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Maintaining pathogens with short infectivity in seasonally structured tick populations: relative importance of three transmission pathways

Etsuko Nonaka

Etsuko Nonaka
Candidate

Mathematics and Statistics
Department

This thesis is approved, and it is acceptable in quality and form for publication:

Approved by the Thesis Committee:

Helen J. Huang, Chairperson

Peter T. Emmet

Stanley Steinberg

MAINTAINING PATHOGENS WITH SHORT INFECTIVITY IN SEASONALLY STRUCTURED TICK POPULATIONS: RELATIVE IMPORTANCE OF THREE TRANSMISSION PATHWAYS

BY

ETSUKO NONAKA

B. A., English, Kansai University of Foreign Studies, 1994
B. S., Forest Science and Biological Aspects of Conservation, University of Wisconsin – Madison, 2000
M. S., Forest Science, Oregon State University, 2003

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ABSTRACT

Infectivity periods of different tick-borne pathogens in host species can vary widely, and the variation affects how the pathogens are maintained in tick populations. In addition to systemic and vertical transmission, cofeeding transmission has been proposed as an important route for the persistence of pathogens with short infectivity (e.g., tick-borne encephalitis causing viruses, TBEv). Because cofeeding transmission requires ticks to feed simultaneously, the temporal dynamics of tick populations become important. Existing models of tick-borne diseases do not fully incorporate all three transmission pathways (systemic, vertical, and cofeeding transmission) and tick seasonality. We developed a comprehensive stage-structured population model that includes seasonality and evaluated the relative importance of the three transmission pathways for pathogens with short infectivity. We used the next generation matrix method to calculate R_0 and performed elasticity analyses for complex disease systems. We found that cofeeding transmission is a critically important route for such pathogens to persist in seasonal tick populations over the reasonable range of parameter values. At higher but still plausible rates of vertical transmission, our model suggests that vertical transmission can be a strong enhancer of pathogen prevalence when it operates in combination with cofeeding transmission. We discuss potential mechanisms behind consistent but low prevalence of TBEv observed in tick populations in the field.

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Chapter 1

Introduction

Tick populations endemically carry multiple pathogens, some of which are more prevalent than others. In infected areas, *Borrelia burgdorferi*, the agent of Lyme disease, is often prevalent in up to 40% of the tick population (Ebel et al. 1999, Randolph et al. 2002), while flaviviruses (Powassan and deer tick virus) that cause tick-borne encephalitis (TBE) are typically present at less than 5% prevalence (Randolph et al. 2002). These pathogens also cause different levels of viraemia and infectivity in host individuals. Host vertebrates (often small to medium mammals and some reptiles) infected with *B. burgdorferi* are viraemic over a period of several months, if not chronically infected. On the other hand, TBE-causing viruses (TBEv) usually have a short infectivity period in host individuals (2 – 3 days), allowing much shorter windows for pathogen transmission. Compared to *B. burgdorferi*, the maintenance of TBEv from one generation of ticks to the next appears to be difficult. Recently, cofeeding transmission (Jones et al. 1987) between infected and uninfected ticks feeding in close proximity on non-viraemic hosts has been proposed to be the key pathway that can sustain TBEv in ticks (Randolph et al. 2002, Randolph et al. 1996). Cofeeding transmission can be potentially effective because ticks show aggregated distributions among host individuals in such a way that 75% of ticks feed on 20% of the host population (Randolph et al. 1999).

Because cofeeding transmission requires individual ticks to feed in close proximity on the host, temporal dynamics of tick populations become important. Tick activity is unarguably seasonal in temperate regions (Ostfeld et al. 1996, Goodwin et al.

2001), and tick seasonal life cycles have been incorporated in Lyme disease models (Proco 1999, Schauber and Ostfeld 2002) in contrast to TBEv models (but see Ogden et al. 2007). The existing Lyme disease models do not include cofeeding transmission because viraemia in the host is so long that systemic transmission (transmission between a tick and its host via blood meal) serves as the major route. Rosà and Pugliese (2003, 2007) have developed models for TBEv including cofeeding transmission, but tick seasonality was not included. In addition to cofeeding and systemic transmission, pathogens can be passed via vertical transmission (transmission from adult female ticks to their eggs). Although evidence shows a small amount of vertical transmission for TBEv in ticks, this route could amplify infection significantly because of high fecundity of adult female ticks (~ 2000 eggs per female). Potentially, cofeeding and vertical transmission could amplify each other substantially, but existing models do not examine the interaction of cofeeding and vertical transmission. There is a need for a comprehensive mathematical model which incorporates all three transmission pathways and seasonal tick population dynamics.

Previously, the emphasis of incorporating seasonality in TBEv disease models has been on including the environmental variables (e.g., moisture and temperature) which are known to affect development rates and mortality in ticks (Ogden et al. 2008, Randolph 2004). We agree with the opinion that more process-based models need to be developed to account for the known correlations between climate and tick activities especially for future predictions under climate change. However, it seems prudent to first understand the population-level effects of seasonality in tick life cycles on disease spread and persistence, using basic population models.

Randolph and colleagues (Randolph et al. 1999, 2000) have put forward the proposition that cofeeding transmission between larvae and nymphs is critically important and vertical transmission has an insignificant role in TBEv persistence in the European ixodid tick, *Ixodes ricinus*. If vertical transmission is not important, overlap between cohorts of ticks must provide the critical link for the pathogen to be passed from one generation to the next via horizontal transmission. For TBEv, horizontal transmission by the systemic route is highly limited due to the short infectivity of the pathogen in the host. Hartemink et al (2008) quantitatively evaluated the theory using a non-dynamic model and provided further support. A study that explicitly considers seasonality in tick life cycle could provide stronger support for the proposition, and evaluate the quantitative effects of inter-cohort overlap on pathogen prevalence.

The objective of this paper is to develop a comprehensive mathematical model that incorporates tick seasonality and evaluate the relative importance of the three transmission pathways for TBEv. In addition, we examine the effects of inter-cohort overlap on pathogen persistence and prevalence. Through this work, we hope to shed light on the mechanisms for low but consistent prevalence of TBEv observed in the field both in the United States (Ebel et al. 1999, Ebel, *unpublished data*) and in Europe (Randolph et al. 2002). To achieve these goals, we build a discrete-time, stage-structured population model and utilize the next generation matrix method to calculate R_0 and to assess the sensitivity of R_0 to the values of input parameters (Diekmann et al. 1990, Hartemink et al. 2008). We use the ecology of the transmission cycle of TBEv involving the black-legged or deer tick (*Ixodes scaluparis*) in the upper Midwest to northeastern

region of the United States as a model system, although it is intended to inform broader situations.

Chapter 2

Methods

Tick life cycle

In the upper Midwest to the northeastern part of the United States, black-legged ticks typically have a two year life cycle (Fig. 1). The timings for emergence and the onset of diapause may vary geographically and from year to year (Ostfeld et al. 1996). For simplicity, we assume an average condition. The larvae emerge in mid to late summer and quest for 3-4 months and then molt followed by diapause in fall until next spring. The nymphs emerge in late spring and quest for 3-4 months before they molt into adults in fall. The adults emerge in fall and quest until late spring except during the coldest months when they undergo diapause. In our model, the larvae are active from July to October, the nymphs from May to August, and the adults from October to May except January and February. The larvae and nymphs usually feed on small mammals, mainly rodents, for blood meals, while the adults feed on larger mammals such as deer. The most common rodent host species is the white-footed mouse (*Peromyscus leucopus*), which is competent for TBEv. White-tailed deer (*Odocoileus virginianus)* is abundant in the regions and is incompetent but can feed a large number of ticks and amplify the tick population. Once infected, infection in ticks is usually life long unless it is lost during molting stages, while it lasts only a few days in the competent hosts. Sandberg et al. (1992), who developed a model for their study site on Nantucket Island, Massachusetts, used a more complex life cycle where ticks could survive beyond two years (i.e., if ticks failed to feed during the first year of the larva or nymph stage, they had a second chance). We think such a case is very rare in our study regions.

The model

We transformed and extended the continuous time model developed by Rosà and Pugliese (2007) for TBEv into a discrete-time model to include the seasonal life cycle of the tick, using the multiple matrix model approach introduced by Sandberg et al. (1992) for Lyme disease. The model by Rosà and Pugliese (2007) was modified to also include the three transmission pathways (vertical, cofeeding, and systemic). Our model is composed of monthly matrices representing population processes occurring in each month for different types of ticks and for the host species. The model computes density (per ha) for twelve types of ticks; three life stages (larvae, nymphs, adults), two feeding phases (fed or unfed), and two epidemiological conditions (susceptible or infected). If ticks fail to feed during the questing season, they are assumed to die from starvation. For the hosts, we assume no seasonal life cycle and a constant total population size. For the competent host (able to carry and transmit the pathogen; H_1; 50 individuals total per ha) the density of susceptible, infected, or recovered types changes over time as hosts become infected and recover from the infection with a population turnover rate of about one year. The competent host is born uninfected, and infection only occurs after birth. The incompetent host (H_2) does not get infected so that it is represented as one constant state variable (0.25 individuals per ha). We assume that infection with the pathogen does not affect feeding rates of ticks or demographic characteristics (e.g., mortality) in ticks or hosts.

We parameterized the model with values taken from the literature (Table 1). If available, we utilized studies with the black-legged tick, but otherwise we used values for other ixodid ticks (mainly *I. ricinus*). Parameter values related to pathogen transmission

are mostly from laboratory studies, while many demographic parameters are estimated in field studies. Because transmission rates were measured in laboratory conditions, it is uncertain how well these values represent field conditions. To reflect this uncertainty, we vary the three transmission rates over plausible ranges based on current estimates. For cofeeding transmission, we considered the measured values as theoretical maxima due to the unnatural settings of the experiments (Labuda et al. 1997). The two cofeeding transmission rates are varied simultaneously by a tuning multiplier and are expressed in the figures as fractions of the measured values (i.e., 0.24 and 0.72). For vertical transmission, we used the value referred to in Danielová et al. (2002) and also estimated it from limited field data presented in the paper (4 – 6 larvae out of 419 larvae caught were potentially infected before their first blood meal). We felt that, although the current best (or most accepted) estimate is 0.001, there is some evidence supporting higher values, and varied the vertical transmission rate up to 0.02.

In our model, the feeding rate of the tick and the rate of cofeeding transmission depend on the densities of ticks and hosts (therefore, the values are updated monthly). Encounters (and feeding) between questing ticks and either species of hosts are modeled as mass action (Sandberg et al. 1992, Rosà and Pugliese 2007). The probability that a tick in life stage Z feeds is given by

$$P_f^Z = 1 - \exp\left[-\left(\beta_1^Z H_1 + \beta_2^Z H_2\right)\right]$$

where $\beta_h^Z = \dfrac{t_h^Z \cdot que\_d^Z}{Z_U \cdot atch\_d^Z}$, Z = L, N, A, h = 1, 2

L, N, or A corresponds to the larva, nymph, or adult life stage of the tick, and 1 and 2 refers to the host species 1 (H_1) and host species 2 (H_2), respectively. Z_U is the number

of unfed ticks in life stage Z. The rate of ticks being infected upon feeding on a host is modeled from simple probability rules:

$$P_{\inf}^{Z} = P_{H1^{sr}}^{Z} \cdot P_{ct}^{Z} + P_{H1^{i}}^{Z} \cdot \left(P_{ct}^{Z} + P_{st}^{Z} \cdot \left(1 - P_{ct}^{Z} \right) \right).$$

$P_{H1^{sr}}^{Z}$ is the proportion of susceptible or recovered H_1 hosts, and $P_{H1^{i}}^{Z}$ is the proportion of infected H_1 hosts encountered by ticks of stage class Z. P_{ct}^{Z} and P_{st}^{Z} are the probabilities of cofeeding and systemic transmission in ticks of stage class Z, respectively. Here we assume that cofeeding transmission is the only way in which ticks can be infected by feeding on susceptible or recovered hosts, and that cofeeding and systemic transmission are mutually exclusive but either is possible on infected hosts. For the cofeeding transmission rate, we adopted and modified the formulation used by Rosà and Pugliese (2007) to include the immunity condition (i.e., recovered or not) of the competent host. In our model, we set the parameters such that cofeeding transmission on recovered (i.e., immune) hosts is more difficult than on susceptible or infected hosts as Labuda et al. (1997) found in their experiments. The rate of cofeeding transmission to a larva from a larva becomes, following Rosà and Pugliese (2003, 2007),

$$P_{LL} = 1 - \exp\left(- \frac{L_{Q,t}^{i} P_{f}^{L} \left(\lambda_{LL}^{r} P_{H1^{r}}^{L} + \lambda_{LL}^{si} P_{H1^{s}+H1^{i}}^{L} \right)}{H_1} \right)$$

where $\lambda_{LL}^{r} = \theta_{LL}^{r} \left(1 + \frac{\rho_{LL}}{\sqrt{k^{L} k^{L}}} \right)$ and $\lambda_{LL}^{si} = \theta_{LL}^{si} \left(1 + \frac{\rho_{LL}}{\sqrt{k^{L} k^{L}}} \right)$

The λ's are the probabilities of cofeeding transmission enhanced by aggregation of ticks and reflects the distribution of tick load among host individuals that has been described as negative binomial (Randolph et al. 1999, 2002). The parameter k^{Z} is the aggregation (or

dispersion) parameter of the negative binomial distribution for ticks in life stage Z (Randolph et al. 1999, Brunner and Ostfeld 2008). The parameter $\rho_{ZZ'}$ is the correlation between burdens of ticks in stage Z and those in stage Z' on a host (Rosà and Pugliese 2003). For example, when the same host individuals tend to harbor a large number of larvae and nymphs, the correlation $\rho_{LN}(=\rho_{NL})$ is close to 1. Of course, if Z = Z', correlation is identically 1. The rate of cofeeding transmission to a larva from a nymph is similarly,

$$P_{LN} = 1 - \exp\left(- \frac{N_{Q,t}^{i} P_f^N \left(\lambda_{LN}^{r} P_{H1^r}^N + \lambda_{LN}^{si} P_{H1^s + H1^i}^N \right)}{H_1} \right).$$

Then the total probability of a larva to be infected via cofeeding transmission is $P_{ct}^{L} = P_{LL} + P_{LN}(1 - P_{LL})$. The total probability of a nymph to be infected via cofeeding transmission is modeled similarly. For adult ticks, both the probabilities of systemic and cofeeding transmission are zero since they are assumed to feed only on the incompetent host which supports neither transmission route. The probability of not being infected upon feeding is the complement of that of being infected:

$$P_{non-\inf}^{Z} = 1 - P_{\inf}^{Z} = P_{H1^{sr}}^{Z} \cdot \left(1 - P_{ct}^{Z}\right) + P_{H1^{i}}^{Z} \cdot \left(1 - P_{st}^{Z}\right) \cdot \left(1 - P_{ct}^{Z}\right) + P_{H2}^{Z}$$

The infection rate of the competent host is also modeled as mass action (Rosà and Pugliese 2007):

$$P_{\inf}^{H1} = 1 - \exp\left\{ - \left(q_H^L \beta_1^L L_{Q,t}^{i} + q_H^N \beta_1^N N_{Q,t}^{i} + q_H^A \beta_1^A A_{Q,t}^{i} \right) \right\}.$$

We assume that adult ticks do not feed on the competent hosts ($\beta_1^A = 0$). The host mortality rate was chosen to reflect longevity of about one year, which is typical in small

rodents in the upper Midwest to northeastern United States. The birth rate was set so that the total host density is at equilibrium. Infected host individuals can recover and develop partial immunity to the pathogen with probability, exp(-γ). The host does not infect other host individuals (no direct horizontal or vertical transmission within the host population). We simulate the model until the tick population reaches the stable-stage distribution (Fig. 2).

Next generation matrix and R_0

To compute the basic reproductive number (in epidemiology, the expected number of secondary infections caused by one infected individual), R_0, we utilized the next-generation matrix method (Diekmann et al. 1990, Diekmann and Heesterbeek 2000, Hartemink et al. 2008). Hartemink et al. (2008) applied the method to tick-borne diseases, and we closely follow their steps except that we obtain the expected numbers of new infections (i.e., the elements of the matrix) directly from model simulations. Briefly, the next generation matrix contains the numbers of individuals that are infected by one infected individual of each type-at-birth during its entire life time. Types-at-birth refer, in our model, to ticks or H_1 host that become infected in one of the months they can be infected ("birth" of an infected). The types-at-births of *infecting* individuals are the columns, and those of *infected* individuals are the rows (Table 2). For example, a larva infected in August (L8) could grow into an infected nymph (since larvae are infected upon feeding, the next opportunity to infect other individuals does not come until they feed next time as nymphs.) and infect larvae in August or September, nymphs between June and September, H_1 host between June and September, and/or lay infected eggs.

Since the elements of the matrix represent pathogen transmission between particular pairs of types, we can classify the elements into the three transmission pathways (Hartemink et al. 2008). The nonzero elements in the first row, for instance, represent the number of infections from ticks to eggs, hence vertical transmission. Cofeeding transmission corresponds to the elements representing infections directly from ticks to ticks. The dominant eigenvalue of this matrix can be interpreted as R_0 with the desired property that, when $R_0 > 1$, the disease can spread into a purely susceptible population (Diekmann et al. 1990, Hartemink et al. 2008).

To compute our next generation matrix, we introduce to the population at the "disease-free" stable-stage distribution one infected tick or host of one type-at-birth and calculate the number of newly infected individuals by type-at-birth. All newly infected individuals are immediately removed if the originally infected tick is to subsequently infect more secondary cases (to avoid including the ticks infected by newly infected ticks, tertiary infections). We assume, as in the previous work, that the infectiousness of ticks and hosts is independent of how they acquired the pathogen (i.e., transmission pathways) and distinguished 15 types-at-birth. There is one type-at-birth for every tick life stage at which infection can be acquired, for every month when they are actively searching a host. There is another type-at-birth for the competent host for each month they can be bitten by ticks (Table 2). We label the types-at-birth as 1) ticks infected as an egg (via vertical transmission; column 1), 2) ticks infected as larvae (through their first blood meal; columns 2-5, August – November), 3) ticks infected as nymphs (through their second blood meal; columns 6-9, June – September), and 4) systemically infectious competent host (columns 10-15, June – November).

The next generation matrix, **K**, will be a 15 x 15 matrix. Each element of the matrix, k_{ij}, indicates the expected number of secondary infections in type-at-birth i caused by one infected individual of type-at-birth j during its entire infectious period. Some of the elements are zero because not all types can infect all other types. The host cannot infect tick eggs and directly infect other individuals of the host, for example. Since we assumed adult ticks do not feed on the competent host, ticks infected during their second blood meal (i.e., nymphs) do not have an opportunity to infect other ticks except via their own eggs. Because ticks infected during their first blood meal (i.e., larvae) feed and possibly infect other individuals only after they molt into nymphs, elements in columns 2-5 corresponding to the months when no nymphs feed are zero.

Non-overlapping generations

To examine the effects of inter-cohort overlap (i.e., larvae and nymphs), we shift the feeding seasons of larvae (one month backward) and nymphs (one month forward) to remove the overlap between two generations. This caused the next generation matrix to become 17 x 17 by increasing the types-at-births for the hosts by two. The basic structure of the matrix is the same except that there is no longer inter-cohort cofeeding transmission from ticks infected as larvae to larvae of the subsequent cohort (i.e., no overlap between larvae and nymphs).

Sensitivity and elasticity analyses

Another utility of the next generation matrix is the ease of computing sensitivity and elasticity values of the matrix elements and of the model parameters (Caswell 2001,

Hartemink et al. 2008). Sensitivities quantify how R_0 changes in response to small changes in the value of a matrix element or a model parameter, while elasticities are normalized sensitivities and measure the proportional change in R_0 in response to a proportional change in an element or a parameter. For matrix elements, the element-wise elasticities sum to unity and each elasticity value indicates the relative importance of a particular transmission route between two types-at-birth. Using this property, we can conveniently sum appropriate elements to calculate the relative importance of vertical, cofeeding, and systemic transmission pathways. For model parameters, elasticity is a more convenient metric to assess sensitivity of R_0 to a small change in a parameter because input values of parameters can vary by orders of magnitude.

Chapter 3

Results

The effect of the three transmission pathways on pathogen prevalence and R_0

The effect of each transmission pathway on prevalence and R_0 was assessed by turning off one pathway at a time and varying the rates of the other pathways (Fig. 3, 4). The model outputs show that prevalence and R_0 are qualitatively in close agreement. Some discrepancy may appear because prevalence reflects endemic conditions (i.e., some hosts are immune), while all secondary infections are removed in the R_0 calculation (i.e., all hosts are susceptible). In the absence of either vertical or systemic transmission, the pathogen persists in the tick population at or above the observed level of >0 – 5% (Fig. 3a, c), while in the absence of cofeeding transmission the pathogen cannot be maintained (Fig. 3b). When cofeeding transmission is the only pathway (Fig 3a, c, at zero for systemic transmission), the pathogen can still be maintained at intermediate or higher cofeeding transmission rates. Although the pathogen can persist without vertical transmission, a small amount can boost the effectiveness of cofeeding transmission greatly (Fig. 3c). On the other hand, systemic transmission is of less importance (Fig. 3a). In summary, neither vertical nor systemic transmission alone can maintain the pathogen, but cofeeding transmission can. Cofeeding transmission is necessary and can be sufficient by itself to sustain the pathogen in the tick population.

When the two tick cohorts (i.e., larvae and nymphs) do not overlap, the pathogen does not persist without vertical or cofeeding transmission (Fig. 3d, e). Persistence is only plausible when both cofeeding and vertical transmission pathways take place (Fig. 3f). Hence, overlap between cohorts has a large impact when there is no vertical transmission,

whereas the effect is much less dramatic in the presence of both vertical and cofeeding transmission.

Relative importance of the three transmission pathways

Elasticity analysis on the next generation matrix quantifies the relative importance of transmission pathways with respect to R_0 for a given set of parameter values. The elasticity value can be interpreted as the proportional contribution to R_0 from each transmission route. We performed analysis with two levels of vertical transmission rates (0.001 and 0.01; Fig. 5). In both cases, relative importance of the three pathways varies over the parameter space, notably cofeeding and systemic transmission exchanging relative importance as the cofeeding transmission rate increases. The relative importance of vertical transmission is less variable for the majority of the space. As expected, an increase in the vertical transmission rate increases its relative importance. Cohort overlap did not qualitatively change the results, but vertical transmission increased its relative importance by 10-15% (Fig. 6).

Sensitivity and elasticity analyses for the input parameters

We examined the cases with and without cohort overlap for two sets of vertical and cofeeding transmission rates; 1) lower vertical and higher cofeeding transmission and 2) higher vertical and lower cofeeding transmission. We chose the vertical and cofeeding transmission rates so that the prevalence is roughly the same (except the non-overlapping case with a low vertical transmission). For low vertical/high cofeeding transmission rates with overlap, the elasticities of the parameters related to nymphs (t_1^N, que_d^N,

$atch\_d^N$, ε^L) are much higher, indicating that nymphs play the critical role in determining R_0 (Fig. 7a). The cofeeding transmission parameter (λ_{si}) has a high elasticity, and it is dominated by the route from nymphs to larvae (λ_{si}^{LN}). With a higher value of vertical transmission, the elasticities of the nymph-related parameters decrease and those of the larva-related slightly increase (Fig. 7b). The elasticity of λ_{si}^{LN} decrease, and instead those of the intra-cohort cofeeding transmission parameters increase (λ_{si}^{LL} and λ_{si}^{NN}). For the case with no overlap, elasticity values do not change much between the two sets of transmission rates (Fig. 7c, d). Many more parameters become more important without cohort overlap. In particular, the parameters related to adult feeding (t_2^A, que_d^A, $atch\_d^A$), the number of viable eggs (a^T, $viab$) and trans-stadial (pathogens are maintained through the molting process) transmission rates (m^L, m^N) become more important, reflecting that pathogen transmission cannot rely as much on inter-cohort transmission. Many of the current cohort need to carry the pathogen over to the next stage or generation for the pathogen to persist in the tick population. In the absence of cohort overlap, R_0 depends on all the stage classes more or less equally (i.e., parameters for all stage classes have more or less similar elasticity values).

Chapter 4

Discussion

We incorporated tick seasonality and all three proposed transmission pathways in a comprehensive epidemiological model to examine the relative importance of the pathways and the effects of cofeeding transmission in overlapping two cohorts of ticks. Our results clearly show that cofeeding transmission is a critically important route for TBE-causing pathogens to persist over the reasonable range of vertical transmission rates (Fig. 3b). Without this transmission route, the pathogens would not be maintained in tick populations, supporting the widely accepted theory for TBEv persistence proposed by Randolph et al. (1996). In addition, our model provides further support for Randolph (2004) that vertical transmission is merely an accessory pathway at very low vertical transmission rates (0.001, Danielová et al. 2002). At higher but still plausible rates of vertical transmission, however, our model suggests that vertical transmission can be a strong enhancer of pathogen prevalence when it operates in combination with cofeeding transmission (Fig. 3c). Inter-cohort overlap has significant impacts only at low vertical transmission rates (Fig. 3f). In the northeastern United States, where larvae and nymphs usually overlap in late summer (Ostfeld et al. 1996), cofeeding transmission alone can be a sufficient mechanism to maintain TBEv. At the time of this writing, we are not aware of any study which reports either vertical or cofeeding transmission rates in *I. scapularis* in field or laboratory populations.

Tick seasonality and cofeeding opportunities

Introducing seasonality in the tick life cycle into a TBEv epidemiological model

may increase or decrease cofeeding opportunities in ticks. In existing non-seasonal models (Rosà and Pugliese 2003, 2007, Hartemink et al. 2008), population densities are computed by using demographic parameters representing some average rates. In our seasonal model, demographic parameters are applied to appropriate months where the demographic processes occur (i.e., egg hatching, molting), creating distinct peaks in the population size. On one hand, the seasonal model appears to increase cofeeding opportunities because many ticks are feeding at the same period. However, given the high mortality due to failing to find a host (i.e., intensive intraspecific competition in ticks), cofeeding opportunities are probably reduced in our model relative to the continuous counterparts. Our model results show that the relative importance of vertical transmission is not quite as low as it was suggested previously (Hartemink et al. 2008) (Fig. 5a). This indicates that circulation of TBEv may rely more on vertical transmission than what would be expected from non-seasonal models. Seasonality in tick life cycle imposes constraints on pathogen persistence, which may have implications for the evolution of host-pathogen interactions.

Mechanisms for the consistent but low prevalence of TBEv in tick populations

TBEv are known to occur at relatively consistent, low prevalence in tick populations (Randolph et al. 2002). In northern Wisconsin, the prevalence usually stays at around 2 – 5% (Ebel et al. 1999, Ebel, *unpublished data*). How TBEv are stably maintained has not yet been quantitatively accounted for, but measuring various transmission rates in field conditions is a formidable challenge. In such situations, models are useful tools to gain insights. For a model to reasonably represent the robust tick-

pathogen system, it should predict a sufficiently large region of >0 – 5 % prevalence in the plausible parameter space. If the region is too narrow, stability would be unlikely observed in nature. As we increase the systemic transmission rate to the observed level of 0.9 (Ebel and Kramer 2004), the region of >0 – 5 % prevalence becomes larger and occurs at intermediate cofeeding transmission rates (Fig. 8a). The figure suggests that the cofeeding transmission rate in the field must be quite stable at the intermediate level to achieve the robustness. It is conceivable that vertical and systemic transmission rates in the field could be relatively stable and similar to measured values in the laboratory. On the other hand, cofeeding transmission can occur at much lower rates in the field than the measured values from laboratory experiments. In laboratory experiments by Labuda et al. (1997), ticks fed on a mouse in dense clusters (~50 ticks) in glass chambers. In the field, ticks may attach to multiple locations on the host body (eyes, ears, neck, chin, etc) in much sparser clusters (Fig. 9) with or without infected ticks. Grooming activities by the host would make cofeeding in dense clusters even more difficult. Also, cofeeding transmission probably depends on stochastic factors and could be collectively (as a population) quite stable because numerous ticks are feeding on many mice. If these assumptions are reasonable, the model suggests that low, steady prevalence in TBEv could be achieved by small vertical, intermediate cofeeding, and high systemic transmission rates. When cohorts happen not to overlap, this region of the parameter space can lead to zero prevalence. Hence, the set of values is consistent with the explanation that intermittent patterns of TBEv occurrences are due to the “fragile” link between cofeeding larvae and nymphs (Randolph and Rogers 2000).

The elasticity analysis of input parameters can also elucidate some of the

particular routes contributing to the persistence of the pathogen. When cohorts overlap with the vertical transmission rate at 0.001 (Fig. 7a), cofeeding transmission from nymphs to larvae serves as the major route (Fig. 10a). The pathogen is passed from nymphs to larvae via cofeeding, larvae become nymphs with the pathogen retained (i.e., trans-stadial transmission, ε^L) and then pass it to the larvae of the next generation. In this scenario, nymphs become the integral part of the transmission process, which corroborates with the conclusion from Hartemink et al. (2008). With a higher vertical transmission (0.01), in addition to the above route, the importance of the two intra-cohort cofeeding transmission pathways increases (Fig. 10b). Larvae and nymphs infected through these pathways will feedback to other routes, reinforcing the entire cycle. In this scenario, all stage classes play key roles in transmission. When inter-cohort overlap is removed, the larva-nymph cofeeding pathway disappears, and the intra-cohort pathways will maintain the pathogen with increased importance of the survival of the pathogen within ticks (Fig. 10c). It is interesting that, when vertical transmission is at the higher rate, multiple feedback loops support pathogen persistence, which might make persistence more robust to external perturbations.

The two views for TBEv persistence in tick populations

We believe that our results can shed some light on two opposing views regarding TBEv persistence in the European ixodid tick, *I. ricinus*, in the literature. One view is that vertical transmission is negligible and cofeeding transmission between larvae and nymphs is the key mechanism for TBEv persistence (Randolph et al. 1999, 2000). The other view emphasizes the importance of vertical transmission and intra-cohort (i.e.,

larvae – larvae) cofeeding transmission and dismisses inter-cohort cofeeding transmission (Danielová et al. 2002). Vertical and cofeeding transmission pathways are alternative routes where pathogens can be passed from one generation to the next. Our result shows synergistic effects of the two transmission routes with increased prevalence as both increase (Fig. 3c). Our model indicates that which hypothesis is more plausible depends on the assumed value of vertical transmission. It shows pathogen extinction at vertical transmission rates of 0.001 with no cohort overlap, supporting the first view (Fig. 8b). It also shows pathogen persistence at intermediate (> 0.003) vertical transmission rates with no cohort overlap (Fig. 8b). Therefore, our model points out the need for more accurate measurements of vertical transmission rates in the field to evaluate the two propositions.

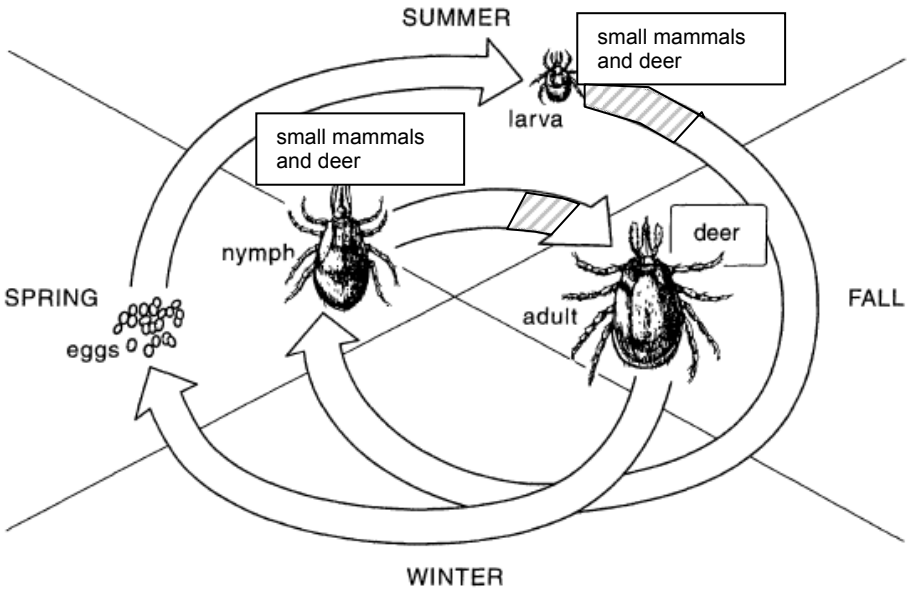


Figure 1. The typical life cycle of the black-legged or deer tick (*Ixodes scapularis*). The shaded areas on the arrows indicate the time period where two cohorts can potentially overlap. Modified from Van Buskirk and Ostfeld (1998).

Figure 2. A stable-stage distribution of the tick population with overlapping cohorts. LUS = susceptible unfed larva, LFS = susceptible fed larva, LUI = infected unfed larva, LFI = infected fed larva, NUS = susceptible unfed nymph, NFS = susceptible fed nymph, NUI = infected unfed nymph, NFI = infected fed nymph, AUS = susceptible unfed adult, AFS = susceptible fed adults, AUI = infected unfed adult, AFI = infected fed adult, S = susceptible host, I = infected host, R = recovered host. The dashed line in the susceptible host figure is the total host population (constant at 50 individuals per ha).

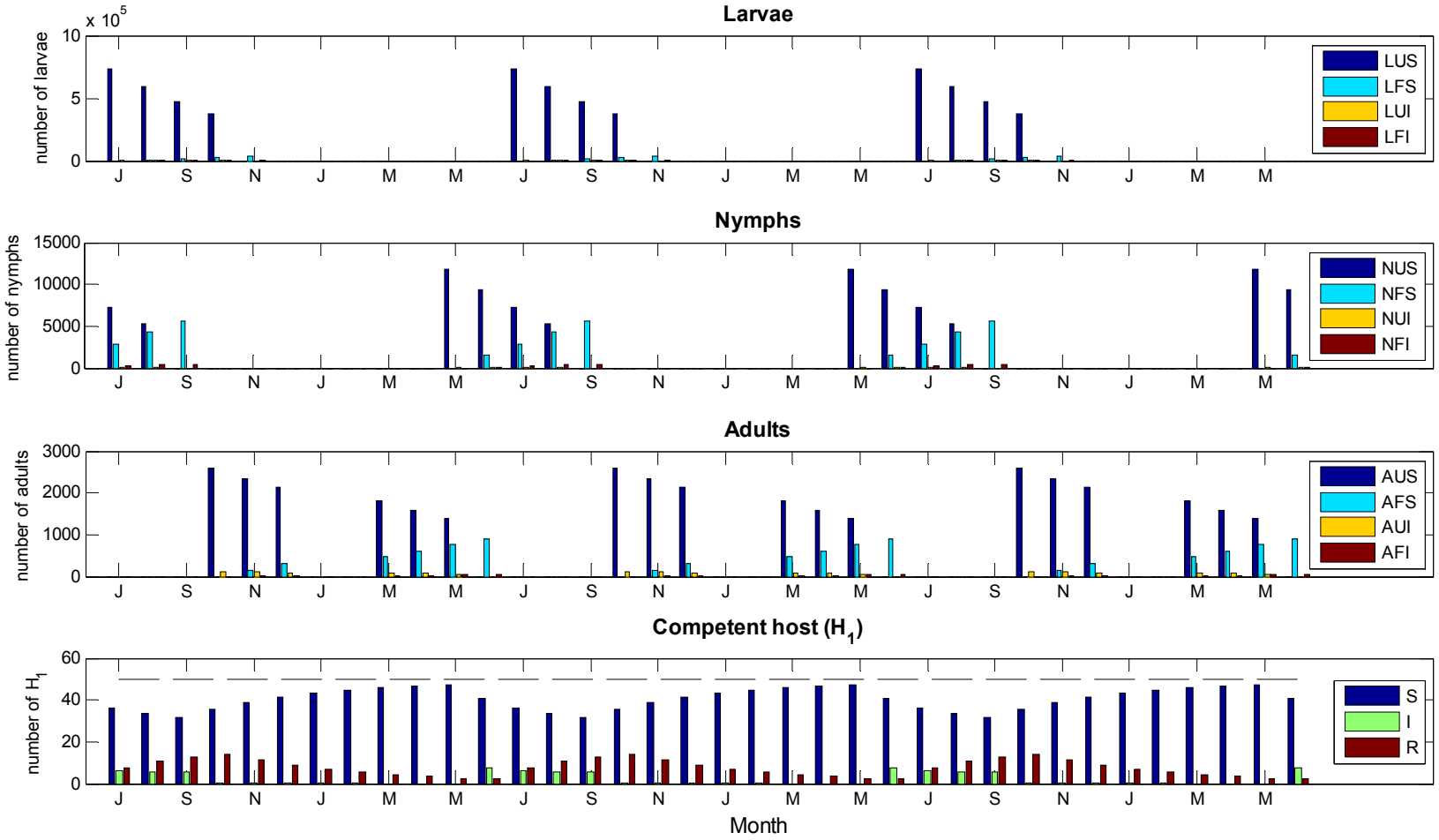


Figure 3: Pathogen prevalence in adult ticks in October when the two cohorts (larvae and nymphs) overlap (the top row) and do not overlap (the bottom row); a, d) without vertical transmission ($\varepsilon^0 = 0$), b, e) without cofeeding transmission (all θ's = 0), and c, f) without systemic transmission (p_1^L and $p_1^N = 0$). The blank color means prevalence = 0. Cofeeding transmission is expressed as the multiples of the baseline rates (0.24 and 0.72).

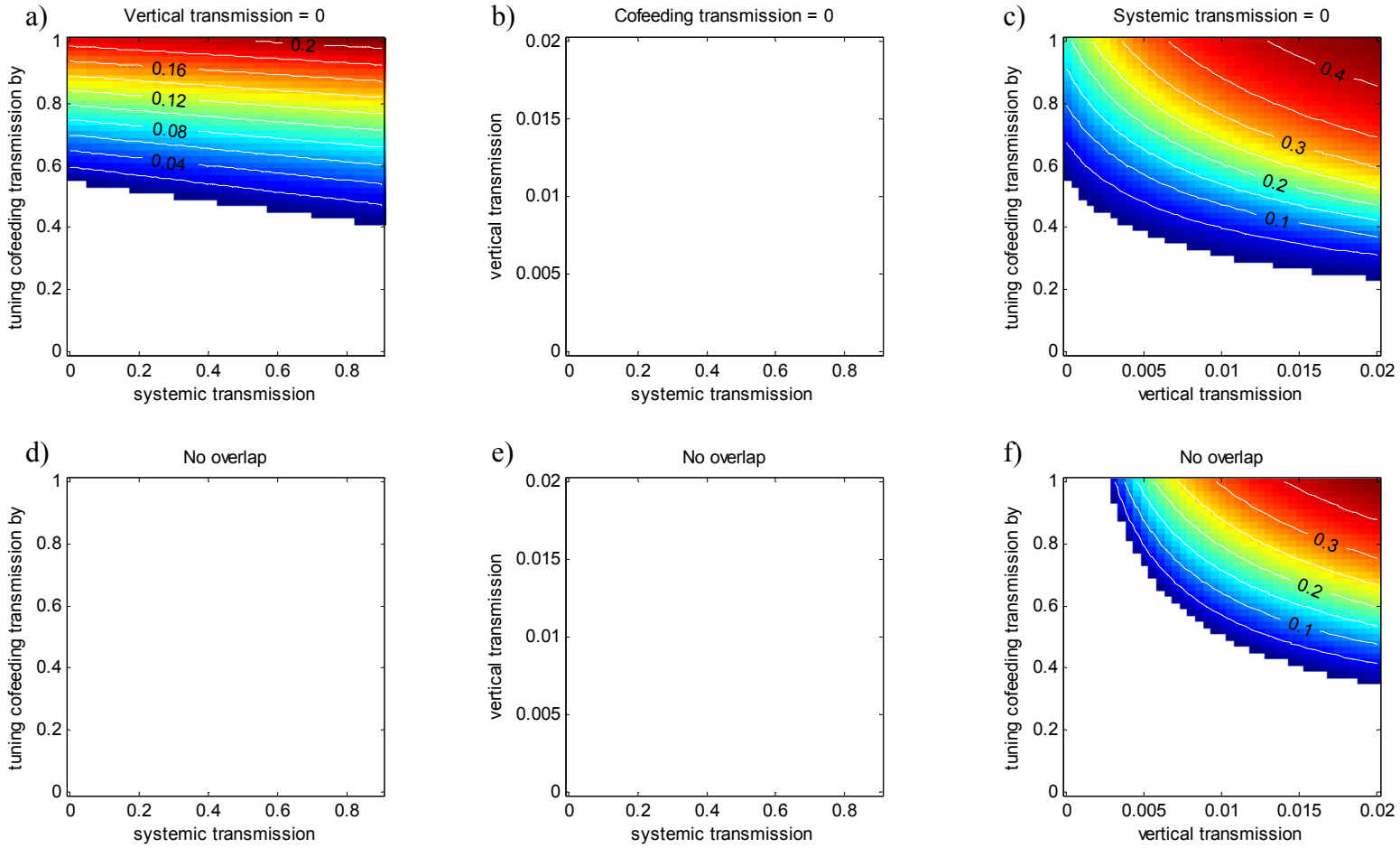


Figure 4: R_0 of the pathogen. See the figure legend for Fig. 3. When $R_0 < 1$, the pathogen would not persist in the population following an initial invasion into a purely susceptible population of ticks and the hosts.

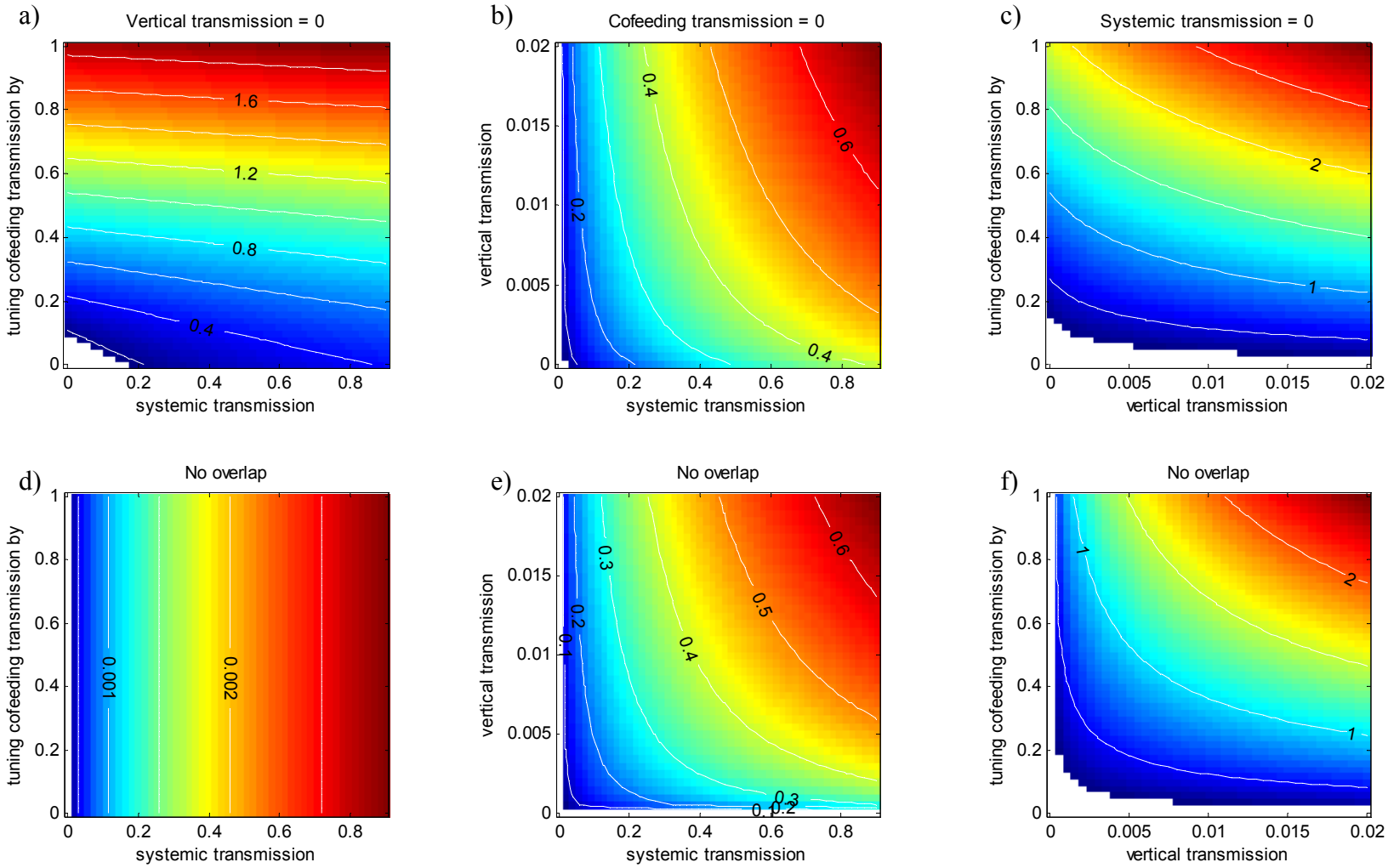


Figure 5: Elasticity (relative importance) values when two cohorts overlap for vertical (left), cofeeding (middle), and systemic transmission (right) with the vertical transmission rate 0.001 (top) and 0.01 (bottom).

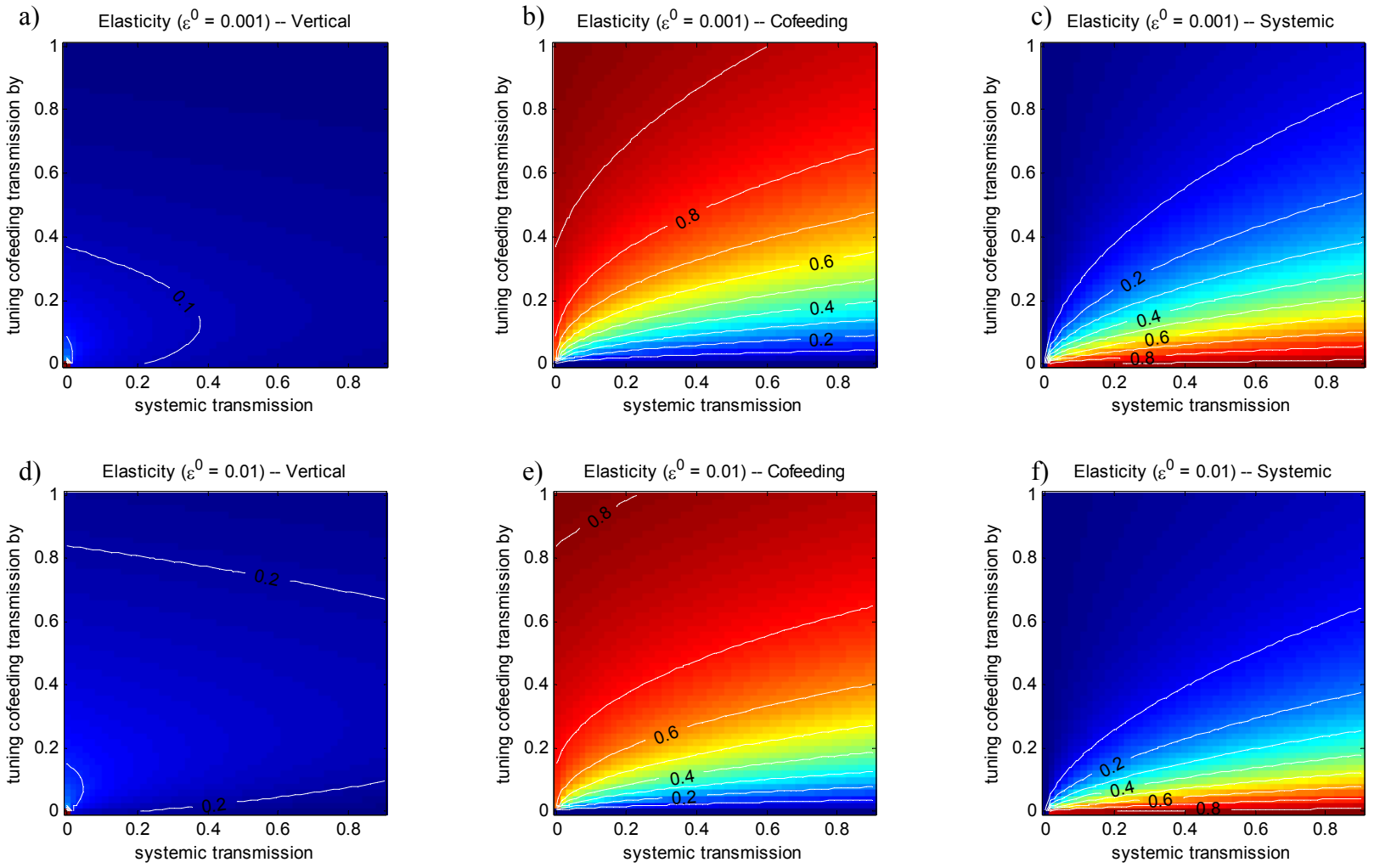


Figure 6. Elasticity (relative importance) values when two cohorts do not overlap for vertical (left), cofeeding (middle), and systemic transmission (right) with the vertical transmission rate 0.001 (top) and 0.01 (bottom).

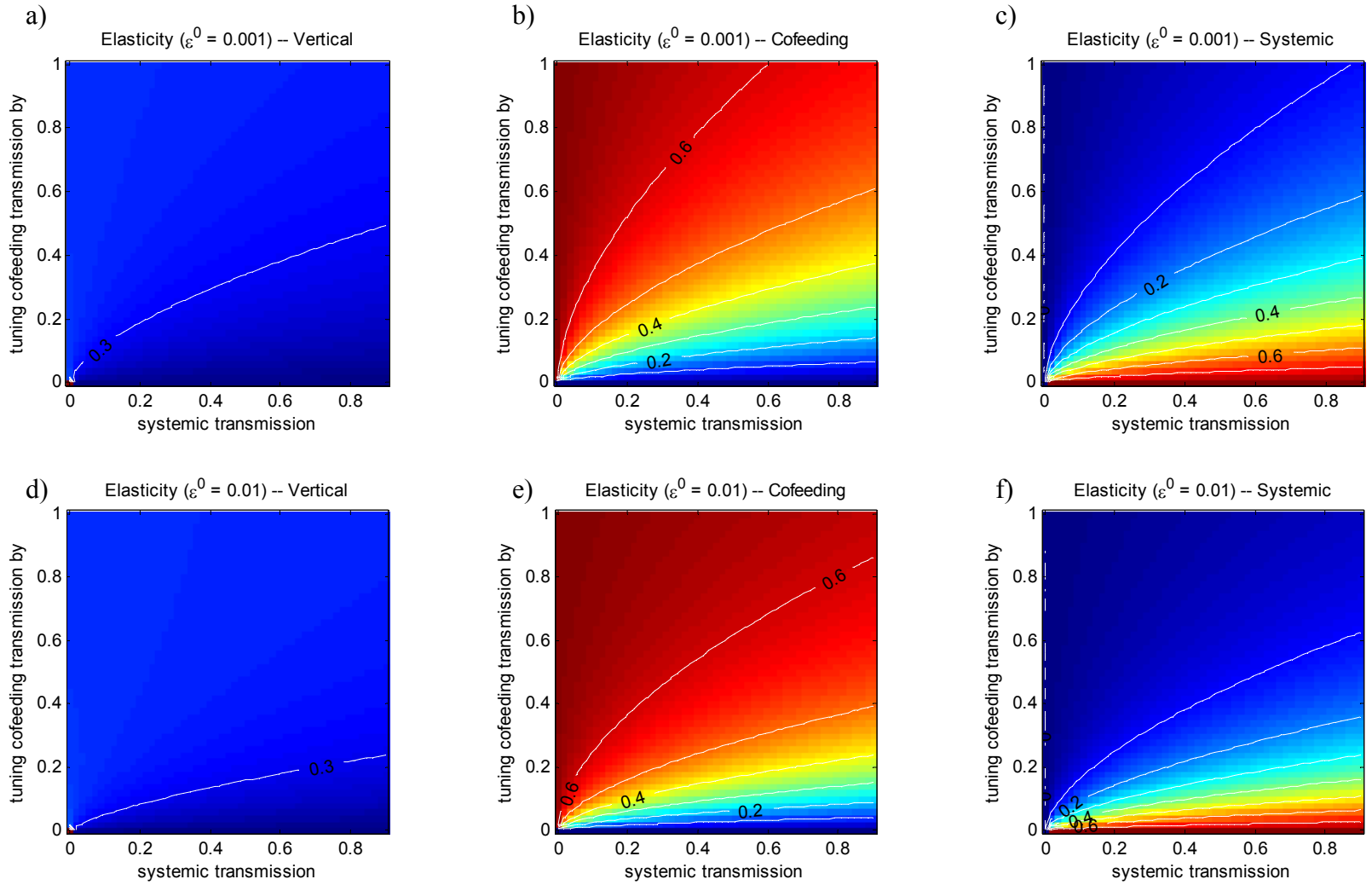
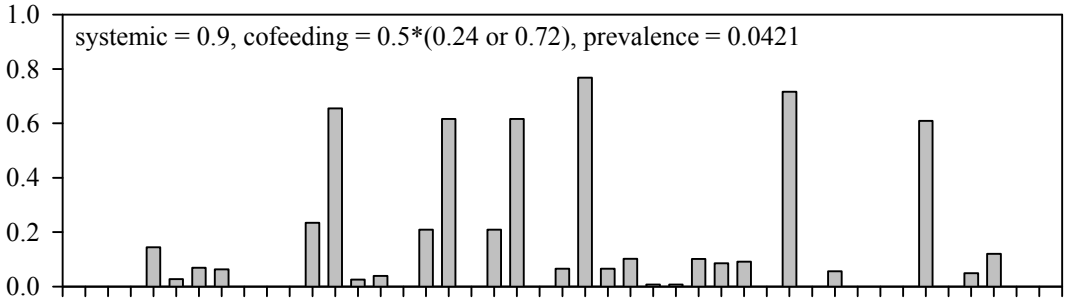
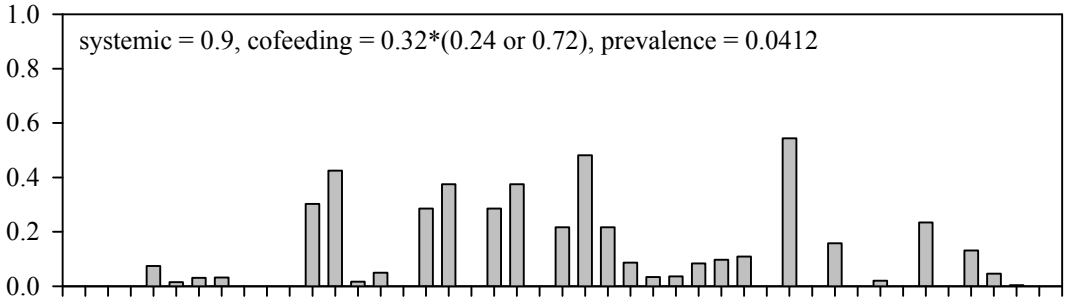


Figure 7. Elasticity values of the input parameters with inter-cohort overlap (a, b) and without (c, d).

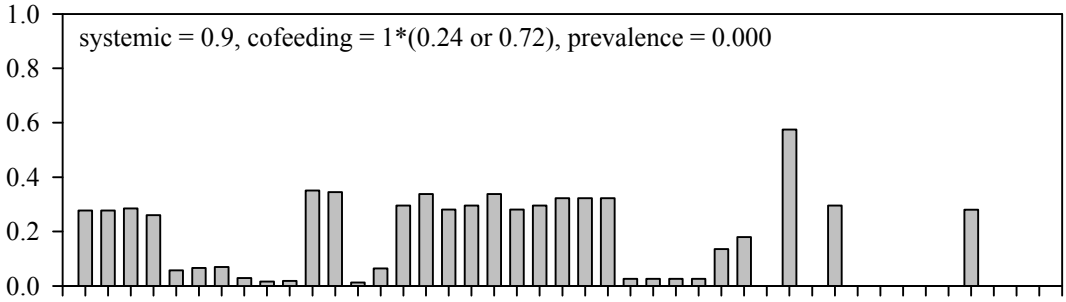
a) With overlap, vertical transmission (ε^0) = 0.001



b) With overlap, vertical transmission (ε^0) = 0.01



c) No overlap, vertical transmission (ε^0) = 0.001



d) No overlap, vertical transmission (ε^0) = 0.01

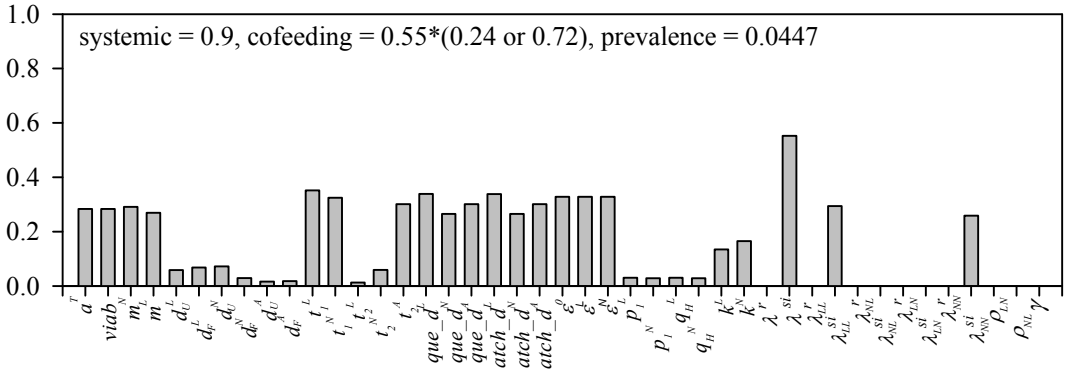


Figure 8. Prevalence of the pathogen with (a) and without (b) inter-cohort overlap and systemic transmission = 0.9. These figures show the regions of prevalence <0 – 5% in the parameter space.

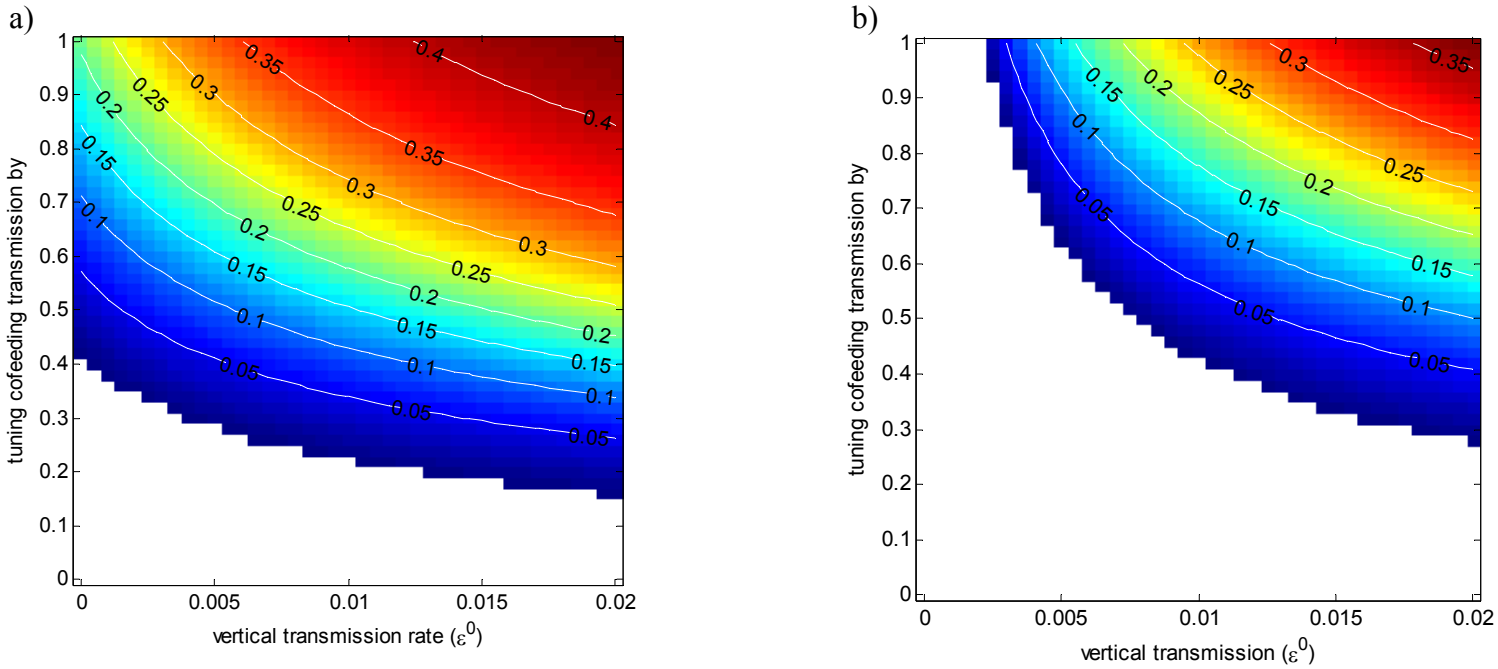
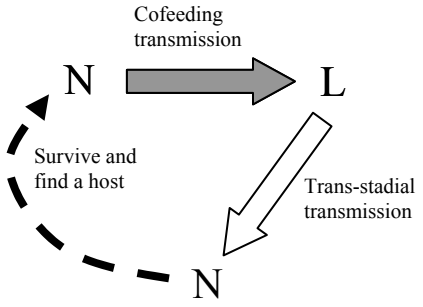


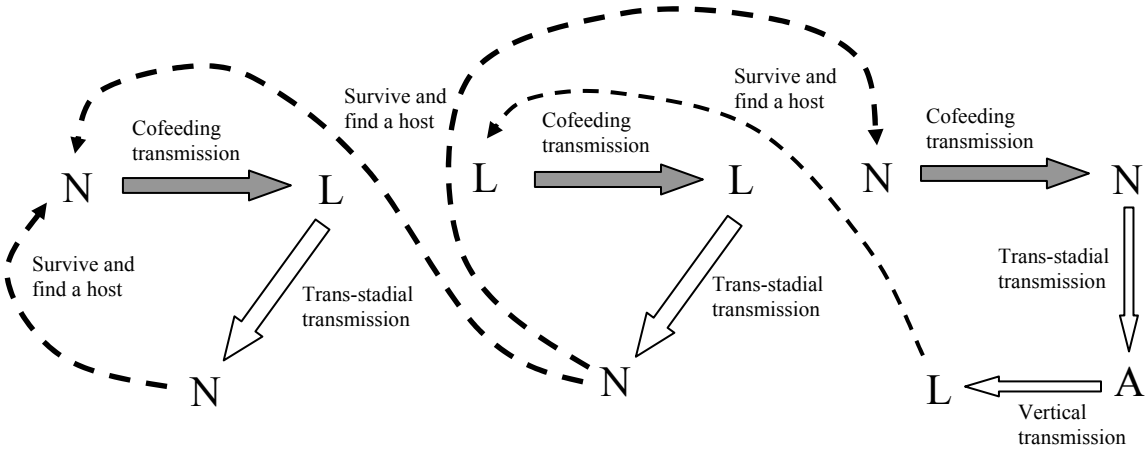
Figure 9. An adult white-footed mouse (*Peromyscus leucopus*) feeding many larval blacklegged ticks (*Ixodes scapularis*). Photo credit: J. L. Brunner. Adopted from Brunner and Ostfeld (2008).

Figure 10. The major transmission pathways inferred from the results of the elasticity analyses. The relative thickness of arrows reflects the magnitude of elasticity qualitatively.

a) With inter-cohort overlap, vertical transmission = 0.001



b) With inter-cohort overlap, vertical transmission = 0.01



c) With no inter-cohort overlap

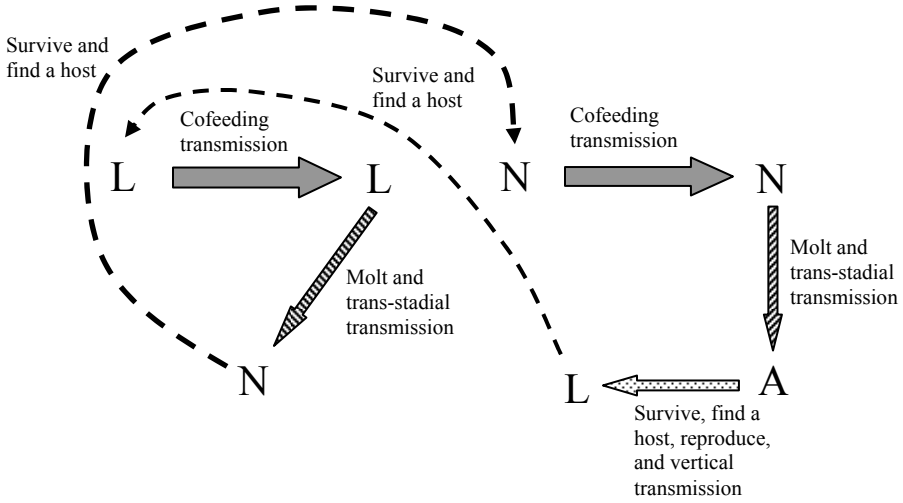


Table 1. Parameter definitions and the values used in the simulation. All the rates are per month. Parameters with an asterisk (*) were varied in simulations (the ranges in brackets).

Parameter	Definition	Value	Source
a_T	Number of eggs laid per female tick	2000	Sandberg et al. 1992, Randolph and Rogers 1997
m^N	Probability of female nymph-to-adult molting	0.5·exp(-0.9)	50/50 sex ratio; Randolph and Rogers 1997, LoGiudice et al. 2003
m^L	Probability of larva-to-nymph molting	exp(-0.09)	Randolph and Rogers 1997
d_U^L	Mortality rate of unfed larvae	$-\log((1-0.0067)\text{^}30)$	Randolph 2004
d_F^L	Mortality rate of fed larvae	$-\log((1-0.00208)\text{^}30)$	Randolph 2004
d_U^N	Mortality rate of unfed nymphs	$-\log((1-0.0021)\text{^}30)$	Randolph 2004
d_F^N	Mortality rate of fed nymphs	$-\log((1-0.0007)\text{^}30)$	Randolph 2004
d_U^A	Mortality rate of unfed adults	$-\log((1-0.00095)\text{^}30)$	Randolph 2004
d_F^A	Mortality rate of fed adults	$-\log((1-0.0006)\text{^}30)$	Randolph 2004
d_H	Mortality rate of host 1 (H_1)	exp(-0.25)	Longevity of mice is about 1 year
t_1^L	Number of larvae on a H_1 individual	27.8	LoGiudice et al. 2003
t_1^N	Number of nymphs on a H_1 individual	5	Ostfeld et al. 1996, Proco 1999, Schmidt et al. 1999
t_1^A	Number of adults on a H_1 individual	0	By assumption
t_2^L	Number of larvae on a H_2 individual	239	LoGiudice et al. 2003
t_2^N	Number of nymphs on a H_2 individual	239	LoGiudice et al. 2003
t_2^A	Number of adults on a H_2 individual	239	LoGiudice et al. 2003
que_d^L	Number of questing days per month of larvae	30	Based on Sandberg et al. 1992
que_d^N	Number of questing days per month of nymphs	30	Based on Sandberg et al. 1992
que_d^A	Number of questing days per month of adults	30	Based on Sandberg et al. 1992

$atch\_d^L$	Number of days larvae remain attached on a host	3	Mather and Spielman 1986, Sandberg et al. 1992
$atch\_d^N$	Number of days nymphs remain attached on a host	5	Mather and Spielman 1986, Sandberg et al. 1992
$atch\_d^A$	Number of days adults remain attached on a host	10	Mather and Spielman 1986, Sandberg et al. 1992
γ	Recovery rate of H_1	exp(-0.3·(30))	By assumption that hosts are viramic only for 2 – 3 days
ε^0	Probability of vertical transmission	0.001*	Costero and Grayson 1996, Danielova et al. 2002
ε^L	Probability of larva-nymph trans-stadial transmission	0.22	Ebel and Kramer 2004
ε^N	Probability of nymph-adult trans-stadial transmission	0.54	Costero and Grayson 1996
p_1^L	Probability of H_1-to-larva systemic transmission	0.9* [0, 0.9]	Ebel and Kramer 2004, Hartemink et al. 2008
p_1^N	Probability of H_1-to-nymph systemic transmission	0.9* [0, 0.9]	Ebel and Kramer 2004, Hartemink et al. 2008
q_H^L	Probability of larva-to-H_1 systemic transmission	0.8	Ebel and Kramer 2004, Hartemink et al. 2008
q_H^N	Probability of nymph-to-H_1 systemic transmission	0.8	Ebel and Kramer 2004, Hartemink et al. 2008
q_H^A	Probability of adult-to-H_1 systemic transmission	0.8	Ebel and Kramer 2004, Hartemink et al. 2008
k^L	Aggregation parameter of the negative binomial distribution for larvae	1.19	Brunner and Ostfeld 2008
k^N	Aggregation parameter of the negative binomial distribution for nymph	0.56	Brunner and Ostfeld 2008
ρ_{LL}	Correlation coefficient of larvae	1	Rosa et al. 2003, Rosa and Pugliese 2007
ρ_{LN}	Correlation coefficient of larvae and nymphs	0.2	Brunner and Ostfeld 2008
ρ_{NN}	Correlation coefficient of	1	Rosà et al. 2003,

	nymphs		Rosà and Pugliese 2007)
θ^r $\left(\theta^r_{LL}, \theta^r_{LN}, \theta^r_{NL}, \theta^r_{NN}\right)$	Probability of cofeeding transmission on a recovered H_1	0.24* [0, 0.24]	Labuda et al. 1997 Note: assumed cofeeding transmission the same between any stages of ticks
θ^{si} $\left(\theta^{si}_{LL}, \theta^{si}_{LN}, \theta^{si}_{NL}, \theta^{si}_{NN}\right)$	Probability of cofeeding transmission on a susceptible or infected H_1	0.72* [0, 0.24]	Labuda et al. 1997 Note: assumed cofeeding transmission the same between any stages of ticks

Table 2. The next generation matrix for the case with cohort overlap. This is a 15 x 15 matrix. The figure shows the blocks of elements which represent one of the transmission pathways. If the block contains a zero, all the elements in the block are zero.

<table>
<tr><th></th><th>Egg</th><th colspan="4">L8 L9 L10 L11</th><th colspan="4">N6 N7 N8 N9</th><th colspan="6">H6 H7 H8 H9 H10 H11</th></tr>
<tr><td>Egg</td><td>vertical</td><td colspan="4">vertical</td><td colspan="4">vertical</td><td colspan="6">0</td></tr>
<tr><td>L8
L9</td><td rowspan="3">cofeeding
Egg → L</td><td colspan="4">cofeeding L → L</td><td colspan="4" rowspan="2">0</td><td colspan="6" rowspan="2">systemic H → L</td></tr>
<tr><td>L10
L11</td><td colspan="4">0</td></tr>
<tr><td>N6
N7
N8
N9</td><td>cofeeding
Egg → N</td><td colspan="4">cofeeding L → N</td><td colspan="4">0</td><td colspan="6">systemic H → N</td></tr>
<tr><td>H6
H7
H8
H9</td><td rowspan="3">systemic
Egg → H</td><td colspan="4">systemic L → H</td><td colspan="4" rowspan="2">0</td><td colspan="6" rowspan="2">0</td></tr>
<tr><td>H10
H11</td><td colspan="4">0</td></tr>
</table>

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Appendix. The model components and equations.

The rate of feeding on any host = $P_f^Z = 1 - \exp\left[-\left(\beta_1^Z H_1 + \beta_2^Z H_2\right)\right]$

where $\beta_h^Z = \dfrac{t_h^Z \cdot que\_d^Z}{Z_U \cdot atch\_d^Z}$, Z = L, N, A, h = 1, 2

L, N, or A corresponds to the larva, nymph, or adult life stage of the tick, and 1 and 2 refers to the host species 1 (H_1) and host species 2 (H_2), respectively.

Let P_{st}, P_{ct} the probability of systemic transmission and cofeeding transmission, respectively;

The rate of feeding but not being infected (*FEED_NOT_INFECTED*^{Z})

$$= P_f^Z \cdot \left(P_{H1^{sr}}^Z \cdot \left(1 - P_{ct}^Z\right) + P_{H1^i}^Z \cdot \left(1 - P_{st}^Z\right) \cdot \left(1 - P_{ct}^Z\right) + P_{H2}^Z\right)$$

The rate of feeding and being infected (*FEED_AND_INFECTED*^{Z})

$$= P_f^Z \cdot \left(P_{H1^{sr}}^Z \cdot P_{ct}^Z + P_{H1^i}^Z \cdot \left(P_{ct}^Z + P_{st}^Z \cdot \left(1 - P_{ct}^Z\right)\right)\right)$$

The rate of cofeeding transmission from a larva to a larva

$$= P_{LL} = \left[1 - \exp\left(-\frac{L_{Q,t}^i P_f^L \left(\lambda_{LL}^r P_{H1^r}^L + \lambda_{LL}^{si} P_{H1^s + H1^i}^L\right)}{H_1}\right)\right]$$

The rate of cofeeding transmission from a nymph to a larva

$$= P_{LN} = \left[1 - \exp\left(-\frac{N_{Q,t}^i P_f^N \left(\lambda_{LN}^r P_{H1^r}^N + \lambda_{LN}^{si} P_{H1^s + H1^i}^N\right)}{H_1}\right)\right]$$

The rate of cofeeding transmission from a nymph to a nymph

$$= P_{NN} = \left[1 - \exp\left(-\frac{N_{Q,t}^i P_f^N \left(\lambda_{NN}^r P_{H1^r}^N + \lambda_{NN}^{si} P_{H1^s + H1^i}^N\right)}{H_1}\right)\right]$$

The rate of cofeeding transmission from a larva to a nymph

$$= P_{NL} = \left[1 - \exp\left(-\frac{L_{Q,t}^i P_f^L \left(\lambda_{NL}^r P_{H1^r}^L + \lambda_{NL}^{si} P_{H1^s + H1^i}^L\right)}{H_1}\right)\right]$$

where,

$$\lambda_{LL}^{r} = \theta_{LL}^{r}\left(1+\frac{\rho_{LL}}{\sqrt{k^{L}k^{L}}}\right),\ \lambda_{LL}^{si} = \theta_{LL}^{si}\left(1+\frac{\rho_{LL}}{\sqrt{k^{L}k^{L}}}\right)$$

$$\lambda_{LN}^{r} = \theta_{LN}^{r}\left(1+\frac{\rho_{LN}}{\sqrt{k^{L}k^{N}}}\right),\ \lambda_{LN}^{si} = \theta_{LN}^{si}\left(1+\frac{\rho_{LN}}{\sqrt{k^{L}k^{N}}}\right)$$

$$\lambda_{NN}^{r} = \theta_{NN}^{r}\left(1+\frac{\rho_{NN}}{\sqrt{k^{N}k^{N}}}\right),\ \lambda_{NN}^{si} = \theta_{NN}^{si}\left(1+\frac{\rho_{NN}}{\sqrt{k^{N}k^{N}}}\right)$$

$$\lambda_{NL}^{r} = \theta_{NL}^{r}\left(1+\frac{\rho_{NL}}{\sqrt{k^{N}k^{L}}}\right),\ \lambda_{NL}^{si} = \theta_{NL}^{si}\left(1+\frac{\rho_{NL}}{\sqrt{k^{N}k^{L}}}\right)$$

represent the aggregation-corrected cofeeding transmission rates on recovered (*r*) or susceptible/infected (*si*) hosts. LL = from a larva to a larva, LN = from a nymph to a larva, NN = from a nymph to a nymph, NL = from a larva to a nymph.

and,

$$P_{H1}^{Z} = \text{Proportion of } H_1 \text{ hosts encountered} = \frac{\beta_1^{Z} H_1}{\beta_1^{Z} H_1 + \beta_2^{Z} H_2}$$

$$P_{H2}^{Z} = \text{Proportion of } H_2 \text{ hosts encountered} = \frac{\beta_2^{Z} H_2}{\beta_1^{Z} H_1 + \beta_2^{Z} H_2}$$

$$P_{H1^r}^{Z} = \text{Proportion of } H_1^r \text{ hosts encountered} = \frac{\beta_1^{Z} H_1^r}{\beta_1^{Z} H_1 + \beta_2^{Z} H_2}$$

$$P_{H1^s+H1^i}^{Z} = \text{Proportion of } H_1^s \text{ or } H_1^i \text{ hosts encountered} = \frac{\beta_1^{Z}\left(H_1^s + H_1^i\right)}{\beta_1^{Z} H_1 + \beta_2^{Z} H_2}$$

$$P_{H1^i}^{Z} = \text{Proportion of } H_1^i \text{ hosts encountered} = \frac{\beta_1^{Z} H_1^i}{\beta_1^{Z} H_1 + \beta_2^{Z} H_2}$$

$$P_{H1^s+H1^r}^{Z} = \text{Proportion of } H_1^s \text{ or } H_1^r \text{ hosts encountered} = \frac{\beta_1^{Z}\left(H_1^s + H_1^r\right)}{\beta_1^{Z} H_1 + \beta_2^{Z} H_2}$$

Then, the rate of cofeeding transmission of larvae

$$= P_{LL} + P_{LN}\left(1 - P_{LL}\right) = P_{LN} + P_{LL}\left(1 - P_{LN}\right)$$

$$= \left[1 - \exp\left(-\frac{L^i_{Q,t} P^L_f \left(\lambda^r_{LL} P^L_{H1^r} + \lambda^{si}_{LL} P^L_{H1^s + H1^i}\right)}{H_1}\right)\right]$$

$$+ \left[1 - \exp\left(-\frac{N^i_{Q,t} P^N_f \left(\lambda^r_{LN} P^N_{H1^r} + \lambda^{si}_{LN} P^N_{H1^s + H1^i}\right)}{H_1}\right)\right]$$

$$\cdot \exp\left(-\frac{L^i_{Q,t} P^L_f \left(\lambda^r_{LL} P^L_{H1^r} + \lambda^{si}_{LL} P^L_{H1^s + H1^i}\right)}{H_1}\right)$$

That of nymphs

$$= P_{NN} + P_{NL}\left(1 - P_{NN}\right) = P_{NL} + P_{NN}\left(1 - P_{NL}\right)$$

$$= \left[1 - \exp\left(-\frac{N^i_{Q,t} P^N_f \left(\lambda^r_{NN} P^N_{H1^r} + \lambda^{si}_{NN} P^N_{H1^s + H1^i}\right)}{H_1}\right)\right]$$

$$+ \left[1 - \exp\left(-\frac{L^i_{Q,t} P^L_f \left(\lambda^r_{NL} P^L_{H1^r} + \lambda^{si}_{NL} P^L_{H1^s + H1^i}\right)}{H_1}\right)\right]$$

$$\cdot \exp\left(-\frac{N^i_{Q,t} P^N_f \left(\lambda^r_{NN} P^N_{H1^r} + \lambda^{si}_{NN} P^N_{H1^s + H1^i}\right)}{H_1}\right)$$

These rates are zero for adult ticks.

<u>The monthly equations of the ticks (with cohort overlap)</u>

July

$$L^s_{U,t+1} = a_T \cdot viab \cdot \left(A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)\right) + \left(1 - \varepsilon^0\right) a_T \cdot viab \cdot \left(A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)\right)$$

$$L^s_{F,t+1} = 0$$

$$L^i_{U,t+1} = a_T \cdot viab \cdot \varepsilon^0 \left(A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)\right)$$

$$L^i_{F,t+1} = 0$$

$$N^s_{U,t+1} = N^s_{U,t} \cdot \left(1 - P^N_f\right) \cdot \exp\left(-d_U{}^N\right)$$

$$N^s_{F,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right) \cdot FEED\_NOT\_INFECTED^N + N^s_{F,t} \cdot \exp\left(-d_F{}^N\right)$$

$$N^i_{U,t+1} = N^i_{U,t} \cdot \left(1 - P^N_f\right) \cdot \exp\left(-d_U{}^N\right)$$

$$N^i_{F,t+1} = N^i_{U,t} \cdot P_f^N \cdot \exp\left(-d_U{}^N\right) + N^s_{U,t} \cdot FEED\_AND\_INFECTED^N \cdot \exp\left(-d_U{}^N\right)$$
$$+ N^i_{F,t} \cdot \exp\left(-d_F{}^N\right)$$
$$A_{t+1} = 0$$

August

$$L^s_{U,t+1} = L^s_{U,t} \cdot \left(1 - P_f^L\right) \cdot \exp\left(-d_U{}^L\right)$$
$$L^s_{F,t+1} = L^s_{U,t} \cdot \exp\left(-d_U{}^L\right) \cdot FEED\_NOT\_INFECTED^L$$
$$L^i_{U,t+1} = L^i_{U,t} \cdot \left(1 - P_f^L\right) \cdot \exp\left(-d_U{}^L\right)$$
$$L^i_{F,t+1} = L^i_{U,t} \cdot P_f^L \cdot \exp\left(-d_U{}^L\right) + L^s_{U,t} \cdot FEED\_AND\_INFECTED^L \cdot \exp\left(-d_U{}^L\right)$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \left(1 - P_f^N\right) \cdot \exp\left(-d_U{}^N\right)$$
$$N^s_{F,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right) \cdot FEED\_NOT\_INFECTED^N + N^s_{F,t} \cdot \exp\left(-d_F{}^N\right)$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \left(1 - P_f^N\right) \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = N^i_{U,t} \cdot P_f^N \cdot \exp\left(-d_U{}^N\right) + N^s_{U,t} \cdot FEED\_AND\_INFECTED^N$$
$$\cdot \exp\left(-d_U{}^N\right) + N^i_{F,t} \cdot \exp\left(-d_F{}^N\right)$$
$$A_{t+1} = 0$$

September

$$L^s_{U,t+1} = L^s_{U,t} \cdot \left(1 - P_f^L\right) \cdot \exp\left(-d_U{}^L\right)$$
$$L^s_{F,t+1} = L^s_{U,t} \cdot \exp\left(-d_U{}^L\right) \cdot FEED\_NOT\_INFECTED^L + L^s_{F,t} \cdot \exp\left(-d_F{}^L\right)$$
$$L^i_{U,t+1} = L^i_{U,t} \cdot \left(1 - P_f^L\right) \cdot \exp\left(-d_U{}^L\right)$$
$$L^i_{F,t+1} = L^i_{U,t} \cdot P_f^L \cdot \exp\left(-d_U{}^L\right) + L^s_{U,t} \cdot FEED\_AND\_INFECTED^L \cdot \exp\left(-d_U{}^L\right)$$
$$+ L^i_{F,t} \cdot \exp\left(-d_F{}^L\right)$$
$$N^s_{Q,t+1} = 0$$
$$N^s_{F,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right) \cdot FEED\_NOT\_INFECTED^N + N^s_{F,t} \cdot \exp\left(-d_F{}^N\right)$$
$$N^i_{Q,t+1} = 0$$
$$N^i_{F,t+1} = N^i_{U,t} \cdot P_f^N \cdot \exp\left(-d_U{}^N\right) + N^s_{U,t} \cdot FEED\_AND\_INFECTED^N \cdot \exp\left(-d_U{}^N\right)$$
$$+ N^i_{F,t} \cdot \exp\left(-d_F{}^N\right)$$
$$A_{t+1} = 0$$

October

$$L^s_{U,t+1} = L^s_{U,t} \cdot \left(1 - P^L_f\right) \cdot \exp\left(-{d_U}^L\right)$$
$$L^s_{F,t+1} = L^s_{U,t} \cdot \exp\left(-{d_U}^L\right) \cdot FEED\_NOT\_INFECTED^L + L^s_{F,t} \cdot \exp\left(-{d_F}^L\right)$$
$$L^i_{U,t+1} = L^i_{U,t} \cdot \left(1 - P^L_f\right) \cdot \exp\left(-{d_U}^L\right)$$
$$L^i_{F,t+1} = L^i_{U,t} \cdot P^L_f \cdot \exp\left(-{d_U}^L\right) + L^s_{U,t} \cdot FEED\_AND\_INFECTED^L \cdot \exp\left(-{d_U}^L\right)$$
$$+ L^i_{F,t} \cdot \exp\left(-{d_F}^L\right)$$
$$N_{t+1} = 0$$
$$A^s_{U,t+1} = {m^N} \cdot \left(N^s_{F,t} \cdot \exp\left(-{d_F}^N\right)\right) + \left(1 - \varepsilon^N\right) \cdot {m^N} \cdot \left(N^i_{F,t} \cdot \exp\left(-{d_F}^N\right)\right)$$
$$A^s_{F,t+1} = 0$$
$$A^i_{U,t+1} = \varepsilon^N \cdot {m^N} \cdot \left(N^i_{F,t} \cdot \exp\left(-{d_F}^N\right)\right)$$
$$A^i_{F,t+1} = 0$$

November

$$L^s_{U,t+1} = 0$$
$$L^s_{F,t+1} = L^s_{U,t} \cdot \exp\left(-{d_U}^L\right) \cdot FEED\_NOT\_INFECTED^L + L^s_{F,t} \cdot \exp\left(-{d_F}^L\right)$$
$$L^i_{U,t+1} = 0$$
$$L^i_{F,t+1} = L^i_{U,t} \cdot P^L_f \cdot \exp\left(-{d_U}^L\right) + L^s_{U,t} \cdot FEED\_AND\_INFECTED^L \cdot \exp\left(-{d_U}^L\right)$$
$$+ L^i_{F,t} \cdot \exp\left(-{d_F}^L\right)$$
$$N_{t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-{d_U}^A\right)$$
$$A^s_{F,t+1} = A^s_{U,t} \cdot \exp\left(-{d_U}^A\right) \cdot FEED\_NOT\_INFECTED^A$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-{d_U}^A\right)$$
$$A^i_{F,t+1} = A^i_{U,t} \cdot P^A_f \cdot \exp\left(-{d_U}^A\right) + A^s_{U,t} \cdot FEED\_AND\_INFECTED^A \cdot \exp\left(-{d_U}^A\right)$$

December

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = {m^L} \cdot L^s_{F,t} \cdot \exp\left(-{d_F}^L\right) + \left(1 - \varepsilon^L\right) \cdot {m^L} \cdot L^i_{F,t} \cdot \exp\left(-{d_F}^L\right)$$
$$N^s_{F,t+1} = 0$$
$$N^i_{U,t+1} = \varepsilon^L \cdot {m^L} \cdot L^i_{F,t} \cdot \exp\left(-{d_U}^L\right)$$
$$N^i_{F,t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-{d_U}^A\right)$$

$$A^s_{F,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right) \cdot FEED\_NOT\_INFECTED^A + A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \left(1 - P_f^A\right) \cdot \exp\left(-d_U{}^A\right)$$
$$A^i_{F,t+1} = A^i_{U,t} \cdot P_f^A \cdot \exp\left(-d_U{}^A\right) + A^s_{U,t} \cdot FEED\_AND\_INFECTED^A \cdot \exp\left(-d_U{}^A\right)$$
$$+ A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

January

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^s_{F,t+1} = 0$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \left(1 - P_f^A\right) \cdot \exp\left(-d_U{}^A\right)$$
$$A^s_{F,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right) \cdot FEED\_NOT\_INFECTED^A + A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \left(1 - P_f^A\right) \cdot \exp\left(-d_U{}^A\right)$$
$$A^i_{F,t+1} = A^i_{U,t} \cdot P_f^A \cdot \exp\left(-d_U{}^A\right) + A^s_{U,t} \cdot FEED\_AND\_INFECTED^A \cdot \exp\left(-d_U{}^A\right)$$
$$+ A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

February

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^s_{F,t+1} = 0$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right)$$
$$A^s_{F,t+1} = A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \exp\left(-d_U{}^A\right)$$
$$A^i_{F,t+1} = A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

March

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right)$$

$$N^s_{F,t+1} = 0$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right)$$
$$A^s_{F,t+1} = A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \exp\left(-d_U{}^A\right)$$
$$A^i_{F,t+1} = A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

April

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^s_{F,t+1} = 0$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-d_U{}^A\right)$$
$$A^s_{F,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right) \cdot FEED\_NOT\_INFECTED^A + A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-d_U{}^A\right)$$
$$A^i_{F,t+1} = A^i_{U,t} \cdot P^A_f \cdot \exp\left(-d_U{}^A\right) + A^s_{U,t} \cdot FEED\_AND\_INFECTED^A \cdot \exp\left(-d_U{}^A\right)$$
$$+ A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

May

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^s_{F,t+1} = 0$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = 0$$
$$A^s_{U,t+1} = A^s_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-d_U{}^A\right)$$
$$A^s_{F,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right) \cdot FEED\_NOT\_INFECTED^A + A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = A^i_{U,t} \cdot \left(1 - P^A_f\right) \cdot \exp\left(-d_U{}^A\right)$$

$$A^i_{F,t+1} = A^i_{U,t} \cdot P_f^A \cdot \exp\left(-d_U{}^A\right) + A^s_{U,t} \cdot FEED\_AND\_INFECTED^A \cdot \exp\left(-d_U{}^A\right)$$
$$+ A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

June

$$L_{t+1} = 0$$
$$N^s_{U,t+1} = N^s_{U,t} \cdot \left(1 - P_f^N\right) \cdot \exp\left(-d_U{}^N\right)$$
$$N^s_{F,t+1} = N^s_{U,t} \cdot \exp\left(-d_U{}^N\right) \cdot FEED\_NOT\_INFECTED^N$$
$$N^i_{U,t+1} = N^i_{U,t} \cdot \left(1 - P_f^N\right) \cdot \exp\left(-d_U{}^N\right)$$
$$N^i_{F,t+1} = N^i_{U,t} \cdot P_f^N \cdot \exp\left(-d_U{}^N\right) + N^s_{U,t} \cdot FEED\_AND\_INFECTED^N \cdot \exp\left(-d_U{}^N\right)$$
$$A^s_{U,t+1} = 0$$
$$A^s_{F,t+1} = A^s_{U,t} \cdot \exp\left(-d_U{}^A\right) \cdot FEED\_NOT\_INFECTED^A + A^s_{F,t} \cdot \exp\left(-d_F{}^A\right)$$
$$A^i_{U,t+1} = 0$$
$$A^i_{F,t+1} = A^i_{U,t} \cdot P_f^A \cdot \exp\left(-d_U{}^A\right) + A^s_{U,t} \cdot FEED\_AND\_INFECTED^A \cdot \exp\left(-d_U{}^A\right)$$
$$+ A^i_{F,t} \cdot \exp\left(-d_F{}^A\right)$$

z

<u>The host equations</u>

$$H^s_{1,t+1} = a_H \cdot H^{all}_{1,t} + H^s_{1,t} \cdot \exp\left(-d^H\right) \cdot \exp\left\{-\left(q^L_H \beta^L_1 L^i_{Q,t} + q^N_H \beta^N_1 N^i_{Q,t} + q^A_H \beta^A_1 A^i_{Q,t}\right)\right\}$$

$$H^i_{1,t+1} = H^s_{1,t} \cdot \left(1 - \exp\left\{-\left(q^L_H \beta^L_1 L^i_{Q,t} + q^N_H \beta^N_1 N^i_{Q,t} + q^A_H \beta^A_1 A^i_{Q,t}\right)\right\}\right) \cdot \exp\left(-d^H\right)$$
$$+ H^i_{1,t} \cdot \exp\left(-d^H\right) \cdot \exp(-\gamma)$$
$$H^r_{1,t+1} = H^i_{1,t} \cdot \left(1 - \exp(-\gamma)\right) \cdot \exp\left(-d^H\right) + H^r_{1,t} \cdot \exp\left(-d^H\right)$$

Since the competent hosts are infective only for 3 days, only 10th of $H^i_{1,t}$ is actually infective in any given time. The rest of $H^i_{1,t}$ were equally partitioned into $H^s_{1,t}$ and $H^r_{1,t}$