

CONCEPTS & SYNTHESIS

EMPHASIZING NEW IDEAS TO STIMULATE RESEARCH IN ECOLOGY

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HOW VIRULENT SHOULD A PARASITE BE TO ITS VECTOR?

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Abstract. Vector-borne parasites are commonly predicted to be less virulent to the vector than to the definitive host as the parasite gains little by harming its main route of transmission. Here we assess the empirical evidence from systems in which insects are vectors for vertebrate, plant, and invertebrate parasites. The body of evidence supports lower (but nonzero) parasite virulence to vectors than to plant or invertebrate hosts, but not to vertebrate hosts. We consider why this might be by assessing evolutionarily stable strategies for an insect parasite that can infect both predator and prey (or vector and definitive host) and can have distinct virulences in these two potential hosts. In a homogeneous environment, the parasite is predicted to be equally virulent to predator and prey. However, in a patchy environment it is predicted to become benign toward the more mobile of the two potential hosts, provided interpatch movement of free parasites is low and competitive displacement among strains in a patch is weak. This prediction meets reality in that the vector is usually more mobile between patches than is the definitive host in plant and invertebrate systems, but not necessarily in vertebrate hosts.

Key words: dispersal; evolution of virulence; free parasite; superinfection; vector-borne disease.

INTRODUCTION

Vector-borne parasites and pathogens are among the most damaging of disease-causing organisms, be they of medical, veterinary, or agricultural importance (Power 1992, Ewald 1994, Dieckmann et al. 2002). Management of these diseases has traditionally been from a population dynamical stance, principally directed at controlling populations of the vectors or enhancing the resistance of the hosts. The likely impact of such interventions upon the evolution of parasite virulence has recently received theoretical attention (Gandon et al. 2001) and is part of a growing field that seeks to manage the virulence of disease-causing organisms (Dieckmann et al. 2002). Despite this interest, the only general predictions that have been made for vector-borne diseases are (1) that they will be more virulent than non-vector-borne parasites and (2) that parasites will have a lower virulence to their vectors than to their main hosts (Ewald 1994). Whatever the

validity of these generalizations, they rest upon some critical assumptions and have yet to be updated in the light of a body of theoretical work on the evolution of virulence over the last decade or so (but see also Day [2001, 2002b]). Our aim in this review is to question some of these assumptions and provide a framework within which modern theory can be applied to given systems so as to generate testable hypotheses.

Critical to our approach is the recognition that many parasites reproduce in the vector as well as the main host and that this may harm not only the main host but also the vector. There will thus be selection upon the parasite's virulence toward the vector just as there is toward the host. Indeed, definitions of the "vector" and its converse, the "main" or "definitive" host, serve to ascribe functions to what are, in effect, two potential hosts on different trophic levels (i.e., where one feeds upon the other, perhaps as a "micropredator"). A parasite can therefore have two distinct virulences to these two hosts, and our contention is that these virulences are so intimately related that consideration of one requires consideration of both. These two virulences will be subject to natural selection due to a range of factors, for example, spatial heterogeneity of hosts, their mobility and life histories, or competi-

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tion between parasite strains. A further justification for our approach is that survival of the vector and its ability to transmit the parasite are key factors in the dynamics of vector-borne diseases, both liable to be influenced heavily by harmful effects of the parasite.

We consider three classes of vector-borne diseases, namely vertebrate, plant, and invertebrate diseases. Common to all is that it is an arthropod that serves as the vector. However, we modify the definition of vector and consider both potential hosts as potential vectors. For this, invertebrate diseases serve as a starting point as the two potential hosts will be broadly similar, particularly in their life histories.

We build our discussion on a general Evolutionarily Stable Strategy (ESS) model based on predator–prey interactions but with the inclusion of a parasite (see Appendices A and B). In this model we investigate the effects of spatial heterogeneity, host mobility, and superinfection (the ability of strains to replace one another in a patch) on parasite virulence to predator and prey (or classically, vector and main host). We then turn to the three classes of system and consider how the different biological features of these systems will influence selection on virulence, in the light of the model and current theory. We relate this to empirical results from the literature, both to identify what patterns are already apparent and to highlight hypotheses that seem to merit particular attention. Our intention is not to generate a set of specific hypotheses but rather to emphasize particular questions that need addressing empirically and theoretically.

PATCHINESS, MOBILITY, AND VIRULENCE

In his book *Evolution of Infectious Diseases*, Ewald (1994, p. 47) gave an explanation for the apparently lower virulence of parasites in vectors than in main hosts: “. . . vectorborne parasites should specialize on their vertebrate hosts as resource bases for amplifying their numbers and on their vector hosts as agents of dispersal.” This makes good intuitive sense. However, to subvert it somewhat, the parasite is just as reliant upon the main host for transmission to new vectors as the reverse. So, which potential host is more important to the parasite? At the heart of this and other predictions is that the vector represents mobility to the parasite. This therefore serves as the first biological feature to consider: how does the mobility of *either* host affect the ESS virulences of the parasite? This requires a consideration of the patchiness of the hosts so we include this in our ESS analysis. We use an insect–parasite system in which a herbivore represents the main host and a predator represents the vector; the parasite can infect either. As a justification, there is accumulating evidence that predators can serve as vectors between patches of prey (Lee and Fuxa 2000, Roy and Pell 2000, Castillejos et al. 2001). We assume no cost to dispersal, only horizontal transmission, and allow competition in the form of superinfection but not coinfection. Dis-

persal is by movement of infected hosts (predator or prey) and also by free parasite propagules, the latter to preserve generality of the model and allow comparisons between systems. We investigate ESS virulences to the two potential hosts, this virulence being defined as the parasite-induced instantaneous mortality rate (see Day [2002a] for a discussion of how different measures of virulence may affect predictions or interpretation). The model is presented in Appendices A and B.

We find that in an unstructured population of potential hosts, the ESS virulence to predator and prey is equal (Appendix A). In this case, the parasite relies as much on the host for transmission to the vector as the converse. Once we introduce spatial heterogeneity in the form of multiple patches, each containing predator and prey, we find that optimal virulence is lowest in the vector, *whether this is predator or prey*. This is to be expected as the vector must live long enough to leave the patch and reach a new one. However, this intuitively reasonable result is sensitive to two conditions: (1) there is limited movement of free parasite between patches (Fig. 1a) and (2) patches are occupied by no more than a single strain of parasite (Fig. 1b). If we allow free parasite movement, the ESS virulences to predator and prey rapidly converge, as the value of vectors is lessened. If we increase the rate at which co-occurring parasite strains can outcompete one another, virulences also converge, but to a limited degree when only predators disperse pathogen between patches. This is because the parasite must exploit the patch before losing it to the competitor. The important information contained in these two parameters is that differential virulence is only expected when the parasite depends on live hosts for movement between patches (vs. free parasite) or has some degree of exclusivity in its exploitation of the patch (vs. superinfection). So only in a patchy environment, with little competition between parasite genotypes and a dependence on live hosts for transmission between patches, will we expect a lower virulence to the more mobile host. Why, then, are vectors generally considered to be little affected by the parasites they bear? Are the conditions set out in this ESS analysis common features of biological systems, or must we look for other differences between the potential hosts to explain differences in virulence? Is there actually any empirical evidence of lower parasite virulence in vectors, or is there a bias in the diseases that are studied or in how they are studied? To address these questions, we now consider the three classes of vector-borne disease.

INVERTEBRATE DISEASES

The first vector-borne disease system we consider is of predatory insects vectoring parasites between their herbivore prey, as in the ESS model (Appendix A). The emphasis in these systems has been their potential for biological control of herbivores. As such, consider-

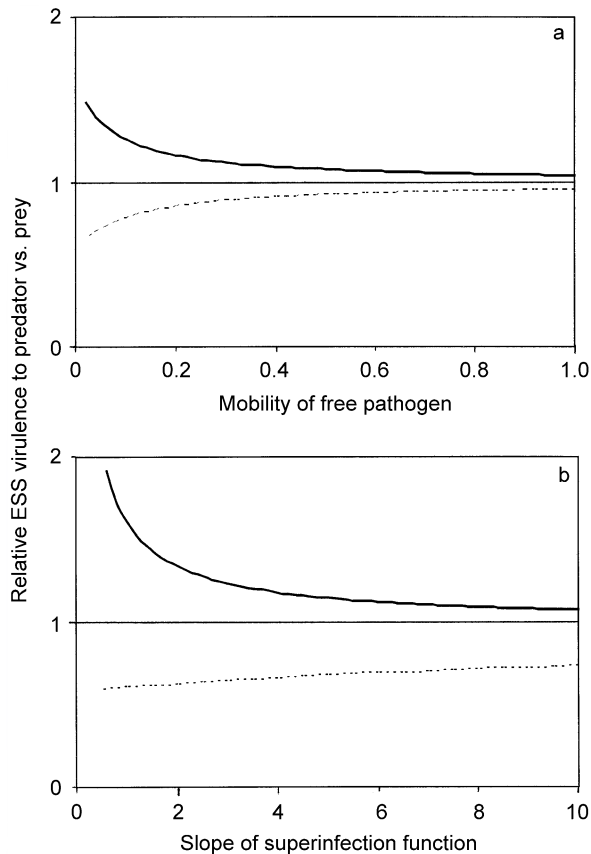


FIG. 1. Model predictions of relative Evolutionarily Stable Strategy (ESS) virulence of a parasite to predators vs. prey in relation to (a) mobility of free pathogen and (b) slope of the superinfection function. (Bold lines, prey only move between patches; dashed lines, predators only move between patches.) The model is summarized in Appendix A and is presented in full in Appendix B.

ations of parasite virulence toward predators has emphasized possible unwanted effects of biocontrol programs (e.g., Poprawski et al. 1998, Chilcutt and Tabashnik 1999, Sajap et al. 1999). However, there is mounting evidence that predators and parasitoids can serve as vectors of herbivore parasites (Vasconcelos et al. 1996, Sajap et al. 1999, Lee and Fuxa 2000, Roy and Pell 2000, Castillejos et al. 2001). Given the broadly similar life histories of these two potential hosts, the ESS prediction is of lower virulence in the more mobile of the two hosts. For this system, we would expect the predator generally to be the more mobile, as many predators move from prey to prey, or prey patch to prey patch, whereas the herbivore prey will generally spend their lifetime in a single location. There has so far been no objective empirical test for differences in virulence of parasites to predators and prey. However, if parasites are indeed less virulent to the more mobile predators, we might expect fewer parasites to have been recorded from predators than from prey. To see if this is the case, we examined a database of isolates of insect-parasitic

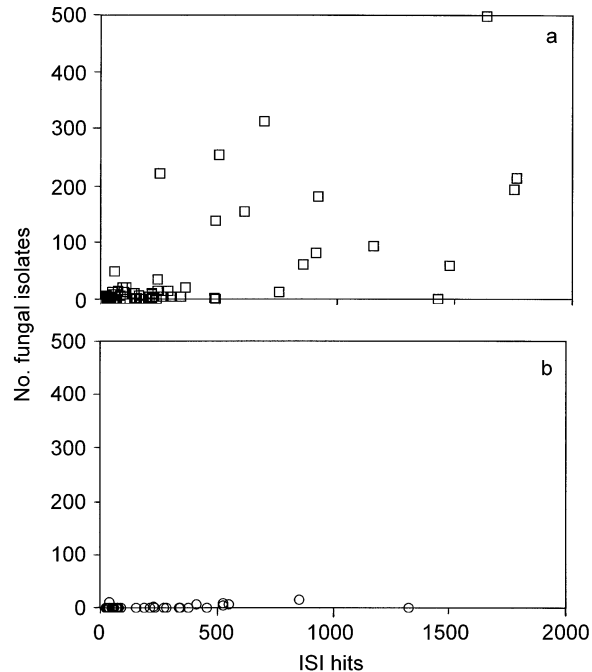


FIG. 2. We expect that there are more parasites in predators (including parasitoids) than in herbivores. We took a list of all nonsynonymical insect families ($N = 980$) from a database of the Smithsonian National Museum of National History.⁵ To estimate "scientific interest" in each family, we conducted a search for each of these in the titles and abstracts of papers in the Institute for Scientific Information (ISI) Web of Science database from 1988 to 3 November 2000.⁶ Families that gave <10 (an arbitrary value) "hits" were subsequently ignored. An estimate was made of the degree to which these families are subject to attack by parasites. This first employed the catalogue of arthropod-parasitic fungi held in the USDA-ARS Collection of Entomopathogenic Fungal Cultures (ARSEF) at Cornell University, Ithaca, New York, USA (compiled 15 October 1998).⁷ We counted from this the total number of isolates held for each host family: (a) pathogens of herbivores; (b) pathogens of predators.

fungi held at the USDA-ARS Collection of Entomopathogenic Fungal Cultures (ARSEF) at Cornell University, Ithaca, New York, USA. For each insect family that is largely herbivorous or predatory on herbivores, we plotted the number of fungal isolates or genera against the number of citations in the literature to correct partially for scientific interest (Fig. 2). There are of course biases in the data (biocontrol workers will examine more herbivores than predators), but the correction accounts to some degree for this. As detection of these fungi would generally result from their killing the host once removed from the field, this relates to instantaneous mortality rates induced by the parasite, the form of virulence used in our model, and to some

⁵ URL: <http://entomology.si.edu/Entomology/FamList/search.lasso>

⁶ URL: <http://wos.mimas.ac.uk/>

⁷ URL: http://www.ppru.cornell.edu/mycology/ARSEF_Culture_Collection.htm

degree ameliorates the potential that highly virulent infections go unnoticed as they remove hosts from the population sampled. Bearing these considerations in mind, the result is consistent with a pattern of higher virulence towards herbivores than to their natural enemies.

PLANT DISEASES

Given the lower mobility of plants than insects, a low virulence of plant parasites toward their vectors might be expected. However, many vector-borne plant parasites do invade and migrate within the vector, often multiplying as well (Nault 1997, Fletcher et al. 1998), which will come at a cost to the vector. This is exemplified by the elicitation of an immune response in *Drosophila* vectors by the bacterial plant pathogen *Erwinia* (Basset et al. 2000) and by cytopathological effects of mollicutes to a range of insect vectors (Fletcher et al. 1998). There is a dearth of studies of the direct effects of plant parasites on their vectors (Purcell 1982, Power 1992, Lee et al. 2000): the usual approach has been to rear insects on infected plants, so indirect effects via host plant quality are not excluded. However, whether direct effects are examined explicitly (Wijkamp et al. 1996) or not, fitness effects on vectors can be positive or negative and are predominantly expressed as relatively minor effects on survival times or fecundity (Granados and Meehan 1975, Madden and Nault 1983, Wijkamp et al. 1996, De Almeida et al. 1997, Beanland et al. 2000, Ebbert and Nault 2001). While these measures of virulence complicate comparisons between insect and plant hosts (Day 2002a), they are in contrast with a range of virulences found in plant hosts, from relative benignity to lethality (Power 1992, Lee et al. 2000). The pattern appears then to be one of lower virulence toward insect vectors than toward plants, but direct comparisons, with the same measures of virulence, are absent. The suggestion that parasite and vector even have a mutualistic interaction has been raised (e.g., Power 1992, Ebbert and Nault 2001), and this viewpoint may be behind the lack of explicit tests of virulence to vectors. It may also be a real pattern.

Plant systems most closely fit our model prediction of lower virulence to the more mobile of the two potential hosts (Fig. 1). It is only seed- or pollen-borne viruses that can be transmitted to a new patch by a dispersing plant host; these viruses appear to be the least virulent to the plant (Power 1992). While this has been explained as the vertical transmission route leading to selection for low virulence (Power 1992), the greater value of the plant as a means of dispersal for the parasite may also provide an explanation (Fig. 1). One of the conditions for differential virulence, i.e., low dispersal as free propagules, is supported in plant viruses and mollicutes that are effectively not transmitted as free propagules. A further factor likely to be crucial to plant parasites is that they may well depend

upon insect vectors multiplying on the plant to provide future means of dispersal to new patches, in contrast with vectors of vertebrate parasites, so this may also contribute to a low relative virulence to the insect vectors. It has been proposed that many plant viruses originated as insect pathogens and subsequently adapted to plant pathogenicity (Nault 1997). We may even see a midpoint in such a shift in a range of mollicutes found on plant surfaces but pathogenic to insect vectors (Whitcomb 1981, Clark 1982, Fletcher et al. 1998). Indeed, this last group of parasites may prove of great value in assessing the balance of virulence between the two potential hosts.

VERTEBRATE DISEASES

Parasite effects on vectors have been most studied with vertebrate diseases. As with many plant parasites, we would expect an effect on the vector as the parasite must pass through host tissues and use host resources for multiplication (Randolph 1998, Welburn and Maudlin 1999, Ghosh et al. 2000, Kollien and Schaub 2000), both of which are liable to cause some harm to the vector (Mims et al. 1966, Lam and Marshall 1968, Maier et al. 1987, Beier 1998, Zieler and Dvorak 2000, Ferguson and Read 2002). Such effects could partly explain the development of resistance (“refractoriness” or “incompetence”) in vectors (Yan et al. 1997, Welburn and Maudlin 1999). Arboviruses can negatively affect the development time, survivorship, or lifespan of their mosquito vectors (Turell et al. 1985, Faran et al. 1987). While the evidence from malarial parasites in mosquitoes has been ambiguous (Chege and Beier 1990) and the experiments conducted have been criticized for use of unrealistically high infection rates and a lack of field corroboration (Chege and Beier 1990, Taylor and Read 1997), the overall pattern is of malarial parasites reducing mosquito survival (Ferguson and Read 2002). Even though a bias towards diseases of particular virulence to vertebrates may be expected, case-fatality rates in vertebrates can be as low as 1% (e.g., Snow et al. 1999). No concerted effort has been made to compare virulences in a vector and a vertebrate host, experiments are clearly complicated by practical and ethical issues, and we could find little such work with vertebrates other than humans. However, some degree of virulence has been shown in vectors, sometimes in subtle forms such as reductions in fecundity, as with mosquitoes and blackfly (Turell et al. 1985, Hurd et al. 1995). These effects can be seen as an adaptation of the parasite as fecundity effects would not hamper parasite transmission (unlike plant parasites whose vectors multiply on the plant host before dispersing and vectoring parasites). We must therefore question whether predictions of lower virulence to vectors of vertebrate diseases have any empirical basis and explore why this may not be the case.

RECIPES FOR CHALLENGING PREDICTIONS

We have quite blatantly sought conditions in which predictions of lower virulence toward vectors than “main” hosts will hold, but the ESS model predicts it to be highly subject to specific conditions of spatial heterogeneity, differential mobility of the two hosts, limited dispersal as free propagules, and weak competition between parasite genotypes. While empirical evidence of such a difference is limited, there does appear to be some from plant and invertebrate systems, but not vertebrate systems. We have proposed that this can be explained in the first two by differential mobility of the potential hosts. For vertebrate systems, however, a critical question emerges: what are patches and how mobile are the hosts between them? If patches are human habitations then we may expect greater vector mobility between these than human mobility. However, if patches are human villages or towns, then human mobility between these will almost certainly be greater than vector mobility. We can therefore expect selection on virulence to act in opposing directions at the two spatial scales.

An additional concern arises in the light of recent work demonstrating potentially contrasting predictions if one considers parasite-induced instantaneous mortality rate (as in our model) vs., for example, case mortality or other measures such as mass loss (Day 2002a). This is a particular problem if the interaction times of the parasite are different in the different hosts, especially where this could lead to increased host recovery due to defenses. As Day states, we must interpret comparisons between theoretical and empirical results with a degree of caution, until a consensus is reached between the two bodies of work on which measures of virulence are being described.

However, our exploration of spatial heterogeneity and host mobility as selective forces on parasite virulence are intended principally as illustrative of what may be key issues. How important these are in the evolution of parasite virulence requires more critical tests and alternative explanations. More critical tests may be obtained by focusing on parasite virulence to the vector; our model predicts non-zero virulence and the extent to which this differs from virulence to the main host, and we have argued that these two virulences are intimately related. Host specialization and trade-offs are likely to reinforce differences in virulence, while virulences may be manifested subtly, in that the parasite may affect vector reproduction rather than life span, for example. Parasite virulence may reduce the mobility of one of the hosts, generating positive feedback as this in turn selects for higher virulence towards this host.

Parasite control over hosts or host patches in the face of competition is likely to be critical. We have dealt with superinfection as this is mathematically more tractable than multiple infection, but both represent the

degree to which a parasite controls the host in the face of competition. There have been efforts to assess multiple infection of individuals or patches in the field (Lam and Marshall 1968, Power 1996, Raybould et al. 1999, Armstrong and Rico-Hesse 2001). For invertebrate diseases, it may be too early to apply our predictions to individual systems given the lack of empirical data on parasite competition. However, one recent study has shown competitive displacement of fungal pathogen strains in locusts (Thomas et al. 2003), and it would be valuable to determine the degree to which this occurs in invertebrate pathogens that fit the model of vector-borne disease. Competitive displacement has also been found in plants, as well as multiple infections of plant and insect hosts or patches (Power 1996, 2000, Raybould et al. 1999, Lee et al. 2000). However, with only the insects dispersing parasites, parasite competitiveness is the least sensitive of the parameters in the model (Fig. 1), for which we do not have an explanation.

Competitive displacement of a strain of dengue virus has been observed in the field (Armstrong and Rico-Hesse 2001), while the sequential replacement of malarial parasite strains in humans has been shown, fitting very closely competitive displacement as in superinfection (Bruce et al. 2000). We urge further work along these lines, especially where it compares vector with “main” host (Power 1996). The expectation would be of greater parasite virulence in the host with the greater degree of multiple or superinfection.

General theory on the evolution of virulence gives us a range of other ecological factors that are liable to select for higher or lower virulence in the two hosts (Ewald 1994, Dieckmann et al. 2002). Principal among these are host life spans and background mortality. Predictions specific to vector-borne diseases have been made and have some empirical support: (1) a diseased vector may be less able to locate a new host and effect transmission, while a diseased host may be more vulnerable to attack by the vector (Ewald 1994); (2) multiple infections, widely held to select for high virulence, may be less likely in the vector than in the definitive host (Power 1996, Lee et al. 2000), and (3) vertical transmission, held to select for low virulence, may be more likely between vectors than between definitive hosts (Ewald 1994). The value of these predictions will depend upon the biologies of specific systems so cannot explain broad patterns, but may well hold for many systems. Thus, while vertical transmission may occur in vectors of vertebrate diseases (Burgdorfer and Brinton 1975, Fine 1975, Aitken et al. 1979, Miller et al. 2000), it is not the rule and is actually more common in plants than in their vectors (Power 1992, Nault 1997).

Testing these multiple factors promises to be both challenging and rewarding. Broader predictions, such as the importance of patchiness, mobility, and free parasite are probably best explored in systems in which

host life histories are similar (i.e., insect pathogens). Where parasites may not be so mild to the vector (as in vertebrate diseases), testing the various predictions may yield more avenues for disease management. For example, reducing vector mobility may increase virulence to the vector in addition to direct protection of the main host, while it may also decrease multiple infection in both vector and main host.

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APPENDIX A

A GENERAL EVOLUTIONARILY STABLE STRATEGY (ESS) ANALYSIS FOR VIRULENCE OF VECTOR-BORNE PARASITES

The model, presented in full in Appendix B, is based upon an insect predator–prey system in which a parasite can exploit either host. Thus, the predator represents the classical “vector” and the prey the “definitive host” and their trophic status is the only biological difference (i.e., transmission may occur through predation). The parasite may exploit either host for reproduction and dispersal and may have separate virulences in each. There is also a free parasite stage that is transmitted by excretion and ingestion, so infectiousness of either host is proportional to the shedding of free parasite. We assume that the parasite does not regulate the population of uninfected predators and predator and prey are at equilibrium, so optimal parasite virulence is found by invasion analysis where the uninvadable strain is that which minimizes the equilibrium population of susceptible prey.

In a single patch (i.e., homogeneous) environment, the ESS virulence in predator and prey is equal, which holds when

there is no free parasite, as in a classical vector system.

In a multi-patch (i.e., heterogeneous) environment, we make a simplifying assumption that within-patch transmission is via free parasite alone, but the results hold for transmission via unsuccessful predation alone (as with a classical vector system). All patches are occupied by both potential hosts, with equal probabilities of patch extinction, and the infection rapidly reaches equilibrium once in a patch. To define the equilibrium, we assume for susceptible prey: logistical growth in the absence of predators and parasites, death from abiotic causes, death from predation by uninfected predators (which appears not to affect the predictions), and infection by contact with free pathogen. This leads to a classic meta-population model in which we assume that a patch harbors only one parasite at a time (i.e., superinfection, Mosquera and Adler [1998]). The effects of free parasite and superinfection on parasite virulence are presented in Fig. 1.

APPENDIX B

A full presentation of a general Evolutionarily Stable Strategy (ESS) analysis for virulence of vector-borne parasites is available in ESA's Electronic Data Archive: *Ecological Archives* E084-065-A1.