

REPORT

## How should environmental stress affect the population dynamics of disease?

Kevin D. Lafferty<sup>1\*</sup> and Robert D. Holt<sup>2</sup>

<sup>1</sup>USGS, Western Ecological Research Center, Marine Science Institute, University of California, Santa Barbara, CA 93106-6150, USA

<sup>2</sup>Department of Zoology, 223 Bartram Hall, PO Box 118525, University of Florida, Gainesville, FL 32611-8525, USA

\*Correspondence: E-mail: [lafferty@lifesci.ucsb.edu](mailto:lafferty@lifesci.ucsb.edu)

### Abstract

We modelled how stress affects the population dynamics of infectious disease. We were specifically concerned with stress that increased susceptibility of uninfected hosts when exposed to infection. If such stresses also reduced resources, fecundity and/or survivorship, there was a reduction in the host carrying capacity. This lowered the contact between infected and uninfected hosts, thereby decreasing transmission. In addition, stress that increased parasite mortality decreased disease. The opposing effects of stress on disease dynamics made it difficult to predict the response of disease to environmental stress. We found analytical solutions with negative, positive, convex and concave associations between disease and stress. Numerical simulations with randomly generated parameter values suggested that the impact of host-specific diseases generally declined with stress while the impact of non-specific (or open) diseases increased with stress. These results help clarify predictions about the interaction between environmental stress and disease in natural populations.

### Keywords

Disease, dynamics, host, infectious, model, pollution, population, stress, transmission.

*Ecology Letters* (2003) 6: 654–664

### INTRODUCTION

In our rapidly changing world, a variety of stresses may affect the functioning of organisms, ranging from toxins to the vicissitudes of climate change. The ultimate impact of such stress, however, depends upon the dynamic behaviour of the stressed system. One arena in which this issue is particularly important is in evaluating the joint impacts of environmental stress and infectious diseases. There is growing evidence that infectious diseases play a major role in the dynamics of many natural populations and communities (Holmes 1996). One can predict that increasing stress either aggravates or moderates impacts of infectious disease, depending upon what aspect of the system one emphasizes.

Consider, for instance, the interplay of stress and disease from the perspective of an individual host affected by a host-specific parasite. Immune systems are costly to maintain and stressed animals may lack sufficient energy to mount an effective defence (Rigby & Moret 2000). Toxic chemicals in pollution (Khan 1990), malnutrition (Beck & Levander 2000) and thermal stress from climate change (Harvell *et al.* 1999) are all examples of stressors hypothesized to increase individual susceptibility to infectious diseases. Hence, quite generally, stressed individuals should

be more susceptible to infection (Scott 1988; Holmes 1996), although the exact impact of any stressor is likely to vary by genotype within a species (Blanford *et al.* 2003). This line of thought suggests that infectious disease should be aggravated by environmental stress.

An opposing prediction emerges from considering the population dynamic context of infection. A key component of infectious disease models is that the likelihood and impact of an epidemic increases with host density (Anderson & May 1986). Outside stressors that depress population density, therefore, should reduce the chance of an epidemic, or even the ability of a parasite to persist at all, because factors that reduce host density also reduce contact rates between infected and uninfected individuals. This dependence of infection upon density is one of the key intersections of epidemiology and conservation biology. Threats to biodiversity, which are generally mediated through reductions in abundance, should normally indirectly reduce risk to host-specific infectious diseases (Lafferty & Gerber 2002). Direct reduction of host density should reduce disease. Culling of seal populations reduces intestinal nematode parasites by reducing host-density below transmission thresholds (Des Clers & Wootten 1990). Fishing can similarly reduce parasites in

fish populations (Arneberg *et al.* 1998). A swim bladder nematode was apparently extirpated from native trout in the Great Lakes after a variety of stressors reduced trout populations to very low levels (Black 1983). Alternatively, some stressors may increase parasitism by increasing host density. The stress most commonly observed to be associated with increased parasitism in fishes and invertebrates is eutrophication (Lafferty 1997). The addition of nutrients to aquatic systems increases primary productivity that indirectly increases some grazers and predators. Such increases in host density could facilitate disease invasion. It is also possible that nutrients or associated pollutants could increase individual susceptibility.

A third prediction arises when we consider the direct effects of stressors on parasites themselves. Stressors may more negatively impact parasites than their hosts. Toxic chemicals and metals have a relatively consistent negative effect across studies of intestinal helminths (Lafferty 1997). Selenium, for example, is more toxic to tapeworms than to their fish hosts (Riggs *et al.* 1987). A pollutant may also kill sensitive free-living stages of the parasite (Evans 1982). For example, trace metals in sewage-sludge reduce survival of free-living cercariae and miracidia, leading to a lower prevalence of a trematode in intermediate-host snails (Siddall & Clers 1994). Alternatively, parasitic infection may make the host more susceptible to toxins (Guth *et al.* 1977; Stadnichenko *et al.* 1995). For instance, cadmium was much more toxic to amphipods infected with larval acanthocephalans than uninfected amphipods (Brown & Pascoe 1989). While this latter effect decreases the spread of an epidemic through a population, it also increases the impact of disease on infected individuals.

Stress may have multiple effects on hosts and parasites such as increasing susceptibility to disease while decreasing host vital rates, such as reproduction. As top predators, marine mammals bioaccumulate lipophilic toxins that can affect the immune system (Swart *et al.* 1994); for example, harbour seals fed fish from polluted areas have lower killer cell activity, decreased responses to T and B cell mitogens and depressed antibody responses (DeStewart *et al.* 1996). Such immunosuppression may be a cofactor in mass mortalities associated with morbillivirus (Van Loveren *et al.* 2000) and there is some correlative evidence for the hypothesis that marine contaminants may increase sea otter susceptibility and exposure to infectious diseases (Lafferty & Gerber 2002; Miller *et al.* 2002). Along with effects on susceptibility to disease, sea lions suffer lower reproductive success when subject to high contaminant concentrations and this may have limited sea lion abundance in some areas (O'Shea & Brownell 1998). In these cases, it is difficult to predict the overall effect of stress on disease.

A similar scenario occurs for gill ciliates of fishes. Intensities or prevalences of ciliates increase with oil

pollution (Khan 1990), pulp mill effluent (Lehtinen 1989; Axelsson & Norrgren 1991; Khan *et al.* 1994) industrial effluent (Dabrowska 1974; Vladimirov & Flerov 1975; Overstreet & Howse 1977) and thermal effluent (Esch *et al.* 1976; Nilsen 1995). This appears to be due to an increase in host susceptibility because toxic conditions impair mucus production; a fish's main defence against gill parasites (Khan 1990). In addition, poor water quality can affect fish vital rates. For example, exposure to petroleum induces liver disease and affects reproduction and growth (Johnson 2001).

Stress can simultaneously increase parasite mortality and impair host vital rates, making it more likely that parasites will be extirpated by stress. Blooms of diatoms containing domoic acid (a neurotoxin that passes up the food chain) have been implicated in mass mortalities of marine mammals (Lefebvre *et al.* 1999). But these toxins may affect some parasites as well. In small doses, domoic acid (from macroscopic red algae) has been traditionally used in Japan to cure roundworm (nematode) infections in humans (Daigo 1959). Dolphins that died of domoic acid poisoning in California in 2002 were remarkably free of intestinal parasites (Krista Fahy, pers. comm.). Because both parasites and domoic acid transmit through the food chain (even in the same food items), there may be important interactions between harmful algal blooms and helminth infections in marine mammals.

This heterogeneous array of potential effects of stress on infectious disease makes it unclear how a particular stressor should affect the overall course of an epidemic in a host population, or endemic levels of a disease. Although stressed individuals should be more susceptible to infection if exposed, the stressor could simultaneously reduce opportunities for infection because the contact rate between infected and uninfected individuals will decline with the extent that the stressor reduces host density. In addition, populations of some parasites that are susceptible to the stressor may not be able to persist at all. It would also appear *a priori* that stress can either aggravate or diminish the population-level impact of a host-specific infectious disease organism upon its host.

To explore this issue formally, we used analytical models of infectious disease dynamics to examine how the effects of stress on host vital rates, such as births, deaths and density dependence, interact with effects of stress on host susceptibility and recovery. Initially, the response to stress that we consider is the likelihood that a disease can invade a host population (a likelihood that increases with the extent that the host carrying capacity exceeds the host-threshold density for transmission). We solved more complicated models numerically to examine the general patterns of association between the impact of disease and stress across a wide range of parameter values.

## A BASIC INFECTIOUS DISEASE MODEL INCLUDING STRESS

We used simple microparasite (SIR) models (Anderson & May 1986) to investigate the opposing effects of increased susceptibility, decreased contact rate and increased parasite mortality associated with a stressor. These models come with several simplifying assumptions, such as a lack of genetic variation for susceptibility or virulence and density-dependent (as opposed to frequency dependent) transmission (explorations of these assumptions indicate, for example, that changes in environmental quality can lead to changes in virulence; Koella 2000). One key assumption we imposed was that there existed a host carrying capacity, in the absence of disease, set by resource limitation on host birth rates or space acquisition.

The rate of change of the infected portion of the population is as follows:

$$\frac{dI}{dt} = \beta SI - LI \quad (1)$$

Here, the variable  $S$  is the density of susceptible hosts (which at equilibrium, in the absence of infection, reaches a carrying capacity,  $K$ ).  $I$  is the density of infected hosts,  $\beta$  is the classic epidemiological transmission efficiency, and  $L$  is the loss rate of infected hosts (e.g. infected host mortality and recovery rate). The intrinsic growth rate of the infection when rare and host population size is constant at  $S$  is  $\lambda = \beta S - L$ . If  $w$  is a parameter associated with the magnitude of a stressor, the net effect of a small increase in stress upon the initial rate of spread of the disease is

$$\frac{\partial \lambda}{\partial w} = \left( \frac{\partial \beta}{\partial w} \right) S + \beta \left( \frac{\partial S}{\partial w} \right) - \frac{\partial L}{\partial w} \quad (2)$$

Given the facts presented above, the first term will usually be positive because stress makes it more likely individual hosts can become infected. However, the second term may be positive, zero, or negative, depending on how the stressor affects host abundance. If stressors strongly reduce host abundance, this can greatly reduce the potential for disease spread. Finally, the third term may also be positive or negative. All else being equal, the first term will tend to dominate when hosts are very abundant.

If  $S$  remains constant at  $K$ , we can easily solve eqn 1, for the basic reproductive 'rate' of a disease,  $R_0$ , which is defined as the expected number of secondary infections generated from a single infected host individual. A disease can invade an uninfected population when  $R_0 > 1$  because an infected individual introduced into an uninfected population will infect at least one other host, on average, before this individual dies or recovers. Moreover, given that the disease invades, an increasing magnitude of  $R_0$  generally (though not always) implies increased prevalence and impact

of a disease (an assumption we later investigate). Because of our assumption of density-dependent disease transmission, the expression for  $R_0$  also implies a host-threshold density below which a disease will not invade, setting a minimal host carrying capacity ( $H_t$ ) that permits the disease to persist. By finding the conditions resulting in  $R_0 = 1$ , we will below utilize a simple graphical depiction of how the opposing effects of stress interact to determine the invasibility of a specialist disease.

It is clear that stress can affect many population parameters at the same time, and that the effects of stress may vary among these parameters. To represent this multiplicity of effects in a more concrete model, stress was entered as a multiplier,  $w$ , that acted independently on each parameter according to that parameter's sensitivity to stress. We use as an illustrative example an expression for susceptibility under stress of  $\beta(1 + w\beta')$  where  $w$  is the level of stress associated with a stressor in the environment (increasing from zero) and  $\beta'$  (increasing from zero) is the extent that stress increased susceptibility. This allowed us to independently vary the level of stress in the environment and the sensitivity of different parameters to stress. While we assumed that stress always increased susceptibility to infection, we assumed that stress could either reduce [using a similar functional form of  $K/(1 + wK')$ ] or increase [ $K(1 + wK')$ ] the carrying capacity because stress could reduce host vital rates, reduce resources or even increase resources (as in eutrophication; stress could also reduce the frequency of intraspecific, density-dependent mechanisms such as territoriality or aggression, thereby indirectly permitting an increase in population size). We also allowed stress to either increase or decrease loss rates [to  $L(1 + wL')$  or  $L/(1 + wL')$ , respectively], as stress might either kill parasites in hosts, increase mortality of infected hosts (increasing the rate of host recovery) or impair immune responses (thus, slowing recovery). We also considered that stress might not act on all the parameters in the model (e.g. any combination of  $\beta'$ ,  $K'$  or  $L'$  could be zero). This creates 18 qualitatively different models for the relationship between stress and  $R_0$ , several of which imply complex associations between parasite growth and stress. From these, we sought a simple analytical solution for the association between  $R_0$  and stress.

Taking the first derivative of  $R_0$  with respect to  $w$  (the slope of  $R_0$  with respect to stress) provides a convenient measure of how an increase in stress influences this facet of disease dynamics. We placed the potential relationships into four categories. If the initial slope (at  $w = 0$ ) was positive and the final slope ( $w$  large) was not negative,  $R_0$  increased with stress, so stress would augment the ability of the disease to persist. If the initial slope was negative and the final slope was not positive,  $R_0$  decreased with stress. If the initial slope was positive and the final slope was

negative,  $R_0$  was highest at intermediate levels of stress, creating a convex (hump-shaped) association. If the initial slope was negative and the final slope was positive,  $R_0$  was lowest at intermediate levels of stress, leading to a concave (U-shaped) association. We then identified the analytical solutions to the relationships between  $R_0$  and stress as defined by the relative sensitivities of  $\beta$ ,  $L$  and  $K$  to stress.

Our approach allows analytical exploration but has a number of limitations. First, although  $R_0$  is associated with the potential for disease impacts, it does not represent the impact of a disease per se. In particular, if stress increases parasite-induced host mortality, the impact of a disease on host population size increases, even while  $R_0$  decreases. Second, our simple expressions for host carrying capacity and parasite loss mask several important features of population dynamics that could be affected by stress (e.g. interdependence between mortality and carrying capacity, density dependence in parasitized populations, non-additive effects of stress on parasite loss).

A more complete model that allows us to address these issues is as follows:

$$\frac{dS}{dt} = b(S + R + jI)(1 - cN) - (m + qN)S + gR + uI - \beta SI \quad (3)$$

$$\frac{dI}{dt} = \beta SI - (m + \alpha)(1 + qN)I - uI - aI \quad (4)$$

$$\frac{dR}{dt} = aI - m(1 + qN)R - gR \quad (5)$$

Here, the variable  $S$  is the density of susceptible hosts,  $I$  is the density of infected hosts and  $R$  is the density of recovered immune hosts ( $N = S + I + R$ ). The parameter  $b$  is the birth rate of uninfected hosts,  $j$  is the proportion of the uninfected birth rate experienced by infected hosts,  $m$  is uninfected host death rate,  $m + \alpha$  is infected host death rate,  $c$  gauges the strength of direct density dependence in host birth rates,  $q$  likewise scales direct density dependence in host death rates,  $\beta$  is the classic epidemiological transmission efficiency,  $u$  is the recovery rate of infected hosts that does not lead to immunity,  $a$  is the rate at which individuals both recover and become immune, and  $g$  measures the loss rate of immunity. For convenience, Table 1 compiles these variables and parameters. We assumed that stress increased susceptibility to infection, host death rates and the loss of immunity. We also assumed that stress decreased intrinsic host birth rates. We allowed stress to either increase or decrease recovery rates as stress might either kill parasites in hosts (increasing the rate of host recovery) or impair immune responses (thus, slowing recovery). We assumed that intensity of density dependence could increase with stress that decreases resources or that density dependence could decrease with eutrophication. Equations 3–5 were

**Table 1** Description of parameters and variables

$a$	Instantaneous, per capita rate of change from infected to immune hosts (parasite mortality)
$b$	Instantaneous, per capita rate of uninfected host birth
$c$	Effect of density dependence on host birth rate
$g$	Instantaneous, per capita rate of loss of immunity
$H_t$	Host-threshold density
$I$	Density of infected hosts
$jb$	Instantaneous, per capita rate of infected host birth
$K$	Equilibrium host density in the absence of disease
$m$	Instantaneous, per capita rate of uninfected host death
$N$	Number of hosts ( $S + I + R$ )
$q$	Effect of density dependence on host death rate
$R$	Density of recovered (immune) hosts
$R_0$	Net reproductive rate of disease
$S$	Density of susceptible hosts
$u$	Instantaneous, per capita rate of change from infected to susceptible hosts (parasite mortality)
$v$	Density of disease causing particles for an open, non-specific or non-infectious disease
$w$	Level of stress in the environment
$x'$	Susceptibility of a parameter $x$ , to stress
$\alpha + m$	Instantaneous, per capita rate of death for infected hosts
$\beta$	Transmission efficiency

solved numerically to determine equilibrium conditions of host populations for disease in the presence of stress.

The responses of various parameters to stress in natural populations are unknown and unlikely to be completely independent. One strategy in the face of such uncertainty is to generate random combinations of parameters, constrained to satisfy the non-trivial equilibrial conditions of the model, and with distributions directly or indirectly scaled to the host birth rate (which in effect defines a time-scale for the model). This approach has the ability to identify if certain relationships hold true only for a relatively narrow combination of parameter ranges.

SIR parameter values were assigned as follows. The host birth rate ( $b$ ) was first randomly selected from a uniform distribution between 0 and 1. In order to have a positive carrying capacity, the host mortality rate ( $m$ ) was randomly selected from a uniform distribution between 0 and  $b$ . Each density dependence parameter was randomly selected from an exponential distribution with a mean of  $m/1000$ . This resulted in a diverse set of carrying capacities and growth rates. Parameter values for disease were chosen as follows. The proportional birth rate of infected hosts,  $j$ , was randomly selected from a uniform distribution between 0 and 1. Additional infected host mortality ( $\alpha$ ), recovery rates ( $u$  and  $a$ ) and the loss rate of immunity ( $g$ ) were randomly selected from an exponential distribution with a mean of  $m/5$ . Constraints were imposed on the value of  $\beta$  so that  $R_0$

was a uniform random number between 1 and 10 in the absence of stress.

Several different scenarios of the effects of stress were run through this procedure and these are listed in Table 2. Values for all stress coefficients (e.g.  $\beta'$ ) were randomly selected from an exponential distribution with a mean equal to 1. For each scenario, we found non-trivial local equilibria via sequential iteration of eqns 3–5. This was repeated across a 10-step range of stress from 0 to the maximum value of stress that would cause the host population to go extinct in the absence of disease. We used 10 000 randomly selected parameter sets (with parameters values obtained as

above) and evaluated each across a range of 10 levels of stress ( $w$ ). We then calculated the shape of the association between stress and  $R_0$  and the impact of disease (where proportional impact of disease was expressed as the decrease in total host density affected by a disease relative to the carrying capacity of the population in the absence of disease, or  $[K - N]/N$ ).

### Stress and non-specific diseases

Several diseases of conservation concern do not fit the assumptions of a standard SIR model. The dynamics of

**Table 2** The association between stress and disease (measured as  $R_0$  and Impact) under different scenarios

Scenario	Parameters affected	Stress association	
		$R_0$	Impact
<i>General</i>			
Simple model (approximation)	Decrease in: $b, j$	58% N	34% N
	Increase in: $\beta, c, g, \alpha$	21% H	38% H
	Increase or decrease in: $u, a$	21% P	25% P
		0.1% U	3% U
Random effect size on all parameters with reduction in resources	Decrease in: $b, j$	92% N	65% N
	Increase in: $\beta, c, q, g, m, \alpha$	8% H	34% H
Open, non-specific or non-infectious Replace $\beta SI$ with $\beta S'v$	Increase or decrease in: $u, a$		1% N
			13% H
	Decrease in: $b, j$		86% P
<i>Case studies</i>			
Eutrophication that increases resources available for reproduction in fishes or invertebrates	Decrease in: $c$	100% P	1% N
			19% H
			74% P
			6% U
Culling that increases mortality in mammals; Fishing that increases mortality in fish; Heavy metal that differentially increases death of infected amphipods	Increase in: $m$ and/or $\alpha$	100% N	64% N
			29% H
			4% P
			3% U
Toxins, such as heavy metals, that kills parasites in fishes, snails or marine mammals	Increase in: $a$ or $u$	100% N	61% N
			30% H
			1% P
			8% U
Heavy metal that increases susceptibility to disease and decreases reproduction in mammals; Oil pollution that increases susceptibility to ciliates and decreases fish reproduction	Decrease in: $b$ Increase in: $\beta$	51% N	25% N
		17% H	34% H
		32% P	38% P
			3% U
Domoic acid that increases parasite mortality and mammal mortality	Increase: $u$ and/or $a$	100% N	61% N
			30% H
			1% P
			8% U

Letter codes refer to the shape of the association: N for negative, H for hump-shaped (or convex), P for positive association, U for U-shaped (or concave).

some diseases are decoupled from host density (i.e. are 'open') if they are (1) non-infectious, (2) not host specific (and if other hosts that can sustain the parasite are not affected by stress) or (3) at the spatial scale under study, have open recruitment (i.e. infective stages that enter the host population come from outside the host population, and not from infected individuals within the focal host population). We modified the above model to accommodate these scenarios by substituting  $\beta SI$  with  $\beta S\nu$ , where  $\nu$  was a constant representing the density of disease causing stages/particles in the environment. In this modified model, because all transmission occurs from sources external to the focal host, the issue of parasite persistence (as gauged by  $R_0$ ) does not arise, but such diseases could nonetheless have strong effects on population size. We explored this with numerical simulations of the above model with appropriate substitutions for the transmission terms. This protocol permits us to assess how having an open source of disease affects the patterns of association between disease impacts and stress.

## RESULTS

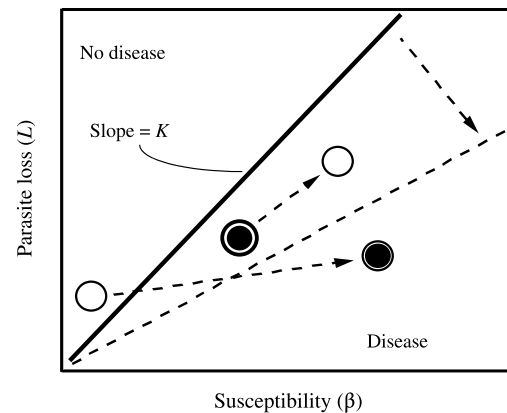
If the host is at its carrying capacity, eqn 1 (disease without stress) leads to:

$$R_0 = \beta K/L \quad (6)$$

$$H_t = L/\beta \quad (7)$$

We graphically represented how the  $R_0 = 1$  isocline separated conditions where a disease could and could not invade. We represent this as a line with slope =  $K$ , according to the degree of susceptibility,  $\beta$  (on the horizontal axis) and parasite 'loss',  $L$  (on the vertical axis) (Fig. 1). This provides a simple analytical illustration for how variations in these parameters (such as might occur with stress) might increase or decrease the ability of a disease to invade. Stress-associated impairment in host vital rates (decreased  $K$ ) decreases opportunities for disease by reducing the slope of the  $R_0 = 1$  isocline (eutrophication would increase the slope). By contrast, increased susceptibility moves populations out into higher  $R_0$  space (more disease). Movement along the vertical axis is more complicated, because stress can act in either direction on this axis. Stress that increases parasite mortality rates decreases disease, whereas stress that impairs host recovery increases disease.

The analytical solutions for the initial and final slopes of the association between  $R_0$  and  $w$  are easiest to describe verbally (with examples to follow). Given that stress coefficients are positive, the initial slope is the same sign as that of the sum of the values of the stress coefficients that increase disease, minus the sum of the values of the stress coefficients that decrease disease. The final slope is the same



**Figure 1** Disease in parameter space. In this graphical representation of eqn 6, the line dividing the parameter space represents  $R_0 = 1$  (no intrinsic rate of increase for an infectious disease entering an uninfected host population). The disease can only invade regions of parameter space to the right of the  $R_0 = 1$  line (where  $R_0 > 1$ ). Increases in susceptibility increase  $R_0$  as do increases in host carrying capacity (host equilibrium in the absence of disease). Increased parasite death rates (either due to increased host recovery rate or increased mortality of infected hosts) decrease  $R_0$ , making it more difficult for a disease to invade. Dashed arrows indicate hypothetical effects of stress on where populations reside in parameter space (stress can shift the location of a population in parameter space or, by reducing the carrying capacity, such as from thick to dashed diagonal line, lower the slope of the line separating disease space from no-disease space). Filled circles represent diseased populations and open circles represent populations without disease. Stress can expose an uninfected population to disease (particularly if effects on susceptibility are greater than effects on parasite mortality) or it can lead to the extirpation of a disease (if effects on host carrying and/or parasite mortality are strong).

sign as the count of the stress coefficients that increase disease, minus the count of the stress coefficients that decrease disease. If there are an equal number of coefficients that increase and decrease disease, the final slope is equal to the initial slope. As the initial and final slope of  $w$  with  $R_0$  can be negative, or positive (or zero for limited situations), negative, positive, concave and convex relationships between stress and disease are all feasible, depending on the number and magnitude of stress coefficients that increase or decrease disease.

The following examples illustrate this result. For a population where susceptibility increases with stress, but loss rates and the carrying capacity are unaffected by stress,  $R_0$  always increases with stress. If stress also decreases carrying capacity (decreasing disease),  $R_0$  will increase with disease if  $\beta' > K'$  or decrease with disease for  $K' > \beta'$ . For a population where stress increases susceptibility (increases disease), decreases carrying capacity (decreases disease) and

increases parasite loss (decreases disease), the final slope between stress and  $R_0$  is always negative. The initial slope is negative for  $\beta' < K' + L'$  (resulting in a negative association between stress and  $R_0$ ). The initial slope is positive for  $\beta' > K' + L'$  resulting in a convex association between stress and  $R_0$ . Finally, for a population where stress increases susceptibility (increases disease), decreases carrying capacity (decreases disease) and decreases parasite loss (increases disease), the final slope between stress and  $R_0$  is always positive. The initial slope is negative for  $K' > \beta' + L'$  (resulting in a concave association between stress and  $R_0$ ). The initial slope is positive for  $K' < \beta' + L'$  resulting in a positive association between stress and  $R_0$ .

We present the analytical solution above graphically in Fig. 2. If stress increases the carrying capacity, such as through eutrophication, the association between stress and  $R_0$  is always positive unless stress increases parasite loss rates and  $L' > \beta'$  (in which case the association is concave). If stress decreases loss rates, the association between stress and  $R_0$  is always positive, unless stress substantially reduces host carrying capacity such that  $K' > \beta'$  (in which case the association is concave). If stress decreases host density and increases parasite loss rates, the association is negative unless  $\beta' > K' + L'$  (in which case the association is convex).

Plotting carrying capacity ( $K$ ) and host-threshold density ( $H_t$ ) independently illustrates how a convex association between disease and stress can result from a linear decrease in  $K$  with stress combined with a non-linear (asymptotic) decrease in  $H_t$  with stress (Fig. 3). A lack of disease in such a population could be explained by either of two mechanisms: (1) at low stress, individual hosts are less susceptible and epidemics are less likely; (2) with high stress, host density is low and contact rates between infected and susceptible hosts are insufficient to maintain an invading epidemic. Disease is likely to be most noticeable in this case at intermediate levels of stress.

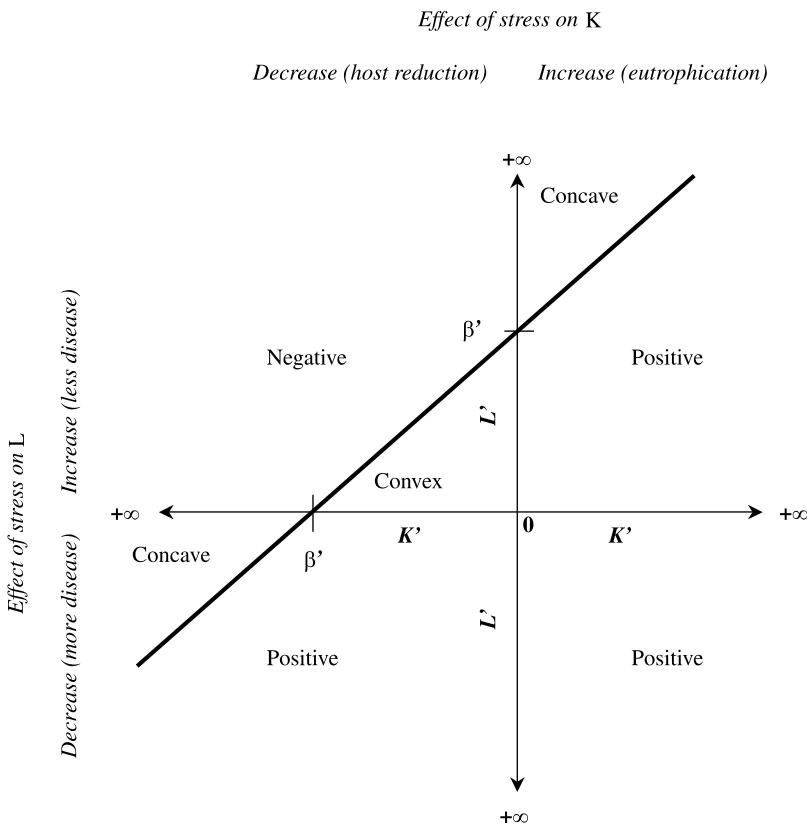
Solutions for the more complex model were cumbersome so we limit our presentation to  $R_0$ ,  $K$  and  $H_t$  in the absence of stress.

$$R_0 = \frac{\beta K}{qK + m + \alpha + u + a} \tag{8}$$

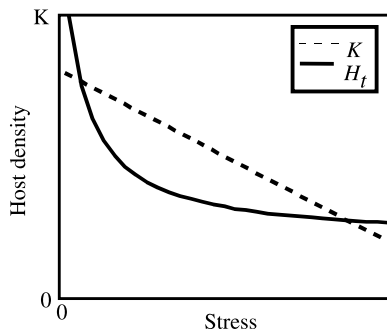
$$K = \frac{b - m}{c + q} \tag{9}$$

$$H_t = \frac{a + u + m + \alpha}{\beta - q} \tag{10}$$

When we examined the numerical simulations for an association between disease impact and stress, we found



**Figure 2** How the shape of the association between stress and  $R_0$  changes in  $\beta' - K' - L'$  space. This illustration shows the four associations between stress and disease in five distinct regions of  $\beta' - K' - L'$  space. Here,  $K'$  and  $L'$  can either increase or decrease disease as stress increases, depending on the quadrant in  $K'-L'$  space. The solution is kept in two dimensions by representing  $\beta'$  in  $L'$  and  $K'$  space.

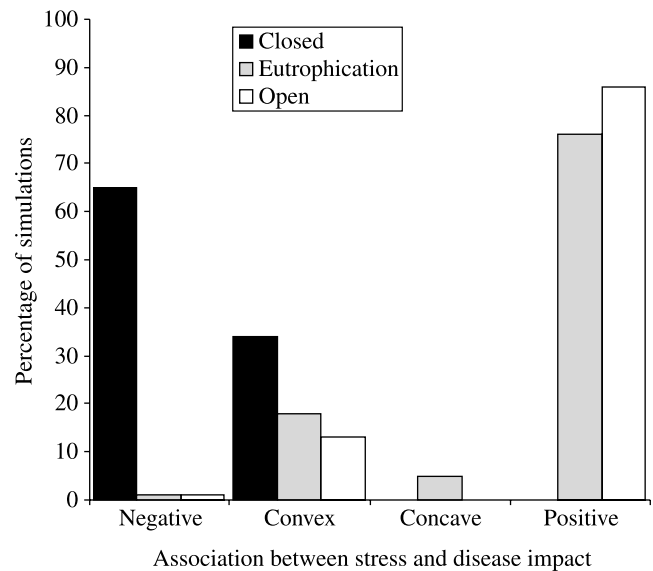


**Figure 3** How opposing effects of stress can make a convex association between stress and disease. An example of an association between  $K$  (dashed line) and stress and  $H_t$  (host-threshold density) and stress that would lead to a convex association between stress and disease. The disease will only invade for values of the dashed line ( $K$ ) above the solid lines ( $H_t$ ).

the results depended strongly on the scenario. We started by looking at each of the parameters separately to be sure that the simulations were consistent with simple expectations. There was a negative association between stress and  $R_0$ , if stress reduced the carrying capacity or increased parasite loss rates (i.e. stress increased  $\alpha$ ,  $m$ ,  $a$ ,  $u$ ,  $q$ , or  $c$  or decreased  $b$ ,  $j$ ). A positive association was found when stress increased transmission, decreased loss rates, or increased the carrying capacity (i.e. stress increased  $\beta$  or decreased  $a$ ,  $u$ ,  $c$ , or  $q$ ). Increases in  $g$  (loss rate of immunity) did not affect  $R_0$ , but had a mostly positive relationship with disease impact (65% positive, 1% negative, 23% convex, 11% concave). Although the association between stress and  $R_0$  was the same as the most frequent association between stress and disease impact, the results for  $R_0$  were never identical to the results for impact. In general, impact showed a greater diversity of associations with stress than did  $R_0$ , with a consistently high frequency of convex associations.

For scenarios involving opposing effects of stress, we begin with the one most closely matching the simple model (Table 2). Here, the association between stress and  $R_0$  exhibited all four possible shapes, but was mostly negative. Convex and positive associations were equally common and concave associations occurred rarely, as they did in all scenarios. The pattern for impact differed in that convex associations were most common, followed by negative, positive and concave associations.

For our complete model (stress affecting all parameters), negative associations between stress and disease were also most common (Table 2, Fig. 4). Positive and concave associations between stress and disease were extremely rare or absent. High levels of stress nearly always extirpated the disease (95%) but rarely extirpated the host earlier than expected (four of 100 000 runs). Similar scenarios of this



**Figure 4** The estimated percentage of the association between the impact of disease (not  $R_0$ , per se) and stress under three scenarios. The standard SIR model showed largely negative associations between stress and disease. Eutrophication showed a greater frequency of positive associations with the impact of disease. The open model showed largely positive associations.

model found that altering the effect of stress on density dependence affected the associations between disease and stress in the expected manner; stress that reduced resources increased negative associations between stress and disease, while increases in resources associated, with stress (such as for eutrophication) increased convex associations.

Altering our simulations to mimic a non-specific, non-infectious or 'open' disease revealed a strongly positive pattern of associations between disease impact and stress (Table 2, Fig. 4). This makes sense in that the per-capita risk of exposure was unrelated to the number of infected individuals in the population, so that when population density declined, the per-capita risk of infections was unaffected. In contrast to the closed model, at high levels of stress it was not rare for host populations to go extinct (15% of runs), and it was not common for parasite populations to go extinct (27%) (Fig. 4).

Customizing the simulations to look at specific scenarios mentioned in our introduction revealed diverse associations between stress and disease (Table 2). Culling of seals, overfishing and heavy metals decreased parasitism, and had negative or convex associations with the impact of disease. Heavy metal and oil pollution had more complex effects on disease in marine mammals and ciliates in fish, including a large proportion of positive interactions. Domoic acid had negative effects on parasites and largely negative or convex effects on the impact of disease. Eutrophication had mostly



positive associations with disease even in the absence of any effects on host susceptibility (Fig. 4).

## DISCUSSION

The array of qualitatively distinct theoretical possibilities suggested by our simple deterministic models seems matched by an equal diversity of known impacts of stress of disease in natural populations. We were able to incorporate opposing predictions about the effects of stress on infectious disease dynamics by using simple SIR models and explicitly considering how stress might affect various parameters. Figure 1 provides a simple graphical portrayal for how the net reproductive rate of the disease ( $R_0$ ) varies in multidimensional parameter space. Stress seems most likely to enhance the ability of the disease to increase when rare if the main effect of stress is to increase host susceptibility, with little effect on host abundance. If stress instead decreases host carrying capacity, the disease is more likely to be extirpated. Disease will also decrease if stress increases parasite loss rates. Because of the diversity of effects of stress at the individual host and population levels, one can observe complex interactions between stress and disease.

We often wish to know more about disease dynamics than simply whether a disease will invade or not. Because a highly pathogenic parasite with a moderate  $R_0$  will have a greater impact than will a non-pathogenic parasite with any  $R_0$ , it is clear that  $R_0$ , though convenient for our analytical analysis, may not always provide a sufficiently robust assay of stress impacts. Solving for the impact of disease on the host population revealed patterns that were similar to those for  $R_0$ , but as a whole more diverse. In particular, convex associations with stress were much more frequent for impact, than for  $R_0$ . We are unaware of any existing empirical data regarding infectious disease along gradients in stress that would be appropriate to analyse to assess the utility of our theoretical conclusions.

In the above SIR models, the combination of a continuous time formulation with direct, non time-lagged density-dependence generally leads to stable equilibria (e.g. >90% of runs in our general model quickly converged to a stable equilibrium). More broadly, one can imagine alternative scenarios. For instance, with appropriate time-lags and density-dependence, stress may destabilize a host equilibrium, leading to a counterintuitive increase in average host density. An increase in average host density, even if the host population is unstable, can lead to a long-term increase in average  $R_0$  for a parasite, facilitating the initial invasion of a disease and later magnifying the rate at which the host population subsequently declines. It can also generate temporary drops in host density below the host-threshold density so that the parasite population goes extinct in cases

where it would ordinarily persist at equilibrium in a stable host population. In our general simulation, instability favoured parasite extinction more than stability did, a phenomenon facilitated by setting  $K > H_i$  at  $w = 0$ .

Simple models without direct density-dependence indicate how disease itself can generate sustained population oscillations. For example, Anderson & May (1981, pp. 480–482) describe a model where healthy hosts become infected by absorbing or ingesting free-living infective stages. Infected hosts give rise to free-living infective stages at a constant rate. This free-living pool of infective stages, in effect, introduces a time-lag into the dynamics of infection and this can generate sustained, stable limit cycles. A stable point equilibrium can occur if parasite pathogenicity (extra mortality because of infection, such as might occur with stress) exceeds the host intrinsic growth rate, but not by very much. In this state, the disease will persist at a defined chronic level. But if pathogenicity is high, stable limit cycles occur, in which the disease will exhibit periodic outbreaks. As with the basic SIR model discussed above, stress can affect a variety of parameters in the model, with a corresponding diversity of potential impacts upon disease prevalence and dynamics. If stress increases the pathogenicity of the disease (with little effect upon other parameters), then the Anderson–May model suggests that, in stressful environments, the destabilizing effect of the free-living pool of infective stages can be made manifest, so that an increase in stress may be marked by the emergence of periodic outbreaks of an infectious disease.

Our randomized parameters generated some qualitative predictions for the effects of stress on disease in natural populations. For most of our simulations, increased stress eventually decreased disease, simply because reductions in host density made transmission less efficient. This contrasts with the effects of stress at the level of the individual, where stress usually has a negative effect on health. In some cases, low levels of stress will increase disease, but higher levels reduce disease, leading to a convex association between stress and the impact of a disease. Positive and, in particular, concave relationships between stress and disease were infrequent. However, some diseases, particularly sexually transmitted ones, normally have frequency-dependent transmission. Under these conditions, stress-induced reductions in host density are less likely to impair disease. Similarly, a reduction in host carrying capacity resulting from stress is of much less consequence if the infectious disease is not host specific. For these cases, as well as for open or non-infectious diseases, our models generally predicted a positive association between stress and disease because transmission efficiency does not decline as host populations become rare. This is clearly the situation that is of greatest concern

for conservation biologists. Many of the diseases of conservation concern are not host-specific, especially those for which domestic animals serve as reservoir hosts (Lafferty & Gerber 2002). Here, the target population of concern may continue to suffer disease even as it becomes vanishingly rare. This observation suggests that a full accounting of the synergistic roles of stress and disease as factors in species conservation requires careful attention to the community context of disease maintenance, transmission, and dynamics.

In many systems, one expects systematic spatial variation in the intensity of stresses. Along geographic gradients, stress may be most intense, for instance, near the edge of species' ranges. Low host productivity at range margins because of unfavourable conditions should indirectly reduce the impact of specialist parasites upon hosts, particularly if such effects are mediated primarily through the host's own demography, rather than through vulnerability to the parasite (Koella 2000; Hochberg & Holt 2002; Holt & Hochberg 2002). Our results amplify this conclusion so as to encompass the ecological impacts of stresses even in central populations.

As noted in the Introduction, there are many systems where stress seems to increase the vulnerability of healthy hosts to infection. We should note that, in principle, some responses to stress might also reduce transmission. For instance, if disease requires close contact between individuals, and stressed individuals move less (e.g. in systems where encounters with conspecifics carries risks because of aggressive interactions), then stress may indirectly reduce contact rates and so dampen disease transmission. If so, this would make it even more likely that stress could indirectly 'benefit' a host population via the depression of specialist infectious diseases.

In conclusion, available data suggest that stressed individuals are more likely to be infected by a host-specific disease on a per capita basis if exposed, whereas stressed populations may tend towards densities that are too low to be invaded by specialist diseases (provided transmission is density-dependent). An additional but realistic complexity is that stress may also increase mortality for parasites (because of negative effects on parasites or infected hosts), thus mitigating the impact of both the stress and the parasite. The results of the simple models presented here help resolve the opposing predictions stemming from these alternative effects. Stress is most likely to reduce the impact of closed, host-specific infectious diseases, and increase the impact of other types of disease. These complex responses to stress suggest that it may be difficult to extrapolate the population level effects of a stressor on disease solely from a study of the effects of that stressor on a particular host vital rate. Future studies might

consider these opposing effects as exciting hypotheses in need of testing.

## ACKNOWLEDGEMENTS

This work was conducted as part of the Diseases and Conservation Biology Working Group supported by the National Center for Ecological Analysis and Synthesis, the University of California, and the University of California, Santa Barbara. H. McCallum, R. Hechinger, M. Rigby, O. Bjornstadt, A. Dobson, K. Phillips and T. Huspeni made helpful comments. This manuscript has also benefited from support received from the National Science Foundation through the NIH/NSF Ecology of Infectious Disease Program (DEB-0224565), and from the University of Florida Foundation, and has also been supported by a grant from the US Environmental Protection Agency's Science to Achieve Results (STAR) Estuarine and Great Lakes (EaGLe) program through funding to the Pacific Estuarine Ecosystem Indicator Research (PEEIR) Consortium, US EPA Agreement #R-882867601. However, it has not been subjected to any EPA review and therefore does not necessarily reflect the views of the Agency, and no official endorsement should be inferred.

## REFERENCES

- Anderson, R.M. & May, R.M. (1986). The invasion, persistence and spread of infectious diseases within animal and plant communities. *Philos. Trans. R. Soc. Lond., Ser. B: Biol. Sci.*, 314, 533–570.
- Arneberg, P., Skorping, A., Grenfell, B. & Read, A. (1998). Host densities as determinants of abundance in parasite communities. *Proc. R. Soc. Lond. B*, 265, 1283–1289.
- Axelsson, B. & Norrgren, L. (1991). Parasite frequency and liver anomalies in 3-spined stickleback, *Gasterosteus aculeatus* (L), after long term exposure to pulp mill effluents in marine mesocosms. *Arch. Environ. Contam. Toxicol.*, 21, 505–513.
- Beck, M.A. & Levander, O.A. (2000). Host nutritional status and its effect on a viral pathogen. *J. Infect. Dis.*, 182, S93–S96.
- Black, G.A. (1983). Taxonomy of a swimbladder nematode, *Cystidicola stigmatura* (Leidy), and evidence of its decline in the Great Lakes. *Can. J. Fish. Aquat. Sci.*, 40, 643–647.
- Blanford, S., Thomas, M., Pugh, C. & Pell, J. (2003). Temperature checks the Red Queen? Resistance and virulence in a fluctuating environment. *Ecol. Lett.*, 6, 2–5.
- Brown, A.F. & Pascoe, D. (1989). Parasitism and host sensitivity to cadmium: an acanthocephalan infection of the freshwater amphipod *Gammarus pulex*. *J. Appl. Ecol.*, 26, 473–487.
- Dabrowska, H. (1974). An attempt to evaluate the state of health of fish from the Lyna and Walsza Rivers in connection to their pollution. *Przegląd Zoologii*, 18, 390–395.
- Daigo, K. (1959). Studies on the constituents of *Chondria armata*. II. Isolation of an anthelmintical constituent. *Yakugaku Zasshi (J. Pharm Soc Jpn)*, 79, 353–356.

- Des Clers, S. & Wootten, R. (1990). Modelling the population dynamics of the sealworm *Pseudoterranova decipiens*. *Neth. J. Sea Res.*, 25, 291–299.
- DeStewart, R.L., Ross, P.S., Voss, J.G. & Osterhaus, A.D.M.E. (1996). Impaired immunity in harbour seals (*Phoca vitulina*) fed environmentally contaminated herring. *Vet. Q.*, 18, S127–S128.
- Esch, G.W., Hazen, T.C., Dimock, R.V. & Gibbons, J.W. (1976). Thermal effluent and epizootiology of ciliate epistylis and bacterium aeromonas in association with centrarchid Fish. *Trans. Am. Microsc. Soc.*, 95, 687–693.
- Evans, N.A. (1982). Effects of copper and zinc on the life cycle of *Notocotylus attenuatus* (Digenea, Notocotylidae). *Int. J. Parasitol.*, 12, 363–369.
- Guth, D.J., Blankespoor, H.D. & Cairns, J. (1977). Potentiation of zinc stress caused by parasitic infection of snails. *Hydrobiologia*, 55, 225–229.
- Harvell, C.D., Kim, K., Burkholder, J.M., Colwell, R.R., Epstein, P.R., Grimes, D.J. *et al.* (1999). Review: Emerging marine diseases: climate links and anthropogenic factors. *Science*, 285, 1505–1510.
- Hochberg, M.E. & Holt, R.D. (2002). Biogeographical perspectives on arms races. In: *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management* (eds Dieckmann, U., Metz, J.A.J., Sabelis, M.W. & Sigmund, K.). Cambridge University Press, Cambridge, pp. 197–209.
- Holmes, J.C. (1996). Parasites as threats to biodiversity in shrinking ecosystems. *Biodivers. Conserv.*, 5, 975–983.
- Holt, R.D. & Hochberg, M.E. (2002). Virulence on the edge: a source-sink perspective. In: *Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management* (eds Dieckmann, U., Metz, J.A.J., Sabelis, M.W. & Sigmund, K.). Cambridge University Press, Cambridge, pp. 104–120.
- Johnson, L.L. (2001). An analysis in support of sediment quality thresholds for polycyclic aromatic hydrocarbons to protect estuarine fish. US Dept. Commer., NOAA, p. 30.
- Khan, R.A. (1990). Parasitism in marine fish after chronic exposure to petroleum hydrocarbons in the laboratory and to the Exxon Valdez oil spill. *Bull. Environ. Contam. Toxicol.*, 44, 759–763.
- Khan, R.A., Barker, D.E., Williamsryan, K. & Hooper, R.G. (1994). Influence of crude oil and pulp and paper mill effluent on mixed infections of *Trichodina cottidarium* and *T. saintjohnsi* (Ciliophora) parasitizing *Myoxocephalus octodecemspinosus* and *M. scorpius*. *Can. J. Zool. – Rev. Can. Zool.*, 72, 247–251.
- Koella, J.C. (2000). Coevolution of parasite life cycles and host life-histories. In: *Evolutionary Biology of Host-Parasite Relationships: Theory Meets Reality* (eds Poulin, R., Morand, S. & Skorping, A.). Elsevier, Amsterdam, pp. 185–200.
- Lafferty, K.D. (1997). Environmental parasitology: what can parasites tell us about human impacts on the environment? *Parasitol. Today*, 13, 251–255.
- Lafferty, K.D. & Gerber, L. (2002). Good medicine for conservation biology: the intersection of epidemiology and conservation theory. *Conserv. Biol.*, 16, 593–604.
- Lefebvre, K.A., Powell, C.L., Busman, M., Doucette, G.J., Moeller, P.D.R., Silver, J.B. *et al.* (1999). Detection of domoic acid in northern anchovies and California sea lions associated with an unusual mortality event. *Natural Toxins*, 7, 85–92.
- Lehtinen, K.J. (1989). Survival, growth and disease of 3-spined stickleback, *Gasterosteus aculeatus* L, brood exposed to bleached kraft mill effluents (bkme) in mesocosms. *Ann. Zool. Fennici*, 26, 133–143.
- Miller, M.A., Gardner, I.A., Kreuder, C., Paradies, D.M., Worcester, K.R., Jessup, D.A. *et al.* (2002). Coastal freshwater runoff is a risk factor for *Toxoplasma gondii* infection of southern sea otters (*Enhydra lutris nereis*). *Int. J. Parasitol.*, 32, 997–1006.
- Nilsen, F. (1995). Description of *Trichodina hippoglossi* N-Sp from farmed Atlantic halibut larvae *Hippoglossus hippoglossus*. *Dis. Aquat. Organ.*, 21, 209–214.
- O'Shea, T.J. & Brownell, R.L. (1998). California sea lion (*Zalophus californianus*) populations and sigma-DDT contamination. *Mar. Pollut. Bull.*, 36, 159–164.
- Overstreet, R.M. & Howse, H.D. (1977). Some parasites and diseases of estuarine fishes in polluted habitats of Mississippi. *Ann. New York Acad. Sci.*, 298, 427–462.
- Rigby, M.C. & Moret, Y. (2000) Life-history trade-offs with immune defenses. In: *Evolutionary Biology of Host-Parasite Relationships: Theory Meets Reality* (eds Poulin, R., Morand, S. & Skorping, A.). Elsevier Science, B.V. Amsterdam, pp. 129–142.
- Riggs, M.R., Lemly, A.D. & Esch, G.W. (1987). The growth, biomass, and fecundity of *Bothriocephalus acheilognathi* in a North Carolina cooling reservoir. *J. Parasitol.*, 73, 893–900.
- Scott, M.E. (1988). The impact of infection and disease on animal populations: implications for conservation biology. *Conserv. Biol.*, 2, 40–56.
- Siddall, R. & Clers, S.D. (1994). Effect of sewage sludge on the miracidium and cercaria of *Zoogonoides viviparus* (Trematoda: Digenea). *Helminthologia (Bratislava)*, 31, 143–153.
- Stadnichenko, A.P., Ivanenko, L.D., Gorchenko, I.S., Grabinskaya, O.V., Osadchuk, L.A. & Sergeichuk, S.A. (1995). The effect of different concentrations of nickel sulphate on the horn snail (Mollusca: Bulinidae) infected with the trematode *Cotylurus cornutus* (Strigeidae). *Parazitologiya (St Petersburg)*, 29, 112–116.
- Swart, R.L., Ross, P.S., Vedder, L.J., Timmerman, H.H., Heisterkamp, S., Loveren, H.V. *et al.* (1994). Impairment of immune function in harbor seals (*Phoca vitulina*) feeding on fish from polluted waters. *Ambio*, 23, 155–159.
- Van Loveren, H., Ross, P.S., Osterhaus, A. & Vos, J.G. (2000). Contaminant induced immunosuppression and mass mortalities among harbor seals. *Toxicol. Lett.*, 112, 319–324.
- Vladimirov, V.L. & Flerov, B.A. (1975). Susceptibility to ichthyophthiriasis in fish following exposure to phenol and polychloroprene poisoning. *Biologiya Vnutrennikh Vod Informatsionnyi Byulleten*, 25, 35–37.

Editor, P. Thrall

Manuscript received 12 February 2003

First decision made 18 March 2003

Manuscript accepted 29 April 2003