The Basic Reproduction Number for Complex Disease Systems: Defining R_0 for Tick-Borne Infections

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ABSTRACT: Characterizing the basic reproduction number, R_0, for many wildlife disease systems can seem a complex problem because several species are involved, because there are different epidemiological reactions to the infectious agent at different life-history stages, or because there are multiple transmission routes. Tick-borne diseases are an important example where all these complexities are brought together as a result of the peculiarities of the tick life cycle and the multiple transmission routes that occur. We show here that one can overcome these complexities by separating the host population into epidemiologically different types of individuals and constructing a matrix of reproduction numbers, the so-called next-generation matrix. Each matrix element is an expected number of infectious individuals of one type produced by a single infectious individual of a second type. The largest eigenvalue of the matrix characterizes the initial exponential growth or decline in numbers of infected individuals. Values below 1 therefore imply that the infection cannot establish. The biological interpretation closely matches that of R_0 for disease systems with only one type of individual and where infection is directly transmitted. The parameters defining each matrix element have a clear biological meaning. We illustrate the usefulness and power of the approach with a detailed examination of tick-borne diseases, and we use field and experimental data to parameterize the next-generation matrix for Lyme disease and tick-borne encephalitis. Sensitivity and elasticity analyses of the matrices, at the element and individual parameter levels, allow direct comparison of the two etiological agents. This provides further support that transmission between cofeeding ticks is critically important for the establishment of tick-borne encephalitis.

Keywords: R_0, next-generation matrix, Lyme borreliosis, tick-borne encephalitis, elasticity analysis, wildlife disease.

The basic reproduction number, R_0, is one of the most important concepts in the field of infectious diseases epidemiology (Anderson and May 1990; Diekmann and Heesterbeek 2000). It is most often defined as the average number of secondary cases caused by one infectious individual placed in a population consisting entirely of susceptibles. Knowledge of R_0 for a particular pathogen in a particular population has numerous applied benefits. (1) It is a threshold quantity such that if $R_0 > 1$, an outbreak is possible if the pathogen is introduced, whereas if $R_0 < 1$, it will certainly die out. (2) When an outbreak is possible, then R_0 is also a measure of the risk that an outbreak will actually occur. (3) If there is an outbreak, then R_0 will determine the initial exponential increase in the number of infecteds. (4) It determines the fraction of a population that would need to be vaccinated in order to avoid an outbreak.

Deriving R_0 for natural systems of infectious agents among wildlife is complicated. The reason is the high level of heterogeneity that is of epidemiological importance: differences between individual host species and host individuals cause differences in susceptibility, infectivity, and contacts, and such differences can also exist for a single individual in different stages of its life history. Apart from being generally multispecies systems, there are also (as a rule) multiple transmission routes for the infectious agent. A method exists in the mathematical biology literature to characterize R_0 even in systems with such complexity: the next-generation matrix method (Diekmann et al. 1990; Diekmann and Heesterbeek 2000). This approach has the advantage that the steps to reach an estimate of R_0 and the matrix elements of the next-generation matrix have a clear biological basis. We give an intuitive and detailed explanation of the approach, catering to a more general ecological audience.

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In order to illustrate the full usefulness of the method, we have constructed our article around the problem of characterizing R_0 for tick-borne infections, where all the complexities we have mentioned are present. Peculiarities in tick biology, such as the fact that hard ticks feed only once in each stage and are not infective until they bite again as the next stage, make ticks different from insect vectors (Randolph and Craine 1995; Randolph 1998). Modeling of tick-borne infections also needs to deal with the complexity of the tick life cycle and the fact that only some of the host species that ticks may feed on are competent transmitters of any particular pathogen. A third source of complexity is that there are three routes of transmission (systemic and nonsystemic horizontal transmission and transovarial vertical transmission), and the life stage of the tick when it first became infected determines which of these routes of transmission is possible for any individual tick. It is therefore not surprising that many different expressions for R_0 have been published for tick-borne diseases (Randolph 1998; Randolph et al. 1999; Caraco et al. 2002; Ghosh and Pugliese 2004; Foppa 2005); the most detailed contributions were by Norman et al. (1999), Rosà et al. (2003), and Rosà and Pugliese (2007).

However, we see some drawbacks in previously used approaches for tick-borne infections. The first is that most models assume a biting rate, as in models for insect vectors. A lower biting rate gives a lower value for R_0. For ticks, however, which bite only once per life stage, the biting rate sensu stricto influences the duration of the life stage but not necessarily R_0. A second problem is that many of the derived expressions are threshold quantities that are based on stability analysis of the infection-free steady state. This indeed leads to quantities with the desired threshold property (Diekmann and Heesterbeek 2000), but they are, in general, different from R_0 in that they cannot be interpreted as an average number of secondary cases, and they often indeed completely lack a biological interpretation at the individual level. This precludes easy biological comparison of different infections. Also, the quantitative differences in such threshold quantities are not the same as differences in R_0. This is because the value of R_0 can be used to gauge both the risk of establishment and the control effort required to prevent establishment. Hence, if one is interested in gauging the quantitative effect of changes in key parameters, then one would prefer R_0. That is, the actual increase in R_0 caused by, say, a 10% increase in a parameter is interesting in its own right, whereas an increase in another threshold quantity is not.

In this article, we derive an expression for R_0 for tick-borne pathogens on the basis of the next-generation matrix approach. We parameterize the next-generation matrix for the two most important tick-borne zoonoses in northern temperate zones: tick-borne encephalitis (TBE) and Lyme borreliosis (Randolph 2001). As for matrix population models used to study generation-based growth in animal and plant populations (De Kroon et al. 1986, 2000; Caswell 2001), the sensitivity and elasticity of R_0 to changes in the elements of the matrix or to changes in individual parameters provide additional insight, particularly when two species or populations can be compared. In the case of TBE and Lyme borreliosis, the next-generation matrices have the same structure and differ only in the values taken by the elements of the matrix. This means direct comparisons are possible, and so we illustrate that parameterizing a next-generation matrix can lead to benefits beyond those traditionally associated with the basic reproduction ratio.

Biological Framework

In Europe, Lyme borreliosis is caused by a group of spirochetal bacteria *Borrelia burgdorferi* s.l., and TBE is caused by TBE virus; both are transmitted by the bite of infected ticks of the species *Ixodes ricinus*. The life cycle of *I. ricinus* involves three postegg instars (larvae, nymphs, and adults), and it can take several years to complete. The larvae hatch from eggs and after a while feed on any vertebrate hosts whose feet touch the ground, such as rodents, ground-feeding birds, sheep, and deer, after which they molt to nymphs. The nymphs then take another blood meal before they become adults. Female adult ticks take yet one more blood meal to lay eggs; male adults do not engorge (Gray 2002). Because nymphs and adults quest at increasingly higher distances from the ground, they contact and feed on successively larger host species (Gigon 1985).

Several transmission routes have been described for tick-borne pathogens. In the systemic (either bacteremic or viremic) route, tick-borne pathogens are transmitted during the blood meals from feeding ticks to a host, establish systemic infections, and are then transmitted back to any other feeding ticks. A second route is nonsystemic transmission (Jones et al. 1987). For TBE virus, this route depends on a particular cellular mechanism involving the Langerhans cells of the host's immune system and immunogenic stimuli from the ticks' saliva, which set up circumscribed routes of transmission limited to tick feeding sites (Labuda et al. 1993*b*, 1996). For *B. burgdorferi* s.l., nonsystemic transmission occurs before (in mice) or without (in sheep) the development of systemic infections, as a result of limited dissemination of the spirochetes (Gern and Rais 1996; Ogden et al. 1997). Because this involves donor and recipient ticks feeding at very nearby sites, this is also referred to as cofeeding transmission. Nonsystemic transmission is thought to be of great importance for the maintenance of the TBE virus cycle (Randolph et al. 1996, 1999). Nonsystemic viral infections were observed to cause lower host mortality than systemic in-

fection, therefore permitting rodents to survive long enough for ticks to complete their blood meals (Labuda et al. 1993*b*), which could allow this route of transmission to confer an evolutionary advantage. In contrast, there is debate about the quantitative contribution that nonsystemic transmission makes to the maintenance of Lyme borreliosis spirochetes (Richter et al. 2002, 2003; Randolph and Gern 2003).

A third mode of amplification of tick-borne agents is vertical or transovarial transmission from an infected adult female tick to her offspring (Danielova et al. 2002). Although this typically results in only a small percentage of the eggs/larvae becoming infected (Matuschka et al. 1998), it may still be numerically important because (1) larvae are much more abundant than nymphs and adults and (2) infection is thought to be lifelong (though see Kurtenbach et al. 2002), which means that ticks infected as eggs would also have the most opportunities (blood meals) to transmit the infection, provided they survive until adulthood.

Not all hosts that ticks feed on support transmission. Rodents are competent hosts (although with species-specific variation); they facilitate nonsystemic transmission between cofeeding ticks and may also develop systemic infections that are long-lasting (months) for Lyme spirochetes but last only 2–3 days for TBE virus. Deer are noncompetent hosts for both pathogens, whereas birds are competent hosts for some types of *B. burgdorferi* s.l. but not for TBE virus. Sheep are difficult to classify; they are competent hosts for *B. burgdorferi* s.s. but support only nonsystemic infections (Ogden et al. 1997). They are not taken into account here because throughout most of the range of Lyme borreliosis, sheep do not play a major role.

The Next-Generation Matrix and R_0

For directly transmitted diseases in a single-species population, the definition provided at the beginning of this article is perfectly clear: R_0 is the average number of secondary cases produced by one primary case in a totally susceptible population. For vector-borne disease, the interpretation of R_0 is less intuitive because there are different infected types involved in transmission, that is, hosts and vectors. The average number of hosts infected by a vector and vice versa, the number of vectors infected by a host, should then be "averaged." This is straightforward in the case of a single host–single vector system without additional transmission routes (i.e., pure vector transmission); in that case, the product of the host-to-vector and vector-to-host reproduction numbers gives the average number of infected hosts generated by one newly infected host.

In a system with more host or vector species and/or additional transmission routes, this direct method breaks down, but the principle remains. We regard "causing new infections" on a generation basis, akin to generating offspring in a demographic sense. In this context, the so-called next-generation matrix (Diekmann et al. 1990; Diekmann and Heesterbeek 2000) provides a means of obtaining R_0. The first step is to identify the different, so-called types-at-birth (or "types" for short) in the system, that is, to categorize individuals by their state at the moment they become infected. These types-at-birth differ with respect to their ability to produce secondary cases (e.g., through differences in infectivity, contacts, life history, and/or transmission route). For vector-borne diseases, there are essentially at least two types-at-birth (one host and one vector species), but in tick-borne infections, there are more. The principle is now to regard generations of infected individuals, distributed over the different types that have been identified. The next-generation matrix then gives the size of the next generation distributed over the different types given in the present generation. If the generations grow in size, this translates as an increase in infected numbers for all types. All elements of the matrix are reproduction numbers for pairs of types, just as in the host-vector example above. For matrices like the next-generation matrix, the elements of which are all nonnegative by their biological interpretation, one has a mathematical convergence result: after sufficient generations, the distribution of infecteds over the different types becomes fixed (i.e., there are fixed ratios of numbers of infecteds over the various types), and per generation, there is one fixed growth factor with which each type in a generation grows. This growth factor is given by the largest eigenvalue of the next-generation matrix. It has precisely the desired mathematical interpretation (when it is larger than 1, generations grow in size; when it is smaller than 1, generations decline in size) and biological interpretation (the per generation growth factor in the number of infecteds). This eigenvalue therefore is R_0. This applies to any infection-host system with an arbitrarily large finite number of types-at-birth. The same reasoning applies when there are an infinite number of types, for example, in the case when the age of an individual is an epidemiologically important trait. We will now illustrate in detail the procedure in the multiple type-at-birth case of tick-borne infections.

A Next-Generation Matrix for Tick-Borne Infections

Assuming that the infectiousness of individuals is independent of the transmission route via which the infection was acquired, we distinguish five types-at-birth. The term type-at-birth refers specifically to the birth of the infection in the individual rather than the individual. In this case, there is one type-at-birth for every tick life stage at which

infection can be acquired and a fifth type-at-birth to take into account systemic infections in vertebrate hosts. We label these types as follows: (1) tick infected as an egg (via transovarial transmission), (2) tick infected as a larva (while taking its first blood meal), (3) tick infected as nymph (while taking its second blood meal), (4) tick infected as adult female (while taking its third blood meal), (5) systemically infectious vertebrate host.

The noncompetent host is not included as a sixth type-at-birth as it cannot become infected: their role in this system is restricted to being a source of "dilution" (from the perspective of the pathogen, a bite on a noncompetent host is a wasted transmission opportunity) but also an important provider of blood meals for ticks. We do not distinguish between an "unfed" and a "fed" type-at-birth for each tick life stage since nothing of interest for pathogen transmission happens until a tick has molted into the next stage. That is, from an epidemiological point of view, a fed larva is the same as an unfed nymph. We also assume that being infected does not influence any of the probabilities of survival, feeding, mating, or cofeeding with other ticks.

For a system with five types-at-birth, the next-generation matrix, **K**, will be a 5×5 matrix. Each of the elements k_{ij} represents the expected number of new cases of type-at-birth i caused by one infected individual of type-at-birth j during its entire infectious period. For example, k_{13} is the average number of eggs (type-at-birth 1) infected by one tick that was infected while feeding as a nymph (type-at-birth 3). Hence k_{13} is a component of transovarial transmission, and it must take into account that not all ticks infected while feeding as a nymph survive to become adult ticks.

It has to be emphasized that the types-at-birth should not be confused with the actual life stages. The type-at-birth for infected ticks refers to the life stage at the moment of infection and is a "characteristic" of the tick that remains the same from the moment of infection onward, irrespective of its future. It should also be kept in mind that because of the fact that ticks take only one blood meal per life stage, in order to be infectious, a tick must have been infected in an earlier life stage.

We will now explain the derivation of each (group of) matrix elements in some detail, with some examples; the complete list of expressions for the elements k_{ij} can be found in appendix A. Some elements equal 0 because not all types-at-birth infect all other types-at-birth. For example, female ticks infected as adults during their third blood meal (type-at-birth 4) do not feed again after they have been infected, and so they do not produce types-at-birth 2, 3, or 4 (representing ticks infected as a larva, nymph, and adult, respectively), nor can they produce type-at-birth 5 (vertebrate hosts with systemic infection). This means that k_{24}, k_{34}, k_{44}, and k_{54} are 0. Elements k_{15} and k_{55} are also 0 because infected vertebrate hosts cannot possibly infect the eggs of ticks, nor can they infect other vertebrate hosts. This gives the matrix

$$\mathbf{K} = \begin{bmatrix} k_{11} & k_{12} & k_{13} & k_{14} & 0 \\ k_{21} & k_{22} & k_{23} & 0 & k_{25} \\ k_{31} & k_{32} & k_{33} & 0 & k_{35} \\ k_{41} & k_{42} & k_{43} & 0 & k_{45} \\ k_{51} & k_{52} & k_{53} & 0 & 0 \end{bmatrix}. \quad (1)$$

The remaining, nonzero elements are described below, grouped according to the transmission route that they represent. The definitions of parameters, as well as their estimates for TBE and Lyme borreliosis, can be found in tables 1 and 2.

Systemic Transmission

The transmission efficiencies from larvae, nymphs, and adult ticks to competent hosts are denoted by q_L, q_N, and q_A, respectively. The probability of feeding on a competent host, or fraction of blood meals taken on competent hosts, is denoted by h_c. Although h_c will most likely increase with the fraction of hosts in a certain area that are competent, there is no simple parity because differential tick feeding probabilities depend also on host body size and tick questing behavior. The number of hosts that receive a systemic infection from a tick infected as an egg (via transovarial transmission) is the sum of hosts infected during its first, second, and third blood meals, weighted by the likelihood that it survives to take these blood meals. A tick that became infected when feeding as a larva can infect a host only in its second and third blood meals; likewise, a tick that became infected as a nymph infects a host only during its third blood meal. The probability that a tick survives to a certain stage is accounted for by three survival probabilities, s_L, s_N, and s_A, with the obvious interpretation of the subscripts. Note though that the survival probability s_A represents the probability of the tick being female as well as the probability of surviving. This is because adult males do not take a third blood meal. So, for example, the number of vertebrate hosts infected by a tick infected as an egg (type-at-birth 1) is

$$k_{51} = (s_L q_L + s_L s_N q_N + s_L s_N s_A q_A) h_C. \quad (2)$$

The transmission efficiencies from a vertebrate host with a systemic infection to larval, nymphal, and adult ticks are denoted by p_L, p_N, and p_A, respectively. The number of ticks that feed on the host during its infectious period depends on the average number of ticks of that stage on a host (N_{LH}, N_{NH}, or N_{AH}), the duration of attachment (D_L,

Table 1: Tick-related parameters

Parameter	Description	Estimate
E	Average no. eggs per adult	2,000[1,2]
s_L	Survival probability from egg to feeding larva	.05[1]
s_N	Survival probability from feeding larva to feeding nymph	.1[1]
s_A	Survival probability from feeding nymph to feeding adult	.1[1,a]
C_{LL}	Mean no. larvae cofeeding with a larva	30[3]
C_{NL}	Mean no. nymphs cofeeding with a larva	2[4]
C_{AL}	Mean no. adults cofeeding with a larva	.01[4]
C_{LN}	Mean no. larvae cofeeding with a nymph	20[2,3]
C_{NN}	Mean no. nymphs cofeeding with a nymph	1[4]
C_{AN}	Mean no. adults cofeeding with a nymph	.01[4]
C_{LA}	Mean no. larvae cofeeding with an adult	.01[4]
C_{NA}	Mean no. nymphs cofeeding with an adult	.01[4]
C_{AA}	Mean no. adults cofeeding with an adult	.01[4]
N_{LH}	Average no. larvae on competent host	6[3,5,6]
N_{NH}	Average no. nymphs on competent host	.2[5,6]
N_{AH}	Average no. adults on competent host	.001[4]
D_L	Days of attachment of larva	2.5[5]
D_N	Days of attachment of nymph	3.5[4]
D_A	Days of attachment of adult	12[4]

Sources: Superscript numbers correspond to the following references: 1, Randolph and Craine 1995; 2, Randolph 2004; 3, Randolph et al. 1999; 4, S. E. Randolph, unpublished manuscript; 5, Gray 2002; 6, Humair et al. 1999.

[a] Assuming half of the 20% survivors mentioned by Randolph and Craine (1995) will be female.

D_N, or D_A), and the duration of the infective period (i). It seems reasonable to assume that transmission takes place when the blood meal is taken, most likely on the last day of attachment when engorgement occurs. Hence, we multiply the average number of ticks per host with the probability that it is engorged (the reciprocal of the period of attachment); for example, if there are 12 ticks attached and the duration of attachment is 3 days, then on average four (i.e., 12 divided by three) of these ticks will be taking their blood meal on a specific day and be exposed to infection. This means, for example, that one systemically infected vertebrate host (type-at-birth 5) will then on average infect

$$k_{25} = \frac{p_L i N_{LH}}{D_L} \tag{3}$$

feeding larvae (type-at-birth 2).

Nonsystemic Transmission

Nonsystemic transmission is possible for all infectious ticks except those infected as an adult. Transmission events of this type for a tick infected as an egg (type-at-birth 1) may occur during its first, second, or third blood meal to, respectively, larvae (k_{21}), nymphs (k_{31}), or adult ticks (k_{41}), which is why these elements are the sum of three terms. Analogously, transmission from a tick infected as a larva (k_{22}, k_{32}, and k_{42}) consists of two terms, whereas a tick infected as a nymph (k_{23}, k_{33}, and k_{43}) has only one chance to pass on the infection, namely during the final blood meal that it takes as an adult. When calculating the number of "neighboring" ticks, which we denote C, the negative binomial distribution of the ticks over the hosts is taken into account, since it is known that ticks are not distributed evenly over hosts (Randolph et al. 1999; Perkins et al. 2003). The efficiency of transmission toward a cofeeding tick in stage j for a tick in stage i is θ_{ij}. In the calculations, all values of θ are assumed to be the same, since more detailed information is not available. As an example, a tick infected as an egg (type-at-birth 1) can infect nymphs while taking its first, second, and third blood meals:

$$k_{31} = (s_L\theta_{LN}C_{NL} + s_L s_N \theta_{NN} C_{NN} + s_L s_N s_A \theta_{AN} C_{NA}) h_C, \tag{4}$$

where, once again, the terms are weighted by the chances that a tick survives each life stage. The critical difference between systemic and nonsystemic transmission is that the former produces a new reservoir of infection (i.e., individuals of the fifth host type), while the latter is a means by which ticks may infect each other directly.

Transovarial Transmission

Transovarial transmission occurs when infected females that had either hatched from an infected egg themselves

Table 2: Pathogen-specific parameters

Parameter	Description	Lyme spirochetes	TBE virus
i	Systemic infection duration	120 days[1]	2 days[1]
θ^a	Efficiency from tick to tick	.56[2]	.55[3,4]
p_L	Efficiency from competent host to larva	.5[5]	.8[6]
p_N	Efficiency from competent host to nymph	.5[6]	.8[6]
p_A	Efficiency from competent host to adult	.4[7]	.8[6]
q_L	Efficiency from larva to competent host	.8[6]	.9[6]
q_N	Efficiency from nymph to competent host	.8[6]	.9[6]
q_A	Efficiency from adult to competent host	.8[6]	.9[6]
r_A	Efficiency from adult to egg	.10[8]	.001[9]

Sources: Superscript numbers correspond to the following references: 1, Randolph et al. 1996; 2, Gern and Rais 1996; 3, Labuda et al. 1993*a*; 4, Labuda et al. 1997; 5, Randolph and Craine 1995; 6, S. E. Randolph, unpublished manuscript; 7, Kurtenbach et al. 1994; 8, Hubálek and Halouzka 1998; 9, Danielova et al. 2002.

[a] Because of the lack of data, we assumed all transmission efficiencies between cofeeding ticks to be the same.

(k_{11}) or become infected as feeding larva (k_{12}), nymph (k_{13}), or adult (k_{14}) go on to produce infected eggs. We assume E eggs per female and a transmission probability of r_A. The expected number of infected eggs per individual is then the probability that the originally infected tick survives to be a female adult tick multiplied by Er_A. Hence the expected number of infected eggs laid by a tick that was infected itself via transovarial transmission equals

$$k_{11} = s_L s_N s_A E r_A, \tag{5}$$

where the survival probability s_A takes into account that only half of the ticks surviving to adulthood are female.

The Next-Generation Matrix

Summarizing then, we give the following general interpretation of the elements of the next-generation matrix. The elements k_{11}, k_{12}, k_{13}, and k_{14} all arise from transovarial transmission. The elements k_{21}, k_{22}, and k_{23}, as well as k_{31}, k_{32}, k_{33}, k_{41}, k_{42}, and k_{43}, involve nonsystemic transmission between ticks (cofeeding). And the nonzero elements in the fifth column (k_{25}, k_{35}, and k_{45}) and the fifth row (k_{51}, k_{52}, and k_{53}) represent transmission from systemic infected host to ticks and transmission from ticks to hosts, respectively. A schematic way of representing the next-generation matrix therefore is

$$\begin{bmatrix} \text{transovarial} & \text{transovarial} & \text{transovarial} & \text{transovarial} & 0 \\ \text{cofeeding} & \text{cofeeding} & \text{cofeeding} & 0 & \text{host} \rightarrow \text{L} \\ \text{cofeeding} & \text{cofeeding} & \text{cofeeding} & 0 & \text{host} \rightarrow \text{N} \\ \text{cofeeding} & \text{cofeeding} & \text{cofeeding} & 0 & \text{host} \rightarrow \text{A} \\ \text{tick} \rightarrow \text{host} & \text{tick} \rightarrow \text{host} & \text{tick} \rightarrow \text{host} & 0 & 0 \end{bmatrix}.$$

Application to TBE and Lyme Borreliosis

For TBE and Lyme borreliosis, the next-generation matrix described above was parameterized with values taken from the literature or based on expert knowledge (see tables 1, 2). Of course, many parameters are dependent on local circumstances, such as density and composition of the host populations, temperature, humidity, and other factors. However, for the sake of illustrating the method described here and for highlighting the differences between the two diseases, we use fixed point estimates. The fraction of blood meals taken on competent hosts (h_c) can vary substantially, so rather than reporting a single number for each infection, R_0 is shown as a function of h_c (fig. 1). We have also plotted the hypothetical curves for R_0 as they would be without the contribution from the nonsystemic transmission route; hence there are four curves.

The values of R_0 are substantially higher for Lyme borreliosis than for TBE and are largely insensitive as to whether nonsystemic transmission occurs. For TBE, however, values of $R_0 > 1$ are not reached unless nonsystemic transmission is included, implying that without this route of transmission, TBE would be able to neither establish nor persist. Our parameterization of the next-generation matrix suggests that even with nonsystemic transmission, a large fraction of blood meals must be taken from competent hosts for TBE to persist. The precise level of this fraction, however, may not be quite as high as suggested here on the basis of parameter values that are no more than current best guesstimates.

In the context of next-generation matrices, the sensitivity and elasticity of R_0 to changes in the reproduction numbers, k_{ij}, or the parameters defining them can be calculated with relative ease (see Caswell 2001, pp. 207–257). Sensitivities quantify how R_0 changes in response to small shifts in the value of a parameter, while elasticities quantify the proportional change in R_0 in response to a propor-

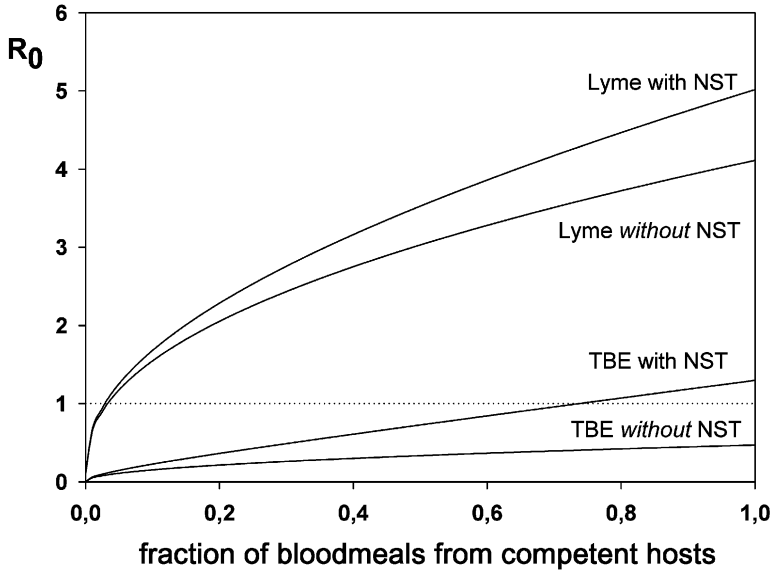

Figure 1: R_0 plotted as a function of the fraction of blood meals taken on competent hosts (h_c) for Lyme borreliosis and tick-borne encephalitis (TBE). For each disease, two curves are shown: R_0 with and without nonsystemic transmission (*NST*). Lyme borreliosis has a higher value of R_0 than TBE and is less dependent on nonsystemic transmission to establish.

tional change in a parameter. We note here that both sensitivities and elasticities are based on local linearization at the point estimate of the parameter, given the point estimates of all the other parameters. This means that extrapolation away from the parameter value (e.g., to estimate the effect of control measures) is not always justified (De Kroon et al. 2000).

Taken together, the set of sensitivity and elasticity values may be used to judge which parameters are important to measure accurately and where variation in parameters will translate into variation in R_0. In figure 2, we show the parameters with the highest sensitivity and elasticity values. We do this for two different values of the fraction of blood meals taken from competent hosts ($h_c = 0.2$ and 0.8).

Interpretation of these sensitivity and elasticity values is as follows. When looking at TBE, we see that the sensitivity of R_0 to the survival rate of nymphs (s_N) is very high, and the high elasticity value for this parameter supports this; apparently, changes in s_N will result in relatively large changes in R_0. In contrast, the transovarial transmission parameter (r_A) has a high sensitivity but a low elasticity value. An absolute change in a parameter with a small value like this ($r_A = 0.001$) has a large impact, whereas a proportional change in a parameter with a low value has little effect. Note that parameters that appear only in the entries of the next-generation matrix as a product (e.g., r_A and E) have equal elasticities. When judging the relative importance of parameters, elasticities are in a way more appropriate, since some of the parameters (such as s_N and r_A) are limited to the interval (0,1) while others (such as C_{LN} and i) are numbers of ticks or numbers of days (see Caswell 2001, pp. 207–257).

For TBE, the elasticities of R_0 to θ_{NL} and C_{LN} are relatively high. These two parameters refer to the transmission from infective nymphs to cofeeding larva. The high elasticities of efficiency of transmission from host to larva (p_L) and from nymph to host (q_N) suggest that systemic transmission from a nymph to a host and from a host to larvae could make an important contribution to the total transmission.

The results for Lyme borreliosis give a vastly different picture. The sensitivities and elasticities of R_0 are relatively high for a much broader set of parameters: s_N, s_L, s_A, E, r_A, and q_L, as well as all those just listed for TBE. The parameters relating to cofeeding (C_{LN} and θ_{NL}) feature less prominently for Lyme borreliosis.

As R_0 increases with the fraction of blood meals taken on competent hosts (h_c), for both diseases, sensitivity values also increase with h_c. Elasticity values can either increase or decrease (see, e.g., C_{LN} and p_L in fig. 2*D*). This effect is stronger for TBE than for Lyme borreliosis, which can be related to the result that the contribution that the different transmission routes make to the overall transmission is rather constant over h_c for Lyme borreliosis, whereas it changes significantly with h_c for TBE (as shown in fig. 3).

For field studies, the parameters that are absent from this discussion are also interesting. These results suggest

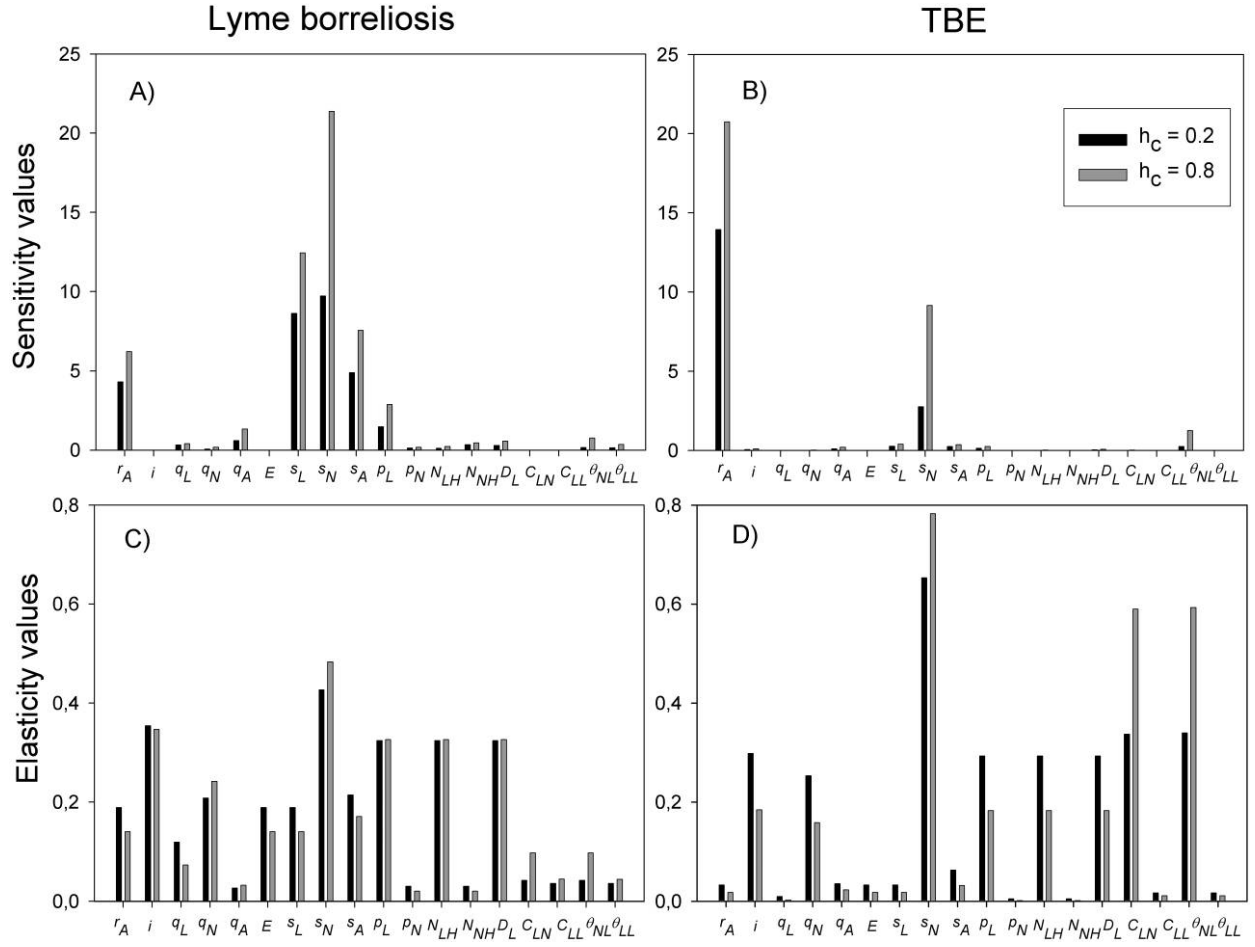

Figure 2: Parameters with the highest sensitivity and elasticity values for Lyme borreliosis and tick-borne encephalitis. The values are computed for two values for the fraction of blood meals taken on competent hosts: $h_c = 0.2$ (*black*) and $h_c = 0.8$ (*gray*). A parameter was included in the subset shown in the figure if either of the sensitivity values was larger than 1 or if either of the elasticity values was larger than 0.03.

that for both diseases, if one is interested in measuring R_0, then rough estimates for D_N, D_A, most of the θ's, most of the C's, and q_A will be adequate.

The elasticities of R_0 with respect to the elements of the next-generation matrix (the k_{ij}) provide another means of comparing the two tick-borne infections. These elasticities may be interpreted as relative contributions to R_0 (De Kroon et al. 1986). This is particularly useful because the contribution of each element may be classified as arising from either systemic, nonsystemic, or transovarial transmission (only one type of transmission is possible between any two types). Hence, we show for each of the three transmission routes the respective contributions to R_0 (i.e., the sum of the elasticities of the elements that relate to the transmission route) in figure 3. This figure clearly depicts the contrast between the two disease systems: Lyme borreliosis is maintained by systemic transmission, whereas (when h_c is large enough so that $R_0 > 1$) TBE depends on nonsystemic transmission. Finally, we note that we could reproduce the switch between relying mostly on systemic transmission and relying mostly on nonsystemic transmission just by changing the duration of infection either from 120 to 2 days (in the next-generation matrix for TBE) or from 2 to 120 days (in the next-generation matrix for Lyme disease).

Discussion and Conclusion

We have presented a method to calculate the basic reproduction number, R_0, for complex disease systems, with multiple types-at-birth and several transmission routes. We used this method to derive an expression for R_0 for tick-borne infections. This number captures the growth in the number of infecteds on a generational basis and hence has a biological interpretation very close to that of R_0 for

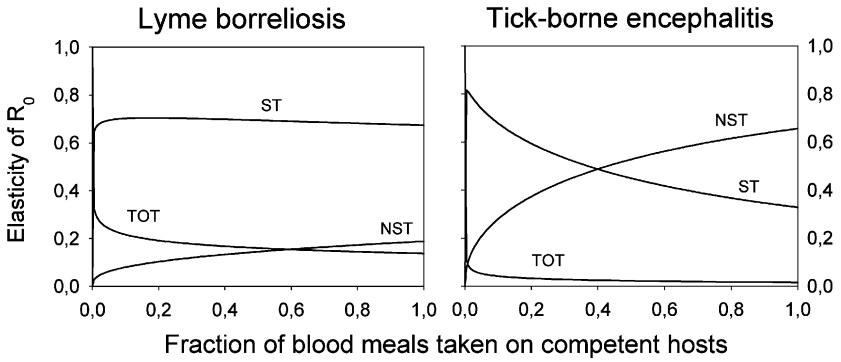

Figure 3: Relative contributions to R_0 from systemic transmission (*ST*), nonsystemic transmission (*NST*), and transovarial transmission (*TOT*). The contributions shift with the fraction of blood meals taken on competent hosts (h_c). Note that in our system, R_0 for tick-borne encephalitis is <1 for most values of h_c.

simpler disease systems. This alone sets the work apart from previous attempts (Randolph and Craine 1995; Norman et al. 1999; Rosà et al. 2003) to express R_0 for tick-borne infections.

For TBE virus, a basic reproduction number based on a next-generation matrix was published by Foppa (2005), but this approach is restrictive in the sense that longitudinal tick infestation data are a prerequisite and (in the words of the author) the constituent parameters are, for all practical purposes, unobservable. These difficulties arise, at least in part, because Foppa (2005) divided the tick population into types-at-birth using an abstract index that was said to capture the relevant epidemiological heterogeneity but was otherwise left undefined.

In contrast to Foppa (2005), we divided the population of infectious ticks into a small set of types-at-birth on the basis of the fact that ticks bite only once per life stage. This led to a set of next-generation matrix elements with a clear biological interpretation and with all parameters having a clear biological definition. This point is well illustrated by the fact that parameterization of the next-generation matrix was possible for both Lyme borreliosis and TBE. The elements of the matrix also have the useful property that they reflect transmission of only one type.

Our results indicate that Lyme borreliosis has a considerably higher R_0 than TBE, which is consistent with earlier findings (Randolph et al. 1996) and the well-recorded much more patchy distribution of TBE, indicating a more fragile transmission cycle (Randolph and Rogers 2000). The elasticity analysis reveals that the contribution made by the transmission routes differs substantially between the disease systems; TBE virus depends on nonsystemic transmission, whereas *Borrelia burgdorferi* s.l. is maintained by systemic transmission. This difference in contributions between the two diseases has been related to the difference in duration of the systemic infection in the host (Randolph et al. 1996). Indeed, just by changing the duration of infection in the next-generation matrix, we can switch the major contribution to R_0 from systemic transmission to nonsystemic transmission and vice versa. For TBE, which causes a very short period of systemic infection, nonsystemic transmission is crucial for transmission between ticks. Lyme borreliosis, on the contrary, causes long-lasting systemic infection in a host, which will in time infect a large number of ticks. The occasional cofeeding event is then of smaller relative importance, although it permits rapid transmission before systemic infections develop (Gern and Rais 1996). This difference between the two pathogens is consistent with earlier findings (Labuda et al. 1993*a*; Randolph et al. 1996). More specifically, our analysis at the parameter level indicated that the cofeeding between larvae and nymphs is very important for TBE. This is possible only when larvae and nymphs show synchronous seasonal feeding activity, which occurs only under certain seasonal temperature conditions (Randolph et al. 2000), thereby explaining the focal distribution of TBE in Europe. It may also be one factor, but only one among many others, in the recent upsurges in TBE observed in much of Europe coincident with climate change (Sumilo et al. 2007).

The sensitivity and elasticity analysis on parameter level also indicates that having accurate measures for some parameters, such as the survival from larval to nymph stage (s_A), is much more important than, for instance, accurately estimating the transmission efficiencies of combinations of cofeeding ticks that hardly ever occur (e.g., two adult ticks cofeeding on a competent host).

We have made a number of simplifications in order to represent the complex pathogen transmission systems for tick-borne diseases as a set of constant elements in a next-

generation matrix. For example, the efficiency of nonsystemic transmission is assumed to be a constant, regardless of the distance between ticks, whereas, for instance, ticks feeding on different ears of a mouse are known to offer reduced potential for nonsystemic transmission. Host densities are implicitly assumed to be constant because it was assumed that all the parameters that depend on host density and species composition of hosts—such as the survival probabilities, the numbers of ticks per host, and the numbers of cofeeding ticks—are constants. A next step would be to include the interactions in the population dynamics of ticks and hosts. We have also not represented any of the tick-host interactions that are observed, for example, the host immune response to tick infestation. In endemic areas, host immune responses to pathogens play a role (Kurtenbach et al. 1994; Ogden et al. 2002), but for R_0, which by definition reflects establishment in a totally susceptible population, this can be ignored. The TBE-related mortality in infected hosts is implicitly taken into account by assuming a very short duration of systemic infection (infection ends either by death of the host or by loss of infectiousness). Future work will be needed to improve the parameterization of this model, especially for the complex Lyme borreliosis system in which a wide range of hosts contributes to spirochete transmission, each of which characteristically feeds different numbers of each tick stage.

The next-generation matrix presented here can also be parameterized with relationships between parameters and climatic variables such that R_0 itself is a function of those variables. Seasonality and spatial heterogeneity in a wide range of environmental conditions is known to be important for vector-borne diseases in general, and this also applies to tick-borne diseases (Randolph and Rogers 2000). Hence, for example, if relationships between temperature variables and tick survival probabilities are known, then predictions may be made about the effect of climate change on the establishment of tick-borne diseases. This can further translate into predictions about the spatial distribution of tick-borne disease resulting from a given climate change scenario. The resulting maps would go beyond predicting future absence and presence since the magnitude of R_0 is also a measure of the risk of establishment, given that a single infected individual has been introduced.

Through the detailed description of the calculation of R_0 for tick-borne infections, we have illustrated the procedure to characterize the basic reproduction ratio for systems involving multiple species, multiple transmission routes, and multiple life-history stages. This procedure, while well known and much used in the biomathematical literature, has not been used to its full potential in the more biological literature and studies of the ecology of infectious disease (but see Hudson et al. 2002; Hartemink et al. 2007). We hope that our more biological description of the procedure and its formal background will help in promoting the proper calculation of this very useful quantity.

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APPENDIX A

Description of Elements of the Next-Generation Matrix

Each of the elements k_{ij} represents the expected number of new cases of type-at-birth i caused by one infected individual of type-at-birth j during its entire infectious period. The type-at-birth refers to the type at the moment of infection and should not be confused with the type at the moment at which an individual infects a new individual. The interpretation of the elements is given in some detail in the main text.

$$k_{11} = s_{\mathrm{L}} s_{\mathrm{N}} s_{\mathrm{A}} E r_{\mathrm{A}},$$

$$k_{12} = s_{N} s_{\mathrm{A}} E r_{\mathrm{A}},$$

$$k_{13} = s_{\mathrm{A}} E r_{\mathrm{A}},$$

$$k_{14} = E r_{\mathrm{A}},$$

$$k_{15} = 0,$$

$$k_{21} = (s_{\mathrm{L}} \theta_{\mathrm{LL}} C_{\mathrm{LL}} + s_{\mathrm{L}} s_{\mathrm{N}} \theta_{\mathrm{NL}} C_{\mathrm{LN}} + s_{\mathrm{L}} s_{\mathrm{N}} s_{\mathrm{A}} \theta_{\mathrm{AL}} C_{\mathrm{LA}}) h_{\mathrm{C}},$$

$$k_{22} = (s_{\mathrm{N}} \theta_{\mathrm{NL}} C_{\mathrm{LN}} + s_{\mathrm{N}} s_{\mathrm{A}} \theta_{\mathrm{AL}} C_{\mathrm{LA}}) h_{\mathrm{C}},$$

$$k_{23} = (s_{\mathrm{A}} \theta_{\mathrm{AL}} C_{\mathrm{LA}}) h_{\mathrm{C}},$$

$$k_{24} = 0,$$

$$k_{25} = \frac{p_{\mathrm{L}} i N_{\mathrm{LH}}}{D_{\mathrm{L}}},$$

$$k_{31} = (s_L\theta_{LN}C_{NL} + s_Ls_N\theta_{NN}C_{NN} + s_Ls_Ns_A\theta_{AN}C_{NA})h_C,$$

$$k_{32} = (s_N\theta_{NN}C_{NN} + s_Ns_A\theta_{AN}C_{NA})h_C,$$

$$k_{33} = (s_A\theta_{AN}C_{NA})h_C,$$

$$k_{34} = 0,$$

$$k_{35} = \frac{p_N i N_{NH}}{D_N},$$

$$k_{41} = (s_L\theta_{LA}C_{AL} + s_Ls_N\theta_{NA}C_{AN} + s_Ls_Ns_A\theta_{AA}C_{AA})h_C,$$

$$k_{42} = (s_N\theta_{NA}C_{AN} + s_Ns_A\theta_{AA}C_{AA})h_C,$$

$$k_{43} = (s_A\theta_{AA}C_{AA})h_C,$$

$$k_{44} = 0,$$

$$k_{45} = \frac{p_A i N_{AH}}{D_A},$$

$$k_{51} = (s_Lq_L + s_Ls_Nq_N + s_Ls_Ns_Aq_A)h_C,$$

$$k_{52} = (s_Nq_N + s_Ns_Aq_A)h_C,$$

$$k_{53} = s_Aq_Ah_C,$$

$$k_{54} = 0,$$

$$k_{55} = 0.$$

APPENDIX B

Sensitivity and Elasticity Analysis

Sensitivity

The sensitivity s_{ij} of a matrix element k_{ij} is defined as the change in the eigenvalue (R_0) as a result of a change in k_{ij}:

$$s_{ij} = \frac{\partial R_0}{\partial k_{ij}}.$$

The sensitivity values s_{ij} together form a sensitivity matrix $\mathbf{S}_{ij}$ that can be calculated from the left and right eigenvectors of the next-generation matrix corresponding to the dominant eigenvalue R_0 (Caswell 2001). A computer program that calculates the eigenvalues of a matrix also supplies the corresponding eigenvectors.

Elasticity

The elasticity e_{ij} of matrix element k_{ij} is defined as the proportional change in R_0 due to a proportional change in the matrix element:

$$e_{ij} = \frac{k_{ij}}{R_0}\frac{\partial R_0}{\partial k_{ij}}.$$

Sensitivity and Elasticity to Individual Parameters

The sensitivity of R_0 to changes in an individual parameter a is calculated as the sum of the partial derivatives of the element to a, multiplied by the sensitivity value of R_0 to the element, for each element in which a is present:

$$\text{Sensitivity}_a = \sum_{\text{all elements with } a} \frac{\partial k_{ij}}{\partial a}\frac{\partial R_0}{\partial k_{ij}}.$$

Once the sensitivity of R_0 to a parameter a has been calculated, a simple multiplication with a/R_0 will give the elasticity value.

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