate) shared the biological characteristics of this species, i.e. they were infective to gerbils *in vivo* and could be cultured in cattle, human and sheep red blood cells *in vitro* (Malandrin et al., 2010). In fact, all European *B. divergens* human isolates were homologous with U16370 by at least 99.94%. In contrast, other isolates, although 99.77% identical with U16370 and morphologically and serologically indistinguishable from *B. divergens*, were not infective to gerbils and could only be maintained in roe and fallow deer red blood cells. On the basis of these biological characteristics

they were identified as *B. capreoli* (reference sequence AY726009), a species that is not considered to be zoonotic due to its inability to develop in human red blood cells *in vitro* (Malandrin et al., 2010). Only a very small number of deer isolates in the database, all from red deer, are over 99.9% homologous with *B. divergens* (Zintl et al., 2011) indicating that the role of red deer as a potential reservoir host for *B. divergens*, warrants further investigation. With regard to *B. venatorum*, isolates 100% identical to the reference sequence AY046575have only ever been identified from roe deer, the accepted reservoir host for this species.

Considering the high degree of genetic homology between *B. divergens* and *B. capreoli* in spite of their marked biological differences, it is possible that at least some of the numerous isolates that have been described in deer represent species in their own right. Unless they are assessed for their ability to infect human red blood cells, we cannot evaluate their potential public health risk. Furthermore the lack of sequence data for zoonotic babesias (currently there are only six human 18S rRNA isolates in the database), should be addressed in order to determine their relationship with *Babesia* strains or species harboured by deer.

5. Directions for future research and conclusion

There is a tendency in the published literature to extrapolate from knowledge gained from intensively researched VBD to other less well-known pathogens. However, as this review shows, the relationship between pathogens, vector and wildlife hosts are often highly specific requiring a much more focused approach.

Moreover, effective and timely action in response to endemic and emerging zoonotic wildlife pathogens is only possible if potential hosts are routinely monitored (Mörner et al., 2002). This is not the case for the vast majority of VBD, particularly those that are not considered of major public health importance. Mannelli et al. (2012), reviewing surveillance activities by competent authorities across Europe, concluded that the only vector-borne zoonotic pathogens for which sufficient data

was being collected were *Francisella tularensis* and West Nile virus, although some others (including *Borrelia burgdorferi*, *L. infantum*, tick-borne encephalitis virus, Crimean-Congo haemorrhagic fever virus) were also being recorded.

We propose that this conflict between the considerable research effort needed to monitor rare VBD and the lack of resources generally available for 'neglected pathogens' may be addressed, at least in part, by developing standardised guidelines for data collection and analysis, and a pan-European repository where up-to-date surveillance data is made available to all stakeholders. The logistics and organisation of this network could replicate those of other similar European collaborations such as the EFSA/ECDC funded VectorNet initiative (https://vectornet.ecdc.europa.eu/), created to monitor the geographic distribution of arthropod disease vectors. This network could also be used to identify surveillance gaps and overlaps and further improve cost effectiveness by establishing links between researchers and organisations that routinely capture and/or cull wildlife (e.g. bird ringing, wildlife vaccination or rehabilitation centres, hunting management centres).This will no doubt result in significant cost savings as well as a better understanding of the current status of VBD.

From a technical point of view, most studies have relied chiefly on the molecular screening of potential vectors and wildlife hosts for the presence of certain pathogens. Recent years have seen the development of various novel blood meal analysis tools, such as stable isotope analysis, high-throughput sequencing, MALDI-TOF MS and high-resolution melting analysis (Schmidt et al., 2011; Campana et al., 2016; Collini et al., 2016; Niare et al., 2017). These methods, in addition to more traditional PCR-based assays, can be used to identify the last host a vector has fed on. Inclusion of these novel tools in standard VBD surveys would thus contribute vital information on vector feeding habits and transmission cycles.

Finally, it is incumbent on the scientific community to demonstrate to policy makers and funding bodies the inherent value of disease surveillance and research into wildlife, as it shares many living spaces, pathogens and arthropod vectors with us.

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Table 1. List of the zoonotic pathogens that are discussed in this review and their known (suspected) vectors and reservoir hosts

Vector borne pathogen	**Known (suspected) vectors**	**Known (suspected) reservoir hosts**	**Reference**
Anaplasma phagocytophilum	*Ixodes ricinus (I. hexagonus, I. trianguliceps)*	Wild ruminants, (small mammals such as rodents and insectivores; birds)	Stuen et al., 2013a (Bown et al., 2003 and 2011; Silaghi et al., 2012b; Lommano et al., 2014)
***Babesia* spp.**			
Babesia divergens	*I. ricinus*	Cattle, (red deer)	Zintl et al., 2003
Babesia venatorum	*I. ricinus*	Roe deer	Herwaldt et al., 2003
Babesia microti	*I. ricinus*	(rodents)	Gray et al., 2002; Häselbarth et al., 2007
***Bartonella* spp.**			
B. elizabethae	*Xenopsylla cheopis*	rat	Loftis et al., 2006
B. grahamii	*Ctenophthalmus nobilis*	bank vole and wild mice	Bown et al., 2004
B. quintana	*Pediculushumanushumanus* (cat and rodent fleas)	Humans (cats, rodents)	Raoult and Roux, 1999(Rolain et al., 2003; Mariè et al., 2006)
B. koehlerae	*Ctenocephalides felis*(rodent	Cat	Avidor et al.,

	fleas)	(rodents)	2004 (Mariè et al., 2006)
Leishmania infantum	*Phlebotomus ariasi,* *P. balcanicus,* *P. kandelakii,* *P. langeroni* *P. neglectus,* *P. perfiliewi,* *P. perniciosus,P. tobbi.*	Canids, lagomorphs and rodents	Alten et al., 2016
***Rickettsia* spp.**			
R. conorii	*Rhipicephalus sanguineus (Rh. pusillus)*	Lagomorphs	Ruiz-Beltrán et al., 1992
R. slovaca	*Dermacentor* spp.	Lagomorphs, mice and voles	Rehácek et al., 1976, 1978, 1992
R. helvetica	*I. ricinus*	(Lizards)	De Sousa et al., 2012