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Should we expect population thresholds for wildlife disease?

James O. Lloyd-Smith[1,2], Paul C. Cross[1,3], Cheryl J. Briggs[4], Matt Daugherty[4], Wayne M. Getz[1,5], John Latto[4], Maria S. Sanchez[1], Adam B. Smith[6] and Andrea Swei[4]

[1]Department of Environmental Science, Policy and Management, University of California at Berkeley, Berkeley, CA 94720-3114, USA
[2]Biophysics Graduate Group, University of California at Berkeley, Berkeley, CA 94720-3200, USA
[3]Northern Rocky Mountain Science Center, United States Geological Survey, 229 A.J.M. Johnson Hall, Bozeman, MT 59717, USA
[4]Department of Integrative Biology, University of California at Berkeley, Berkeley, CA 94720-3140, USA
[5]Mammal Research Institute, Department of Zoology and Entomology, University of Pretoria, 0002 South Africa
[6]Energy and Resources Group, University of California at Berkeley, Berkeley, CA 94720, USA

Host population thresholds for the invasion or persistence of infectious disease are core concepts of disease ecology and underlie disease control policies based on culling and vaccination. However, empirical evidence for these thresholds in wildlife populations has been sparse, although recent studies have begun to address this gap. Here, we review the theoretical bases and empirical evidence for disease thresholds in wildlife. We see that, by their nature, these thresholds are rarely abrupt and always difficult to measure, and important facets of wildlife ecology are neglected by current theories. Empirical studies seeking to identify disease thresholds in wildlife encounter recurring obstacles of small sample sizes and confounding factors. Disease control policies based solely on threshold targets are rarely warranted, but management to reduce abundance of susceptible hosts can be effective.

Introduction

Ideas about threshold levels of host abundance for invasion or persistence of infectious diseases are central to the theory and practice of disease ecology [1–3], but have their roots in human epidemiology. The notion of a threshold population for invasion (N_T) (see Glossary) is a founding principle of epidemiological theory [4–6], and the critical community size (CCS) required for disease persistence dates back to Bartlett's seminal analyses of measles data [7]. Evidence of population thresholds in wildlife disease systems has been described as 'rare' [8] and 'weak' [9], yet these concepts underpin all efforts to eradicate wildlife diseases by reducing the numbers of susceptible hosts through controversial methods such as culling, sterilization, or vaccination (e.g. [10–12]). Recent empirical studies have sought to identify invasion and persistence thresholds in wildlife with mixed success [8,9,12–15]. Here, we consider these findings in the context of theoretical models of disease spread, which reveal that abrupt population thresholds are not expected for many disease-host systems. Moreover, even when thresholds are expected, demographic stochasticity makes them difficult to measure under field conditions. We discuss how conventional theories underlying population thresholds neglect many factors relevant to natural populations such as seasonal births or compensatory reproduction, raising doubts about the general applicability of standard threshold concepts in wildlife disease systems. These findings call into question the wisdom of centering control policies on threshold targets and open important avenues for future research.

Corresponding author: Lloyd-Smith, J.O. (jls@nature.berkeley.edu).

Glossary

Basic reproductive number (R_0): the expected number of secondary cases caused by the first infectious individual in a wholly susceptible population. This acts as a threshold criterion because disease invasion can succeed only if $R_0 > 1$.
Critical community size (CCS): the host population size above which stochastic fadeout of a disease over a given period is less probable than not. Because disease dynamics do not change abruptly with population size, the CCS is traditionally set by subjective assessment or arbitrarily chosen criteria. Originally defined in the context of epidemic fadeout, the CCS is now often used as a general term for all population thresholds for disease persistence.
Demographic stochasticity: the variation evident in dynamics of small populations owing to the probabilistic nature of individual processes, such as birth, death or transmission.
Deterministic model: a mathematical or simulation model in which chance has no role; thus, the results are determined entirely by model structure, parameter values and initial conditions.
Effective reproductive number (R_{eff}): the expected number of secondary cases caused by each infectious individual in a partially immune population. In well-mixed populations, $R_{eff} = sR_0$, where s is the fraction of the population that is susceptible.
Endemic fadeout: extinction of the disease from a stable endemic state owing to random fluctuations in the number of infected individuals (represented by the quasi-stationary distribution of I).
Epidemic fadeout: extinction of the disease during the period following an epidemic when the pool of susceptibles is depleted, reducing the potential for ongoing transmission. This can result from random fluctuations in the number of infected individuals or from a protracted period with $R_{eff} < 1$.
Herd immunity: phenomenon whereby disease can be excluded from a population in spite of the presence of some susceptibles because the proportion of individuals that are immune is sufficient to ensure that $R_{eff} < 1$.
Quasi-stationary distribution: the stationary distribution of a stochastic variable conditional on not having gone extinct yet. This concept is used to describe 'equilibrium' behaviour in stochastic models where extinction is assured as time goes to infinity. See [35] for details.
Stochastic model: mathematical or simulation model incorporating chance events; it is particularly important when small numbers of individuals exert a strong influence on dynamics (as in invasions) or when fluctuations around mean behaviour are important.
Threshold population for invasion (N_T): the minimum host population size required for a disease to be able to invade a host population successfully.

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Setting the stage

We first introduce some general concepts to frame the discussion.

Numbers, densities and transmission models

Population abundance can be quantified in terms of either numbers or densities of individuals. Active debate in disease ecology centers on which measure is preferable for species with various social systems or for different scales of measurement, and on the consequences for modeling disease transmission [16–21]; although important, this topic is beyond the scope of this article. In considering population thresholds, the central question is whether transmission rates increase with population abundance (N) or remain constant, reflecting some behavioral limit to contact rates [2,22]. The relevant measure of abundance might be determined by the ecology of the host species, the modeling framework employed, or the units of a suspected threshold being evaluated. Because in-depth discussion of thresholds requires stochastic models, which are posed naturally in terms of counts, N represents population size throughout most of this article. In our brief discussion of deterministic models relevant to large, well-mixed populations, N represents a density. Both abundance measures arise in the empirical studies reviewed.

We contrast two classic models of disease transmission, in which the hazard rate of infection for each susceptible individual scales linearly either with the number or density of infectious individuals (yielding density-dependent transmission) or with the proportion of infectious individuals in the population (yielding frequency-dependent transmission, which is independent of N). These are idealizations that are sometimes thought to depict transmission at low and high population abundances, respectively, but the boundary between those regimes is not well characterized [2,16,19]. Numerous empirical studies have demonstrated that disease transmission or prevalence increases with N (e.g. [23–25]), but others have found greater support for frequency-dependent transmission [18,26,27].

Reproductive numbers and disease spread

The basic reproductive number (R_0) of a disease is the expected number of secondary cases caused by a typical infectious individual in a wholly susceptible population [4,28,29]. If $R_0<1$, then each case does not replace itself on average and the disease will die out. If $R_0>1$, then the invasion can succeed. When only a fraction, s, of the population is susceptible (e.g. if some hosts are immune as a result of a previous infection or vaccination), disease spread is described by the effective reproductive number R_{eff}, which equals sR_0 for a well-mixed population. Again, $R_{\text{eff}}<1$ implies that the disease will decrease in prevalence and eventually die out. The value of R_0 (and R_{eff}) depends on all the factors that influence transmission, including the rate of contact among hosts, mixing patterns, factors affecting infectiousness and susceptibility, and the length of the infectious period (Box 1) [4,28,29].

Population thresholds for disease invasion

We begin by describing the conceptual basis for invasion thresholds, and then use simulations to illustrate the challenges in identifying them.

Deterministic foundations

Invasion thresholds are conceptually straightforward: if R_0 is an increasing function of N, as in density-dependent transmission, then the invasion threshold N_T is that population abundance for which $R_0=1$ (Box 1). In deterministic models, populations with $N>N_T$ can sustain major disease invasions ($R_0>1$), whereas those with $N<N_T$ cannot. If R_0 is independent of N, as in frequency-dependent transmission, then no threshold population abundance for invasion exists. In both cases, however, if some individuals are immune, there is a threshold minimum proportion of susceptibles, $s_T=1/R_0$, for an invasion to succeed; this is the principle underlying herd immunity [30].

Stochastic complications

When the number of individuals carrying the disease is small, such as during the early phases of disease invasion or when total population size is small, chance events can have a significant influence. Stochastic models show that an invasion can fail by chance even when $R_0>1$ [29,31]. Observing failed invasions, therefore, does not necessarily imply a population below the invasion threshold (Figure 1). In the simplest models, where individuals leave the infectious state at a fixed *per capita* rate, the probability of a failed invasion when $R_0>1$ is $(1/R_0)^{I_0}$, where I_0 is the initial number of infected individuals [29]. Thus, a disease with $R_0=3$ introduced by a single infected case, has 33% chance of dying out. In more realistic models incorporating non-random mixing or heterogeneous infectiousness, this complication is heightened because stochastic extinction can become much more probable for a given R_0 ([32], J. Lloyd-Smith *et al.*, unpublished).

Random variation in outbreak size (i.e. the total number of individuals infected) can blur the distinction between successful and failed invasions. When $R_0\gg1$ or the well-mixed population is relatively large, the distribution of outbreak sizes is bimodal with distinct peaks corresponding to successful and failed invasions (Figure 1). As R_0 approaches 1, or as the population size decreases, this clear distinction is lost and classifying any given outbreak as a success or failure becomes difficult. Even if many outbreaks are observed, it can be difficult to discern when the invasion threshold has been crossed; there is little difference between outbreak size distributions for $R_0=0.9$ versus $R_0=1.1$ (or even $R_0=1.5$ in small populations). One proposed solution to this problem is to define the threshold as the point where the distribution changes from monotonically decreasing to bimodal [33], but, in practice, it will be nearly impossible to obtain enough replicate outbreaks to characterize borderline cases.

Stochastic fadeout and thresholds for disease persistence

After a disease has successfully invaded a population, it can still go extinct or 'fade out' owing to random

Box 1. Insights from simple deterministic models

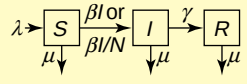
Basic principles of disease spread are illustrated clearly by deterministic models that divide a population into compartments based on disease status and depict disease transitions as predictable flows among groups. Here, we consider a non-fatal disease, without a significant latent period, from which individuals recover to a state of permanent immunity. We therefore use the so-called SIR model, named after the three disease compartments (susceptible, infectious, recovered). Owing to the crucial role of the transmission process in determining population thresholds, we analyze the model for density-dependent and frequency-dependent transmission. Because inflow of new susceptibles is essential to the long-term persistence of such a disease, we include a simple treatment of demographic dynamics. The models are given in Table I.

For both models, the total population size has a stable equilibrium at $N^* = \lambda/\mu$. The units of β differ between the two models [17].

We immediately gain several insights from these models. Because R_0 increases with N in the model with density-dependent transmission, we predict a population threshold for invasion of $N_T = \frac{\gamma+\mu}{\beta}$. Conversely, there is no population threshold for invasion in the frequency-dependent model because R_0 depends only on rate parameters [16,18,58].

Regarding persistence, we first ask whether an endemic equilibrium is possible. For both models, non-zero values of I^* exist whenever $R_0 > 1$: if a disease can invade, it will reach an endemic steady state in the deterministic model [28]. Therefore, for density-dependent transmission, the existence of an endemic equilibrium depends on population density, whereas for frequency-dependent transmission it does not. Another important question is how far the endemic equilibrium is from $I = 0$. Deterministic models do not include random fluctuations, but in real populations there is greater danger of stochastic fadeout when I is small (just as for population fluctuations of severely endangered species). All else being equal, the disease will persist longer for larger values of I^*. The endemic equilibria for both models can be written $S^* = \frac{N^*}{R_0}$ and $I^* = \frac{N^*}{\alpha}\left(1 - \frac{1}{R_0}\right)$, where $\alpha = \frac{\gamma+\mu}{\mu}$ is the ratio of mean host lifespan to mean infectious period [35]. For a given value of $R_0 > 1$, therefore, we expect I^* to increase with N^* in both models, and hence we expect persistence times to increase gradually with N^*. I^* also decreases as α increases, so transient diseases are predicted to be more vulnerable to stochastic fadeout.

Table I. Basic SIR models for disease spread



S, I, R = densities of Susceptible, Infectious, and Recovered hosts ($N = S + I + R$)
λ = input of new susceptibles
μ = death rate not associated with disease
γ = recovery rate of infectious individuals
β = transmission coefficient

Transmission	**Density-dependent (βI)**	**Frequency-dependent ($\beta I/N$)**
Model equations	$\frac{dS}{dt} = \lambda - \mu S - \beta IS$	$\frac{dS}{dt} = \lambda - \mu S - \frac{\beta I}{N} S$
	$\frac{dI}{dt} = \beta IS - (\gamma + \mu) I$	$\frac{dI}{dt} = \frac{\beta I}{N} S - (\gamma + \mu) I$
	$\frac{dR}{dt} = \gamma I - \mu R$	$\frac{dR}{dt} = \gamma I - \mu R$
R_0	$R_0 = \frac{\beta N}{\gamma + \mu}$	$R_0 = \frac{\beta}{\gamma + \mu}$
Steady-state values of S and I at endemic equilibrium	$S^* = \frac{\gamma + \mu}{\beta}$, $I^* = \frac{\beta\lambda - \mu(\gamma + \mu)}{\beta(\gamma + \mu)}$	$S^* = \frac{\lambda(\gamma + \mu)}{\mu\beta}$, $I^* = \frac{\lambda[\beta - (\gamma + \mu)]}{\beta(\gamma + \mu)}$

fluctuations in the number of infected individuals. Two types of stochastic fadeout are distinguished chiefly by their starting conditions: endemic fadeout refers to the extinction of a disease from a relatively stable endemic state (Figure 2a) [28], whereas epidemic fadeout describes extinction occurring after a major outbreak depletes the available number of susceptibles (Figure 2b) [28]. Both concepts address persistence of an established disease, and thus are distinct from the invasion threshold N_T governing the initial growth of an outbreak.

The notion of a CCS, above which disease can persist, arose from studies of measles that suggested high probabilities of fadeout between biennial epidemics in communities smaller than 250 000–300 000 people, but probable persistence in larger communities [7,34]. The term CCS has since come to describe population thresholds for endemic or epidemic fadeout [35]. Further studies of measles have reinforced the CCS paradigm [28,36–38], encouraging researchers to look for persistence thresholds in other systems (Table 1). However, the CCS has proven challenging to theorists, resisting calculation or even rigorous definition, although substantial progress has been made recently [29,35]. We review these developments and present illustrative simulations to show why abrupt thresholds for persistence should not be expected.

Endemic fadeout

Endemic fadeout is less probable when the equilibrium abundance of infectious individuals (I^*) is high, and deterministic models show that I^* increases with population abundance (Box 1). Stochastic models reveal that disease persistence in finite populations is inherently temporary because fluctuations always cause extinction over very long timescales [35,39]. Analysis of endemic fadeout therefore focuses on the expected time to extinction, T_E, beginning from the quasi-stationary distribution of the number of susceptible and infectious individuals (roughly, the steady state of the stochastic process before disease extinction) [35,39,40]. The time to extinction from quasi-stationarity is distributed exponentially, with mean T_E increasing with N (Figure 2c) [35,39–41]. Thus, we expect longer persistence in larger populations, with stochastic fadeout becoming a very remote possibility for sufficiently large N, although no particular threshold value of N exists

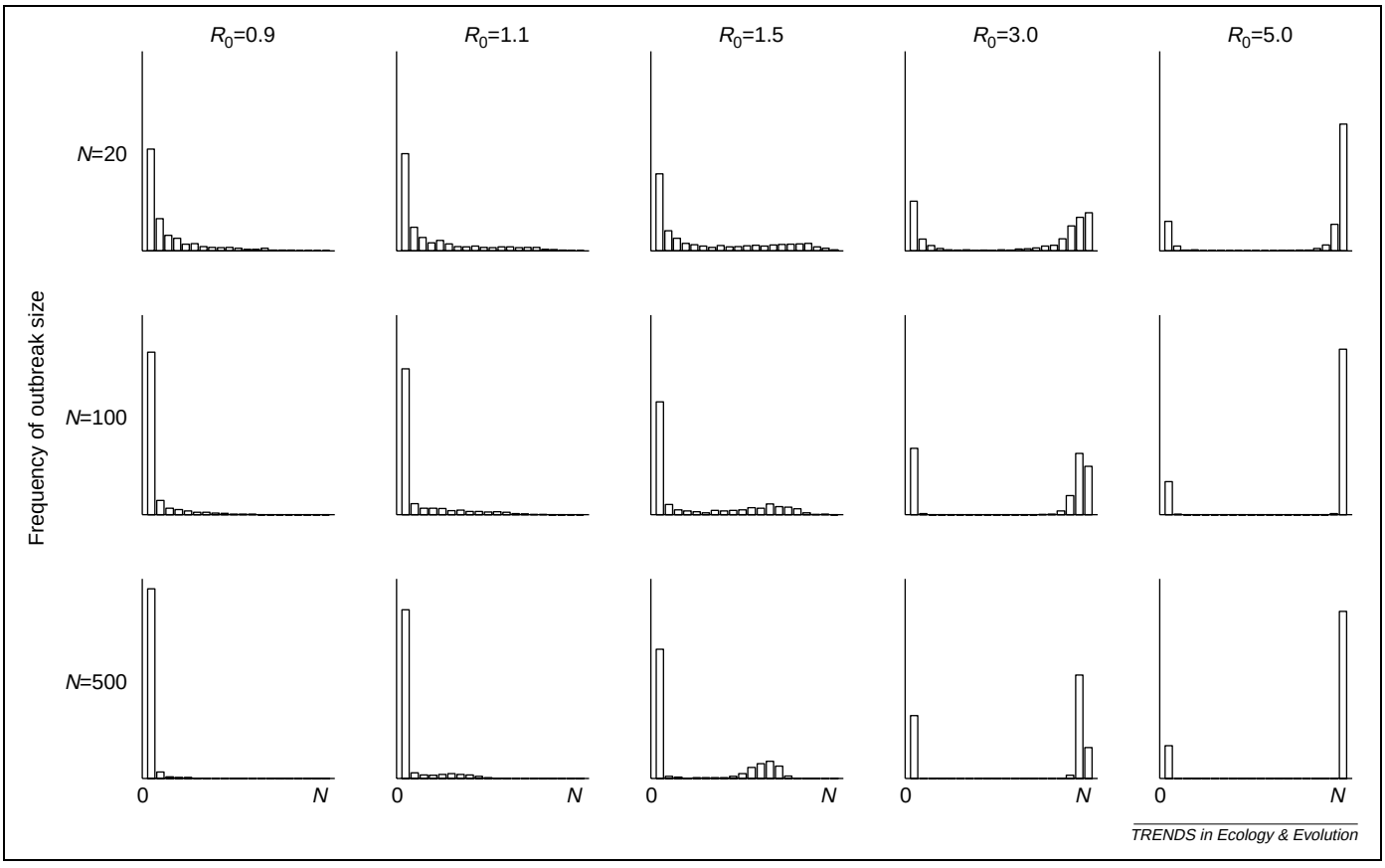


Figure 1. Stochasticity and the invasion threshold. We used a stochastic simulation of disease invasion to characterize the distribution of outbreak sizes for diseases with different R_0 values and host population sizes. Histograms show the total number of individuals infected in each of 1000 simulated SIR (see Box 1) outbreaks. The population is closed (i.e. no births and deaths) with S susceptible individuals, I infectious individuals, and R recovered (immune) individuals. In each time step, two processes can occur: each susceptible individual can become infected with probability $1-\exp(-\beta I/N)$ (reflecting frequency-dependent transmission with transmission coefficient β), and each infectious individual can recover with probability $1-\exp(-\gamma)$ (where γ is the instantaneous recovery rate). In these simulations, $\gamma=0.1$ and $\beta=\gamma R_0$, and the initial conditions for each outbreak simulation were $S=N$ and $I=1$. This is the discrete-time analogue of the frequency-dependent model in Box 1, but, because N was fixed, the same results would be obtained from a model with density-dependent transmission with infection probability $1-\exp(-\beta' I)$, where $\beta'-\gamma R_0/N$.

that distinguishes populations where disease can or cannot persist (however, an arbitrary threshold can be defined by choosing a particular probability of fadeout over a given period [35]). Furthermore, T_E depends strongly on the relative timescales of disease and demographic processes (Figure 2c) as summarized by the ratio of mean host lifespan to mean infectious period (Box 1) [35]. For given values of R_0 and N, faster demographic turnover favours longer disease persistence; timescales of demographics versus disease also affect the range of N for which T_E becomes very large. These effects occur partly because I^* increases as the lifespan-to-infectious-period ratio decreases (Box 1), but the influence of relative timescales on fluctuations in the number of infected individuals needs further research.

Epidemic fadeout

Epidemic fadeout presents still more complications than endemic fadeout, involving stochastic fluctuations in the number of infected individuals superimposed on a changing epidemic curve (Figure 2b). As a major epidemic declines, R_{eff} drops below 1 owing to depletion of susceptibles, and transmission will slow or stop. The susceptible pool is replenished via birth, immigration, or the loss of protective immunity, and, if the disease can persist until R_{eff} again exceeds 1, then another epidemic can occur. This cycle repeats, generating a series of periodic epidemics (with diminishing intensity in simple models, but see [28,35]). Persistence through the 'troughs' between the epidemics depends on the duration of the waning tail of the initial outbreak, the number of individuals that escaped infection, and the rate of replenishment of the susceptible pool. These factors all depend on N in complex ways, particularly in wildlife (Box 2), but even the simplest models exhibit no abrupt threshold in population size (Figure 2d). Instead, epidemic fadeout depends fundamentally on timescales, because rapid demographic turnover speeds replenishment of susceptibles and aids persistence (Figure 2d) [29,35,42], and also on the intensity of the initial epidemic (which is governed by disease and demographic timescales and the infectiousness of the disease), because more individuals escaping infection initially leaves a greater pool of susceptibles [7,31]. The detectable CCS for measles, with its short infectious period and high transmissibility, might be the exception rather than the rule. In general, fadeout rates are determined by relationships between N and the timescales of demography and transmission [29,35,40,42], yielding gradual dependence on N, but often no abrupt threshold effects.

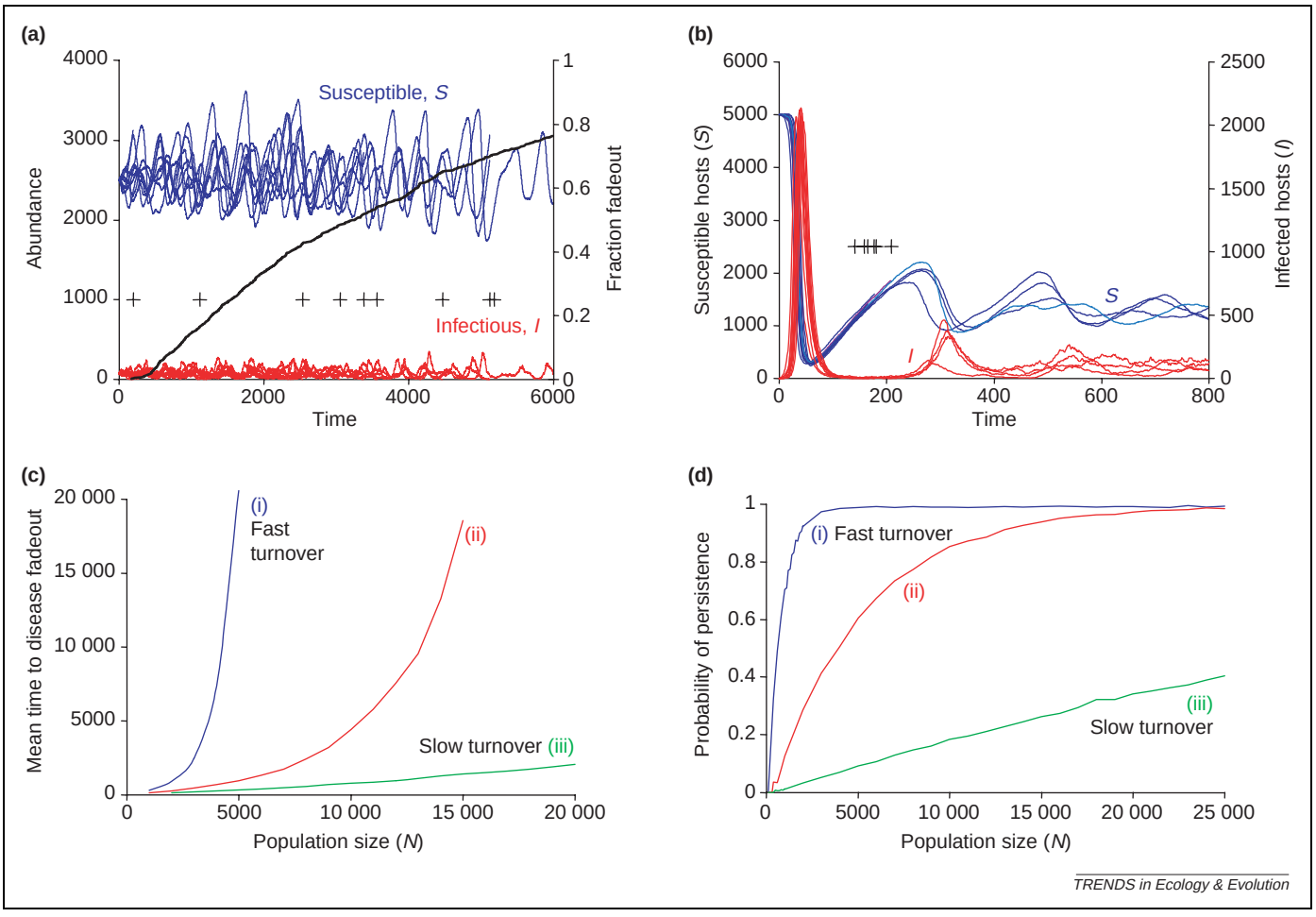


Figure 2. Endemic and epidemic fadeout and the absence of abrupt persistence thresholds illustrated using a stochastic simulation of disease spread. Results demonstrate that both types of fadeout depend strongly on demographic rates and vary gradually with N rather than showing abrupt thresholds. The simulation model tracks the numbers of S, I and R individuals and extends the model used in Figure 1 to include population recruitment and death. For all simulations, $R_0=4$ and recovery rate $\gamma=0.1$; **(a)** Endemic fadeout: ten stochastic simulations of endemic disease dynamics, begun from endemic equilibrium conditions (see Box 1). + signs indicate instances of endemic fadeout when I fluctuated to zero. The black line shows the cumulative fraction of runs with disease fadeout, out of 1000 stochastic simulations. The ratio of the mean host lifespan to mean infectious period, α, equals 101. **(b)** Epidemic fadeout: 10 stochastic simulations of epidemic disease dynamics, begun with $S=4999$, $I=1$, $R=0$. + signs indicate instances of epidemic fadeout during the trough in I following the first epidemic peak. α equals 34.3. **(c)** Average time to endemic fadeout (out of 1000 runs started at the endemic equilibrium) as a function of population size and the relative rate of demographic turnover. For curves (i), (ii) and (iii), α equals 51, 101 and 201, respectively. **(d)** Probability of persisting through the first inter-epidemic trough as a function of population size and the relative rate of demographic turnover, estimated from the fraction of 10 000 runs that persisted (starting with $S=N^*-1$, $I=1$, and $R=0$, conditional on successful invasion of the disease). For curves (i), (ii) and (iii), α equals 21, 34.3 and 51, respectively; when $\alpha=101$, no runs persisted through the first trough. For full details, please see Online Supplementary Information.

Detecting thresholds in natural populations: observations and challenges

Several recent studies have investigated population thresholds in wildlife disease systems (Table 1). These studies represent major investments in field research and analysis, but their ability to draw definitive conclusions has been limited by the inherent challenges described above and additional complexities of real disease-host interactions (Box 3). Here, we review their substantial contributions and identify recurring obstacles.

Shortcomings in available data

The most obvious challenge to detecting thresholds for wildlife disease is a low level of replication in wildlife studies compared with human datasets, which limits the ability of field workers to detect a threshold when one does exist (Figure 1). Combined with sampling error and stochastic extinctions, it also raises the possibility of spurious claims of thresholds. A related limitation is that documentation of failed invasion or persistence is frequently lacking. For rabies in red foxes, *Vulpes vulpes*, a frequently cited dataset suggests a threshold in rabies prevalence that is associated with the number of foxes killed in a region, itself a controversial metric of relative density [43]. However, because there were no observed densities (whether infected or not) below the putative threshold of 0.4 foxes killed km^{-2}, the validity of the threshold is ambiguous. Another oft-cited example of wildlife disease thresholds suggested that brucellosis could neither invade nor persist in bison, *Bison bison*, herds of <200 individuals, but, of the 18 herds studied, only one had ~ 200 bison (with seroprevalence near zero) and none were smaller than this [12]. By contrast, analysis of phocine distemper in harbour seals, *Phoca vitulina*, illustrates that, if a CCS exists, it is well above the estimated population size [14]. To demonstrate disease thresholds requires documenting not only successful invasion or persistence at high host population sizes, but also failure of the disease to invade or persist in populations with N below the putative threshold. Failed

Table 1. Selected empirical studies testing for population thresholds for wildlife disease

Host	Pathogen(s)	Sampling unit (no. individuals per unit)	Study duration (y)	Type of evidence (and conclusion)	Observations	Refs
Great gerbils, *Rhombomys opimus*	Plague, *Yersinia pestis*	Two populations	40	Prevalence over time; statistical model (Periods of plague absence suggest a population threshold for invasion and persistence)	Strong data, but model did not distinguish between invasion and persistence thresholds; possible effects of vector; two-year lag between host abundance and disease	[9]
Bank voles, *Clethrionomys glareolus*, and wood mice, *Apodemus sylvaticus*	Cowpox	15 populations (5–140)	2	Prevalence as a function of host densities and numbers; estimates of movement (Evidence for 'fuzzy' invasion and persistence thresholds in one host species in population number, but not density)	Limited replication relative to the large effects of stochasticity in small populations; possible alternative hosts; unknown effect of background populations in single mainland patch	[8]
Semi-feral dogs, *Canis familiaris*	Rabies	Three populations	3–5	Rabies presence or absence as a function of host density and number (Evidence for CCS in population density, but not number)	Limited replication; possible alternative reservoirs; no temporal replication	[13]
Harbour seals, *Phoca vitulina*	Phocine distemper virus	Pooled datasets for 25 sub-populations	1–2	Observed fade-outs; mathematical modeling (If CCS exists, it is much larger than the entire population)	Only mathematical support of CCS; possible alternative hosts	[14]
American bison, *Bison bison*	*Brucella abortus*	Pooled datasets for 18 herds (200–3200)	45+	Prevalence as a function of host density (*Brucella* fails to invade herds of $<$200 individuals)	No data below putative threshold; only one herd without brucellosis; possible alternative hosts.	[12]
African lion, *Panthera leo*	Six feline viruses	Two populations (40–260)	20–25	Outbreaks over time as a function of the number of susceptibles (Certain viruses invade only after buildup of susceptibles)	Possible alternative hosts (source of diseases is unknown); sparse sampling in one of two populations	[15]
Humans, *Homo sapiens*[a]	Measles	60 cities, (10^4–3×10^6)	22	Number of cases over time; mathematical modeling (Disease does not persist in isolated populations of $<$250 000 individuals)	Strongest example of CCS to date	[37,38]

[a]This classic example is included for comparison of wildlife studies to human disease systems.

invasions, by their very nature, are difficult to observe, compounding the difficulty of identifying these thresholds.

Alternative hosts

The confounding effects of environmental reservoirs or multiple host species arise in several studies (Table 1). An invasion threshold was suggested for parvovirus and calicivirus in lions, *Panthera leo*, based upon a susceptible pool that was assumed to equal the number of animals born between one outbreak and the next (thus neglecting immigration or animals that escaped previous infection) [15]. The authors acknowledge, however, that a crucial determinant of outbreak timing – and thus of all thresholds estimated from cumulative births between outbreaks – is introduction of the pathogen, so the patterns they observe could arise from disease dynamics within the unknown reservoir. The specter of unknown alternative host species looms over many wildlife disease studies, although some recent research has inferred the role of unstudied reservoirs from disease dynamics in their focal species [44,45]. Definitive documentation of thresholds for a multi-host disease requires measuring the abundances of all important host species and their intra- and interspecific transmission rates (e.g. [27,46]).

Success stories, but puzzles persist

Even the most exhaustive studies demonstrating thresholds are beset by these fundamental problems. Analysis of a 30-year time series convincingly showed a threshold density of great gerbils, *Rhombomys opimus*, below which infection by plague, *Yersinia pestis*, was not present [9]. However, the authors could not distinguish between invasion and persistence thresholds, and the cause of an observed two-year lag between gerbil abundance and plague outbreak remains unclear. Ongoing and extensive research of cowpox dynamics in a two-species rodent metapopulation [8,26,27] recently reported evidence of separate invasion and persistence thresholds for one host species, but only when abundances were measured in numbers, not as densities [8]. Although compelling, these data are confounded somewhat by interspecies transmission (including an unstudied third host species [27]), and by possible differences in movement and mixing behaviour between island and mainland populations.

Thresholds in disease control: applications and evidence

Wildlife diseases usually spread unchecked, but are sometimes managed if they pose risks to humans, livestock or sensitive species. Control efforts typically aim to reduce the susceptible host population through culling, sterilization or vaccination [3,23,47–54]. These measures represent the most important application of threshold concepts and the best potential source of large-scale experimental data testing those concepts.

When links to theory are stated explicitly, most vaccination and population reduction targets seem to be aimed at reducing R_{eff} below 1, rather than on the more-ambiguous CCS [47,54,55]. Seeking eradication through herd immunity by vaccinating a threshold proportion of the population is sound in principle, provided that the population is well-mixed. Otherwise, targeted vaccination

Box 2. Density dependence and the critical community size (CCS)

A core assumption underlying the CCS is that the rate of susceptible replenishment (usually owing to birth and/or immigration) increases with population size [7,34,37]. In human systems, the population growth rate generally satisfies this assumption (Figure Ia). In wildlife systems, however, density-dependent effects can dominate recruitment, such that the replenishment rate of new susceptibles might decrease as N increases (Figure Ib). Many different curves (some highly non-linear) can describe the relationship between wildlife population size and recruitment rates, and death rates often also exhibit density dependence [59]. Immigration and emigration can vary similarly when animals distribute themselves via density-dependent habitat selection [60].

These ecological complexities contribute uncertainty to the already loosely-defined CCS [35], casting doubt on its general applicability in wildlife disease systems. They also introduce the potential for perverse outcomes of control efforts: culling programs might increase birth rates (through compensating recruitment) or immigration (as conspecifics recolonize a cleared habitat; sometimes termed the 'vacuum effect' [47]), thus increasing the chance of disease persistence [42,47]. Finally, disease-induced mortality of a host species might itself interact with density-dependent effects, generating complex dynamics and possible feedback cycles with unpredictable effects on disease persistence.

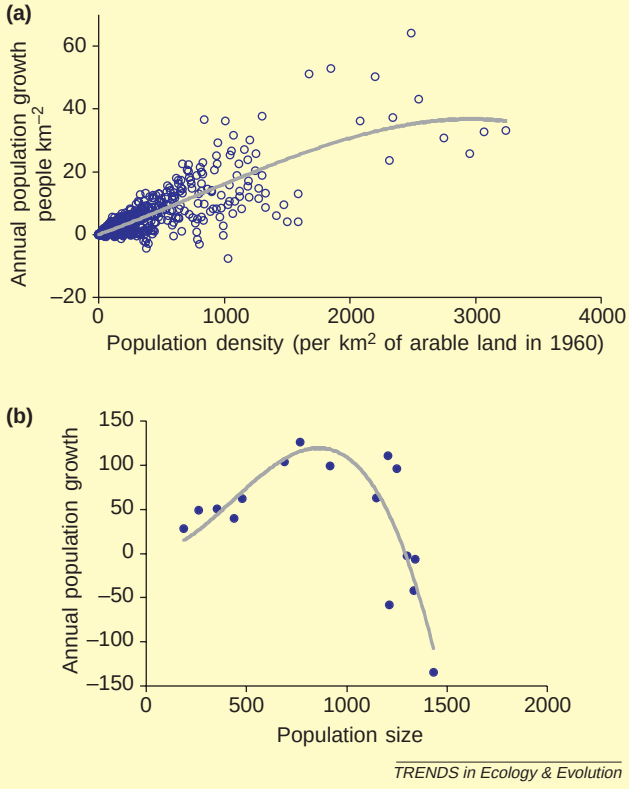


Figure I. Annual population growth for **(a)** humans from 187 countries from 1960 to 2000 and **(b)** wildebeest in the Serengeti. Human recruitment generally increases with N, whereas density-dependent effects make wildlife recruitment more complicated. Reduction of wildlife population size might increase the rate of population growth, thus aiding disease persistence by replenishing the susceptible pool. Third-order polynomials were fit to the data with the y-intercept set to zero (grey line). (Data from [61].)

policies might be required, focusing on regions [49,56] or pursuing thresholds calculated for specific groups [57]. Disease control by culling is theoretically more effective under some circumstances [47], but is less reliable owing to both its basic assumption that R_0 increases with N (Box 1) and the unpredictable effects of population change, such as compensating reproduction (Box 2) or social perturbation [10]. Some wildlife control programs have achieved the ultimate success of regional eradication [48,54], notably fox rabies in Europe [53], whereas

Box 3. Future directions

Although significant progress has been made, many outstanding questions surround population thresholds for disease.

Real-world complexities

The foundations of threshold theory apply chiefly to well-mixed host populations in constant environments with single directly transmitted pathogens and no alternative host species. Complexities of real disease systems, both human and wildlife, present important challenges:

- Spatial or social structure in a population impedes disease invasion [32] and can help or hinder persistence [14,62,63]. Research is needed into how metapopulation structure impacts our ability to detect thresholds and should consider different patterns of between-group movement [64] and possible group-level heterogeneities [28]. This topic links to fundamental questions surrounding abundance measures and transmission [16–21].
- Impacts of wildlife population dynamics (e.g. large fluctuations, density dependence, trophic interactions and seasonal births [47,61]) on disease invasion and persistence are largely unstudied.
- Host-pathogen coevolution can influence disease invasion (via pathogen adaptation to the new host [65]) or persistence (via immune escape mechanisms or evolution of virulence [66,67]), but is not incorporated in current thinking on thresholds.
- Many pathogens have mechanisms to favour persistence, including reactivation of infections, extended latent or infectious periods, asymptomatic carrier states, environmental reservoirs or alternative host species [1,3,27,45,68]. The influence of these factors on possible thresholds should be examined.
- Environmental or behavioral variation can cause transmission to vary seasonally, potentially coupling with natural timescales of disease-host interactions, with unknown impacts on disease thresholds [37,38,69,70].
- Disease-host systems involving additional complexities, including macroparasitic and vector-borne diseases, or those with free-living stages, can exhibit altered or additional thresholds that are not well understood [2,42].

The search for thresholds

Empirical studies seeking disease thresholds in wildlife systems are challenged by the indistinct nature of their target and by issues of sample size versus stochasticity and confounding ecological factors. Future empirical research can follow two parallel paths. Top-down studies seeking to identify invasion or persistence thresholds for wildlife must address the recurring methodological issues listed in the main text, compiling well-replicated disease datasets over a range of host abundances, and, for persistence, also tracking mortality, recruitment and migration of hosts and identifying possible reservoirs. These are challenging standards that will be met only under rare circumstances. Bottom-up mechanistic studies, meanwhile, can investigate the processes underlying thresholds (e.g. transmission, birth, death and immigration), particularly the density dependence that is common in wildlife systems. These complementary approaches, linked by new theory appropriate for wildlife disease, represent the surest path to well-grounded empirical evidence of disease thresholds.

others have reduced disease incidence [53,54] and a few have increased disease spread [10].

Control programs that manipulate the abundance of susceptible hosts could, in principle, provide unique information about the validity of population threshold concepts in wildlife disease. Unfortunately, these programs suffer from the same methodological issues as the field studies described above. Individual studies rarely include replication or a range of control effort and thus do not enable correct estimation of thresholds. For example, a New Zealand trial regionally eradicated bovine TB, *Mycobacterium bovis*, by culling brushtail possum, *Trichosurus vulpecula*, densities to 22% of pre-control levels for ten years [48]. This outcome is consistent with a model-predicted threshold at 40% of pre-control levels [55], but yields no further information regarding a precise threshold level. Efforts to pool results from multiple control programs can be frustrated by inconsistent reporting practices and by the lack of comparability between different control methods. For decades, fox rabies control (by culling and, more recently, vaccination) has been extensive throughout Europe, but programs rarely give results from a range of fox densities and frequently do not report densities at all [53]; local eradications have been achieved, but programs failing to eradicate rabies (which are essential to determining thresholds) are probably under-reported.

Conclusions and the way forward

The concept of population thresholds for wildlife disease has the potential to guide or mislead us and should be applied with caution in research and control efforts. Four major points arise from our review:

(1) Population thresholds for disease are not abrupt in most natural systems: there are no 'magic numbers' separating dynamical regimes. Invasion thresholds exist if R_0 of a disease increases with N and the host population is large and well-mixed, but they are blurred by stochasticity and finite population effects (Figure 1). Persistence of disease against endemic or epidemic fadeout increases gradually with population size, and depends as strongly on the timescales of demographic and transmission processes as on N (Figure 2). Therefore CCS thresholds should be viewed as ranges of host abundance or can be defined precisely using arbitrary criteria.

(2) Efforts to identify thresholds for wildlife disease are impeded by limited replication and biased datasets, complex population structures, alternative host species and other complications. Influences of many factors arising in wildlife ecology require study (Boxes 2,3).

(3) Control policies predicated solely on thresholds are not supported by evidence. Distinct targets are alluring to policy-makers and can have other benefits, but the likely benefits of final, incremental steps toward a supposed threshold should be weighed against their often-escalating costs.

(4) Despite points 1–3, threshold concepts provide a useful framework for characterizing and controlling epidemics, and further research into theoretical and applied questions is essential (Box 3).

The relationship between host abundance and transmission is a central question of disease ecology, and understanding transitions in disease dynamics as N changes (including gradual changes, which can be characterized as 'soft thresholds') will aid in interpreting observed patterns and designing control measures. Management policies aimed at reducing susceptible populations can lower prevalence or eradicate disease, but unintended outcomes are possible. Regardless of outcome, all control programs should monitor and publish their results because they represent a crucial opportunity to better our understanding of population thresholds and the dependence of wildlife disease on host population abundance.

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Supplementary data

Supplementary data associated with this article can be found at doi:10.1016/j.tree.2005.07.004

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Online Supplementary Information

Should we expect population thresholds for wildlife disease?

James O. Lloyd-Smith[1,2], Paul C. Cross[1,3], Cheryl J. Briggs[4], Matt Daugherty[4], Wayne M. Getz[1,5], John Latto[4], Maria S. Sanchez[1], Adam B. Smith[6] and Andrea Swei[4]

[1]Department of Environmental Science, Policy and Management, University of California at Berkeley, Berkeley, CA 94720-3114, USA
[2]Biophysics Graduate Group, University of California at Berkeley, Berkeley, CA 94720-3200, USA
[3]Northern Rocky Mountain Science Center, United States Geological Survey, 229 A.J.M. Johnson Hall, Bozeman, MT 59717, USA
[4]Department of Integrative Biology, University of California at Berkeley, Berkeley, CA 94720-3140, USA
[5]Mammal Research Institute, Department of Zoology and Entomology, University of Pretoria, 0002 South Africa
[6]Energy and Resources Group, University of California at Berkeley, Berkeley, CA 94720, USA
Corresponding author: Lloyd-Smith, J.O. (jls@nature.berkeley.edu).

Figure 2 (expanded). Endemic and epidemic fadeout and the absence of abrupt persistence thresholds illustrated using a stochastic simulation of disease spread. Results demonstrate that both types of fadeout depend strongly on demographic rates and vary gradually with N rather than showing abrupt thresholds. The simulation model tracks the numbers of S, I and R individuals and extends the model used in Figure 1 to include population recruitment and death. For all simulations, R_0=4 and recovery rate γ=0.1; full details are given below. **(a)** Endemic fadeout: ten stochastic simulations of endemic disease dynamics, begun from endemic equilibrium conditions (see Box 1). + signs indicate instances of endemic fadeout when I fluctuated to zero. The black line shows the cumulative fraction of runs with disease fadeout out of 1000 stochastic simulations. The *per capita* death rate is μ=0.001, so the ratio of mean host lifespan to mean infectious period is $\alpha=(\gamma+\mu)/\mu$=101. λ=10 new susceptibles were recruited per time step, yielding equilibrium population size $N^*=\lambda/\mu$=10 000. **(b)** Epidemic fadeout: 10 stochastic simulations of epidemic disease dynamics, begun with S=4999, I=1, R=0. + signs indicate instances of epidemic fadeout during the trough in I following the first epidemic peak. Parameters: λ=15, μ=0.003, so $N^*=\lambda/\mu$=5000 and $\alpha=(\gamma+\mu)/\mu$=34.3. **(c)** Average time to endemic fadeout (out of 1000 runs started at the endemic equilibrium) as a function of population size and the relative rate of demographic turnover. Along each curve, the equilibrium population size, $N^*=\lambda/\mu$, was varied by changing the input of new susceptibles, λ, while keeping the death rate, μ, constant. Different rates of demographic turnover (i.e. different curves at a given population size) were achieved by varying λ and μ simultaneously, while keeping the ratio $N^*=\lambda/\mu$ constant. Thus, μ varies between curves, which alters the timescale ratio $\alpha=(\gamma+\mu)/\mu$. For curve (i), μ=0.002, $\alpha=(\gamma+\mu)/\mu$=51; for (ii), μ=0.001, $\alpha=(\gamma+\mu)/\mu$=101; and for (iii), μ=0.0005, $\alpha=(\gamma+\mu)/\mu$=201. **(d)** Probability of persisting through the first inter-epidemic trough as a function of population size and the relative rate of demographic turnover, estimated from the fraction of 10 000 runs that persisted (starting with $S=N^*-1$, I=1, and R=0, conditional on successful invasion of the disease). Equilibrium population size and demographic turnover rates were varied as in (c). For curve (i), μ=0.005, $\alpha=(\gamma+\mu)/\mu$=21; for (ii), μ=0.003, $\alpha=(\gamma+\mu)/\mu$=34.3; and for (iii), μ=0.002, $\alpha=(\gamma+\mu)/\mu$=51. With μ=0.001, $\alpha=(\gamma+\mu)/\mu$=101 and no runs persisted through the first trough. In all panels, simulations were based on the frequency-dependent model from Figure 1, with four processes occurring in each time step: each susceptible individual can become infected with probability $1-\exp(-\beta I/N)$, with transmission coefficient $\beta=(\gamma+\mu)R_0$; each infectious individual can recover with probability $1-\exp(-\gamma)$; every individual can die with probability $1-\exp(-\mu)$; and λ new susceptibles are recruited to the population.