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Thresholds for disease persistence in models for tick-borne infections including non-viraemic transmission, extended feeding and tick aggregation

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Abstract

Lyme disease and Tick-Borne Encephalitis (TBE) are two emergent tick-borne diseases transmitted by the widely distributed European tick *Ixodes ricinus*. The life cycle of the vector and the number of hosts involved requires the development of complex models which consider different routes of pathogen transmission including those occurring between ticks that co-feed on the same host. Hence, we consider here a general model for tick-borne infections. We assumed ticks feed on two types of host species, one competent for viraemic transmission of infection, the second incompetent but included a third transmission route through non-viraemic transmission between ticks co-feeding on the same host. Since a blood meal lasts for several days these routes could lead to interesting nonlinearities in transmission rates, which may have important effects.

We derive an explicit formula for the threshold for disease persistence in the case of viraemic transmission, also for the case of viraemic and non-viraemic transmission. From this formula, the effect of parameters on the persistence of infection can be determined. When only viraemic transmission occurs, we confirm that, while the density of the competent host has always a positive effect on infection persistence, the density of the incompetent host may have either a positive effect, by amplifying tick population, or a negative (''dilution'') effect, by wasting tick bites on an incompetent host. With non-viraemic transmission, the ''dilution'' effect becomes less relevant. On the other hand, if the nonlinearity due to extended feeding is included, the dilution effect always occurs, but often at unrealistically high host densities. Finally, we incorporated the effects of tick aggregation on the hosts and correlation of tick stages and found that both had an important effect on infection persistence, if non-viraemic transmission occurred.

Keywords: Mathematical model; Tick-borne infection; Persistence threshold; Co-feeding transmission; Tick aggregation

1. Introduction

Tick-borne diseases, such as Lyme disease and Tick-Borne Encephalitis (TBE), have become a significant problem to human populations inhabiting woodland areas in many parts of Europe, the former USSR and North America. The increase in prevalence of these diseases, not recorded more than 30 years ago, is probably associated with the abandonment of fields and pastures coupled with the expansion of woodland which have favoured the spread and the increase in the densities of both deer and rodents. Hence, tick populations have increased and with them their potential for disease transmission. This increased tick population coupled with people having more leisure time has lead to an increase in the exposure of people to infection.

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Concern over tick-borne diseases has stimulated the development of several mathematical models for either tick-borne infections, or tick population dynamics. The important first step was to develop mathematical models for tick population dynamics (e.g. Sandberg et al., 1992; Kitron and Mannelli, 1994; Randolph and Rogers, 1997). The second to develop models for tick-borne infections and these have often been set, for ease of analysis, in continuous time: see, for instance, Hudson et al. (1995) and O'Callaghan et al. (1997). Norman et al. (1999) and more recently Gilbert et al. (2001) proposed a model where ticks are subdivided into the three stages (larvae, nymphs and adults) with stage progression only through a blood meal on a vertebrate host and transmission is only viraemic (i.e. from infected tick to susceptible host, and vice versa). They computed the value of the basic reproduction number, R_0, and showed the so-called dilution effect: when two alternative hosts exist for ticks, only one of which is competent for transmission (e.g. mice and deer for Lyme diseases) an increase in the density of the incompetent host (deer in this example) may shift R_0 from above to below 1, and thus cause pathogen extinction. A similar model has been applied by Caraco et al. (1998) to the deer, tick Borrellia system in the USA, while qualitatively similar results have been obtained by Van Buskirk and Ostfeld (1995) and Mannelli (in press) in computer-based models.

It has been demonstrated in a number of tick-borne systems that certain tick hosts, which do not produce a viraemic response, will permit non-viraemic transmission between co-feeding ticks (Labuda et al., 1993, Jones et al., 1987; Ogden et al., 1997). Moreover, Randolph et al. (1996, 1999, 2002) have shown the importance of co-feeding (transmission between ticks feeding together on an incompetent host) and temporal coincidence of different tick stages in the maintenance of TBE.

In this paper we build on the model by Norman et al. (1999). We introduce general rules for the encounter rates between hosts and ticks, that take into account the duration of feeding. More importantly, we consider specifically the possibility of non-viraemic transmission which is thought to be crucial in the maintenance of several infections such as TBE. We also consider the distribution of tick stages among hosts, which will have extremely important effects on transmission via co-feeding. In fact, in certain parts of the vector's range, patterns of tick infestation on hosts (e.g. rodents) are such that they facilitate co-feeding transmission. Specifically, both immature tick stages show highly aggregated distribution on their host and these aggregated distributions are coincident rather than independent (Perkins et al. in MS); those hosts which were feeding larvae were simultaneously feeding the greatest number of nymphs. As a result, about 20% of hosts feed about three-quarters of both larvae and nymphs and the number of susceptible larvae feeding alongside potentially infected nymphs is twice as many as it would be if the distribution were independent (Randolph et al., 2002; Perkins et al. in MS).

For these different models we compute, using matrix theory, the threshold quantity for infection persistence. Thus, we may understand the effect of different parameters on disease persistence.

2. The model

Following Norman et al. (1999), ticks were classified according to their stage as larvae (L), nymphs (N), and adults (A). Each immature stage (larvae and nymphs) requires a blood meal from a suitable vertebrate host. The adult female requires a meal before producing eggs. The model considers two types of hosts: viraemic hosts (H_1) that acquire and transmit the disease, and non-viraemic hosts (H_2) that simply sustain the tick population without amplifying the pathogen. Here, H_2 is assumed to be at constant density while H_1 hosts are classified as being either susceptible (H_{1s}), infected (H_{1i}) or immune (H_{1r}), and their density may vary as a consequence of infection. We assume no trans-ovarial transmission of infection in ticks (reported as negligible in TBE but cannot recall reference), while the pathogen is transmitted inter-stadially, so once an immature stage is infected the subsequent stages can transmit the pathogen to a susceptible host. Then, nymphs and adults are classified as either susceptible (N_s and A_s) or infected (N_i and A_i). In the model, the principal route of infection is viraemic transmission, we also consider non-viraemic transmission since there is growing evidence that this is crucial in several tick-borne diseases (Randolph et al., 2002).

2.1. Tick–hosts interactions

Ticks change stage by feeding on a host, hence, a key factor in the dynamics is the encounter rate between hosts and ticks (in the different stages). We assume throughout a mass-action law, that is, the encounter rate between hosts (whose density will be denoted by H) and, for instance, nymphs will be proportional to the product HN_Q, where N_Q, denotes the density of questing nymphs.

In a complete model, we may include N_F (the density of feeding nymphs) and N_Q as variables, as done by Mwambi et al. (2000) which consider only tick population dynamics. In the simplest approximation, it has instead often been

assumed (Caraco et al., 1998; Norman et al., 1999) that both are proportional to the density N of ticks. As an intermediate step, we use here a quasi-steady-state assumption (see, for instance, Segel and Slemrod, 1989).

Assuming that questing nymphs become feeding nymphs by encountering hosts (at rate β^N), and that feeding nymphs drop off hosts at rate σ^N (so the average duration of a blood meal is $1/\sigma^N$). Then we have the two equations:

$$\dot{N}_{F_j} = \beta_j^N H_j N_Q - \sigma_j^N N_{F_j} = \beta_j^N H_j (N - N_{F_1} - N_{F_2}) - \sigma_j^N N_{F_j}, \tag{1}$$

where N_{F_j} represents the density of nymphs which are feeding on host H_j with $j = 1, 2$ (definition of all the parameters are shown in Table 1). We assume now that the feeding process is faster than all other processes (deaths, births, stage progression), so that we set $\dot{N}_{F_j} = 0$ and from Eq. (1) we obtain

$$N_{F_j} = \frac{c_j^N H_j N}{1 + c_1^N H_1 + c_2^N H_2} \quad \text{and} \quad N_Q = \frac{N}{1 + c_1^N H_1 + c_2^N H_2}, \tag{2}$$

where $c_j^N = \beta_j^N / \sigma_j^N$.

From these assumptions, we can write equations for the densities of each stage. For instance, we obtain

$$\frac{\mathrm{d}A}{\mathrm{d}t} = m^N (\beta_1^N H_1 + \beta_2^N H_2) \frac{N}{1 + c_1^N H_1 + c_2^N H_2} - (\beta_1^A H_1 + \beta_2^A H_2) \frac{A}{1 + c_1^A H_1 + c_2^A H_2} - b_T A,$$

where the first term represents the nymphs becoming adults, the second term the adults that start a blood meal and therefore exit the compartment (it is assumed here that adults reproduce only once in their life, as is usual in the *Ixodidae* ticks) and the third the deaths of questing adults (b_T is ticks' death rate, assumed to be the same in all stages).

Table 1
Notation used to denote the various variable and parameters included in the model

Variable or rate	Description
L	Larval density
N	Nymph density
A	Adult density
$T = (L + N + A)$	Total tick density
H_1	Total viraemic host density
H_{1s}	Susceptible viraemic host density
H_{1i}	Infected viraemic host density
H_{1r}	Immune viraemic host density
H_2	Non-viraemic host density
a_T	Birth rate of larvae per adult tick
b_T	Natural death rate of ticks (the same for all stages)
a_1	Birth rate for viraemic host
b_1	Natural death rate for viraemic host
α	Rate at which viraemic hosts die from the disease
γ	Rate at which viraemic hosts recover to immunity
β_j^z	Encounter rate between questing ticks in stage $z (z = L, N, A)$ and hosts $H_j (j = 1, 2)$
σ_j^z	Dropping rate of ticks in the stage $z (z = L, N, A)$ feeding on host $H_j (j = 1, 2)$
c_j^z	$= \beta_j^N / \sigma_j^N$ for $z = L, N, A$ and $j = 1, 2$
ψ^z	$= 1/(1 + c_1^z H_1 + c_2^z H_2)$ for $z = L, N, A$
g^z	$= \psi^z (\beta_1^z H_1 + \beta_2^z H_2)$ for $z = L, N, A$
m^z	Moulting success probability for ticks in stage z $(z = L, N)$
p^N	Probability of becoming infected for a nymph feeding on an infectious host
p^A	Probability of becoming infected for an adult feeding on an infectious host
q^N	Probability of becoming infected for a viraemic host bitten by an infectious nymph
q^A	Probability of becoming infected for a viraemic host bitten by an infectious adult
θ_{NL}	Non-viraemic transmission coefficient for infected nymphs and larvae
θ_{AL}	Non-viraemic transmission coefficient for infected adults and larvae
θ_{NN}	Non-viraemic transmission coefficient for infected nymphs and susceptible nymphs
θ_{AN}	Non-viraemic transmission coefficient for infected adults and susceptible nymphs
k^L	Aggregation parameter of the negative binomial distribution for larvae
k^N	Aggregation parameter of the negative binomial distribution for nymphs
k^A	Aggregation parameter of the negative binomial distribution for adults
ρ_{NL}	Correlation coefficient for nymphs and larvae
ρ_{AL}	Correlation coefficient for adults and larvae
ρ_{AN}	Correlation coefficient for adults and nymphs

The parameters m^N represent the probability of moulting success for nymphs after feeding. In practise, m^N may depend on the host species (Humair et al., 1999) so to be accurate we should use m_1^N and m_2^N. However, when we do, the formulae become awkward, and so in this presentation we stick to the case of a single m^N.

For ease of notation, it will be convenient to introduce the following functions:

$$\psi^z(H_1,H_2)=\frac{1}{1+c_1^zH_1+c_2^zH_2}\quad\text{and}\quad g^z(H_1,H_2)=\frac{\beta_1^zH_1+\beta_2^zH_2}{1+c_1^zH_1+c_2^zH_2},$$

where $z=L,N$ or A. Note that if $\beta_j^zH_j\ll\sigma_j^z$ (as it appears likely) the functions ψ^z are very close to 1, so that g^z are practically linear over most of the reasonable range of H_1 and H_2.

2.1.1. Density dependence in ticks and hosts

Detecting density dependence in the demographic parameters of ticks is rather complex because of the complexity of their life cycle (Hudson et al., 2002). However, without introducing any density-dependent factor, the tick population would grow (or decrease) exponentially unrealistically making it difficult to identify any meaningful persistence threshold.

Randolph and Rogers (1997) present a model where the mortalities of the larval-to-nymph and nymphal-to-adult stages are a function of the initial densities of larvae and nymphs, respectively.

Here, for the sake of simplicity, we assume, like Norman et al. (1999), that only the production of larvae per feeding adult tick $a_T(T)$ is density dependent, where $a_T(T)$ is a decreasing function of the total number of ticks present in the system. Furthermore, to simulate logistic growth of the viraemic host H_1 (the non-viraemic host is assumed to be at a constant size H_2) we assumed that the birth rate $a_1(H_1)$ is a decreasing function of the total density, while the death rate b_1 is assumed to be constant. The effect of these assumptions is examined in the Discussion.

2.2. Infection

2.2.1. Viraemic transmission

Initially, we model viraemic transmission as in Norman et al. (1999). In particular, we assume that viraemic transmission can occur only on one species of host, usually H_1.

We assume that a proportion q^z of the hosts being bitten by infected ticks become infected; here z may be equal to N or A, since questing larvae cannot pass on virus until they become nymphs.

Hence, the rate at which susceptible hosts become infected will be equal to

$$q^N\beta_1^NH_{1s}N_i\psi^N(H_1,H_2)+q^A\beta_1^AH_{1s}A_i\psi^A(H_1,H_2),$$

where H_{1s} is the density of susceptible hosts, N_i and A_i those of infected nymphs and adults.

Analogously, we assume that a proportion p^z of ticks (here z may be equal to L or N) become infected while feeding on hosts and then switching from larvae to infected nymphs or from susceptible nymphs to infected adults. Hence, the rate at which larvae become infected will be equal to

$$m^Lp^L\beta_1^LH_{1i}L\psi^L(H_1,H_2)$$

and the rate at which susceptible nymphs become infected will be equal to

$$m^Np^N\beta_1^NH_{1i}N_s\psi^N(H_1,H_2),$$

where H_{1i} is the density of infected hosts, L and N_s those of larvae and susceptible nymphs respectively, while m^z is the probability of moulting success for ticks in stage z ($z=L,N$).

2.2.2. Non-viraemic transmission

Modelling the rate of non-viraemic transmission adds another level of complexity, but a level we suspect is important. It is reasonable to assume that, once an infected nymph (for instance) arrives on a host, it will infect a certain proportion of the other ticks feeding on the same host over the whole duration of the blood meal. Assuming that this quantity is proportional to the mean number of ticks present on the same host of a given feeding tick, it implies that the rate at which new infections are produced by infected nymphs (for instance) through the co-feeding route is proportional to the product of two quantities: first the encounter rate of infected nymphs, and second the mean number of other ticks present on the same host of a given feeding nymph.

We have already considered the first term. As for the second, it is easy to see that the mean number of nymphs present on a random host will be equal to the number of feeding nymphs, given by expression (2), over the number of hosts. However, the mean number of other nymphs present on the same host of a given feeding tick may be different from the mean number of nymphs present on a given host. To understand that from a statistical point of view, let p_i be

the proportion of hosts carrying i nymphs; then, the probability that, on the same host of a randomly selected feeding nymph, there are i nymphs (including the one from which we started) is $q_i = ip_i/\sum_l lp_l$; in fact, we select a nymph at random and so it will be more likely to find a host that carries many nymphs. The average number of nymphs on that host is therefore

$$\sum_i iq_i = \frac{\sum_i i^2 p_i}{\sum_l lp_l} = \frac{E(N^2)}{E(N)} = E(N) + \frac{V(N)}{E(N)},$$

where $E(N) = \sum_i ip_i$ represents the mean number of nymphs on a randomly selected host, $V(N)$ is the variance of that number. In order to get the mean number of *other* nymphs present on the same host of a given feeding nymph, we must subtract 1 (the nymph we started with) obtaining

$$E(N) + \frac{V(N)}{E(N)} - 1. \tag{3}$$

Note that, if the distribution of the nymphs is Poisson, the variance is equal to the mean, and the mean number of other ticks present on the same host of a random feeding nymph is equal to the mean number of nymphs present on a random host. On the other hand, if the distribution were aggregated (for instance, a negative binomial distribution that is described by the mean and the parameter k), then the variance is equal to $V(N) = E(N)(1 + E(N)/k)$, so that the mean number of other ticks present on the same host of a given feeding nymph is equal to $E(N)(1 + 1/k)$. We will follow this latter assumption, which is used in models for macroparasites (Anderson and May, 1978), hence the distribution of each stage will be assumed to be a negative binomial with a given k.

Putting all the ingredients together, the encounter rate of infected nymphs with hosts of species 2 is $\beta_2^N H_2 N_i \psi^N(H_1, H_2)$; the mean number of susceptible nymphs on a host of species 2 is, using Eq. (2), $c_2^N N_s \psi^N(H_1, H_2)$ so that the rate at which nymphs get infected by other nymphs through co-feeding is

$$m^N \theta_{NN} N_i N_s H_2 [\psi^N(H_1, H_2)]^2 \left(1 + \frac{1}{k^N}\right), \tag{4}$$

where θ_{NN} is a proportionality constant that includes the probability for a nymph of being in a co-feeding group, the probability of being infected in that case, the probability of the infection being maintained trans-stadially and the constants β and c.

Clearly, one could also include the last factor in θ_{NN} but we preferred to keep it apart , to explore the role of aggregation.

When we consider inter-stadial (for instance, nymphs to larvae) transmission by co-feeding, we need to know the mean number of larvae on the same host of a given feeding nymph. Let p_{ij} be the proportion of hosts carrying i larvae and j nymphs; then the probability that the host on which a given nymph is feeding will carry i larvae and j nymphs is equal to $jp_{ij}/\sum_{k,l} lp_{kl}$. Hence, the average number of larvae on that host is equal to

$$\frac{\sum_{i,j} ijp_{ij}}{\sum_{k,l} lp_{kl}} = \frac{E(LN)}{E(N)} = E(L) + \frac{Cov(L, N)}{E(N)}. \tag{5}$$

As expected, the mean number of larvae on the same host of a given feeding nymphs is influenced by the covariance between larvae and nymphs. To proceed, we assume that the association between stages are fixed constants; although the assumption that each stage is distributed in a negative binomial with fixed parameter means

$$V(t) = E(t) + \frac{(E(t))^2}{k} \cong \frac{(E(t))^2}{k},$$

so, from Eq. (5) we obtain

$$E(L) + \frac{Cov(L, N)}{E(N)} = E(L) + \frac{\rho_{LN}\sqrt{V(N)V(L)}}{E(N)} \cong E(L) + \frac{\rho_{LN} E(L)}{\sqrt{k^L k^N}}.$$

We can then say that the rate at which larvae get infected by nymphs through co-feeding is

$$m^L \theta_{NL} N_i L H_2 \psi^N(H_1, H_2) \psi^L(H_1, H_2) \left(1 + \frac{\rho_{LN}}{\sqrt{k^L k^N}}\right), \tag{6}$$

where θ_{NL} has the same interpretation as θ_{NN}. Note that, formally, Eq. (4) is a special case of Eq. (6) with $\rho_{NN} = 1$.

2.3. The equations

From the previous assumptions, we obtain the following equations:

$$
\begin{aligned}
\frac{dL}{dt} &= g^A(H_1,H_2)a_T(T)(A_i+A_s) - b_T L - g^L(H_1,H_2)L,\\
\frac{dN_s}{dt} &= m^L g^L(H_1,H_2)L - m^L\beta_1^L p^L H_{1i}\psi^L(H_1,H_2)L - b_T N_s - g^N(H_1,H_2)N_s\\
&\quad -m^L\theta_{NL}N_i L H_2\psi^N(H_1,H_2)\psi^L(H_1,H_2)\left(1+\frac{\rho_{NL}}{\sqrt{k^N k^L}}\right) - m^L\theta_{AL}A_i L H_2\psi^A(H_1,H_2)\psi^L(H_1,H_2)\left(1+\frac{\rho_{AL}}{\sqrt{k^A k^L}}\right),\\
\frac{dA_s}{dt} &= m^N g^N(H_1,H_2)N_s - m^N\beta_1^N p^N H_{1i}\psi^N(H_1,H_2)N_s - b_T A_s - g^A(H_1,H_2)A_s\\
&\quad - m^N\theta_{NN}N_i N_s H_2[\psi^N(H_1,H_2)]^2\left(1+\frac{1}{k^N}\right) - m^N\theta_{AN}A_i N_s H_2\psi^A(H_1,H_2)\psi^N(H_1,H_2)\left(1+\frac{\rho_{AN}}{\sqrt{k^A k^N}}\right),\\
\frac{dN_i}{dt} &= m^L p^L\beta_1^L H_{1i}\psi^L(H_1,H_2)L - b_T N_i - g^N(H_1,H_2)N_i + m^L\theta_{NL}N_i L H_2\psi^N(H_1,H_2)\psi^L(H_1,H_2)\left(1+\frac{\rho_{NL}}{\sqrt{k^N k^L}}\right)\\
&\quad + m^L\theta_{AL}A_i L H_2\psi^A(H_1,H_2)\psi^L(H_1,H_2)\left(1+\frac{\rho_{AL}}{\sqrt{k^A k^L}}\right),\\
\frac{dA_i}{dt} &= m^N p^N\beta_1^N H_{1i}\psi^N(H_1,H_2)N_s + m^N g^N(H_1,H_2)N_i - b_T A_i - g^A(H_1,H_2)A_i\\
&\quad + m^N\theta_{NN}N_i N_s H_2[\psi^N(H_1,H_2)]^2\left(1+\frac{1}{k^N}\right) + m^N\theta_{AN}A_i N_s H_2\psi^A(H_1,H_2)\psi^N(H_1,H_2)\left(1+\frac{\rho_{AN}}{\sqrt{k^A k^N}}\right),\\
\frac{dH_{1i}}{dt} &= q^N\beta_1^N H_{1s}\psi^N(H_1,H_2)N_i + q^A\beta_1^A H_{1s}\psi^A(H_1,H_2)A_i - (b_1+\gamma+\alpha)H_{1i},\\
\frac{dH_{1r}}{dt} &= \gamma H_{1i} - b_1 H_{1r},\\
\frac{dH_{1s}}{dt} &= a_1(H_1)H_1 - b_1 H_{1s} - q^N\beta_1^N H_{1s}\psi^N(H_1,H_2)N_i - q^A\beta_1^A H_{1s}\psi^A(H_1,H_2)A_i.
\end{aligned}
\tag{7}
$$

Most of the assumptions that lead to these equations have already been discussed. In addition, it has been assumed that ticks have no impact on the demography of either H_1 or H_2 (whose density is assumed to be constant), while infected hosts have an additional death rate α. It should also be noted that infected nymphs (and adults) that become infected through co-feeding must be subtracted from susceptible nymphs (or adults) since they correspond to feeding susceptible larvae (nymphs) that do not develop into susceptible nymphs (adults). The model without non-viraemic transmission analysed by Norman et al. (1999) is a special case of the model presented here: one needs only set all parameters θ equal to 0 and $\psi(H_1,H_2)$ equal to 1.

3. Basic reproduction numbers (R_0)

R_0 is a measure of the maximum reproductive potential of a parasite between one generation and the next for a susceptible host population in a given environment. R_0 is one of the most important and useful concepts in epidemiology since it determines whether or not a parasite has the potential to spread in a host population, the difficulty of eradication and also produces an estimate of parasite fitness. For microparasites (virus and bacteria), R_0 is defined as the average number of secondary cases which one case can produce in a population consisting only of susceptible individuals. If $R_0 > 1$ a chain reaction of new cases will result leading to an epidemic outbreak, but if $R_0 < 1$ the number of infected hosts will fall and eventually be lost from population.

For macroparasites, and in particular for ticks, the idea of R_0 is the same, but the definition is subtly different. In this instance, R_0 is defined as the number of new female parasites produced by a female parasite when there are no density-dependent constraints acting anywhere in the life cycle of the parasites (Hudson et al., 2002).

Mathematically, R_0 works as a threshold quantity for the stability of the disease-free equilibrium. In fact, it makes the disease-free equilibrium (for microparasites) or the parasite-free equilibrium (for macroparasites) stable when $R_0<1$ or unstable when $R_0>1$.

A very useful tool in the computation of the thresholds for disease persistence in epidemic models is the Perron–Frobenius theory (see the application to epidemic models in Diekmann and Heesterbeek, 2000). Using this theory, we derive, in the following sections, the thresholds for the persistence of both ticks and the disease distinguishing the cases with and without non-viraemic transmission. We will write these in the form $R_0>1$ where the R_0 are explicit quantities related to the transmission of the infection. We remark that, although we used the symbol R_0 for these threshold quantities, they are not always exactly equal to the basic reproduction number defined in Diekmann and Heesterbeek (2000) as the spectral radius of the ''next-generation matrix''. The spectral radius cannot be computed explicitly, and we believe that our quantity has a useful interpretation. In either case, the conditions for persistence are the same with both methods.

3.1. The case with only viraemic transmission

Here we consider only the viraemic route of the infection. This means that a susceptible tick can only become infected when feeding on an infected viraemic hosts (H_{1i}). At the same time the transmission could pass from infected ticks to susceptible hosts (H_{1s}) while non-vireamic hosts (H_2) do not take part in the infection process. Thus, in this case we set all of the parameters concerned with non-viraemic transmission to zero ($\theta_{NL}=\theta_{AL}=\theta_{NN}=\theta_{AN}=0$). The special case with all the quantities $\psi^z(H_1,H_2)=1$ has been already analysed by Norman et al. (1999) and Gilbert et al. (2001).

3.1.1. Tick-free equilibrium

Through the study of the local stability of the tick-free equilibrium (see Appendix A) we derived the following basic reproduction number for the tick population:

$$R_0^{ticks}=a_T(0)\frac{m^Lg^L(H_1,H_2)}{b_T+g^L(H_1,H_2)}\frac{m^Ng^N(H_1,H_2)}{b_T+g^N(H_1,H_2)}\frac{g^A(H_1,H_2)}{b_T+g^A(H_1,H_2)}. \tag{8}$$

This quantity represents the threshold condition for the persistence of ticks in the system. When $R_0^{ticks}>1$ the ticks will persist and, from numerical simulation, it appears that tick and host populations will settle to a positive coexistence equilibrium. The quantity R_0^{ticks} has a rather obvious biological interpretation in that if the product of the losses from each tick stage is greater than the product of the gains to each stage, then the ticks will die out, if not, they will persist. In particular, the expression of R_0^{ticks} in Eq. (8) is the result of three multiplicative factors whose biological interpretations are the following:

(i) $m^Lg^L(H_1,H_2)/(b_T+g^L(H_1,H_2))$ is the probability of a larva becoming a nymph,
(ii) $m^Ng^N(H_1,H_2)/(b_T+g^N(H_1,H_2))$ is the probability of a nymph becoming an adult and
(iii) $a_T(0)\,(g^A(H_1,H_2)/(b_T+g^A(H_1,H_2))$ is the number of larvae produced per adult.

3.1.2. Disease-free equilibrium

Through the study of the local stability of the disease-free equilibrium in the case with only viraemic transmission (see Appendix B) we found that the disease-free equilibrium is stable if and only if the following condition is satisfied:

$$\begin{aligned}R_0^{vir}=&\frac{m^Lp^L\beta_1^L\psi^L(H_1,H_2)L}{(b_1+\gamma+\alpha)}\frac{q^N\beta_1^NH_1\psi^N(H_1,H_2)}{(b_T+g^N(H_1,H_2))}+\frac{m^Lp^L\beta_1^L\psi^L(H_1,H_2)L}{(b_1+\gamma+\alpha)}\frac{m^Ng^N(H_1,H_2)}{(b_T+g^N(H_1,H_2))}\\&\times\frac{q^A\beta_1^AH_1\psi^A(H_1,H_2)}{(b_T+g^A(H_1,H_2))}+\frac{m^Np^N\beta_1^N\psi^N(H_1,H_2)N}{(b_1+\gamma+\alpha)}\frac{q^A\beta_1^AH_1\psi^A(H_1,H_2)}{(b_T+g^A(H_1,H_2))}<1.\end{aligned} \tag{9}$$

If we follow an infected host we see that it produces on average $m^Lp^L\beta_1^L\psi^LL/(b_1+\gamma+\alpha)$ infected nymphs. Each nymph will infect a host with probability $q^N\beta_1^NH_1\psi^N/(b_T+g^N)$, and can also develop to infected adult with probability $m^Ng^N/(b_T+g^N)$ and then infect a host as adult with probability $q^A\beta_1^AH_1\psi^A/(b_T+g^A)$. Finally, an infected host produces also $m^Np^N\beta_1^N\psi^NN/(b_1+\gamma+\alpha)$ infected adults that infect a host with probability $q^A\beta_1^AH_1\psi^A/(b_T+g^A)$.

3.2. The case with non-viraemic transmission

Here, we consider horizontal transmission between ticks. This means that a susceptible tick can become infected not only by feeding on an infected viraemic host but also when co-feeding with other infected ticks present on the same

non-viraemic host. In our model the parameters measuring non-viraemic transmission are $\theta_{NL}, \theta_{AL}, \theta_{NN}$ and θ_{AN} depending on the different tick stages that are co-feeding (Table 1).

Through the study of the local stability of the disease-free equilibrium in the case with non-viraemic transmission (see Appendix C) we obtained a joint condition for the stability of the disease-free equilibrium that means disease extinction.

The disease-free equilibrium is stable if the following three condition are satisfied:

$$R_{0,ad}^{non-vir} = \frac{m^N \theta_{AN} N H_2 \psi^A \psi^N (1 + \rho_{AN}/\sqrt{k^A k^N})}{b_T + g^A} < 1, \tag{10}$$

$$R_{0,nym}^{non-vir} = \frac{m^L \theta_{NL} L H_2 \psi^N \psi^L (1 + \rho_{NL}/\sqrt{k^N k^L})}{b_T + g^N} < 1, \tag{11}$$

$$\begin{aligned} R_0^{all} = {} & \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{1}{1 - R_{0,nym}^{non-vir}} \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N} + \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{m^N g^N + m^N \theta_{NN} N H_2 [\psi^N]^2 (1 + (1/k^N))}{(b_T + g^N)(1 - R_{0,nym}^{non-vir})} \\ & \times \frac{q^A \beta_1^A H_1 \psi^A}{(b_T + g^A)(1 - R_{0,nym}^{non-vir})} + \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \frac{1}{1 - \mathrm{R}_{0,ad}^{non\text{-}vir}} \frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A} + \frac{m^N p^N \beta_1^N \psi^N N}{b_1 + \gamma + \alpha} \\ & \times \frac{m^L \theta_{AL} L H_2 \psi^A \psi^L (1 + (\rho_{AL}/\sqrt{k^A k^L}))}{(b_T + g^A)(1 - \mathrm{R}_{0,ad}^{non\text{-}vir})} \frac{q^N \beta_1^N H_1 \psi^N}{(b_T + g^N)(1 - \mathrm{R}_{0,nym}^{non\text{-}vir})} + R_0^{non-vir} < 1, \end{aligned} \tag{12}$$

where

$$R_0^{non-vir} = \frac{m^L \theta_{AL} L H_2 \psi^A \psi^L (1 + \rho_{AL}/\sqrt{k^A k^L})}{b_T + g^A} \frac{m^N \theta_{NN} N H_2 [\psi^N]^2 (1 + 1/k^N)}{b_T + g^N} \frac{1}{1 - R_{0,nym}^{non-vir}} \frac{1}{1 - R_{0,ad}^{non-vir}}. \tag{13}$$

Conditions (10) and (11) are threshold conditions for horizontal transmission between ticks. Eq. (10) means that each infected adult tick produces less than 1 infected adult tick, by infecting nymphs through co-feeding. Eq. (11) analogously means that each infected nymph produces less than 1 infected nymph, by infecting larvae through co-feeding.

The expression of R_0^{all}, shown in Eq. (12), is more complex but the terms all have a biological interpretation. The first three terms correspond to those in the reproduction number with only viraemic transmission (see Eq. (9)), but they are changed due to non-viraemic transmission. In fact, we must consider that each nymph infected by a host will on average produce $R_{0,nym}^{non-vir}$ infected nymphs by infecting co-feeding larvae that, after moulting, will become infected nymphs; all of these will produce through co-feeding $(R_{0,nym}^{non-vir})^2$ other infected nymphs; summing over all generations of infections, the "progeny" via co-feeding of an infected nymphs is equal to $1/(1 - R_{0,nym}^{non-vir})$ infected nymphs (remember that we are under conditions (10) and (11)). Hence, when we count how many infected hosts an infected host produces through infected nymphs and back, we must multiply the average number of infected nymphs produced by an infected host, that is $m^L p^L \beta_1^L \psi^L L/(b_1 + \gamma + \alpha)$, by the "co-feeding nymph progeny" of each infected nymph, that is $1/(1 - R_{0,nym}^{non-vir})$, by the average number of hosts infected by each nymph, that is $q^N \beta_1^N H_1 \psi^N/(b_T + g^N)$, obtaining thus the first term in Eq. (12). The changes in the second and third terms are analogous, noting that now the number of infected adults produced by an infected nymph is not given simply by its probability of getting to the adult stage, but we must also add the number of adults produced from nymphs by co-feeding. The fourth term is the reciprocal of the second and describes transmission from a host to an adult, then transmission from adults to nymphs by co-feeding, and finally viraemic transmission from nymphs to hosts. The last term, denoted by $R_0^{non-vir}$, computes the total transmission potential (between and within nymphs and adults) of the non-viraemic route. It should be noted that several terms can disappear in the special cases considered below.

3.3. Special cases

An interesting special case, based on the transmission dynamics of *Borrelia* or of louping ill, occurs when adult ticks do not feed on H_1 (e.g. mice for *Borrelia*), and larvae do not feed on H_2 (e.g. deer). In this case we have $\beta_1^A = \beta_2^L = 0$ and, as there are no larvae on the non-viraemic host, non-viraemic transmission cannot occur through larvae and consequently θ_{NL} and θ_{AL} will be 0.

Under this assumption the threshold for disease persistence assumes the following form, which is identical to the case with only viraemic transmission:

$$R_0^{vir} = \frac{m^L p^L \beta_1^L \psi^L L}{b_1 + \gamma + \alpha} \frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N}. \tag{14}$$

However, note that we also have the extra condition for stability (see Eqs. (10) and (11)). In this case we have two separate epidemic processes. The first is through the viraemic (or spirochaetaemic for *Borrelia*) route: infected nymphs biting susceptible hosts which are then bitten by larvae: the threshold condition for this process is $R_0^{vir} > 1$ with R_0^{vir} given in Eq. (14). The second epidemic is purely non-viraemic: infected adults infecting susceptible nymphs via co-feeding; the threshold condition for this process is in Eq. (10). The second epidemic has no effect on the first, since infected adults do not participate in viraemic transmission as they do not feed on H_1 ($\beta_1^A = 0$). Hence, the two threshold conditions can be considered independently. Note, that if R_0 in Eq. (14) is less than 1 but Eq. (10) is violated, only adult ticks will be infected, while nymphs and hosts will not be infected

Another interesting special case occurs with only non-viraemic transmission in the system. This means that there are no competent hosts in the system and the reservoir of the diseases are exclusively the ticks. In this case all the parameters concerning the viraemic transmission have to be set to 0. Now, R_0^{all} of Eq. (12) reduces to $R_0^{non-vir}$ shown in Eq. (13). In this case the disease-free equilibrium is unstable (the pathogen persists in the system) when at least one among $R_{0,nym}^{non-vir}$, $R_{0,ad}^{non-vir}$ or $R_0^{non-vir}$shown respectively in Eqs. (10), (11) and (13) is larger than 1. From these expressions it can be seen that a high value of the correlation coefficients ρ, or a low value of the aggregation parameters k, make pathogen persistence more likely. As a consequence, non-viraemic transmission among highly aggregated ticks could be sufficient to make the pathogen persist in the system even without hosts that sustain the infection.

4. Results and discussion

4.1. Persistence–extinction boundary with only viraemic transmission

If we set R_0^{vir} to 1 in Eq. (9) and plot H_1 against H_2 for a chosen set of parameter values we can determine the densities of viraemic and non-viraemic host that must be present for the pathogen to persist (Figs. 1A and B). Both figures show that a minimum density of viraemic host (H_1) is needed in order to make the pathogen persist in the system.

The effect of the density of non-viraemic hosts H_2 is more complex; in fact, it has already been observed (Norman et al., 1999) that their density may have either a positive effect on infection transmission, by amplifying tick population, or a negative (“dilution”) effect, by wasting tick bites on incompetent hosts. Indeed, the shape of the persistence–extinction boundary may differ with only slightly changes in the parameter values (see Figs. 1A and B, which differ only in the value of the encounter rate between questing nymphs and viraemic hosts, β_1^N). In the case of Fig. 1A, only the dilution effect of H_2 occurs: starting from a point $(H_1, 0)$ where $R_0^{vir} > 1$, an increase of the

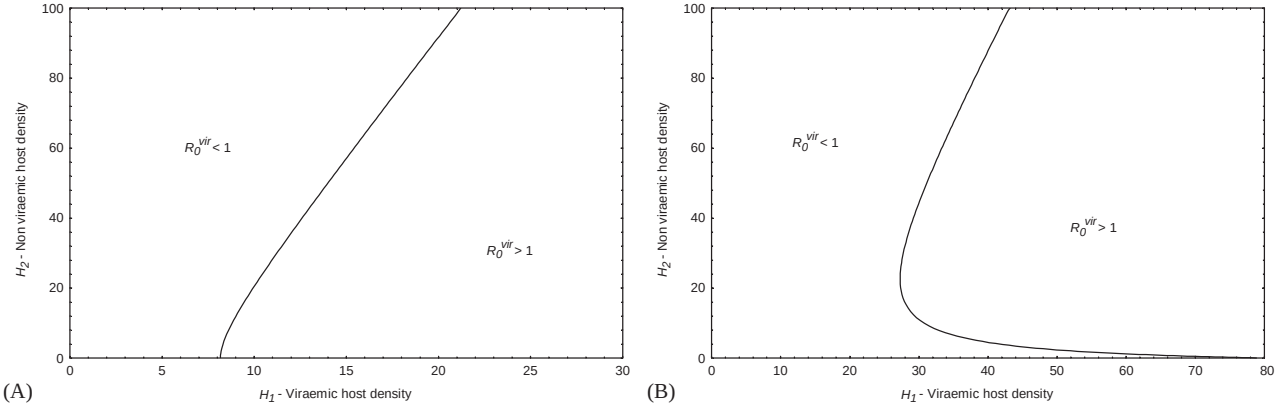

Fig. 1. The effect of hosts densities on R_0^{vir} in the case without non-viraemic transmission. In (A) $\beta_1^N = 10^{-5}$, while in (B) $\beta_1^N = 10^{-6}$. The other parameters are: $\beta_1^L = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8, N = 10^6, \gamma = 0.5775, \alpha = 2.31, b_1 = 0.087$, $b_T = 0.0277, q^A = q^N = 1, p^L = p^N = 1, \psi^L = \psi^N = 1, m^L = m^N = 1, \theta_{NL} = \theta_{AL} = \theta_{NN} = \theta_{AN} = 0$. The parameter values are purely illustrative, though elaborated from Hudson et al. (1995) and Norman et al. (1999), measuring time in months and densities in km^{-2}.

non-viraemic hosts makes the R_0^{vir} decrease till it becomes lower than 1 and the disease dies out; furthermore, if we start from a point $(H_1, 0)$ with $R_0^{vir} < 1$, R_0^{vir} will remain lower than 1 for any density H_2 of the non-viraemic hosts.

In Fig. 1B, if we start from a point $(H_1, 0)$ with H_1 in an intermediate region (between 30 and 60), an initial increase of H_2 makes the pathogen persist (R_0^{vir} moves from below 1 to above 1) but a further increase of H_2 causes a decrease of R_0^{vir} and again the dilution effect of H_2 is observed.

We then see that the net effect of H_2 on R_0^{vir} depends on the quantitative strength of the two effects, and it is difficult to predict the outcome a priori. One may note that the decrease of β_1^N of an order of magnitude from Fig. 1A to Fig. 1B makes the ticks more dependent on H_2 for amplification; thus, it is not surprising the positive effect of H_2 on R_0^{vir} is more apparent in Fig. 1B.

4.2. Effect of non-viraemic transmission

From the expression of R_0^{all} in Eq. (12) with non-viraemic transmission we see that the effect of non-viraemic transmission terms is to increase the basic reproduction number of the disease.

In terms of host densities, the boundary between the persistence and extinction regions in the (H_1, H_2)-plane shifts upwards and to the left with increasing non-viraemic terms (see Fig. 2, where the effect of θ_{AN}, the parameter of non-viraemic transmission between nymphs and adults, is shown; the other parameters have a similar effect). For high enough values of the non-viraemic terms, the dilution effect completely disappears and the disease can persist in the absence of the viraemic host. The effect of all the non-viraemic terms on R_0^{all} are explored in Fig. 3. R_0^{all} increases particularly when terms involving the larval stage (θ_{AL} and θ_{NL}) are included in the model. This is quite understandable, since a tick which is infected as a larva will have two opportunities to transmit the infection, while a tick infected as a nymph will have just one opportunity.

In Figs. 2 and 3 we assumed that all c_j^z are equal to 0 for all the tick stages ($z = L, N, A$) and for both host species, $j = 1, 2$. We mentioned that this assumption is a good approximation for the cases in which the transmission rate is much less than the detachment rate of ticks $\beta_j^z H_j \ll \sigma_j^z$, which seems likely in many systems. If $c_j^z > 0$ but small, still the functions ψ^z are very close to 1 and g^z are practically linear over most of the reasonable range of H_1 and H_2. However, as shown in Fig. 4, if $c_2^L > 0$, R_0 always drops below 1 when the density of the non-viraemic host becomes very high (note the logarithmic scale of H_2 axis). This is because with a very high density of non-viraemic hosts, almost all ticks will feed on H_2 hosts, but each individual host will be carrying very few ticks, so that the probability of finding co-feeding ticks will be relatively low; hence, non-viraemic transmission will become insignificant while viraemic transmission on H_2 hosts is, by assumption, impossible. Probably, the host densities at which this effect occurs are unrealistically high for most reasonable parameter values, so that this effect, whilst interesting mathematically, is practically irrelevant.

4.3. Effect of aggregation on R_0

We have not yet considered either the aggregation of the tick distribution among hosts or the correlation between different stages of ticks feeding on the same host in the figures presented in the previous sections. However, it is well

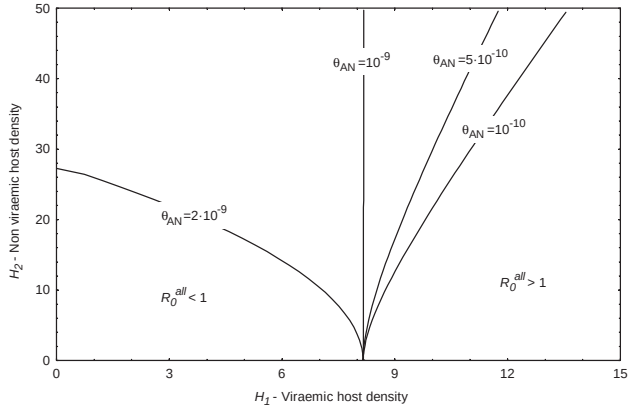

Fig. 2. Effect of non-viraemic terms θ_{AN} on R_0^{all}. The other non-viraemic terms are set to 0 and the rest of parameters are: $\beta_1^L = 10^{-5}$, $\beta_1^N = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8$, $N = 10^6$, $\gamma = 0.5775$, $\alpha = 2.31$, $b_1 = 0.087$, $b_T = 0.0277$, $q^A = q^N = 1$, $p^L = p^N = 1$, $\psi^L = \psi^N = 1$, $m^L = m^N = 1$, $k^N = \infty$, $\rho_{NL} = \rho_{AN} = \rho_{AL} = 0$.

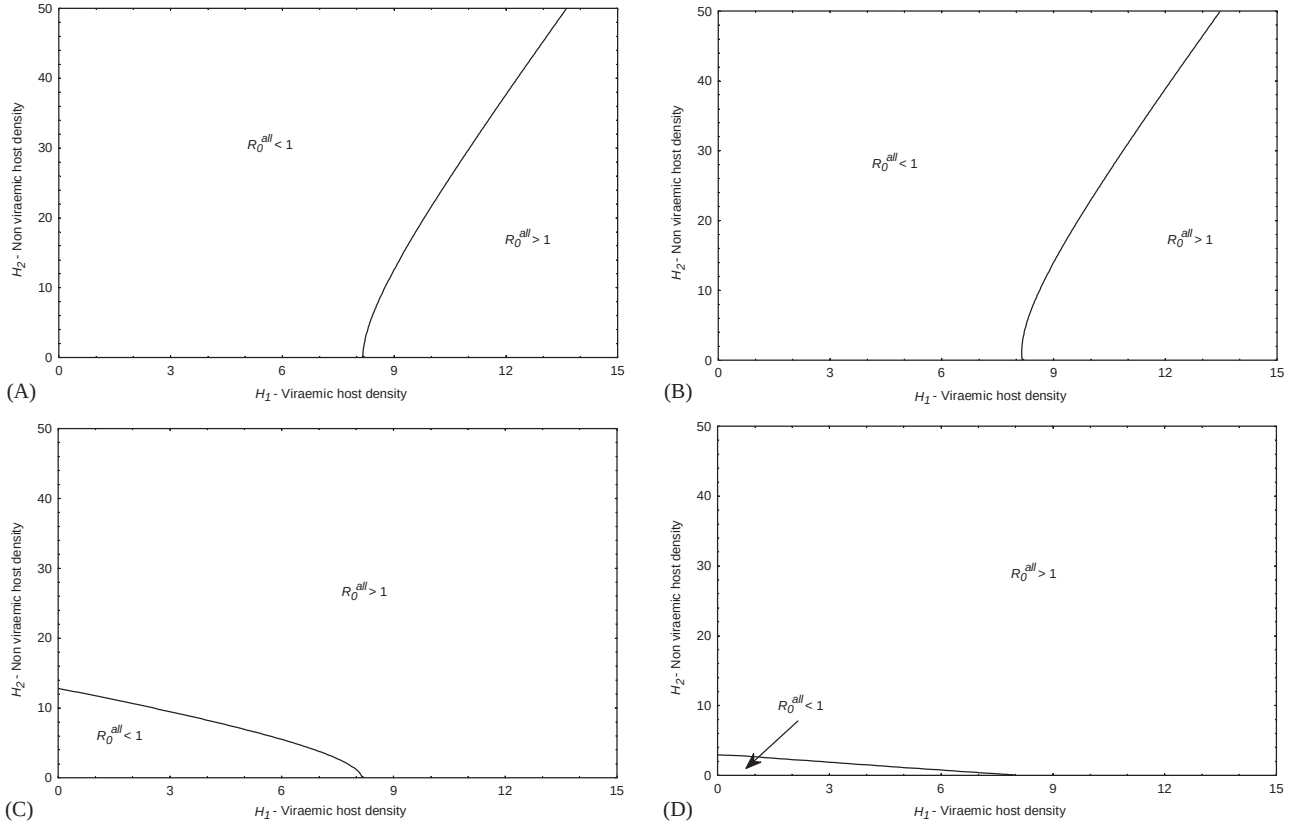

Fig. 3. Effect of different non-viraemic terms on R_0^{all}. The effect of θ_{AN} is shown in (A), θ_{NN} in (B), θ_{AL} in (C) and θ_{NL} in (D). In all the figures the non-viraemic term takes the values 10^{-10}, while the others are set to 0. The other parameters are: $\beta_1^L = 10^{-5}$, $\beta_1^N = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8, N = 10^6, \gamma = 0.5775, \alpha = 2.31, b_1 = 0.087, b_T = 0.0277, q^A = q^N = 1, p^L = p^N = 1, \psi^L = \psi^N = 1, m^L = m^N = 1, k^N = \infty, \rho_{NL} = \rho_{AN} = \rho_{AL} = 0$.

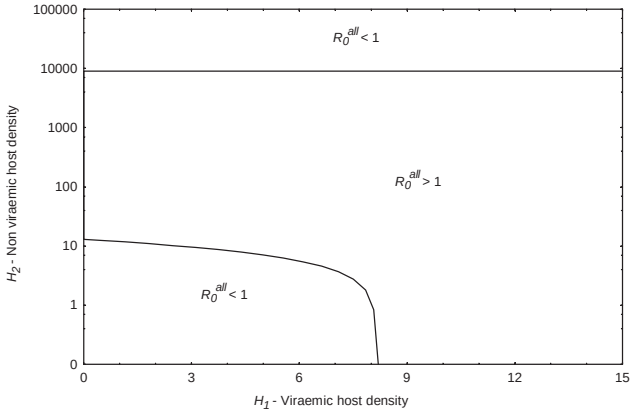

Fig. 4. Effect of $c_2^L = \beta_2^L/\sigma_2^L$ on R_0^{all}. The parameters values are: $\beta_1^L = 10^{-5}$, $\beta_1^N = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8, N = 10^6, \gamma = 0.5775, \alpha = 2.31, b_1 = 0.087, b_T = 0.0277, q^A = q^N = 1, p^L = p^N = 1, \psi^L = \psi^N = 1, m^L = m^N = 1, \theta_{AL} = 10^{-10}, \theta_{AN} = \theta_{NN} = \theta_{NL} = 0, \rho_{AL} = 0, c_2^L = 10^{-3}$. We remark that the lower boundary line is indistinguishable by the corresponding boundary in the case with $c_2^L = 0$ (Fig. 3C).

known in the literature (see, for instance, Randolph et al., 2002) that each tick stage shows highly aggregated distributions on their host population; moreover, these aggregated distributions are coincident rather than independent: those hosts feeding large number of larvae were simultaneously feeding the greatest number of nymphs. It has been surmised that this pattern of tick infestation facilitates transmission via co-feeding and thus significantly increases the basic reproductive number R_0 of the pathogen (Randolph et al., 1999).

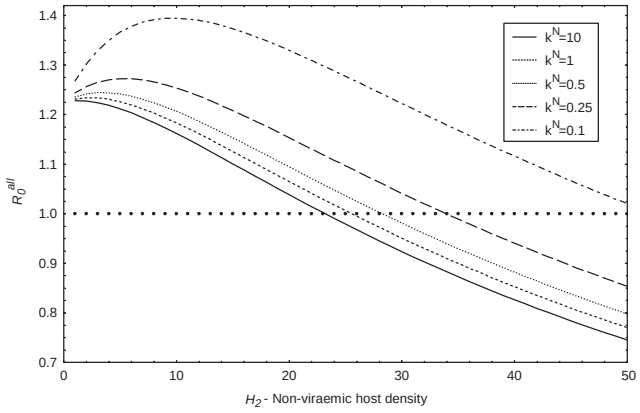

Fig. 5. Graph to show the effect of H_2 on R_0^{all} for different values of k^N, when H_1 is supposed to be constant (in this case $H_1 = 10$). $\theta_{NN} = 10^{-10}$, while the other non-viraemic terms are set to 0. The other parameters are: $\beta_1^L = 10^{-5}$, $\beta_1^N = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8, N = 10^6, \gamma = 0.5775, \alpha = 2.31, b_1 = 0.087, b_T = 0.0277, q^A = q^N = 1, p^L = p^N = 1, \psi^L = \psi^N = 1, m^L = m^N = 1$.

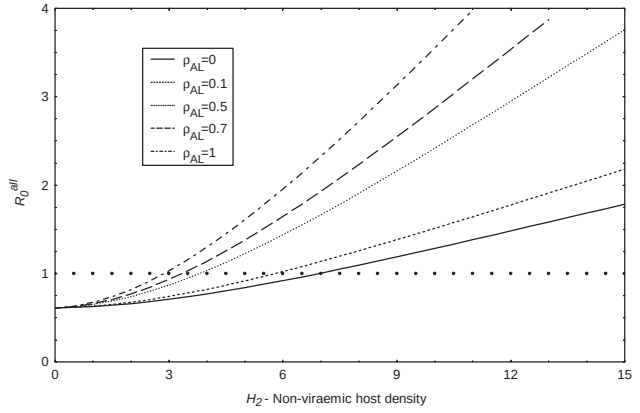

Fig. 6. Graph to show the effect of H_2 on R_0^{all} for different values of ρ_{AL}, when H_1 is supposed to be constant (in this case $H_1 = 5$). $\theta_{AL} = 10^{-10}, k^L = 1, k^N = 0.1$ while the other non-viraemic terms are set to 0. The other parameters are: $\beta_1^L = 10^{-5}$, $\beta_1^N = 10^{-5}$, $\beta_1^A = 10^{-5}$, $\beta_2^N = 10^{-3}$, $\beta_2^A = 10^{-3}$, $L = 10^8, N = 10^6, \gamma = 0.5775, \alpha = 2.31, b_1 = 0.087, b_T = 0.0277, q^A = q^N = 1, p^L = p^N = 1, \psi^L = \psi^N = 1, m^L = m^N = 1$.

In Figs. 5 and 6 we show the quantitative effect of tick distribution on R_0^{all} for the parameter values used in Fig. 3. Fig. 5 corresponds to Fig. 3B with H_1 fixed at 10; hence, we are in the region where the dilution effect holds: increasing the density of H_2 would make R_0^{all} drop below 1; as can be seen in Fig. 5, a strong aggregation in nymph distribution ($k^N \ll 1$) increases significantly R_0^{all} and may double the density of H_2 at which the dilution effect occurs.

Fig. 6 corresponds to Fig. 3C with $H_1 = 5$, where, on the other hand, increasing the density of H_2 makes R_0^{all} grow above 1. In this case, a strong correlation between adults and larvae ($\rho_{AL} \approx 1$) causes a big increase in R_0^{all}.

On the whole, the expressions shown in this paper for the threshold for disease persistence of tick-borne infections clarify the possible role of the different pathways in sustaining the infection, as well as the importance of tick distributions in the case of non-viraemic transmission, and the possible relevance of the encounter rates in the case of multiple hosts. This understanding may help in identifying possible strategies for disease control, and assessing their possible results. Finally, the assumptions made on the density-dependence factors have no real consequence on the threshold quantities computed in the text (although they may affect the overall dynamics of the system). In fact, if a_T were constant, one would only need to substitute this constant for the quantity computed at the relevant equilibrium. Conversely, if some quantity, for instance the moulting success m^z, were a function of the density of all ticks, or some stage of, one would use its value at the relevant equilibrium. In the future, we plan to use models of this structure to complement observational and experimental work on tick-borne infections in the region of Trentino, Italy. Certainly, many parameters of this model have not yet been measured experimentally, so that mainly qualitative trends can be gained by this modelling effort. One of the factors missing in this model, which has instead a profound effect on

infection transmission is seasonality (see, for instance, Randolph et al., 1999); we shall introduce seasonality in the model, although probably explicit expressions will no longer be computable.

Acknowledgements

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Appendix A. Stability of tick-free equilibrium

System (7) has a tick-free equilibrium $L = N_i = N_s = A_i = A_s = H_{1i} = H_{1r} = 0$; $H_{1s} = H_1 > 0$. In the linearization of Eq. (7) at the tick-free equilibrium, the equations for tick dynamics decouple from those for infection transmission, so that the linearized equations essentially become:

$$\begin{aligned}
\frac{dL}{dt} &= g^A(H_1, H_2)a_T(0)A - b_T L - g^L(H_1, H_2)L,\\
\frac{dN}{dt} &= m^L g^L(H_1, H_2)L - b_T N - g^N(H_1, H_2)N,\\
\frac{dA}{dt} &= m^N g^N(H_1, H_2)N - b_T A - g^A(H_1, H_2)A.
\end{aligned} \tag{A.1}$$

Which can be written, using matrix notation, as

$$\frac{d}{dt}\begin{pmatrix} L \\ N \\ A \end{pmatrix} = A_{11}\begin{pmatrix} L \\ N \\ A \end{pmatrix},$$

where

$$A_{11} = \begin{pmatrix} -b_T - g^L(H_1, H_2) & 0 & a_T(0)g^A(H_1, H_2) \\ m^L g^L(H_1, H_2) & -b_T - g^N(H_1, H_2) & 0 \\ 0 & m^N g^N(H_1, H_2) & -b_T - g^A(H_1, H_2) \end{pmatrix}.$$

Formally, this follows from the fact that the Jacobian of Eq. (7) at the tick-free equilibrium can be written in the following form:

$$J = \begin{pmatrix} A_{11}^{3\times 3} & A_{12}^{3\times 5} \\ 0^{5\times 3} & A_{22}^{5\times 5} \end{pmatrix}, \tag{A.2}$$

where

$$A_{22} = \begin{pmatrix} -b_T - g^N & 0 & 0 & 0 & 0 \\ m^N g^N & -b_T - g^A & 0 & 0 & 0 \\ q^N \beta_1^N H_1^* \psi^N & q^A \beta_1^A H_1^* \psi^A & -(\gamma + b_1 + \alpha) & 0 & 0 \\ 0 & 0 & \gamma & -b_1 & 0 \\ -q^N \beta_1^N H_1^* \psi^N & -q^A \beta_1^A H_1^* \psi^A & a_1'(H_1^*) + a_1(H_1^*) & a_1'(H_1^*) + a_1(H_1^*) & a_1'(H_1^*) + a_1(H_1^*) - b_1 \end{pmatrix}.$$

From Eq. (A.2), we see that the eigenvalues of J are the eigenvalues of A_{11} and of A_{22}. Since A_{22} is triangular, its eigenvalues are the terms on the diagonal, which are all negative, since at equilibrium $a_1(H_1^*) = b_1$ and $a_1(H_1)$ is a decreasing function. Then the study of the local stability of the tick-free equilibrium reduces to the study of Eq. (A.1).

In order to see whether all the eigenvalues of a matrix have a negative real part, we apply here (and in the other cases) the following theorem, that is a special case of Theorem 6.13 in Diekmann and Heesterbeek (2000).

Theorem A.1. *Let T be a non-negative matrix and D a positive diagonal matrix. Let r denote the spectral bound of the matrix $T-D$ and let R_0 the dominant eigenvalue of the positive matrix $K = TD^{-1}$. Then $r<0 \Leftrightarrow R_0<1$.*

We split the matrix A_{11} in the form $A_{11} = T - D$ with T and D, respectively:

$$T = \begin{pmatrix} 0 & 0 & a_T(0)g^A(H_1,H_2) \\ m^L g^L(H_1,H_2) & 0 & 0 \\ 0 & m^N g^N(H_1,H_2) & 0 \end{pmatrix},$$

$$D = diag \begin{pmatrix} b_T + g^L(H_1,H_2) \\ b_T + g^N(H_1,H_2) \\ b_T + g^A(H_1,H_2) \end{pmatrix}.$$

Now, we compute the eigenvalues of the matrix TD^{-1} that assumes the following form:

$$TD^{-1} = \begin{pmatrix} 0 & 0 & a_T(0)\dfrac{g^A(H_1,H_2)}{b_T + g^A(H_1,H_2)} \\ \dfrac{m^L g^L(H_1,H_2)}{b_T + g^L(H_1,H_2)} & 0 & 0 \\ 0 & \dfrac{m^N g^N(H_1,H_2)}{b_T + g^N(H_1,H_2)} & 0 \end{pmatrix}. \tag{A.3}$$

As the hypotheses of Theorem A.1 are satisfied, the stability condition for the tick-free equilibrium is that the spectral radius of TD^{-1} is less than 1. The solutions of the characteristic equation of (A.3) are the three cubic roots of

$$R_0^{ticks} = a_T(0)\frac{m^L g^L(H_1,H_2)}{b_T + g^L(H_1,H_2)}\frac{m^N g^N(H_1,H_2)}{b_T + g^N(H_1,H_2)}\frac{g^A(H_1,H_2)}{b_T + g^A(H_1,H_2)}.$$

It is clear that they are in module larger than one if and only if $R_0^{ticks} > 1$. Note that, using the definition of Diekmann and Heesterbeek (2000) one would define the basic reproduction number as $\sqrt[3]{R_0^{ticks}}$, which obviously gives the same threshold; we believe that the condition $R_0^{ticks} > 1$ is much easier to interpret.

Appendix B. Stability of disease-free equilibrium with only viraemic transmission

When $R_0^{ticks} > 1$ system (7) has a disease-free equilibrium with $N_i = A_i = H_{1i} = H_{1r} = 0$ and the other components at some positive value. In this case too, in the linearization of Eq. (7) at the disease-free equilibrium, the equations for tick dynamics decouple from those for infection transmission; the linearized equations for the infected compartments are:

$$\begin{aligned} \frac{dN_i}{dt} &= m^L p^L \beta_1^L H_{1i} \psi^L(H_1,H_2)L - [b_T + g^N(H_1,H_2)]N_i, \\ \frac{dA_i}{dt} &= m^N p^N \beta_1^N H_{1i} \psi^N(H_1,H_2)N + m^N g^N(H_1,H_2)N_i - [b_T + g^A(H_1,H_2)]A_i, \\ \frac{dH_{1i}}{dt} &= q^N \beta_1^N H_1 \psi^N(H_1,H_2)N_i + q^A \beta_1^A H_1 \psi^A(H_1,H_2)A_i - (\gamma + b_1 + \alpha)H_{1i}, \end{aligned}$$

which can be written, using matrix notation, as

$$\frac{d}{dt}\begin{pmatrix} N_i \\ A_i \\ H_{1i} \end{pmatrix} = A \begin{pmatrix} N_i \\ A_i \\ H_{1i} \end{pmatrix},$$

where

$$A = \begin{pmatrix} -b_T - g^N(H_1,H_2) & 0 & m^L p^L \beta_1^L \psi^L(H_1,H_2)L \\ m^N g^N(H_1,H_2) & -b_T - g^A(H_1,H_2) & m^N p^N \beta_1^N \psi^N(H_1,H_2)N \\ q^N \beta_1^N H_1 \psi^N(H_1,H_2) & q^A \beta_1^A H_1 \psi^A(H_1,H_2) & -(b_1+\gamma+\alpha) \end{pmatrix}.$$

In fact, the Jacobian at the disease-free equilibrium can again be written in the form (A.2) (see Appendix A), so that we need only to find the sign of the eigenvalues of A_{11} and A_{22}.

First, we study the sign of the eigenvalues of the block A_{11} that in this case assumes the following form:

$$A_{11} = \begin{pmatrix} a_T'(T^*)A^* g^A - (b_T + g^L) & a_T'(T^*)A^* g^A & a_T'(T^*)A^* g^A + g^A a_T(T^*) \\ m^L g^L & -b_T - g^N & 0 \\ 0 & m^N g^N & -b_T - g^A \end{pmatrix}.$$

Using the Routh–Hurwitz criterion we have that the eigenvalues of A_{11} are negative if the following three conditions are satisfied:

(i) $tr\, A_{11} < 0$
(ii) $det\, A_{11} < 0$
(iii) $M^*\ tr\, A_{11} - det\, A_{11} < 0$,

where M^* is the sum of the minors of A_{11}. As $a(T)$ is a decreasing function condition (i) is trivially satisfied. Using the conditions at the equilibrium for L^*, N^* and A^* we obtain the following identity:

$$m^L m^N g^L g^N g^A a_T(T^*) = (b_T + g^L)(b_T + g^N)(b_T + g^A),$$

from which it is easy to see that the determinant of A_{11} is always negative (condition (ii)). Finally, it is not difficult to show that also condition (iii) is always satisfied; thus the eigenvalues of A_{11} have all negative real part.

As for the matrix A_{22}, it can be written as

$$A_{22} = \begin{pmatrix} A^{3x3} & 0^{3x2} \\ B^{2x3} & C^{2x2} \end{pmatrix}, \tag{B.1}$$

where

$$C = \begin{pmatrix} -b_1 & 0 \\ a_1'(H_1^*) + a_1(H_1^*) & a_1'(H_1^*) + a_1(H_1^*) - b_1 \end{pmatrix}$$

is a triangular matrix with both negative eigenvalues, since at equilibrium $a_1(H_1^*) = b_1$. Then the study of the local stability of the disease-free equilibrium reduces to the study of the sign of the eigenvalues of the matrix A.

Also in this case, the hypotheses of the Theorem A.1 (see Appendix A) are satisfied; hence, using the same procedure as for the tick-free equilibrium (Appendix A), we split the matrix A in the form $A = T - D$, where TD^{-1} is

$$TD^{-1} = \begin{pmatrix} 0 & 0 & \dfrac{m^L p^L \beta_1^L \psi^L(H_1,H_2)L}{(b_1+\gamma+\alpha)} \\ \dfrac{m^N g^N(H_1,H_2)}{(b_T + g^N(H_1,H_2))} & 0 & \dfrac{m^N p^N \beta_1^N \psi^N(H_1,H_2)N}{(b_1+\gamma+\alpha)} \\ \dfrac{q^N \beta_1^N H_1 \psi^N(H_1,H_2)}{(b_T + g^N(H_1,H_2))} & \dfrac{q^A \beta_1^A H_1 \psi^A(H_1,H_2)}{(b_T + g^A(H_1,H_2))} & 0 \end{pmatrix}. \tag{B.2}$$

The characteristic equation of Eq. (B.2) is

$$f(\lambda) = -\lambda^3 + \lambda\left(\frac{m^L p^L \beta_1^L \psi^L(H_1,H_2)L}{(b_1+\gamma+\alpha)}\frac{q^N \beta_1^N H_1 \psi^N(H_1,H_2)}{(b_T + g^N(H_1,H_2))} + \frac{m^N p^N \beta_1^N \psi^N(H_1,H_2)N}{(b_1+\gamma+\alpha)}\frac{q^A \beta_1^A H_1 \psi^A(H_1,H_2)}{(b_T + g^A(H_1,H_2))}\right)$$
$$+ \frac{m^L p^L \beta_1^L \psi^L(H_1,H_2)L}{(b_1+\gamma+\alpha)}\frac{m^N g^N(H_1,H_2)}{(b_T + g^N(H_1,H_2))}\frac{q^A \beta_1^A H_1 \psi^A(H_1,H_2)}{(b_T + g^A(H_1,H_2))} = 0.$$

From the signs of the coefficients of the cubic, one easily sees that the dominant eigenvalue of TD^{-1} is larger than 1 if and only if $f(1) > 0$, that is

$$\frac{m^L p^L \beta_1^L \psi^L L}{b_1+\gamma+\alpha}\frac{m^N g^N}{b_T + g^N}\frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A} + \frac{m^L p^L \beta_1^L \psi^L L}{b_1+\gamma+\alpha}\frac{q^N \beta_1^N H_1 \psi^N}{b_T + g^N} + \frac{m^N p^N \beta_1^N \psi^N N}{b_1+\gamma+\alpha}\frac{q^A \beta_1^A H_1 \psi^A}{b_T + g^A} > 1.$$

The LHS of this expression is equal to R_0^{vir} as defined in Eq. (9). Hence the stability condition can be stated as $R_0^{vir}<1$.

Appendix C. Stability of disease-free equilibrium with non-viraemic transmission

In the case with non-viraemic transmission we have that all the blocks of the matrix J are the same of those in the case with only viraemic transmission (Appendix B) except for A_{12} and A_{22} which contain the non-viraemic terms. For the same reasons as in Appendix B, the study of the stability of the disease-free equilibrium reduces to the study of the sign of the eigenvalues of the matrix A that in this case assumes the following form:

$$A=\begin{pmatrix} -b_T-g^N+m^L\theta_{NL}LH_2\psi^L\psi^N\left(1+\dfrac{\rho_{NL}}{\sqrt{k^Lk^N}}\right) & m^L\theta_{AL}LH_2\psi^A\psi^L\left(1+\dfrac{\rho_{AL}}{\sqrt{k^Ak^L}}\right) & m^Lp^L\beta_1^L\psi^LL \\ m^Ng^N+m^N\theta_{NN}NH_2[\psi^N]^2\left(1+\dfrac{1}{k}\right) & -b_T-g^A+m^N\theta_{AN}NH_2\psi^A\psi^N\left(1+\dfrac{\rho_{AN}}{\sqrt{k^Ak^N}}\right) & m^Np^N\beta_1^N\psi^NN \\ q^N\beta_1^NH_1\psi^N & q^A\beta_1^AH_1\psi^A & -(b_1+\gamma+\alpha) \end{pmatrix}.$$

Splitting the matrix A in the form $A=T-D$, as in Appendix B, we choose

$$T=\begin{pmatrix} 0 & m^L\theta_{AL}LH_2\psi^A\psi^L(1+\rho_{AL}/\sqrt{k^Ak^L}) & m^Lp^L\beta_1^L\psi^LL \\ m^Ng^N+m^N\theta_{NN}NH_2[\psi^N]^2(1+1/k^N) & 0 & m^Np^N\beta_1^N\psi^NN \\ q^N\beta_1^NH_1\psi^N & q^A\beta_1^AH_1\psi^A & 0 \end{pmatrix}$$

and

$$D=diag\begin{pmatrix} b_T+g^N-m^L\theta_{NL}LH_2\psi^L\psi^N(1+\rho_{NL}/\sqrt{k^Lk^N}) \\ b_T+g^A-m^N\theta_{AN}NH_2\psi^A\psi^N(1+\rho_{AN}/\sqrt{k^Ak^N}) \\ b_1+\gamma+\alpha \end{pmatrix}.$$

In this case the hypothesis of the Theorem A.1 (see Appendix A) are not always satisfied: in fact, the elements of D may not be positive. Therefore, before computing the eigenvalues of the matrix TD^{-1} as in the case with only viraemic transmission, we must consider the cases when the elements of D are not positive. Note that it would be possible to split the matrix A in a form $A=T-D$ in such a way that the diagonal D is strictly positive. Indeed, this is required in the definition of R_0 given by Diekmann and Heesterbeek (2000) who also suggest the use of a transition matrix Σ, writing $A=T+\Sigma-D$; however, the computations appear much simpler using the present form.

Using results of loop analysis (Puccia and Levins, 1985), we study the stability of the disease-free equilibrium when the diagonal elements of the matrix A are not negative.

To do that, we apply the stability criteria based on the loop model notation (Puccia and Levins, 1985), to the matrix A.

The following three cases have to be considered:

Case 1: The first two diagonal elements of A are positive ($a_{11},a_{22}>0$) while the third is negative ($-a_{33}<0$). In this case the feedbacks at levels 1 and 2 (Puccia and Levins, 1985) become

$$F_1=a_{11}+a_{22}-a_{33},$$
$$F_2=a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}-a_{11}a_{22}+a_{11}a_{33}+a_{22}a_{33}.$$

The stability condition at level 1, $F_1<0$ (Puccia and Levins, 1985), implies that $a_{33}>a_{11}+a_{22}$. Inserting this inequality in the feedback at level 2 we obtain

$$\begin{aligned} F_2 &> a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}-a_{11}a_{22}+a_{11}(a_{11}+a_{22})+a_{22}a_{33} \\ &= a_{12}a_{21}+a_{13}a_{31}+a_{23}a_{32}+(a_{11})^2+a_{22}a_{33}>0. \end{aligned}$$

Thus, the stability condition at level 2, $F_2<0$ (Puccia and Levins, 1985), is not met and the equilibrium is unstable.

Case 2: The first diagonal element of A is positive ($a_{11} > 0$) while the second and third are negative ($-a_{22}, -a_{33} < 0$). In this case the feedbacks are

$$F_1 = a_{11} - a_{22} - a_{33},$$
$$F_2 = a_{12}a_{21} + a_{13}a_{31} + a_{23}a_{32} + a_{11}a_{22} + a_{11}a_{33} - a_{22}a_{33},$$
$$F_3 = a_{12}a_{23}a_{32} + a_{21}a_{32}a_{13} - a_{11}a_{23}a_{32} + a_{22}a_{13}a_{31} + a_{33}a_{12}a_{21} + a_{11}a_{22}a_{33}.$$

The stability condition at level 2, $F_2 < 0$, implies that $a_{22}a_{33} > a_{12}a_{21} + a_{13}a_{31} + a_{23}a_{32} + a_{11}a_{22} + a_{11}a_{33}$. Inserting this inequality in the feedback at level 3 we obtain

$$\begin{aligned} F_3 &> a_{12}a_{23}a_{32} + a_{21}a_{32}a_{13} - a_{11}a_{23}a_{32} + a_{22}a_{13}a_{31} + a_{33}a_{12}a_{21} + a_{11}(a_{12}a_{21} + a_{13}a_{31} + a_{23}a_{32} + a_{11}a_{22} + a_{11}a_{33}) \\ &= a_{12}a_{23}a_{32} + a_{21}a_{32}a_{13} + a_{22}a_{13}a_{31} + a_{33}a_{12}a_{21} + a_{11}a_{12}a_{21} + a_{11}a_{13}a_{31} + (a_{11})^2(a_{11} + a_{22}) > 0. \end{aligned}$$

Thus the stability condition at level 3, $F_3 < 0$ (Puccia and Levins, 1985), is not met and the equilibrium is unstable.

Case 3: The second diagonal element of A is positive ($a_{22} > 0$) while the first and third are negative ($-a_{11}, -a_{33} < 0$). In this case feedbacks assume the following form:

$$F_1 = a_{22} - a_{11} - a_{33},$$
$$F_2 = a_{12}a_{21} + a_{13}a_{31} + a_{23}a_{32} + a_{11}a_{22} - a_{11}a_{33} + a_{22}a_{33},$$
$$F_3 = a_{12}a_{23}a_{32} + a_{21}a_{32}a_{13} + a_{11}a_{23}a_{32} - a_{22}a_{13}a_{31} + a_{33}a_{12}a_{21} + a_{11}a_{22}a_{33}.$$

The stability condition at level 2, $F_2 < 0$, implies that $a_{11}a_{33} > a_{12}a_{21} + a_{13}a_{31} + a_{23}a_{32} + a_{11}a_{22} + a_{22}a_{33}$. Inserting this inequality in the feedback at level 3 we obtain

$$\begin{aligned} F_3 &> a_{12}a_{23}a_{32} + a_{21}a_{32}a_{13} + a_{11}a_{23}a_{32} - a_{22}a_{13}a_{31} + a_{33}a_{12}a_{21} + a_{22}(a_{12}a_{21} + a_{13}a_{31} + a_{23}a_{32} + a_{11}a_{22} + a_{22}a_{33}) \\ &= a_{12}a_{23}a_{32} + a_{21}a_{32}a_{13} + a_{11}a_{23}a_{32} + a_{22}a_{12}a_{21} + a_{22}a_{23}a_{32} + (a_{22})^2(a_{11} + a_{33}) > 0. \end{aligned}$$

Thus the stability condition at level 3 is not met and the equilibrium is unstable. We conclude that in all three cases the disease-free equilibrium is unstable.

We now consider the case where the hypotheses of Theorem A.1 are satisfied; then the matrix TD^{-1} assume the following form, where all the denominators are strictly positive:

$$TD^{-1} = \begin{pmatrix} 0 & \dfrac{m^L\theta_{AL}LH_2\psi^A\psi^L(1+\rho_{AL}/\sqrt{k^Ak^L})}{b_T + g^A - m^N\theta_{AN}NH_2\psi^A\psi^N(1+\rho_{AN}/\sqrt{k^Ak^N})} & \dfrac{m^Lp^L\beta_1^L\psi^LL}{b_1+\gamma+\alpha} \\ \dfrac{m^Ng^N + m^N\theta_{NN}NH_2[\psi^N]^2(1+1/k^N)}{b_T + g^N - \theta_{NL}m^LLH_2\psi^N\psi^L(1+\rho_{NL}/\sqrt{k^Nk^L})} & 0 & \dfrac{m^Np^N\beta_1^N\psi^NN}{b_1+\gamma+\alpha} \\ \dfrac{q^N\beta_1^NH_1\psi^N}{b_T + g^N - m^L\theta_{NL}LH_2\psi^N\psi^L(1+\rho_{NL}/\sqrt{k^Nk^L})} & \dfrac{q^A\beta_1^AH_1\psi^A}{b_T + g^A - m^N\theta_{AN}NH_2\psi^A\psi^N(1+\rho_{AN}/\sqrt{k^Ak^N})} & 0 \end{pmatrix}.$$

From Theorem A.1 (Appendix A) we get that, in the case with non-viraemic transmission, the threshold condition for disease extinction is, given the positivity of the matrix D, the following:

$$\begin{aligned} R_0^{all} = &\frac{m^Lp^L\beta_1^L\psi^LL}{b_1+\gamma+\alpha}\frac{m^Ng^N + m^N\theta_{NN}NH_2[\psi^N]^2(1+(1/k^N))}{b_T + g^N - m^L\theta_{NL}LH_2\psi^N\psi^L(1+(\rho_{NL}/\sqrt{k^Nk^L}))}\frac{q^A\beta_1^AH_1\psi^A}{b_T + g^A - m^N\theta_{AN}NH_2\psi^A\psi^N(1+(\rho_{AN}/\sqrt{k^Ak^N}))} \\ &+\frac{m^Lp^L\beta_1^L\psi^LL}{b_1+\gamma+\alpha}\frac{q^N\beta_1^NH_1\psi^N}{b_T + g^N - m^L\theta_{NL}LH_2\psi^N\psi^L(1+(\rho_{NL}/\sqrt{k^Nk^L}))} \\ &+\frac{m^Np^N\beta_1^N\psi^NN}{b_1+\gamma+\alpha}\frac{q^A\beta_1^AH_1\psi^A}{b_T + g^A - m^N\theta_{AN}NH_2\psi^A\psi^N(1+(\rho_{AN}/\sqrt{k^Ak^N}))} \\ &+\frac{m^Ng^N + m^N\theta_{NN}NH_2[\psi^N]^2(1+(1/k^N))}{b_T + g^N - m^L\theta_{NL}LH_2\psi^N\psi^L(1+(\rho_{NL}/\sqrt{k^Nk^L}))}\frac{m^L\theta_{AL}LH_2\psi^A\psi^L(1+(\rho_{AL}/\sqrt{k^Ak^L}))}{b_T + g^A - m^N\theta_{AN}NH_2\psi^A\psi^N(1+(\rho_{AN}/\sqrt{k^Ak^N}))} \\ &+\frac{m^Np^N\beta_1^N\psi^NN}{b_1+\gamma+\alpha}\frac{m^L\theta_{AL}LH_2\psi^A\psi^L(1+(\rho_{AL}/\sqrt{k^Ak^L}))}{b_T + g^A - m^N\theta_{AN}NH_2\psi^A\psi^N(1+(\rho_{AN}/\sqrt{k^Ak^N}))} \\ &\times\frac{q^N\beta_1^NH_1\psi^N}{b_T + g^N - m^L\theta_{NL}LH_2\psi^N\psi^L(1+(\rho_{NL}/\sqrt{k^Nk^L}))} < 1. \end{aligned}$$

By some very simple algebra, it can be seen that this expression is identical to that shown in Eq. (12) to make the biological interpretation more transparent.

Conversely, the disease-free equilibrium will be unstable, and the disease will persist, if D is not positive or $R_0^{all} > 1$.

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