

ARTICLE

Disease Ecology

The circulation of *Anaplasma phagocytophilum* ecotypes is associated with community composition of vertebrate hosts

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Funding information

European Interreg North Sea Region programme; Naturvårdsverket, Grant/Award Numbers: NV-01337-15, NV-03047-16, NV-08503-18; Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Grant/Award Number: 022.005.021

Handling Editor: Tad A. Dallas

Abstract

Anaplasma phagocytophilum is a tick-borne pathogen that has been detected in many tick and vertebrate species. It is among the most widespread tick-borne pathogens in animals in Europe. The bacterium can be genetically divided into four ecotypes, which are linked to distinct but overlapping host species. However, knowledge about the transmission dynamics of the enzootic cycles of the different ecotypes is limited. Here, we quantified the link between the ecotypes of *A. phagocytophilum*, the different life stages of the tick *Ixodes ricinus*, and vertebrate host groups through a meta-analysis. We extracted data on the mean *I. ricinus* burden and the *A. phagocytophilum* infection prevalence in both hosts and feeding *I. ricinus* from 197 papers on 77 wildlife species. With this information, we modeled the relative importance of different host taxonomic groups for the circulation of the different ecotypes of *A. phagocytophilum* in a theoretical assemblage of hosts with varying presence of red deer (*Cervus elaphus*) and densities of small mammals. We showed that the composition of the vertebrate community affects the relative abundance of different ecotypes of *A. phagocytophilum* in the different life stages of *I. ricinus*. The presence of red deer is likely to increase the infection prevalence of Ecotype 1 in ticks, while small mammal densities drive the prevalence in ticks of mainly Ecotype 3, and to a lesser extent Ecotype 1. In Europe, vertebrate communities are changing, with an increase in red deer abundance and changes in the population dynamics of small mammals. Our results suggest that these changes could imply an increase in the circulation of *A. phagocytophilum* and thus an increase in the risk for public and veterinary health.

KEYWORDS

anaplasmosis, host assemblage, *Ixodes ricinus*, tick, tick-borne pathogen, transmission dynamics

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INTRODUCTION

Communities of vertebrate species are changing across Europe as a consequence of changes in distribution and population size of many species following changes in climate and land use, as well as increased legal protection. Among the species that show changes in distribution or population size are several of the hosts for *Ixodes ricinus*, the most important vector for tick-borne pathogens in Europe (Piesman & Eisen, 2008). For example, most ungulate species, that function as important hosts for adult *I. ricinus* (Hofmeester et al., 2016), have increased in both population size and distribution across Europe (Apollonio et al., 2010). These increases in abundance of ungulates have been linked to the increase in abundance of *I. ricinus* (Medlock et al., 2013). Simultaneously, population cyclicity in small mammals, which function as important hosts for larval *I. ricinus* (Hofmeester et al., 2016), has been flattened in the last decades and densities of small mammals in peak years have decreased (Cornulier et al., 2013). Densities of small mammals may vary widely over years due to population cyclicity, with densities in peak years 2–3 orders of magnitude higher than in low-phase years (Andreassen et al., 2021). In many rodent-borne pathogen systems, pathogen transmission and prevalence are dependent on host density (e.g., Khalil et al., 2019; Stenseth et al., 2006). Thus, the flattened cyclicity and decreased densities in peak years might also influence tick-borne pathogen dynamics (e.g., Krawczyk et al., 2020). It is thus important to study the role of different vertebrate hosts in a community perspective to better understand how changes in vertebrate populations might influence the transmission of tick-borne diseases.

Anaplasma phagocytophilum (previously known as a combination of *Ehrlichia phagocytophilia*, *Ehrlichia equi*, and *Ehrlichia* “HE agent”) (Dumler et al., 2001) is a tick-borne pathogen that can cause granulocytic anaplasmosis in humans and anaplasmosis or tick-borne fever in domestic ruminants (Stuen et al., 2013). In Europe, it is mainly transmitted by *I. ricinus* and found to infect a wide array of wildlife species, including both ungulates and small mammals (reviewed in Stuen et al., 2013). The prevalence of *A. phagocytophilum* in questing *I. ricinus* nymphs has been linked to the availability of red deer (*Cervus elaphus*) and fallow deer (*Dama dama*), and to some extent roe deer (*Capreolus capreolus*) (Takumi et al., 2021). Similarly, rodents seem to play an important role in the transmission of *A. phagocytophilum* (Bown et al., 2009). However, both groups of species might function as hosts in ecologically distinct transmission cycles.

Several ecotypes of *A. phagocytophilum* have been proposed (Jahfari et al., 2014), based on the genetic differences in the *groEL* gene. These ecotypes may have different

transmission cycles because each of them has been linked to a distinct range of vertebrate hosts (Bown et al., 2009; Jaarsma et al., 2019; Jahfari et al., 2014). Ecotype 1 has been found in many host species, including humans and livestock, while Ecotypes 2, 3, and 4 were mainly found in roe deer, rodents, and birds, respectively (Jahfari et al., 2014). Ecotype 1, therefore, seems to be the most important ecotype for human and veterinary health.

Management of anaplasmosis in humans and livestock would benefit from a better understanding of the links between the different ecotypes and the different species or taxonomic groups of the vertebrate host. Such an understanding could, for example, identify areas with an increased risk for anaplasmosis and provide insight into the consequences of environmental changes for disease risk, such as the consequences of changing wildlife communities. However, there are still many knowledge gaps regarding the enzootic transmission cycles of the different ecotypes, and even though the ecotypes have been found in specific host species, the relative contribution of these species in the transmission of the different ecotypes is unresolved.

In this study, we used a meta-analysis approach to quantify the role of different vertebrate host species in the circulation of different *A. phagocytophilum* ecotypes. First, we investigated the relationship between (1) the *I. ricinus* burden and infection prevalence of *A. phagocytophilum* in hosts and (2) this infection prevalence and the infection prevalence of *A. phagocytophilum* in feeding ticks of different life stages. Then, we quantified the role of the community composition of vertebrate hosts in the maintenance of the different ecotypes of *A. phagocytophilum* in *I. ricinus* in a theoretical host assemblage. Because of the expected relevance of small mammals and red deer in the transmission cycle of *A. phagocytophilum* and the fact that these species are showing large changes in their population size and distribution in Europe, we tested for the effect of changes of these species in several scenarios. In these scenarios, we changed (1) the density of small mammals to mimic peak years versus low-phase years and (2) the presence versus absence of red deer.

METHODS

We performed a systematic literature search in PubMed, Scopus, and Web of Science, to collect data on the *I. ricinus* burden on vertebrate species and the prevalence of *A. phagocytophilum* in vertebrate species and feeding *I. ricinus* (see Appendix S1 for the search string and other details). We only included papers that investigated vertebrate species in Europe during 1945–2018. Following the PRISMA guidelines for systematic reviews (Moher et al., 2009), and to correct for potential observation errors,

each paper was read by minimally two authors (all authors participated in this effort) who independently extracted the data, after which the data were compared and cross-checked, as well as double-checked when found to differ. From the 11,015 unique papers identified by the search string, we extracted data from 197 papers on 77 vertebrate species. The other papers were excluded based on our exclusion criteria (Appendix S1). We calculated the mean tick burden per vertebrate species, the mean infection prevalence of *A. phagocytophilum* in the vertebrate species, and the mean infection prevalence of *A. phagocytophilum* in feeding ticks, as defined by Kahl et al. (2002) (see Appendix S1 for these calculations).

We used an approach similar to Hofmeester et al. (2016) to quantify the relative importance of a vertebrate host species for producing engorged *I. ricinus* infected with *A. phagocytophilum*. This relative importance is defined as the proportional contribution of a particular host species to the total number of engorged *I. ricinus* infected with *A. phagocytophilum* in a certain area in relation to that of other host species (extension of the definition for relative reservoir capacity by Kahl et al., 2002). The relative importance of a host species (among all n species) for producing engorged *I. ricinus* ticks infected with the different ecotypes of *A. phagocytophilum* was calculated using Formula 1 (adjusted from Hofmeester et al., 2016). We explain this formula for larvae:

$$\psi_{ix} = \frac{\sigma_i D_i \chi_i e_x}{\sum_{j=1}^n \sigma_j D_j \chi_j e_x}, \quad (1)$$

where ψ_{ix} is the relative importance of species i for producing engorged larvae infected with *A. phagocytophilum* ecotype x , σ_i is the mean larval burden of species i , D_i is the density (number per square kilometer) at which species i occurs, χ_i is the infection prevalence in feeding larvae on host species i , and e_x is the proportion of infected ticks that are expected to be infected with ecotype x . The denominator, $\sum_{j=1}^n \sigma_j D_j \chi_j e_x$, is the total number of feeding larvae infected by all species within a host assemblage, as determined by their mean larval burden, their densities, the infection prevalence in feeding larvae, and the expected proportion of ticks infected with ecotype x . The relative importance of species i for producing engorged *A. phagocytophilum* infected nymphs or adults is obtained through the same formula, with appropriate interpretation of the parameters in Formula 1. For visualization and interpretation purposes, we determined the total number of ticks infected during feeding, which is the denominator of Formula 1, as well as the relative importance of each host species or taxonomic group. Furthermore, we calculated the proportion of ticks infected during feeding per life stage on all host species

within the theoretical host assemblage in relation to all feeding ticks of that life stage using Formula 2. For larvae, this formula reads as follows:

$$I = \frac{\sum_{j=1}^n \sigma_j D_j \chi_j e_x}{\sum_{j=1}^n \sigma_j D_j}, \quad (2)$$

where I is the proportion of feeding larvae infected with *A. phagocytophilum* ecotype x within a host assemblage, $\sum_{j=1}^n \sigma_j D_j \chi_j e_x$ is the total number of feeding larvae that get infected on all host species within a host assemblage, and the denominator, $\sum_{j=1}^n \sigma_j D_j$, is the total number of larvae fed by all species within a host assemblage. The proportion of feeding nymphs and adults infected with *A. phagocytophilum* ecotype x was obtained through the same formula, with appropriate interpretation of the parameters in Formula 2.

The relative importance of a host species depends on which other potential host species are present in a host community and at what densities. Therefore, we selected host species to include in a theoretical host assemblage to perform our calculations. For ease of visualization and interpretation purposes, we grouped host species in taxonomic groups: small mammals (<1 kg), medium-sized mammals (1–20 kg), ungulates and medium-sized birds (22–42 cm). We only selected species for which we obtained the mean tick burden of all tick life stages and the infection prevalence with *A. phagocytophilum* in hosts in our meta-analysis ($n = 18$; Appendix S2: Table S1). We thus included four ungulate species that are dominant in different parts of Europe, the red fox (*Vulpes vulpes*) as medium-sized mammal, four dominant small mammal species in northwestern Europe, and one dominant medium-sized bird species in the theoretical host assemblage (Table 1; Bjärvall & Ullström, 1995; Cramp & Perrins, 1994; Ecke & Hörnfeldt, 2021). For each of the species included in the theoretical host assemblage, we determined the order of magnitude of their density (number per square kilometer) based on data from published literature (Table 1; Cramp & Perrins, 1994; Hörnberg, 2001; Niethammer & Krapp, 1978). Due to lack of data, we unfortunately could not include fallow deer and a large number of other common vertebrate host species, including many medium-sized mammals and birds, in our theoretical host assemblage.

To determine the potential changes in *A. phagocytophilum* transmission dynamics due to the introduction of red deer and population fluctuations of small mammals, we created four different scenarios that change part of our theoretical host assemblage. These scenarios differed to include all combinations of two changing factors: (1) two density estimates for small mammals—a density for the low phase and a density for the high phase that were modeled

TABLE 1 Constitution of the theoretical host assemblage with their taxonomic class and the order of magnitude of the density for the vertebrate species used in the calculations.

Species	Taxonomic class	Density (no. km ⁻²)				Density reference
		With red deer		No red deer		
		Low	Peak	Low	Peak	
<i>Alces alces</i>	Ungulate	10 ⁰	10 ⁰	10 ⁰	10 ⁰	Hörnberg (2001)
<i>Apodemus sylvaticus</i>	Small mammal	10 ²	10 ³	10 ²	10 ³	Niethammer and Krapp (1978)
<i>Capreolus capreolus</i>	Ungulate	10 ¹	10 ¹	10 ¹	10 ¹	Niethammer and Krapp (1978)
<i>Cervus elaphus</i>	Ungulate	10 ⁰	10 ⁰	0	0	Niethammer and Krapp (1978)
<i>Microtus agrestis</i>	Small mammal	10 ²	10 ³	10 ²	10 ³	Niethammer and Krapp (1978)
<i>Myodes glareolus</i>	Small mammal	10 ²	10 ³	10 ²	10 ³	Niethammer and Krapp (1978)
<i>Sorex araneus</i>	Small mammal	10 ²	10 ³	10 ²	10 ³	Niethammer and Krapp (1978)
<i>Sus scrofa</i>	Ungulate	10 ⁰	10 ⁰	10 ⁰	10 ⁰	Niethammer and Krapp (1978)
<i>Turdus merula</i>	Medium-sized bird	10 ²	10 ²	10 ²	10 ²	Cramp and Perrins (1994)
<i>Vulpes vulpes</i>	Medium-sized mammal	10 ⁰	10 ⁰	10 ⁰	10 ⁰	Niethammer and Krapp (1978)

Note: Low, density of small mammals in low-phase density; Peak, density of small mammals in peak phase density.

with a 10-fold difference (see Table 1); and (2) with and without red deer present in the theoretical host assemblage. The presence and density of all other host species were equal in all scenarios. We did not explore scenarios without roe deer present, because we were mainly interested in changes in abundances of hosts that play a role in the transmission of the zoonotic Ecotype 1, and because in Europe there are generally no areas where roe deer do not occur (yet) and *I. ricinus* do. Therefore, excluding roe deer would violate our assumption that tick densities were similar among scenarios.

We used generalized linear models with a binomial distribution to test for a relationship between the *I. ricinus* burdens per tick life stage and the *A. phagocytophilum* infection prevalence in hosts, and between the infection prevalence in hosts and the infection prevalence in feeding ticks of each life stage. We log₁₀-transformed the tick burden of all tick stages in these models to adjust for overdispersion in the data. To adjust for the presence of zeroes, we replaced these with the lowest potential non-zero tick burden (i.e., in total, one tick feeding on all sampled individuals of the host species). Infection prevalence of *A. phagocytophilum* in feeding *I. ricinus* was only available for a few vertebrate species and tick stages (Appendix S2: Table S1). Therefore, we used the relationships that we found between infection prevalence in hosts and infection prevalence in feeding ticks (Figure 1d–f) to predict the infection prevalence in feeding ticks for all the host species that we included in our theoretical host assemblage. These predicted values were used in subsequent analyses (Table 2).

Only a few papers (8 of 197) reported the specific ecotype of *A. phagocytophilum* infections. Jaarsma et al.

(2019), not included in our literature review, sequenced *A. phagocytophilum* positive samples from multiple vertebrate species and ticks. Based on the results from this study, and the ecotypes that were reported in the papers included in our literature review, we predicted the ecotype of the *A. phagocytophilum* positive ticks that fed on the host species that were included in our theoretical host assemblages (Table 2; see Appendix S1 for details behind these predictions).

We performed all analyses and visualizations in R version 3.6.0 (R Core Team, 2019) using the packages *tidyverse*, *ggpubr*, *grid*, and *gridExtra* (Auguie & Antonov, 2017; Kassambara, 2020; Murrell, 2019; Wickham and Rstudio, 2017). We used an α value of 0.05, unless stated otherwise.

RESULTS

Overall, we extracted data on *I. ricinus* burden, *A. phagocytophilum* infection prevalence in the host, and/or *A. phagocytophilum* infection prevalence in feeding *I. ricinus* for 77 vertebrate species from published studies. Of these 77 species, larval, nymphal, and/or adult *I. ricinus* burden could be estimated for 50 species (Appendix S2: Table S1). The highest mean larval and nymphal burden were found on mountain hare (*Lepus timidus*; 416 larvae and 87 nymphs per individual, based on two studies), while European roe deer had the highest mean adult burden with 18 adults per individual (based on eight studies; Appendix S2: Table S1).

The *A. phagocytophilum* infection prevalence in hosts was estimated for 46 vertebrate species, of which the

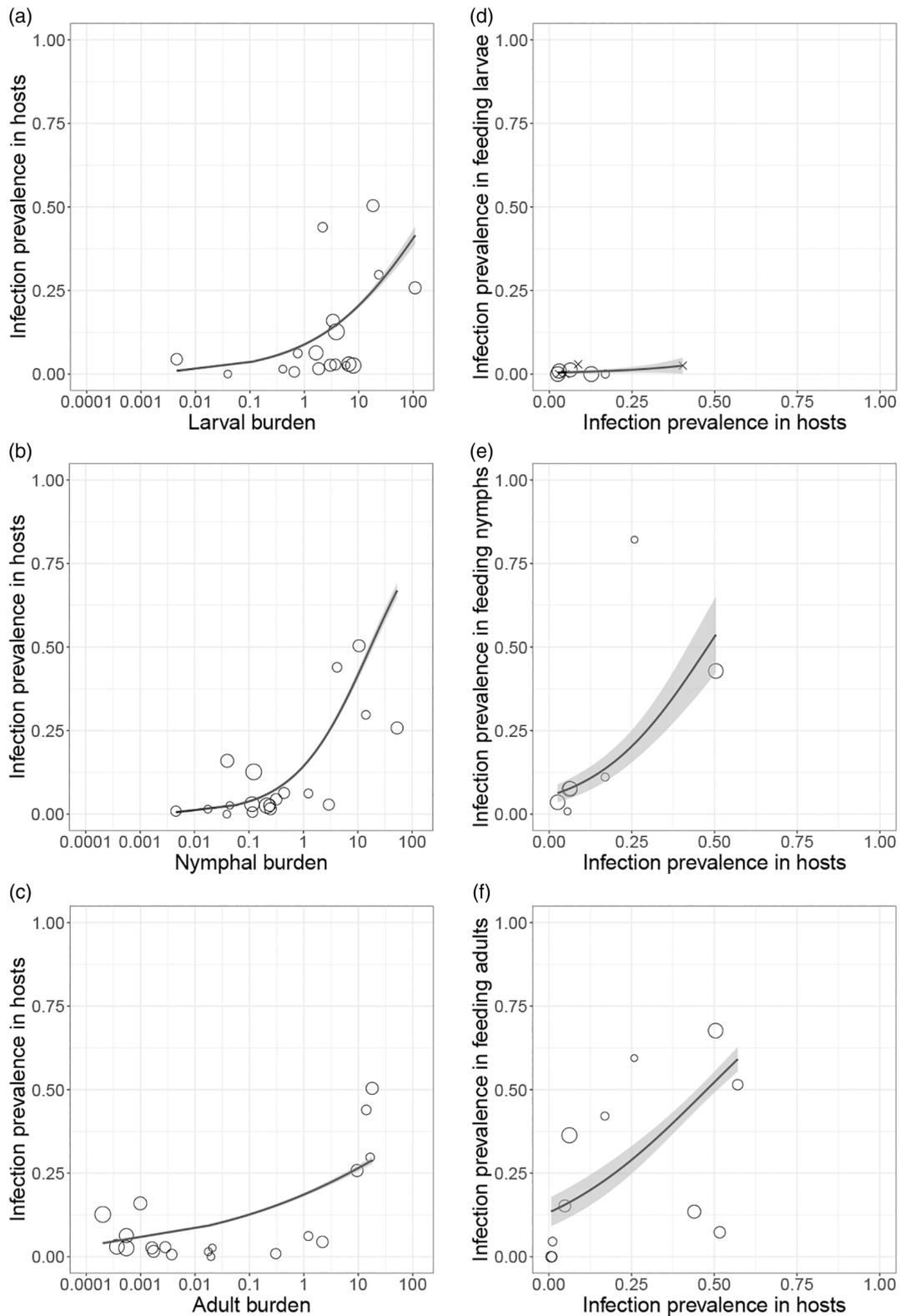


FIGURE 1 Correlations among mean *Ixodes ricinus* burden and the mean *Anaplasma phagocytophilum* infection prevalence in vertebrate hosts and feeding *I. ricinus*, per host species. *A. phagocytophilum* infection prevalence in hosts as a function of (a) larval burden, (b) nymphal burden, and (c) adult burden. Infection prevalence in (d) feeding larvae, (e) feeding nymphs, and (f) feeding adults as a function of the infection prevalence in hosts. For each graph, the sample size of the value on the y-axis is represented by the size of the circles in the plot, and the 95% CI is given with gray shading. In (d), the values of the infection prevalence in hosts that were predicted according to the correlation between the infection prevalence in hosts and the nymphal burden are shown as × (see main text for more details).

TABLE 2 Constitution of the theoretical host assemblage with predicted the tick burden per species.

Species	Tick burden			Predicted infection prevalence in feeding ticks			Predicted proportion of ecotypes			
	L	N	A	L	N	A	1	2	3	4
<i>Alces alces</i>	23.4	14.1	16.6	0.02	0.26	0.33	0.65	0.35	0.00	0.00
<i>Apodemus sylvaticus</i>	6.5	0.1	0.0	0.00	0.06	0.15	0.07	0.04	0.88	0.02
<i>Capreolus capreolus</i>	18.2	10.5	18.0	0.04	0.54	0.53	0.15	0.85	0.00	0.00
<i>Cervus elaphus</i>	2.2	4.2	14.0	0.03	0.44	0.46	0.94	0.06	0.00	0.00
<i>Microtus agrestis</i>	1.6	0.4	0.0	0.01	0.08	0.16	0.07	0.04	0.88	0.02
<i>Myodes glareolus</i>	3.9	0.1	0.0	0.01	0.11	0.20	0.07	0.04	0.88	0.02
<i>Sorex araneus</i>	3.3	0.0	0.0	0.01	0.13	0.22	0.07	0.04	0.88	0.02
<i>Sus scrofa</i>	0.8	1.2	1.2	0.01	0.08	0.16	0.94	0.06	0.00	0.00
<i>Turdus merula</i>	3.7	2.9	0.0	0.00	0.06	0.15	0.56	0.05	0.00	0.39
<i>Vulpes vulpes</i>	0.0	0.3	2.2	0.01	0.07	0.15	1.00	0.00	0.00	0.00

Note: These values are used to calculate the relative importance of the different host species within the theoretical host assemblage (see Formula 1). Abbreviations: A, adult; L, larval; N, nymphal.

highest infection prevalence was found in the European roe deer (50%, based on 44 studies), fallow deer (52%, based on 15 studies), and mouflon (*Ovis orientalis*; 57%, based on 9 studies) (Appendix S2: Table S1). *A. phagocytophilum* infection prevalence in hosts increased with the *I. ricinus* burden for all life stages (larvae: $\beta = 0.97$, 95% CI = 0.90–1.05, $p < 0.001$; nymphs: $\beta = 1.45$, 95% CI = 1.39–1.50, $p < 0.001$; adults: $\beta = 0.46$, 95% CI = 0.43–0.48, $p < 0.001$; Figure 1a–c).

We estimated the *A. phagocytophilum* infection prevalence in feeding larval, nymphal, and adult *I. ricinus* for 9, 10, and 13 vertebrate species, respectively (Appendix S2: Table S1). The highest infection prevalence was found in feeding larvae from the common nightingale (*Luscinia megarhynchos*; 3%, based on one study), in nymphs from the western European hedgehog (*Erinaceus europaeus*; 82%, based on one study) and European roe deer (43%, based on two studies), and in adults from European roe deer (68%, based on three studies), the western European hedgehog (59%, based on one study), and mouflon (52%, based on one study). *A. phagocytophilum* infection prevalence in feeding nymphs and adults increased with host infection prevalence (nymphs: $\beta = 5.96$, 95% CI = 4.54–7.44, $p < 0.001$; adults: $\beta = 3.94$, 95% CI = 3.18–4.75, $p < 0.001$; Figure 1e,f), but not for larvae ($\beta = -6.87$, 95% CI = -53.55 to 20.56, $p = 0.671$), for which we note the low sample size ($n = 5$ species). As we wanted to include the predicted infection prevalence in feeding ticks in our estimates of relative importance based on these correlations, we tried to utilize the available data as much as possible. We thus wanted to include the four species for which infection prevalence in larvae was available, but data on the infection prevalence in the host were lacking. Based on the relation between the

nymphal burden and the *A. phagocytophilum* infection prevalence in hosts, we predicted the infection prevalence in host species for which we had data on the nymphal burden and the infection prevalence in feeding larvae but lacked data on the host infection prevalence ($n = 4$ bird species). After including these predicted values, infection prevalence in feeding larvae increased with host infection prevalence ($\beta = 4.51$, 95% CI = 0.34–8.74, $p = 0.035$; Figure 1d).

In our theoretical host assemblages, the number and proportion of feeding ticks that got infected with *A. phagocytophilum* Ecotypes 1, 2, and 4 increased from larvae to nymphs (Figure 2). In contrast, the number of feeding ticks infected with *A. phagocytophilum* Ecotype 3 decreased from larvae to nymphs, while the proportion increased (Figure 2). From nymphs to adults, the proportion of ticks infected with Ecotype 1 increased, just as the number and proportion of ticks infected with Ecotype 2 (Figure 2). For *A. phagocytophilum* Ecotypes 3 and 4, the number and proportion of feeding ticks decreased to negligible levels from nymphs to adults (Figure 2). When small mammals occurred in high densities, the number of feeding larvae and nymphs infected with *A. phagocytophilum* Ecotypes 1, 2, or 3 were higher than when they occurred in low densities, while there were no differences for Ecotype 4 (Figure 2). The presence of red deer only increased the number of feeding adults infected with *A. phagocytophilum* Ecotype 1, while the proportion of feeding adults infected with Ecotype 1 or 2 both increased (Figure 2). We want to highlight that the relative importance of the different taxonomic host groups for producing feeding ticks infected with *A. phagocytophilum* Ecotype 1 varied among the life stages of *I. ricinus*. In contrast, for Ecotypes 2, 3, and

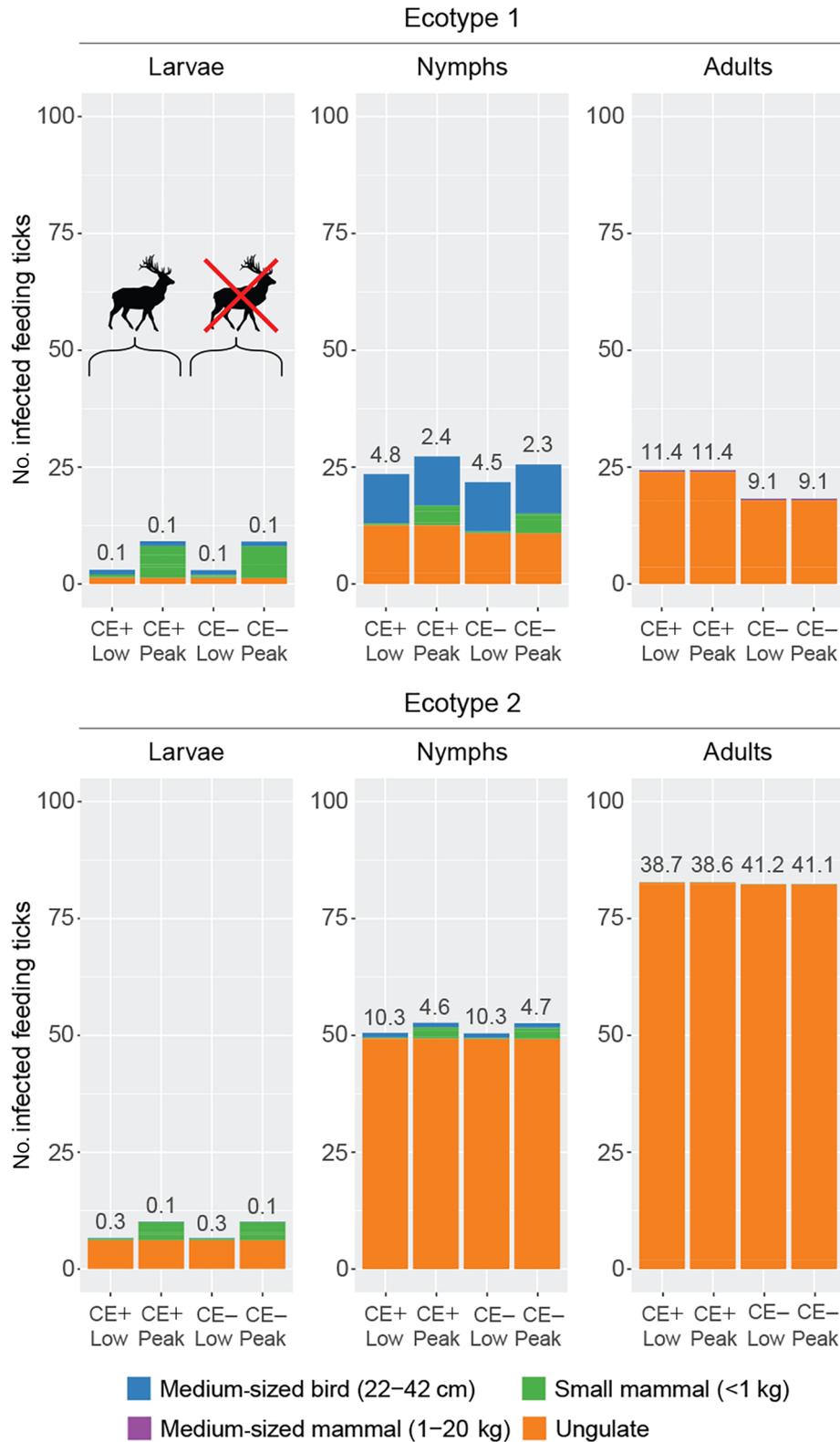


FIGURE 2 The expected number of feeding *Ixodes ricinus* infected with *Anaplasma phagocytophilum* per life stage in four host communities, per ecotype, and the relative contribution of different host taxonomic groups to the production of these engorged infected *I. ricinus*. Values on top of bars represent the percentage of feeding ticks that are infected within a host assemblage. CE+ denotes host assemblages with red deer (*Cervus elaphus*) included, while CE– denotes host assemblages where red deer is excluded. In host assemblages denoted with low, small mammal species were modeled at low-phase densities, while in host assemblages denoted with peak, they were modeled at peak phase densities. Silhouettes by Sander Vink.

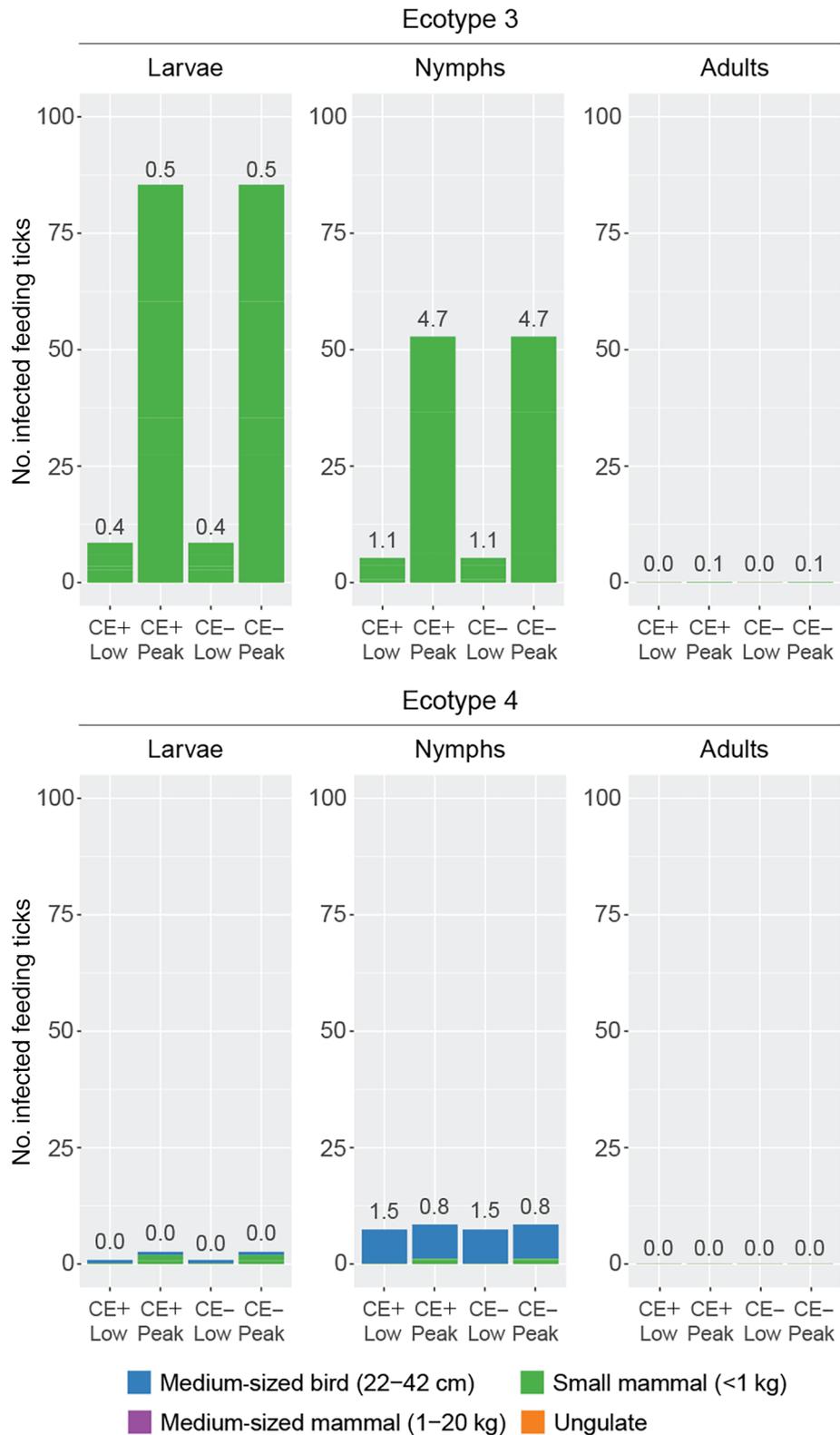


FIGURE 2 (Continued)

4, the relative importance is mainly dominated by one taxonomic group for all life stages of *I. ricinus*: Ecotype 2 by ungulates (varying from 61% to 100%), Ecotype 3 by small

mammals (100%), and Ecotype 4 by medium-sized birds (varying from 26% to 98%) (Figure 2; Appendix S2: Table S2).

DISCUSSION

To manage anaplasmosis in humans and livestock, and potentially identify areas with an increased risk for anaplasmosis, it is important to quantify links between vertebrate hosts and *A. phagocytophilum*. This is specifically important at the level of ecotypes, since these have different pathogenic properties for humans and (domestic) animals (Jahfari et al., 2014). In this study, we quantified for the first time how different host species occurring at different densities could influence the presence of ticks infected with the different ecotypes of *A. phagocytophilum*. A previous review, Stuenkel et al. (2013), described that, both in the United States and in Europe, two large groups of vertebrates have been identified to be infected with *A. phagocytophilum*, namely ungulates and small mammals. We confirmed these results and found that these two groups had the highest relative importance for producing ticks infected with *A. phagocytophilum*, specifically for Ecotypes 1, 2, and 3. Furthermore, ungulates and small mammals have also been described as important hosts for feeding *I. ricinus* ticks, where ungulates feed the majority of adults and small mammals the majority of larvae (Hofmeester et al., 2016).

We found that, for all life stages of *I. ricinus*, the *A. phagocytophilum* infection prevalence in host species increased with the tick burden (Figure 1). This correlation can be interpreted in two, not mutually exclusive, ways. First, it indicates that the chance of a host to get infected with *A. phagocytophilum* likely increases when it feeds on more ticks, but second it also indicates that if an individual is infected with *A. phagocytophilum*, it likely feeds on more ticks that could become infected. The latter is further amplified by the fact that the infection prevalence in feeding nymphs and adults increased with the infection prevalence in hosts (Figure 1). For larvae this pattern was less strong, possibly because we found a generally low infection prevalence in larvae. These correlations seem very similar to what was previously suggested for *Borrelia burgdorferi* s.l., albeit with a stronger focus on nymphs and adults (Hofmeester et al., 2016). The increase of *A. phagocytophilum* infection prevalence in hosts with larval burden needs an explanation as questing larvae are thought to be uninfected with *A. phagocytophilum* due to the absence or inefficiency of transovarial transmission in *I. ricinus* (Hauck et al., 2020). We expect that the correlation with larval burden was likely caused by general positive correlations of the tick burden of the three life stages (Appendix S2: Table S1), as well as the previous finding that tick burden of all life stages increased with host body mass (Hofmeester et al., 2016). This indicates that hosts are likely infected by

either of the later stages and the positive correlation with larval burden is spurious.

The host species that we could include in our analyses were limited because some species are highly understudied. Hofmeester et al. (2016) identified several common vertebrate species as understudied, and we did not see an increase in studies on these species. These include Eurasian jay (*Garrulus glandarius*), Eurasian red squirrel (*Sciurus vulgaris*), European badger (*Meles meles*), European pine marten (*Martes martes*), great spotted woodpecker (*Dendrocopos major*), and Eurasian pygmy shrew (*Sorex minutus*). Furthermore, we identified two new species for which data were lacking, fallow deer and western European hedgehog. In recent years, some papers have been published regarding some of these species, which we either included in our meta-analysis (Coipan et al., 2018; Jahfari et al., 2017; e.g., Myrsterud et al., 2015) or which did not fulfill our selection criteria (e.g., Dziemian et al., 2015; Fabri et al., 2021; Furness & Furness, 2018; Hofmeester et al., 2018; Marsot et al., 2012; Myrsterud et al., 2021). In addition, our knowledge on infection prevalence of feeding *I. ricinus* with *A. phagocytophilum* is especially limited, with only data for 19 vertebrate host species (of the 77 species included in this study). For this reason, and the limited sample sizes, we had to predict the infection prevalence in *I. ricinus* for the species in our theoretical host assemblage. This prediction, however, does not take into account the difference among the host species in their efficiency to transmit the pathogen. This means that for species that are less efficient in their transmission, the infection prevalence in *I. ricinus* might be overpredicted, while for species that are more efficient, it is underpredicted. However, the general results should be robust even though the exact numbers and importance of individual host species will differ among study areas as a consequence of many factors including the population history of different host species, interactions among host species, indirect effects of hosts on tick populations, and other factors that we did not consider in our theoretical host assemblage.

The presence of red deer had a positive effect on the number and proportion of feeding ticks infected with *A. phagocytophilum* Ecotype 1 (Figure 2). Consequently, this also means that there was a positive effect on the proportion of questing ticks infected with *A. phagocytophilum* of the next life stage, under the assumption that the pathogen does not alter the survival of the tick. This positive effect of the presence and high density of red deer has been shown before in field studies (Rosef et al., 2009; Takumi et al., 2021), although others failed to find this relationship (Bown et al., 2008; Myrsterud et al., 2013). According to Takumi et al. (2021), not only red deer but also fallow deer, and to some extent roe deer, determined

the density of questing nymphal *I. ricinus* infected with *A. phagocytophilum*. However, due to insufficient data on fallow deer, we could not include this species in our analyses, and we decided not to explore scenarios excluding roe deer, since that would violate our assumption of similar tick densities among scenarios. We also found an effect of different densities of small mammals on the number and proportion of feeding ticks infected with multiple ecotypes of *A. phagocytophilum*. In general, the number of feeding ticks infected with *A. phagocytophilum* increased with higher densities of small mammals, as expected (Figure 2). This increase was more pronounced for Ecotype 3, where small mammals had a higher relative importance for producing feeding ticks infected with *A. phagocytophilum*. To our knowledge, no field studies have been published that investigated the relationship between the density of small mammals and the density of questing *I. ricinus* ticks infected with *A. phagocytophilum*. It has been shown, however, that the density of questing nymphs as well as the density of questing nymphs infected with *B. burgdorferi*, *Borrelia afzelli*, and *Neoehrlichia mikurensis* can increase with small mammal density (Krawczyk et al., 2020; Ostfeld et al., 2001), but not always (Hofmeester et al., 2017).

The vertebrate host communities in Europe are constantly changing. Therefore, the effects of the presence of red deer and the densities at which small mammals occur on the number and proportion of feeding ticks infected with *A. phagocytophilum* could have important implications for public and veterinary health. An increase in the abundance of red deer, but also of other ungulate species, has been observed in Europe (Apollonio et al., 2010). Furthermore, cyclicity and outbreaks of small mammal densities occur throughout Europe, although the drivers behind these dynamics might differ from region to region (Andreassen et al., 2021). Densities of small mammals can also differ significantly between geographically close areas due to differences in ecological drivers of small mammal population dynamics (e.g., Ecke et al., 2010). The exact implications of these changes for the circulation of *A. phagocytophilum* cannot be determined with this meta-analysis, partly due to a lack of data. There is thus a clear need for further studies on the role of red and fallow deer, but also other deer species like roe deer, in the circulation of *A. phagocytophilum* Ecotype 1, and how their densities and distribution are related to the density of ticks infected with *A. phagocytophilum* Ecotype 1. The relationship between small mammal densities and the density of questing nymphs infected with *A. phagocytophilum* also needs further investigation.

Our results show that the proportion of feeding ticks infected with *A. phagocytophilum* Ecotype 1 or 2 in the whole host community increased greatly from larvae to nymphs, and again from nymphs to adults (Figure 2). These results suggest that for both Ecotypes 1 and 2, ticks mainly become infected while feeding as nymphs or adults. However, the infections of feeding adults will likely not influence the dynamics of *A. phagocytophilum* since transovarial transmission in ticks is absent or inefficient (Hauck et al., 2020). Furthermore, the proportion of feeding larvae and nymphs infected with *A. phagocytophilum* Ecotypes 1 and 2 was low. Therefore, we suspect that Ecotypes 1 and 2 are maintained through the high infection prevalence in hosts as a result of their high relative importance for feeding the adult stage (Hofmeester et al., 2016). Because of this high relative importance, only a few immature ticks need to be infected to maintain the high infection prevalence in a few key host species. This is comparable to that proposed previously for *Borrelia garinii* circulating between larvae and nymphs (Hofmeester et al., 2016). Furthermore, it is in line with the suggestion that *A. phagocytophilum* Ecotypes 1 and 2 mainly circulate between *I. ricinus* nymphs and adults (Takumi et al., 2019). In contrast, the number of feeding adults infected with *A. phagocytophilum* Ecotype 3 was negligible, and this raises the hypothesis that the circulation of Ecotype 3 is maintained by *I. ricinus* larvae and nymphs, similar to what has been suggested for the circulation of *B. afzelli* (Hofmeester et al., 2016). We, however, cannot exclude the role of other tick species in the circulation of *A. phagocytophilum* Ecotype 3. Bown et al. (2008) found evidence for *Ixodes trianguliceps*, but not *I. ricinus*, transmitting *A. phagocytophilum* Ecotype 3. This could indicate that *I. trianguliceps* plays a bigger role in the circulation of *A. phagocytophilum* Ecotype 3 than *I. ricinus*. Because of the generally low infection prevalence of *A. phagocytophilum* Ecotype 4 in *I. ricinus*, we expect that other tick species maintain the circulation of this ecotype. *A. phagocytophilum* Ecotype 4 has been found in *Ixodes frontalis* feeding on birds and in questing *Ixodes ventralis* (Jaarsma et al., 2019).

Few studies have looked at the different ecotypes of *A. phagocytophilum* in wildlife and *I. ricinus* feeding on wildlife (Chastagner et al., 2017; Hildebrand et al., 2018; Hofmeester et al., 2018; Kazimírová et al., 2018). Therefore, we had to predict the ecotype distribution in feeding *I. ricinus* for our models based on the presence of the different ecotypes in host species according to the literature (Chastagner et al., 2017; Jaarsma et al., 2019; Jahfari et al., 2014; Kazimírová et al., 2018). With this method, we assumed that the distribution of the ecotypes among the feeding *I. ricinus* is the same as the distribution

of the ecotypes among the host species as published in previous studies (Jaarsma et al., 2019; Jahfari et al., 2014). However, the number of studies on which we based our assumptions was limited and we cannot rule out that different ecotypes have different species-specific transmission rates. This should be a priority research area to improve our predictions on how different wildlife species maintain different ecotypes of *A. phagocytophilum*.

CONCLUSIONS

In this meta-analysis, we show that only a few vertebrate host taxa are involved in the circulation of the different ecotypes of *A. phagocytophilum* in *I. ricinus* ticks. Specifically, we show that the presence of red deer likely increases the prevalence of Ecotype 1 in feeding ticks, while small mammal densities drive the prevalence of mainly Ecotype 3 in feeding ticks. We hypothesize that this is also the case for the prevalence of these ecotypes in questing nymphs and adults, but this needs to be investigated further. Our results suggest that the increase in distribution and population size of red deer, which has been observed in many parts of Europe (Apollonio et al., 2010), could lead to an increase in questing *I. ricinus* infected with *A. phagocytophilum* Ecotype 1 and thus an increased risk to public and veterinary health. A similar pattern might be true for fallow deer that show a similar increase in distribution and population size throughout Europe (Apollonio et al., 2010), although data on tick burdens and *A. phagocytophilum* infection prevalence for this species are sparse. A recent study, however, found that fallow deer likely play an important role in the transmission of *A. phagocytophilum* (Fabri et al., 2021). Furthermore, our results suggest an important role for fluctuations in small mammal densities in determining the prevalence of mainly *A. phagocytophilum* Ecotype 3, but also of Ecotype 1. As small mammal populations in Europe are experiencing changes in their population dynamics (Cornulier et al., 2013), this might have important implications for the circulation of Ecotype 3 and, to a lesser extent, of Ecotype 1. However, we also identified a large knowledge gap when it comes to the prevalence of the different ecotypes of *A. phagocytophilum* in wildlife vertebrate hosts and feeding *I. ricinus* ticks. We thus urge for more studies of the changing dynamics of this seemingly increasing microorganism that is of importance for both public and veterinary health.

ACKNOWLEDGMENTS

The study received support from the Swedish Environmental Protection Agency (Naturvårdsverket, NV-01337-15/NV-03047-16/NV-08503-18). Hein Sprong was supported by a grant from the European Interreg North Sea

Region program, as part of the NorthTick project. Nannet Doreen Fabri was supported by a grant from the Dutch Research Council (NWO; 022.005.021). The authors thank Chantal van de Poel, Maaïke de Jong, Kas Swinkels, and Aleksandra Krawczyk for their contributions in the data collection, and Sander Vink for drawing the silhouettes used in this paper.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data and code (Fabri, 2022) are available from Zenodo: <https://doi.org/10.5281/zenodo.6645193>.

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How to cite this article: Fabri, Nannet Doreen, Hein Sprong, Hans Heesterbeek, Frauke Ecke, Joris Petrus Gerardus Marinus Cromsigt, and Tim Ragnvald Hofmeester. 2022. “The Circulation of *Anaplasma Phagocytophilum* Ecotypes is Associated with Community Composition of Vertebrate Hosts.” *Ecosphere* 13(9): e4243. <https://doi.org/10.1002/ecs2.4243>