Effect of host populations on the intensity of ticks and the prevalence of tick-borne pathogens: how to interpret the results of deer exclosure experiments

A. PUGLIESE[1]* *and* R. ROSÀ[2]

[1] *Department of Mathematics, University of Trento, Povo (TN), Italy*
[2] *Centre for Alpine Ecology, Edmund Mach Foundation, Viote del Monte Bondone (TN), Italy*

(*Received 25 July 2007; revised 13 November 2007, 3 March 2008; accepted 3 March 2008; first published online 28 April 2008*)

SUMMARY

Deer are important blood hosts for feeding *Ixodes ricinus* ticks but they do not support transmission of many tick-borne pathogens, so acting as dead-end transmission hosts. Mathematical models show their role as tick amplifiers, but also suggest that they dilute pathogen transmission, thus reducing infection prevalence. Empirical evidence for this is conflicting: experimental plots with deer removal (i.e. deer exclosures) show that the effect depends on the size of the exclosure. Here we present simulations of dynamic models that take into account different tick stages, and several host species (e.g. rodents) that may move to and from deer exclosures; models were calibrated with respect to *Ixodes ricinus* ticks and tick-borne encephalitis (TBE) in Trentino (northern Italy). Results show that in small exclosures, the density of rodent-feeding ticks may be higher inside than outside, whereas in large exclosures, a reduction of such tick density may be reached. Similarly, TBE prevalence in rodents decreases in large exclosures and may be slightly higher in small exclosures than outside them. The density of infected questing nymphs inside small exclosures can be much higher, in our numerical example almost twice as large as that outside, leading to potential TBE infection risk hotspots.

Key words: Mathematical model, tick-host interactions, tick-borne pathogens, dilution effect, deer exclosure, infection hot spots.

INTRODUCTION

Tick-borne infections are caused by pathogens transmitted between hosts by ticks that become infected following a blood meal. Among the zoonotic tick-borne diseases, tick-borne encephalitis (TBE), Lyme disease, rickettsiosis and ehrlichiosis are emerging as international human health threats (Hudson *et al*. 2002).

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 distribution and temporal dynamics. Tick distribution is certainly influenced by meteorological factors, so that accurate information about microclimate conditions has been correlated with tick population dynamics and the distribution of TBE (Randolph *et al*. 2000). However, tick-borne foci of infection tend to occur at a fine scale determined by the spatial distribution and abundance of competent host species for tick-borne pathogen transmission in relation with non-competent host species (Van Buskirk and Ostfeld, 1995; Ostfeld and Keesing, 2000). As ticks can feed on many different animals and every host species has a unique reservoir competence or ability to carry and transmit pathogens, the presence of different blood hosts might affect disease incidences. For Lyme disease in the USA, 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* spp. (Ostfeld and Keesing, 2000); this phenomenon has been named the 'dilution effect' (Van Buskirk and Ostfeld, 1995; Norman *et al*. 1999), meaning that the presence of non-competent hosts, such as white-tailed deer, dilutes the transmission of tick-borne pathogens, decreasing their prevalence and subsequent disease risk to humans.

Several mathematical models have been developed (Hudson *et al*. 1995; O'Callaghan *et al*. 1998; Caraco, Gardner and Szymanski, 1998; Norman *et al*. 1999; Rosà *et al*. 2003; Rosà and Pugliese, 2007) that demonstrate theoretically the possibility of the dilution effect, and the conditions under which it may occur for tick-borne infections. Keesing, Holt and Ostfeld (2006) give a general presentation of the possible ways in which species diversity might decrease infection risk both for directly-transmitted, and for vector-borne infections ('dilution effect' *sensu lato*); they also present the existing evidence which is widespread but rarely conclusive.

* Corresponding author: Andrea Pugliese, Department of Mathematics, University of Trento, Via Sommarive 14, 38050 Povo (TN) – Italy. Tel: +39 0461 881519. Fax: +39 0461 881624. Email: pugliese@science.unitn.it

Parasitology (2008), **135**, 1531–1544.
doi:10.1017/S003118200800036X Printed in the United Kingdom

A method to study the relevance of the 'dilution effect' is to alter experimentally host densities. One of the simplest ways to modify host densities is to build exclosures that prevent the entrance of large mammals, such as deer. Several experiments of this type have been performed in different parts of the world (a subset of which is presented by Perkins *et al*. 2006); however, the exclosure data have yielded equivocal outcomes, some resulting in tick reduction, others in tick amplification. Recently, Perkins *et al*. (2006) performed a meta-analysis of a sub-set of the published studies, showing that the results did indeed depend on the scale of the exclosures. They found that small exclosures generally resulted in tick amplification, while large exclosures caused reductions in tick intensity, with the switch from tick amplification to reduction occurring when exclosures were larger than about 2·5 hectares. The general prediction from this meta-analysis was confirmed by results from some small experimental exclosures (less than 2·5 hectares in size), where rodent density, tick intensity and tick-borne encephalitis (TBE) prevalence were repeatedly measured inside and outside the exclosures. Perkins *et al*. (2006) found that the intensity of feeding nymphs and adult female ticks on rodents, but not larval intensity, were higher within deer exclosures than outside; moreover, rodents positive for TBE were found only where deer were absent.

Understanding of the mechanisms that create tick amplification and a TBE hotspot at this small spatial scale remains elusive. Clearly, if deer are absent, ticks that are present in the exclosures will be more likely to feed on rodents, increasing tick load and the potential for infection transmission. On the other hand, the absence of deer, a very important blood host for feeding adult ticks, will in the long term reduce tick population abundance, and this may also decrease tick load on rodents. The balance between these two forces may in principle depend on rodent density and size of the exclosure compared to the typical scale of rodent movement; in fact, ticks may be carried on animals inside small exclosures, while this factor should be less important for large exclosures.

Here we explore the possible role of host density and exclosure size in increasing or decreasing rodent tick load and infection prevalence through the use of (deterministic) mathematical models. First, we consider a model for tick population dynamics, based on Rosà and Pugliese (2007), and investigate the predicted effect of host densities on tick population dynamics. Then, by extending the model with patches from which deer are assumed to be absent, we study whether the model can help explain the experimental results of Perkins *et al*. (2006). Finally, we consider the dynamics of a tick-borne infection transmitted both systemically and non-systemically through co-feeding ticks (Randolph *et al*. 2002*a*), analysing the likely effect of deer exclosures.

This modelling methodology can be a first step towards understanding the role of space in tick-borne infections. Even though many interesting empirical results come from patchy habitats (for instance Allan, Keesing and Ostfeld (2003) show how rodent density, and especially borreliosis prevalence, increase in small forested fragments), most models consider a homogeneous setting. These models do not allow an understanding of whether local differences will be swamped by host movement or actually generated through restricted host movement, as in the case analysed here. Although the models analysed here are tailored for the case of artificial exclosures, the results can provide insights into the behaviour of tick density and tick-borne infections in patchy habitats.

MATERIALS AND METHODS

Mathematical models

Model 1: Basic model for tick demography. To examine *Ixodes ricinus* (Acari: Ixodidae) dynamics we used a basic tick demography model following Rosà and Pugliese (2007). This model explores the dynamics of three tick stages: larvae (L), nymphs (N) and adults (A) by explicitly modelling questing (with subscript Q) and feeding (with subscript F) phases (see Appendix). It is assumed that ticks feed on two kinds of blood hosts: small mammals (e.g. rodents), indicated with H_1, and medium to large-sized mammals (e.g. deer), indicated with H_2. For each tick stage (e.g. larvae) we then distinguish between those feeding on hosts of type 1 (L_{F_1}) and those feeding on hosts of type 2 (L_{F_2}).

The overall flow diagram is shown in Fig. 1. All transitions in the diagram are assumed to be density-independent, except for the production of larvae per feeding adult ticks which is a decreasing function of the number of ticks feeding on hosts of type i, $T_{F_i}(i=1, 2)$; this assumption corresponds to the observation that past tick load stimulates host resistance to tick feeding, resulting in reduced egg production (Wikel, 1996). The rationale for this or other types of density dependence is discussed at length in Rosà and Pugliese (2007).

Neglecting, for the sake of simplicity, seasonality in the tick-host interaction, and all developmental stages between one tick stage and the next, one arrives at the first system of differential equations (A.1) reported in the Appendix. A full list of parameters with their biological interpretation, nominal values and units, is given in Table 1.

Model 2: Model for tick demography with deer exclosure. We add to the previous model a deer exclosure, assuming that deer (H_2) are present only outside the exclosure, while rodents (H_1) may move freely from and into the exclosure. We do not

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Table 1. Numerical values and biological interpretation of population parameters

Symbol	Description	Value (units)
H_1	Rodent density	15 (ha^{-1}) [in Models 1 and 2], variable [in Model 3]
K_1	Carrying capacity of rodents	15 (ha^{-1}) [in Model 3]
b_1	Natural birth rate of rodents	0·00821 (day^{-1}) [in Model 3]
d_1	Natural death rate of rodents	0·0037 (day^{-1}) [in Model 3]
H_2	Roe deer density	0·1 (ha^{-1})
r^T	Average egg production per fed adult tick	2000
s^T	Density-dependent death rate of ticks	0·25 (ha $ticks^{-1}$)
d^L	Death rate of larvae	0·0365 (day^{-1})
d^N	Death rate of nymphs	0·015 (day^{-1})
d^A	Death rate of adult ticks	0·00625 (day^{-1})
σ^L	Detachment rate of larvae	0·28 (day^{-1})
σ^N	Detachment rate of nymphs	0·22 (day^{-1})
σ^A	Detachment rate of adult ticks	0·12 (day^{-1})
m^L	Moulting success probability for larvae	0·15
m^N	Moulting success probability for nymphs	0·15
β_1^L	Encounter rate between questing larvae and rodents	0·015 ($host^{-1}$ day^{-1})
β_1^N	Encounter rate between questing nymphs and rodents	0·0005 ($host^{-1}$ day^{-1})
β_1^A	Encounter rate between questing adults and rodents	0·00002 ($host^{-1}$ day^{-1})
β_2^L	Encounter rate between questing larvae and roe deer	0·08 ($host^{-1}$ day^{-1})
β_2^N	Encounter rate between questing nymphs and roe deer	0·25 ($host^{-1}$ day^{-1})
β_2^A	Encounter rate between questing adults and roe deer	0·25 ($host^{-1}$ day^{-1})
λ	Probability of getting infected via co-feeding	0·55
α	Disease-related death rate of rodents	0·33 (day^{-1})
γ	Recovery rate of rodent host	0·3 (day^{-1})
ρ	Exit rate of rodents from the exclosures	0–1 (day^{-1})
scale	Ratio of areas inside and outside the exclosure	≈ 0

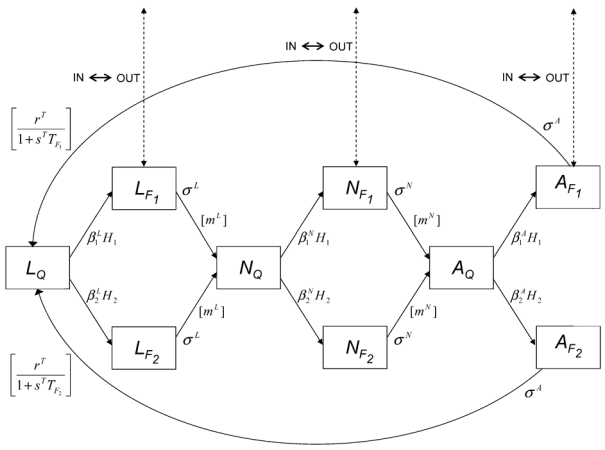

Fig. 1. Flow chart of models. Model (1) is obtained when disregarding the dashed lines; the symbols over the arrows represent the rate at which the transition occurs; the symbols in square brackets represent the conversion factor from one compartment to the next. Model (2) would consist of two flow charts like the one represented here (with the chart representing the inside compartment of the exclosure lacking the L_{F_2}, N_{F_2} and A_{F_2} components i.e. no feeding on deer) coupled by the dashed lines.

explicitly take account of space in the model, assuming that within each compartment (the exclosure and the rest of the habitat) interactions are homogeneous. Moreover, we assume that (except for the existence of a fence) the habitat is homogeneous, so that rodent density is the same inside and outside the exclosure.

Parameter ρ quantifies the movement of rodents from and into the exclosure and it is strictly related with the size of the exclosure: for instance, a value of ρ is equal to 0·1 means that 10% of the rodents initially present inside the exclosure move, per unit time, outside of the exclosure. Clearly ρ depends on the ratio between the typical distance (in the time unit) of rodents' movement and the size of the exclosure: the higher the value of ρ, the smaller is the size of the exclosure. Furthermore, to keep rodent density constant inside and outside the exclosure (neglecting stochastic fluctuations), we need to assume that, for each rodent that moves out of the exclosure, another one moves inside.

Rodents that move will carry the ticks feeding on them; hence, ticks feeding on type 1 hosts will move inside and outside the exclosure at the same rates as rodents. On the other hand, questing ticks will remain in the compartment in which they have developed, and there will be ticks feeding on type 2 hosts only in the outside compartment (a sketch of the resulting flow chart can be inferred from Fig. 1 by considering that the dashed lines connect two sections such as the one depicted but with the section representing the inside compartment of the exclosure lacking the L_{F_2}, N_{F_2} and A_{F_2} components – i.e. no feeding on deer).

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In order to balance the equations properly, a further parameter is necessary, here called *scale*, representing the ratio of areas inside and outside the exclosure. This parameter will affect the change of outside densities due to rodent emigration from the exclosure; when *scale* is set to zero (as we do in all simulations presented in this paper, meaning that the area of the exclosures is extremely small relative to that of the outside habitat), the movement of rodents to and from the exclosure does not affect rodent or tick density outside deer exclosure. (Qualitative results obtained when relaxing this assumption are discussed below.)

These assumptions lead to a modification of system (1). We need to consider the densities of all tick stages inside (indicated with superscript IN) and outside (with superscript OUT) the exclosure, and we obtain the equation system (A.2) reported in the Appendix.

Model 3: Model for tick-borne infections with deer exclosure. Finally, we consider the dynamics of a tick-borne infection. Tick-borne infections may have different competent hosts, and different infection pathways (Randolph, Gern and Nuttall, 1996; Randolph *et al*. 2002*a*). Here we consider the case where both systemic and non-systemic (through co-feeding ticks) transmission takes place only on rodents (competent hosts) while deer feed the tick population without amplifying the pathogen. These assumptions are adequate to describe the transmission of tick-borne encephalitis virus (TBEv) (Randolph *et al*. 2002*a*).

The system is built over the structure shown in Fig. 1, but distinguishes between susceptible, infected and infectious ticks, as well as susceptible, infective and immune rodents. Ticks are born susceptible to TBEv and may become infected via a blood meal from an infectious host or a co-feeding tick; after developing to the next stage, the infected tick will become infectious. Analogously, rodents are born susceptible and may become infected when an infective tick feeds on them; after a short infectious period (during which they suffer extra-mortality caused by the infection) they become permanently immune. We disregard localized infection of hosts that could, without a systemic infection, infect ticks for a few weeks following the infected tick bite, at least for borreliosis (Gern and Rais, 1996).

The equations, reported in the system (A.3) of the Appendix, have been analysed in Rosà and Pugliese (2007). Here, we consider a slightly more general case, letting adult ticks feed not only on deer but also on rodents; although it is usually thought that adult ticks rarely feed on rodents, this does seem to occur in the field: a total of 32 adult ticks were found on the 2988 *Apodemus flavicollis* (Rodentia: Muridae) trapped in the years 2000–2004 (unpublished observations) in the long-term study reported by Rosà *et al*. (2007), and adult ticks feeding on rodents were also observed by Perkins *et al*. (2006). The equations presented in Rosà and Pugliese (2007) include explicit parameters for the probability of a tick [or a host] getting infected after a blood meal on [by] an infective host [tick]; since here we are mainly interested in qualitative effects on prevalence, we fix these probabilities to 1, as in Foppa (2005).

The final modelling step is to introduce the exclusion of deer into model (3), distinguishing, as in model (2), tick and rodent host stages between the inside (IN) and outside (OUT) of the deer exclosure (compartments). The resulting system (not shown), consists of 32 differential equations and is available on the Web as supplemental material.

Parameter values

The models are calibrated with parameter values pertaining to *Ixodes ricinus* and tick-borne encephalitis in Trentino (northern Italy) considering the following main host species: the most abundant rodent host, the yellow-necked mouse (*Apodemus flavicollis*), and the main ungulate host, roe deer (*Capreolus capreolus* (Mammalia: Cervidae)). The full list of parameters values is given in Table 1, where we measure time in days and densities in hectares^{-1} (ha^{-1}). Carrying capacity for rodents is set to 15 mice ha^{-1} while deer density is set to 0·1 ha^{-1}, according to densities observed during field experiments (Rosà *et al*. 2007). The mean lifespan of *A. flavicollis* is considered to be 270 days and the average number of offspring is assumed to be 6 year^{-1}, implying that type 1 host mortality, d_1, is 0·0037 day^{-1} and type 1 host birth rate, b_1, assuming 1 : 1 sex ratio, is 0·00821 day^{-1} (Ferrari *et al*. 2007).

Concerning ticks' demographic parameters, adult females are thought to produce up to 5000 eggs in their unique oviposition (International Scientific-Working Group on TBE: http://www.tbe-info.com/tbe.aspx); hence, r_T is taken as 2000, around half of that value to take into account the presence of male and female ticks. As for the parameter s_T, describing density-dependent tick mortality, we set it to 0·25 in order to find equilibrium densities for feeding ticks comparable with those observed in the field (Rosà *et al*. 2007). Tick mortalities are different for each life stage (Sonenshine, 1991; Randolph and Rogers, 1997) and are computed as the reciprocal of the average survival period of ticks on vegetation which have not found a host (see Table 1 for values). The detachment rate of ticks, σ, is given by the reciprocal of the average duration of feeding time [1/(feeding time)] and depends on tick stages (Sonenshine, 1991; International Scientific Working Group on TBE: http://www.tbe-info.com/tbe.aspx) (see Table 1 for values). Parameters m^L and m^N represent the probability of successful moulting for larvae and nymphs,

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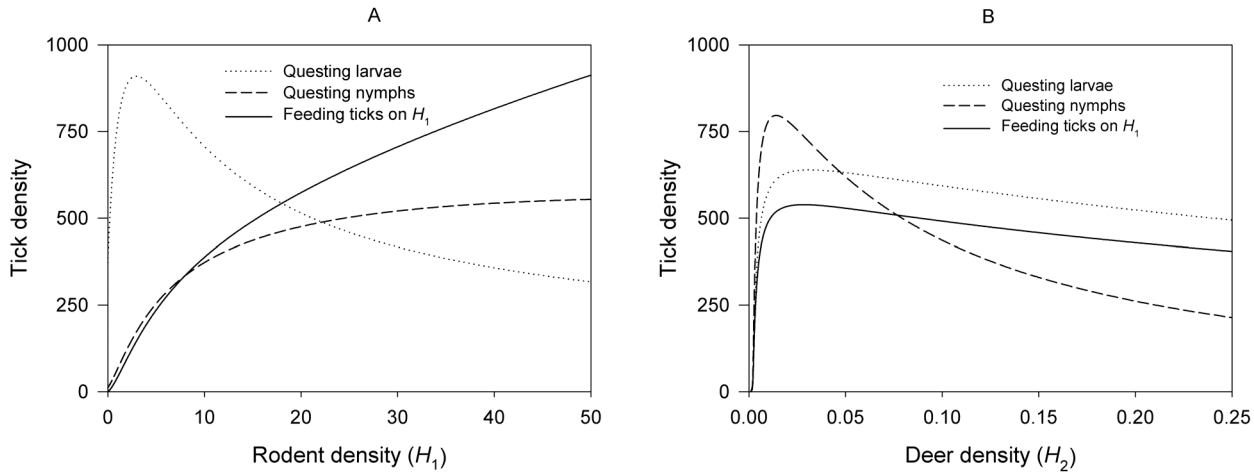

Fig. 2. Effect of rodent density (left panel, A) and deer density (right panel, B) on the density of questing larvae (dotted lines); questing nymphs (dashed lines), and rodent-feeding ticks (solid lines). Parameter values are those listed in Table 1.

respectively, after feeding. In practice, the values of m^L and m^N may depend on the host species upon which they feed (Humair *et al*. 1999), but, for the sake of simplicity, here we choose the same values for both host types and we also choose the same value for larvae and nymphs, setting $m^L = m^N = 0{\cdot}15$ (Humair, Rais and Gern, 1999).

Empirical data on the densities of larvae and nymphal ticks questing and feeding on rodents were used to estimate encounter rates between rodents and ticks in different stages (Rosà, 2003; Rosà and Pugliese, 2007). No comparable measures existed to estimate the encounter rates of ticks with deer. An experiment with tracer animals (domesticated goats) was carried out obtaining the numerical values reported in Rosà and Pugliese (2007). Since ticks may be better adapted to their natural host, roe deer, than to domesticated goats, we used in this paper default values for the tick-deer encounter rates that were higher than those estimated from the experiment; these are reported in Table 1, while in Fig. 3 we show the difference in results obtained when comparing the two sets of coefficients.

The probability of transmission of tick-borne encephalitis virus (TBEv) through co-feeding ticks, λ is set to 0·55 in accordance with values measured in laboratory experiments by Labuda *et al*. (1993). Here, for the sake of simplicity, we assumed the same value for all possible co-feeding transmission among different tick stages: infected nymphs to larvae, infected to susceptible nymphs, and infected adults to susceptible nymphs.

Finally TBEv-induced rodent mortality rate (α) is taken from Randolph *et al*. (1996), while the recovery rate from infection (γ) is an average of the values reported by Randolph *et al*. (1996), Foppa (2005), and the International Scientific Working Group on TBE (http://www.tbe-info.com/tbe.aspx).

A very important parameter in the model with exclosures is ρ, the rate at which rodents exit the exclosures. As discussed above, this is inversely related to exclosure size; this relation can be quantified using estimates for rodent home ranges. Home ranges for *A. flavicollis* have been determined by Schwartzenberger and Klingel (1995) to be around 1·5 ha for males and 0·38 ha for females, during the breeding season. Recent observations in the Trentino study area (A. Stradiotto and F. Cagnacci, unpublished data) show a dramatic change in home range between years of high or low rodent density: calculated home ranges are close to the estimates by.Schwartzenberger and Klingel (1995) in high-density years, but may be around 4·2 ha (for males) and 1·9 ha (for females) in low-density years. Taking an average of these measures, and assuming that a rodent explores half its home range in 1 day, we can roughly say that $\rho = 1$ corresponds to an exclosure's size of around 0·75–1 ha, and $\rho = 0{\cdot}1$ to an exclosure's size of around 7·5–10 ha.

RESULTS

Effect of hosts on tick densities

Fig. 2 shows how the equilibrium densities of questing larvae and nymphs, and of ticks feeding on rodents, change with densities of rodents (left panel) and of deer (right panel). Increasing host densities makes it easier for a tick to find a host and, because of the values of encounter rates, questing larvae are especially sensitive to rodent densities, while questing nymphs are more sensitive to deer densities. This observation may help in understanding the shapes of the curves shown in Fig. 2. When hosts are scarce, finding a host is a limiting component for tick populations; hence, at low host densities, all curves increase with either host type density. On the other hand, in model (1) it is assumed that the ticks' reproductive success decreases with feeding tick density; hence, at high host densities, equilibrium tick density will reach a saturation level and will only

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marginally be affected by further increases in host densities. This fact causes the humped shape of the curves of questing larvae with respect to rodent densities and of questing nymphs with respect to deer densities. The humped shape is a general feature under this type of density dependence (see Rosà and Pugliese, 2007) and can be explained as follows: when rodent hosts are extremely abundant, the total number of ticks is almost independent of host densities due to the saturation effect; hence, the rate at which new larvae are recruited is almost constant; the rate at which larvae feed on rodents (and thus leave the questing phase) is a strongly increasing function of rodent density (H_1), since rodent hosts will be easier to find. An almost constant entry rate and an always increasing exit rate make the equilibrium level smaller and smaller, as clearly shown in Fig. 2. A similar argument holds for questing nymphs (and more weakly for larvae) and deer densities. In turn, equilibrium densities of questing nymphs continue increasing with rodent densities (at least over the reasonable range shown in Fig. 2), because the entry rate in the compartment (resulting from larvae feeding increasingly on rodents) augments faster than the exit rate (nymphs' feeding rates are less sensitive to rodent densities). The shape, at high host densities, of the curves of feeding ticks can be easily explained by a competition effect: at an almost constant total level of ticks, increasing rodent densities will make more ticks feed on rodents (and less on deer), as seen in the left panel of Fig. 2; increasing deer densities will make less ticks feed on rodents (and more on deer), as seen in the right panel of Fig. 2.

Effect of deer exclosure on tick dynamics

We show (Fig. 3) the effect of the size of deer exclosure on tick populations taking the parameter *scale* equal to 0, i.e. assuming that the area outside the exclosure is much larger than the inside area; hence, densities outside do not depend on the presence of the exclosure or the exchange rate ρ. Other simulations (not shown) with a positive value of the parameter *scale* yield qualitatively similar results, although in that case outside tick densities will depend on parameter ρ. Fig. 3 shows the densities of ticks feeding on rodents (inside and outside deer exclosures) against the value of parameter ρ (the proportion of rodents exiting the exclosure per unit time, hence it is an inverse measure of the size of exclosure: the higher the value of ρ the smaller the area within the deer exclosure).

We used two different sets of values for the encounter rates between deer and ticks (β_2); on the left panel of Fig. 3, results are shown that use lower values of β_2 (estimated from the observations on goats as proxy for deer as described above and used by Rosà and Pugliese, 2007), on the right hand side, results correspond to higher values of β_2, which assume more encounters per unit time with natural hosts (Table 1). It can be seen that, in both cases, densities of feeding larvae (top row of Fig. 3) are lower inside the exclosure than outside, with the difference decreasing as the exclosure becomes smaller (ρ increases). Only when the exclosure is large, the densities of feeding adults are lower inside than outside; for smaller exclosures (about $\rho > 0{\cdot}1$) there are more adult ticks feeding on rodents inside than outside the exclosure (bottom row of Fig. 3), though the effect is rather weak especially for higher values of β_2 (right hand panel). Finally, the effect of exclosure size on the densities of feeding nymphs (middle row of Fig. 3) depends strongly on the values of β_2: when they are smaller (left hand side), densities are higher outside than inside, similarly to what happens for larvae; in the case of higher β_2 values (right panel), densities inside the exclosure may be much higher (by above 10%) inside a small exclosure than outside, while a reduction in tick density is reached only with large exclosures.

The previous results were obtained assuming that parameters were exactly the same outside and inside exclosures, except for the absence of deer. It is possible, although no real evidence exists that, in the absence of deer, rodent density H_1 increases, as well as the rate β_1^A at which adult ticks attach to rodents. Fig. 4 shows the effect of exclosure size under these two assumptions. Comparing Fig. 4 to Fig. 3, an increase in β_1^A results, as expected, in a substantial increase in the density of feeding adults and no changes in the other stages. An increase in H_1 results in a strong increase in the density of both feeding adults and nymphs. The conjecture that parameters are the same inside as outside exclosures is a conservative assumption that reduces the possible effects of exclosures.

Fig. 3 shows only the densities obtained in the exclosures at equilibrium. It may be of interest to also study the transient effects. Fig. 5 shows the temporal dynamics of feeding nymph density on rodents after the introduction of deer exclosure. The right panel of Fig. 5 shows a simulation with a smaller exclosure size ($\rho = 0{\cdot}5$) while on the left panel the simulation of a larger exclosure is shown ($\rho = 0{\cdot}05$). The removal of deer always results in a transient increase of feeding nymphs on rodents, but this effect lasts only for small exclosures (right panel of Fig. 5) while for larger exclosures (left panel of Fig. 5), a reduction in tick densities is observed after a short period of time (around one month in the simulation).

Effect of host densities on the prevalence of a tick-borne infection

Rosà and Pugliese (2007) discuss in detail the effects of host densities on the persistence of a

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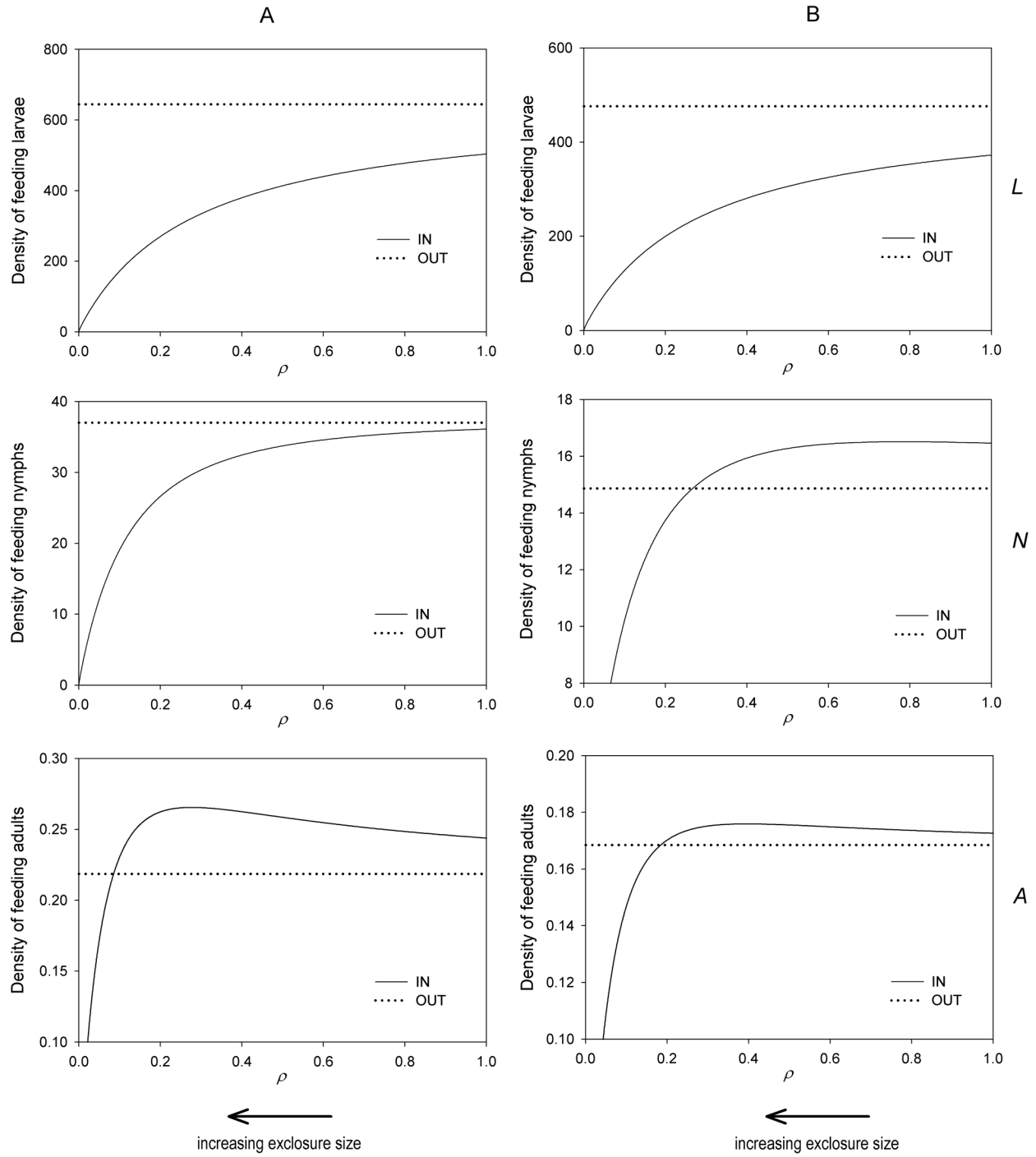

Fig. 3. Effect of varying ρ (the rate of exchange of rodents between the inside (*IN*) and outside (*OUT*) compartments of the exclosure; an inverse measure of exclusure size, see text for details), on equilibrium densities of various stages of rodent-feeding ticks: larvae (*L*, top); nymphs (*N*, middle); and adults (*A*, bottom). For results of the simulations shown on the left panel (A), encounter rates between ticks and deer are $\beta_2^L = 0{\cdot}05$, $\beta_2^N = 0{\cdot}03$, $\beta_2^A = 0{\cdot}13$, while for those simulations on the right panel (B), values are $\beta_2^L = 0{\cdot}08$, $\beta_2^N = 0{\cdot}25$, $\beta_2^A = 0{\cdot}25$. In all simulations the parameter *scale* (the ratio of areas inside and outside the exclosure, see main text) = 0; remaining parameter values as in Table 1; solid and dotted lines represent, respectively, the inside and outside compartments of the exclosure.

tick-borne infection; they analysed the region (in the 2-dimensional plane of rodent and deer densities) in which the basic reproduction ratio, R_0, is greater than 1, according to the type of transmission of the infection, and the modes of regulation of tick populations.

Here, for the only case of an infection transmitted systemically and by ticks co-feeding on rodents (like TBEv), with density dependence as incorporated in equation system (A.1), we show (Fig. 6) how the equilibrium infection prevalence depends on host densities. As rodent density increases above a

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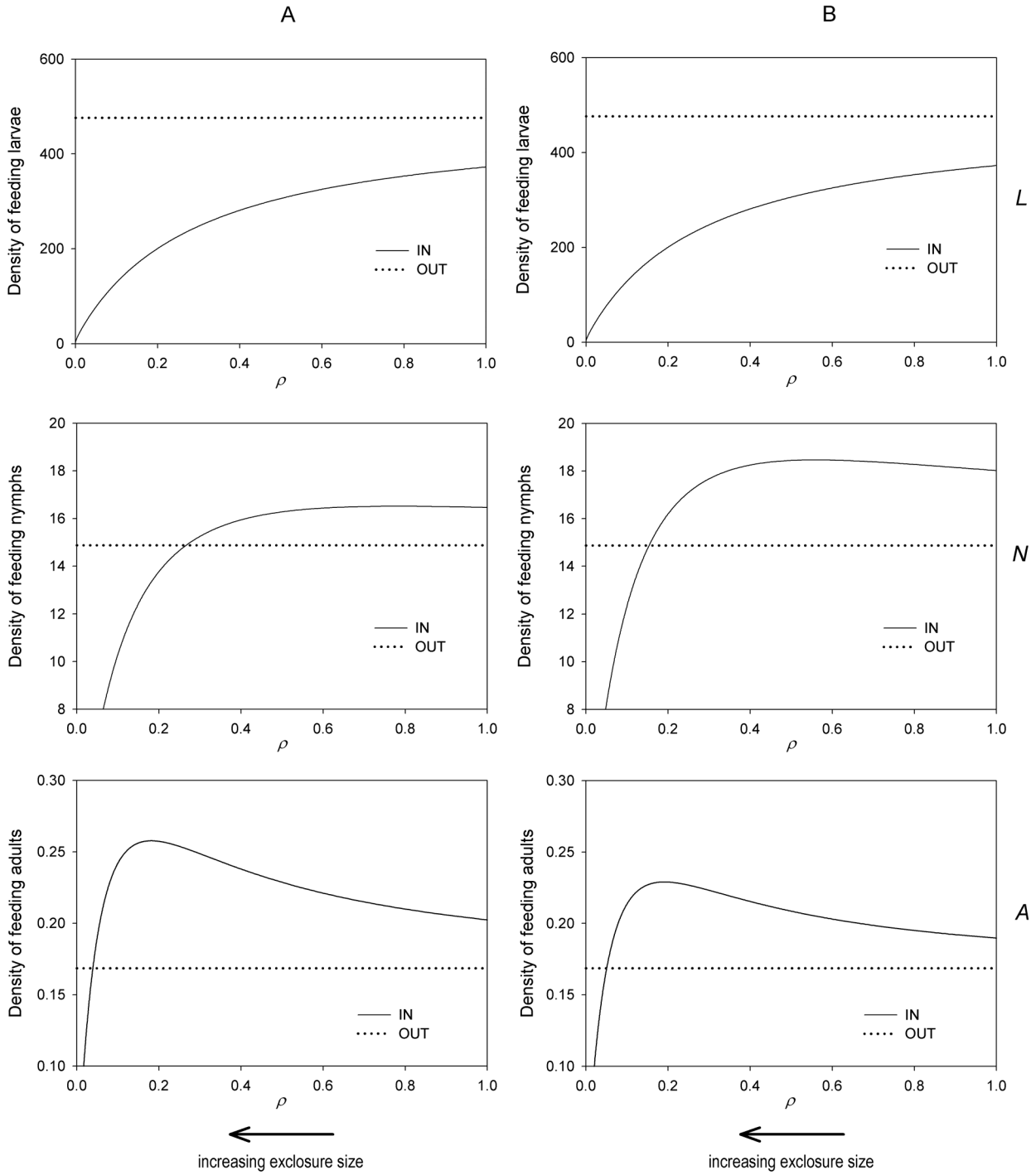

Fig. 4. Effect of varying ρ (see Fig. 3) on equilibrium densities of different rodent-feeding tick stages (top, middle, and bottom rows as in Fig. 3) when using higher values inside than outside the exclosure of β_1^A (the encounter rate between adult ticks and rodents), and H_1 (the density of rodents). On the left panel (A) $\beta_1^{A,IN}=0{\cdot}00005$ and $\beta_1^{A,OUT}=0{\cdot}00002$, on the right panel (B) $H_1^{IN}=25$, $H_1^{OUT}=15$. In all simulations *scale* $=0$; remaining parameter values as in Table 1; solid and dotted lines represent, respectively, the inside and outside compartments of the exclosure.

minimum threshold density (around 9/ha with the chosen parameter values), the prevalence of TBE in rodents and the density of infected questing nymphs (the stage that represents a higher risk of transmission to humans) increase steadily. Prevalence increases with deer density only when such density is extremely low (less than 0·03/ha); further increases cause a reduction in infection prevalence, up to the point that, for deer density above an upper threshold (around 0·14/ha with the parameter values used), the infection cannot persist. This constitutes the 'dilution' effect: an increase in density of a blood host species not competent for an infection dilutes the possibility of effective infection transmission and makes its persistence more difficult. Clearly the exact values obtained for the upper threshold of deer

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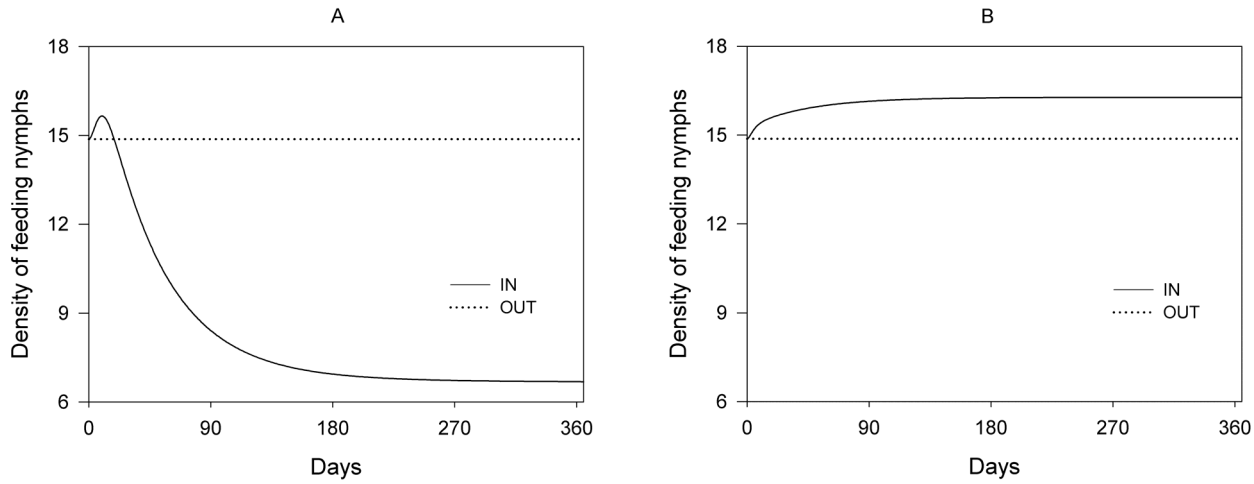

Fig. 5. Temporal dynamics of the densities of rodent-feeding nymphs after the introduction of deer exclosure. Two examples with different exclosure size are depicted: left panel (A), larger exclosure ($\rho = 0{\cdot}05$); right panel (B), smaller exclosure ($\rho = 0{\cdot}5$). In both panels $scale = 0$; remaining parameter values as in Table 1; solid and dotted lines represent, respectively, the inside and outside compartments of the exclosure.

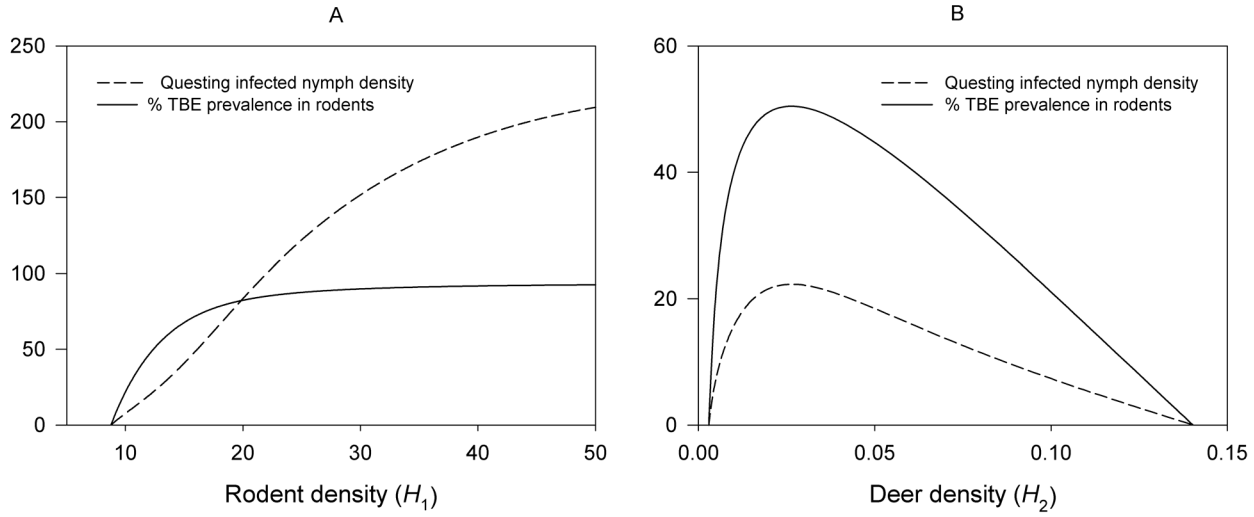

Fig. 6. Effect of rodent density, left panel (A) and deer density, right panel (B) on the equilibrium levels of questing, infected nymph density (dashed lines), and TBE prevalence in rodents (solid lines). Parameter values as in Table 1.

density and, more generally, for disease prevalence depend on the parameter values used and also on the assumption that systemic transmission is perfect. Conditions allowing for the persistence of TBEv are analysed more thoroughly by Randolph *et al.* (2002*a*), Foppa (2005) and Rosà and Pugliese (2007).

Finally, it must be noted that it is theoretically possible that a dilution effect holds for rodents as well: if rodent densities were extremely high, the tick/host ratio would decrease, making infection transmission less likely (Rosà and Pugliese, 2007). Indeed, if the axis displaying rodent density (on the left panel of Fig. 6) were extended up to densities around 500 rodents/ha, one would see a decrease in infection prevalence, and the curve would be similar to that of the right panel. However, this phenomenon depends on the assumption that tick populations are limited by density-dependent factors other than rodent density (see Rosà and Pugliese, 2007, for a more thorough discussion of this issue), and in any case, this would occur only for densities of rodents unrealistically high, so that it has no practical relevance.

Effect of deer exclosure on infection dynamics

Finally, we simulated the effect of exclosure size (varying ρ) on tick-borne encephalitis (TBE) infection, with particular attention to the density of infected questing nymphs inside and outside deer exclosures (left panel of Fig. 7) as this represents the most important variable in terms of human infection risk. The right panel of Fig. 7 shows the effect of exclosure size on TBE prevalence detected in rodents inside and outside deer exclosures. TBE prevalence in rodents decreases in large exclosures (about

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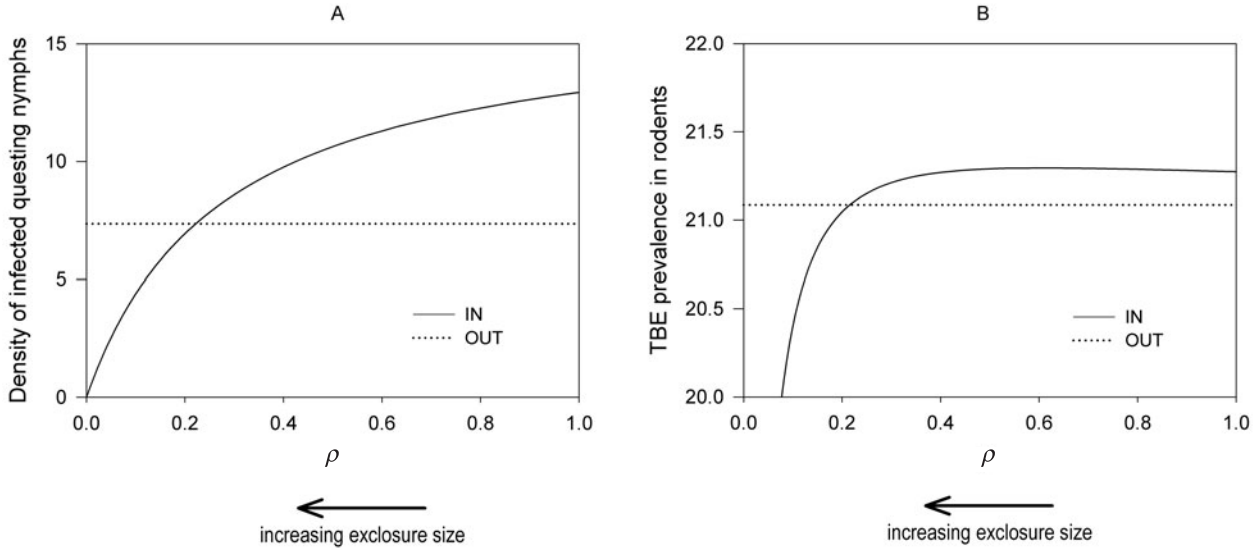

Fig. 7. Effect of varying ρ (see Fig. 3) on equilibrium densities of questing infected nymphs (left panel, A) and TBE prevalence in rodents (right panel, B) inside and outside the deer exclosure. In both panels $scale = 0$; remaining parameter values as in Table 1; solid and dotted lines represent, respectively, the inside and outside compartments of the exclosure.

$\rho < 0{\cdot}2$), and is slightly higher inside than outside in small exclosures (right panel). Similarly, but with a much stronger effect, the density of infected questing nymphs in small exclosures is much higher than that outside the exclosure. When the exclosure is very small ($\rho \approx 1$, corresponding to around $0{\cdot}75-1$ ha), the density of infected questing nymphs inside is almost twice as high as that outside, leading to the potential for a TBE risk hotspot.

DISCUSSION

Several observations (Ostfeld and Keesing, 2000) indicate that the density and diversity of tick blood hosts are important determinants of the presence and intensity of tick-borne infections. However, experiments in which host densities have been directly altered by setting plots from which larger mammals (especially deer) were excluded have yielded equivocal results, with tick densities sometimes higher and sometimes lower, inside the experimental plots than outside.

Perkins *et al*. (2006) have suggested that a general trend could be inferred from the experimental plots: small exclosures tend to result in higher tick densities, large exclosures in lower tick densities. We show in the present paper that this rule is compatible with the predictions of the mathematical models used in recent years to describe tick-host interactions, when they are modified to allow for the presence of a deer exclosure. It is certainly possible that deer removal results in a different type of habitat, for instance with a different vegetation cover, hence with different tick and host survival and tick-host encounter rates. Thus, differences in tick densities could be explained on this basis. While it is very likely that deer removal will change several features of the habitat, these differences should not be highly influenced by the size of the exclosure plot. Thus, it seems difficult to explain the patterns shown by Perkins *et al*. (2006) on this basis alone.

Here, we have shown instead that, assuming that there is no habitat difference between inside and outside the plots, the basic mechanisms of tick-host interactions predict density effects in qualitative agreement with experimental data: large exclosures should result in lower densities of ticks in all stages, while small exclosures can result in relevant increases of tick densities, depending on parameter values and the tick stage (larva, nymph, questing, feeding).

Thus, simple mathematical models seem to agree with the general pattern observed in experimental results of deer exclosures, although certainly more detailed information (e.g. on the habitat or host species) would be necessary to describe better each specific experiment. Thus, the analysis of the exclosure experiments seems to be in agreement with the assumption that tick populations are strongly influenced by host densities. A particularly striking result of the simulations shown in this paper is the potential increase in the densities of infected questing nymphs in small areas from which deer are excluded (left panel of Fig. 7). Although the model was built to describe experimental exclosures, it shows that there exists potentially the risk that infective tick stages concentrate in small areas in which, for whatever reason, hosts that are important 'tick amplifiers' but that are not competent for the infection are absent.

It must certainly be recognized that several aspects of the model presented here are not particularly realistic. The models are deterministic, based on

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differential equations with constant coefficients, thus disregarding seasonality and developmental delays, two features that are central in the dynamics of tick populations in temperate habitats (Randolph *et al*. 2002*b*; Rosà *et al*. 2007). Models that take into account the existence of discrete growing seasons are considerably more complex to analyse (Ghosh and Pugliese, 2004; Ogden *et al*. 2007), but their predictions should differ from those obtained with differential equation models mainly in the dynamic properties and not in the equilibria, which have been the main subject of analysis here. Indeed, since the aim of the present models is not an accurate quantitative prediction of densities of ticks, hosts, and pathogens, but rather the elucidation of mechanisms that could produce a concentration of infected ticks in deer exclosures (or similar natural areas), we believe that adding too much detail would risk obscuring the issue. It has already been noted that the equilibrium values predicted by the model for ticks (questing or feeding) in the various stages (Figs. 2, 3) are similar to values observed in the study site in Trentino (Rosà *et al*. 2007), indicating that the parameter values used correspond to realistic scenarios.

Central to the present analysis is the role of space in models for the dynamics of tick populations and tick-borne infections. However, the exclosures and the remaining habitat have been described only as homogeneous compartments with a fixed exchange of rodents between them; an explicit spatial variable is absent. This kind of modelling precludes the possibility of identifying boundary areas around the exclosure, which are affected by the experiments, and more general spatial features of tick distribution. On the other hand, an explicitly spatial model would require better knowledge of animal movement rules, and the estimation of additional parameters. Moreover, differences between outside and inside areas would have to be inferred from results deriving from a more complex series of experiments. We believe that the present approach to modelling of exclosures, though based on somewhat simplifying assumptions, is quite adequate to the aim of qualitatively explaining the consequences of deer exclosures on tick densities. A similar approach, using different rules for animal movement, could be used to model fragmented habitats, as exemplified by the study of Allan *et al*. (2003). This method would allow us to study how the impact of deer (or other non-competent blood hosts) serving as tick amplifiers or reducing encounters with competent hosts (Keesing *et al*. 2006) may act over different ranges, potentially creating local hot spots of infection transmission.

ACKNOWLEDGMENTS

We thank Sarah Perkins for providing useful comments and suggestions on the manuscript; Anna Stradiotto and Francesca Cagnacci for providing unpublished information about rodent behaviour, two anonymous reviewers for stimulating comments, and Maria-Gloria Basáñez for organizing the very interesting workshop from which this special issue originates and for performing a detailed and valuable editing of the final version of the manuscript.

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APPENDIX

Model 1: Model for tick dynamics without deer exclosure

$$
\begin{aligned}
\frac{dL_Q}{dt} &= \frac{r^T}{1+s^T T_{F_1}}\sigma^A A_{F_1} + \frac{r^T}{1+s^T T_{F_2}}\sigma^A A_{F_2} - (\beta_1^L H_1 + \beta_2^L H_1)L_Q - d^L L_Q \\
\frac{dL_{F_1}}{dt} &= \beta_1^L H_1 L_Q - \sigma^L L_{F_1} \\
\frac{dL_{F_2}}{dt} &= \beta_2^L H_2 L_Q - \sigma^L L_{F_2} \\
\frac{dN_Q}{dt} &= m^L \sigma^L (L_{F_1} + L_{F_2}) - (\beta_1^N H_1 + \beta_2^N H_1)N_Q - d^N N_Q \\
\frac{dN_{F_1}}{dt} &= \beta_1^N H_1 N_Q - \sigma^N N_{F_1} \\
\frac{dN_{F_2}}{dt} &= \beta_2^N H_2 N_Q - \sigma^N N_{F_2} \\
\frac{dA_Q}{dt} &= m^N \sigma^N (N_{F_1} + N_{F_2}) - (\beta_1^A H_1 + \beta_2^A H_1)A_Q - d^A A_Q \\
\frac{dA_{F_1}}{dt} &= \beta_1^A H_1 A_Q - \sigma^A A_{F_1} \\
\frac{dA_{F_2}}{dt} &= \beta_2^A H_2 A_Q - \sigma^A A_{F_2}.
\end{aligned}
\tag{A.1}
$$

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Model 2 : Model for tick dynamics with deer exclosure

$$\frac{dL_Q^{IN}}{dt} = \frac{r^T}{1+s^T T_{F_1}^{IN}}\sigma^A A_{F_1}^{IN} - \beta_1^L H_1 L_Q^{IN} - d^L L_Q^{IN}$$

$$\frac{dL_{F_1}^{IN}}{dt} = \beta_1^L H_1 L_Q^{IN} + \rho L_{F_1}^{OUT} - \rho L_{F_1}^{IN} - \sigma^L L_{F_1}^{IN}$$

$$\frac{dL_Q^{OUT}}{dt} = \frac{r^T}{1+s^T T_{F_1}^{OUT}}\sigma^A A_{F_1}^{OUT} + \frac{r^T}{1+s^T T_{F_2}^{OUT}}\sigma^A A_{F_2}^{OUT} - (\beta_1^L H_1 + \beta_2^L H_2) L_Q^{OUT} - d^L L_Q^{OUT}$$

$$\frac{dL_{F_1}^{OUT}}{dt} = \beta_1^L H_1 L_Q^{OUT} + scale \cdot \rho L_{F_1}^{IN} - scale \cdot \rho L_{F_1}^{OUT} - \sigma^L L_{F_1}^{OUT}$$

$$\frac{dL_{F_2}^{OUT}}{dt} = \beta_2^L H_2 L_Q^{OUT} - \sigma^L L_{F_2}^{OUT}$$

$$\frac{dN_Q^{IN}}{dt} = m^L \sigma^N L_{F_1}^{IN} - \beta_1^N H_1 N_Q^{IN} - d^N N_Q^{IN}$$

$$\frac{dN_{F_1}^{IN}}{dt} = \beta_1^N H_1 N_Q^{IN} + \rho N_{F_1}^{OUT} - \rho N_{F_1}^{IN} - \sigma^N N_{F_1}^{IN}$$

$$\frac{dN_Q^{OUT}}{dt} = m^L \sigma^L (L_{F_1}^{OUT} + L_{F_2}^{OUT}) - (\beta_1^N H_1 + \beta_2^N H_2) N_Q^{OUT} - d^N N_Q^{OUT} \tag{A.2}$$

$$\frac{dN_{F_1}^{OUT}}{dt} = \beta_1^N H_1 N_Q^{OUT} + scale \cdot \rho N_{F_1}^{IN} - scale \cdot \rho N_{F_1}^{OUT} - \sigma^N N_{F_1}^{OUT}$$

$$\frac{dN_{F_2}^{OUT}}{dt} = \beta_2^N H_2 N_Q^{OUT} - \sigma^N N_{F_2}^{OUT}$$

$$\frac{dA_Q^{IN}}{dt} = m^N \sigma^N N_{F_1}^{IN} - \beta_1^A H_1 A_Q^{IN} - d^A A_Q^{IN}$$

$$\frac{dA_{F_1}^{IN}}{dt} = \beta_1^A H_1 A_Q^{IN} + \rho A_{F_1}^{OUT} - \rho A_{F_1}^{IN} - \sigma^A A_{F_1}^{IN}$$

$$\frac{dA_Q^{OUT}}{dt} = m^N \sigma^N (N_{F_1}^{OUT} + N_{F_2}^{OUT}) - (\beta_1^A H_1 + \beta_2^A H_2) A_Q^{OUT} - d^A A_Q^{OUT}$$

$$\frac{dA_{F_1}^{OUT}}{dt} = \beta_1^A H_1 A_Q^{OUT} + scale \cdot \rho A_{F_1}^{IN} - scale \cdot \rho A_{F_1}^{OUT} - \sigma^A A_{F_1}^{OUT}$$

$$\frac{dA_{F_2}^{OUT}}{dt} = \beta_2^A H_2 A_Q^{OUT} - \sigma^A A_{F_2}^{OUT}.$$

Model 3 : Model for tick-borne infections without deer exclosure

$$\frac{dL_Q}{dt} = \frac{r^T}{1+s^T T_{F_1}}\sigma^A A_{F_1} + \frac{r^T}{1+s^T T_{F_2}}\sigma^A A_{F_2} - (\beta_1^L H_1 + \beta_2^L H_2) L_Q - d^L L_Q$$

$$\frac{dL_F^e}{dt} = \beta_1^L L_Q H_1^i + \beta_1^L L_Q (H_1^s + H_1^r)[1 - exp(-\lambda N_{F_1}^i / H_1)] - \sigma^L L_F^e$$

$$\frac{dL_F^s}{dt} = [\beta_1^L (H_1^s + H_1^r) exp(-\lambda N_{F_1}^i / H_1) + \beta_2^L H_2] L_Q - \sigma^L L_F^s$$

$$\frac{dN_Q^i}{dt} = m^L \sigma^L L_F^e - d^N N_Q^i - (\beta_1^N H_1 + \beta_2^N H_2) N_Q^i$$

$$\frac{dN_Q^s}{dt} = m^L \sigma^L L_F^s - d^N N_Q^s - (\beta_1^N H_1 + \beta_2^N H_2) N_Q^s$$

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$$\frac{dN^i_{F_1}}{dt} = \beta^N_1 H_1 N^i_Q - \sigma^N N^i_{F_1}$$

$$\frac{dN^i_{F_2}}{dt} = \beta^N_2 H_2 N^i_Q - \sigma^N N^i_{F_2}$$

$$\frac{dN^e_F}{dt} = \beta^N_1 N^s_Q H^i_1 + \beta^N_1 N^s_Q (H^s_1 + H^r_1)[1 - exp(-\lambda N^i_{F_1}/H_1)] - \sigma^N N^e_F$$

$$\frac{dN^s_F}{dt} = [\beta^N_1 (H^s_1 + H^r_1) exp(-\lambda N^i_{F_1}/H_1) + \beta^N_2 H_2] N^s_Q - \sigma^L N^s_F$$

$$\frac{dA^i_Q}{dt} = m^N \sigma^N (N^i_{F_1} + N^i_{F_2} + N^e_F) - d^A A^i_Q - (\beta^A_1 H_1 + \beta^A_2 H_2) A^i_Q$$

$$\frac{dA^s_Q}{dt} = m^N \sigma^N N^s_F - d^A A^s_Q - (\beta^A_1 H_1 + \beta^A_2 H_2) A^s_Q \tag{A.3}$$

$$\frac{dA_F}{dt} = (\beta^A_1 H_1 + \beta^A_2 H_2)(A^i_Q + A^s_Q) - \sigma^A A_F$$

$$\frac{dH^s_1}{dt} = b_1 H_1 - d_1(H_1) H^s_1 - \beta^N_1 N^i_Q H^s_1$$

$$\frac{dH^i_1}{dt} = \beta^N_1 N^i_Q H^s_1 - (d_1(H_1) + \alpha + \gamma) H^i_1$$

$$\frac{dH^r_1}{dt} = \gamma H^i_1 - d_1(H_1) H^r_1,$$

where

$$d_1(H_1) = d_1 + (b_1 - d_1) H_1 / K_1.$$

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