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Effects of tick population dynamics and host densities on the persistence of tick-borne infections

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Abstract

The transmission and the persistence of tick-borne infections are strongly influenced by the densities and the structure of host populations. By extending previous models and analysis, in this paper we analyse how the persistence of ticks and pathogens, is affected by the dynamics of tick populations, and by their host densities. The effect of host densities on infection persistence is explored through the analysis and simulation of a series of models that include different assumptions on tick–host dynamics and consider different routes of infection transmission. Ticks are assumed to feed on two types of host species which vary in their reservoir competence. Too low densities of competent hosts (i.e., hosts where transmission can occur) do not sustain the infection cycle, while too high densities of incompetent hosts may dilute the competent hosts so much to make infection persistence impossible. A dilution effect may occur also for competent hosts as a consequence of reduced tick to host ratio; this is possible only if the regulation of tick populations is such that tick density does not increase linearly with host densities.

Keywords: Tick-borne infections; Tick population dynamics; Basic reproduction number; Host density; Dilution effect

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1. Introduction

Tick-borne zoonotic diseases constitute an important public health problem that has increased over the past 20 years as people increasingly spend leisure time near woodlands and countryside. These infections are characterized by an intricate set of ecological and epidemiological relationships between pathogen, tick vector, vertebrate hosts, and humans, which largely determine their spatial and temporal dynamics.

Several authors have used mathematical models to investigate the effects of various biotic and abiotic factors on temporal and spatial population dynamics of ticks [1,2].

Detailed models based on information about local climate conditions in a specific tick-infested area have been developed with this specific aim. By using meteorological data from satellites, accurate up-to-date information about microclimate conditions from one month to the next can be obtained, and these might be correlated with what is happening to the tick population.

For instance a consistent correlation has been found between how rapidly the temperature cools in the autumn and the feeding patterns of the larval and nymphal stages of the tick the following year; this factor is considered to be very important in the transmission of tick-borne encephalitis [3].

Many studies, mainly in the United States, have focussed instead on the effect of biotic factors such as biodiversity, in terms of species richness, on the persistence of Lyme disease [4–6]. As ticks can feed on many different animals and every species has a unique reservoir competence, or ability to carry and transmit the pathogen, the presence of different food sources might affect disease incidences. For Lyme disease in the US, where the most important reservoir is the white-footed mouse, it has been shown that the greater the relative abundance of non-mouse hosts, the lower the percentage of ticks infected with Borrelia [5]. This suggests that the preservation of vertebrate biodiversity and community composition can reduce the incidence of Lyme disease [6].

An important advance in our understanding of how tick-borne pathogens persist in natural systems, was the discovery of non-systemic transmission of infection through co-feeding ticks on some host species [7]; this kind of transmission is considered to be crucial for the persistence of some infections, notably the tick-borne encephalitis virus complex [8].

On the other hand, trans-ovarial transmission, from adult ticks to offspring, may occur but its frequency is very low and its contribution to transmission is generally thought to be negligible [9].

Because of the special features of tick dynamics, over the recent years several mathematical models have been devoted to either tick population dynamics (e.g. [10–13]), or tick-borne infections [14–18].

A basic concept in epidemic theory is the reproduction number, R_0, defined in [19] as the spectral radius of the next-generation matrix, that specifies the expected number of cases in the next generation of infections given the distribution of infectious individuals in the present generation. In most models, the epidemics can persist only if $R_0 > 1$. Sometimes, other threshold quantities S are derived studying the Jacobian matrix at the infection-free steady state; this will be unstable (and the epidemic will persist) only if $S > 1$. Such quantities have the same threshold behaviour of R_0, even though they do not have the same biological interpretation [20].

Norman et al. [17] computed a threshold value for tick-borne infections and showed the so-called dilution effect: when two alternative hosts exist for ticks (e.g. mice and deer), only one of which is competent for transmission (mice in the case of Lyme diseases), an increase in the density

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of the incompetent host (deer in this example) may cause pathogen extinction. Qualitatively similar results have been obtained in computer-based models [21,22].

Foppa [23] has suggested a method to estimate R_0 for TBE (or better an upper bound for R_0) from easily empirically observation on the distributions of ticks and hosts.

In a previous paper [24], we have extended the model of [17] by allowing also for non-systemic transmission and extended feeding periods, and computed threshold values for pathogen persistence in such cases. Here, we build on that analysis, choosing to consider the feeding period, by explicitly modelling the questing and feeding phases of ticks; we explore in greater detail the dilution effect, showing that it is theoretically possible that R_0 drops below 1 at high densities of the competent hosts too. Indeed, some recent results [25] show that the prevalence of tick-borne encephalitis (TBE) may be negatively correlated also with the density of the host species considered more competent for infection transmission (*Apodemus flavicollis*).

We analyse how the structure of density-dependence in tick demography, and the various transmission routes, affect the occurrence of the dilution effect.

Using the persistence thresholds and parameter estimates obtained from the literature, we are also able to assess the potential role of trans-ovarial and co-feeding transmission in the persistence of TBE infections.

2. Tick population dynamics

The life cycle of ixodid ticks includes three post-embryonic developmental stages: larva (L), nymph (N) and adult (A). Each stage can be subdivided in turn according to the phases of activity: 'questing', in which the unfed tick seeks a host and 'feeding', in which the attached tick feeds, becomes engorged and drops off. After dropping off their hosts, ticks go through a period of development, after which they emerge as questing ticks at the next stage (or eggs hatch, if the feeding ticks are adult females).

Ticks are found on many vertebrate hosts; usually adults have a more restricted host range than larvae and nymphs [26]. Nevertheless, the generally accepted view is that, at least in Europe and Eastern US, the dynamics of ticks and tick-borne diseases (e.g. Lyme disease and TBE) depends largely on two classes of hosts: small rodents such as mice and voles, and larger mammals such as ungulates [2,27]. The former class, which will be indicated in the following model as H_1, is the most common host species for immature stages of ticks (larvae and nymphs) while adults are generally found on medium-sized and large mammals (H_2); among them, deer are the most important.

Under these assumptions, we build a simple model for the dynamics of tick populations, assuming that host populations are fixed at given densities H_1 and H_2. The dynamics is described through a continuous model, thus disregarding seasonality, as generally done in models for tick-borne infections (but see [23] and [28]).

Differently from other models for tick-borne infections, we divide ticks at each stage into questing and feeding as in [12]. On the other hand, we do not consider the trans-stadial development stage, thus assuming that stage transitions are instantaneous. Developmental stages would act as a delay, that might influence the dynamical properties of a system, but not its equilibria, which are the focus of the present paper.

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2.1. The basic model for tick demography

We start by considering the model for tick dynamics only, without considering any infection; this will then be the foundation for the transmission models. The variables of the model are L_Q, N_Q and A_Q (the densities of questing larvae, nymphs and adults, respectively) and L_F, N_F and A_F (the density of the same stages in the feeding phase). Encounters between questing ticks and hosts of either class are governed by mass-action; i.e. the corresponding encounter rate is given by the product $(\beta_1^N H_1 + \beta_2^N H_2)N_Q$, in the case of questing nymphs, and similarly for the other stages. A tick–host encounter results in the transition of the tick to the feeding stage. Questing larvae, nymphs and adults die respectively at rate d^L, d^N and d^A. Mortality in the feeding period, which lasts on average $1/\sigma$ days, is neglected. The parameters m^L (m^N) represent the probability of moulting success for larvae (nymphs) after feeding. In practice, m^L and m^N may depend on the host species [29] but here, for the sake of simplicity, we stick to the case of a single parameter.

The final parameter needed is the production of larvae per feeding adult tick, a_T. If all parameters were constant, the tick population would grow or decrease exponentially, in contrast to the usual observations of fairly constant population densities [30]. Hence, following [14,17], we assume that larva production a_T is a decreasing function of tick density T, hence $a_T(T)$; in the next Section, we discuss more thoroughly the issue of density-dependence in tick demography.

The resulting equations that describe tick population dynamics are the following:

$$\begin{aligned}
\dot{L}_Q &= \sigma^A a_T(T) A_F - d^L L_Q - (\beta_1^L H_1 + \beta_2^L H_2) L_Q \\
\dot{L}_F &= (\beta_1^L H_1 + \beta_2^L H_2) L_Q - \sigma^L L_F \\
\dot{N}_Q &= m^L \sigma^L L_F - d^N N_Q - (\beta_1^N H_1 + \beta_2^N H_2) N_Q \\
\dot{N}_F &= (\beta_1^N H_1 + \beta_2^N H_2) N_Q - \sigma^N N_F \\
\dot{A}_Q &= m^N \sigma^N N_F - d^A A_Q - (\beta_1^A H_1 + \beta_2^A H_2) A_Q \\
\dot{A}_F &= (\beta_1^A H_1 + \beta_2^A H_2) A_Q - \sigma^A A_F.
\end{aligned} \tag{1}$$

Simple matrix algebra (Appendix A.2) shows that the tick-free equilibrium of (1) is stable if $\rho(K) < 1$, where

$$K = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 & \sigma^A a_T(0) \\
\frac{\beta^L}{d^L+\beta^L} & 0 & 0 & 0 & 0 & 0 \\
0 & m^L & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{\beta^N}{d^N+\beta^N} & 0 & 0 & 0 \\
0 & 0 & 0 & m^N & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{\beta^A}{d^A+\beta^A} & 0
\end{pmatrix}, \tag{2}$$

with $\beta^L = \beta_1^L H_1 + \beta_2^L H_2$, $\beta^N = \beta_1^N H_1 + \beta_2^N H_2$ and $\beta^A = \beta_1^A H_1 + \beta_2^A H_2$.

It is easy to see that $\rho(K) = \sqrt[6]{S_0^{\text{ticks}}}$ with

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$$S_0^{\text{ticks}} = \frac{m^L \beta^L}{d^L + \beta^L} \cdot \frac{m^N \beta^N}{d^N + \beta^N} \cdot \frac{\beta^A}{d^A + \beta^A} a_T(0). \tag{3}$$

In order to intepret (3), let

$$s^L = \frac{m^L \beta^L}{d^L + \beta^L}, \qquad s^N = \frac{m^N \beta^N}{d^N + \beta^N}, \qquad b^A(T) = \frac{\beta^A}{d^A + \beta^A} a_T(T), \tag{4}$$

where s^L [s^N] is the probability that a questing larva [nymph] feeds and moults into a questing nymph [adult], while $b^A(T)$ is the average number of larvae expected to be produced by a questing adult, when T is ticks' population density. Hence, $S_0^{\text{ticks}} = s^L \cdot s^N \cdot b^A(0)$ represents the expected number of larvae produced by a larva, when density-dependent effects are absent [24].

When $S_0^{\text{ticks}} > 1$, we show below that there exists a unique positive equilibrium T^* of system (1). When no confusion arises, we will denote by T^* both the six-dimensional equilibrium of (1), and the total tick density $T^* = L^* + N^* + A^*$. Setting the RHS of (1) equal to 0, we see that the total densities of each stage L^*, N^*, and A^* satisfy the relations:

$$L^* = (1 + c_1^L H_1 + c_2^L H_2) L_Q^* = \frac{c_1^L H_1 + c_2^L H_2}{1 + c_1^L H_1 + c_2^L H_2} L_F^* \tag{5}$$

with $c_j^L = \beta_j^L / \sigma^L$, $j = 1, 2$, and analogously for the other stages. Moreover, we have

$$\begin{aligned} N^* &= \frac{m^L \beta^L}{1 + c_1^L H_1 + c_2^L H_2} \cdot \frac{1 + c_1^N H_1 + c_2^N H_2}{d^N + \beta^N} L^* \\ A^* &= \frac{m^N \beta^N}{1 + c_1^N H_1 + c_2^N H_2} \cdot \frac{1 + c_1^A H_1 + c_2^A H_2}{d^A + \beta^A} N^* \\ L^* &= \frac{a_T(T^*) \beta^A}{1 + c_1^A H_1 + c_2^A H_2} \cdot \frac{1 + c_1^L H_1 + c_2^L H_2}{d^L + \beta^L} A^*. \end{aligned} \tag{6}$$

Finally, inserting the first equation of (6) in the second and then the second in the third, it is not difficult to see that T^* must satisfy

$$s^L \cdot s^N \cdot b^A(T^*) = \frac{a_T(T^*)}{a_T(0)} S_0^{\text{ticks}} = 1. \tag{7}$$

Since $a_T(\cdot)$ has been assumed to be a decreasing function, it is clear that the system has a unique positive equilibrium if and only if $S_0^{\text{ticks}} > 1$.

Almost the same equations for the equilibrium and for S_0^{ticks} have been found in [24], using time-scales arguments. The slight difference between the two expressions arises from the assumption in [24] that questing and feeding ticks have the same death rate, while here we neglect the death rate of feeding ticks.

We cannot prove the stability of T^*, if $S_0^{\text{ticks}} > 1$, as was done in [24]; in this case the system is six-dimensional, and the computations become awkward. However, we investigated the stability numerically, using parameter values in the range considered to be reasonable for *Ixodes ricinus* in northern Italy (see Section 4) and did not find any parameter set that makes the equilibrium unstable. Then, when computing threshold conditions for pathogen persistence, we will take for granted that the positive equilibrium T^* is stable for system (1).

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2.2. Modelling density-dependence in tick population dynamics

As discussed above, in case of no density-dependence in tick demography, there would be an exponential growth or decrease of tick population. Instead, ixodid ticks are typified by remarkably constant population sizes, varying annually by considerably less than one order of magnitude [30].

Population regulation of ticks about fairly constant equilibrium level can be brought only if the rates of one or more of the demographic processes vary with population density. Death rates must increase, or birth rates must decrease with increasing density [30]. In [17] and [24] it is assumed that density-dependence occurs through a reduction of the birth rate of ticks: the production of larvae per feeding adult tick, $a_T(T)$, was assumed to be a linear decreasing function of the total number of ticks present in the system. A consequence of this assumption is that at high densities ticks would have a negative birth rate; in order to avoid this incongruity, here we assume $a_T(T)$ to be a negative exponential function of the total number of ticks, as follows:

$$a_T(T) = r_T \exp\{-s_T T\}, \tag{8}$$

where r_T is the maximum egg production of adult ticks (taking sex ratio into account), while s_T measures the strength of density-dependence.

Density-dependence in ticks may occur also in other parts of the tick cycle such as moulting probability, the probability that an immature feeding tick survives and develops to the next stage [1]. One can then assume that the moulting probabilities m^L and m^N to depend on the number of ticks, T, similarly to (8):

$$m^L(T) = r_L \exp\{-s_L T\}, \quad m^N(T) = r_N \exp\{-s_N T\}. \tag{9}$$

Few data exist in the literature about the exact nature of population regulation in ticks; however, it is generally thought that the regulation arises mainly through host immunity rather than because of tick predation or parasitism [30]. Indeed, hosts acquire resistance to tick feeding as a result of repeated infestation [31,32], as observed both in tick-cattle and tick-rodent interaction [33,34]. Several effects of acquired resistance in hosts have been observed, such as the reduced engorgement weight of ticks, increased duration of feeding, decreased number of ova, reduced viability of these ova and blocked moulting and death of engorging ticks [31,32,35]. The decrease of the average blood meal might affect tick fecundity, as it varies directly with meal size [36]. This empirical evidence indicates that the production of larvae from adult females, a_T, should depend on the immune status of the host on which the adult fed. A model that takes into account individual tick loads and immune histories would be very complex (see [37]); using a mean field approach, one could assume that adult fecundity depends on past history of average tick load; simplifying further, we let adult fecundity depend on the instantaneous average tick load, rather than on total tick density as done in (8). Using again a negative exponential model, the alternative form for the production of larvae per feeding adult is:

$$a_T(T) = r_T \exp\left\{-s_T \frac{T}{uH_1 + vH_2}\right\}, \tag{10}$$

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where the two parameters u and v weigh the contributions of the two host species to tick population dynamics. If this type of density-dependence occurs in moulting probabilities, as in (9), $m^L(T)$ and $m^N(T)$ assume the following form:

$$m^L(T) = r_L \exp\left\{-s_L \frac{T}{uH_1 + vH_2}\right\}, \quad m^N(T) = r_N \exp\left\{-s_N \frac{T}{uH_1 + vH_2}\right\}. \tag{11}$$

2.3. Effect of host densities on tick equilibrium densities

What is the effect of host densities on tick dynamics? When hosts are abundant, ticks are more likely to find a host, hence there is an increase in the rates at which ticks progress from stage to stage and reproduce. However, if, as assumed in (8), ticks' reproductive success decreases with tick density, equilibrium density will saturate with increasing host density. The left panel of Fig. 1 shows a numerical example. It can be seen, and it is a general feature under assumption (8), that the equilibrium density of questing larvae depends in a non-monotonous way on the density of hosts 1 (the ones on which larvae mainly feed). A biological interpretation of this result is presented in Section 5.

When we let instead tick fecundity depend on average tick load ($a_T(T)$ given by (10)), the effect of host densities on tick equilibrium density changes substantially, as shown in the right panel of Fig. 1. In this case, the equilibrium density of ticks increases almost linearly with host density without reaching a plateau. Since tick fecundity is regulated by ticks-to-hosts ratio, we can say that ticks' carrying capacity increases linearly with host densities. In the right panel of Fig. 1, one can see that the equilibrium density of larvae too goes on increasing with host density H_1 (the same occurs for H_2), as well as the equilibrium densities of the other tick stages (not shown).

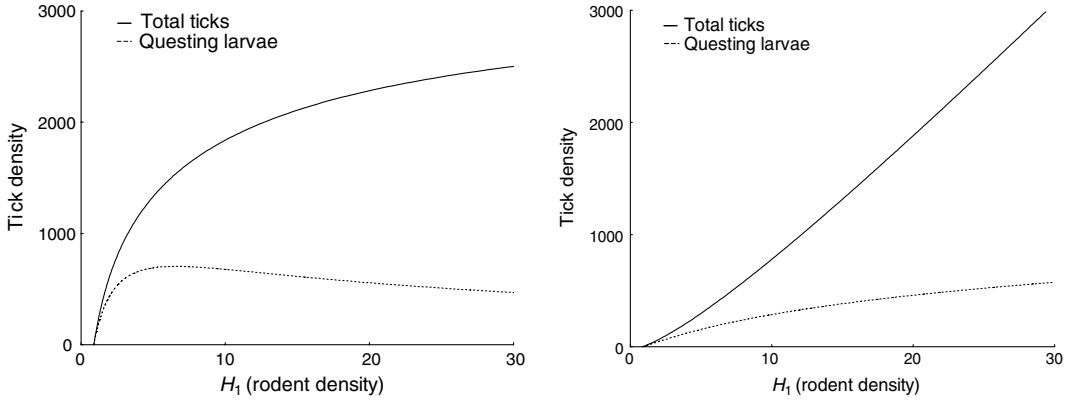

Fig. 1. Effect of H_1 on tick equilibrium densities (total ticks and questing larvae) using different choices for $a_T(T)$: on the left, $a_T(T)$ is given by (8), on the right by (10). Parameter values are: $\beta_1^L = .015$, $\beta_1^N = .0005$, $\beta_1^A = 0$, β_2^L=.05, $\beta_2^N = .03$, $\beta_2^A = .13$, $d^L = .0365$, $d^N = .015$ $d^A = .00625$, r_T=2000, $s_T = .001$, $m^L = m^N = .15$, $\sigma^L = .28$, $\sigma^N = .22$, $\sigma^A = .12$, $H_2 = .06$, $u = .04$, $v = .4$.

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Finally, we studied the model with density-dependence in the moulting success for the various tick stages, (9) or (11). The results are not shown, since the resulting figures are very similar to those in Fig.1, according to the choice of (9) (left panel) or (11) (right panel).

An important theoretical difference is that, using (9) or (11), it is possible to find examples of $m_N(\cdot)$ and $m_L(\cdot)$ such that multiple positive equilibria occur, as well as cases where a unique equilibrium is unstable (see [28] for proof of this in a discrete – continuous setting). However, these examples have only been found for unusual parameter values; using realistic parameter values, it appears that the positive equilibrium is always unique and stable.

3. Models for the dynamic of tick-borne infections

As discussed in the Introduction, different tick-borne infections have different competent hosts, and different infection pathways. Here we consider two cases, that model infections of public health relevance and allow for computations of biologically interpretable threshold quantities for infection persistence.

We start, in Section 3.1, considering the case where systemic transmission takes place only in one host species (competent hosts), H_1, including also vertical (trans-ovarial) transmission in ticks from infected adults to eggs/larvae.

Afterwards, in Section 3.2, we introduce the non-systemic route of transmission through co-feeding ticks; both transmission routes take place in the same host species, H_1.

Other cases, for instance an infection to which both types of hosts are competent, like *Anaplasma*, could be handled similarly.

3.1. Systemic transmission in H_1

We start by considering the case, in which the infection is only transmitted systemically between ticks and one single competent host species (assumed to be H_1) at blood meals. Precisely, we will assume that a tick feeding on an infected host (of type 1) has probability p_1^z ($z = L$, N or A) of becoming infected, and a host fed on by an infected tick has probability q_1^z of becoming infected. For simplicity, both infections will be assumed to occur exactly at the beginning of the blood meal, so that the infection rate of hosts will be proportional to the contact rate of questing infective ticks (of the various stages) with susceptible hosts, while ticks will become infected (in a feeding stage) at a rate proportional to the contact rate of susceptible questing ticks (at that stage) with infective hosts. The model considered does not contain an incubation period for the infection; however, the assumption about infection transmission makes it impossible that, as a host becomes infected, it infects the ticks already feeding on it; therefore, effectively a sort of incubation period is implicit in the model.

The model equations are built on the structure of (1), dividing all tick stages (questing or feeding larvae, nymphs and adults) between susceptibles and infected (denoted by a superscript i or s). Furthermore, hosts of class 1 will be divided into susceptible, infective and immunes (s, i or r) and their densities will change following infections and recoveries; moreover, since we allow for an infection causing mortality in the hosts, host demography needs to be modelled explicitly, and it is then necessary to assume density-dependence in the hosts too, for simplicity operating only

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through the fertility term $a_1(H_1)$. Finally, trans-ovarial transmission from adult female ticks to eggs is also included introducing the parameter ε that measures the proportion of infected eggs laid by an infected female adult. Using these assumptions, it is not difficult to modify system (1) and obtain the following system:

$$
\begin{aligned}
\dot{L}^i_Q &= \varepsilon\sigma^A a_T(T)A^i_F - d^L L^i_Q - (\beta^L_1 H_1 + \beta^L_2 H_2)L^i_Q\\
\dot{L}^s_Q &= (1-\varepsilon)\sigma^A a_T(T)A^i_F + \sigma^A a_T(T)A^s_F - d^L L^s_Q - (\beta^L_1 H_1 + \beta^L_2 H_2)L^s_Q\\
\dot{L}^i_F &= (\beta^L_1 H_1 + \beta^L_2 H_2)L^i_Q + p^L_1\beta^L_1 H^i_1 L^s_Q - \sigma^L L^i_F\\
\dot{L}^s_F &= (\beta^L_1 (H_1 - p^L_1 H^i_1) + \beta^L_2 H_2)L^s_Q - \sigma^L L^s_F\\
\dot{N}^i_Q &= m^L\sigma^L L^i_F - d^N N^i_Q - (\beta^N_1 H_1 + \beta^N_2 H_2)N^i_Q\\
\dot{N}^s_Q &= m^L\sigma^L L^s_F - d^N N^s_Q - (\beta^N_1 H_1 + \beta^N_2 H_2)N^s_Q\\
\dot{N}^i_F &= (\beta^N_1 H_1 + \beta^N_2 H_2)N^i_Q + p^N_1\beta^N_1 H^i_1 N^s_Q - \sigma^N N^i_F\\
\dot{N}^s_F &= (\beta^N_1 (H_1 - p^N_1 H^i_1) + \beta^N_2 H_2)N^s_Q - \sigma^N N^s_F\\
\dot{A}^i_Q &= m^N\sigma^N N^i_F - d^A A^i_Q - (\beta^A_1 H_1 + \beta^A_2 H_2)A^i_Q\\
\dot{A}^s_Q &= m^N\sigma^N N^s_F - d^A A^s_Q - (\beta^A_1 H_1 + \beta^A_2 H_2)A^s_Q\\
\dot{A}^i_F &= (\beta^A_1 H_1 + \beta^A_2 H_2)A^i_Q + p^A_1\beta^A_1 H^i_1 A^s_Q - \sigma^A A^i_F\\
\dot{A}^s_F &= (\beta^A_1 (H_1 - p^A_1 H^i_1) + \beta^A_2 H_2)A^s_Q - \sigma^A A^s_F\\
\dot{H}^s_1 &= a_1(H_1)H_1 - d_1 H^s_1 - (q^L_1\beta^L_1 L^i_Q + q^N_1\beta^N_1 N^i_Q + q^A_1\beta^A_1 A^i_Q)H^s_1\\
\dot{H}^i_1 &= (q^L_1\beta^L_1 L^i_Q + q^N_1\beta^N_1 N^i_Q + q^A_1\beta^A_1 A^i_Q)H^s_1 - (d_1 + \gamma_1 + \alpha_1)H^i_1\\
\dot{H}^r_1 &= \gamma_1 H^i_1 - d_1 H^r_1.
\end{aligned}
\tag{12}
$$

System (12) has an infection-free equilibrium, corresponding to the equilibrium T^* of system (1). We will denote it still by the name T^*: at the equilibrium, $H^s_1 = H^*_1$ solution of $a_1(H_1) = d_1$, while all the susceptibles in the various tick stages are given by the corresponding values in (5) and (6), and all the infective components (and H^r_1) are equal to 0.

As shown in Appendix A.3, T^* is stable if $\rho(K) < 1$ where

$$
K = \begin{pmatrix} 0 & 0 & \varepsilon b^A(T^*) & p^A(T^*) \\ s^L & 0 & 0 & p^L \\ 0 & s^N & 0 & p^N \\ q^L & q^N & q^A & 0 \end{pmatrix}. \tag{13}
$$

In (13), s^L, s^N and b^A are given in (4), while the entries

$$
q^L = \frac{q^L_1\beta^L_1 H^*_1}{d^L + \beta^L}, \qquad q^N = \frac{q^N_1\beta^N_1 H^*_1}{d^N + \beta^N}, \qquad q^A = \frac{q^A_1\beta^A_1 H^*_1}{d^A + \beta^A}, \tag{14}
$$

represent the probability that an infected questing larva (or nymph or adult) infects a host. Finally,

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$$p^L = \frac{m^L p_1^L \beta_1^L L_Q^*}{d_1 + \gamma_1 + \alpha_1}, \qquad p^N = \frac{m^N p_1^N \beta_1^N N_Q^*}{d_1 + \gamma_1 + \alpha_1}, \qquad p^A(T) = \frac{\varepsilon a_T(T) p_1^A \beta_1^A A_Q^*}{d_1 + \gamma_1 + \alpha_1}, \tag{15}$$

represent the average number of infected questing nymphs [adults, larvae] produced by an infected host over its infectious period, taking into account that vertical transmission is necessary for a host to infect tick larvae, after being bitten by an adult.

Although the matrix K is obtained in Appendix A.3 using matrix algebra, it can be seen that it can be considered the next-generation matrix [19], using as types-at-birth infected questing larvae L_Q^i, nymphs N_Q^i, and adults A_Q^i, together with the infected competent hosts, H_1^i. Hence, we may write $R_0 = \rho(K)$.

In this case, we know no explicit expression for $R_0 = \rho(K)$; it is possible however to write the following threshold quantity S_0,

$$S_0 = S_0^{\text{syst}} + S_0^{\text{vert}} + \varepsilon, \tag{16}$$

where

$$S_0^{\text{syst}} = p^L \cdot q^N + p^L \cdot s^N \cdot q^A + p^N \cdot q^A \tag{17}$$

and

$$S_0^{\text{vert}} = p^A(T^*)\left(q^L + s^L q^N + s^L s^N q^A\right) + p^N \varepsilon b^A(T^*)\left(q^L + s^L q^N\right) + p^L s^N \varepsilon b^A(T^*) q^L. \tag{18}$$

S_0^{syst} represents the average number of hosts infected by an infected host going through systemic transmission host-to-tick, and then tick-to-host. Analogously S_0^{vert} represents the average number of hosts infected by an infected host going through a single trans-ovarial transmission. Finally, the term ε is the average number of infected larvae [nymphs, adults] produced by an infected larva [nymph, adult] purely through vertical transmission.

The threshold $S_0 < 1$ can be understood, since

$$S_0 < 1 \quad \Longleftrightarrow \quad \frac{S_0^{\text{syst}} + S_0^{\text{vert}}}{1 - \varepsilon} < 1.$$

The fraction $1/(1-\varepsilon)$ represents the whole infected (through vertical transmission) progeny, including itself, of an infected tick. Hence, $\frac{S_0^{\text{syst}} + S_0^{\text{vert}}}{1-\varepsilon}$ represents the average number of hosts infected by an infected host going host-to-tick, then considering all ticks infected through vertical transmission, and then tick-to-host.

Indeed, one can compute the quantity T_1 (relatively to infected hosts) introduced by [20]. Moving the fourth row and column to first in (13), and making the necessary computations, one obtains

$$T_1 = \frac{S_0^{\text{syst}} + S_0^{\text{vert}}}{1 - \varepsilon}. \tag{19}$$

Although R_0, S_0 and T_1 are different quantities, they have the same threshold behaviour: $R_0 > 1$ if and only if $S_0 > 1$ if and only if $T_1 > 1$ [20].

Without transovarial transmission ($\varepsilon = 0$), the threshold reduces to $S_0^{\text{syst}} > 1$. Essentially, the same threshold for pathogen persistence has been found in the model studied in [24], as can be seen using the relation (5) between L^* and L_Q^*.

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Adult ticks do not usually feed on rodents (H_1 in this case), so that it can be assumed $\beta_1^A = 0$, so that $q^A = p^A(T^*) = 0$. Under this condition, the threshold simplifies to

$$S_0 = p^L \cdot q^N + \varepsilon b^A(T^*)[p^N(q^L + s^L q^N) + p^L s^N q^L] > 1. \tag{20}$$

3.2. Systemic and non-systemic transmission in H_1

We consider here a further route of infection, usually called non-systemic infection, which takes place horizontally between co-feeding ticks. This means that a susceptible feeding tick can get the infection not only from an infected host but also from other infected feeding ticks that are co-feeding on the same host [8]. We restrict here to the empirically relevant case where both systemic and non-systemic infections can occur only in hosts of class 1. In addition, to keep under control the computations, we do not include trans-ovarial transmission and we assume that adult ticks feed only on hosts 2.

These assumptions simplify considerably the mathematics, and appear adequate to describe the transmission of *Borrelia burgdorferi* or TBEv, assuming hosts 1 to be small rodents, and hosts 2 to be mainly deer [2]. In fact, successful TBE virus transmission, between co-feeding ticks, seems to be strongly species specific. Empirical investigations have found wild rodents, in particular *Apodemus* spp., to be the most competent transmission hosts, whilst investigations of other species (e.g. deer, hedgehog, pheasant) have found no evidence of virus transmission [38–40].

In the model, non-systemic transmission is described by the parameters λ_{LN} (transmission from infective nymphs to larvae) and λ_{NN} (transmission from infective nymphs to susceptible nymphs). We do not consider co-feeding transmission in the adult tick stages since we assume no adult ticks feed on H_1. Precisely, λ_{LN} (and similarly λ_{NN}) represents the probability that a larva gets infected, provided it starts feeding on a host on which an infective nymph is also feeding. This probability includes the probability for a larva to be in the same co-feeding group, the probability that the infection is then transmitted and the probability of the infection being maintained trans-stadially; estimates for all these probabilities, in the case of TBE virus, may be found in the literature [7,39,40].

Then the probability for a larva to get infected through non-systemic transmission, as it starts feeding on a host of class 1, is given by

$$1 - \exp\left\{-\lambda_{LN}\frac{N^i_{F_1}}{H^s_1 + H^i_1 + H^r_1}\right\} \tag{21}$$

where $N^i_{F_1}/H_1$ represents the average nymph load over hosts of class 1, and we assumed independence in the distribution of ticks over hosts. It is well known, however, that the distributions of ticks on hosts are aggregated, and that there is a positive correlation between the distributions of larvae and nymphs [8,41]. In [24], assuming that tick stages are distributed according to a negative binomial distribution, and that ρ_{LN} represents the correlation coefficient between larvae and nymphs on hosts, we showed that (21) still holds with

$$\lambda_{LN} = \theta_{LN}(1 + \rho_{LN}/\sqrt{k^L k^N}), \tag{22}$$

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where k^L and k^N are the aggregation parameters k of the negative binomial for larvae and nymphs, respectively, while θ_{LN} is the probability that a larva gets infected, provided it starts feeding on a host on which an infective nymph is already feeding. Analogously λ_{NN} can be written as $\theta_{NN}(1+1/k^N)$ (see [24]). Hence, we always use formula (21) for the probability that a larva that starts feeding on a host of class 1 gets infected; biologically, λ_{LN} may be interpreted according to (22).

Summing up, the rate at which larvae get infected non-systemically is given by

$$\beta_1^L H_1 L_Q \left(1-\exp\left\{-\frac{\lambda_{LN}N_{F_1}^i}{H_1}\right\}\right).$$

Note that in [24] the simpler expression $\beta_1^L L_Q \lambda_{LN} N_{F_1}^i$ had been used for the infection rate [always remembering the relations (5)]. That expression is not feasible, since it yields infection probabilities larger than 1 when the density of infected nymphs is high; however, the linearization at the infection – free equilibrium is the same, so that the computation of R_0 in [24] is correct.

For this model, in order to avoid unrealistic transmission routes, it becomes necessary to distinguish between ticks that have been infected but are not yet infectious (they will be denoted as *exposed*), and ticks that are infectious, i.e. capable to transmit the infection to a host or to co-feeding ticks. Precisely, we assume that ticks that get infected during a blood meal become 'exposed' and they will become infectious only after moulting [26].

Hence, we will divide feeding larvae into susceptible (L_F^s) and exposed (L_F^e) (i.e., those being infected in that blood meal), that will moult into susceptible (N_Q^s) and infectious (N_Q^i) questing nymphs; feeding nymphs will be susceptible, infectious (those infected as feeding larvae) or exposed (those being infected in that blood meal). In addition, we need to distinguish between infected nymphs feeding on host 1 ($N_{F_1}^i$) and host 2 ($N_{F_2}^i$) as we assume that co-feeding transmission can occur only on host 1.

Using the variables and assumptions described above, we obtain, taking into account that ticks feeding on infectious hosts may get infected by both transmission routes, the following system:

$$\begin{aligned}
\dot{L}_Q &= \sigma^A a_T(T) A_F - d^L L_Q - (\beta_1^L H_1 + \beta_2^L H_2) L_Q \\
\dot{L}_F^e &= \beta_1^L L_Q H_1^i \left(1-(1-p_1^L)\exp\left\{-\frac{\lambda_{LN}N_{F_1}^i}{H_1}\right\}\right) + \beta_1^L L_Q (H_1^s + H_1^r)\left(1-\exp\left\{-\frac{\lambda_{LN}N_{F_1}^i}{H_1}\right\}\right) \\
&\quad - \sigma^L L_F^e \\
\dot{L}_F^s &= \left[\beta_1^L\left(H_1^s + H_1^r + (1-p_1^L)H_1^i\right)\exp\left\{-\frac{\lambda_{LN}N_{F_1}^i}{H_1}\right\} + \beta_2^L H_2\right] L_Q - \sigma^L L_F^s \\
\dot{N}_Q^i &= m^L \sigma^L L_F^e - d^N N_Q^i - (\beta_1^N H_1 + \beta_2^N H_2) N_Q^i \\
\dot{N}_Q^s &= m^L \sigma^L L_F^s - d^N N_Q^s - (\beta_1^N H_1 + \beta_2^N H_2) N_Q^s \\
\dot{N}_{F_1}^i &= \beta_1^N H_1 N_Q^i - \sigma^N N_{F_1}^i \\
\dot{N}_{F_2}^i &= \beta_2^N H_2 N_Q^i - \sigma^N N_{F_2}^i
\end{aligned}$$

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$$
\begin{aligned}
\dot{N}^e_F &= \beta^N_1 N^s_Q H^i_1 \left(1-(1-p^N_1)\exp\left\{-\frac{\lambda_{NN}N^i_{F_1}}{H_1}\right\}\right)+\beta^N_1 N^s_Q (H^s_1+H^r_1)\left(1-\exp\left\{-\frac{\lambda_{NN}N^i_{F_1}}{H_1}\right\}\right)\\
&\quad -\sigma^N N^e_F\\
\dot{N}^s_F &= \left[\beta^N_1\left(H^s_1+H^r_1+(1-p^N_1)H^i_1\right)\exp\left\{-\frac{\lambda_{NN}N^i_{F_1}}{H_1}\right\}+\beta^N_2 H_2\right]N^s_Q-\sigma^N N^s_F\\
\dot{A}^i_Q &= m^N\sigma^N(N^i_{F_1}+N^i_{F_2}+N^e_F)-d^A A^i_Q-\beta^A_2 H_2 A^i_Q\\
\dot{A}^s_Q &= m^N\sigma^N N^s_F-d^A A^s_Q-\beta^A_2 H_2 A^s_Q\\
\dot{A}_F &= \beta^A_2 H_2(A^i_Q+A^s_Q)-\sigma^A A_F\\
\dot{H}^s_1 &= a_1(H_1)H_1-d_1 H^s_1-q^N_1\beta^N_1 N^i_Q H^s_1\\
\dot{H}^i_1 &= q^N_1\beta^N_1 N^i_Q H^s_1-(d_1+\gamma_1+\alpha_1)H^i_1\\
\dot{H}^r_1 &= \gamma_1 H^i_1-d_1 H^r_1.
\end{aligned}
\tag{23}
$$

Although the previous system seems utterly complicated, simple matrix algebra (Appendix A.4) shows that the condition for the stability of the infection-free equilibrium of (23) is that the spectral radius $\rho(K)<1$ with

$$
K=\begin{pmatrix}
0 & 0 & \frac{\beta^L_1 p^L_1 L^*_Q}{d_1+\gamma_1+\alpha_1} & \frac{\beta^L_1 L^*_Q \lambda_{LN}}{\sigma^N}\\
m^L & 0 & 0 & 0\\
0 & q^N & 0 & 0\\
0 & \frac{\beta^N_1 H^*_1}{d^N+\beta^N} & 0 & 0
\end{pmatrix}.
\tag{24}
$$

As its third and fourth columns, and rows, are proportional, one eigenvalues of K in (24) is *0*; the others are the three cubic roots of

$$
S_0=p^L\cdot q^N+\frac{m^L\beta^N_1 H^*_1}{d^N+\beta^N}\cdot\frac{\lambda_{LN}\beta^L_1 L^*_Q}{\sigma^N}.
\tag{25}
$$

Then, the condition for the stability of the infection-free equilibrium can be written as $S_0<1$.

Note that K might be considered the next generation matrix, using as types-at-birth L^e_F, N^i_Q, H^i_1 and $N^i_{F_1}$; we would then obtain $R_0=\rho(K)=\sqrt[3]{S_0}$.

On the other hand, if (perhaps more closely to the concept of next-generation matrix developed in [19]) one chooses as types-at-births N^i_Q and H^i_1, the next-generation matrix becomes a 2×2 matrix, that, after some thoughts, can be written as

$$
K=\begin{pmatrix}
\frac{\beta^N_1 H^*_1}{d^N+\beta^N}\frac{\lambda_{LN}\beta^L_1 L^*_Q}{\sigma^N}m^L & p^L\\
q^N & 0
\end{pmatrix}.
\tag{26}
$$

Then $R_0=\rho(K)$ can be found, solving a second-degree equation, while S_0 corresponds to T_1, as defined in [20].

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The expression (25) for S_0 can be read as the expected number of 'exposed' larvae produced (in a wholly susceptible population) by a newly infected (hence 'exposed') larva over its infectious period: the first term $p^L \cdot q^N$ computes those infected through the systemic route (recall in fact the definitions (14) and (15), with the relative interpretations); the second term computes those infected through the non-systemic route: $\frac{m^L \beta_1^N H_1^*}{d^N + \beta^N}$ is the probability of surviving moulting, and finding a host 1, $\frac{\beta_1^L L_Q^*}{\sigma^N}$ is the average number of larvae that start feeding on that host while the index tick is feeding and λ_{LN} is the probability of infecting each co-feeding larva.

4. Effect of host densities on infection persistence

Parameter values used for simulations are based on estimates obtained in Trentino (northern Italy) for the following species: the most abundant tick (*Ixodes ricinus*), the most abundant rodent host, yellow-necked mouse (*A. flavicollis*), named H_1, and the main ungulate host, roe deer (*Capreolus capreolus*), named H_2. Empirical data were used to estimate tick and host densities and the encounter rates between hosts and ticks in different stages [42]. Parameter values concerning tick biology (such as mortality, fertility, duration of feeding, moulting probabilities) were derived from previously published studies [11,29,43]. The probabilities of infection of ticks and hosts were calibrated to tick-borne encephalitis virus (TBEv), and estimated from the literature; for systemic and non-systemic transmission from [7,8,39,40] while for transovarial transmission from [44]. Time is measured in *days* while density in $hectare^{-1}$.

We start by considering the case of systemic transmission only in hosts 1 (rodents) with $\beta_1^A = 0$, so that S_0 is given by (20). Fig. 2 shows the effect of H_1 on S_0 for different levels of trans-ovarial transmission (measured by the parameter ε), using density-dependence $a_T(T)$ given by (8) in the left panel and (10) in the right panel. Both panels show that a minimum density of rodents (H_1) and a large enough probability of trans-ovarial transmission (ε) are needed for the pathogen to persist ($S_0 > 1$). The shape of the curves in the left panel of Fig. 2 show a dilution effect due to rodents: when rodent density is too high, S_0 always goes below 1 so that the infection dies out. This does not happen in the right panel of the figure where S_0 always grows with rodent density.

The same qualitative pattern is observed in Fig. 3 where non-systemic transmission is considered. The figure shows the effect of H_1 on S_0 in (25) for different levels of transmission through co-feeding ticks (measured by the parameter λ_{LN}) and the two types of density-dependence. It is interesting to note that with our parameter set, calibrated on TBE virus in Trentino, the infection cannot persist ($S_0 < 1$) when only systemic transmission is considered (curves with ε=0 in Fig. 2, and λ_{LN}=0 in Fig. 3), in accordance with the general view of that infection [8].

In order to assess the relative importance of trans-ovarial and non-systemic transmission routes, we compare the two figures. Using reasonable values of rodent density (below 20–30 heads per hectare) the probability of trans-ovarial transmission (ε) needed to make the virus persists ($S_0 > 1$) must be higher than 10 per cent; this value is one order of magnitude higher than reported estimates [44]. Conversely, the minimum value needed for non-systemic transmission (λ) is between 0.3 and 0.4, which is comparable with values reported in literature [39].

The relative densities of both hosts that allow the pathogen to persist can be shown through the persistence-extinction boundary in the plane $H_1 - H_2$ [17]; in that plane we plot the curve $S_0 = 1$

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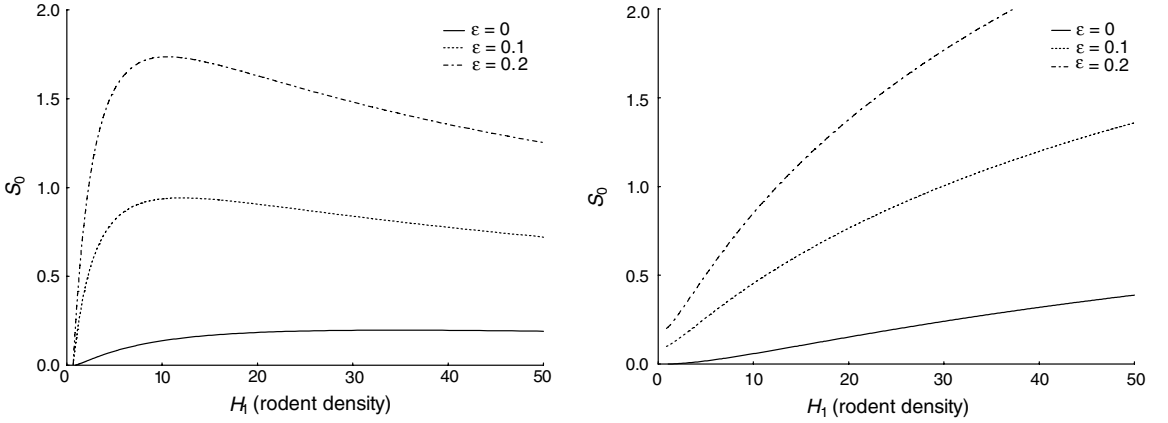

Fig. 2. Effect of H_1 on S_0 in (20) for different values of ε using different choices for $a_T(T)$: on the left, $a_T(T)$ is given by (8), on the right by (10). Tick demographic parameters are the same as in Fig. 1; the others are $d_1 = 0.0037$, γ_1=0.3, $\alpha_1 = 0.33$, $p_1^L = p_1^N = p_1^A = .5$, $q_1^L = q_1^N = q_1^A = .5$.

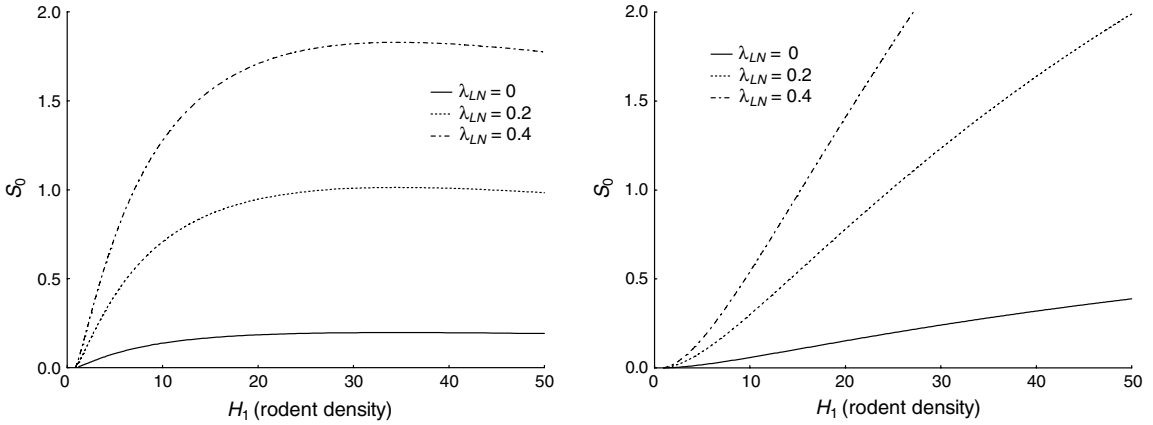

Fig. 3. Effect of H_1 on S_0 in (25) for different values of λ_{LN} using different choices for $a_T(T)$: on the left, $a_T(T)$ is given by (8), on the right by (10). Parameter values are the same as in Fig. 2; the other are: $\rho_{LN} = .25$, $k^L = 1$, $k^N = .1$.

that will divide the region (of host densities) where the infection persists from the region in which the infection goes extinct. Focussing on the effect of roe deer density (H_2), that are assumed to be incompetent to transmission, one can see in both panels (differing in the assumptions about the density-dependent tick fertility $a_T(T)$) of Fig. 4, that H_2 has a double effect on pathogen persistence: the pathogen persists when H_2 density is in a range above a minimum density, needed for tick persistence, and below a maximum. Above the latter density, the incompetent hosts prevent the transmission of the disease, by acting as a pathogen sink that looses more pathogens from the system than the competent rodent hosts may produce, and let S_0 drop below unity (Fig. 4). Concerning the effect of rodents on pathogen persistence, in Fig. 4 we can see (as already observed

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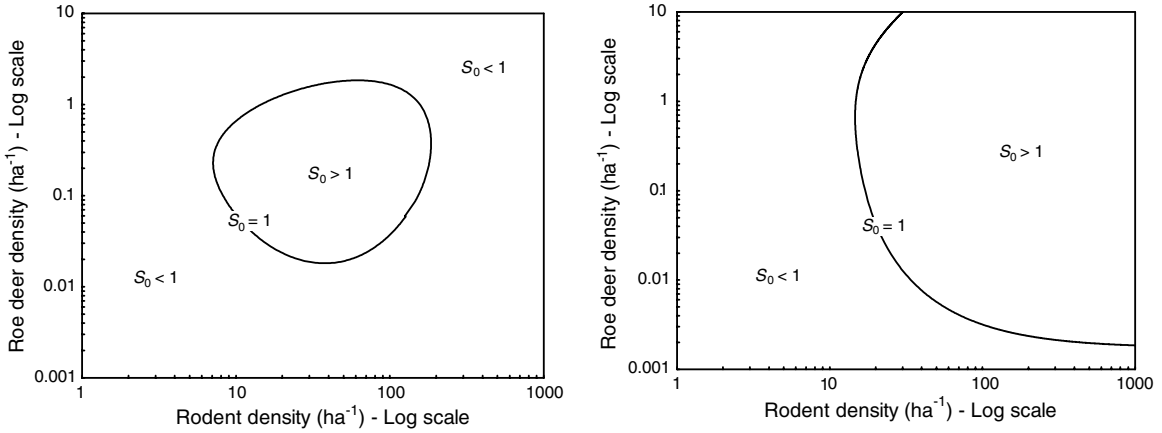

Fig. 4. Effect of host densities on S_0 in (25) using different choices for $a_T(T)$: on the left, $a_T(T)$ is given by (8), on the right by (10). All the parameters are the same as in Fig. 3 with $\lambda_{LN} = .3$.

in Fig. 3) that the effect of rodents depends on the structure of density-dependence. A negative effect of high rodent density is shown in the left panel of Fig. 4 that uses $a_T(T)$ in (8) while it does not occur in the right panel with $a_T(T)$ in (10) .

5. Discussion

In this paper, we have assessed, with the help of different mathematical models, how changes in the relative densities of the main host species can influence the persistence of tick-borne infections. The models considered differ in the assumptions about tick population dynamics, and the different infection pathways occurring between hosts and ticks.

The tool used to investigate the persistence of pathogens has been the computation, using matrix algebra, of the threshold for the stability of the infection-free equilibrium for the models considered. For some of the cases considered, the threshold had been already computed, but the present paper has improved the realism, by considering in detail the transition between tick stages and their phases of activity. In other cases, such as that with trans-ovarial transmission, the present paper shows a new explicit formula for computing the persistence threshold.

As widely known, a threshold for the stability of the infection-free equilibrium can generally be written as $R_0 < 1$, where R_0 is the basic reproduction number, defined in [19] as the spectral radius of the next-generation matrix. While we acknowledge the great theoretical importance and the heuristic value of the concept of R_0, we deem that sometimes other threshold quantities (that we denoted here as S_0) can be more practical, because explicit computation of eigenvalues of large matrices is unlikely and because there may be ambiguities in identifying the correct next-generation matrix (see for instance (24) and (26)). For this reason, we aimed at obtaining, in the various cases, threshold quantities S_0 that were simple to write and interpret. Often, the value obtained coincides with the quantity T_l, defined in [20], the relevant quantity when, in a pathogen multi-host system, attention is focussed on some hosts only.

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Apart from these technical issues, the focus of this paper is on the effect of host densities on the persistence of tick-borne pathogens. We found that the effect depends strongly on the way tick population is regulated; indeed, the conclusions differ significantly in case (8) or (10) is used to model density-dependent tick fecundity.

Using (8), overall tick density saturates with increasing host density, while equilibrium larval density actually decreases when rodent (H_1) density increases beyond a minimum (left panel of Fig. 1); on the other hand, using (10), overall tick density increases about linearly with increasing host density, while larval density increases more slowly (right panel of Fig. 1).

The decrease of larval density using (8) can be explained as follows: at large host densities, the equilibrium total number of ticks is almost independent of host densities; hence, the rate at which new larvae are recruited is almost constant. On the other hand, the rate at which larvae feed (and thus leave the stage) is a strongly increasing function of the density of H_1, since hosts will be easier to find. An almost constant input together with an increasing output results in a decreasing equilibrium density.

There exist very little information on what mainly regulates tick populations in the field. Several studies demonstrate that hosts' immune status strongly affects tick survival and fecundity, and, as discussed above, this indirect regulation may better be modelled through the function (10) rather than through (8).

Some indirect evidence about the mechanisms of tick demography may be found by comparing tick densities in systems that are ecologically similar but with different host densities. Kirby et al. [45] report a significant increase in tick burden of red grouse over a period of 20 years in which deer density appears to have increased. Allan et al. [46] have instead monitored tick densities in forest fragments of different size with the smaller fragments having higher mice densities; they found that questing nymph density decreases significantly with fragment area (thus increases with mice density), but questing larvae density does not differ among fragments of different sizes. Overall, it appears to be a result intermediate between that predicted through (8) and that predicted through (10) (left and right panels of Fig. 1).

The influence of host densities on infection persistence, under the two assumptions (8) or (10), was already discussed in Section 4 and can be seen in Fig. 4. When host densities are too low for ticks to persist, no tick-borne infection can persist: this explains the lower and left boundaries of the persistence regions in Fig. 4. One can also see a negative effect of high densities of non-competent hosts (the upper boundaries in Fig. 4); this can be explained on the basis of 'wasted' tick bites [14]. The possibility of a dilution effect on the transmission of tick-borne infections caused by non-competent hosts had already been found theoretically [17,18] and seems to be confirmed in [6] on the detailed study on Lyme disease in North-Eastern United States where the effect of host diversity and community composition on disease risk was examined.

A new result arising from this paper is that the dilution effect might occur at high density of competent hosts too. The effect is the same with or without non-systemic transmission; indeed, the expressions (20) (without trans-ovarial transmission) and (25) have exactly the same qualitative dependence on the densities H_1 and H_2, differing only in the quantitative values.

This dilution effect strongly depends on the type of regulation of tick population; indeed, using (8), tick (and especially larval) density does not increase much with increasing H_1 (left panel of Fig. 1), so that tick-per-host ratio will strongly decrease with increasing H_1. Thus, when hosts are abundant, each host will have the opportunity to infect only a few larvae; although each

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infected larva will then have a high probability of finding, as nymph, a host, the overall effect is to decrease the reproduction number below 1, as shown by the left panel of Fig. 4. For $a_T(T)$ as in (10), the number of ticks per rodent does not decrease significantly for increasing values of rodent density, and then generally the reproduction number does not go below 1 at high densities of H_1 (right panel of Fig. 4).

Since the exact nature of density-dependence in tick demographic parameters is largely unknown, better information on tick demography would be needed, before being able to conclude whether this second dilution effect is relevant in natural systems. It has to be remarked that, recently, an inverse density-dependence between competent mice density, tick loads and prevalence of tick-borne encephalitis has been recorded by [25].

The quantitative results shown in Figs. 2 and 3 show that the tick-borne encephalitis virus would not be able to persist in many areas, for instance in Trentino, without trans-ovarial or co-feeding transmission; indeed, many authors [2,8] argue that tick-borne encephalitis is mainly transmitted through co-feeding ticks. Our quantitative analysis seems to support this view, since for R_0 to be larger than 1, trans-ovarial transmission should be about one order of magnitude higher than current estimates [44], while a probability of transmission via co-feeding around the values measured in laboratory experiments [39] would suffice for persistence.

Foppa [23] too discusses the mechanisms that allow for the persistence of TBE. His approach is to find an empirical estimate for R_0 for TBEv, assuming only systemic transmission; his expression (2) for R_0 is, if monthly variations are neglected, exactly $p^L \cdot q^N$ in our notation (14) and (15), like (20). His estimates for q^N and p^L differ slightly from ours, because Foppa implicitly assumes $q_1^N = p_1^L = 1$ (probability 1 of getting infected upon encounter with the virus), and has somewhat different rules about which larval ticks get infected, upon contact with an infectious host. Overall, his estimates and confidence intervals for R_0 are generally below 1, with point estimates of 0.66 or 0.91, according to the site. Hence, he supports the view that, to explain the persistence of TBEv, other competent hosts must be present.

Our estimate for R_0 with only systemic transmission is around 0.15, depending on host density (see Fig. 2 with $\varepsilon = 0$). Considering that we use $q_1^N = p_1^L = 0.5$, and that his procedure for estimating α is actually an over-estimate, the two estimates seem rather similar. In the present paper, we have shown that co-feeding transmission at a reasonable rate seems to be enough to explain the persistence of TBEv [8]. Certainly, considering the seasonality, as in [23], could improve the computation of persistence thresholds.

Indeed, as discussed in the Introduction, seasonality has definitely an important role in tick-transmitted infections; in particular, for co-feeding transmission, uninfected larvae must feed alongside infected nymphs; hence coincidental timing of emergence is crucial for infection persistence. These effects are not considered in the present model setting, except for the fact that the equations (22) for non-systemic transmission contain, as a parameter, the correlation coefficient ρ_{NL} between nymphs and larvae. If ρ_{NL} is positive, as often empirically observed [8,41], the reproductive number will be increased. On the other hand, without coincidental feeding, ρ_{NL} would be negative, and the reproductive number would be decreased.

Although the estimate for R_0 will certainly depend on the seasonal patterns of tick (and host) populations, we believe that the effect of host densities on the persistence of tick-borne infections would be qualitatively similar in constant and seasonal environments. Indeed, a dilution effect with increasing densities of competent hosts has been found also in a model with discrete growing

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seasons [28]. Studying the issue in an equilibrium setting allows for clearer and simpler conclusions. A more complex situation would arise with seasonality coupled with multi-annual fluctuations of host (and tick) populations, as seems to be the case in Trentino [47]; it is difficult to predict the effects, without an explicit modelling investigation.

An important aspect of tick populations are the heterogeneities in tick–host interactions; these are indirectly present in our models, through the aggregation indices, k^N and k^L, that appear in equation (22) to compute the probability of non-systemic infection transmission. Aggregation of ticks on few hosts would be relevant also for systemic transmission, if the same hosts always tend to be fed on by ticks, hence would be more likely than the population average infected by tick-borne infections. It is not clear to us whether this kind of heterogeneities (apparently usual in tick–host interactions [47]) would simply increase the values of R_0 computed in this paper, or would also change the qualitative effects discussed. Probably, for a reliable answer, it would be helpful to develop individual-based models where static and dynamic (for instance, because of age, social status, or immune histories) heterogeneities can be modelled and monitored. The present computations of R_0 constitute anyway a background against which to compare more detailed models.

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Appendix A. Local stability of equilibria

A.1. Two useful tools

Many Jacobian matrices (or parts of them) that determine the stability of the equilibria of the systems considered in the text can be written in the form $J = T - D$ where T is an irriducible non-negative matrix, and D is a positive diagonal matrix. For such matrices Diekmann and Heesterbeek [19] show the following property:

Lemma 1. *Let $J = T - D$ where T is an irriducible non-negative matrix, and D is a positive diagonal matrix. Then*

$$s(J) > [<]0 \quad \Longleftrightarrow \quad \rho(TD^{-1}) > [<]1, \tag{27}$$

where $s(J)$ is the maximum of the real part of the eigenvalues of J, and $\rho(TD^{-1})$, the spectral radius of TD^{-1}, is the maximum of the moduli of the eigenvalues of TD^{-1}.

Since the (local) stability of an equilibrium is generally determined by the sign of $s(J)$, the previous lemma yields a criterion for determining the stability.

When applying the previous result to some of the cases analysed in the text, it turns out that the dimension of the matrix TD^{-1} is relatively large, so that computation of its spectral radius is awkward. In some cases, it is possible to reduce the dimensionality of the problem, applying the following

Lemma 2. *Let A be a non-negative irreducible matrix such that*

$$A = \begin{pmatrix} 0 & 0 & M \\ Q & 0 & 0 \\ B & P & 0 \end{pmatrix} \tag{28}$$

where M, Q, B and P represent submatrices of arbitrary dimension, while 0 represent 0-matrices of appropriate dimension. Then

$$\rho(A) > [<]1 \iff \rho(K) > [<]1 \quad \text{with } K = \begin{pmatrix} MB & MP \\ Q & 0 \end{pmatrix}. \tag{29}$$

Proof. Let R be the spectral radius of A, and let v be a corresponding eigenvector, which can be chosen to be positive. Setting $v = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \end{pmatrix}$ with v_i of appropriate dimension, the identity $A\,v = R\,v$ can be written, using (28), as

$$\begin{cases} Mv_3 = Rv_1 \\ Qv_1 = Rv_2 \\ Bv_1 + Pv_2 = Rv_3 \end{cases}$$

Using the first equation in the third one multiplied by M, we can rewrite the third and second equation as

$$\begin{cases} MBv_1 + MPv_2 = R^2 v_1 \\ Qv_1 = Rv_2 \end{cases} \tag{30}$$

Now if $R < 1$, we have from (30), using $R^2 < R$,

$$K\begin{pmatrix} v_1 \\ v_2 \end{pmatrix} \leqslant R\begin{pmatrix} v_1 \\ v_2 \end{pmatrix}.$$

This implies ([48], Theorem 2.1.11) that $\rho(K) \leqslant R < 1$.

On the other hand, if $R > 1$, we have, using $R^2 > R$,

$$K\begin{pmatrix} v_1 \\ v_2 \end{pmatrix} \geqslant R\begin{pmatrix} v_1 \\ v_2 \end{pmatrix}.$$

This implies ([48], Theorem 2.1.11) that $\rho(K) \geqslant R > 1$.

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We have then proved the thesis.

A.2. Stability of tick-free equilibrium

System (1) has a tick-free equilibrium $L_Q = L_F = N_Q = N_F = A_Q = A_F = 0$. The Jacobian J, obtained linearizing (1) at the tick-free equilibrium, can be split in the form $J = T - D$ where T is the non-negative matrix:

$$T = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \sigma^A a_T(0) \\ \beta^L & 0 & 0 & 0 & 0 & 0 \\ 0 & m^L\sigma^L & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta^N & 0 & 0 & 0 \\ 0 & 0 & 0 & m^N\sigma^N & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta^A & 0 \end{pmatrix}, \tag{31}$$

and D is the positive diagonal matrix:

$$D = \operatorname{diag} \begin{pmatrix} d^L + \beta^L \\ \sigma^L \\ d^N + \beta^N \\ \sigma^N \\ d^A + \beta^A \\ \sigma^A \end{pmatrix}. \tag{32}$$

TD^{-1} is exactly the matrix K in (2) (see the text) and its eigenvalues are the six sixth roots of S_0^{ticks} in (3). Because of Lemma 1, the stability condition for the tick-free equilibrium is that the spectral radius of TD^{-1} is less than 1, so that it can be stated as $S_0^{\text{ticks}} < 1$.

A.3. Stability of infection-free equilibrium with only systemic transmission

We wish to study the stability of T^* relatively to system (12). Before computing its Jacobian, it is useful to choose a suitable order of the components; we choose the order:

$$L_Q^i, N_Q^i, A_Q^i, H_1^i, L_F^i, N_F^i, A_F^i, H_1^r, H_1^s, L_Q^s, L_F^s, N_Q^s, N_F^s, A_Q^s, A_F^s$$

This ordering yields a nice simplification of the Jacobian matrix that assumes the form:

$$\begin{pmatrix} A_1 & 0 & 0 \\ B_1 & A_2 & 0 \\ B_2 & B_3 & J^* \end{pmatrix} \tag{33}$$

where A_1 and A_2 will be written down below, J^* is a 6×6 matrix and B_i are matrices of the appropriate dimensions. Since the Jacobian is block-triangular, its eigenvalues are the eigenvalues of A_1, A_2 and J^*. J^* is the Jacobian of (1) at T^*; by assumption (see the text), all its eigenvalues have

negative real part. Hence, in order to study the stability of T^* we need only to look at the eigenvalues of A_1 and A_2:

$$A_1 = \begin{pmatrix} -(d^L+\beta^L) & 0 & 0 & 0 & 0 & 0 & \varepsilon\sigma^A a_T(T^*) \\ 0 & -(d^N+\beta^N) & 0 & 0 & m^L\sigma^L & 0 & 0 \\ 0 & 0 & -(d^A+\beta^A) & 0 & 0 & m^N\sigma^N & 0 \\ q_1^L\beta_1^L H_1^* & q_1^N\beta_1^N H_1^* & q_1^A\beta_1^A H_1^* & -(d_1+\gamma_1+\alpha_1) & 0 & 0 & 0 \\ \beta^L & 0 & 0 & p_1^L\beta_1^L L_Q^* & -\sigma^L & 0 & 0 \\ 0 & \beta^N & 0 & p_1^N\beta_1^N N_Q^* & 0 & -\sigma^N & 0 \\ 0 & 0 & \beta^A & p_1^A\beta_1^A A_Q^* & 0 & 0 & -\sigma^A \end{pmatrix}$$

$$A_2 = \begin{pmatrix} -d_1 & 0 \\ a_1'(H_1^*)H_1^* + a_1(H_1^*) & a_1'(H_1^*)H_1^* + a_1(H_1^*) - d_1 \end{pmatrix}.$$

A_2 is a triangular matrix; hence, its eigenvalues are the elements on the diagonal, all of which are negative, since $a_1(\cdot)$ is decreasing and at equilibrium $a_1(H_1^*) = d_1$. Hence, we see that the equilibrium T^* is exponentially asymptotically stable if and only if the eigenvalues of A_1 have negative real part.

$A_1 = T_1 - D_1$ with T_1 non-negative and D_1 a positive diagonal matrix; hence from Lemma 1, we look at the spectral radius of $T_1 D_1^{-1}$. We note that $T_1 D_1^{-1}$ can be written in the form (28) with

$$M = \begin{pmatrix} 0 & 0 & \varepsilon\sigma^A a_T(T^*) \\ m^L & 0 & 0 \\ 0 & m^N & 0 \end{pmatrix} \quad Q = \begin{pmatrix} q^L & q^N & q^A \end{pmatrix}$$

$$B = \begin{pmatrix} \frac{\beta^L}{d^L+\beta^L} & 0 & 0 \\ 0 & \frac{\beta^N}{d^N+\beta^N} & 0 \\ 0 & 0 & \frac{\beta^A}{d^A+\beta^A} \end{pmatrix} \quad P = \begin{pmatrix} \frac{p_1^L\beta_1^L L_Q^*}{d_1+\gamma_1+\alpha_1} \\ \frac{p_1^N\beta_1^N N_Q^*}{d_1+\gamma_1+\alpha_1} \\ \frac{p_1^A\beta_1^A A_Q^*}{d_1+\gamma_1+\alpha_1} \end{pmatrix}.$$

Hence, we can apply Lemma 2 and compute the spectral radius of the matrix $K = \begin{pmatrix} MB & MP \\ Q & 0 \end{pmatrix}$ that is (13) (see the text).

Letting $G(\lambda)$ be the characteristic polynomial of K, it is easy to see that $G(\lambda) = \lambda^4 - a\lambda^2 - b\lambda - c$ with a, b and c positive; from the signs of the coefficients, one can conclude that G has a unique positive root. Since K is non-negative, $\rho(K)$ is the largest positive root of $G(\lambda)$; hence $\rho(K) < [>]1$ if and only $G(1) > [<]0$; the condition $G(1) < 0$ is exactly $S_0 > 1$ with S_0 in (16).

A.4. Both systemic and non-systemic infection

When also non-systemic infection on H_1 is considered, we compute the Jacobian using the following order of the components:

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$$L_F^e, N_Q^i, H_1^i, N_{F_1}^i N_{F_2}^i, N_F^e, A_Q^i, H_1^r, H_1^s, L_Q, L_F^s, N_Q^s, N_F^s, A_Q^s, A_F.$$

The Jacobian of (23) can be written in the same form of (33) where all the sub-matrices are the same except for A_1 and A_2, that in this case are the following 4×4 matrices:

$$A_1 = \begin{pmatrix} -\sigma^L & 0 & p_1^L \beta_1^L L_Q^* & \beta_1^L \lambda_{LN} L_Q^* \\ m^L \sigma^L & -(d^N + \beta^N) & 0 & 0 \\ 0 & q_1^N \beta_1^N H_1^* & -(d_1 + \gamma_1 + \alpha_1) & 0 \\ 0 & \beta_1^N H_1^* & 0 & -\sigma^N \end{pmatrix}.$$

$$A_2 = \begin{pmatrix} -\sigma^N & 0 & 0 & 0 \\ 0 & -\sigma^N & 0 & 0 \\ m^N \sigma^N & m^N \sigma^N & -(d^A + \beta^A H_2) & 0 \\ 0 & 0 & 0 & -d_1 \end{pmatrix}.$$

As in the previous case, A_2 is a triangular matrix with all negative elements on the diagonal. Thus, we study the matrix $A_1 = T_1 - D_1$, where D_1 is a diagonal positive matrix and T_1 is a non-negative matrix. The matrix $K = T_1 D_1^{-1}$ is (24) (see the text). Because of Lemma 1, the stability condition for the infection-free equilibrium is $\rho(TD^{-1})$, i.e. $S_0 < 1$, as shown in the text.

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