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336

Claire Cayol

Eco-Epidemiology of Tick- and Rodent-Borne Pathogens in Boreal Forests

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Editors
Jari Haimi
Department of Biological and Environmental Science, University of Jyväskylä
Pekka Olsbo, Ville Korkiakangas
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ABSTRACT

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Infectious diseases are amongst the ten major causes of human mortality worldwide, 60% of them being animal-borne. Variations of abiotic and biotic conditions are likely to modify the transmission of parasites and pathogens within reservoir species, and, as a consequence, alter the zoonotic risk for human. My thesis aims at elucidating the dynamics and mechanisms of the maintenance of ticks, tick-borne pathogens (TBPs) and the Puumala hantavirus (PUUV) in the reservoir host, the bank vole (*Myodes glareolus*, BV). In Northern Europe, tick-borne diseases are growing in importance to human because of the latitudinal expansion of the tick *Ixodes ricinus*. Field monitoring revealed that *I. ricinus* was the only species found in the vegetation in Central Finland. The abundance of immature *I. ricinus* in nature was positively associated with the BV abundance. The highest risk periods for tick bites on humans were May–June and September. *Ixodes ricinus* was positively associated with open water coverage and human density, which might offer suitable moisture conditions and anthropogenic modifications favouring the species. The infection of BV with the zoonotic *B. burgdorferi* s.l. was associated with the abundance of *I. ricinus* at the site, indicating that this tick species was required for the transmission and persistence of this pathogen. An experiment revealed, for the first time, that *B. afzelii* can modify the behaviour and the breeding success of its host, and these effects are both sex- and size-specific and density-dependent. Space-state modelling of longitudinal field data revealed that PUUV infection likelihood was the lowest in BV previously infested with vectors in comparison to *Anaplasma phagocytophilum* infected BV, or individuals without any previous infections. Altogether, this study shows how seasonality, co-infecting pathogens and host population density influence the risk of tick-borne pathogens and the zoonotic risk in Central Finland.

Keywords: *Borrelia burgdorferi s.l.*; disease ecology; eco-epidemiology; *Myodes glareolus;* Puumala hantavirus; reservoir; tick-borne pathogens.

Claire Cayol, University of Jyväskylä, Department of Biological and Environmental Science, P.O. Box 35, FI-40014 University of Jyväskylä, Finland

Author's address

Claire Cayol
Department of Biological and Environmental Science
P.O. Box 35
FI-40014 University of Jyväskylä
Finland
claire.c.cayol@jyu.fi

Supervisors

Dr. Eva Kallio
Department of Ecology and Genetics,
P.O. Box 3000
FI-90014 University of Oulu
Finland

Dr. Esa Koskela
Department of Biological and Environmental Science
P.O. Box 35
FI-40014 University of Jyväskylä
Finland

Dr. Tapio Mappes
Department of Biological and Environmental Science
P.O. Box 35
FI-40014 University of Jyväskylä
Finland

Reviewers

Dr. Muriel Vayssier-Taussat
UMR BIPAR, INRA-Anses-ENVA
22 rue Pierre et Marie Curie
94701 Maisons-Alfort Cedex, France

Prof. Atle Mysterud
CEES, Dept. of Biosciences
University of Oslo
P.O. Box 1066 Blindern, NO-0316 Oslo, Norway

Opponent

Prof. Annapaola Rizzoli
Centro Ricerca e Innovazione - Fondazione Edmund Mach
via E. Mach 1, 38010 San Michele all'Adige (TN), Italy

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LIST OF ORIGINAL PUBLICATIONS

I have substantially contributed to the study design (Chapt. I, II, III, IV), data collection (Chapt. I, III & IV), statistical analysis (Chapt. I, II, III & IV) and writing (Chapt. I, II, III & IV) of the manuscripts presented in my thesis. The original ideas of chapters I, II, IV were from Eva R. Kallio. In study IV, the statistical modelling was performed collaboratively with Andrés López-Sepulcre, with whom I share the first authorship.

I Cayol, C., Koskela, E., Mappes, T., Siukkola, A. & Kallio, E.R. 2017. Temporal dynamics of the tick *Ixodes ricinus* in northern Europe: epidemiological implications. *Parasites and Vectors* 10: 166.

II Cayol, C., Jääskeläinen, A., Koskela, E., Kyröläinen, S., Mappes, T., Siukkola, A., Kallio, E.R. 2017. Spatial heterogeneities and the role of two sympatric *Ixodes*-tick species in pathogens transmission within rodent populations. Submitted manuscript.

III Cayol, C., Giermek, A., Gómez-Chamorro, A., Hytönen, J., Kallio, E.R., Mappes, T., Salo, J., Voordouw, M.J., Koskela, E. 2017. The Lyme disease pathogen alters breeding success in a rodent reservoir host. Submitted manuscript.

IV Cayol, C., López-Sepulcre, A., Fenton, A., Koskela, E., Kyröläinen, S., Mappes, T., Sironen, T., Vapalahti, O., Kallio, E.R. 2017. Coinfection dynamics of Puumala hantavirus and vector-borne pathogens in the reservoir host: A state-space modelling approach. Manuscript.

1 INTRODUCTION

1.1 Epidemiology & ecological epidemiology

1.1.1 Epidemiology

The concept of epidemiology appeared in the scientific literature in the early 1870s and was defined as a 'method of reasoning about disease phenomena that deals with biological inferences derived from observations in populations' (Lilienfeld 1978 p. 89). Epidemiological studies initially targeted humans, and progressed secondarily to productive livestock (Lilienfeld 1978, Martin *et al.* 1987). Since the early stages of epidemiology, mathematical modelling has been used for the prediction and comprehension of epidemiological issues, despite imperfect data drawn, for instance, from imperfect diagnosis tests (Nokes and Anderson 1988, Keeling 2005). The basic model in epidemiology of infectious diseases is the susceptible/infected/recovered model (SIR), which describes the transition between infectious states (Fig. 1) (Anderson and May 1979, May and Anderson 1979, Anderson 1991).

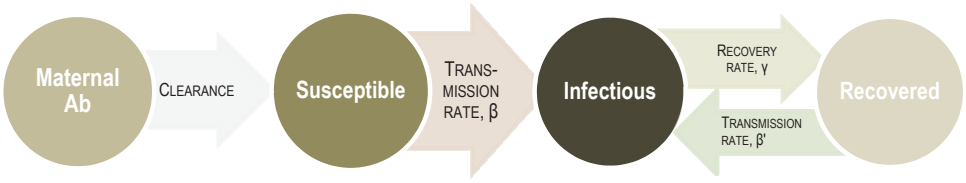


FIGURE 1 An example of the SIR model (after Anderson 1991).

Basic reproduction number (R0) is another key concept in epidemiology. R0 is the maximum reproductive potential of a parasite between one generation and the next for a given naïve host population in a given environment. For instance, for directly transmitted pathogens, R0 depends on the pathogen transmission rate, the host population size, the recovery rate, the mortality rate due to

infection and the background mortality level in the host population (Anderson 1991, Cooch *et al.* 2012, McCallum 2012).

1.1.2 Eco-epidemiology

The alterations that contribute to the development of disease take place at the molecular level, at the anatomical level, at the population level, while including interactions within and between populations, and the environment. The need for epidemiological studies to encompass all these components was theorised in the 1990s, with the emergence of the field of eco-epidemiology (Susser and Susser 1996). The environment plays a key role in the dynamics of human infectious diseases. Indeed, a large majority of pathogens can infect several host species. In particular, 60% of human pathogens are naturally maintained in an animal species, with the majority of them being found in a wild species (Taylor *et al.* 2001, Woolhouse *et al.* 2001). The dynamics of a wild host population and its pathogens are intertwined in permanent interactions (Anderson and Thresh 1988, Begon 2009). Understanding the dynamics of a pathogen in its wild host(s) and clarifying the circumstances for human exposure and infection is critical, especially in the context of fast and global environmental change (Anderson 1991, Tompkins and Wilson 1998).

In my thesis, I investigate the ecology of infectious diseases in a natural host, with an emphasis on zoonotic pathogens. The aim of my work is to understand the ecological processes that lead to the establishment and maintenance of zoonotic pathogens in their natural hosts. The host studied is the bank vole (*Myodes glareolus*), and the pathogens are the directly transmitted Puumala hantavirus, and the tick-borne pathogen *Borrelia burgdorferi* s.l.

1.1.3 The need for eco-epidemiology in an era of biological safety

After the consolidation of the germ theory of diseases in the 19th century, by Louis Pasteur and Robert Koch, the fields of bacteriology and infectious diseases rapidly evolved, creating a sense that human infectious diseases would be eradicated in the 20th century (Lederberg 2000). The discovery of antibiotics in the 20th century, the globalisation of vaccination, the development of sterilisation, and pasteurisation fostered a feeling of biological safety (Lederberg 2000, Bush 2010). However, recent developments (outlined below) have demonstrated that the issue of infectious diseases is more complex than expected and far from resolved.

One of the main uncertainties concerning the future of infectious diseases is linked with temperature variations associated with global climate change. Temperature is clearly identified as a potential driver of virulence in pathogens (Harvell *et al.* 2002, Blanford *et al.* 2003, Mitchell *et al.* 2005, Semenza and Menne 2009). Nevertheless, predicting the effect of climate change on infectious risk is challenging, and, given that the effect of warmer temperatures on hosts and pathogens are species-specific and can be divergent (Lafferty 2009), this requires in-depth studies for individual host–pathogen systems. In the case of

tick-borne pathogens (TBP), the association of a milder climate with increased deer populations might modify the geographical distribution of ticks in Northern Europe, bringing vectors and their pathogens to naïve populations (Jaenson *et al.* 2012, Medlock *et al.* 2013). The speed and intensity of human movements can favour rapid and large-scale circulation of infectious agents and vectors (Tatem *et al.* 2006, Kilpatrick and Randolph 2012). Specifically, human migrations linked with climate change are expected to cause a redistribution of pathogens (Martens and Hall 2000, Soto 2009, Black *et al.* 2011).

Moreover, socio-economic conditions can participate in the spread of infectious diseases (Godfrey and Randolph 2011). For instance, the opening of new export markets for berries and mushrooms in Central Europe have modified human behaviour, leading to increased human exposure to ticks in areas where the tick-borne encephalitis virus (TBE) is prevalent (Randolph 2010). Furthermore, several factors can result in the emergence of new infectious human diseases in an area. Real emergence occurs when pathogens affecting animal species jump the species barrier and affect humans (Cleaveland *et al.* 2001, Haydon *et al.* 2002, Woolhouse *et al.* 2005, Childs *et al.* 2007). These real emergences can occur when land-cover or land-use are altered and contacts between humans and wildlife are increased (Daszak *et al.* 2001, Bradley and Altizer 2007, Karesh *et al.* 2012, Brearley *et al.* 2013). On the other hand, geographical emergence occurs when pathogens are encountered in new areas, after introduction and acclimation of pathogens or their vectors (Randolph and Rogers 2010, Kilpatrick and Randolph 2012).

Additionally, it has been hypothesised that biodiversity loss is likely to increase the risk of infectious disease (Keesing *et al.* 2006, Wood *et al.* 2014). For example, this hypothesis was verified in North America, where an altered biodiversity increased the risk of Lyme borreliosis (Ostfeld and Keesing 2000, Logiudice *et al.* 2008). Finally, bacterial resistance to antibiotics and immunosuppressive diseases such as AIDS create conditions for the maintenance of infectious diseases (Karesh *et al.* 2012, Lewis 2012). In summary, in the 21st century, we are faced with the persistence of old infectious disease issues (*e.g.* tuberculosis), and the emergence and circulation of new infectious pathogens on a global scale (*e.g.* SARS) (Han *et al.* 2016).

1.2 A theoretical framework for infection in natural hosts

Some pathogens affect only their natural host, but the large majority of pathogens can affect several host species (Woolhouse *et al.* 2001). In epidemiology, a reservoir can be defined as 'one or more natural host populations epidemiologically connected, where the pathogen is maintained and from which the pathogens are transmitted to the "target" population, or species of concern, generally human or domestic species (Haydon *et al.* 2002 p. 1469).

Pathogens that are naturally maintained in a host population are in a dynamic balance between exploitation of the host resources and host defences. This equilibrium reflects a co-evolutionary process between the host and the pathogen (Combes 2001, Schmid-Hempel 2011, Medzhitov *et al.* 2012). The exploitation of the host resource by a pathogen (so-called pathogen virulence) and the defence deployed by the infected organism are energetically costly for the host (Schmid-Hempel 2011). They can generate fitness loss in the host that might be translated into host and pathogen population dynamics (Anderson and May 1979, May and Anderson 1979, Hudson *et al.* 2002, Cattadori *et al.* 2005, McCallum 2012, Patterson *et al.* 2013). For example, the population cycles observed in some red grouse populations are caused by the infestation with the parasitic nematode *Trichostrongylus tenui* (Hudson *et al.* 1998, Tompkins and Begon 1999, Burthe *et al.* 2006). Nevertheless, the theory of virulence predicts that optimal pathogen virulence is a moderate level of host exploitation, which allows pathogen transmission, but which does not exclude some detrimental effect to the host (Schmid-Hempel 2011). Moreover, pathogen virulence varies with host characteristics, with the pathogen itself and with the environment. The disease triangle theorises the interaction within this triad (Scholthof 2007 see Fig. 2). For example, temperature variation or resource availability can affect the host–pathogen relationship (Blanford *et al.* 2003, Wolinska and King 2009). As a result, the way a pathogen can alter the Darwinian fitness (survival and reproductive success) of its host is not absolute but can vary depending on the host and the environment. In my thesis, I explore the effect of abiotic and biotic variations on infectious diseases in a wild rodent host, with an emphasis on the host population density and parasitic coinfections.

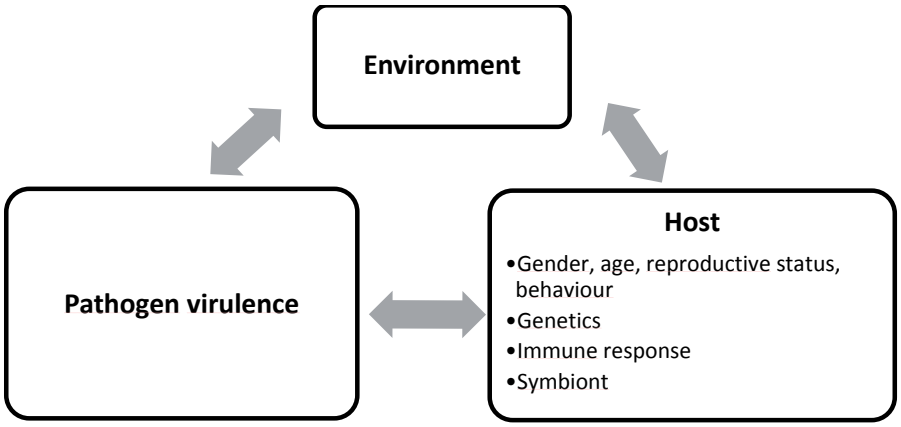


FIGURE 2 The disease triangle (after Scholthof 2007).

1.3 Coinfections

Hosts are typically infected with different parasites and pathogens that can coexist in a stable community (May and Nowak 1995, Petney and Andrews 1998). The composition of the parasite community is not random but depends on the host and the environment (Lello *et al.* 2008). Moreover, the composition of the parasite community is structured by interactions among members of this community (Petney and Andrews 1998). Ecosystem ecology gives a useful framework to study these interactions. In this approach, the host is considered as an ecosystem where various species of pathogens and symbionts interact. The host constitutes the environment, the resource and the host's immune system constitutes the predator for the species in the community (Rynkiewicz *et al.* 2015). Similar to ecosystems, resource-based interactions (*e.g.* competition for resource or space) and predator-based interactions (by the host's immune system) shape the parasite species community (Graham 2008, Telfer *et al.* 2010). Consequently, current and previous infections determine the physical and immunological environment in which a new parasite will attempt to establish (Pedersen and Fenton 2007, Behnke 2008, Telfer *et al.* 2010).

1.4 The specificities of vectorial transmission

1.4.1 Vectorial transmission

Vector-borne transmission is an indirect horizontal transmission route that involves a vector, generally a hematophagous arthropod, which transmits pathogens among hosts during its blood meal (Antonovics *et al.* 2017, Wilson *et al.* 2017). Vectors usually have a limited effect on the fitness of their hosts (Hersh *et al.* 2014, Wilson *et al.* 2017 but see Lehmann 1993, Norte *et al.* 2013). Vectorial transmission introduces a layer of complexity into pathogen transmission and dynamics. Indeed, the relationship between vectors and their pathogens is likely to influence the transmission of these pathogens to the vertebrate host (Sonenshine 1994). Vector competency, *i.e.* the ability of the vector to acquire and transmit an infection, varies with the vector species, the pathogen species and with physiological and ecological factors (Sonenshine 1994). Moreover, the population dynamics of the vector have a direct influence on the dynamics of the pathogens transmitted. Vectors are ectothermic, which means that they are sensitive to environmental conditions, and their occurrence is commonly seasonal and limited to geographical areas that offer optimal habitat, abiotic conditions and suitable hosts (Sonenshine 1994, Reisen 2010). As a result, the dynamics of vector-borne infections mostly follow the seasonality and geographical range of their vectors (Reisen 2010).

1.4.2 Ticks as vectors

1.4.2.1 Life cycle

Ticks (Acari: Ixodoidea) are considered the primary vector of infectious diseases in the Northern Hemisphere in humans and domestic animals (Sonenshine 1994, Estrada-Peña and Jongejan 1999). The superfamily Ixodoidea comprises approximately 900 species (Guglielmone *et al.* 2013). Here, we will illustrate the characteristics of ticks as vectors, with two examples of hard ticks (Ixodidae): *Ixodes ricinus*, the most important vector in Europe, and *I. trianguliceps* (de la Fuente *et al.* 2008, Pfaffle *et al.* 2013). Both species present lifecycles with three life-stages (larvae, nymphs and adults), and for both species, the transition from one stage to another requires a blood meal on a vertebrate host. *Ixodes ricinus* is a generalist or bridge species, which feeds on various hosts (see Fig. 3), whereas all stages of *I. trianguliceps* feed on small mammals (Cotton and Watts 1967, Ulmanen 1972, Randolph 1975a, Gray 1982, Dobson *et al.* 2011, Schmidt *et al.* 2011). The monitoring of small vertebrate species provides an insight into the dynamics of immature life-stages of *I. ricinus* (Pfaffle *et al.* 2013).

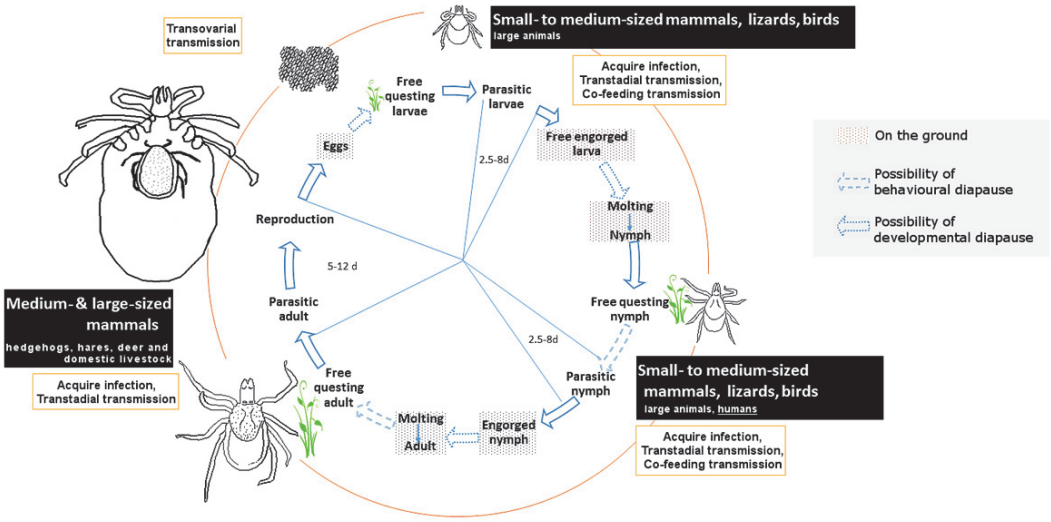


FIGURE 3 *Ixodes ricinus* life cycle (drawn based on Gray 1982, Randolph 1998, Estrada-Peña *et al.* 2005, Gray *et al.* 2016).

Ticks are characterised by a long lifespan (several years), but the relative length of interaction with the vertebrate host is short (Randolph 1998). As a result, a large part of the tick life cycle is spent in a free stage in the environment. In the case of *I. ricinus*, the environment is the vegetation (during the host-seeking phase, so-called "questing") or the soil or litter (during the moulting, diapause or rehydration phases). When *I. trianguliceps* are in the free stage, they live inside rodents' burrows (Cotton and Watts 1967, Randolph 1998, Dobson *et al.* 2011). Ixodid ticks have very limited mobility, and their dispersion relies mainly on their host (Randolph 1998). They are extremely sensitive to abiotic

conditions, such as temperature (which determines their development rate) and humidity (which determines their survival), and depend on host availability (Daniel *et al.* 1977, Randolph and Storey 1999, Estrada-Peña *et al.* 2004, Ogden *et al.* 2004, Randolph 2004). As a result, their occurrence in time and space is extremely scattered (Estrada-Peña 2003, Randolph 2004, Dobson *et al.* 2011, Perez *et al.* 2016). When abiotic conditions are not favourable, Ixodid ticks can enter diapause, which delays their activity (and infectious potential) for several months or even years (Gray 1982, Belozerov *et al.* 2002, Ogden *et al.* 2004, Gray *et al.* 2016).

1.4.2.2 Hosts and pathogens

The distribution of ticks in their host population is not random: generally, 20% of the host population carries 80% of the tick population (Randolph 1975b, 2009, Randolph *et al.* 1999). Indeed, host sex, age and immunological status, fitness and behaviour modify the exposure and susceptibility to ticks (Nilsson 1988, Hughes and Randolph 2001, Randolph 2009, Harrison and Bennett 2012). Pathogen transmission occurs during the blood meal from a contaminated host to a tick and from a contaminated tick to a naïve host. Moreover, co-feeding transmission, *i.e.* the transmission of pathogens between one infected tick (typically a nymph) and one naïve tick (typically a larva) feeding concomitantly on the same uninfected host, has been described (Rais and Gern 1996, Labuda *et al.* 1997, Voordouw 2015). This transmission route is essential for the persistence of pathogens with transient viremia in the host, such as that which occurs in TBE. The synchronous activity of larvae and nymphs dictates the occurrence of this pathogen in nature (Rais and Gern 1996, Labuda *et al.* 1997, Randolph 2008a, 2009, Nonaka *et al.* 2010, Voordouw 2015).

1.4.2.3 Basic reproductive number for TBP

The singularities of ticks as vectors generates many non-linearities in the tick-borne transmission route (Randolph 1998, 2008a). The basic transmission rate for tick-borne pathogens reflects these non-linearities, and highlights the need for knowledge on tick life-cycle and tick and host abundance in an area to predict the transmission of tick-borne pathogens in this area:

$$Ro = \frac{N}{H}\frac{f\beta_{VT}\beta_{TT}\beta_{TV}p^{n}F}{r+h},$$

where N/H = ratio vector to host, f = probability of a tick feeding on a vertebrate host, β_{VT} = pathogen transmission coefficient from vertebrate host to tick, β_{TT} = pathogen transmission coefficient within the tick, β_{TV} = pathogen transmission coefficient from tick host to vertebrate host, p = tick daily survival probability, n = tick interstadial development period (days), F = tick reproduction rate, h = vertebrate host daily mortality rate, r = daily rate of loss of infectivity in the vertebrate host (Randolph *et al.* 1999, Hartemink *et al.* 2008, Harrison *et al.* 2011, Tonetti *et al.* 2015).

1.4.3 Focus on *Borrelia burgdorferi* s.l.

1.4.3.1 The human disease

Lyme disease caused by *Borrelia burgdorferi* s.l. is considered the most common vector-borne disease of the Northern Hemisphere nowadays (Hubalek and Halouzka 1997, Piesman and Gern 2004, Randolph 2009). The disease was described in the 1970s in the USA, but it is suspected that it had been present in North America before the arrival of the first European settlers (Burgdorfer *et al.* 1983, Barbour and Fish 1993). In Europe, erythema chronicum migrans, a pathognomonic skin rash that expands centrifugally, was first described in 1908 by the Swedish physician Arvid Afzelius (Burgdorfer *et al.* 1983). Since then, Lyme disease has been reported in 26 European countries with variations in the type of manifestation, severity and frequency of the disease. These diverse clinical forms have been linked to the genetic diversity of the *B. burgdorferi* s.l. complex (Piesman and Gern 2004). *B. burgdorferi* s.s. shows tropism for joints and causes arthritis, *B. afzelii* is responsible for skin diseases and *B. garinii* infects the nervous system and is associated with neurological disease (Wang *et al.* 1999, Piesman and Gern 2004, Stanek *et al.* 2012). While the cycle of Borrelia is maintained in nature by hard ticks and a broad spectrum of vertebrate host species, humans are considered as dead-end hosts, and some domestic animals, such as dogs, are regarded as incidental hosts not involved in the enzootic cycle of the bacteria (Radolf *et al.* 2012). Larvae are generally disease free, hence nymphs appear to be the most effective stage for the transmission of *B. burgdorferi* s.l. to humans due to their small size and short feeding periods (Bunikis *et al.* 2004a, Stanek *et al.* 2012, Hajdušek *et al.* 2013).

1.4.3.2 The bacterium

The *Borrelia burgdorferi* sensu lato complex belongs to the spirochetes phylum, which is characterised by flagellated helically shaped bacteria (Barbour and Hayes 1986). The complex has large genetic diversity, although the genetic variation is more important in Europe compared with North America (Piesman and Gern 2004, Margos *et al.* 2011, Franke *et al.* 2013). Within the *Borrelia burgdorferi* complex, 20 genospecies have been described, and seven are involved in public health issues (Piesman and Gern 2004, Wodecka *et al.* 2010, Rudenko *et al.* 2011, Radolf *et al.* 2012, Franke *et al.* 2013). The bacteria is transmitted between vertebrate hosts by at least four species of hard ticks (Bunikis *et al.* 2004a, Radolf *et al.* 2012). Strain diversity is also described, based on the polymorphism of the outer protein OspC, for example (Brisson and Dykhuizen 2004, Bunikis *et al.* 2004a). About 20 OspC major groups (oMG) can be defined in each Borrelia genospecies, with distinct levels of pathogenicity and lack of cross-immunity between strains, which makes vaccination strategies complicated (Baranton *et al.* 2001, Bunikis *et al.* 2004b, Baum *et al.* 2012). Infection with multiple strains is common in the vertebrate host (Bunikis *et al.* 2004a, Andersson *et al.* 2013, Durand *et al.* 2015).

1.4.3.3 Ecological epidemiology

The occurrence of Lyme disease in an area requires the presence of competent vectors and competent wild reservoir hosts (Barbour and Hayes 1986, Gray 1998). The maintenance of Borrelia in nature is permitted by permanently infected hosts and overwintering ticks (Bunikis *et al.* 2004b). In the tick vector, the infection is maintained transtadially, but there is no transovarial transmission (Bellet-Edimo *et al.* 2005). The observed rate of infection in nymphs is 25%, and it is 50% in adult ticks, which can acquire infection from the nymph stage or can retain it from the larval stage (Barbour and Fish 1993, Randolph 2009). Species community structure is critical when defining the risk of Lyme disease in an area. Rodents, insectivores and birds are keystone species in Borrelia transmission and maintenance (Franke *et al.* 2013). In the rodent host, the infection with Borrelia is permanent, and it generates an early (IgM) and late and permanent (IgG) immune response (Magnarelli *et al.* 1988, 1997, 2006, 2013, Schwan *et al.* 1989). Medium- and large-sized mammals can also be involved in the cycle. Lizards play the main role in the cycle of *B. lusitaniae*, whereas the rodent-associated *B. afzelii* has also been detected in bird-feeding ticks (Kurtenbach *et al.* 1998, Gern 2008, Franke *et al.* 2013).

The presence of species competent for ticks but incompetent for borrelia modifies the prevalence of the bacteria in ticks, as well as the presence of enzootic cycles involving other non-bridge vector species (Barbour and Fish 1993). For example, deer are important hosts for the dynamics of ticks but are incompetent for Borrelia; therefore, they have a negative impact on Borrelia prevalence in questing ticks (Tälleklint and Jaenson 1996a, Franke *et al.* 2013). Because of variation in host competence in Borrelia, the concept of the dilution effect was defined as the reduced infection prevalence in ticks found in ecosystems with high species diversity. As a result, high species diversity reduces the risk of disease for humans (Ostfeld and Keesing 2000, LoGiudice *et al.* 2003, Keesing *et al.* 2006).

1.5 The bank vole as a reservoir

1.5.1 Why rodents?

Rodents are efficient reservoirs of zoonotic pathogens, with around 11% of rodent species carrying 85 unique zoonotic pathogens (Meerburg *et al.* 2009, Han *et al.* 2016). Moreover, around 40% of rodent reservoir species are considered hyperreservoirs, *i.e.* they carry more than one zoonotic pathogen (Han *et al.* 2015). This overrepresentation of rodents in reservoir species is explained by the large species richness found in the order and by their ubiquitous distribution favouring frequent contact with humans (Han *et al.* 2015, Meerburg 2015). Within the order, species with fast life-history and early and frequent reproduction are the most efficient reservoirs of zoonotic pathogens (Han *et al.* 2015, 2016).

1.5.2 The bank vole

The bank vole, *Myodes glareolus*, is a ubiquitous rodent species widely distributed in western Palearctic forests from France to Central Asia and from Southern Spain to South-West Ireland (Wilson and Reeder 2005). Bank voles occupy a wide range of habitats, but they are commonly found in woodland with dense plant cover, which provides food and shelter against predators (Tanton 1969, Mazurkiewicz 1994, Bellamy *et al.* 2000, Torre and Arrizabalaga 2008). In Northern Europe, they inhabit coniferous spruce forests where they feed mainly on epiphytic lichen and to a lesser extent on berries and seeds (Viro and Sulkava 1985). Classified as least concern in the IUCN Red List of Threatened Species (Amori *et al.* 2008), the bank vole is considered as a potential pest in many European countries, due to damage to seeds and young trees (Hansson and Zejda 1977, Huitu *et al.* 2009). Bank voles are polyandrous, and females optimise their fitness by mating several times and with high-quality males (Oksanen *et al.* 1999, Ratkiewicz and Borkowska 2000, Klemme *et al.* 2007, 2008, Borkowska 2010). In Fennoscandia, reproduction takes place from mid-May to mid-September, and young females can postpone their reproduction to the next breeding season (Cayol *et al.* unpub., Wiger 1979, Kaitala *et al.* 1997, Prévot-Julliard *et al.* 1999, Koivula *et al.* 2003, Kallio *et al.* 2015). Male bank voles have large home ranges that connect with other male home ranges and that cover the territories of several females. Females are mainly territorial, and their territories can be contiguous but do not overlap (Bondrup-Nielsen and Karlsson 1985, Ims 1987, Koskela *et al.* 1997).

1.5.3 Population dynamics

In some regions of their geographic range, bank vole populations show large cyclic fluctuations of their population size (Middleton 1930, Krebs and Myers 1978, Hansson and Henttonen 1985). A north–south geographic gradient in regularity and amplitude of these fluctuations variation has been described, with the northernmost Fennoscandian populations showing the highest amplitude of fluctuations (Hansson and Henttonen 1985, Hansson *et al.* 2000). cduring the decline phase of a cycle might participate in the reduction of population abundance directly, or through interactions with predators or food supply (Soveri *et al.* 2000, Hakkarainen *et al.* 2007, Huitu *et al.* 2007, Forbes *et al.* 2015). The mechanism of the cycle consists of lower survival in young individuals between the peak and decline phases of the cycle in late summer and early autumn (Norrdahl and Korpimäki 2002). Recently, an attenuation in the intensity and amplitude of the cycles has been observed in several cyclic populations (Ims *et al.* 2008, Cornulier *et al.* 2013).

1.5.4 Population dynamics & reservoir competence

My thesis tackle the eco-epidemiology of the Puumala hantavirus (PUUV), a zoonotic virus hosted by the bank vole, which is responsible for haemorrhagic

fever with renal syndrome in humans (Brummer-Korvenkontio *et al.* 1980, Vapalahti *et al.* 2003). Moreover, more than 100 species of ectoparasites have been found in small mammals in Fennoscandia, including ticks and fleas (Brinck-lindroth *et al.* 1975). My study focuses on *Borrelia* spp., presented above, and on three other vector-borne pathogens: *Anaplasma phagocytophilum*, *Babesia microti*, *Bartonella* spp. The genus *Bartonella* encompasses a large group of proteobacteria that can be transmitted through both flea and tick bites (Bown *et al.* 2004, Chan and Kosoy 2010, Reis *et al.* 2011, Buffet *et al.* 2013). The bacteria cause transient infection of erythrocytes (Bown *et al.* 2004, Telfer *et al.* 2007). *Anaplasma phagocytophilum* is a Gram-negative obligate intracellular bacteria from the family Anaplasmataceae (Doudier *et al.* 2010, Rar and Golovljova 2011). *Anaplasma phagocytophilum* has the ability to manipulate or highjack the host immune response and can then thrive inside the immune cells. The main cells targeted are neutrophil granulocytes, the first line of the innate immune response against infectious diseases (Bown *et al.* 2003, Kumar and Sharma 2010, Rikihisa 2010, Rar and Golovljova 2011). The protozoa *Ba. microti* causes permanent infection in erythrocytes (Chauvin *et al.* 2009, Yabsley and Shock 2013).

The potential role of infectious diseases on their host population density has been discussed above. However, the way a disease will develop and affect a host (or level of pathogen virulence) in a particular host population density also deserves attention from disease ecologists. First, the transmission of many pathogens is density-dependent (Anderson and May 1979). Second, a high host population density can generate intra-specific competition for limited resources, such as space, food and mating partners (Krebs 1970, Ostfeld 1985, Ostfeld *et al.* 1993, Bown *et al.* 2009). Therefore, in a high population density, more aggressive interactions and higher stress levels are expected (Wolff 1993, Koskela *et al.* 1997, Bartolomucci 2007, Kallio *et al.* 2007, Forbes *et al.* 2016). High host density is therefore expected to exacerbate pathogen virulence (Kallio *et al.* 2007, 2015, Burthe *et al.* 2008, Beldomenico and Begon 2010). A possible vicious circle between host condition (linked, for example, with population density) and disease susceptibility has been highlighted (Beldomenico and Begon 2010). However, Wilson *et al.* (1998, 2002) have demonstrated the opposite assumption in insect species. For this hypothesis, natural selection should favour individuals that invest more in mechanisms of resistance as population density increases. Consequently, susceptibility to disease should decline when population density is high (Wilson and Reeson 1998, Wilson *et al.* 2002).

1.5.5 The PUUV

Puumala hantavirus (PUUV; genus Hantavirus, family Bunyaviridae) is a zoonotic virus occurring in large part of Europe and western parts of Russia (Vapalahti *et al.* 2003, Olsson *et al.* 2010, Heyman *et al.* 2011). The genus Hantavirus contains species associated with different species of micromammals from all continents excepted the Oceanian region (Henttonen *et al.* 2008,

Yanagihara *et al.* 2014). Around 20 species from the genius are considered as zoonotic (Jonsson *et al.* 2010).

Every year, thousands of human cases of nephropathia epidemica, a mild form of haemorrhagic fever with renal syndrome, are recorded in human in Europe (Brummer-Korvenkontio *et al.* 1980, Vapalahti *et al.* 2003). The disease is endemic to Northern Europe, with between 1500 and 2000 human cases reported in Finland every year (Rose *et al.* 2003, Vapalahti *et al.* 2003). The disease pattern reflects the host population dynamics: epidemic events follow rodent outbreaks (Mills and Childs 1998, Olsson *et al.* 2003, Davis *et al.* 2005, Kallio *et al.* 2009, Voutilainen *et al.* 2016). Because of possible complication during the acute phase of the disease and long term complications, the impact of PUUV on public health is non-negligible (Makary *et al.* 2010, Vaheri *et al.* 2013).

In the rodent host, the virus is horizontally transmitted, by the respiratory route or direct contact (Meyer and Schmaljohn 2000, Vapalahti *et al.* 2003). Direct and indirect contacts between individuals, resulting from *e.g.* mating, aggressive encounters, communal nesting or high population density increase the likelihood of PUUV infection (Escutenaire *et al.* 2002, Olsson *et al.* 2002, Voutilainen *et al.* 2016). Since viral particles can persist in the environment for several weeks, transmission can also be delayed (Kallio *et al.* 2006a). Individuals remain infected for their lifetime, and infected individuals mount a lifelong antibody response, which peaks 4–5 weeks after infection (Yanagihara *et al.* 1985, Voutilainen *et al.* 2016). Protective maternal antibodies postpone infection in young individuals for up to 80 days (Kallio *et al.* 2006b, 2010, 2013, Voutilainen *et al.* 2016).

1.6 Aim and scopes of the thesis

The global scope of my thesis is the ecology of infectious and parasitic diseases in nature, with an emphasis on zoonotic pathogens. My ultimate goal is to inform about the zoonotic risk and to generate epidemiological knowledge for public health purposes. In this respect, this work can be seen as part of the One Health initiative, an integrative framework that aims to reduce the risk of infectious diseases at the animal–human–ecosystem interface (Zinsstag *et al.* 2011, Dantas-Torres *et al.* 2012). My thesis focuses on host–parasite interactions and on the ecological processes that lead to the establishment and maintenance of pathogens in their natural hosts. This work will therefore contribute to the understanding of infection dynamics in a wild host, in relation to seasonal biotic, abiotic variation and cyclic fluctuations of the host population. Ubiquitous rodents such as voles are ideal species for epidemiological studies. They feed several ectoparasite species and host a large range of potentially zoonotic micro-pathogens, including vector-borne pathogens. The geographical repartition of the main European tick vector is undergoing both short- and long-term changes particularly visible on the northern edge of its distribution,

for instance, in Northern Europe. My study contributes to the understanding of these dynamics in Fennoscandia, at the edge of geographical range of the main European tick species.

With this in mind, in the first chapter of the thesis, I identify the tick species present in the vegetation and on bank voles in our study area of Central Finland. I explain their temporal dynamics, while taking into account abiotic variation and host population dynamics. I discuss similarities between our study system and the nearest systems studied (Southern Finland and Southern Sweden) (Tälleklint and Jaenson 1997, Sormunen *et al.* 2016, Laaksonen *et al.* 2017). Since studies concerning ticks in Finland are scarce, I contribute to the knowledge of the dynamics of tick vectors in Fennoscandia.

Since the first chapter characterised the tick species present, in the second chapter of this thesis, I explain the local distribution of the two tick species found in our study area, with respect to habitat characteristics and anthropic pressures. Vector diversity and interactions between coinfesting ectoparasites can impact pathogen diversity (Cumming and Guégan 2006); I thus elucidate the consequences of co-existing vector species for the circulation of several vector-borne pathogens, especially the zoonotic pathogen *Borrelia burgdorferi* s.l., in the rodent host.

In the third chapter of the thesis, I test experimentally the hypothesis that the infection with *Borrelia afzelii* can impair the fitness of its natural host. In doing so, I shed new light on the intimate relationship between the TBP *B. afzelii* and its rodent host. Parasites take advantage of the resources of their hosts and can therefore impair the fitness of their host. As a result, they exert a selection pressure on the host population. Moreover, altering the host fitness might modify the dynamics of the pathogen itself. In this chapter, I clarify the consequences of the infection with *B. afzelii* on the fitness of its main rodent host, the bank vole, in varying environmental conditions.

In the fourth chapter of the thesis, I acknowledge that single infections rarely exist in nature and that most hosts are infected with several pathogens simultaneously. Concomitant infections modify the physical and immunological framework in which a new pathogen will attempt to establish (Telfer *et al.* 2008, 2010). I address the risk of infection of the bank vole with the Puumala hantavirus, an endemic zoonotic virus in Finland, while taking into account preceding infection status with ticks, fleas and three vector-borne pathogens. The study of coinfection is challenging, and there is a dire need for new analytical tools. I propose a state-space model with a Bayesian approach, a thus-far underused technique in the study of coinfections.

2 METHODS

2.1 Longitudinal capture-mark-recapture (CMR)

There are several advantages to repeating capture and sampling of identified individuals from a population over time (so-called individual longitudinal sampling) (Clutton-Brock and Sheldon 2010). This sampling strategy controls for genetic variability and removes some inter-individual noise (Cohen *et al.* 2015). Moreover, longitudinal trapping reflects causality well, as the observation at a given sampling point can be related to previous observations (Telfer *et al.* 2008, Cohen *et al.* 2015). These trapping strategies are indispensable in disease ecology to unravel patterns of pathogen transmission in the natural environment, as an alternative to or together with experimental infections (Hofmeister *et al.* 1999, Birtles *et al.* 2001, Bunikis *et al.* 2004b, Telfer *et al.* 2007, 2008, Behnke 2008, Fenton *et al.* 2014). New tools, such as Markov models or state-space models, allow hidden processes responsible for the observations to be inferred from this longitudinal data (Clark and Bjørnstad 2004, Cooch *et al.* 2012, Buhnerkempe *et al.* 2015).

Chapters I, II and IV of my thesis are based on longitudinal field monitoring of wild populations of bank vole populations from Central Finland. Chapter I is based on a four-year longitudinal rodent monitoring study in urban forests (2012–2015). Chapter II analyses data from a one-year longitudinal rodent monitoring study in urban and semi-urban forests (2012). Chapter IV was based on a two-year longitudinal monitoring study, but only one year is included in the analysis (See also Fig. 4). All trappings took place between snow melt (May) and first snow (November).

In all longitudinal monitoring studies, bank voles were live-trapped with Ugglan Special multiple-capture live traps (Grahnab Company, Sweden) monthly (or every 4 weeks in study IV). Each trapped individual was identified with a microchip inserted under the skin at the first capture. Biometric measurements were taken at each capture. These consisted of body mass and head width measurements. Each individual was sampled for blood and tissue.

Ectoparasite presence and abundance were assessed (ticks and fleas). In Chapters I and II, all the ticks identified from the fur were removed and stored in alcohol. In study IV, ticks were counted but not removed. Thereafter, all trapped individuals were released back to their capture area.

In addition, questing ticks were collected from the vegetation using the flag dragging technique in Chapters I and II. All ticks collected (from voles or vegetation) were identified to species and life-stage levels under a binocular microscope, using standard morphological identification keys (Arthur 1963, Filippova 1977, Snow 1978).

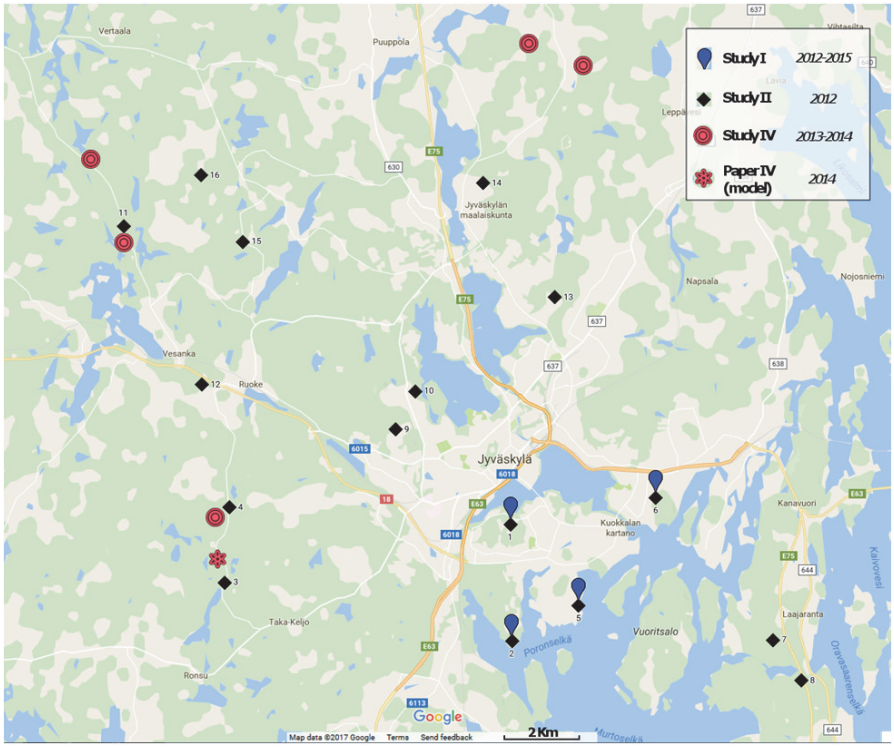


FIGURE 4 Summary of the longitudinal trappings, with locations (Map data2017 Google).

2.2 Pathogens identification

Laboratory screening was performed from the samples collected for the detection of infection with PUUV, *A. phagocytophilum*, *Ba. microti*, *Bartonella* spp. and *B. burgdorferi* s.l. The detection of PUUV relied on an indirect test, based on antibody detection. DNA of *A. phagocytophilum*, *Ba. microti*, *Bartonella* spp. was detected from DNA extracted from blood or skin samples (See Table 1).

TABLE 1 Laboratory techniques used for the detection of pathogens from bank voles.

Pathogen	Sample; DNA extraction	Detection method	Reference
PUUV	Whole blood; No DNA extraction	immunofluorescent antibody test (IFAT)	(Kallio-Kokko *et al.* 2006)
A. phagocytophilum	Whole blood; alkaline extraction, dilution (1:50) (Bown *et al.* 2003)	qPCR	(Courtney *et al.* 2004)
Ba. microti	Whole blood; alkaline extraction, dilution (1:50) (Bown *et al.* 2003)	qPCR	(Bown *et al.* 2008)
***Bartonella* spp.**	Whole blood; alkaline extraction, dilution (1:50) (Bown *et al.* 2003)	qPCR	(Diaz *et al.* 2012)
***B. burgdorferi* s.l.**	Skin; Laird extraction (Laird *et al.* 1991)	nested PCR	(Wodecka *et al.* 2009)

2.3 Covariates and modelling

In Chapter I, the abiotic conditions during tick flagging days (daily average humidity (in percent) and daily average temperature (in °C)) were collected. Data originated from records at the nearest meteorological station located few kilometres from the study sites. We modelled the abundance of tick life stage by tick species on rodents and in the vegetation with general linear mixed models (GLMM), as a function of seasonality (Month and Year) or abiotic conditions during flagging, of bank vole abundance, and of abundance of other life stages. We modelled the tick burden on bank voles while taking into account season, individual bank vole characteristics, the presence of other ectoparasite species or life-stages, and bank vole abundance.

For Chapter II, infection with *A. phagocytophilum*, *B. microti* and *B. burgdorferi* s.l. were detected. Pathogens detection was cross-sectional and occurred only at the first capture. Moreover, we computed the inland open water coverage (in ha) or "open water coverage" around the trapping area (including lakes, ponds and rivers) in a circular area with a 1 km radius (3.14 km2) around each trapping area. Within the same circular area, we computed the "human density" in humans per km^2, using the database LandScan (Dobson *et al.* 2000). We used a GLMM to model the relationship between questing tick abundance, human density and open water coverage in an area. We also explained tick parasitism on bank voles with the same covariates. At the individual level, we explained tick presence and infection on bank voles with the three pathogens mentioned above, especially with *B. burgdorferi* s.l., with individual characteristics (sex, body mass), presence of the two tick species found and presence of other pathogens.

In Chapter IV, the infection status with PUUV, *A. phagocytophilum*, *Ba. microti*, *Bartonella* spp. and tick and fleas was detected at each capture for each individual. A state-space model was computed. The model contained two layers. First, an observation level: for instance, the capture of an individual at session *t* infected or uninfected, according to the results of the diagnosis test.

Second, a process level, including hidden processes such as the transmission of pathogens from their vectors and assay performance. The processes were based on SI models for infections and infestations. These models allowed the inference of the likelihood of infection with PUUV at time *t* knowing infection and infestation statuses with other pathogens at *t-1*. Moreover, transmission rates of all pathogens, recovery rates, trappability and survival were assessed. Finally, prevalence and incidence (for permanent infection) were also derived from the model.

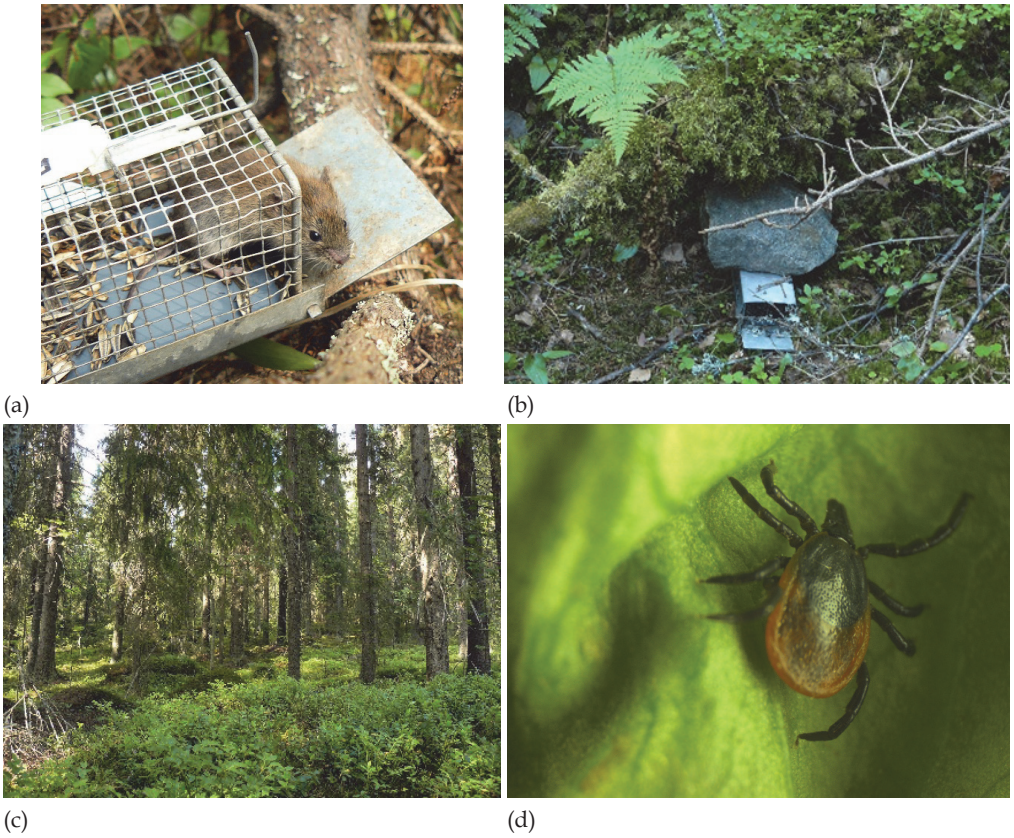
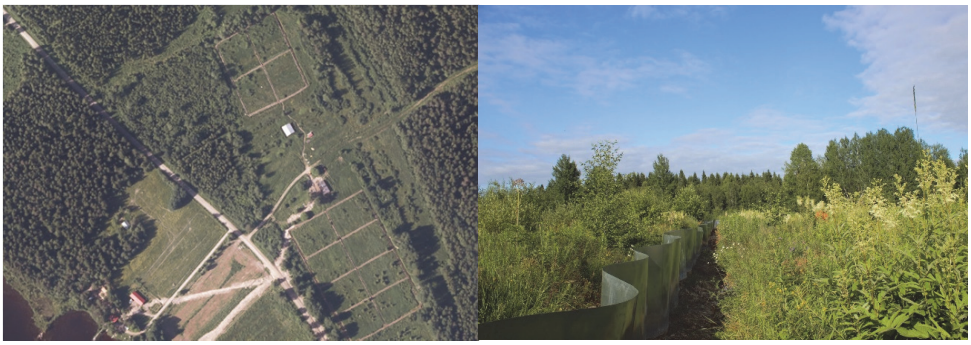


FIGURE 5 (a) Wild-caught bank vole released in its capture area after measurements and sampling. (b) Ugglan Special multiple-capture live-traps, prebaited 2 to 3 days before capture to optimise trapping efficiency. (c) Typical spruce dominated forest. (d) Questing Ixodes tick. (Photographs by C. Cayol).

2.4 Experimental infection in semi-natural conditions

In Chapter III, we experimentally infected adult bank voles from a laboratory colony with *Borrelia afzelii*. We monitored infected and uninfected individuals (sham-treated) released in vegetated outdoor enclosures for 18 days, in high

and low population densities. We monitored survival, physiological parameters (body mass, body fat content, ankle width, haematocrit and Borrelia IgG antibody concentration), reproductive success ('probability of reproduction', 'male siring success', 'male fertilization success', 'female whelping success', 'female polyandry index' and 'parturition delay') and home range size for each individual. We explained the impact of infection and varying population density on these factors in GLMMs and LMMs (linear mixed models).



(a) (b)

FIGURE 6 (a) Aerial view of the outdoor enclosures used in the experimental infection (Pukara, Konnevesi, Finland, from https://www.retkikartta.fi/). (b) Fence between two enclosures (By C. Cayol).

3 COMMENTED RESULTS

3.1 The risk periods for ticks in urban forests

Ixodes ricinus was the only species found in the vegetation. Larvae were mostly found in June. Nymphs as well as nymphs and females were the most abundant in May–June and September. This defines the highest risk periods for tick bites on humans in the area. Questing adults (males and females) were more abundant in May–June and August–September, and their abundance varied between years (Chapters I, II).

Two tick species parasitised bank voles: *I. trianguliceps*, the vole tick and *I. ricinus*. Approximately 76% of hosts were infested with ticks. We found that *I. ricinus* larvae were the most abundant on bank voles in June, but inter-year fluctuations were revealed by the model. Bank vole infestation with *I. ricinus* nymphs was maximal in May and did not show inter-year fluctuations (Chapter I). In Chapter II, in which 16 sites were studied, we found a marked uneven spatial distribution of *I. ricinus* on bank voles, whereas *I. trianguliceps* showed an even distribution.

Overall, our data might indicate that for *I. ricinus*, the life-history strategy observed in our study area consists of an early summer blood meal for larvae followed by postponed activity until the next spring when nymph emergence is observed after a behavioural diapause (Tälleklint and Jaenson 1996b, Randolph 2004, Dobson *et al.* 2011) (Chapter I). Moreover, our study shows synchronous early summer questing activity between larvae and nymphs, which is relevant from an epidemiological point of view, especially for pathogens transmitted by co-feeding (Chapter I).

3.2 The distribution and occurrence of two tick species explained

The abundance of larvae and nymphs in the vegetation was positively associated with bank vole abundance. This positive relationship might arise

from better engorgement success for larvae in high bank vole abundance, but it remains unclear for nymphs. Moreover, variations in abiotic conditions modified the abundance of questing larvae and adults. The abundance of larvae was explained with the abundance of adults in the vegetation in the previous flag dragging session. Nymph and adult abundance increased simultaneously (Chapter I).

In Chapter II, we found that the abundance of questing *I. ricinus* adults and nymphs was further explained by the total water coverage and the human population density in the area. These areas might constitute the first steps of a recent spread of *I. ricinus* in the region. The area was considered as part of the edge of the distribution of the species in Finland as early as 1961 (Öhman 1961), while a recent survey provided evidence for the occurrence of Ixodes ticks up to 550 km north of our study area (Laaksonen *et al.* 2017). It can be hypothesised that areas with large open water, thus able to offer favourable moisture conditions, are more likely to be colonised (Gray 1998, Gray *et al.* 1998, Bunnell *et al.* 2003). Moreover, several anthropic modifications linked with human settlements are favourable to tick establishment, including increased temperature (Gallo *et al.* 1996, Bradley and Altizer 2007), garden resource provisioning for important hosts such as deer (Kilpatrick and Spohr 2000), and lower species diversity, favouring ubiquitous species such as rodents (Bradley and Altizer 2007, Brearley *et al.* 2013).

Infestation of bank voles with *I. ricinus* nymphs and larvae was positively associated with bank vole abundance. Moreover, infestation with larvae was positively associated with the number of questing larvae observed in the environment, but this relationship was not observed for nymphs, confirming that small rodents are the main host for larvae, but not nymphs, in our study area (Chapter I). Infestation with *I. ricinus* increased with age (in a nonlinear manner for nymphs), and males were more frequently infested than females. Coinfestation with other life stages of *I. ricinus* or *I. trianguliceps* increased the likelihood of infestation (Chapter I). The aggregation of species and life-stages on the rodent host is particularly relevant to pathogen transmission: pathogen transmission from infected nymphs to susceptible larvae can occur via simultaneous feeding on the same host, even without systemic infection of the host. This co-feeding transmission pathway is important for several zoonotic TBP, especially those with short-lived or non-systemic infections in the rodent host, such as *A. phagocytophilum* or tick-borne encephalitis virus (TBEV), respectively (Randolph *et al.* 1996, 2000, Randolph 2008b, Harrison and Bennett 2012). In Chapter II, we found that the probability of infestation with *I. trianguliceps* larvae was highest in the youngest individuals, whereas nymphs infested males more frequently. We further found that open water coverage in the area was positively correlated with the burden of bank voles with *I. ricinus* but not with *I. trianguliceps*.

3.3 Vector diversity alters pathogen occurrence

Infestation with *I. trianguliceps* mainly concerned young bank voles, whereas older individuals were more likely to be infested with *I. ricinus* (Chapter I and II). Moreover, old male bank voles were the most susceptible to be infected with *B. burgdorferi* s.l. The infection was associated with the general abundance of *I. ricinus* observed at the site, but *I. trianguliceps* infestation decreased the probability of being infected with *B. burgdorferi* s.l (Chapter III). In addition, *B. burgdorferi* s.l. infection did not show any relationship with *A. phagocytophilum* or *Ba. microti* infections, whose local strains have been shown to be transmitted by *I. trianguliceps* (Bown *et al.* 2008, Kallio *et al.* 2014). Our results do not exclude that *I. trianguliceps* may contribute to the transmission of *B. burgdorferi* s.l. among rodent hosts (Hubbard *et al.* 1998). However, another tick species, such as *I. ricinus* or *I. persulcatus* is required to support the transmission and persistence of this pathogen (Kovalevskii *et al.* 2013, Korenberg *et al.* 2015).

3.4 *B. afzelii* impairs the rodent host fitness

For the first time, we show evidence of altered fitness in a natural host infected with *B. afzelii*. We found that large uninfected male bank voles had significantly higher mating success than large *B. afzelii*-infected males (Chapter III). Moreover, effects of infection on male reproductive success were observed in the low population density: infected males sired a lower proportion of offspring and fertilised a lower proportion of females than control males. Moreover, in the low-density treatment, the home range surface of infected males was much smaller compared to uninfected individuals. This density-dependent cost of infection at low population density suggests that uninfected males invested more energy to explore a larger home range than infected males. As female bank voles are territorial and hyperdispersed (Ostfeld 1985, Erlinge *et al.* 1990, Wolff 1993, Koskela *et al.* 1998), the uninfected control males may encounter and mate with more females compared to the infected males. Furthermore, infected females reproduced 2.9 days earlier than uninfected females independently of the population density. The terminal investment hypothesis might explain the faster reproduction in females (Chapter III).

On the other hand, we found that infection with *B. afzelii* had little effect on host survival, body mass or body fat percentage. Typical symptoms of infection, such as swollen joints or haematocrit variation, were not observed (Chapter III).

3.5 Coinfection matters

The best model explaining the probability of contracting PUUV at time *t* was the model that took into account the infection status with *A. phagocytophilum* and vectors (ticks or fleas) at time *t-1*. Based on our finding (Chapter IV), the probability of becoming infected with PUUV is the lowest in individuals that were previously infested with ectoparasite but not infected with *A. phagocytophilum*. In individuals infected with *A. phagocytophilum*, the presence of vectors did not modify the probability of becoming infected with PUUV. In individuals previously infected and uninfested, the probability of contracting PUUV was similarly high.

The incidence rate and prevalence of PUUV showed the same patterns in males and females. In particular, the prevalence was highest at the beginning of the study period and decreased steadily during the monitoring period. Some macroparasitic infections have been shown to alter the susceptibility to microparasites. Indeed, the Th2 immune pathway triggered by some macroparasites, such as ticks and fleas, and the Th1 pathway triggered after many microparasite infections are antagonistic (Cox 2001, Kovář *et al.* 2002, Fenton *et al.* 2008, Skallová *et al.* 2008). Our results might suggest that the Th2 path response observed against ticks might be effective in reducing infection risk with PUUV, and open another avenue for research on this issue.

In summary, while the critical need for new analytical tools and high-quality datasets in the study of the effect of parasite communities on transmission risk is expressed, in Chapter IV, we demonstrated the utility of the Bayesian state-space model for studying coinfection (LaDeau *et al.* 2011, Cooch *et al.* 2012, Buhnerkempe *et al.* 2015). Hidden processes were revealed: infection rates, recovery rates and survival were inferred by the model.

4 CONCLUSION AND FUTURE DIRECTIONS

My thesis shows that in Northern European urban forests, the population dynamics of bank voles and questing *I. ricinus* larvae and nymphs are related, suggesting higher tick abundance and, consequently, a higher risk of TBP for humans during the rodent population peak. Moreover, larvae and nymphs showed synchronous activity in the vegetation and on voles. These conditions are prerequisite for the maintenance of pathogens such as TBEV. However, our study area presents a low caseload of locally acquired TBE in humans. Between 1996 and 2017, only three cases of TBE were recorded, whereas the number of cases of Borrelia infection detected and recorded for Central Finland was 348 (Anon 2017). Therefore, other parameters, for instance, a tick abundance threshold, could be explored to understand the so far absence of TBEV in this area. Theoretical modelling and between-systems comparisons might be necessary to address this point.

We propose that anthropogenic factors affect the patchy distribution of *I. ricinus* and that *I. trianguliceps* alone is not sufficient to support the circulation of *B. burgdorferi* s.l. in the rodent host populations (Chapter II). These results need to be considered when planning public health policies, by increasing awareness of the general public to the risk of tick bites in urban areas, close to open water. Moreover, an avenue for research is the study of cross-immunity between these tick species (reviewed by Nelson *et al.* 1977). The effect of an early bank vole exposure to the nidicoulous *I. trianguliceps* on late exposure with *I. ricinus* requires attention, as it could impact the basic reproductive number of tick-borne pathogens transmitted by *I. ricinus*.

The demonstration of a cost of infection of Borrelia pathogens is relevant for understanding the evolution of resistance in vertebrate reservoir hosts. Indeed, recent field studies of bank voles have suggested that a genetic polymorphism for a receptor of the innate immune response (the toll-like receptor 2, TLR2), is associated with a varying level of resistance to *B. afzelii* (Tschirren *et al.* 2011, 2013). A study of the TLR2 polymorphism in bank vole populations across Europe found that the resistance allele against *B. afzelii* (C2) was more common in countries with a high incidence of human Lyme disease

(Tschirren 2015). Our demonstration that infection with *B. afzelii* reduces host fitness reinforces the hypothesis that this pathogen drives selection on the TLR2 gene in bank vole populations.

Moreover, a deeper exploration of the effect of Borrelia infection on sexual selection, suggested by our study, is needed. When infected, individuals able to afford the cost of both infection and reproduction were small males, but these individuals are not favoured by sexual selection when they are uninfected (Boratyński and Koteja 2009). A mate choice experiment could determine the outcome of male–male competition and female choice between infected and uninfected individuals. Furthermore, the predation risk by small carnivores generally increases with vole mobility (Norrdahl and Korpimäki 1998). By affecting home range size, infection with *B. afzelii* could reduce predation risk by small carnivores in male bank voles. This directional predation would not affect bank vole population dynamics, but it might increase the infection prevalence within a bank vole population.

We have considered the effect of Borrelia infection in isolation and without the tick vector. For the sake of completeness, our study would require either an experimental infection with the tick vector or the capture of naturally infected and control individuals. Both cases raise some experimental issues. In the first case, as the transmission from tick to bank vole is not systematic, the experimental set-up would require a large sample size to ensure enough infected individuals. In the second case, the variation in infection "age" and strain diversity in wild-caught individuals could be a source of variability and reduced statistical power. Moreover, we have considered the effect of the early stages of a Borrelia infection of one particular strain (oMG 3). A similar study could be performed with individuals in a chronic stage of infection and infected with other strains, and even coinfection with several strains could be considered.

We advocate for the use of state-space models in coinfection studies. These models also allow the estimation of hidden processes (so-called "epidemiological dark-matter"), such as missing data, lack of capture or uncertainty in the detection of pathogens (Lachish *et al.* 2011, Strelioff *et al.* 2013, Viana *et al.* 2014, Buhnerkempe *et al.* 2015).

Furthermore, to be comprehensive, the study of a catholic tick species such as *I. ricinus* requires the integration of other vertebrate species that participate in the tick life cycle. The involvement of migratory birds and seabirds in the circulation of Borrelia (Dietrich *et al.* 2011), as well as in the introduction of new strains should be considered. The abundance and the role of deer, other rodent species, hedgehogs, lagomorphs and wild carnivores could be assessed in our system for example with GPS or ratio-tracking for the large species. The participation of domestic animals (dog, cats) should also be estimated. Moreover, given the cyclic population dynamics of the bank vole, the main rodent species in our study area, longer time series are necessary to complete the understanding of our system (Clutton-Brock and Sheldon 2010).

Finally, we have only determined a small proportion of the role of factors such as landscape level parameters and urbanisation in tick dynamics in our system. Habitat connectivity and other landscape attributes, host species assemblage and soil characteristics are also important determinants of *I. ricinus* occurrence (Estrada-Peña 2003), but have not been considered in our study.

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Shakespeare said, "*All the world's a stage, And all the men and women merely players*". My PhD was one of these stages where comedy and tragedy were played alternately. I drifted between genuine laughs in a blue Toyota lab-van, while handling hundreds of cute voles in the middle of picturesque coniferous forests and profound moments of uncertainty and doubt about me as a scientist, as a colleague, as a friend. I can't deny that this play has taught me a lot.

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"Il faut toujours connaître les limites du possible. Pas pour s'arrêter, mais pour tenter l'impossible dans les meilleures conditions."Romain Gary.

YHTEENVETO (RÉSUMÉ IN FINNISH)

Puutiaisten ja jyrsijöiden levittämien taudinaiheuttajien eko-epidemiologia boreaalisissa metsissä

Epidemiologian ala tutkii tautien esiintymistä ja runsauden vaihteluita populaatiotasolla, kun taas eko-epidemiologia huomioi tauteihin vaikuttavat tekijät molekyyleistä yhteisöihin ja ympäristöön. Huolimatta viime vuosisadan bakteriologisten tutkimusten nopeasta kehityksestä tartuntataudit ovat edelleen ihmisten kuolleisuuden tärkeimpiä syitä maailmanlaajuisesti. Vaikka monet taudinaiheuttajat kiertävät luonnostaan luonnonvaraisissa isäntälajeissa, zoonoottiset taudinaiheuttajat voivat tarttua ihmisen ja eläimen välillä. Onkin arvioitu, että noin 60 % ihmisen taudinaiheuttajista on zoonoottisia. Abioottisten ja bioottisten olosuhteiden vaihtelut voivat muuttaa lois-isäntä –suhdetta ja näin ollen vaikuttaa zoonoottisten taudinaiheuttajien ihmiselle aiheuttamaan riskiin. Luonnonvaraisten eläimien välittämien taudinaiheuttajien kiertokulun tunteminen luonnossa on kriittinen askel zoonoosien aiheuttamien sairauksien epidemiologian ymmärtämisessä.

Väitöskirjatyöni tavoitteena oli selvittää zoonoottisten taudinaiheuttajien dynamiikkaa ja luonnollista kiertoa säilymöisännissä. Pohjois-Euroopassa zoonoottiset puutiaisten välittämät taudit lisääntyvät, mikä johtuu ensisijaisesta *Ixodes ricinus* -puutiaisen levinneisyyden muutoksista, jotka johtuvat pääsääntöisesti abioottisten olosuhteiden muutoksista. Erityisesti Lymen tauti (Borrelioosi), joka on yleisimpiä puutiaisten aiheuttamia sairauksia, on kasvava ongelma taudinaiheuttajan monimutkaisen ekologian sekä sen ihmiselle aiheuttamien monimutkaisten oireiden vuoksi. Puutiaisvälitteisten taudinaiheuttajien kiertokulku luonnossa tapahtuu tyypillisesti luonnonvaraisten isäntälajien ja puutiaisten välillä. Tyypillisesti *I. ricinus* –puutiaisten nuoruusvaiheet aterioivat jyrsijöissä mahdollistaen puutiaisvälitteisten taudinaiheuttajien kiertokulun. Valtaosan elämästään puutiaiset kuitenkin elävät riippumattomina isäntäeläimistään. Puutiaiset ovat siten riippuvaisia isännän saatavuudesta, mutta myös erittäin herkkiä elinympäristön abioottisille vaihteluille. Puutiaislajit, jotka eivät aterioi ihmisellä eivätkä siten levitä taudinaiheuttajia suoraan ihmiseen, saattavat osaltaan vaikuttaa puutiaisvälitteisten taudinaiheuttajien kiertokulkuun luonnossa. Jyrsijät ovat avainasemassa useiden puutiaisvälitteisten taudinaiheuttajien kiertokulussa luonnossa.

Väitöskirjatyöni keskittyy (1) metsämyyrän (*Myodes glareolus*), joka on Keski-Suomen runsaslukuisin jyrsijälaji sekä zoonoottisen Puumala hantaviruksen (PUUV) isäntälaji, (2) puutiaisten ja (3) puutiais- ja jyrsijävälitteisten taudinaiheuttajien välisiin vuorovaikutussuhteisiin. Tutkimus tehtiin alueella, joka sijaitsee *I. ricinus* -puutiaisen esiintymisalueen pohjoisrajalla, missä ympäristöolot ja myyrätiheydet vaihtelevat suuresti. Siten ensimmäisenä hypoteesinani oli, että puutiaisten ja puutiaisvälitteisten taudinaiheuttajien esiintymisessä on selviä alueellisia ja ajallisia vaihteluita, jotka liittyvät abioottisiin oloihin ja jyrsijöiden runsauden vaihteluihin (luvut I ja II). Toisena hypoteesinani oli, että yksi

Borrelioosin aiheuttajista, *Borrelia afzelii*, vaikuttaa sen isäntäeläimen kelpoisuuteen, ja että tämä vaikutus on isäntäpopulaatiotiheydestä riippuva (luku III). Kolmanneksi tunnistin, että luonnossa isäntäyksilöitä infektoi useat taudinaiheuttajat, jotka voivat olla vuorovaikutuksessa keskenään kilpailemalla resursseista tai epäsuorasti isännän immuunijärjestelmän kautta, ja testasin oletusta, että myyrän todennäköisyyteen saada infektio vaikuttaa muut taudinaiheuttajat ja ulkoloiset (IV luku).

Ensimmäistä hypoteesia koskien tarkastelin puutiaisten ajallista runsautta 4-vuotisen myyrä- ja puutiaispyynnin avulla, joka otteutettiin neljällä tutkimusalueella boreaalisissa kaupunkimetsissä. *I. ricinus* oli ainoa kasvillisuudessa löydetty laji, kun taas metsämyyrää loisi kaksi puutiaislajia: *Ixodes trianguliceps* ja *I. ricinus*. Loisittujen metsämyyräyksilöiden osuus oli 76 %, mutta vanhat koiraat olivat useammin *I. ricinus* -puutiaisen loisimia. Puutiaisten esiintyminen oli erittäin kausiluonteista, ja suurin riski ihmiselle tulla puutiaisen puremaksi oli touko-kesäkuussa ja jälleen syyskuussa. Puutiaisten nuoruusvaiheet aterioivat samanaikaisesti metsämyyrillä vaikuttaen osaltaan puutiaisvälitteisten taudinaiheuttajien kiertokulkuun alueella. Puutiaisten määrä korreloi positiivisesti metsämyyrän runsauden kanssa.

Lisäksi tarkastelin puutiaisten ja puutiaisvälitteisten taudinaiheuttajien esiintymiseen vaikuttavia tekijöitä käyttäen myyrä- ja puutiaispyynneistä saatua aineistoa, joka kerättiin 16 näytteenottopaikalta, jotka sijaitsivat erilaisilla etäisyyksillä ihmisasutuksesta. Havaitsin, että *I. ricinus* esiintyi epätasaisesti tutkimusalueella, kun taas *I. trianguliceps* esiintyi kaikilla näytteenottopaikoilla. *I. ricinus* oli runsaampi alueilla, joilla vesistöjä oli runsaasti ja ihmistiheys oli korkea. Näillä alueilla kosteusolot ja antropogeeniset tekijät saattavat suosia *I. ricinus* -puutiaisen esiintymistä. *Borrelia burgdorferi* s.l. esiintyi myyrissä vain alueilla, joilla oli runsaasti *I. ricinus* –puutiaisia. Tämä viittaa siihen, että tämä puutiaislaji tarvittiin kyseisen taudinaiheuttajan tarttumiseen ja pysyvyyteen alueella, kun taas *I. triangulicep*s ei ainakaan yksin kyennyt ylläpitämään kyseisen taudinaiheuttajan kiertokulkua luonnossa.

Seuraavaksi tarkastelin hypoteesia, jonka mukaan *B. afzelii* vaikuttaa isäntälajina toimivan metsämyyrän kelpoisuuteen, kokeellisella infektiolla luonnollisissa olosuhteissa, joissa myyrien populaatiotiheys vaihteli. *B. afzelii* -infektio vaikutti metsämyyrän lisääntymiseen, mutta infektion vaikutus riippui isännän sukupuolesta ja populaatiotiheydestä. Tämä infektion aiheuttama tiheydestä riippuva kustannus havaittiin koirailla, joita pidettiin alhaisessa populaatiotiheydessä, ja siihen liittyi muuttunut liikkuvuus. Lisäksi havaitsin, että vaikka suuri kehon koko suosi lisääntymistä infektoimattomilla koirailla, tämä koko tuoma hyöty katosi, jos yksilö oli infektoitunut. Tartunnan saaneita naaraat puolestaan lisääntyivät aikaisemmin kuin infektoimattomat naaraat.

Lopulta tutkin hypoteesia siitä, vaikuttavatko ko-infektiot metsämyyrän todennäköisyyteen saada Puumala-virustartunta. Tähän käytin epätavallista analyyttistä työkalua, Bayesialaista tila-avaruusmallia käyttäen pitkittäistutkimusaineistoa. Tämä yhden kenttäkauden kattava aineisto käsitti yksilökohtaiset tiedot eri tartuntojen tilasta. Havaitsin, että Puumala-virus tartunta oli epäto-

dennäköisin yksilöissä, joilla oli aikaisemmin ollut ulkoloistartunta, mutta jotka eivät olleet saaneet *Anaplasma phagocytophilum* tartuntaa. *A. phagocytophilum* -infektoiduilla yksilöillä puutiaisten ja kirppujen läsnäolo ei muuttanut todennäköisyyttä saada Puumala-virustartuntaa. Esitän, että puutiaisia vastaan havaittu immuunivaste saattaa olla tehokas infektioriskin pienentämisessä Puumala-viruksen suhteen, kun taas *A. phagocytophilum* –infektion ja Puumala-virusinfektion välillä ei havaittu vuorovaikutusta.

Kokonaisuudessaan väitöstutkimukseni osoittaa kuinka vuodenaikaisuus, taudinaiheuttajat ja isäntälajin populaatiotiheys vaikuttavat puutiaisten, puutiais- ja jyrsijävälitteisten taudinaiheuttajien ja niiden isäntinä toimivan metsämyyrän väliseen vuorovaikutussuhteeseen boreaalisessa ympäristössä, jossa olosuhteet vaihtelevat vuodenaikaisesti. Nämä vuorovaikutussuhteet voivat välittyä ihmisen riskiin saada puutiais- tai jyrsijävälitteisiä tartuntatauteja. Tästä syystä tuottamani tieto on ensiarvoista ymmärtääksemme zoonoottisten tartuntatautien aiheuttamia riskejä eläinten, ihmisten ja ekosysteemin rajapinnassa.

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ORIGINAL PAPERS

I

TEMPORAL DYNAMICS OF THE TICK *IXODES RICINUS* IN NORTHERN EUROPE: EPIDEMIOLOGICAL IMPLICATIONS

by

Claire Cayol, Esa Koskela, Tapio Mappes, Anja Siukkola & Eva R. Kallio 2017

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RESEARCH Open Access

Temporal dynamics of the tick *Ixodes ricinus* in northern Europe: epidemiological implications

Claire Cayol*, Esa Koskela, Tapio Mappes, Anja Siukkola and Eva R. Kallio

Abstract

Background: Tick-borne pathogens pose an increasing threat to human and veterinary health across the northern hemisphere. While the seasonal activity of ticks is largely determined by climatic conditions, host-population dynamics are also likely to affect tick abundance. Consequently, abundance fluctuations of rodents in northern Europe are expected to be translated into tick dynamics, and can hence potentially affect the circulation of tick-borne pathogens. We quantified and explained the temporal dynamics of the tick *Ixodes ricinus* in the northernmost part of its European geographical range, by estimating (i) abundance in vegetation and (ii) infestation load in the most common rodent species in the study area, the bank vole *Myodes glareolus*.

Results: *Ixodes ricinus* nymphs and adult females, the life stages responsible for the most of tick bites in humans, peaked in May-June and August-September. Larvae and nymphs were simultaneously active in June and abundance of questing larvae and nymphs in the vegetation showed a positive association with bank vole abundance. Moreover, infesting larvae and nymphs were aggregated on bank voles, and the infestation of bank voles with *I. ricinus* larvae and nymphs was positively associated with bank vole abundance.

Conclusion: Our results indicate early summer and early autumn as periods of increased risk for humans to encounter *I. ricinus* ticks in boreal urban forests and suggest a 2 years life-cycle for *I. ricinus* with two cohorts of ticks during the same year. Moreover, we identified a simultaneous activity of larvae and nymphs which allows co-feeding on the rodent host, which in turn supports the transmission of several important zoonotic tick-borne pathogens. Finally, we showed that a high density of the rodent host may enhance the risk that ticks and, potentially, tick-borne pathogens pose to human health.

Keywords: *Ixodes ricinus*, Rodent host, Seasonality, Public health, Population dynamics

Background

Tick-borne pathogens are a growing burden for European public health policies [1–3]. The current observed increase in tick-borne disease incidence in Europe may be explained by the geographical expansion of *Ixodes ricinus*, the growing share of space between humans and wild animals, and the improvement of diagnostics tools [4–6]. The epidemiology of tick-borne zoonoses, such as Lyme borreliosis, anaplasmosis or tick-borne encephalitis (TBE), depends on tick abundance and population dynamics, infection prevalence within the tick population, and land use that may affect human exposure to ticks [7, 8]. In order to predict the risks that tick-borne diseases pose to humans, an assessment of factors underlying the temporal variation of tick abundance is necessary.

The abundance of *I. ricinus* varies in time and space and is highly dependent on environmental conditions, including habitat quality, host availability, and abiotic conditions [9–12]. In northern Fennoscandia, at the northernmost part of the European range of *I. ricinus*, abiotic conditions undergo extreme seasonal variation; there are 145 to 160 days of snow cover with short day-lengths, during which ticks are not active. This is followed by a quick elevation in temperature leading to a short summer with long day-lengths [13]. In these

* Correspondence: claire.c.cayol@jyu.fi
Department of Biological and Environmental Science, University of Jyväskylä, P.O. Box 35, FI-40014 Jyväskylä, Finland

conditions, *I. ricinus* activity is likely to show distinctive seasonal patterns, which have not been characterized to date (but see [14] for southwest Finland).

Ixodes ricinus is dependent on vertebrate hosts to complete its life-cycle. Larvae typically feed on small vertebrates, such as rodents; nymphs, the more common biting stage for humans, parasitize mostly medium-sized mammals; and adults feed mainly on large hosts, such as deer [15, 16]. The population dynamics of ticks and rodents are expected to be linked: some studies have indicated delayed density dependence of questing nymphs on rodent abundance, suggesting that high rodent abundance provides augmented opportunities for successful larvae feeding and nymph development [17, 18]. The bank vole (*Myodes glareolus*) is a common rodent species throughout Europe [19]; this species is commonly infested by immature *I. ricinus* [16, 20, 21]. In northern Europe, vole population abundance shows both seasonality, driven by seasonal breeding, and multiannual density fluctuations shaped by predation, food availability and food quality [22–24]. These seasonal and multiannual density fluctuations are likely to be translated into the dynamics of ticks, and consequently, into the epidemiology of tick-borne pathogens. To date, there are few studies that have investigated the association between the dynamics of cyclic small rodents and ticks [25].

The bank vole is also an important reservoir host for many tick-borne pathogens, such as *Borrelia afzelii*, tick-borne encephalitis virus (TBEV) and *Babesia microti* [26, 27]. Typically, tick larvae acquire infections from an infected rodent host that has become infected while feeding infected nymph(s) [10]. Alternatively, larvae acquire infections *via* simultaneous feeding with infected nymphs without systemic infection of the host [28, 29]. Infectivity is transstadially maintained in the tick to the following life stage [30].

Here, we present results from a 4 years of longitudinal bank vole monitoring and tick sampling in central Finland at the northernmost part of the European range of *I. ricinus*, where abiotic conditions undergo extreme seasonal variation. Our primary aim is to characterize temporal dynamics and quantify the importance of host related factors and abiotic conditions on temporal dynamics of *I. ricinus*. We also aim to identify seasonal patterns that are relevant for tick-borne pathogen circulation, with the ultimate goal of providing information concerning the risk of tick-borne diseases in our study area.

Methods

Study area

Sampling took place monthly from May to October in 2012 – 2015 in four periurban forests in the Jyväskylä area in Central Finland: (Kylmänoro (62°13′36.220″, 25°45′1.739″); Jyskänlaakso (62°13′55.398″, 25°49′34.269″); Hämeenlahti (62°12′40.119″, 25°47′11.052″); and Sippulanniemi (62°11′9.019″, 25°44′58.147″) [31]. One trapping period within a month will be referred to as "session" in the following paragraphs. Forests were dominated by Scots pine (*Pinus sylvestris*) and silver birch (*Betula pendula*) or by spruce (*Picea abies*). The herbaceous stratum was typically composed of *Vaccinium myrtillus*, *V. vitis-idaea*, *Maianthemum bifolium*, *Linnaea borealis* and *Oxalis acetosella*.

Tick dragging

Monthly tick dragging was performed during or within a few days of the vole trapping, using a 1 × 1 m cotton flannel flag sewed to a wooden rod [12]. The fabric was randomly dragged over the vegetation for 300 – 500 m per site around the rodent trapping transects and checked every 20–25 m for ticks, which were removed with tweezers and stored in alcohol at -20 °C. No dragging was performed during rain. In October 2014, due to early snow cover, dragging was not performed. Due to the duration, coverage and interval of the dragging (less than 30 min, 300–500 m^2 once a month in each site) it is unlikely that the flag dragging affected the overall tick population abundance and it should not have interfered with the ticks parasitizing rodents in the area.

Vole trapping and tick infestation on voles

As the active tick population consists in parasitizing, questing and resting ticks, sampling targeted questing ticks and parasitizing ticks on their rodent host. This latter buffers the effects of microclimate changes and rodent sampling, in particular, also buffers the effect of the patchy distribution of larvae [32].

Vole trapping was carried out with two lines of 10 Ugglan Special multiple-capture live traps (Grahnab Company, Sweden), positioned 10 – 15 m apart, located near to rodent burrows. Traps were prebaited for 1–3 nights with sunflower seeds (*Helianthus annuus*), after which traps were set with sunflower seeds (for food) and a piece of potato (for water) for two consecutive nights. Wood shavings were provided as bedding in wet or cold weather. Traps were checked once per day and trapped voles were handled and sampled before release close to their capture site. Bycatch of species other than voles, as well as recapture of the same individual during the same session, were released immediately on site.

All trapped voles were marked individually with electronic identification chips (microchip Trovan Unique™), which were injected subcutaneously at their first capture. During each capture, voles were identified, body mass was measured as a proxy for age (as in e.g. [33]), and sex and reproductive condition were recorded. The presence

of fleas was recorded and all voles were examined for ticks, with special attention to the area around the ears and face. All ticks were removed with tweezers and stored in alcohol at -20 °C until further identification. All ticks - both those removed from rodents and those collected from vegetation - were identified to species level and life stage under a dissection microscope using morphological identification keys [34–36]. Species identification of seven ticks identified as *I. ricinus* and three as *I. trianguliceps* was further confirmed with PCR following a method described elsewhere [37]. Briefly, PCR targeted the mitochondrial 16S rRNA gene and the amplicons obtained were successfully sequenced for eight of the ten ticks. Thereafter sequence identity was determined by BLAST search against the NCBI Nucleotide database and the obtained sequences confirmed our morphological tick identification.

We assessed the overall bank vole population abundance by computing the overall minimum number of voles alive (MNA) at a given trapping session (t) as follows: total number of individuals caught at a given trapping session (t) summed with the total number of individuals marked when caught during subsequent sessions, but not caught at (t) [38].

We trapped 658 bank voles, an average of 1.53 times (range 1–6), for a total of 1007observations for which all variables described above were available. The minimum number of voles alive per session varied from 5 (in May 2013) to 120 individuals (in September 2014). Three other rodent species were bycaught, consisting of 52 observations of yellow-necked mouse (*Apodemus flavicollis*), one observation of field vole (*Microtus agrestis*), and two observations of house mouse (*Mus musculus*) (Additional file 1: Figure S3).

Statistical analysis

Ticks in vegetation

We characterized the temporal activity of *I. ricinus* in the vegetation (i.e. collected by flagging), by examining tick questing activity separately for each life stage, i.e. larvae, nymphs, adults (males and females), in relation to the following variables: year (2012 – 2015), month (May-October), estimated bank vole abundance per given session (MNA), abundance of other life stages present during the same session (number of ticks/100 m^2), and the abundance of previous tick life stages collected during the previous session (for larvae: adult, for nymph: larvae, for adults: nymphs). To further identify the effect of current climatic conditions on tick activity, we computed the mean daily saturation deficit (SatDef, in millimetres of mercury) during tick flagging days, based on daily average humidity (in percent) and daily average temperature (in °C) [9, 39, 40] recorded at the meteorological station of Nenäinniemi in Jyväskylä, located 0.72–3.7 km from the study sites (http://www.jyv-weather.info/index.php) (Additional file 1: Figure S1). SatDef was used as an explanatory variable rather than month, with which it showed collinearity. Thus, the second set of models included SatDef and its second-degree polynomial term $SatDef^2$, MNA, current and previous tick abundances as described above. Furthermore, the abundance of nymphs and females pooled together was also modelled with two sets of models: the first one included vole abundance, month and year and the second one included year, vole abundance, SatDef and $SatDef^2$.

Models were fitted using generalized linear mixed models (GLMM) with a negative binomial error distribution (with log-link function) and site was included as a random effect to control for potential pseudoreplication [41]. To take into account the variation in the distance flags were dragged, an offset term (log(distance flagged)/100) was introduced in the models. The model selection (provided in Additional file 1: Table S2) was an automated selection process starting from the full model and based on AICc (Akaike Information Criteria corrected for small sample size [42]), using dredge function in R software. We kept the most parsimonious model that lay within 2AICc difference from the best model fitted [42] (Additional file 1: Tables S1 and S2).

Ticks infesting voles

Ixodes ricinus infestation load on bank voles was examined separately for larvae and nymphs. We assessed whether tick infestation showed seasonality and/or between year variation and whether it was affected by individual host characteristics or by concomitant parasitism (by other tick stages, other tick species or fleas). For that purpose, we fitted a GLMM with a negative binomial error distribution to test the fixed effects of month, year, vole sex, body mass (centred value) and its second order polynomial term, presence of fleas, presence of other life stages of *I. ricinus* and *I. trianguliceps*, body mass*vole abundance (MNA) interaction term and body mass*sex interaction term. 'Trapping site' and 'vole individual nested in the trapping site' were included as random effects in the models. Model selection was performed as described before except that we utilized the function *drop1* in R software (Additional file 1: Tables S4 and S5).

All statistical analyses were performed with R version 3.2.3 (2015, The R Foundation for Statistical Computing), and using the packages *stats* (http://www.R-project.org/), *MASS* (https://cran.r-project.org/web/packages/MASS/index.html), *glmmADMB* (http://glmmadmb.r-forge.r-project.org/) and *MuMIn* (https://cran.r-project.org/web/packages/MuMIn/index.html).

Results

Ticks in vegetation

We sampled and identified 943 *I. ricinus* larvae, 867 nymphs, 239 (adult) females and 294 males from the vegetation. The mean abundance of *I. ricinus* per session and per area varied from 0 to 22.7 ticks/100 m^2 when considering all tick life stages and from 0 to 6.25 ticks/100 m^2 when taking into account only female adults and nymphs. Overall, the density of questing ticks collected from vegetation was 7.1/100 m^2 (Additional file 1: Figure S2). The ratio between *I. ricinus* larvae, nymphs and adults was 3.5:3.3:2.0. In addition, one *I. trianguliceps* nymph was identified.

Models revealed unimodal questing patterns for larvae, which were mostly found in June. Conversely, a bimodal questing pattern was found for nymphs as well as nymph and females modelled together, with the highest abundances found in May-June and September, which therefore appears as the higher risk period for tick bites on humans. Questing adults (males and females) were more abundant in May-June and August-September, and their abundance varied with year, with the highest abundance found in 2015 (Table 1, Fig. 1).

For any given month, the abundances of questing *I. ricinus* larvae and nymphs showed positive associations with vole abundance (Tables 1, 2; Fig. 2; Additional file 1: Figure S4). For each addition of one individual to the bank vole population, an increase of larvae abundance by approximately 3% and of nymph abundance by 1% was predicted (Fig. 2; Additional file 1: Figure S4).

The abundance of questing larvae was positively associated with saturation deficit, while the abundance of questing adults showed a non-linear relationship with saturation deficit. The number of adults found in vegetation was positively associated with saturation deficit until an optimal value (3.16 mm Hg), after which the abundance of adult ticks was negatively affected by any further increase in saturation deficit. Nymph abundance was not associated with saturation deficit in the best model selected (Table 2).

We found a positive relationship between the number of questing larvae and the abundance of adults observed in the vegetation one session before. Nymph abundance increased with adult abundance during the same flagging session whereas adult abundance showed a negative relationship with nymph abundance during the previous session (Table 2).

Ticks infesting voles

From bank voles, two tick species were identified: *I. trianguliceps*, the vole tick and *I. ricinus*. The proportion of infestation with either of these tick species was 75.8%. The ratio of *I. ricinus* larvae to nymphs found feeding on bank voles was 13:1. The total number of ticks

Table 1 Selected best model for the abundance of tick questing in the vegetation with estimated coefficients (in log scale), explained by vole abundance, month (May taken as reference) and year (2012 as reference)

Y = Larva abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	-1.424 (0.667)	-2.13	0.033
June	1.891 (0.742)	2.55	0.011
July	0.003 (0.778)	0.00	0.997
August	-1.100 (0.974)	-1.13	0.259
September	-0.987 (1.035)	-0.95	0.340
October	-1.707 (0.979)	-1.74	0.081
Vole abundance	0.028 (0.013)	2.14	0.032
Random effect: site	$\sigma^2 = 0.46$ (SD = 0.68)		
Negative binomial dispersion parameter	0.38 (SE = 0.07)		
Y = Nymph abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	0.193 (0.375)	0.52	0.607
June	-0.401 (0.275)	-1.46	0.145
July	-1.571 (0.313)	-5.02	<0.005
August	-1.312 (0.351)	-3.74	<0.005
September	-0.628 (0.390)	-1.61	0.107
October	-2.730 (0.404)	-6.76	<0.005
Vole abundance	0.013 (0.004)	2.99	0.003
Random effect: site	$\sigma^2 = 0.38$ (SD = 0.62)		
Negative binomial dispersion parameter	2.88 (SE = 0.70)		
Y = Adult (male + female) abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	-0.766 (0.393)	-1.95	0.051
June	-0.203 (0.226)	-0.90	0.368
July	-0.600 (0.238)	-2.52	0.012
August	0.395 (0.215)	1.84	0.066
September	0.279 (0.214)	1.30	0.192
October	-1.082 (0.292)	-3.71	<0.005
2013	0.288 (0.196)	1.47	0.142
2014	0.306 (0.202)	1.51	0.131
2015	0.923 (0.191)	4.82	<0.005
Random effect: site	$\sigma^2 = 0.39$ (SD = 0.63)		
Negative binomial dispersion parameter	7.48 (SE = 2.81)		
Y = Female + Nymph abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	0.514 (0.350)	1.47	0.142
June	-0.422 (0.227)	-1.86	0.063
July	-1.509 (0.258)	-5.84	<0.005
August	-1.021 (0.282)	-3.62	<0.005
September	-0.599 (0.324)	-1.85	0.064
October	-2.430 (0.323)	-7.53	<0.005
Vole abundance	0.012 (0.004)	3.04	0.002
Random effect: site	$\sigma^2 = 0.37$ (SD = 0.60)		
Negative binomial dispersion parameter	4.42 (SE = 1.10)		

σ^2 is the variance attributable to random effect. Number of observations: Total = 88; Site = 4
Abbreviations: *SD* standard deviation, *SE* standard error

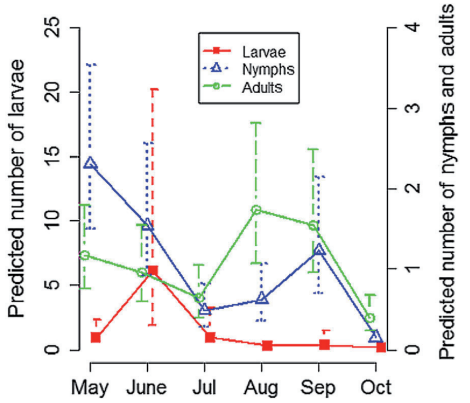

Fig. 1 Predicted number ± standard error (SE) of larvae, nymphs and adults in 100 m^2 of vegetation per month. Predictions are based on GLMM shown in Table 1

sampled from voles was 3564, out of which 14 ticks could not be identified due to poor condition (Additional file 1: Table S3 and Figure S5).

Models revealed a clear seasonal pattern in the infestation burden of *I. ricinus* larvae on bank voles (Table 3, Fig. 4): larval infestation underwent seasonality, with a peak in June and a trough in August-October. The highest infestation level was in 2013 and the lowest in 2014. In addition, bank vole infestation load with *I. ricinus* nymphs underwent seasonal variation, with a peak in May, but was stable between years (Table 4, Fig. 3).

For any given month, nymph infestation on voles was positively associated with bank vole abundance (Table 4). Similarly, larval infestation level increased with bank vole abundance, but the increase was more pronounced among female bank voles than among males (Table 3, Fig. 4). Moreover, infestation with larvae was positively associated with the amount of questing larvae observed in the environment (Table 3), whereas the bank vole infestation load with nymphs was not associated with the amount of questing nymph (i.e. the abundance of questing nymphs was not selected in the best model, Additional file 1: Table S5).

Tick infestation intensity on a host varied with individual characteristics such as age, sex and co-infestation. The oldest male bank voles (i.e. those with highest body mass) were the most intensely infested with larvae (Table 3). Moreover, bank vole infestation load with *I. ricinus* larvae was positively associated with co-infesting *I. trianguliceps* females and nymphs and *I. ricinus* nymphs (Table 3), whereas the infestation with *I. ricinus* nymphs increased with the presence of *I. trianguliceps* larvae and females (Table 4). In addition, the infestation load with nymphs showed a non-linear relationship with body mass: infestation load increased until voles reached 32.4 g, whereupon any further increase in body mass led to a reduction of the infestation burden (Table 4).

Table 2 Selected best model for the abundance of ticks questing in the vegetation with estimated coefficients (in log scale), explained by the vole abundance, the amount of ticks in other stages in vegetation during the previous session and/or during the current session, and the saturation deficit (SatDef) and its second degree polynomial term ($SatDef^2$)

Y = Larva abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	-5.426 (1.002)	-5.41	<0.005
Vole abundance	0.029 (0.009)	3.11	0.002
Amount of adult ticks during the previous session	1.007 (0.308)	3.27	0.001
SatDef	0.969 (0.192)	5.03	<0.005
Random effect: site	$\sigma^2 = 4.59e^{-06}$ (SD = 0.002)		
Negative binomial dispersion parameter	0.34 (SE = 0.06)		
Y = Nymph abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	-0.279 (0.233)	-1.20	0.232
Amount of adult ticks during the same session	0.381 (0.167)	2.28	0.023
Random effect: site	$\sigma^2 = 0.098$ (SD = 0.31)		
Negative binomial dispersion parameter	1.12 (SE = 0.21)		
Y = Adult (male + female) abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	-1.294 (0.461)	-2.81	0.005
SatDef	0.621 (0.239)	2.60	0.009
$SatDef^2$	-0.098 (0.037)	-2.63	0.009
Amount of nymph during the same session	0.222 (0.075)	2.97	0.003
Amount of nymph during the previous session	-0.135 (0.071)	-1.91	0.056
Random effect: site	$\sigma^2 = 0.33$ (SD = 0.57)		
Negative binomial dispersion parameter	3.04 (SE = 0.81)		
Y = Female + nymph abundance	Estimate (SE)	*z*-value	*P*-value
Intercept	0.011 (0.316)	0.04	0.971
Vole abundance	0.006 (0.003)	1.98	0.048
Random effect: site	$\sigma^2 = 0.27$ (SD = 0.52)		
Negative binomial dispersion parameter	1.53 (SE = 0.29)		

σ^2 is the variance attributable to random effect. Number of observations: Total = 88; Site = 4
Abbreviations: *SD* standard deviation, *SE* standard error

Discussion

In this study, we characterized the temporal dynamics of *I. ricinus* by assessing its abundance in the vegetation and its infestation load in one of its main host in the northernmost part of its range. We focused on bank voles, which parasitism provides insightful information concerning the local immature tick communities.

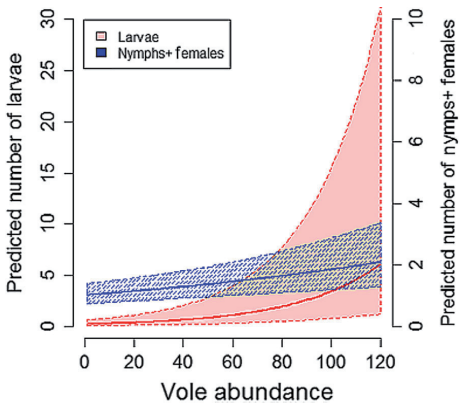

Fig. 2 Predicted number ± standard error (SE) of larvae and pooled nymphs and females in 100 m^2 of vegetation explained by vole abundance. Predictions are based on GLMM shown in Table 2

Moreover, we identified risk periods - when humans are likely to encounter tick bites - in boreal forests and seasonal patterns that might be relevant for tick-borne pathogen circulation.

Tick seasonality

We identified that the highest tick abundance was in early summer (May-June) and early autumn (August-September), which are consequently the periods of increased risk for humans to encounter *I. ricinus* ticks in boreal forests. The same pattern of bimodal questing activity was previously found in southern Finland for nymph and adult ticks in coniferous and deciduous forests, whereas larvae showed a bimodal occurrence with a larger peak in September than in June [14]. Overall, two types of tick questing activity patterns have been described in Europe: in highly seasonal climates, such as those in central Europe, a bimodal questing activity with early spring and autumn peaks has been described for all life stages of *I. ricinus* [43]. However, in milder climates, with less climatic variation between seasons, only one peak of activity was observed for all life stages; in either spring or early summer [43]. In the present study, nymphs and adults showed bimodal activity, whereas larvae showed a unimodal activity pattern. This unimodal activity pattern could arise from egg production during the preceding year, the product of which overwintered as eggs or as larvae [44] or from egg production during the same spring. It could be argued that the inclusion of a year*month interaction term in the model would have captured between year seasonal variations suggested by the raw data (Additional file 1: Figure S1), and would have revealed both unimodal and bimodal activity patterns for larvae. However, data from a longer time series would be needed in order to clarify this point.

Table 3 Selected best model for *I. ricinus* larvae infestation load on an individual bank vole with estimated coefficients (in log scale) explained by month (from May to October, with May as a reference), year (from 2012 to 2015, with 2012 as a reference), sex (female as a reference), body mass in grams (centred values), presence of *I. trianguliceps* females and nymphs, presence of *I. ricinus* nymphs, vole abundance during the same session, questing larvae in vegetation during the same session, the interaction between centred body mass and sex and the interaction between sex and vole abundance. We defined site and individual nested in site as nested random structure

	Estimate (SE)	*z*-value	*P*-value
Intercept	-0.923 (0.318)	-2.91	0.004
June	0.477 (0.243)	1.96	0.050
July	-0.691 (0.277)	-2.49	0.013
August	-0.900 (0.342)	-2.63	0.009
September	-1.734 (0.413)	-4.20	<0.005
October	-2.768 (0.376)	-7.36	<0.005
2013	0.720 (0.150)	4.79	<0.005
2014	-0.688 (0.275)	-2.50	0.012
2015	-0.248 (0.169)	-1.47	0.142
Male	0.996 (0.219)	4.55	<0.005
Body mass	0.020 (0.010)	2.03	0.043
Presence of *I. trianguliceps* female	0.402 (0.154)	2.61	0.009
Presence of *I. trianguliceps* nymphs	0.202 (0.101)	2.00	0.046
Presence of *I. ricinus* nymphs	0.526 (0.132)	3.97	<0.005
Vole abundance	0.033 (0.005)	6.43	<0.005
Amount of questing larvae during the same session	0.027 (0.009)	2.86	0.004
Interaction: Sex(Male)*Body mass	0.048 (0.016)	3.02	0.003
Interaction: Sex (Male)*Vole abundance	-0.009 (0.003)	-3.20	0.001
Random effects			
Site	$\sigma^2 = 0.06$ (SD = 0.25)		
Individual nested in site	$\sigma^2 = 0.22$ (SD = 0.47)		
Negative binomial dispersion parameter	1.70 (SE = 0.24)		

σ^2 is the variance attributable to random effect. Number of observations: Total = 1007; Site = 4, Site:Individual = 658
Abbreviations: *SD* standard deviation, *SE* standard error

Our results seem to indicate the coexistence of two age cohorts of ticks during the same year. Larvae detected on bank voles and in the vegetation in early summer become nymphs in autumn, which can exhibit two different behaviors: immediate questing behavior in autumn; or activity postponed until the next spring after a behavioral diapause [45–47]. In our study, the largest peak of nymphal activity was observed in spring,

Table 4 Selected best model for *I. ricinus* nymph infestation load on an individual bank vole with estimated coefficients (in log scale) explained by month (from May to October, with May as reference), sex (female as reference), presence of *I. trianguliceps* larvae and females and presence of *I. ricinus* larvae, centered body mass and its squared value. We defined site and individual nested in site as nested random structure

	Estimate (SE)	*z*-value	*P*-value
Intercept	-2.994 (0.617)	-4.86	<0.005
June	-1.325 (0.385)	-3.44	<0.005
July	-1.360 (0.429)	-3.17	0.002
August	-2.103 (0.518)	-4.06	<0.005
September	-3.043 (0.643)	-4.73	<0.005
October	-2.956 (0.732)	-4.04	<0.005
Male	1.787 (0.298)	6.00	<0.005
Body mass	0.219 (0.036)	6.14	<0.005
Body mass^2	-0.009 (0.003)	-2.80	0.005
Presence of *I. trianguliceps* larvae	0.709 (0.247)	2.87	0.004
Presence of *I. trianguliceps* female	1.012 (0.318)	3.18	0.002
Vole abundance	0.014 (0.006)	2.30	0.021
Random effects			
Site	$\sigma^2 = 0.75$ (SD = 0.87)		
Individual nested in site	$\sigma^2 = 0.01$ (SD = 0.09)		
Negative binomial dispersion parameter	1.00 (SE = 0.46)		

σ^2 is the variance attributable to random effect. Number of observations: Total = 1,007; Site = 4; Site:Individual = 658
Abbreviations: *SD* standard deviation, *SE* standard error

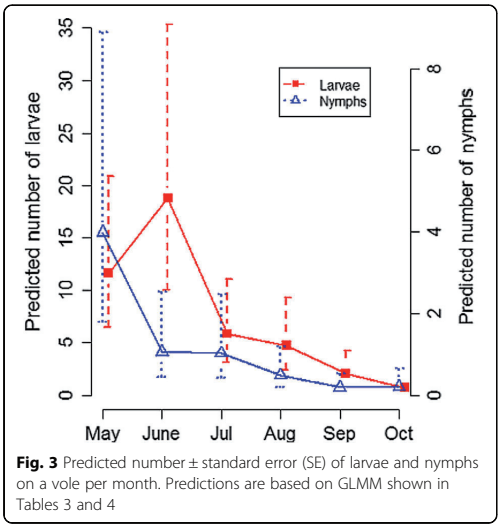

Fig. 3 Predicted number ± standard error (SE) of larvae and nymphs on a vole per month. Predictions are based on GLMM shown in Tables 3 and 4

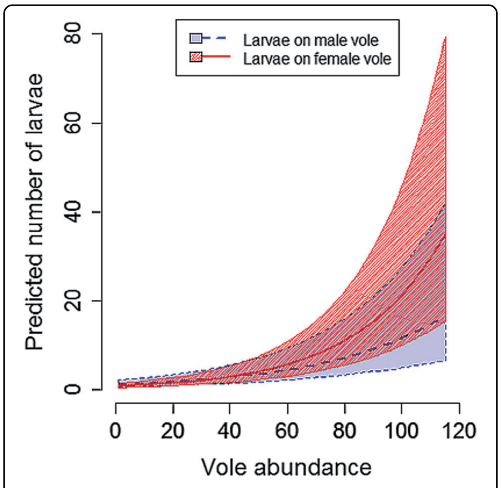

Fig. 4 Predicted number ± standard error (SE) of larvae per bank vole (male and female separated) by vole abundance. Predictions are based on GLMM shown in Table 3

suggesting that the second behavior was predominant [45]. In addition, we found a peak in questing adults 2 years after the largest larval infestation, indicating a probable 2-year period between larvae blood meal and adults, and suggesting a 2 to 3 year life-cycle from egg to adult for *I. ricinus* in our study area. Furthermore, in an additional model, the amount of questing nymphs was explained, amongst others explanatory variables, by the total amount of larvae that fed on bank vole the year before (GLMM negative binomial: *estimate* (± *SE*) = 0.005 ± 0.002, $P = 0.0071$, see Additional file 1: Tables S6 and S7). This model confirmed firstly, that the variation in bank vole larval infestation was translated into nymph abundance and secondly, a 1 year delayed relationship between bank vole larval infestation and questing nymphs.

We observed an effect of saturation deficit on larval and adult questing behavior, but not on nymphs, as described in other studies [40, 45]. Ticks respond to microclimate, but climatic variations measured in this study presumably reflect only roughly microclimatic variations and could explain the lack of association between saturation deficit and nymph activity found in our study. On the other hand, nymphs might also be acclimatized to local conditions and therefore their questing behavior may vary compared to nymphs studied in other locations [48, 49]. This is further supported by the optimal saturation deficit value of 3.16 mm Hg over which the adult questing activity decreased, when an optimum of 4.4 mm Hg has been previously noted elsewhere [9].

Our ratio larvae:nymph:adult was 3.5:3.3:2.0 and was therefore different from theoretical biological expectation (100:10:2) [30], indicating a possible underestimation of nymphs, and particularly of larvae, which show an important patchiness in distribution. Indeed, the blanket dragging technique is limited by variability in sampling efficiency given the nature of the substrate, the wind speed during sampling, and the height, type and growth stage of the vegetation [50, 51]. Moreover, the total tick population is not accessible by flagging given that diapausing ticks, parasitizing ticks, quiescent ticks or rehydrating individual are not questing in vegetation. Associating bank vole screening to the blanket dragging provided a broader view of immature ticks' population by beneficiating from the buffer effect that the host offers against the larvae patchiness and the drop of activity in case of unfavourable microclimate [32]. The two approaches are complementary and had led to similar results supporting further the idea that bank voles play an important role as host for immature ticks in the area.

Dynamics of tick in immature stages and bank vole population are related

Questing and parasitizing abundances of larvae and nymphs showed positive associations with bank vole abundance during a given session. Regarding nymphs, this positive relationship might arise from better engorgement success for larvae in high bank vole abundance. However, regarding larvae, this correlation does not imply a causative relationship since bank voles do not contribute to larvae production, which relies on large mammal availability [52]. Consequently, this positive relationship between the abundance of larvae and bank voles might reflect large-mammal density variations or might reveal a functional response: larvae may increase questing behavior in response to increased chemical signals produced by large bank vole populations [53]. This hypothesis requires further attention and needs to be experimentally quantified. Additionally, abundance of other species known to host adult stages needs to be quantified.

The largest burden of nymph parasitism in voles was observed in May, whereas peaks of questing nymphs in the vegetation were observed in May-June and September. In May, vole populations are mainly composed of overwintered sexually active adults; highly mobile males exhibit large home ranges in their search for receptive females [54]. Therefore, the probability of encountering questing nymphs present at a low level in the recovering spring vegetation is increased [55]. In September, bank vole contact rate with nymphs might be lower due to taller vegetation, which allows nymphs to quest higher on plants, where they can contact larger mammal hosts [47]. Moreover, the bank vole develops an acquired resistance to ticks, leading to a significant reduction of infestation success after the first infestation [56, 57], which could lead to poor infestation success during the second nymph peak in September. However, our data (Table 3) provide little support for this hypothesis as regards larvae infestation that increases with animal weight, which is used here as a proxy for age, when a decrease in the relationship was expected under acquired immunity hypothesis. As a consequence, the main period for larval and nymph co-infestation on bank voles is in early summer. The epidemiological consequences of these co-infestations are discussed below. Concerning larvae, we identified an infestation peak in June, which is in accordance with the peak of larvae questing activity and in accordance with previous surveys [58].

Male bank voles were more commonly infested with nymphs than females and the infestation increased with bank vole abundance. This sex-specific infestation load has been described previously [59] and may not only be due to the immunosuppressing role of testosterone [60–62], but also to sex-specific behavioral differences, e.g. in home range sizes [63]. Surprisingly, we found larvae infestation differs with population density; females carried more larvae at high population density, whereas males carried more nymphs at any population density. A different use of vertical space by bank vole males and females in high population densities can be hypothesized, leading males to come into contact with more nymphs that quest higher in vegetation, whereas females, which exhibit aggressive defensive behavior against intruders during the reproductive season [64], would stay close to the ground, i.e. at larvae level. More attention should be paid to the use of vertical space by bank voles in order to clarify the potential role of vertical space use causing differences between individuals in their tick infestation load.

Our data show a concomitant early summer questing activity between larvae and nymphs, and a parasitic aggregation between larvae and nymphs of *I. ricinus* on bank voles, which are relevant from an epidemiological point of view. The simultaneous activity of larvae and potentially infected nymphs occurs when rapidly rising temperatures in spring allow the simultaneous emergence of larvae and nymphs from overwintering diapause. In these conditions, pathogen transmission from infected nymphs to susceptible larvae can occur *via* simultaneous feeding on the same host, even without systemic infection of the host. This co-feeding transmission pathway is important for several zoonotic tick-borne pathogens, especially those with short-lived or non-systemic infections in the rodent host, such as *Anaplasma phagocytophilum* or tick-borne encephalitis virus (TBEV), respectively [65–68].

Synchronous infestations on bank voles

In addition to aggregation between *I. ricinus* life stages on bank voles, we found a significant aggregation between tick species, with *I. ricinus* infestation load increasing with the presence of *I. trianguliceps*. *I. trianguliceps* is a nidicolous species associated with rodents and insectivores, which does not quest in the vegetation and hence does not come into contact with humans [69]. Even if it is not involved in zoonotic transmission, *I. trianguliceps* is responsible for maintaining the enzootic cycle of potential zoonotic pathogens such as *Anaplasma phagocytophilum* [70, 71] or *Babesia microti* [72, 73]. Both of these pathogens have been identified in Finnish bank voles [74]. *Ixodes trianguliceps* could contribute to the sylvatic cycle of pathogens that the generalist *I. ricinus* could transmit to humans, who are considered as dead-end hosts. Hence, the between-species ectoparasite aggregation is also relevant from an epidemiological point of view.

Conclusion

In northern European urban forests, population dynamics of bank voles and questing *I. ricinus* larvae and nymphs are related, suggesting higher tick abundance and consequently higher risk of tick-borne pathogens for human during the rodent population peak. Larvae and nymphs showed synchronous activity, which increases the transmission opportunity for several pathogens and which are the prerequisite conditions for the maintenance of some pathogens such as TBEV. Further studies should focus on assessing the prevalence of tick-borne pathogens in the bank vole and in questing ticks in order to specify the zoonotic risk. Recent models demonstrate a dampening of vole population cycles in northern Europe [75], which could therefore be translated into the population dynamics of ticks.

Additional file

Additional file 1: Figure S1. Average monthly saturation deficit and temperature during the monitoring years. **Figure S2.** Observed mean abundance of ticks in vegetation per session, from May 2012 to October 2015. **Figure S3.** Mean number of vole captured per trap-night at each session and in each site, from May 2012 to October 2015. **Table S1.** Selection table for models explaining the abundance of ticks questing in the vegetation. **Figure S4.** Predicted number of larvae, nymphs and pooled nymphs and females per 100 m2 of vegetation explained by bank vole abundance. **Table S2.** Selection table for models explaining the abundance of ticks questing in the vegetation. **Table S3.** Total number of ticks (per species and stage) collected on voles. **Figure S5.** Vole infestation per session with *I. ricinus* larvae and nymphs from May 2012 to October 2015. **Table S4.** Selection table for models explaining the abundance of infesting larvae. **Table S5.** Selection table for models explaining the abundance of infesting nymphs. **Table S6.** Additional model for the abundance of nymphs questing in the vegetation. **Table S7.** Selection table for the additional model explaining the abundance of questing nymphs. (DOCX 3706 kb)

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Availability of data and materials

The datasets analysed during the current study are available in the institutional repository of the University of Jyväskylä https://jyx.jyu.fi/dspace/handle/123456789/53330

Authors' contributions

ERK and TM designed the monitoring. CC, AS and ERK collected the field data. CC, ERK, EK and TM performed the statistical analysis. CC drafted the manuscript. ERK, EK and TM critically revised the paper. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval

The trapping methods applied in this study were approved by the Finnish Animal Experiment Board and the Finnish Ministry of the Environment, under the authorization ESAVI/3834/04.10.03/2011 and ESAVI/7256/04.10.07/2014.

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Additional file 1

Content: Figure S1. Average (± SE) monthly saturation deficit and temperature during the monitoring years, measured in the weather station. **Figure S2.** Observed mean abundance of ticks in vegetation per session, from May 2012 to October 2015 (NB: in 2014 ticks were not dragged in October, due to poor weather conditions).**Figure S3.** Mean number of vole captured per trap-night at each session and in each site, from May 2012 to October 2015. **Table S1.** Model selection table for the abundance of ticks questing in the vegetation explained by vole abundance (MNA), month, year, abundance in other stages during the same session (nymph (Ny), adult (Ad), larva (Larv)), abundance of ticks in a previous life-stage collected during the previous session (lag(Ad), Lag(Ny), Lag(Larv)), total amount of larvae that fed on voles during the previous year (LagY(Larv)), total amount of larvae that fed on bank vole during the same early summer (May and June) (LagS(Larv)). **Figure S4.** Predicted number (± SE) of larvae, nymphs and pooled nymphs and females per 100 m2 of vegetation explained by bank vole abundance. Predictions are based on GLMM showed in Table 1. **Table S2.** Model selection table for the abundance of ticks questing in the vegetation, explained by vole abundance (MNA), Saturation deficit (SatDef) and Saturation deficit2 (SatDef2), abundance in other stages during the same session (adult (Ad), nymph (Ny), larva(Larv)), abundance of ticks in a previous life-stage collected during the previous session (lag(Ad), Lag(Ny), Lag(Larv)). **Table S3.** Total number of ticks (per species and stage) collected on voles, with the minimum and maximum tick infestation per vole, the percentage of vole infested with a particular tick stage or species, the mean number of ticks infesting a vole and the mean number of ticks per infested vole. **Figure S5.** Vole infestation per session (± SE) with *I. ricinus* larvae and nymphs from May 2012 to October 2015. **Table S4.** Model selection table for the abundance of infesting larvae, explained by month, year, bank vole sex, centered body mass (cBm) and cBm2, infestation with ticks in other species or other stages (ItL (*I. trianguliceps* larvae), ItF (*I. trianguliceps* female), ItN (*I. trianguliceps* nymph), IrN (*I. ricinus* nymph)) and with fleas,

abundance of questing larvae (Larv), vole abundance (MNA), and the interaction between sex and vole abundance and the interaction between sex and body mass. **Table S5.** Model selection table for the abundance of infesting nymphs, explained by month, year, bank vole sex, centered body mass (cBm) and cBm2, infestation with ticks in other stages or other species (ItL (*I. trianguliceps* larvae), ItF (*I. trianguliceps* female), ItN (*I. trianguliceps* nymph), IrL (*I. ricinus* larvae)) and with fleas, abundance of questing nymphs (Nymph), vole abundance (MNA), the interaction between sex and vole abundance and the interaction between sex and body mass. **Table S6.** Additional model for the abundance of nymphs questing in the vegetation. **Table S7.** Model selection table concerning the abundance of questing nymphs, explained by month, year, vole abundance (MNA), the total amount of larvae that fed on voles the year before (LagY(Larv)), the total amount of larvae that fed on voles during the same summer (May and June) (LagS(Larv)), the amount of larvae (Larv) and adult (Ad) in vegetation during the same session

List of variables in the datasets associated with this manuscript: Date; Month; Year; Session: trapping period within a month; Av_temp, Av_hum, Av_baro: daily average temperature, humidity, atmospheric pressure recorded at the meteorological station of Nenäinniemi; Vole_MNA_general: minimum number of voles alive during the session; areas: location of the sampling areas: 1= Kylmänoro, 2= Sippulanniemi, 3= Hämeenlahti, 4= Jyskänlaakso; ticks: presence/absence of tick in vegetation during the session; irl, irn, irf, irm, irnf, ad, irtot: total number of *I. ricinus* larvae, nymphs, females, males, females and nymphs, males and females, all stages pooled together collected with the flagging method; it: number *of I.trianguliceps* all stages pooled together collected with the flagging method; m: number of meters flagged; satdef: mean saturation deficit during the sampling day; trap: vole trap location; ind: vole identification number; sex: vole sex (1: female, 2: male); weight: vole weight (g); head: vole head width (mm); ticks: presence/absence of ticks on the vole; fleas: presence/absence of fleas on the vole; IrL_TOT,

IrN_TOT, IrF, Ir_TOT: total number of *I. ricinus* larvae, nymphs, females and all stages pooled infesting an individual vole; IrL_PA, IrN_PA, Ir_PA: presence/absence of larvae, nymphs and all stages of *I. ricinus* infesting an individual vole; ItL_TOT, ItN_TOT, ItF_TOT, M_It, It_TOT: total number of *I. trianguliceps* larvae, nymphs, females, males, and all stages pooled infesting an individual vole; ItL_PA, ItN_PA, ItF_PA, It_PA: presence/absence of *I.trianguliceps* larvae, nymphs, females and all stages pooled infesting an individual vole, NoN.identified.ticks: total number of ticks non identified at species level sampled from an individual vole; Tot_Ticks: total number of ticks all stages and all species pooled together infesting an individual vole; irl_100, irn_100, irf_100, irm_100, irnf_100, irtot_100: total number of *I.ricinus* larvae, nymphs, females, males, nymphs and females, all stages pooled together flagged in 100m2 of vegetation during a session; it_100: total number of *I.trianguliceps* flagged in 100m2 of vegetation during session

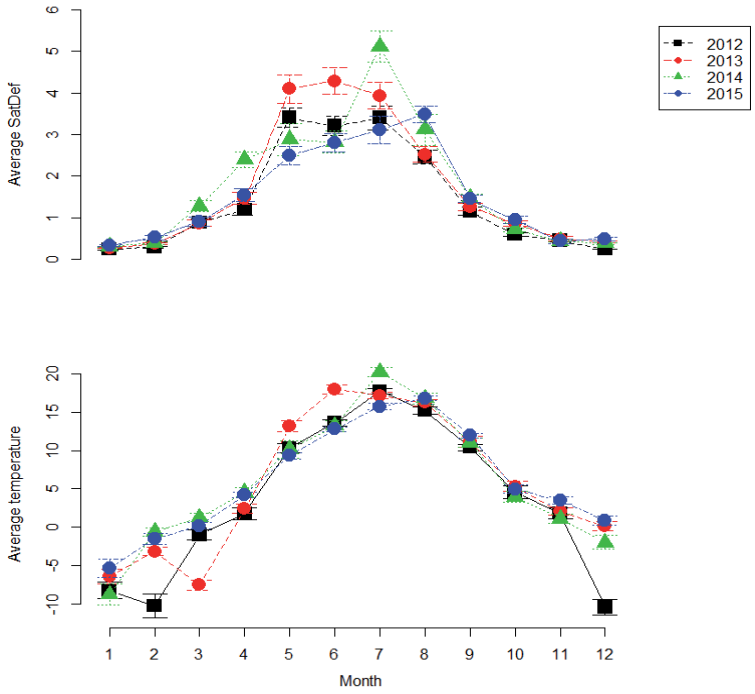

Figure S1. Average (± SE) monthly saturation deficit and temperature during the monitoring years, measured in the weather station

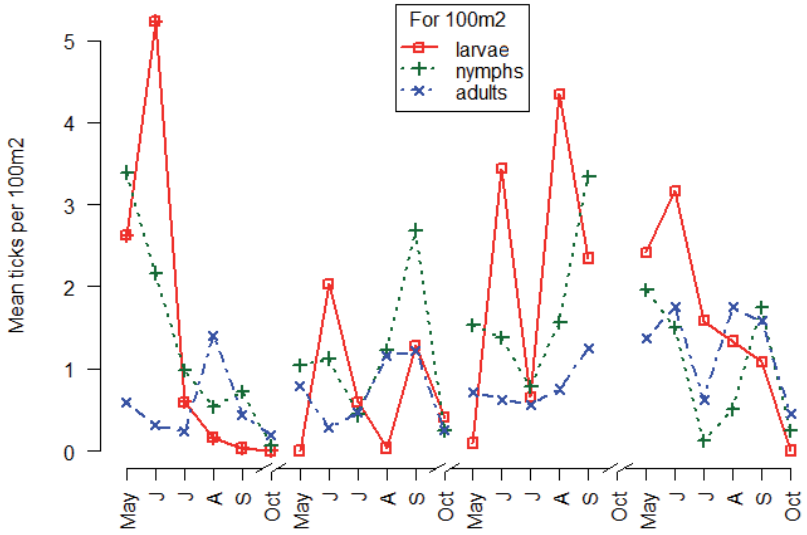

Figure S2. Observed mean abundance of ticks in vegetation per session, from May 2012 to October 2015 (NB: in 2014 ticks were not dragged in October, due to poor weather conditions).

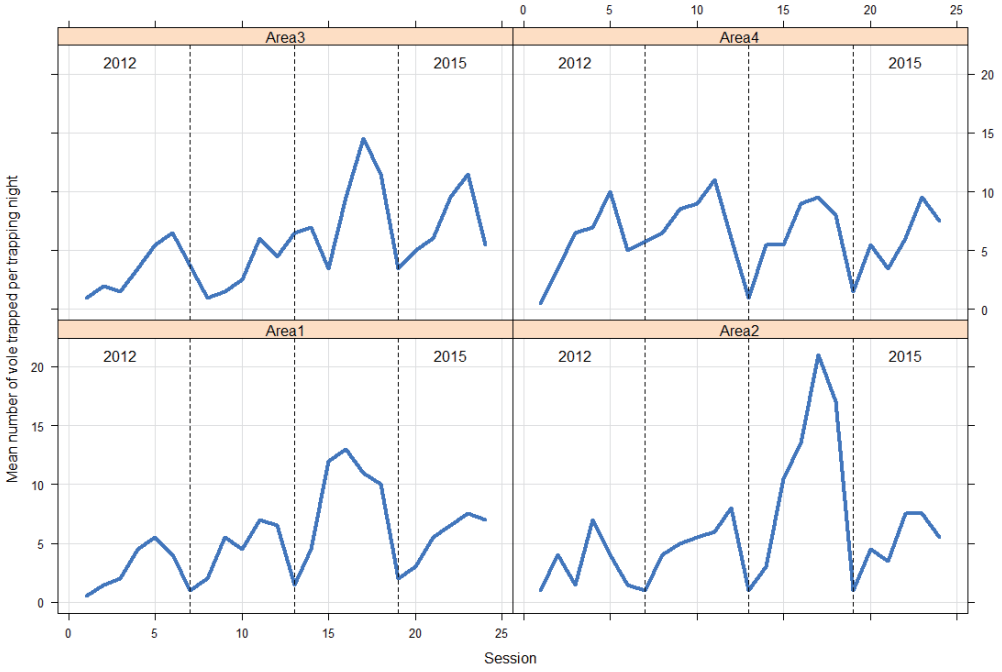

Figure S3. Mean number of vole captured per trap-night at each session and in each site, from May 2012 to October 2015.

Table S1. Model selection table for models showed in Table 1. The abundance of ticks questing in the vegetation was explained by vole abundance (MNA), month, year, abundance in other stages during the same session (nymph (Ny), adult (Ad), larva (Larv)), abundance of ticks in a previous life-stage collected during the previous session (lag(Ad), Lag(Ny), Lag(Larv)), total amount of larvae that fed on voles during the previous year (LagY(Larv)), total amount of larvae that fed on bank vole during the same early summer (May and June) (LagS(Larv)). Full model and all models laying at 2 AICc difference from the lowest AICc are showed with their degree of freedom (Df).

Questing larvae		Df	AICc	Delta
FULL	Lag(Ad)+ Ny+Ad+Year+Month+MNA	15	491.8	7.73
Best	Month+MNA	9	484.1	0.00
	Month+Ny+MNA	10	484.4	0.30
	Month+MNA+lag(Ad)	10	485.3	1.18
	Month+Ny	9	485.4	1.30
	Ad+MNA+Month+Ny	11	485.5	1.40
	Ad+MNA+Month	10	485.8	1.73
Questing nymphs				
FULL	Lag(Larv)+Larv+Ad+Year+Month+MNA	15	521.8	11.71
Best	Month+MNA	9	510.8	0.71
	Lag(Larv)+Month+MNA	10	510.1	0.00
Questing adults				
FULL	Lag(Ny)+Larv+Ny+Year+Month+MNA	15	451.8	5.34
Best	Month+Year	11	447.0	0.58
	Larv+Month+Year	12	446.4	0.00
	Larv+Month+Year+Ny	13	446.5	0.11
	Month+Ny+Year	12	447.5	1.09
	Larv+MNA+Month+Year	13	448.3	1.91
Questing (female+nymph)				
FULL	Month+Year+MNA	12	552.0	6.04
Best	Month+MNA	9	546.0	0.00

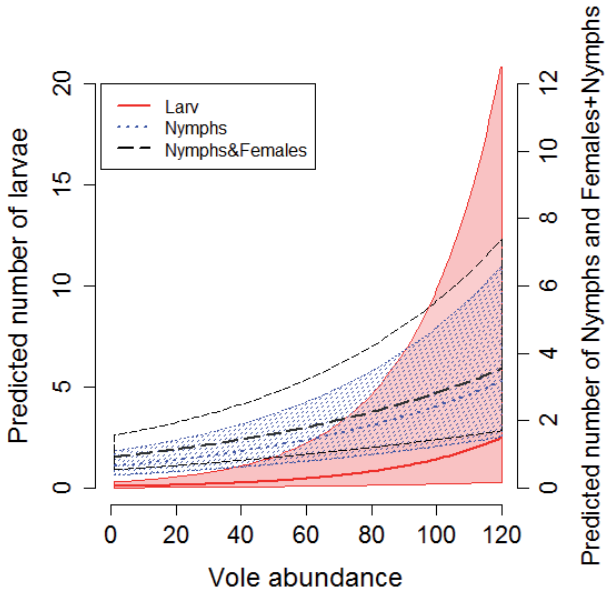

Figure S4. Predicted number (± SE) of larvae, nymphs and pooled nymphs and females per 100 m^2 of vegetation explained by bank vole abundance. Predictions are based on GLMM showed in Table 1.

Table S2. Model selection table for models showed in Table 2. The abundance of ticks questing in the vegetation was explained by vole abundance (MNA), Saturation deficit (SatDef) and Saturation deficit^2 (SatDef^2), abundance in other stages during the same session (adult (Ad), nymph (Ny), larva(Larv)), abundance of ticks in a previous life-stage collected during the previous session (lag(Ad), Lag(Ny), Lag(Larv)). Full model and all models laying at 2 AICc difference from the lowest AICc are showed with their degree of freedom (Df).

Questing larvae		Df	AICc	Delta
FULL	Lag(Ad)+SatDef+SatDef²+MNA+Ny+Ad+Year	12	485.6	8.62
Best	Lag(Ad)+SatDef+MNA	6	477.10	0.00
	Lag(Ad)+SatDef+SatDef²+MNA	7	477.1	0.07
	Lag(Ad)+SatDef+SatDef²+MNA+Ny	8	477.6	0.64
	Lag(Ad)+SatDef+ MNA+Ny	7	478.6	1.55
Questing nymphs				
FULL	Lag(Larv)+SatDef+SatDef²+MNA+Larv+Ad+Year	12	565.5	10.35
Best	Ad	4	555.8	0.69
	Ad+SatDef+MNA	6	555.1	0.00
	Ad+Larv	5	555.4	0.25
	Ad+MNA	5	555.9	0.77
	Ad+MNA+Larv	6	556.0	0.83
	Ad+SatDef²+MNA	6	556.0	0.89
	Ad+Larv+SatDef+MNA	7	556.2	1.05
	Ad+Larv+Year	8	556.8	1.66
	SatDef²+SatDef+MNA+Ad	7	556.8	1.67
	SatDef²+ MNA+Ad+Larv	7	556.9	1.77
	Ad+Year	7	557.0	1.89
Questing adults				
FULL	Lag(Ny)+SatDef+SatDef²+MNA+Larv+Ny+Year	12	459.0	0.47
Best	Satdef+SatDef²+Ny+Lag(Ny)+Year	10	458.9	0.37
	Satdef+SatDef²+Ny+Lag(Ny)+Year+Larv	11	458.5	0.00
	Satdef+SatDef²+Ny+Lag(Ny)+Year+MNA	11	460.0	1.48
Questing (female+nymph)				
FULL	SatDef+SatDef²+MNA+Year	9	603.7	3.70
Best	MNA	4	600.3	0.31
	Satdef+Satdef²+MNA	6	600.0	0.00
	Year	6	600.1	0.04
	Satdef+MNA	5	601.3	1.25
	MNA+Year	7	601.8	1.72

Table S3. Total number of ticks (per species and stage) collected on voles, with the minimum and maximum tick infestation per vole, the percentage of vole infested with a particular tick stage or species, the mean number of ticks infesting a vole and the mean number of ticks per infested vole (SE=standard error, N=1007 observations)**.**

	Range	Total number	% Vole infested	Mean per vole (SE)	Mean per vole infested by the tick stage and species (SE)
I. ricinus					
Larvae	[0; 46]	2290	59.19	2.27 (0.13)	3.84 (0.20)
Nymph	[0; 13]	178	9.83	0.18 (0.03)	1.80 (0.04)
Female	[0; 1]	1	0.099	-	-
Total	[0; 50]	2469	61.17	2.45 (0.15)	4 (0.22)
I. trianguliceps					
Larvae	[0; 27]	718	28.40	0.71 (0.06)	2.51 (0.17)
Nymph	[0; 8]	275	18.47	0.27 (0.02)	1.48 (0.08)
Female	[0; 4]	84	5.86	0.08 (0.012)	1.42 (0.10)
Male	[0; 2]	4	0.40	0.004 (0.002)	1.33 (0.33)
Total	[0;27]	1081	42.9	1.07 (0.07)	2.50 (0.13)

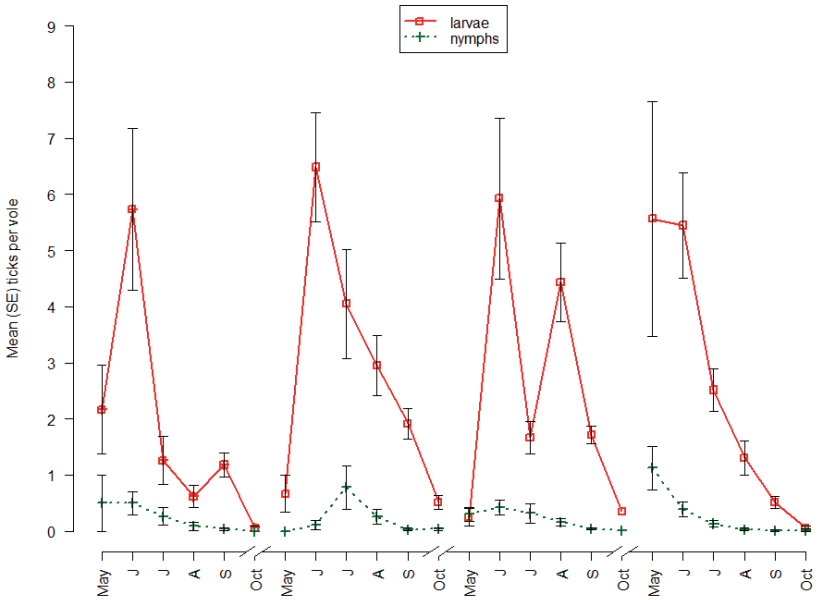

Figure S5. Vole infestation per session (± SE) with *I. ricinus* larvae and nymphs from May 2012 to October 2015

Table S4. Model selection table for models showed in Table 3. The abundance of infesting larvae was explained by month, year, bank vole sex, centered body mass (cBm) and cBm^2, infestation with ticks in other species or other stages (ItL (*I. trianguliceps* larvae), ItF (*I. trianguliceps* female), ItN (*I. trianguliceps* nymph), IrN (*I. ricinus* nymph)) and with fleas, abundance of questing larvae (Larv), vole abundance (MNA), and the interaction between sex and vole abundance and the interaction between sex and body mass

Model	AIC	Df
Full Model: Month + Year + Sex + cBm + cBm^2 + Sex *cBm + ItL + ItF + ItN + IrN + MNA + Larv + Fleas + Sex*MNA	3469.0	19
Month + Year + Sex + cBm + cBm^2 + Sex *cBm + ItL + ItF + ItN + IrN + MNA + Larv + Sex*MNA	3467.0	18
Month + Year + Sex + cBm + Sex *cBm + ItL + ItF + ItN + IrN + MNA + Larv + Sex*MNA	3465.1	17
Month + Year + Sex + cBm + Sex *cBm + ItF + ItN + IrN + MNA + Larv + Sex*MNA	3464.0	16

Table S5. Model selection table for models showed in Table 4. The abundance of infesting nymphs was explained by month, year, bank vole sex, centered body mass (cBm) and cBm^2, infestation with ticks in other stages or other species (ItL (*I. trianguliceps* larvae), ItF (*I. trianguliceps* female), ItN (*I. trianguliceps* nymph), IrL (*I. ricinus* larvae)) and with fleas, abundance of questing nymphs (Nymph), vole abundance (MNA), the interaction between sex and vole abundance and the interaction between sex and body mass

Model	AIC	Df
Full model: Month + Year + Sex + cBm + cBM^2 + ItL + ItN + ItF + IrL + Sex * Bm + Sex * MNA + MNA + Nymph + Fleas	708.55	19
Month + Sex + cBm + cBM^2 + ItL + ItN + ItF + IrL + Sex * Bm + Sex * MNA + MNA + Nymph + Fleas	702.82	16
Month + Sex + cBm + cBM^2 + ItL + ItN + ItF + IrL + Sex * Bm + Sex * MNA + MNA + Nymph	700.83	15
Month + Sex + cBm + cBM^2 + ItL + ItF + IrL + Sex * Bm + Sex * MNA + MNA + Nymph	698.93	14
Month + Sex + cBm + cBM^2 + ItL + ItF + IrL + Sex * Bm + Sex * MNA + MNA	697.15	13
Month + Sex + cBm + cBM^2 + ItL + ItF + IrL + Sex * Bm + MNA	695.96	12
Month + Sex + cBm + cBM^2 + ItL + ItF + Sex * Bm + MNA	695.16	11
Month + Sex + cBm + cBM^2 + ItL + ItF + MNA	695.57	10

Table S6. Additional model for the abundance of nymphs questing in the vegetation

Y = Nymph abundance in vegetation	Estimate(SE)	z-value	p-value
Intercept	-0.108(0.28)	-0.38	0.7028
2014	-0.709(0.38)	-1.85	0.0637
2015	-1.051(0.40)	-2.62	**0.0089**
June	-0.542(0.28)	-1.96	**0.0498**
July	-2.132(0.40)	-5.29	**<0.005**
August	-1.446(0.49)	-2.94	**<0.005**
September	-0.924(0.62)	-1.50	0.1331
October	-2.802(0.54)	-5.23	**<0.005**
Tot amount of larvae that fed on voles the year before	0.005(0.002)	2.69	**0.0071**
Amount of tick larvae questing at the same session	-0.078(0.03)	-2.69	**0.007**
Vole abundance	0.021(0.008)	2.55	**0.0109**
Random effect: site	σ2 = 0.1161 (SD =0.34)		
Negative binomial dispersion parameter	5.6955 (SE = 1.80)		
AIC	390.2		

Additional model for the abundance of *I. ricinus* nymphs questing in the vegetation with estimated coefficients (in log scale), explained by month (from May to October, with May as a reference), year (from 2013 to 2015, with 2013 as a reference), the total amount of larvae that fed on voles the year before, the amount of larvae in vegetation during the current session and the vole abundance. σ^2 is the variance attributable to random effect. Number of observations: total = 68, Site = 4

Table S7. Model selection table concerning the model showed in table S6. The abundance of questing nymphs was explained by month, year, vole abundance (MNA), the total amount of larvae that fed on voles the year before (LagY(Larv)), LagS(Larv): the total amount of larvae that fed on voles during the same summer (May and June), the amount of larvae (Larv) and adults (Ad) in vegetation during the same session

Questing nymphs (2)		Df	AIC	Δ
FULL	Year+Month+MNA+LagY(Larv)+LagS(Larv)+ Larv+Ad	15	400.2	4.61
Best	Month+MNA	9	396.9	1.29
	Larv+Month+MNA	10	395.6	0.00
	Larv+Year+Month+MNA+LagY(Larv)	13	396.9	1.31
	Larv+MNA+Month+ LagS(Larv)	11	397.5	1.89

II

SPATIAL HETEROGENEITIES AND THE ROLE OF TWO SYMPATRIC *IXODES*-TICK SPECIES IN PATHOGENS TRANSMISSION WITHIN RODENT POPULATIONS

by

Claire Cayol, Anu Jääskeläinen, Esa Koskela, Sami Kyröläinen, Tapio Mappes, Anja Siukkola & Eva R. Kallio 2017

Submitted manuscript

III

THE LYME DISEASE PATHOGEN ALTERS BREEDING SUCCESS IN A RODENT RESERVOIR HOST

by

Claire Cayol, Anna Giermek, Andrea Gomez-Chamorro, Jukka Hytönen, Eva R. Kallio, Tapio Mappes, Jemiina Salo, Maarten J. Voordouw, Esa Koskela
2017

Submitted manuscript

IV

COINFECTION DYNAMICS OF PUUMALA HANTAVIRUS AND VECTOR-BORNE PATHOGENS IN THE RESERVOIR HOST: A STATE-SPACE MODELLING APPROACH

by

Claire Cayol, Andrés López-Sepulcre, Andy Fenton, Esa Koskela, Sami Kyröläinen, Tapio Mappes, Tarja Sironen, Olli Vapalahti, Eva R. Kallio 2017

Manuscript