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Population Dynamics of Pathogens with Multiple Host Species

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abstract: Pathogens that can infect multiple host species will have different dynamics than pathogens that are restricted to a single species of host. This article examines the conditions for establishment and long-term population dynamic behavior of pathogens that infect multiple species of hosts. The article attempts to address three major questions in this area: First, under which conditions will increases in the diversity of host species buffer infectious disease outbreaks, and under which conditions will host diversity amplify disease outbreaks? Second, under what conditions is it possible to control an infectious agent by focusing control against only one host species? Third, what role does host species diversity play in maintaining pathogen persistence? The answers to these questions supply some important general insights into the role that biodiversity plays in buffering humans and other species against new and emerging pathogens.

Keywords: pathogen, multihost, mathematical model, R_0, matrix, who acquires infection from whom (WAIFW).

Ecological studies of host-pathogen systems have largely focused on single species of hosts infected with a single species of pathogen (Anderson and May 1991; Grenfell and Dobson 1995). There is a relative paucity of models and empirical data for the dynamics and impact of pathogens that infect multiple species of hosts (Anderson and May 1986; Begon et al. 1992; Norman et al. 1994; Woolhouse et al. 2001) or of multiple species of pathogens that infect a single host (Dobson 1990; Dobson and Roberts 1994; Roberts and Dobson 1995). Important exceptions are either systems where transmission is mediated by a vector (Ostfeld and Keesing 2000*a*, 2000*b*) or studies of plant pathogens in host communities that either are genetically diverse or consist of multiple host species (Garrett and Mundt 1999; Mitchell et al. 2002, 2003). As worries about emerging diseases and pathogen pollution increase (Daszak et al. 2000), a central problem in epidemiology is to develop a framework for examining the population dynamics of pathogens that infect multiple species of hosts.

In this article, I review and develop a set of theoretical analyses that directly address a number of key questions in the dynamics of multiple-host single-pathogen systems. In particular, I focus on three key questions in pathogen ecology. First, under which conditions will increases in the diversity of host species buffer infectious disease outbreaks, and under which conditions will host species diversity amplify disease outbreaks? The model framework developed for these analyses can then be used to briefly examine a second central question in pathogen ecology: under what conditions is it possible to control an infectious agent by focusing control against only one host species? This work on the role of host diversity on pathogen abundance will be complemented by theoretical and empirical analyses that address the third key question in this area, namely, what role does host species diversity play in maintaining pathogen persistence?

The Model

The transient dynamics of pathogens that infect multiple hosts may be explored using multiple sets of coupled differential equations that correspond to the multispecies susceptible-infectious-recovered (SIR) model:

$$\frac{dS_i}{dt} = (b_i - \Delta_i N_i)N_i - d_i S_i - S_i \sum_{j=1,\,n} \beta_{ij} I_j, \quad (1)$$

$$\frac{dI_i}{dt} = S_i \sum_{j=1,\,n} \beta_{ij} I_j - (d_i + \alpha_i + \sigma_i) I_i, \quad (2)$$

$$\frac{dR_i}{dt} = \sigma_i I_i - d_i R_i. \quad (3)$$

Here, we assume that each host population is divided into susceptible, infectious, and recovered (and immune) hosts; these are designated *S*, *I*, and *R*, respectively, and the rest of the model's parameters are defined in table 1. Initially, we will focus on pathogens that are directly transmitted, although I indicate important results that have implications for vector-transmitted pathogens. Models for

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Table 1: Definition of parameters used in the model

Parameter	Definition
b_i	Per capita birth rate of host species i
d_i	Per capita death rate of host species i
Δ_i	Per capita density-dependent reduction in birth rate of host species i
β_{ij}	Per capita rate of pathogen transmission from host species j to host species i
α_i	Per capita additional mortality of host species i when infected with the pathogen
σ_i	Per capita rate of recovery of species i from infection
K_i	Density to which species i equilibrates in the absence of the pathogen (eq. [4])
c_{ij}	Proportional scaling parameter that modifies between-species transmission from an arithmetic mean of their within-species rates
τ_{ij}	Net rate of infection from species j to species i

vector-transmitted pathogens that explicitly include vectors are by definition more complex; some initial models that build on the work described here are described in A. Dobson (unpublished manuscript). The basic models used here assume no competitive or predatory interactions between the host species; under these circumstances and in the absence of the pathogen, each species settles to an equilibrium density, K_i:

$$K_i = \frac{(b_i - d_i)}{\Delta_i}. \tag{4}$$

If the hosts compete for food resources or share common predators, then more complicated dynamics will result; for the sake of clarity, I shall ignore those conditions here and explore their consequences in more detail in a later article. I also assume that interactions between host populations are well mixed and that their dynamics may be captured by the mean field approximation. This assumption can also be relaxed and its consequences explored for specific systems for which empirical data on the spatial distribution of hosts and their pathogens exists.

Models for multihost pathogens have to consider two components of transmission: within-species transmission and between-species transmission. Pathogen transmission is always a complex function of host physiology, behavior, immunity, and ecology. Mathematical ecologists tend to obscure the biological details of this within a single transmission parameter, usually designated β. Here, I will adopt a simple convention and initially assume that interspecific transmission between species varies as the mean of their within-species transmission rates modified by a constant scaling factor that varies between 0 and unity. Thus, transmission from species j to species i will be given by

$$\beta_{ij} = c_{ij}\left(\frac{\beta_{ii} + \beta_{jj}}{2}\right). \tag{5}$$

Here the parameter c_{ij} is a scaling parameter that allows us to adjust the magnitude of between-species transmission rates. The primary advantage of adopting this approach is that it allows us to utilize a single parameter to examine how the dynamics of the system respond to changes in the relative intensity of within- versus between-species transmission. I explicitly assume rates of between-species transmission are lower than rates of within-species transmission; this largely reflects the ecological assumption that species tend to have more interactions with individuals of the same species than with individuals of other species. We can envision hypothetical situations in which rates of between-species transmission are higher than rates of within-species transmission; for example, between-species rates of transmission may be higher in situations where pathogens are transmitted by free-living infective stages whose hosts have sequential usage of pasture. We can easily explore these modifications within our model framework (by including an additional expression for pathogen free-living stages) but feel they are less common than cases where within-species transmission exceeds between-species transmission. We could also use this framework to examine the consequences of within-species transmission being either unusually low, as will occur when the pathogen is unable to develop in the host, or unusually high, as will occur when the hosts sustain infections for a prolonged period of time or live in dense aggregations where transmission rates are high. This latter case closely corresponds to rinderpest in wildebeest and buffalo herds. Here, frequent spillovers from cattle can cause widespread mortality in wildebeest, even though the wild hosts cannot sustain the pathogen in areas where

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cattle populations are vaccinated (Plowright 1982; Dobson 1995).

The simplest next step would be to explore the dynamic properties of models where we allow c_{ij} (between-species transmission scaling) to vary between 0 and unity and assume that between-host transmission is symmetrical and that the individuals of all host species are well mixed. However, there are many interesting empirical situations where between–host species transmission is asymmetrical, particularly the cases where "chains" of species are linked in a unidirectional fashion, the case that arguably corresponds to most "emerging" pathogens. Ultimately the values of c_{ij} will significantly reflect the spatial distribution of the different host species. Thus, asymmetries in the magnitude of c_{ij} and c_{ji} will reflect a complex mix of habitat and resource uses. I will return to this point when we discuss the transient dynamics of multihost pathogen systems, but first let us derive expressions for R_0, the basic reproductive number, for pathogens that infect multiple host species. This will allow us to derive some basic but fundamental properties of symmetrical and asymmetrical multihost pathogen models.

Basic Reproductive Rate for Pathogens That Infect Multiple Hosts

The dynamics of pathogens whose populations are subdivided into age or sex classes can be examined within a matrix framework that characterizes rates of infection between each section of the host community (Anderson and May 1984; Anderson et al. 1989; Gupta et al. 1989). When extending these models to examine the transmission dynamics of pathogens that infect multiple host species, we initially ignore heterogeneities due to social organization or age and sex considerations within each species, and we focus on the dynamic consequences of simple within– and between–host species transmission. These two forms of transmission will have a number of interacting components: the spatial distribution of each host species (mainly driven by the interaction between their social organization and the underlying pattern of resource availability), the within- and between-species contact rates, and two physiological components that determine susceptibility when exposed to infection and the rate at which hosts incubate and produce infective stages.

Between-Species Transmission

Initially, we assume that all of the different components of transmission from individuals of host species j to host species i can be captured by a single transmission parameter, τ_{ij}. This allows us to construct a matrix of transmission values termed a "who acquires infection from whom" (WAIFW) matrix, (Schenzle 1984; Anderson and May 1985). In the case of a simple three-species system, this matrix takes the form

$$\mathbf{W} = \begin{pmatrix} \tau_{i,i} & \tau_{j,i} & \tau_{k,i} \\ \tau_{i,j} & \tau_{j,j} & \tau_{k,j} \\ \tau_{i,k} & \tau_{j,k} & \tau_{k,k} \end{pmatrix}. \tag{6}$$

The elements of the matrix characterize the rates of infection between all possible combinations of species. Plainly, it would be possible to modify each of the τ_{ij} terms to explicitly consider the contact rates between species, the overlap in their spatial distributions, and the physiological components of susceptibility and transmission.

An important result derived by Diekmann, Heesterbeek, and colleagues (Diekmann et al. 1990) allows us to modify this WAIFW matrix and produce an estimate of the basic reproductive rate of the pathogen, R_0. In order to do this, we need to expand each term in the matrix described above so that it corresponds to the rate of transmission between pairs of species times the average duration of infection for an infectious individual of the species transmitting the pathogen. This would give a new matrix, $\mathbf{G}$[1], each of whose elements is the rate of transmission from species i to species j times the duration of time for which an individual of species i is infectious:

$$\mathbf{G} = \begin{pmatrix} \dfrac{\beta_{i,i}p_{i,i}}{(\alpha_i + \delta_i + d_i)} & \dfrac{\beta_{j,i}p_{j,i}}{(\alpha_i + \delta_i + d_i)} & \dfrac{\beta_{k,i}p_{k,i}}{(\alpha_i + \delta_i + d_i)} \\ \dfrac{\beta_{i,j}p_{i,j}}{(\alpha_j + \delta_j + d_j)} & \dfrac{\beta_{j,j}p_{j,j}}{(\alpha_j + \delta_j + d_j)} & \dfrac{\beta_{k,j}p_{k,j}}{(\alpha_j + \delta_j + d_j)} \\ \dfrac{\beta_{i,k}p_{i,k}}{(\alpha_k + \delta_k + d_k)} & \dfrac{\beta_{j,k}p_{j,k}}{(\alpha_k + \delta_k + d_k)} & \dfrac{\beta_{k,k}p_{k,k}}{(\alpha_k + \delta_k + d_k)} \end{pmatrix}. \tag{7}$$

Here, d_i is the mortality rate of host species i, α_i is the pathogen-induced host mortality rate of host species i, and δ_i is the recovery rate of an infected individual of host species i. The p_{ij} terms determine whether transmission is density dependent, frequency dependent, or via a vector. These first two terms have also been called pseudo–mass action and true mass action, respectively, by De Jong (De Jong et al. 1995). Where transmission is frequency dependent, the p_{ij} terms are unity (times the relative proportion of interspecific contacts). Where transmission is density dependent, the p_{ij} terms correspond to the product of the density of species j and the proportion of total

[1] Diekmann et al. (1990) term this matrix **K**; I use **G** to avoid confusion with carrying capacity (eq. [4]).

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contacts that species j has with species i. In the vector-transmitted case, the p_{ij} terms correspond to vector density times the proportion of vectors that first bite species j and then bite species i. Diekmann et al. (1990) show that the spectral radius (dominant eigenvalue) of **W** (and whence **G**) is equivalent to the basic reproductive rate R_0 of a pathogen whose transmission dynamics are described by the coupled sets of differential equations (eqq. [1]–[3]) whose initial dynamics in the presence of a single infected individual are governed by the properties of this matrix, **G** (eq. [7]). Although analytical solutions may only be obtained for the simplest two-host communities (Holt and Pickering 1985; Begon and Bowers 1995; Holt et al. 2003), it is simple to determine qualitative values of R_0 for more complex communities and to derive several important results by inspection. The simplest two-species case provides important insights into the conditions for establishment of a pathogen that infects multiple host species (fig. 1; appendix). In the case of density-dependent transmission, increased abundance of either host species leads to an increase in R_0; however, notice that a doubling of abundance of the host species with the smaller body mass has a much larger impact on R_0. In contrast, addition of a second host species leads to an initial reduction in R_0 when transmission is frequency dependent; this buffering occurs until one of the hosts becomes sufficiently abundant to dominate R_0, when further increases in this host's abundance lead to further increases in R_0. Figure 1 also illustrates that the dynamics of the frequency-dependent model are almost identical to a model that explicitly includes vectors. Here again, initial inclusion of second species always reduces R_0; however, when the second host species becomes sufficiently abundant, further increases in host density lead to an increase in R_0. Here it is also important to notice that R_0 is more sensitive to the abundance of the host with the larger body mass.

Full Multihost Species Case

In the case of pathogens that infect multiple species, all elements of the next-generation matrix, **M** (eq. [7]), will be nontrivial. The basic two-host species of this version of the model has been explored previously by a number of authors (Holt and Pickering 1985; Begon et al. 1992; Begon and Bowers 1994; Greenman and Hudson 1997, 2000; Hudson and Greenman 1998; Holt et al. 2003). Two central results emerge from these earlier models: the presence of shared pathogens can create a powerful form of (frequency dependent) indirect competition that allows species that would otherwise exclude each other to coexist, and coexistence of the hosts and persistence of the pathogen is dependent on rates of within-species transmission exceeding rates of between-species transmission, as was first pointed out by Holt and Pickering (Holt and Pickering 1985; Begon and Bowers 1995). The next-generation matrix approach described above (eq. [7]) allows us to extend these results to the n-species case. Initially, consider a system in which four host species share a common pathogen such as canine distemper, rinderpest, or anthrax; any attempt to model this type of system will be frustrated by the huge numbers of parameters that need to be estimated. One way to simplify this problem is to scale the parameters of the model as allometric functions of the body sizes of the host species.

Allometric Scaling of Multispecies Epidemics

The population density and birth and death rates of most vertebrate species tend to scale allometrically with their body sizes (Charnov 1983; Peters 1983). Work by De Leo and Dobson (1996) suggests that the dynamics of a variety of epidemiological models may be usefully explored by scaling their parameter values as functions of host body size. This approach is particularly helpful for estimating rates of pathogen transmission; because nearly all other parameters of simple SIR pathogens are functions of host body size, transmission rate can usually be estimated at the threshold value that just allows the pathogen to establish ($R_0 = 1$). Two important insights are gained from adopting this approach: first, the interval between disease outbreaks will tend to scale with host body size (this is intuitive because host birth rate is the primary determinant of the rate at which new susceptibles are created); second, minimum transmission rates necessary for pathogen establishment tend to decrease with host body size if transmission is frequency dependent (pure mass action), while they increase with host body size if transmission is density dependent (pseudo–mass action; De Leo and Dobson 1996). This is less intuitive but essentially reflects the strong dependence of transmission efficiency on population density in density-dependent systems, while transmission is more dependent on the longevity of infected hosts in frequency-dependent systems (fig. 1). Recent work (Cable and Enquist 2004) suggests that key epidemiological features of the pathogen's interaction with its host may also illustrate subtle forms of allometric scaling; for example, the incubation periods of rabies, pseudorabies, and anthrax seem to scale with host body size, as do the times to death of hosts infected with these pathogens. Cable and Enquist (2004) argue that these results reflect the underlying cell cycle dynamics between the pathogen and the host's immune systems; if this result is more general, it certainly will be useful for examining the dynamics of pathogens that may infect multiple hosts.

This scaling of parameters to body size allows us to use the next-generation matrices (eq. [7]) to explore the dy-

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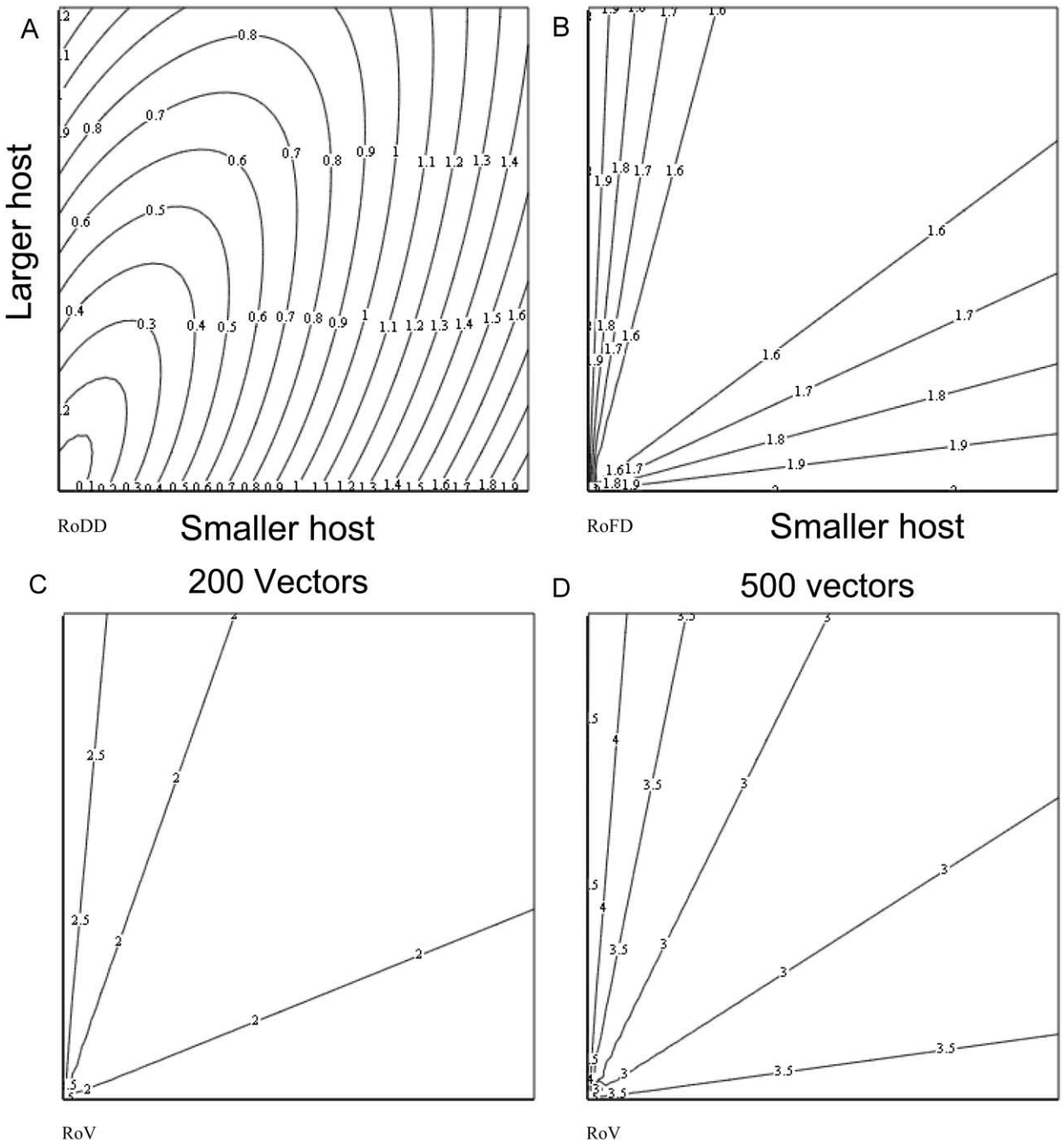

Figure 1: Thresholds for disease establishment in the density-dependent, frequency-dependent, and vector-transmitted cases. *A*, *B*, Cases where transmission is density dependent and frequency dependent, respectively. *C*, *D*, Cases for vector transmission with 200 and 500 vectors, respectively. In each case, the *X*-axis is the magnitude of the host species with smallest mass (here 1 kg), and the *Y*-axis is the abundance of the host with larger body mass (5 kg). The axes are drawn on a linear scale and range from 0 to twice the carrying capacity for a host of this body size. Each host would settle to its carrying capacity in the absence of the pathogen (there is no direct competition between the hosts). The contour lines give the magnitude of R_0 for a pathogen that causes a 50% reduction of life expectancy but has no impact on fecundity. The contours illustrate the expected magnitude of R_0, assuming transmission scales in the way derived by De Leo and Dobson (1996; e.g., $\beta[i, i] = R_0\{0.0247 \times m \times w[i] \wedge 0.44\}$); here m is the proportional increase in mortality of the host due to the presence of the pathogen ($=2.1$ in these simulations, with $R_0 = 1.5$). In all cases, w(i) is the body mass of smallest host species and is set at 1 kg. The expressions for R_0 in each case are derived in the appendix.

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namics of multihost pathogens in regions of parameter space where hosts and pathogen are likely to persist. We can then modify the pathogen or host parameters to examine ways in which biological changes in susceptibility, virulence, or transmission cause persistence of the pathogen or any one of its hosts to break down. Initially, let us use the approach to examine how changes in host diversity affect the basic reproductive number of the pathogen, R_0. The magnitude of this parameter determines whether the pathogen can invade a community of host species. This will allow us to address a central question in the field of biodiversity and conservation biology: Does increased diversity of host species tend to buffer or amplify disease outbreaks? In the simplest case, the potential for disease outbreaks will be determined by the magnitude of R_0. The consequences of increasing host diversity and modifying the relative magnitude of within- and between-species transmission are illustrated in figure 2. Two important results emerge: First, in the density-dependent case, increases in species diversity lead to increases in the number of contacts between infected individuals and potentially susceptible hosts. Increased host diversity will always lead to increased values of R_0 and a greater potential for disease outbreaks, particularly when rates of between-species transmission approach those for within-host transmission. In contrast, where transmission is characterized by frequency-dependent dynamics, increases in interspecific transmission lead to reductions in within-species transmission; this tends to buffer the tendency for outbreaks to occur, and it is possible for increased host species diversity to lead to significant reductions in R_0. This result corresponds to those obtained in studies of tick- or flea-transmitted pathogens (Ostfeld and Keesing 2000*a*, 2000*b*; LoGuidice et al. 2003). In contrast, the density-dependent case is likely to correspond to the case for pathogens such as rinderpest or rabies in East Africa, where the pathogen requires a diversity of hosts in order to establish.

Force of Infection

A second important result that emerges straightaway from the transmission matrices is expressions for the force of infection experienced by each host species and the force of infection exerted by each host species. These are simply the sum of each row and column, respectively, in equation (7). Thus, the force of infection exerted on species j by the rest of the community is

$$\lambda_j = \tau_{ji} + \tau_{jj} + \tau_{jk}. \tag{8}$$

In the same way, we can calculate the force of infection placed on other species due to the presence of infections in species j:

$$\lambda_{Cj} = \tau_{ij} + \tau_{jj} + \tau_{kj}. \tag{9}$$

Calculation of this expression for each host species in the community should allow us to identify the species that makes the largest contribution to epidemic outbreaks. In cases where this expression is significantly larger for one species than for all others in the community, this is the species against which we must focus control efforts to contain the pathogen. A dramatic example of this approach would be the control of rinderpest virus (RPV) in East Africa (Plowright and McCullough 1967; Plowright and Taylor 1967; Plowright 1968). Although RPV infected a large number of artiodactyl species, cattle were the only hosts to be vaccinated. As levels of immunological resistance increased in cattle, RPV disappeared from wild ungulates, suggesting that cattle were the reservoir species that caused frequent spillover infections into wildlife.

Recent work by Fulford, Roberts, and Heesterbeek (Fulford et al. 2002; Roberts and Heesterbeek 2003) provides an important method for examining the efficiency of pathogen control when focused against one stage or host of a pathogen with a complex life cycle. Their approach is based on methods derived from a similar approach to the one described here. Rather than reiterate their results, I will simply point the reader in the direction of these articles and emphasize that the methods can readily be applied to cases where pathogens can infect multiple species of hosts.

Important insights into the dynamics of multihost pathogens may be obtained by even heuristic exploration of equations (8) and (9) for different pathogens. For example, many bird species as well as humans and horses and even crocodilians are all potential hosts for West Nile virus (WNV; Anderson et al. 1999; Bernard et al. 2001). Although the pathogen is vector transmitted by a number of mosquito species, let us assume that this transmission is fast and can be collapsed into the transmission terms of our next-generation matrix (eq. [7]). Humans are incapable of transmitting the pathogen back to mosquitoes and so exert zero force of infection on other host species (although humans have transmitted the pathogen to other humans following tissue transplants). More subtly, many crows found dead have been infected with WNV, and experimental infections suggest they die within days of infection. This led to the suggestion that they were important reservoirs for the pathogen. However, if they only live for a limited time following infection, the force of infection they exert on other species is likely to be low. In contrast, house sparrows *Passer domesticus* show little pathology to WNV but can transmit the pathogen back to mosquitoes; the abundance of house sparrows and their high level of resistance may considerably enhance the force of infection they exert on other species.

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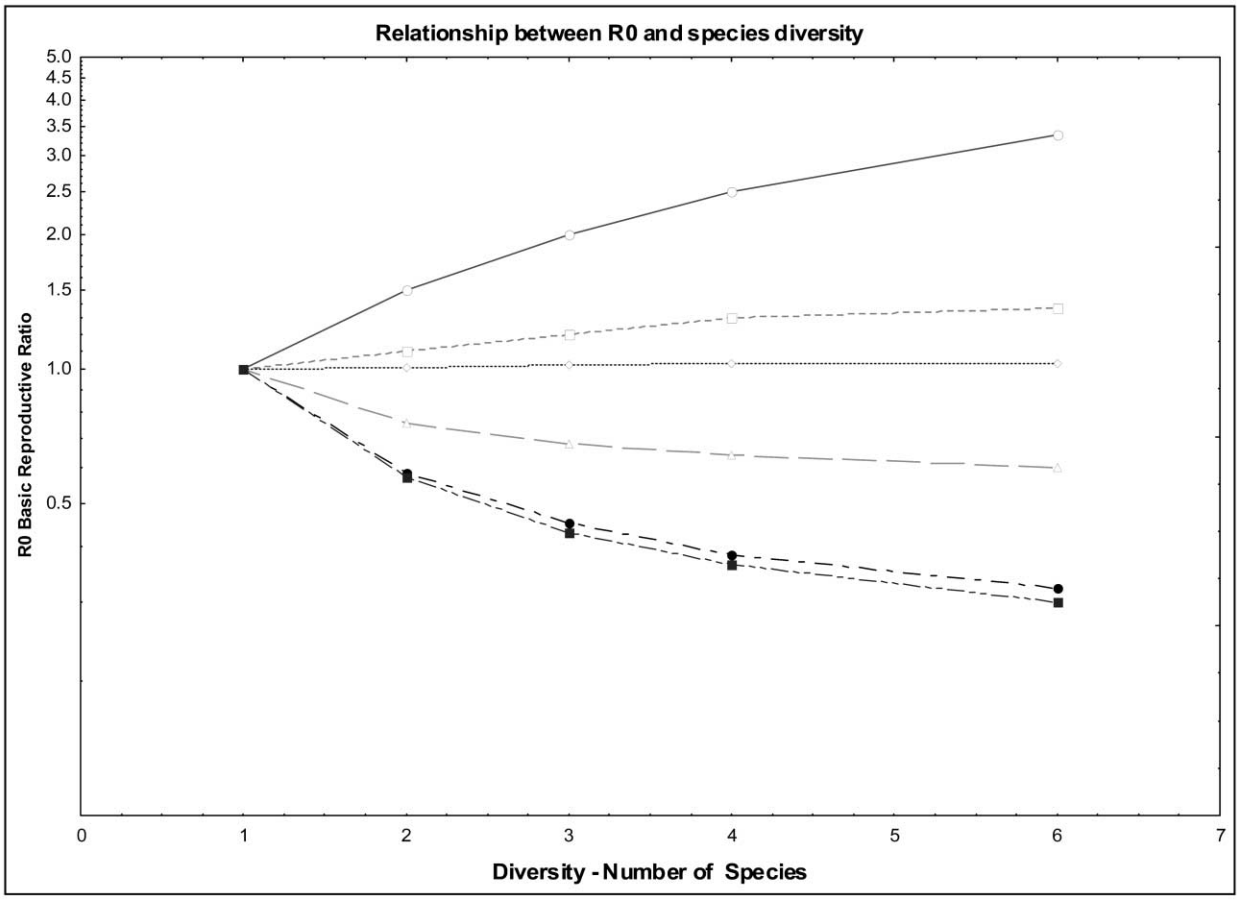

Figure 2: Influence of increasing species diversity on the basic reproductive ratio of a pathogen that is able to infect all of the hosts in the community. The net value of R_0 is estimated for communities of increasing diversity (from one to six host species). The upper three lines correspond to the case for density-dependent transmission, with $c = 0.05$, 0.01, and 0.001; the lower three lines correspond to frequency-dependent transmission for the same c values.

Complications Due to the Presence of Vector Reproduction

Nearly everything described above assumes transmission can be classified as either density dependent or frequency dependent. Vector-transmitted pathogens will be more complicated because we will also have to consider the population dynamics and behavior of the vector. In some situations, vector abundance may be independent of host abundance and diversity. This is probably the case for mosquito-transmitted pathogens, where vector abundance may be a function of suitable pools of water for breeding. In contrast, where ticks act as vectors, their abundance may well be a function of host diversity and abundance; increases in host abundance will lead to increases in the resources available to the vector population (e.g., more blood meals). However, in both cases, vectors will take a finite number of blood meals per lifetime. This will increase the rate at which transmission saturates and will lead to an increased proportion of infectious bites wasted on hosts that may be less viable resources for the pathogen. Whether the dynamics of vector-transmitted pathogens are buffered or amplified by the increased host diversity will depend on whether increases in the size of the vector population are sufficient to compensate for the "wasted" bites on less viable hosts. This has direct implications for the question of whether increased diversity of host species buffers or amplifies disease outbreaks. When vector abundance is independent of host population density, as is the case for many mosquito-vectored diseases such as avian malaria, WNV, or dengue fever, it is likely that the frequency-dependent formulation described above provides a fair description of the dynamics of the pathogen in a multihost system (Dye and Williams 1995). Here, the key result is that increasing host diversity will tend to both reduce rates of disease spread and potentially buffer epi-

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demic outbreaks (fig. 1; appendix). The situation is more complicated in vectored systems where the abundance of the vector is also a function of one or more host species; here, we are specifically concerned with tick-transmitted pathogens such as Lyme disease, Rocky Mountain spotted fever, or the tsetse fly–transmitted sleeping sickness (Rogers 1988). Models for these pathogens have to include the impact of host species abundance on the abundance of the vectors and then have to consider how their suitability as vectors affects rates of transmission between and within host species. A series of results by Ostfeld and colleagues (Ostfeld and Keesing 2000*a*, 2000*b*; Schmidt and Ostfeld 2001; LoGuidice et al. 2003), based on simulation models, again suggest that host diversity can buffer disease outbreaks and reduce transmission rates to incidental hosts (such as humans).

Asymmetrical Matrices and Pathogen Emergence

As we mentioned above, a variety of different (predominantly ecological) mechanisms will ensure that pathogen transmission between species is asymmetrical. For example, consider the situation with two host species where the habitat (or niche) of one is a subset of those used by the other species. Under these circumstances, all of the individuals of the population with the limited range will be exposed to transmission from the other species; in contrast, only the subset of individuals who overlap with the other species will be exposed to interspecific transmission.

Asymmetries in interspecific transmission are of central importance in the emergence of new diseases, particularly those directly transmitted between hosts by either physical contact or aerial plumes. Consider Nipah or Hendra viruses; in both cases, a fruit bat species serves as a reservoir host that maintains the pathogen with few or no signs of pathology. Infrequent chance events allow the bats to transmit the pathogen to domestic livestock: pigs, in the case of Nipah virus, and horses, in the case of Hendra virus (Murray et al. 1995). If the conditions for the pathogen are beneficial, an epidemic outbreak may occur in domestic livestock and may then be transmitted to humans. A crucial point to notice here is that while transmission may occur from bats to pigs or pigs to humans, there is no reciprocal transmission from pigs to bats or from humans to pigs. If we were to write this system down as a WAIFW matrix, all of the elements above the leading diagonal would be 0:

$$\mathbf{W}_{\text{emerging}} = \begin{pmatrix} \tau_{\text{AA}} & 0 & 0 \\ \tau_{\text{BA}} & \tau_{\text{BB}} & 0 \\ 0 & \tau_{\text{CB}} & \tau_{\text{CC}} \end{pmatrix}. \tag{10}$$

For all matrices of this type, the dominant eigenvalue is the largest of the diagonal terms. This essentially implies that the multispecies dynamics consists of three almost independent epidemics: the background endemic infections in the reservoir host, the epidemic that may occur in the first emergent host (B) if the conditions occur to allow transmission from A to B, and the outbreak that occurs in the second emergent host if transmission occurs from B to C. This insight is mathematically trivial, yet it characterizes the vast majority of examples of emergent disease (severe acute respiratory syndrome [SARS]; Nipah, Hendra, and Ebola viruses). In each case, the between-species transmission event reflected a mix of stochastic and deterministic events, usually modification of reservoir host habitat that led to increased contact with a second host species whose numbers may have recently increased. Once the between-host transmission event had occurred, the dynamics of infection were essentially driven by within-host dynamics. Similar mechanisms apply when the close association between domestic livestock and the humans who tend them may spark a second epidemic in the human population. Here again, I should emphasize that these asymmetries will be more pronounced for directly transmitted pathogens than for vector-transmitted pathogens such as malaria, dengue fever, or yellow fever.

Transient Dynamics and Other Fun Extensions

If we return to the symmetrical case where all hosts species are susceptible and overlap in their use of space, we can again use our allometric scaling of parameter values to explore the transient dynamics of equations (1)–(3) for n different species. Initially, let us consider the density-dependent case (transmission dominated by pseudo–mass action) when the pathogen is successfully introduced ($R_0 > 1$). The transient dynamics of the system are dependent upon the relative magnitude of between-species transmission (fig. 3*A*). If interspecific transmission is low, each of the species that are infected will exhibit epidemic outbreaks at frequencies equivalent to those which would be observed in the total absence of interspecific transmission. As rates of interspecific transmission are increased (fig. 3*B*), the epidemic outbreaks are first buffered, and then the system settles to stable patterns of constant abundance with all species containing infected individuals. Further increases in between-species transmission lead to population cycles in all species, but now the cycle period is driven by those in the species with the fastest turnover of susceptibles (usually the species with the smallest body mass). As interspecific transmission is increased still further, the species that can best recover from the impact of the pathogen are able to drive other host species to extinction (fig. 3*C*). Similar patterns of transient dynamics are seen in the frequency-dependent model, although the

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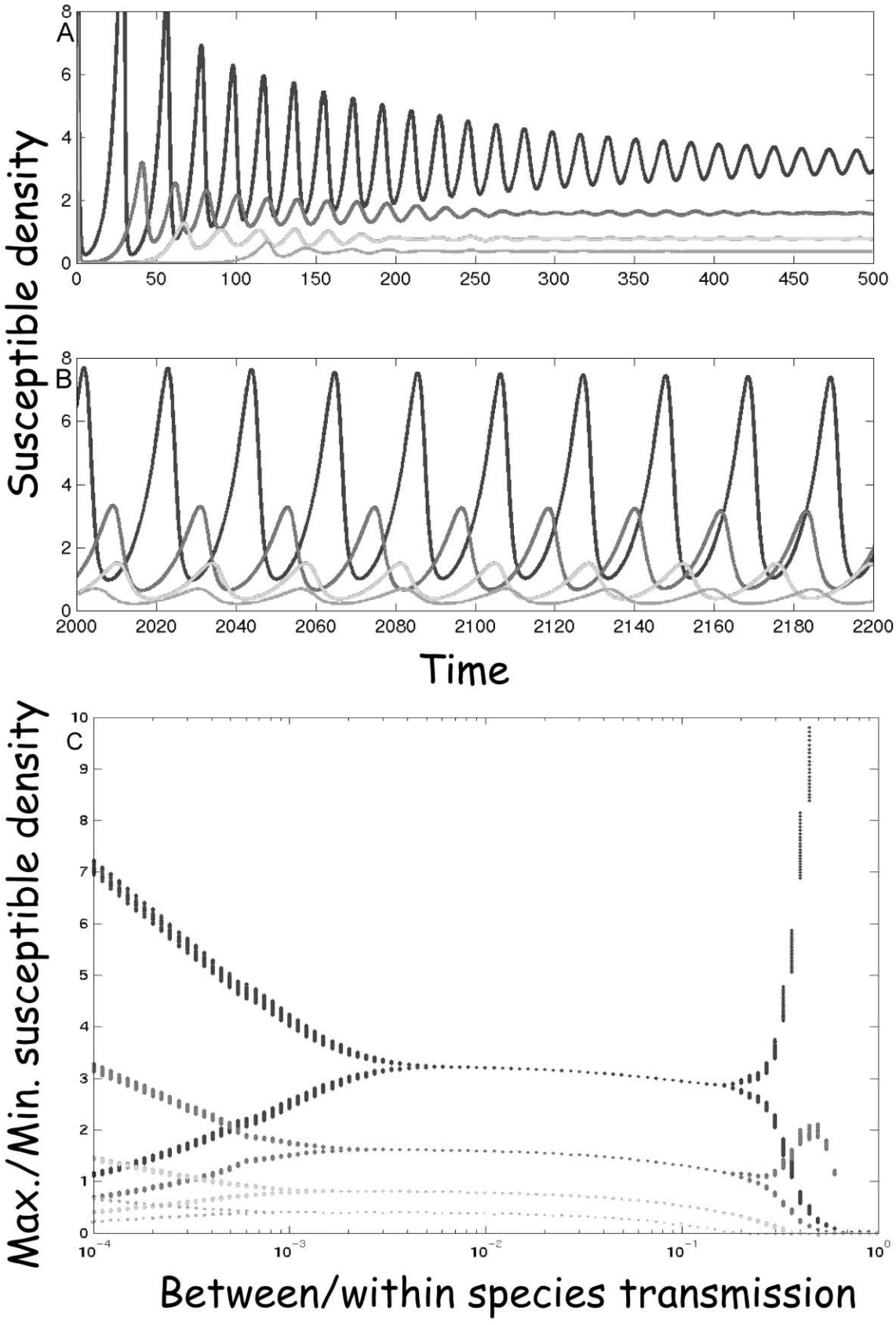

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dynamics are much less violent than in the density-dependent model.

Note that all species are eventually infected in the deterministic case. This would be less likely in the stochastic case when interspecific transmission would occur infrequently but cause epidemic outbreaks whose magnitude varied inversely with the time since interspecific transmission last occurred (Rhodes and Anderson 1996; Woolhouse et al. 2001). This result has important implications for the question, What role does the use of multiple host species play in enhancing the persistence of infectious pathogens? Here, it is worth making a comparison between the dynamics of the pathogen with multiple hosts and the dynamics of pathogens in a single host population split into many subpopulations within a metapopulation. Just as the metapopulation structure of a host population considerably enhances persistence in the single-species case (Swinton 1998; Swinton et al. 1998), it is likely that the presence of multiple host species (with different vital dynamics) will also enhance the persistence of a pathogen with multiple hosts. An interesting problem for the more mathematically gifted reader would be to extend the stochastic persistence model of Swinton (1998) to a multiple host species case. I suspect this could be done using the methods developed in Gibson and Bruck 2000.

Similarly, both the analysis of establishment and of the transient dynamics assumes that each species experiences a similar level of virulence (expressed as a constant proportional reduction in future life expectancy). Where asymmetries occur in the size of host populations, it is likely that the pathogen will evolve levels of virulence that are most adaptive in the host species where the majority of infections occur. This may lead to either increases or decreases in its virulence toward other host species (Woolhouse et al. 2001). Furthermore, in cases where host species diversity increases and levels of between-species transmission are low, the dynamics will come to resemble those of a pathogen within a host metapopulation; under these circumstances, selection may occur for more virulent strains of the pathogen (Boots et al. 2004). These increases in virulence will be increasingly detrimental for rarer species that only experience occasional pathogen outbreaks. When these outbreaks occur, the high proportion of susceptibles that characterize infrequently infected species may significantly increase the size of the outbreaks and increase the total risk of species (or subpopulation) extinction.

Discussion

This article has examined the conditions for establishment of pathogens and their transient dynamics in situations where they infect multiple species of host. In response to the three questions posed in the introduction, the analysis suggests that host species diversity can amplify epidemic outbreaks when transmission is predominantly density dependent, as is the case for pathogens transmitted by aerial plumes or free-living infective stages. In contrast, host species diversity may buffer the potential for epidemic outbreaks when transmission is frequency dependent or mediated by a vector. When it is possible to identify the host species whose presence dominates the transmission terms of the matrix that characterizes pathogen transmission, it may be possible to eradicate the pathogen by focusing vaccination or other forms of control against this species. The long-term transient dynamics of pathogens that infect multiple host species are highly dependent upon the relative magnitude of between- to within-species transmission. When between-species transmission is significant but less than within-species transmission, the pathogen-hosts system may exhibit stable dynamics that may enhance pathogen persistence. As between-host transmission increases to levels observed within a species, the species best able to recover from epidemic outbreaks can drive other

Figure 3: Long-term dynamics of epidemic outbreaks in a pathogen that infects four host species. *A*, Set rates of interspecific transmission at a relatively high level ($c = 0.1$), and the epidemics initially occur simultaneously in all four species; eventually the species with the lowest rates of population growth are driven to extinction by the presence of the pathogen. *B*, Between-species transmission rates are low ($c = 0.0001$), and epidemic outbreaks occur independently within each species; their frequency is determined by the time it takes for a pool of susceptibles to exceed the threshold needed to initiate a new epidemic. Thus, we see more frequent outbreaks in the smaller-bodied species with faster birth rates. The two top graphs show rates of interspecific transmission are high ($c = 0.1$), and the epidemics initially occur simultaneously in all four species; eventually the species with the lowest rates of population growth are driven to extinction by the presence of the pathogen. The rates of population growth of each population are given by standard allometric growth equations: population growth rate, $r(i) = 0.6 \times w(i) \wedge (-0.27)$; host mortality rate (in absence of pathogen), $\mu(i) = 0.4 \times w(i) \wedge (-0.26)$. The intraspecific transmission rates are given by the formula from De Leo and Dobson (1996; see fig. 1). In all cases, $w(i)$ is the body mass of smallest host species (here set at 1 kg); the masses of the other three species are given by the formula $w(i) = ws \times 1.5 \wedge i$. *C*, Bifurcation diagram illustrating the relationship between equilibrium host population size and rates of interspecific pathogen transmission. When rates of interspecific transmission are low, each host population exhibits independent epidemic outbreaks whose magnitude and frequency are determined by their intrinsic rates of birth and death. As rates of interspecific transmission increase, the system first settles to a steady state where the presence of the pathogen causes each species to remain at a constant abundance. Further increases in rates of interspecific transmission lead to the pathogen sequentially driving to extinction the hosts with the slowest rates of increase.

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hosts extinct. This in turn may increase the possibility of the pathogen becoming locally extinct when the system enters an "interepidemic trough"' (sensu Bjørnstad et al. 2002; Grenfell et al. 2002).

In all of the analysis described above, we have assumed that interspecific transmission may be characterized by a single parameter that sets rates of interspecific functions as a proportional value of the mean rate of within-species transmission. Plainly, the first step for further examination of multihost species dynamics is to examine what happens when we relax this assumption. I have argued that the simplest first step in this direction is to examine cases where transmission between species is totally asymmetrical; this case corresponds to that observed in many emerging pathogens (e.g., SARS and the Nipah, Hendra, and Ebola viruses). Further developments in this direction also need to focus on the stochastic nature of the rare events that lead to transmission between one species and another. In particular, we need a better understanding of how anthropogenic modifications of the natural habitat of many wild species may lead to increased rates of transmission to either domestic species or species that spend time in close contact with humans and domestic livestock. Significant emphasis has been placed on the possible role of climate in determining these events, but the fragmentation and destruction of natural habitats may play an equally important role. In the case of recent Nipah and Hendra virus outbreaks in Malaysia and Australia, forest destruction has considerably altered the natural habitat for the fruit bat species that serve as reservoirs of these pathogens. This has restricted their roosting sites and probably increased the frequency with which they utilize the fruit trees that provide shade for domestic livestock.

Further explorations of rates of interspecific transmission need to focus on the roles of spatial distributions and habitat use in creating opportunities for pathogen transmission to occur and on the role that the physiological, immunological, and genetic backgrounds of different host species play in determining susceptibility on the occasions when the spatial opportunity arises for transmission (Lafferty and Holt 2003). This creates a curious ecological irony; perhaps the best way initially to estimate the magnitude of asymmetries in rates of disease transmission between species would be to utilize the techniques developed to measure competitive overlap in resource use by the host species (Hairston et al. 1960; Miller 1967; Abrams 1975; Schoener 1983; Dublin et al. 1990). The framework described above can readily be modified to explore these important modifications. As always, the insights gained will be considerably strengthened if they are accompanied by empirical studies that attempt to differentiate between the different factors that determine rates of susceptibility.

Implications for Global Change: Biodiversity and Climate

The results described in this article have important implications for pathogens whose geographical distribution may change as a consequence of global climate change. Although no consensus has yet emerged about whether pathogens have already begun to change their distributions (Dobson and Carper 1993; Harvell et al. 1999; Patz and Lindsay 1999; Dobson et al. 2003), most workers believe that vector-transmitted pathogens are more likely to respond to climate change than are directly transmitted pathogens (Dobson and Carper 1992; Harvell et al. 2002). Thus, our major worry is that vector-transmitted pathogens presently confined to the tropics may expand their range into the temperate zones. Unfortunately, this expansion will also allow them to move from regions of high alternate host diversity into regions where host diversity is reduced. Because the dynamics of these pathogens will be dominated by frequency-dependent dynamics, they will likely have a bigger impact on susceptible hosts in the temperate zone. Partial evidence in support of this is supplied by work on Lyme disease (Schmidt and Ostfeld 2001; LoGuidice et al. 2003) and West Nile virus (V. Ezenwa, unpublished manuscript); both of these pathogens have had a reduced impact on human populations as they have spread from the northern temperate regions of New England into the southern parts of the United States. This effect will also be particularly important for vector-transmitted pathogens such as dengue fever and malaria, which might move in the opposite direction down the diversity gradient from the tropics into the temperate zone. Essentially, the limited supply of alternate host species in the temperate zone will allow mosquitoes and other vectors to focus their attention on humans or domestic livestock. It is hard to think of a more pragmatic reason for conserving biodiversity in the temperate zone.

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APPENDIX

Basic Reproductive Number for Pathogens with Multiple Hosts

This appendix provides analytical expressions for R_0 for pathogens that infect two host species. The expressions can fairly readily be expanded to the *n*-species case; ironically, this is relatively simple for a vector-transmitted pathogen while less clear-cut for directly transmitted pathogens with density-dependent or frequency-dependent transmission. Initially, let us consider the two directly transmitted cases. The next-generation matrices for these are both of the form

$$\mathbf{G} = \begin{pmatrix} \tau_{aa}A - \lambda & \tau_{ab}Ac \\ \tau_{ba}Bc & \tau_{bb}B - \lambda \end{pmatrix}.$$

Each of the τ expressions has the same general form. In the case of density-dependent transmission, $\tau_{aa} = \beta_{aa}A / (d_a + \alpha_a + \delta_a)(A + B)$, $\tau_{ab} = \beta_{ab}A / (d_b + \alpha_b + \delta_b)(A + B)$, and so on.

In contrast, in the frequency-dependent case, $\tau_{aa} = \beta_{aa}/(d_a + \alpha_a + \delta_a)(A + B)$, $\tau_{ab} = \beta_{ab}/(d_b + \alpha_b + \delta_b)(A + B)$, and so on.

The expression for R_0 is given by the dominant eigenvalue of matrix **G**:

$$R_0 = \frac{\tau_{aa}A + \tau_{bb}B}{2} + \frac{\sqrt{\tau_{aa}^2A^2 + \tau_{bb}^2B^2 + 4\tau_{ab}\tau_{ba}ABc^2 - 2\tau_{aa}\tau_{bb}AB}}{2}.$$

It is also possible to derive analytical expressions for slightly more complex three- and four-host communities; however, numerical solutions can readily be found for more complicated cases. In all the cases described in the main text, I have used the allometric scaled rates of host birth, death, and abundance to estimate appropriate values of allometric scaled transmission and virulence (De Leo and Dobson 1996). These "sets" of parameter values considerably reduce the area of parameter space that needs to be explored to understand the dynamics of these types of system in realistic regions of parameter space.

One additional important case will be considered here, vector-transmitted pathogens that utilize multiple host species. It has been argued that the frequency-dependent transmission mimics vector transmission; here, we illustrate that this is also the case for pathogens with multiple host species; paradoxically, explicitly including the vector allows us to produce a simple expression for R_0 that generalizes for *n* host species.

Consider the next-generation matrix for a pathogen with three host species transmitted by a vector whose abundance is *V*:

$$\mathbf{G}_V = \begin{pmatrix} 0 & 0 & 0 & \frac{V\tau_{\text{vh}}A}{A+B+C} \\ 0 & 0 & 0 & \frac{V\tau_{\text{vh}}B}{A+B+C} \\ 0 & 0 & 0 & \frac{V\tau_{\text{vh}}B}{A+B+C} \\ \frac{V\tau_{\text{hv}}A}{A+B+C} & \frac{V\tau_{\text{hv}}B}{A+B+C} & \frac{V\tau_{\text{hv}}C}{A+B+C} & 0 \end{pmatrix}.$$

Here, $\tau_{\text{vh}} = \beta_{\text{vh}}$ and $\tau_{\text{hv}} = \beta_{\text{hv}}/\mu$, where vector life expectancy is $1/\mu$ and β_{vh} and β_{hv} are the transmission rates of the pathogen to and from the vector. We can again rescale these values by host body sizes with little additional effort. The resultant expression for R_0 is again given by the dominant eigenvalue of **G**v:

$$R_0 = \frac{\sqrt{V\tau_{\text{vh}}\tau_{\text{hv}}(A^2 + B^2 + C^2)}}{A + B + C},$$

which of course generalizes for *n* species of hosts. When the two-species case is plotted graphically, it is seen to closely resemble that for the case of frequency dependent transmission (fig. 1*B*, 1*C*, 1*D*); however, we now have the advantage of also seeing its underlying sensitivity to vector abundance.

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