



A simple model for the establishment of tick-borne pathogens of *Ixodes scapularis*: A global sensitivity analysis of R_0



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AUTHOR HIGHLIGHTS

- We take advantage of a recent breakthrough in defining R_0 for tick-borne infections.
- A global sensitivity analysis is conducted for a simple R_0 model for *B. burgdorferi*.
- R_0 is sensitive to the survival of fed larvae but not tick abundance.
- R_0 is sensitive to the transmission efficiency from mammalian hosts to larval ticks.
- We hence obtain insight into drivers of emergence and approaches to control.

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ABSTRACT

The basic reproduction number of a pathogen, R_0 , determines whether a pathogen will spread ($R_0 > 1$), when introduced into a fully susceptible population or fade out ($R_0 < 1$), because infected hosts do not, on average, replace themselves. In this paper we develop a simple mechanistic model for the basic reproduction number for a group of tick-borne pathogens that wholly, or almost wholly, depend on horizontal transmission to and from vertebrate hosts. This group includes the causative agent of Lyme disease, *Borrelia burgdorferi*, and the causative agent of human babesiosis, *Babesia microti*, for which transmission between co-feeding ticks and vertical transmission from adult female ticks are both negligible. The model has only 19 parameters, all of which have a clear biological interpretation and can be estimated from laboratory or field data. The model takes into account the transmission efficiency from the vertebrate host as a function of the days since infection, in part because of the potential for this dynamic to interact with tick phenology, which is also included in the model. This sets the model apart from previous, similar models for R_0 for tick-borne pathogens. We then define parameter ranges for the 19 parameters using estimates from the literature, as well as laboratory and field data, and perform a global sensitivity analysis of the model. This enables us to rank the importance of the parameters in terms of their contribution to the observed variation in R_0 . We conclude that the transmission efficiency from the vertebrate host to *Ixodes scapularis* ticks, the survival rate of *Ixodes scapularis* from fed larva to feeding nymph, and the fraction of nymphs finding a competent host, are the most influential factors for R_0 . This contrasts with other vector borne pathogens where it is usually the abundance of the vector or host, or the vector-to-host ratio, that determine conditions for emergence. These results are a step towards a better understanding of the geographical expansion of currently emerging horizontally transmitted tick-borne pathogens such as *Babesia microti*, as well as providing a firmer scientific basis for targeted use of acaricide or the application of wildlife vaccines that are currently in development.

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1. Introduction

The basic reproduction number, R_0 , is a key concept in epidemiology with $R_0 = 1$ providing a threshold condition that determines whether a pathogen will spread or fade out. The magnitude

of R_0 is also a measure of the risk of an epidemic (Heffernan et al., 2005) and indicates the level of effort needed to control or prevent an epidemic. In single host systems, R_0 is the expected number of secondary cases produced by one infectious individual in a fully susceptible population; it typically depends on the infectious period, the probability of transmission and the contact rate among individuals (Dietz, 1993). The definition of R_0 for multi-host disease systems is less straightforward because it must somehow average over the various host types (representing, for example,

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different species in the system that can be infected and infectious) to obtain a single number. Furthermore, in multi-host disease systems there are often multiple transmission routes. These issues were resolved by the next-generation matrix approach (Diekmann et al., 1990).

Tick-borne diseases are examples of multi-host disease systems and account for the majority of vector-borne diseases in the United States. Of particular importance are those diseases transmitted by *Ixodes scapularis*, which is undergoing a process of range expansion in the northeastern and upper midwestern United States (White et al., 1991; Diuk-Wasser et al., 2010). Coincident with this range expansion has been the emergence of at least six new zoonotic diseases of humans caused by an array of microbial agents: *Borrelia burgdorferi* (Lyme borreliosis), *Babesia microti* (human babesiosis), *Anaplasma phagocytophilum* (human anaplasmosis), deer tick *Flavivirus* (deer tick encephalitis and Powassan encephalitis), *Borrelia miyamotoi* (*B. miyamotoi* borreliosis), and an *Ehrlichia muris*-like agent (deer tick ehrlichiosis). *Borrelia burgdorferi*, the causative agent of Lyme disease, is by far the most common cause of illness from a tick bite. In the United States cases primarily occur in the Northeast and Upper Midwest (Pepin et al., 2012). Vertebrates, particularly white-footed mice (*Peromyscus leucopus*), are hosts to the larval and nymphal life stages of the black-legged tick (*Ixodes scapularis*), which are the main carriers of these pathogens (Mather et al., 1989; Piesman and Spielman, 1982).

Our model is based on a next-generation matrix approach for tick-borne pathogens (Hartemink et al., 2008) and an extension which included tick seasonal activity patterns (phenology) (Davis and Bent, 2011). Davis and Bent (2011) used loop analysis to establish that for three of the pathogens they investigated – *Borrelia burgdorferi*, *Babesia microti* and *Anaplasma phagocytophilum* – it was just one loop in the transmission graph, involving only two of the host types, that accounts for almost all transmission of the pathogen and generation of new infected hosts. The basis for this simplification is that non-systemic transmission between co-feeding ticks and transovarial transmission from an adult female to her eggs are both either absent or negligible for *Borrelia burgdorferi*, *Babesia microti* and *Anaplasma phagocytophilum* (Piesman and Hopp, 2001; Spielman et al., 1985; Gray et al., 2002; Rollend et al., 2012). This dramatically reduces the number of parameters required to estimate R_0 and, hence, reduces the number of parameter ranges required to define a parameter space over which one can conduct a global sensitivity analysis. We emphasize though, that for other important tick-borne disease systems such as tick-borne encephalitis virus in Europe, the focus on horizontal transmission alone is not at all appropriate and the simplification does not apply (see Davis and Bent, 2011).

While the model here is based on a simplification we also include additional complexity by including infection trajectories in the vertebrate host. Such trajectories plot the efficiency of transmission, from vertebrate host to larval ticks, as a function of the time since infection, and are derived from intensive laboratory work. The trajectories are interesting to include because of the observed variation between pathogens, and between strains, and because of the potential for the dynamics of the trajectories to interact with the tick phenology.

The resulting model is a surprisingly simple expression for R_0 with far fewer parameters compared to those in agent-based or individual based models that have previously been proposed for tick-borne pathogens (see Ogden et al., 2007; Schaubert and Ostfeld, 2002 for examples), or compared to the full R_0 model for tick-borne pathogens (Davis and Bent, 2011). We focus on *Borrelia burgdorferi* in a white-footed mouse only model, which allows us to take full advantage of data arising from laboratory experiments such as those of Derdákóvá et al. (2004) and

Hanincová et al. (2008) and from field work conducted in Connecticut, USA (Diuk-Wasser, unpublished data), to provide meaningful ranges for the parameters. To account for larval ticks feeding on hosts other than white-footed mice in the vertebrate community, we include a parameter for the probability of finding a competent host.

A model for R_0 provides a method to make site-specific or region-specific predictions about whether the pathogen is likely to emerge. Such a model may also be used to explicitly identify threshold targets to stop emergence, even when the method of control affects just one of the host types (Roberts and Heesterbeek, 2003). A global sensitivity analysis of an R_0 model can also inform as to which parameters R_0 is most sensitive to and hence it may shed light on the most effective method for control. The most common methods currently used to reduce human exposure to tick-borne pathogens are spray repellents and protective clothing. Other control approaches deal directly with the vertebrate host system. These include lowering the transmission rate through antibiotic treatment of vertebrate host species (Dolan et al., 2011), vaccination of the main vertebrate host (Tsao et al., 2004, 2012) and the use of acaricide to control ticks by application to vertebrate hosts or area wide spraying (Piesman and Beard, 2012).

We performed global sensitivity analyses to identify the parameters of the model that explain most of the variation in R_0 over the parameter space defined by the parameter ranges. Such analyses suggest which are the key parameters, and hence the key drivers, that might explain variation in emergence and persistence of these pathogens across different sites and indeed across North America.

2. Materials and methods

R_0 for multi-host disease systems is defined to be the dominant eigenvalue of the next-generation matrix (NGM) (Diekmann et al., 1990). The NGM relates the expected numbers of infected (and infectious) individuals (of each host type) in generation $n + 1$ to the numbers of infected (again of each host type) in generation n . If an individual belongs to the n th generation this means that the chain of infection from the primary case to the individual consists of n transmission events. At any point in an epidemic there are of course many overlapping generations. This serves to highlight that the next-generation approach does not attempt to model growth of the infected population over real time, and that R_0 is a number not a rate.

Hartemink et al. (2008) constructed a next-generation matrix for tick-borne pathogens by defining four tick host types and one vertebrate host type. For a subset of tick-borne pathogens in North America, a more complicated next-generation matrix having four tick host types and three vertebrate host types so as to incorporate tick phenology was proposed by Davis and Bent (2011).

In this paper we present a far simpler 2-host type next-generation matrix that only includes the horizontal transmission routes between the predominant vertebrate host, assumed to be white-footed mice (*Peromyscus leucopus*) in the eastern USA (LoGiudice et al., 2003; Schmidt and Ostfeld, 2001), and the black-legged tick (*Ixodes scapularis*). These two host types are shown in the transmission graph in Fig. 1. Host type 1 is defined as a tick that was infected as a larvae, i.e. during its first blood meal. Host type 2 is a vertebrate infected by a nymph. For many tick-borne disease systems this reduction to two host-types is not meaningful or useful because ticks at older life stages may become infected, and through alternative transmission routes such as transovarial transmission contribute to R_0 .

Brunner and Ostfeld (2008) used a set of negative binomial random variables to describe the numbers of larvae and nymphs

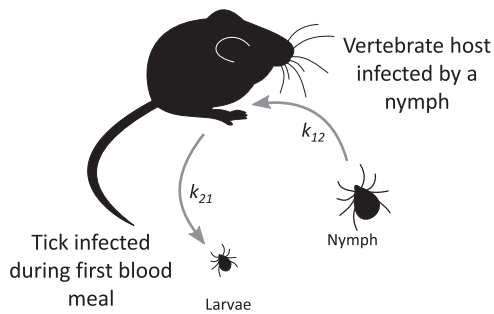


Fig. 1. The transmission graph consisting of two epidemiologically distinct host types: white-footed mice (*Peromyscus leucopus*) infected by an *Ixodes scapularis* nymph and larvae infected by a white-footed mouse. Note that ticks feed only once per life stage and only some vertebrate species are effective transmitters of the pathogens. Directed arcs indicate transmission between the host-types and correspond to non-zero elements of the next-generation matrix.

on a host captured t days since the beginning of the year. We denote these random variables as $Z_L(t)$ and $Z_N(t)$ respectively referring to the numbers of larvae and nymphs, and the *mean* tick burdens (t days since the beginning of the year) as $\bar{Z}_L(t)$ and $\bar{Z}_N(t)$. The mean burden of nymphs is modelled as a right shifted lognormal curve and the mean larvae burden is modelled as an early right shifted normal followed by a later lognormal peak (as set out in Brunner and Ostfeld, 2008). These curves are shown in Fig. 2. The functional forms have easily interpreted parameters that control the timing, height and width of the peak burdens. Given that the degree of aggregation of ticks on particular individuals of the host population is unknown the burden curves represent the expected or average burden on a host, which is currently quantifiable through available field data.

2.1. Formulation of R_0 for tick-borne disease

The directed arcs in Fig. 1 correspond to non-zero elements in the next-generation matrix with k_{ij} defined as the expected number of infected hosts of type i produced by a single infected host of type j . The next-generation matrix is then

$$\begin{bmatrix} 0 & k_{12} \\ k_{21} & 0 \end{bmatrix}$$

and R_0 is the dominant eigenvalue, which in this case is simply the geometric mean of k_{12} and k_{21}

$$R_0 = \sqrt{k_{12}k_{21}}. \quad (1)$$

The expected number of larvae (host type 1) that a mouse (host type 2) will infect over the entire time it is infectious is given by

$$k_{12} = \int_{t=0}^{t=365} a_N(t) \int_{t'=0}^{t'=365-t} \frac{1}{d_L} p(t') \theta^{t'} \bar{Z}_L(t' + t) dt' dt. \quad (2)$$

The expression for k_{12} contains a double integral so that we can account for the seasonal activity of the two relevant life stages of *I. scapularis*. The inner integral gives the average number of larvae infected by a mouse, that was itself infected at time t , where $t=0$ has nominally been chosen as January 1st. Note that t' should be interpreted as the number of days since infection in a single mouse. The inner integral is a function of the tick phenology ($\bar{Z}_L(t)$), mouse survival (θ) and the efficiency of transmission from mouse to tick ($p(t')$). The outer integral weights the value of the inner integral by the proportion of host seeking nymphs $a_N(t)$ that emerge and feed at time t . It is the normalised version of $\bar{Z}_N(t)$. Finally the parameter d_L appears in Eq. (2) which is the number of days of attachment for a larvae taking a blood meal so that counts of feeding larvae over the time a mouse is infected are correctly

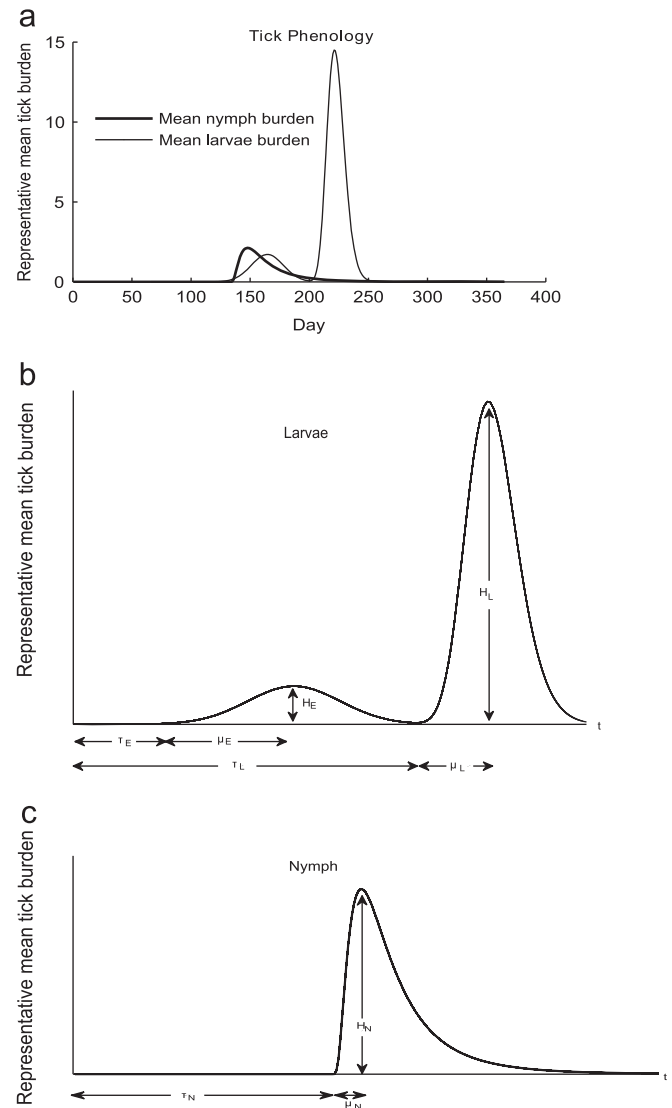


Fig. 2. (a) Burden phenology of white-footed mice. Parameters of (b) the expected larval burden and (c) the expected nymphal tick (*Ixodes scapularis*) burden for white-footed mice (*Peromyscus leucopus*) representing the expected burden on a host at any given time of the year starting January 1. Functional forms of these representative curves can be found in Brunner and Ostfeld (2008) and in Appendix A.

accounted for. The survival of white-footed mice t days after infection is coarsely modelled by a geometric distribution with a mean of 133 days (Schug et al., 1991) and hence the probability that a mice will still be alive t' days after infection is θ raised to the power of t' .

The form of k_{12} here is modified from the previous model of Davis and Bent (2011) because it incorporates transmission efficiency from vertebrate host to larvae as a function of days since infection. This allows us to take advantage of recent laboratory studies on the infectivity of vertebrate hosts as a measurable function, $p(t')$, of days post infection. We note that this function incorporates transtadial transmission because the proportion of ticks infected (after being placed on infected mice) is calculated after the larvae moult and become nymphs. A representative log-normal curve for $p(t')$ is shown in Fig. 3. This function has parameters that control the timing and height of peak transmission efficiency as well as the duration of the infectious period in mice.

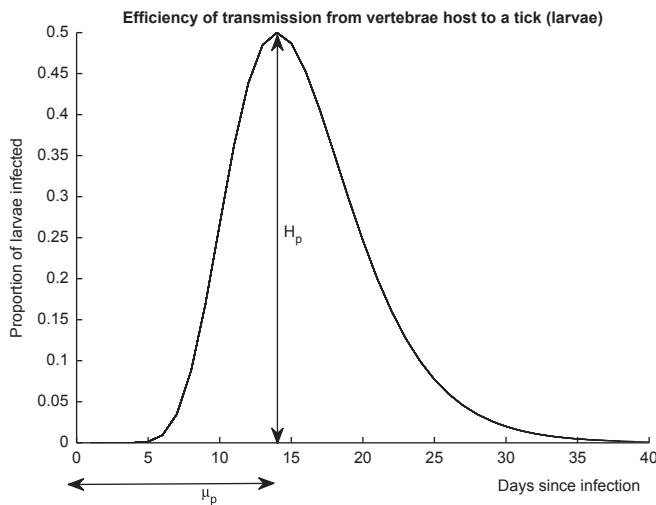


Fig. 3. Representative curve, $p(t')$, of efficiency of transmission from a vertebrate host (white-footed mice *Peromyscus leucopus*) to a tick (*Ixodes scapularis* larvae stage). The function is a log-normal curve with three parameters controlling the height, width and duration.

The formula for k_{21} is much simpler and is given by

$$k_{21} = s_N q_N c \quad (3)$$

where s_N is the proportion of fed larvae that survive and moult to become host-seeking nymphs; c is the proportion of nymphs that find a competent host and q_N is the probability of transmission from an infected nymph to the mouse that it takes its blood meal from, all assumed to be constants.

Combining Eqs. (1)–(3), R_0 takes the form

$$R_0 = \sqrt{s_N q_N c \int_{t=0}^{t=365} a_N(t) \int_{t'=0}^{t'=365-t} \frac{1}{d_L} p(t') \theta^{t'} \bar{Z}_L(t' + t) dt' dt}. \quad (4)$$

2.2. Parameterisation

Listed in Table 1 are the 19 parameters that define the three functions and five constants in Eq. (4). For each parameter we have provided a range and a point estimate. The range for each parameter is based on values given in the literature and in some cases on unpublished data as well. Of the 19 parameters, 11 (the last 11 in Table 1) describe how the average tick burdens on mice (see Fig. 2) change over the course of a year. The timing of these burden curves, when each of the three periods of host-seeking activity first begin, are given by τ_N , τ_E and τ_L , respectively being for the nymph (N), early larvae (E) and late larvae (L) periods of activity. Parameters μ_N , μ_E and μ_L give the period of time from the beginning of these three periods of activity to their corresponding peaks. Finally, the parameters σ_N and σ_L control the width of the peaks in the burden curves (see Appendix A for explicit formulation). The parameters controlling the heights of the tick burden curves at the various peaks are H_E , H_L and H_N .

The timing of the nymph and larvae peak burdens is crucial since the uninfected larvae must feed on a host after the host has been infected by a nymph if there is to be transmission to the next generation of ticks (Gatewood et al., 2009; Kurtenbach et al., 2006). Each burden curve has a peak nymphal or larval count which represents the maximum expected burden on white-footed mice. Suitable parameters were found using published estimates (Brunner and Ostfeld, 2008; Davis and Bent, 2011; Devey and Brisson, 2012) but some ranges were found using unpublished data collected from the white-footed mice in Mansfield,

Connecticut, Block Island and Rhode Island, USA (Diuk-Wasser, unpublished data). Note that the burden curves describe the average burden and that extreme ranges are included to ensure there is no underestimation of the effect that the ratio of ticks to hosts might have on R_0 .

Parameter ranges for transmission efficiency of *B. burgdorferi* (including two different strains) were determined using published estimates (Derdáková et al., 2004) and longitudinal data on transmission efficiency to larval *I. scapularis* ticks (Durland Fish, unpublished data). Note that we have defined ranges for *B. burgdorferi* because this is currently the only pathogen for which we have sufficient data. We have not yet defined separate ranges for *B. microti* and *Anaplasma phagocytophilum*, though the little data available would suggest they are contained within the given ranges for the two strains of *B. burgdorferi*. Transmission efficiency is measured as infectiousness of the vertebrate host and is represented as a lognormal curve with three parameters. These are the maximum transmission efficiency, H_p , the timing of the peak transmission, μ_p (which also controls the incubation period) and a shape parameter, σ_p , which determines the duration of infectivity. Survival of white-footed mice was coarsely estimated using the mean longevity of white-footed mice from Schug et al. (1991) and Snyder (1956), reported as 133 days. For the range for this parameter we used the maximum and minimum recorded values from these two studies.

There are four other parameters in the model: d_L , q_N , c and s_N . The days of attachment for larvae, d_L , has a range of 3–5 days and is well referenced in the literature (see Nazario et al., 1998; Piesman et al., 1987 for example). Point estimates for probability of transmission from nymph to mouse q_N , the survival of *Ixodes* ticks from larvae to nymph, s_N , and the probability of a nymph finding a competent host, c , are rarer. The point estimate for the transmission from nymph to mouse is given as 0.83 in Piesman et al. (1987) with additional references in Mather et al. (1990) and Piesman and Spielman (1982). The survival of engorged *Ixodes* larvae has previously been identified as an important parameter in the next generation matrix model (Hartemink et al., 2008). The large range for this and c in Table 1 reflects the difficulty with measuring this parameter directly and hence the scarcity of relevant literature.

Fixed point values, as well as ranges for all of the parameters appearing in the R_0 formula are given in Table 1. However, many parameters, including those relating to tick phenology, will be locally dependent, so fixed point parameters should be interpreted as representative values only.

2.3. Sensitivity analyses

Local and global sensitivity methods are used for the parameter sensitivity analysis. Local sensitivity measures treat model output (in this case R_0) as a function of a single variable by fixing all other parameters to their point estimates. Using Eq. (4) it is straight forward to look at the local sensitivity of R_0 , given a list of point estimates for the parameters. Local sensitivity can be approximated by the observed change in R_0 relative to a small change in each parameter. In Table 1 we show the change in R_0 in response to a 1% change in each parameter. We similarly approximate the elasticities of R_0 , defined as the proportional change in R_0 in response to a proportional change in the parameter value (a 1% change) with all other parameters fixed. Elasticities are often viewed as a better basis of comparison of sensitivity because they are independent of the units used.

The global sensitivity analysis calculates Sobol's main and total effect indices (Saltelli et al., 2008). The main effect of a parameter x is also known as the first order effect or top-marginal variance and is the average reduction in the variance of model output if x is

Table 1

Parameters appearing in the tick-borne pathogen model relating to (i) white-footed mice (*Peromyscus leucopus*) survival post infection, (ii) nymphal and larval tick (*Ixodes scapularis*) burdens and behaviour and (iii) pathogen transmission efficiency and dynamics and associated references. Global sensitivity results are given as Sobol's main and total effects indices. Literature for given ranges can be found in the associated reference: [Davis and Bent \(2011\)](#), [Nazario et al. \(1998\)](#), [Piesman et al. \(1987\)](#), [Li et al. \(2012\)](#), [Piesman and Spielman \(1982\)](#), [Schug et al. \(1991\)](#), [Snyder \(1956\)](#), [Hanincová et al. \(2008\)](#), [Derdáková et al. \(2004\)](#), [Brunner and Ostfeld \(2008\)](#), [Devevey and Brisson \(2012\)](#) and Diuk-Wasser, unpublished data.

Function	Parameter	Parameter description	Point estimate	Ranges	Reference	Sensitivity	Elasticity	Main effect	Total effect
	d_L	Days of attachment (larvae) (days)	4	3–5	Davis and Bent (2011) , Nazario et al. (1998) , Piesman et al. (1987)	–0.01	–0.05	0.01	0.02
	s_N	Survival from larvae to nymph	0.4	0.1–0.5	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Li et al. (2012)	0.13	0.05	0.09	0.15
	c	Probability of finding a competent host	0.5	0.1–0.99		1.16	0.50	0.18	0.18
	q_N	Probability of transmission (nymph to mice)	0.83	0.57–0.88	Davis and Bent (2011) , Piesman and Spielman (1982)	0.06	0.05	0.01	0.03
θ	ρ	Survival of mice	133	85–185	Schug et al. (1991) , Snyder (1956)	< 0.01	0.01	< 0.01	0.01
$p(t')$	H_P	Height of transmission efficiency curve	0.6	0.2–0.8	Diuk-Wasser (unpublished data), Hanincová et al. (2008)	0.09	0.05	0.07	0.1
	μ_P	Shift to peak transmission efficiency [days]	14	1–21	Diuk-Wasser (unpublished data), Hanincová et al. (2008) , Derdáková et al. (2004)	< 0.01	–0.02	0.15	0.24
	σ_P	Shape parameter transmission efficiency	0.7	0.1–1	Diuk-Wasser (unpublished data), Hanincová et al. (2008)	0.35	0.04	0.21	0.27
$\bar{Z}_N(t)$	μ_N	Shift to peak nymph burden [days]	15	10–20	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	< 0.01	< 0.01	< 0.01
	τ_N	Timing nymph burden [days]	133	120–150	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	0.15	< 0.01	0.01
	σ_N	Shape parameter nymph burden	0.7	0.5–0.9	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	0.04	< 0.01	< 0.01
	H_N	Height nymph burden	2	1–10	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Li et al. (2012) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	0	0	0	0
$\bar{Z}_L(t)$	μ_L	Shift to late peak larvae [days]	49	40–55	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	–0.03	< 0.01	< 0.01
	τ_L	Timing of late peak larvae [days]	172	160–180	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	–0.23	< 0.01	0.01
	τ_E	Timing of early peak larvae [days]	166	150–175	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	0.04	< 0.01	0.02
	σ_L	Shape parameter late larvae peak	0.2	0.1–0.3	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	0.35	0.04	< 0.01	0.02
	μ_E	Shift to early peak larvae [days]	11	5–20	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	–0.04	0.02	0.03
	H_E	Height first larvae peak	1	0.5–50	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	0.01	0.01	0.09	0.1
	H_L	Height second larvae peak	15	5–100	Diuk-Wasser (unpublished data), Davis and Bent (2011) , Li et al. (2012) , Brunner and Ostfeld (2008) , Devevey and Brisson (2012)	< 0.01	0.04	0.03	0.06

fixed to some value x^* , and where the average is taken over the possible values for x^* . The total effect is also known as bottom-marginal variance and includes interaction effects; the total effect should always be greater than or equal to the main effect. Essentially, a main effect index measures the effect of parameter x on R_0 ignoring all other parameters. A main effect index is a measure between $[0, 1]$ where values close to 1 indicate a large influence on R_0 .

The main and total effects indices of the global sensitivity analysis are calculated for each parameter using a Monte Carlo estimation of Sobol's Indices scheme (Saltelli, 2002) using the R package Sensitivity with a uniform distribution (Pujol et al., 2012). The analyses were run with 20,000 uniformly distributed samples with 100 bootstrap replicates.

3. Results

The summary statistics for the set of values of R_0 for *Borrelia burgdorferi* generated by the sampling procedure for the global sensitivity analysis are given in Table 2. The mean of R_0 is different to the fixed point estimate of R_0 at 1.16. The majority of R_0 values occur near the threshold at $R_0=1$ with the middle 50% of values lying in the range 0.8–2.1. The maximum occurs close to 8.

The results of the local and global sensitivity analyses are given in Table 1 and shown graphically in Fig. 4. The results indicate that c , the probability of finding a competent host, is the highest ranked parameter (by sensitivity) in the local sensitivity analysis. This parameter was also ranked highly by the global sensitivity indices. The parameters of $p(t')$, governing the transmission efficiency from mouse to larvae, were also highly ranked by both the main and total effect. The two parameters μ_P and σ_P which respectively control the shift to the peak transmission efficiency and the length of time medium-high transmission efficiency is sustained, both produced larger total effects. The parameter s_N , the proportion of fed larvae that survive to become host-seeking, unfed nymphs, was ranked third by both the main and total effect indices. The height of the transmission efficiency curve, H_P , was similarly ranked. All other parameters produced low main and total effects.

The shape parameter, σ_P of $p(t')$ which controls the duration of medium-high infectivity in mice, is plotted against R_0 in Fig. 5 (where all other parameters have been set to their fixed point estimates). A value of 0.4 for σ_P gives a duration of infectivity of approximately 21 days (estimated from plots of $p(t')$) and when σ_P is 0.95 then low chronic (or long term continuing) infection occurs. In Fig. 5, $R_0 < 1$ when the length of time a mouse is efficiently transmitting to larvae is less than 42 days. The shape parameter may be thought of as controlling the extent to which chronic infection occurs in mice.

The parameter s_N , the survival of *Ixodes* ticks from fed larvae to host-seeking nymphs ranks fourth in importance in the global sensitivity analysis. From Eq. (4) it is easy to deduce that R_0 is directly proportional to $\sqrt{s_N}$. This behaviour is also evident in Fig. 6. Note that if the proportion of larvae that survive to become feeding nymphs is below 0.3 then $R_0 < 1$ at the fixed point estimate and the height of the larvae burden has relatively little

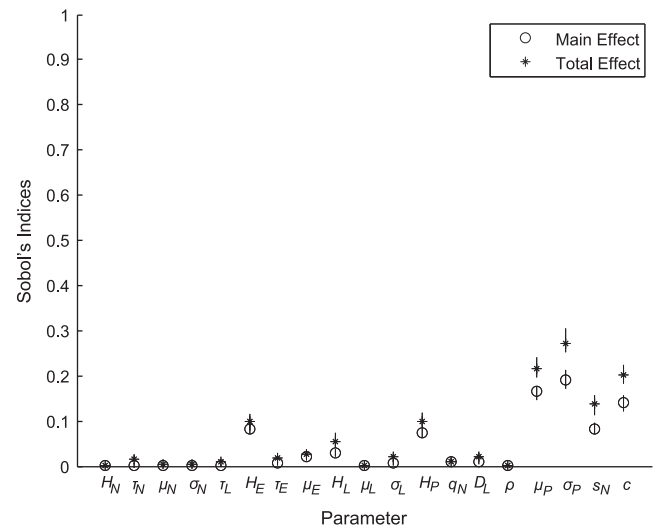


Fig. 4. Results of the global sensitivity analysis of the R_0 model. Main effect measures the sensitivity of R_0 to individual parameters and the total effect measures the sensitivity including interactions. The four highest ranking parameters are survival of fed larvae, the probability of finding a competent host, the number of days to peak infectivity in mice and duration of infectivity in mice.

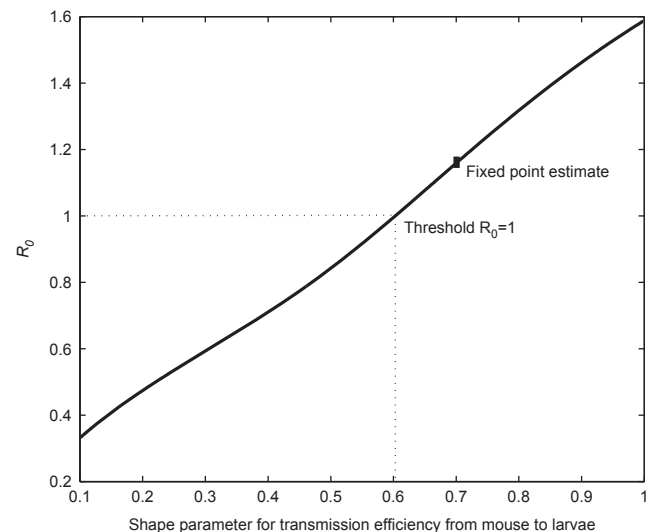


Fig. 5. The parameter σ_P from the function $p(t')$ controls the duration of infectiousness and is here plotted against R_0 as if R_0 was a function of a single variable. At 0.4 the infectivity lasts 21 days, at 0.95 low chronic (continual) infection occurs. The threshold condition for $R_0 < 1$ occurs at 0.42 which corresponds to an infectious period ending at approximately 42 days.

impact. In general, from the repeated sampling of R_0 in Table 2, 95% of R_0 values will be less than one when less than 25% of ticks survive from fed larvae to feeding nymph ($s_N < 0.25$). Equivalently, R_0 is proportional to $\sqrt{c}$ and if at the fixed point estimate the chance of a nymph finding a competent host is less than 0.36 then $R_0 < 1$.

Similarly, vaccination rates of the vertebrate host can be estimated from the repeated sampling of R_0 from Table 2. Vertebrate hosts would need to be vaccinated with a proportion greater than $1-1/R_0^2$ such that, in this multi-host system, the number of secondary vertebrate infections occurs at R_0^2 (see Roberts and Heesterbeek, 2003 for estimation of vaccination rates for a multi-host infectious disease). Using the value of the top 95th percentile of R_0 , indicating considerable confidence that the

Table 2

Summary statistics for the distribution of R_0 values for *Borrelia burgdorferi* and associated with the sampling scheme used to perform the global sensitivity analysis.

Min.	1st quartile	Median	Mean	3rd quartile	Max.
0.03	0.79	1.32	1.57	2.10	8.38

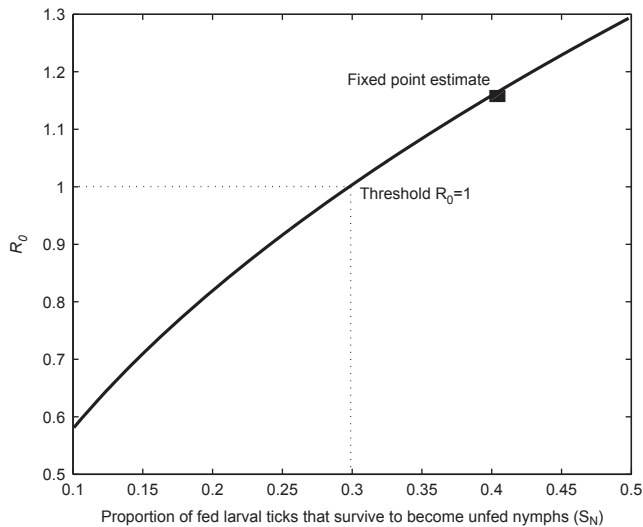


Fig. 6. R_0 plotted against S_N , the survival of *Ixodes* ticks from larvae to nymphs. The threshold condition for $R_0 < 1$ occurs at $S_N = 0.29$.

intervention would reduce R_0 below 1, the proportion of vaccinated white-footed mice would need to be greater than 93%.

There are three functions which have parameters with a total effect index noticeably larger than their associated main effect index, the transmission efficiency function $p(t')$ and the burden curves $\bar{Z}_N(t)$ and $\bar{Z}_L(t)$. These parameters are the timing parameters of the burden curve peaks. The higher total effect index values suggest interactions in the model between $\bar{Z}_N(t)$, $\bar{Z}_L(t)$ and $p(t')$. This is unsurprising since it is clear that all of these timing parameters together determine the extent of the overlap between when larvae are feeding and when mice are likely to be infectious. The time difference in days between the timing of the nymph burden and the first peak of the larvae burden $t = \tau$ are plotted against the two highest ranked parameters of the transmission efficiency function $p(t')$ in Figs. 7 and 8.

From Fig. 7 there appears to be a non-linear relationship between both the peak timing τ and duration μ_p of the transmission curve $p(t')$ and burden curves at the threshold $R_0 = 1$. Also, Fig. 7 indicates the greater the difference in timing (between the nymph and larval activity peaks) then the later the peak of the transmission curve needs to occur to produce a similar range of R_0 values.

The duration of infectivity, controlled by σ_p in $p(t')$ and which is plotted in Fig. 8, produces a similar phenomenon to the timing parameter μ_p , because as the difference in timing between the burdens increases, the shape parameter also has to increase to produce the same range of R_0 values. Fig. 8 is consistent with the appealing rule of thumb that the duration of the infectivity curve must be longer than the difference between the peak nymph and peak larvae burden timing. For example, when the difference in the nymph and larvae burden curves is greater than 21 days, the duration of infectivity, σ_p , must be slightly larger than 21 days (as indicated by 0.4 in the figure) to produce values along the threshold $R_0 = 1$.

4. Discussion

We have presented an R_0 model for a group of tick-borne pathogens for which there is negligible transmission between co-feeding ticks or from an infected adult female to her eggs. This group includes *Borrelia burgdorferi*, *Babesia microti* and *Anaplasma phagocytophilum*. We have also presented sensitivity analyses

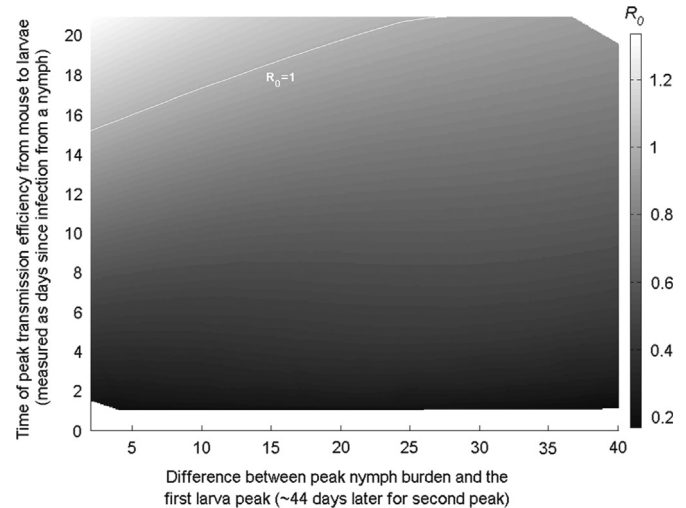


Fig. 7. The parameter μ_p of $p(t')$, which controls the timing of the peak of the transmission efficiency curve, plotted against the difference in the timing of the nymph and larvae burdens (in days). As the difference increases then μ_p must also increase to maintain values of $R_0 > 1$.

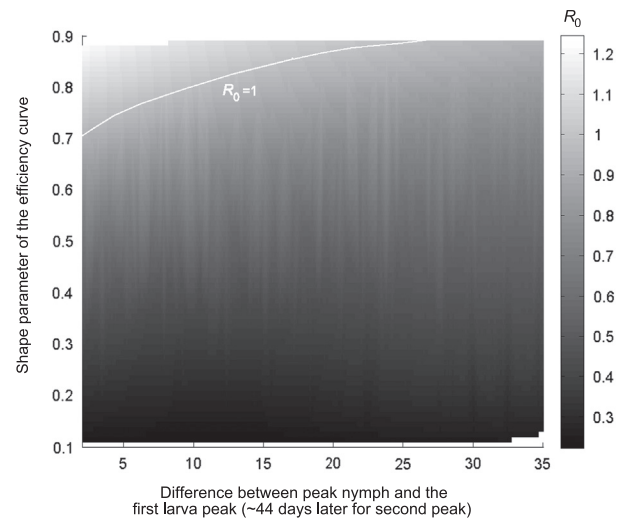


Fig. 8. The shape parameter σ_p of $p(t')$ controls the duration of infectivity and is plotted here against the difference in the timing of the nymph and larvae burdens (measured in days). At 0.4 the duration of infectivity is 21 days and at 0.95 low chronic infection occurs. As the difference increases σ_p must also increase to maintain values of $R_0 > 1$.

using parameter ranges defined for *Ixodes scapularis* ticks transmitting *Borrelia burgdorferi* but which are likely to include relevant ranges for other pathogens carried by *Ixodes scapularis* too. Our results indicate that a key determinant of R_0 for these systems is the proportion of fed larval *Ixodes scapularis* that survive to become host-seeking nymphs and find a competent host. Our analyses have also identified the efficiency of transmission from vertebrate hosts to larval *Ixodes scapularis* as highly important, at least in part because of interaction with tick phenology. This provides a contrast with other vector-borne diseases such as plague and malaria where the proportion or abundance of feeding vectors or the ratio of hosts to vectors is considered critical (see Anderson and May, 1991; Keeling and Rohani, 2008; May and Anderson, 1979 for theory and Macdonald, 1957; Reihners et al., 2012 for examples). This is not to say that tick burden is irrelevant, but that even with the very broad ranges for the numbers of ticks on hosts (see Table 1 and the ranges used for the parameters H_E , H_L

and H_N), the sensitivity analyses consistently ranked other factors as more important.

In terms of public health relevance, the sensitivity analysis suggests possible drivers for the geographical distribution of tick-borne pathogens such as *Borrelia burgdorferi* and *Babesia microti* and identifies possible targets for control. In particular, these results highlight the importance of laboratory studies that measure the infectivity of vertebrate hosts as functions of the time since infection. In particular, we suggest there is a need to better understand whether chronic infection occurs. Clearly, if a pathogen is too rapidly cleared then this can lower R_0 to below one (see Fig. 5). This result gives weight to the need to detect and measure differences in infectivity between pathogens and between strains as there is potential to better understand patterns of emergence of these pathogens at specific sites. Additionally, this result suggests that targeted methods that lower peak infectivity or the duration of infectivity of vertebrate hosts (Richer et al., 2011; Tsao et al., 2004), such as vaccination, show potential to lower R_0 below one.

Current regimes suggest that a vaccination rate of 93% may be unrealisable. The long tail of the R_0 distribution allows us to instead consider a 90% confidence bound on R_0 whereby a much more feasible 67% of vertebrate hosts would need to be vaccinated. A previous vaccination experiment based on injecting individual mice estimated that $79 \pm 4\%$ (in year 1) and $73 \pm 1\%$ in year 2 of the experiment were vaccinated at least once, $68 \pm 16\%$ (year 1) and $57 \pm 7\%$ (year 2) were captured and vaccinated at least twice by the last trapping period (Tsao et al., 2004). However, a more recent study evaluating a new vaccine formulation based on an easily distributable oral bait vaccine (Voordouw et al., 2013) estimated that over 90% of mice would be completely vaccinated within 24 days in a pilot mark recapture study. Tsao et al. (2012) suggests that a baiting regime when used in conjunction with acaricide application and changes in the competent host dynamics, all of which were identified in our results, would be effective. Additionally, vaccination reduces the proportion of infected ticks (Voordouw et al., 2013) and in turn reduces the risk to humans.

The understanding of how R_0 is sensitive to changes in tick phenology might also lead to better control methods. The results of the local sensitivity analysis indicate that near the point estimate of R_0 , tick phenology or more specifically the timing parameters of tick seasonality are predictors of presence or absence. This result is consistent with Gatewood et al. (2009) in that there is a small subset of burden timing parameters that allow for the pathogen to be transmitted which may vary geographically. The interaction of these terms with the infectivity terms emphasizes the complex nature of these pathogens in that rapidly cleared strains may not be disadvantaged compared to persistent strains provided the nymph and larval burdens occur in quick succession. In fact, high overlap of the peak transmission with the larval burden produces a significantly larger R_0 . This result agrees with the more recent results of Haven et al. (2012) which suggest the delay in larval activity strongly interacts with the timing of peak pathogen transmission. We note that although tick phenology was not identified as a significant contributor to the variation in R_0 there is only a relatively small subset of ranges for the timing parameters that produce R_0 values greater than one.

Of perhaps greater public health importance is that s_N , the survival of fed larvae was identified in the analyses as a parameter to which R_0 is sensitive. This is a parameter which possibly can be influenced through the application of acaricides and is a possible control measure to reduce R_0 below one (see Fig. 6). This parameter ranked just behind the parameters of the transmission curve and the probability of a nymph finding a competent host in terms of main and total effect, and is also indicated as

having the highest elasticity value in the original R_0 model (Hartemink et al., 2008). It is perhaps worth emphasising that the demographic rate of a tick life stage is not necessarily strongly related to its abundance because compensatory mechanisms at the population level can occur in wildlife populations which “make-up” for the reduction in some other demographic rate. This in turn means it is possible that reducing the survival of fed larvae may have a dramatic impact on the pathogen (cause it to fade out) but have little discernible effect on the overall abundance of ticks.

The high main and total effect of the probability of a nymph finding a competent host suggests that the composition and abundance of competent vertebrate host species have a marked influence on the magnitude of R_0 . For simplicity, our model includes a single vertebrate species that is considered to be 100% competent. However, in a multi-host community, parameter c would encompass both the probability of finding any host and the relative competence of the host the tick actually fed on. The typical value for the probability of a larva finding a competent host is not known.

In the case of the model and analyses presented here, we emphasise that for some parameters we defined very broad ranges because there was little information about the parameter. This is important to understand because a global sensitivity analysis may rank a parameter as important simply because there is high uncertainty. This is quite different to the case in which high variability, either across sites or across time has been observed for a particular parameter. It may therefore be the case that when the true variation in a parameter is better known, it may be ranked differently.

The range of R_0 values presented here is consistent with other reported ranges of *Borrelia burgdorferi* (see for example Hartemink et al., 2008). Our mean estimates are slightly higher than the original estimate of Davis and Bent (2011) and is significantly lower than what is predicted in Hartemink et al. (2008). This may be due to the different transmission cycle of the European strain of *Borrelia burgdorferi* where the transovarial transmission route contributes significantly to R_0 (Randolph and Craine, 1995).

The estimated values of R_0 presented here and in the previous work of Hartemink et al. (2008) and Davis and Bent (2011) are consistently low (the median value in the present analysis was 1.32). In fact, in a comparison of R_0 for five tick-borne pathogens between the north-eastern and mid-western regions of North America to highlight the impact that tick phenology can have; for one of the pathogens (*Anaplasma phagocytophilum*) R_0 was estimated to be less than 1 for the north-east and greater than 1 for the mid-west (Davis and Bent, 2011). The magnitude of R_0 is an index of the control effort required to eliminate a pathogen. While the widespread success of *Borrelia burgdorferi* rightly reminds us to be cautious, the implication remains that the low R_0 values estimated here imply, at least for these particular pathogens and this particular region, that vaccination, acaricide application or changes in the competent host dynamics may indeed lead to local fade out.

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Appendix A. Description of formula used in the calculation of R_0

- Equations used in quantifying tick phenology

$$\bar{Z}_N(t) = \begin{cases} H_N e^{-(1/2)[\ln((t-\tau_N)/\mu_N)/\sigma_N]^2} & \text{if } t \geq \tau_N, \\ 0 & \text{otherwise.} \end{cases}$$

$$\bar{Z}_L(t) = \begin{cases} H_E e^{-(1/2)((t-\tau_E)/\mu_E)^2} & \text{if } t \leq \tau_L, \\ H_L e^{-(1/2)[\ln((t-\tau_L)/\mu_L)]^2} + H_E e^{-(1/2)((t-\tau_E)/\mu_E)^2} & \text{otherwise,} \end{cases} \quad (\text{A.1})$$

$$a_N(t) = \frac{\bar{Z}_N(t)}{\int_0^{365} \bar{Z}_N(t) dt}. \quad (\text{A.2})$$

- Infectivity of vertebrate hosts

$$p(t') = H_P e^{-(1/2)[\ln(t/\mu_P)/\sigma_P]^2}. \quad (\text{A.3})$$

- Survival of vertebrate hosts

$$\theta(t') = \left(1 - \frac{1}{\rho}\right)^{t'}. \quad (\text{A.4})$$

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