AN ABSTRACT OF THE DISSERTATION OF

Sean M. Moore for the degree of Doctor of Philosophy in Zoology presented on June 8, 2010.

Title:
The Effects of Community Composition, Landscape Structure, and Climate on Host-Pathogen Interactions

Abstract approved: _____
Elizabeth T. Borer

Like other species interactions in ecological systems, host-pathogen interactions are influenced by environmental factors, landscape characteristics and the broader community context. My thesis explores the potential influences of food-web interactions (Chapter 2), climate change (Chapter 3), landscape structure and host movement patterns (Chapter 4), and the combined influences of local community context and regional processes (Chapter 5) on host-pathogen interactions.

Infectious diseases transmitted by vectors depend on the interactions between the vector and other species within the community. In Chapter 2 I develop a theoretical model integrating predator-prey and host-pathogen theory to examine the effect of predator-vector interactions on vector-transmitted diseases. Predation on a vector may drastically slow a pathogen's spread, and increase host abundance by reducing—or eliminating—infection in the host population. The introduction of a predator can lead to a negative relationship between preva-

lence and vector fecundity, with the pathogen being driven out of the system at high rates of predation or fecundity. Chapter 3 examines how temperature influences the biology of a parasite, *Trypanosoma brucei rhodesiense,* and its tsetse fly vector in order to examine the potential effects of global warming on sleeping sickness. Model results indicate that projected warming over the next 50–100 years is likely to significantly shift the distribution of sleeping sickness in Africa. The modeling approach presented in Chapter 3 provides a framework for using the climate-sensitive aspects of vector and pathogen biology to predict changes in disease prevalence and risk due to climate change.

The spread and persistence of generalist pathogens that infect multiple host species are influenced by spatial heterogeneity in host composition and the movement patterns of different host species. Chapter 4 uses a metapopulation disease model to identify the potential effects of landscape connectivity, patch heterogeneity, and host community composition on the spread, prevalence, and persistence of multi-host pathogens at the local and regional scales. In an observational study of barley and cereal yellow dwarf viruses (B/CYDV) in a set of Cascades meadows, I found that patterns of disease prevalence are primarily driven by the diversity and composition of the local host community (Chapter 5).

The Effects of Community Composition, Landscape Structure, and Climate on Host-Pathogen Interactions

by
Sean M. Moore

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APPROVED:

Major Professor, representing Zoology

Chair of the Department of Zoology

Dean of the Graduate School

I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Sean M. Moore, Author

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DEDICATION

In memory of my mother, Rhoda Moore.

The Effects of Community Composition, Landscape Structure, and Climate on Host-Pathogen Interaction

Chapter 1 – General introduction

Our understanding of disease ecology has evolved rapidly since Anderson and May (1979); May and Anderson (1979) began to synthesize the fields of parasitology, epidemiology, and population biology. Pathogens and parasites have been recognized as an important component of many ecological communities. Pathogens can regulate host populations (Tompkins et al., 2002*a*) and influence community structure (Hudson and Greenman, 1998; Collinge and Ray, 2006; Hatcher et al., 2006). The local abundance and diversity of parasites can exceed that of predators (Kuris et al., 2008), which has important implications for trophic interactions and other food web properties (Hudson et al., 2006; Lafferty et al., 2006, 2008). In recent years there has been an increasing appreciation of the importance of studying diseases within the context of the larger ecological community (Collinge and Ray, 2006; Keesing et al., 2006; Hudson et al., 2002; Grenfell et al., 1995; Ostfeld and Holt, 2004). Although there has been an increased emphasis on studying host-pathogen dynamics within a community context, research has largely focused on a limited set of interactions. My thesis explores the potential influences of food-web interactions (Chapter 2), climate change (Chapter 3), landscape structure and host movement patterns (Chapter 4), and the combined influences of local community context and regional processes (Chapter 5) on host-pathogen interactions.

Host-pathogen interactions are influenced by environmental factors, landscape composition and structure, and the broader community context (Guernier et al., 2004; Keesing et al., 2006; Ostfeld et al., 2006*b*; Plantegenest et al., 2007). In particular, diseases that are transmitted by a vector are dependent on the population dynamics of the vector species, as well as the interactions of the vector and host populations with other species within the community(Ostfeld and Keesing, 2000; Keesing et al., 2006; Zavaleta and Rossignol, 2004). Previous theoretical studies have explored the effect of predation on host-pathogen dynamics when a predator and pathogen compete for the host as a resource (Packer et al., 2003; Hall et al., 2005; Holt and Roy, 2007), or when predators influence the abundance of disease reservoirs (Ostfeld and Holt, 2004). Because vector-borne pathogens are dependent on a vector species for disease transmission, pathogen prevalence and persistence may also be affected by predator-vector interactions.

Although recent theoretical work has incorporated vector interactions with pathogen and host species, current models of disease dynamics have not yet considered the potential role of predators in regulating the vector and pathogen populations. In Chapter 2 I develop a mathematical model that integrates predator-prey and host-pathogen theory to examine the indirect effect of predators on pathogen dynamics. The model predicts that predation on a vector may drastically slow the initial spread of a pathogen and decrease the proportion of hosts infected at equilibrium. These results highlight the importance of studying interactions that—within the greater community—may alter our predictions of the outcome of host-pathogen interactions. It also suggests that the introduction of

biological control agents to control vector populations can reduce prevalence or eradicate a pathogen, particularly in productive environments where the vector population experiences a high turnover rate.

Climate warming over the next century is expected to have a large impact on the interactions between pathogens and their animal and human hosts (Harvell et al., 2002; Pascual and Bouma, 2009). Vector-borne diseases are particularly sensitive to warming because temperature changes can alter pathogen and vector development rates and generation times, shift the geographical distribution of vector or reservoir host populations, and alter transmission dynamics (Patz et al., 2000; Gubler et al., 2001). Because climate conditions affect multiple parameters involved in the epidemiology of a particular disease, often in different directions and with different intensities, predicting the impact of climate change on disease transmission and risk requires a framework that specifically incorporates the role of each climate-sensitive parameter. In Chapter 3 I use a modeling framework proposed by Rogers and Randolph (2006) to examine the likely effects of an increase in mean annual temperatures on the epidemiology and risk of trypanosomiasis (sleeping sickness) in Eastern and Southern Africa. The relationships between temperature and several key epidemiological parameters, including the parasite development rate and the vector biting and mortality rates, are used to calculate the sensitivity of the parasite's basic reproductive number, R_0, to temperature. The predicted suitable temperature range for sustained trypanosomiasis transmission is then used to forecast changes to the parasite's geographic range under several climate change scenarios. Model results indicate that projected warming

over the next 50-100 years is likely to significantly shift the distribution of sleeping sickness in Africa. The modeling approach presented in Chapter 3 also provides a framework for using the climate-sensitive aspects of vector and pathogen biology to predict changes in disease prevalence and risk due to climate change.

Disease ecology studies have largely been limited to exploring host-pathogen interactions within a local community, ignoring regional and landscape level processes and patterns. Epidemiological studies that have incorporated spatial dynamics or landscape heterogeneity have largely been restricted to single host-pathogen metapopulation dynamics or the analysis of non-dynamic spatial distributions of disease incidence or risk (Hess et al., 2002; Keeling et al., 2004; Ostfeld et al., 2005). Heterogeneity in community composition and movement patterns of different host species among landscape fragments will influence the spread and persistence of generalist pathogens that infect multiple host species (Smith et al., 2002; Collinge et al., 2005; Real and Biek, 2007). In Chapter 4, I develop a multi-host, multi-patch metapopulation disease model to identify the potential effects of landscape connectivity, patch heterogeneity, and host community composition on the initial spread, prevalence, and persistence of multi-host pathogens at the patch and regional scales. In addition, I also examine how the correlation of host traits associated with resistance to fragmentation, host quality and dispersal ability may affect the invasion and spread of multi-host pathogens in fragmented landscapes. I also review empirical studies of multi-host pathogens and use the model to illustrate the ways that spatial heterogeneity may influence disease dynamics in natural and disturbed communities.

The spread of infectious disease epidemics, as well as spatial patterns of disease incidence, are influenced by the spatial structure of host populations (Hess et al., 2002). Spatial dynamics are particularly important for plant pathogens because natural plant communities exist in spatially heterogeneous landscapes, and host species are often distributed in patches that will influence how pathogens spread and persist (Plantegenest et al., 2007). In Chapter 5 I investigate the role of local community interactions and the effects of landscape structure and regional processes on the dynamics of plant pathogens in the open meadows of the Cascade Mountains of Oregon. Barley and cereal yellow dwarf viruses (B/CYDV) are a group of generalist, aphid-vectored plant viruses that infect over 100 grass species in both agricultural and natural systems (D'Arcy and Burnett, 1995). Host susceptibility to B/CYDV varies, with some species suffering increased mortality and reduced fecundity when infected and other species experiencing little change in their overall fitness (Irwin and Thresh, 1990; Power and Mitchell, 2004; Malmstrom et al., 2005). Studies have also shown that the presence of highly competent reservoir species can increase the prevalence of B/CYDV in local host communities (Power and Mitchell, 2004). Host-aphid interactions also vary by host, with aphids showing preference for and experiencing higher fitness on certain host species (Borer et al., 2009). While the effect of these host community differences have been investigated at the local level their importance for regional patterns of B/CYDV spread and persistence have not been fully explored. Both local, within-field movements and long-distance dispersal by aphids are important for B/CYDV transmission (Irwin et al., 1988; McElhany et al.,

1995), and host-vector interactions at multiple spatial scales may influence local and regional disease dynamics. This complexity of B/CYDV epidemiology makes it an ideal study system for the exploration of spatial community dynamics and disease ecology.

Spatial patterns of pathogen prevalence are determined by ecological processes acting across multiple spatial scales. I used variance components analysis and model selection techniques to partition the sources of variation in B/CYDV prevalence and determine which abiotic and biotic factors influence host-pathogen interactions in a Cascades meadow system. B/CYDV prevalence in Cascades meadows varied by host species identity, with a significantly higher proportion of infected *Festuca idahoensis* individuals than *Elymus glaucus* or *Bromus carinatus*. While there was significant variation in prevalence between host species and between meadows in the same meadow complex, there was no evidence of any significant variation in prevalence between different meadow complexes. Variation in prevalence between meadows was primarily associated with the local community context—host identity, the relative abundance of different host species, and host species richness—and the physical landscape attributes of the meadow.

Predators indirectly control vector-borne disease: linking predator-prey and host-pathogen models

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Chapter 2 – Predators indirectly control vector-borne disease: linking predator-prey and host-pathogen models

Abstract

Pathogens transmitted by arthropod vectors are common in human populations, agricultural systems, and natural communities. Transmission of these vector-borne pathogens depends on the population dynamics of the vector species as well as its interactions with other species within the community. In particular, predation may be sufficient to control pathogen prevalence indirectly via the vector. To examine the indirect effect of predators on vectored-pathogen dynamics, we developed a theoretical model that integrates predator-prey and host-pathogen theory. We used this model to determine whether predation can prevent pathogen persistence or alter the stability of host-pathogen dynamics. We found that, in the absence of predation, pathogen prevalence in the host increases with vector fecundity, whereas predation on the vector causes pathogen prevalence to decline, or even go extinct, with increasing vector fecundity. We also found that predation on a vector may drastically slow the initial spread of a pathogen. The predator can increase host abundance indirectly by reducing or eliminating infection in the host population. These results highlight the importance of studying interactions that, within the greater community, may alter

our predictions when studying disease dynamics. From an applied perspective, these results also suggest situations where an introduced predator or the natural enemies of a vector may slow the rate of spread of an emerging vector-borne pathogen.

2.1 Introduction

Pathogens are a critical component of many ecological communities, often regulating host populations and influencing community structure. In recent years there has been an increasing appreciation of the importance of studying diseases within the context of the larger ecological community (Grenfell et al., 1995; Hudson et al., 2002; Ostfeld and Holt, 2004; Keesing et al., 2006; Collinge and Ray, 2006). In particular, diseases that are transmitted by a vector are dependent on the population dynamics of the vector species as well as the interactions of the vector and host populations with other species within the community (Ostfeld and Keesing, 2000; Keesing et al., 2006; Zavaleta and Rossignol, 2004). Diseases transmitted by arthropod vectors are common in wildlife, agricultural and human communities (Anderson and May, 1991). Zoonotic diseases such as Lyme disease and West Nile Virus are transmitted to humans and animals by arthropod vectors, and many emerging or resurgent infectious diseases are vector-transmitted (Gubler, 1998; Gratz, 1999; Daszak et al., 2000; Dobson and Foufopoulos, 2000; Taylor et al., 2001).

Although there has been an increased emphasis on studying host-pathogen dynamics within a community context, research has largely focused on a limited set of interactions. Community epidemiology studies have tended to focus on interactions between hosts sharing a common pathogen (Holt and Pickering, 1985; Begon et al., 1992; Woolhouse et al., 2001; Holt et al., 2003), or between pathogens that infect the same hosts (Holmes and Price, 1986; Esch et al., 1990; Kuris and Lafferty, 1994). Previous theoretical studies have explored the effect of predation on host-pathogen dynamics when a predator and pathogen compete for the host as a resource (Hochberg et al., 1990; Packer et al., 2003; Ostfeld and Holt, 2004; Hall et al., 2005; Holt and Roy, 2007). Predation intensity on host populations can alter host-pathogen dynamics (Hudson et al., 1992; Packer et al., 2003; Dwyer et al., 2004), and even affect pathogen persistence in the host population (Grenfell et al., 1995; Hall et al., 2005; Duffy et al., 2005). In general, predation often has major impacts on community structure via direct suppression of prey populations and indirect effects such as trophic cascades (Hairston et al., 1960; Paine, 1966; Price et al., 1980; Sih et al., 1985; Schmitz et al., 2000). Because vector-borne pathogens are dependent on a vector species for transmission, pathogen persistence may be affected by predator-vector dynamics in addition to predator-host interactions. For example, a variety of predators consume the larvae of different disease-transmitting mosquito species (see Kumar and Hwang 2006; Floore 2007 for recent reviews), and these predators are capable of regulating mosquito populations (Chase and Knight, 2003; Stav et al., 2005; Juliano, 2007, 2009; Seng et al., 2008). To date, however, there has not been a theoretical

exploration of the impact of predator-vector interactions on the transmission or persistence of vector-borne pathogens.

The potential for predation to prevent pathogen invasion or reduce disease prevalence in a host population also has implications for the biological control of vector populations. Predators have been introduced, or proposed, as biological control agents of vectors for various diseases such as malaria, dengue fever, and Lyme disease (Jenkins, 1964; Legner, 1995; Stauffer et al., 1997; Samish and Rehacek, 1999; Scholte et al., 2005; Kumar and Hwang, 2006; Ostfeld et al., 2006*a*; Walker and Lynch, 2007). Several recent studies suggest that predator introductions led to a decline in local cases of dengue fever in Vietnam and Thailand (Kay and Nam, 2005; Kittayapong et al., 2008), and malaria in India (Ghosh et al., 2005; Ghosh and Dash, 2007). However, many control efforts have been unsuccessful or have had unintended consequences, such as the displacement of native fish species by mosquito fish (*Gambusia affinis*) introduced to control malaria (WHO, 1982; Pyke, 2008). The goal of biological control is not necessarily to eliminate the vector (Murdoch et al., 1985), but to reduce pathogen prevalence and the risk of disease outbreaks in the host population. Natural enemies and introduced predators could accomplish this goal by directly reducing the density of the vector population, or by lowering the infectious proportion of the vector population. The identification of a target vector population threshold density, below which the pathogen cannot persist, is an important step in determining whether predation could sufficiently lower the vector population density. Biological control efforts are often used in concert with other vector control efforts

(WHO, 2004) such as insecticide spraying; therefore it is also important to investigate how predator-vector dynamics may influence or be influenced by additional vector mortality factors.

Although recent theoretical work has incorporated vector interactions with pathogen and host species, current models of disease dynamics have not yet considered the potential role of predators in regulating vector and pathogen populations. Here we developed a mathematical model that integrates predator-prey and host-pathogen theory to examine the indirect effect of predators, via a vector, on pathogen dynamics. Using the model we examined how predation on a vector population may affect disease prevalence as measured by the proportion of infected individuals in a host population. In particular, we investigated the relationship between predation strength and pathogen prevalence. We also determined whether predation can prevent pathogen persistence and examine different scenarios to determine under what conditions predation is most likely to effectively eradicate a pathogen. Lastly, we determined whether the form of disease transmission affects the model results.

2.2 The Model

We designed our model to examine the effects of a vector's predator on disease dynamics, by incorporating both vector population dynamics and a predator. The main version of our model assumes that the host population is at a constant equilibrium and that pathogen transmission is density-dependent (following e.g.,

Anderson and May 1991; Hethcote 2000). We also examined model formulations incorporating host population demographics (Section 2.4), frequency-dependent transmission (Section 2.2.2), host immunity, vector latency, a saturating predator functional response, and selective predation (Appendix C). Incorporating host population demographics can be particularly important because disease-induced mortality and reductions in host fecundity often have a large effect on host-pathogen dynamics. We begin without host dynamics to set a baseline for us to examine the potentially interactive effects of predation and the vector population's growth rate. Predator-vector dynamics are represented by a set of Lotka-Volterra predator-prey equations (Gurney and Nisbet, 1998). For simplicity, the predator is modeled as an obligate dietary specialist, dependent on the vector population for survival. However, this model also adequately represents a generalist predator capable of regulating the vector population.

We initially assumed a constant host population size based on the Ross-MacDonald susceptible-infected (SI) model for malaria (Ross, 1910; Macdonald, 1957; Anderson and May, 1991). We modified the Ross-MacDonald model by adding a predator (P) to the system and making the vector population dynamic:

$$\begin{aligned}
\frac{dI}{dt} &= \beta_{VH}(H-I)V - \gamma I, \\
\frac{dU}{dt} &= b_N(U+V) - \beta_{HV}IU - (m_N + d_N(U+V))U - \alpha UP, \\
\frac{dV}{dt} &= \beta_{HV}IU - (m_N + d_N(U+V))V - \alpha VP, \\
\frac{dP}{dt} &= \epsilon\alpha(U+V)P - m_P P.
\end{aligned} \tag{2.1}$$

In these equations, I represents infected hosts. Because the total host population size is constant, we only need to keep track of infecteds, and represent susceptible hosts as $S = H - I$. β_{VH} is the transmission coefficient for hosts acquiring infection from vectors, and γ represents the removal rate of individuals from the infected class as a result of death or recovery to the susceptible class. Disease transmission from the vector to the host is dependent on the densities of susceptible hosts $(H - I)$ and infectious vectors (V).

Unlike hosts, vectors have a dynamic population size. U and V represent uninfected and infectious vectors, respectively. All vectors are born uninfected into class U with a per-capita birth rate of b_N. Infectiousness does not affect vector birth rate or mortality. Vectors only acquire infection from hosts, with the transmission coefficient β_{HV}. Host-to-vector disease transmission is also density-dependent, determined by the densities of infected hosts (I) and uninfected vectors (U). Vectors in both classes experience density-independent (m_N) and density-dependent (d_N) mortality in addition to death from predation. Vector predators (P) have a conversion efficiency of ϵ, an attack rate of α, and a density-independent mortality rate of m_P. Thus, the vectors experience logistic growth, while their predators have a linear, Type I functional response.

2.2.1 Equilibrium and invasion analysis

The main model with a constant host population has five biologically relevant equilibria (negative equilibrium values are excluded): (i) populations other than

the host (H) are absent; (ii) the host and vector (N) are present, but the pathogen and predator are absent; (iii) vectors (N) and predators (P) are present in the absence of the pathogen; (iv) the pathogen is present in the host and vector populations, but the predator is absent; and (v) all populations including the pathogen coexist at nonzero densities (Table 2.1). Because host density remains constant, the host is present in each of these equilibria as long as the parameter $H > 0$.

Equilibrium (i) is stable and the host population (H) is disease-free if $b_N \leq m_N$. If $b_N > m_N$, then equilibrium (i) is unstable and, at a minimum, the vector population can invade the system. Equilibrium (ii) represents the disease-free, predator-free system where the host population, H, is disease-free (i.e., $I^* = 0$) and the vector population, N, is at equilibrium $N^* = \frac{b_N - m_N}{d_N} \equiv K_V$, which is the vector's carrying capacity. When predation is strong enough to regulate vector dynamics—as determined by the inequality $m_P/\epsilon\alpha < K_V$—the predator can invade and shift the system to equilibrium (iii). When the pathogen is absent, dynamics between the vector and predator are described by the traditional Lotka-Volterra predator-prey model with a self-limiting prey population (Gurney and Nisbet, 1998).

For analyzing the effect of predation on the invasion or persistence of a pathogen, it is useful to consider the pathogen's basic reproduction number, R_0—the number of individuals infected by the initial infectious case in an entirely susceptible population (Diekmann et al., 1990). If $R_0 > 1$, each infectious host will infect more than one susceptible individual, and the pathogen can invade

and persist upon introduction into a susceptible population. If $R_0 < 1$, infected individuals do not fully replace themselves in the population, which leads to the elimination of the pathogen from the host population. Therefore, $R_0 = 1$ serves as a threshold parameter for the invasion of the pathogen into a susceptible population. With the next-generation method (Diekmann et al., 1990; van den Driessche and Watmough, 2002), and the total vector population defined as $N = U + V$ for convenience, the pathogen's basic reproduction number from equation (2.1) is

$$R_0 = \sqrt{NH}\frac{\sqrt{\beta_{VH}\beta_{HV}}}{\sqrt{\gamma(m_N + d_N N + \alpha P)}}. \tag{2.2}$$

This equation for R_0 is sensitive to our initial assumptions; R_0 will be altered when host demographics are included or disease transmission is frequency-dependent. When the predator is absent, as in equilibrium (ii), $R_0 = \sqrt{(N^* H\beta_{VH}\beta_{HV}/\gamma m_N)}$. From this equation we can see that there is a host density threshold $H_T = \gamma b_N / N^* \beta_{VH}\beta_{HV}$, such that $H > H_T$ is required for pathogen invasion and persistence. If the predator is present the host density threshold for a successful pathogen invasion is $H_T = \epsilon\alpha\gamma b_N / m_P \beta_{VH}\beta_{HV}$.

In addition to a host density threshold, there is also a minimum vector density required for pathogen persistence:

$$N_T = \frac{\gamma(m_N + \alpha P^*)}{(H\beta_{VH}\beta_{HV} - d_N\gamma)}. \tag{2.3}$$

The vector density threshold depends on the equilibrium predator density (P^*). In the absence of a predator, the minimum vector density for pathogen persistence simplifies to $N_T = \gamma b_N / H\beta_{VH}\beta_{HV}$.

2.2.2 Frequency-dependent transmission model

The initial model assumed density-dependent transmission, in which the number of contacts between the vector and host is proportional to host density. In contrast, when disease transmission is frequency-dependent, the number of contacts depends on the proportion of infected host individuals rather than host density. It has been argued that the transmission of many vector-borne pathogens is better described by the frequency, rather than the density, of infected individuals in the host population (Getz and Pickering, 1983; Thrall et al., 1993; Antonovics et al., 1995; Rudolf and Antonovics, 2005).

Disease transmission is likely to be frequency-dependent when the vector only feeds on one or a few hosts during its lifetime, a feeding strategy employed by many mosquitoes, ticks, and other arthropods that transmit disease (Antonovics et al., 1995). Many models with frequency-dependent transmission predict host-pathogen dynamics that differ from the results of density-dependent transmission models (Getz and Pickering, 1983; Thrall et al., 1993; Wonham et al., 2006). Therefore we modify our model by making disease transmission frequency-dependent; formulation details for the frequency-dependent transmission model are described in Appendix B.

2.3 Results - Constant host population

Adding a predator reduces the region of pathogen persistence at equilibrium (Figure 2.1). Because an increase in the predator's attack rate, α, or conversion efficiency, ϵ, leads to a decrease in R_0, an increase in predation strength leads to a decrease in the equilibrium proportion of infected hosts (Figure 2.2). In addition to reducing equilibrium infection levels, predation can also delay the onset of an epidemic (Figure 2.3). By decreasing the vector's lifespan, predation decreases the average number of new hosts infected during the lifespan of each infectious vector, thereby slowing the spread of disease. Even the relatively moderate predation rates used in Figure (2.3), decrease the equilibrium pathogen prevalence by 30% and increase the time to equilibrium from 50 to 150 days.

In the absence of predation, an increase in the vector birth rate leads to an increase in the proportion of infected hosts (Figure 2.4a). However, when the predator is introduced into the system, an increase in the vector birth rate leads to a decline in the prevalence of disease in the host population (Figure 2.4a), because an increase in the vector birth rate leads to an increase in the predator population. Predation increases turnover in the vector population, and the average individual vector is infectious for a shorter period because it is alive for a shorter period. In addition, higher vector fecundity leads to more non-infectious vectors, thereby diluting the infectious potential of the vector population. Nonintuitively, in a tri-trophic system, increased vector fecundity leads to reduced host infection. When the predator is present, the proportion of infected hosts at equilibrium

is sensitive to the vector birth rate, b_N, but not to the vector mortality rate, m_N, or density-dependent mortality term, d_N (Figure 2.4b). Increases in the vector mortality rate lead to a gradual reduction in pathogen prevalence in the absence of the predator. However, when a predator is present, moderate increases in the non-predation vector mortality rate do not affect pathogen prevalence, because the predator regulates the vector population. At equilibrium, vector density is determined solely by the predator population's parameter values (Table 2.1). Therefore increasing m_N reduces predator density, but does not change vector density or pathogen prevalence until the additional vector mortality is high enough that the predator cannot persist by feeding on the vector.

Introducing a predator to the system will lower the proportion of infected hosts, except in a narrow parameter range where the vector's birth rate is barely higher than its mortality rate. Equation (2.3) for the minimum vector population threshold, N_T, suggests that an increase in b_N increases the minimum vector density required for pathogen persistence. There is also an inverse relationship between vector productivity (as measured by b_N) and the strength of predation, α. At low vector productivity levels, pathogen persistence is possible except at very high levels of predation. As vector productivity increases, the predation strength needed to exclude the pathogen from the system decreases (Figure 2.1b). Increasing the predator's conversion efficiency, ϵ, also reduces disease prevalence.

The presence of the predator also increases the minimum host density, H_T, required for disease persistence when disease transmission is density-dependent. As the strength of predation increases, H_T also increases. The other parameters

that affect pathogen persistence and prevalence are identifiable by examination of equation (2.2) for R_0. An increase in transmission rates β_{VH} or β_{HV} leads to increased pathogen prevalence. A decrease in the density of the host population causes a decrease in the proportion of infected hosts, and below a critical threshold density, H_T, the pathogen cannot persist in the host population. There is also a negative relationship between the rate of host recovery or turnover, γ, and pathogen persistence. At high recovery rates the pathogen cannot invade and persist in the host population.

Frequency-dependent model results

When disease transmission is frequency-dependent, increasing host density leads to a decrease in disease prevalence. R_0 is no longer positively related to host density, but instead scales with the inverse of host density (see Appendix B). Likewise, the predation strength required to exclude the pathogen is also lower at higher host densities. Except at low host densities, the region of parameter space permitting pathogen persistence will be greater under density-dependent transmission than under frequency-dependent transmission. However, the mode of transmission does not affect the relationship between vector productivity, predation strength, and disease prevalence. An increase in predation strength or the vector birth rate, with predators present, still leads to a decrease in the proportion of infected hosts.

2.4 Dynamic host population model

The assumption of a constant host population is useful for simplifying the dynamics of a relatively complex system and may be justified in the case of a disease with a short infectious period and limited effects on host mortality or fecundity. However, when a pathogen has an effect on host fecundity or mortality, or a long infectious period, the presence of a pathogen can have a large impact on host population dynamics. Including host population dynamics is also appropriate if host and vector population dynamics occur on a similar time scale. Here, the initial model of density-dependent transmission in a constant host population (equation (2.1)) is altered to include host demographics. The host has a per-capita mortality rate, m_H, and a per-capita birth rate, b_H, with a density-dependent control, ϕ. The modified model also explores the effect of the pathogen on host fecundity, ρ, and an additional disease-induced mortality rate, δ:

$$\begin{aligned}
\frac{dS}{dt} &= b_H(1-\phi H)(S+\rho I) - \beta_{VH} SV - m_H S, \\
\frac{dI}{dt} &= \beta_{VH} SV - m_H I - \delta I, \\
\frac{dU}{dt} &= b_N(U+V) - \beta_{HV} IU - (m_N + d_N(U+V))U - \alpha UP, \\
\frac{dV}{dt} &= \beta_{HV} IU - (m_N + d_N(U+V))V - \alpha VP, \\
\frac{dP}{dt} &= \epsilon\alpha(U+V)P - m_P P.
\end{aligned} \tag{2.4}$$

After including host demographics, the pathogen reproduction number is

$$R_0 = \sqrt{NH}\frac{\sqrt{\beta_{VH}\beta_{HV}}}{\sqrt{(\delta + m_H)(m_N + d_N N + \alpha P)}}. \tag{2.5}$$

The only difference between this equation and equation (2.2) is that, instead of $1/\gamma$, the average infectious period of an infected host is now $1/(\delta + m_H)$.

The equilibrium equations for the total host density (H^*) when the pathogen is present are too complex to display succinctly. However, the equilibrium values for the other model equations can be solved as a function of H^* (see Appendix A). The equilibrium solutions to the dynamic-host-population model as a function of H^* are very similar to those for the constant-host-population model, where host density was represented as a parameter, H. In fact, when there is no disease-induced mortality ($\delta = 0$) and no reduction in the fecundity of infected individuals ($\rho = 1$), the equilibrium solutions of the two models are identical when $H^* = H$.

Results - Dynamic host model

Disease-induced changes in host mortality and fecundity decrease the proportion of infected hosts at equilibrium, but they do not modify the qualitative relationship between predation intensity and disease prevalence in the host population compared to the initial model. If infected hosts are subject to additional mortality, the proportion of infected hosts at equilibrium decreases (Figure 2.5a). In addition, an increase in the disease-induced mortality rate leads to a decrease in

the predation intensity required to prevent pathogen persistence. Reducing the fecundity of infected hosts also leads to a reduction in pathogen prevalence, but it does not affect pathogen persistence (Figure 2.5b). Even if infected hosts are sterile ($\rho = 0$), the threshold for pathogen persistence does not change.

When host demographics are included in the model, the pathogen can also affect the equilibrium host density. When the pathogen does not affect host mortality or fecundity, the equilibrium host density is at its carrying capacity, $K_H = (b_H - m_H)/(b_H\phi)$, whether or not the pathogen is present. If infection increases the host mortality rate ($\delta > 0$) or reduces fecundity ($\rho < 1$), the host population density will remain below the carrying capacity when the pathogen is present at equilibrium. Increasing the negative effect of infection on host fecundity reduces the host population density, but the relationship between the disease-induced mortality rate and host density is non-linear. Initial increases in the disease-induced mortality rate reduce the equilibrium host population density; further increases minimally increase host population density, although equilibrium host density remains below the carrying capacity unless the pathogen is extirpated. Equilibrium host population density is higher in the presence of the predator for a given set of parameter values. In addition, increasing the predator attack rate or predator conversion efficiency increases the equilibrium host density (a standard trophic cascade) and decreases pathogen prevalence in the host population as we saw when host population size was constant.

2.5 Discussion

Numerous ecological studies have shown that, in addition to directly affecting their prey, predators often indirectly affect other species in a community (Holt, 1977; Sih et al., 1985; Wootton, 1994; Shurin et al., 2002; Caceres et al., 2009). Our analysis indicates that predators may have important indirect effects on the prevalence or persistence of a vector-borne pathogen in a host population by controlling the vector population. If predation intensity is strong enough, the predator can prevent the establishment of a pathogen in a susceptible population. In addition, introducting a predator into a system where an endemic pathogen is at equilibrium with the host and vector populations can eliminate the pathogen (as long as $R_0 < 1$ in the presence of the predator). These predictions are robust to assumptions about host population dynamics and disease transmission as well as the addition of acquired immunity in the host population, a vector latency period, a saturating response of predation to vector density, and selective predation on infectious or non-infectious vectors (Appendix C).

A non-intuitive prediction of this model is that predation on the vector population reverses the relationship between vector productivity and pathogen prevalence. Pathogen prevalence increases with vector productivity (defined here as the vector's birth rate, b_N) in the absence of predation, whereas in the presence of the predator, pathogen prevalence declines with increasing vector productivity. The effect of predation on pathogen prevalence or persistence is not dependent on whether disease transmission is modeled as density- or frequency-dependent and

provides an indication of situations where natural predation or biological control may successfully control vector-borne diseases. Interestingly, the results of several studies are consistent with this prediction. In particular, vector control methods are essential for managing dengue fever and dengue hemorrhagic fever—a common mosquito-transmitted viral disease in humans—because of limited treatment options and no approved vaccine (Kroeger and Nathan, 2007). Predaceous copepods in the genera *Mesocyclops* and *Macrocyclops* have been used successfully as biological control agents to control *Aedes spp.* mosquitoes that transmit dengue (Marten et al., 1994; Kay et al., 2002; Kay and Nam, 2005; Nam et al., 2005; Kittayapong et al., 2008). In Vietnam, biological control efforts targeted larval breeding sites where the productivity of *Aedes aegypti* was especially high (Kay et al., 2002). These control efforts helped eradicate the vector from 32 of 37 communities; no new dengue cases were reported in any of the treated communities over a period of several years (Kay and Nam, 2005; Nam et al., 2005). The introduction of *Mesocyclops* in combination with other control measures also led to a significant reduction in dengue cases in Chachoengsao Province, Thailand (Kittayapong et al., 2008), and larvivorous fishes significantly reduced the long-term ($>$ 12 months) density of *A. aegypti* in rural Cambodia (Seng et al., 2008).

Targeting sites of high vector productivity is likely to have the largest effect on vector abundance. Our model suggests that introducing a predator to these sites could also lead to large reductions in pathogen prevalence due to a predator-induced reversal in the relationship between vector productivity and pathogen prevalence. In addition to targeting highly productive larval sites for

dengue control, several researchers have suggested that malarial control efforts should target the most productive larval habitats (Gu and Novak, 2005; Gu et al., 2008). Although these efforts are aimed at targeting productive habitats for environmental management and source reduction, our model predicts that these productive habitats could be targets for successful biological control efforts, particularly when elimination of the habitat is not feasible. Although controlling malaria by introducing predators has a controversial history (Pyke, 2008), several recent reviews suggest that native or introduced predators can reduce the abundance of *Anopheles* larvae in certain habitats (Walker and Lynch, 2007; Chandra et al., 2008). For example, Wu et al. (1991) found that introducing carp to rice paddies in Guangxi, China, significantly reduced larval mosquito density and may have reduced malaria transmission at the village and county levels. Kumar et al. (1998) found that replacing DDT and pyrethum treatments with the introduction of *Bacillus thuringiensis* and a native larvivorous fish *Aplocheilus blocki* to the major breeding habitats of *Anopheles stephensi* in Goa, India, led to a significant reduction in larval *A. stephensi* abundance. In addition, malaria incidence declined when compared with nearby towns that did not receive the new treatments. These studies, along with others reviewed by Walker and Lynch (2007) and Chandra et al. (2008), suggest that predator control of *Anopheles* mosquitoes can reduce malaria incidence in certain situations. Although quantitative evaluation of vector productivity is often difficult (Killeen et al., 2005), recent efforts to quantify the productivity of *Anopheles* (Mutuku et al., 2006) and *Aedes* (Kay et al., 2002; Chadee, 2007) mosquitoes show promise and sug-

gest that using measures of habitat-based vector productivity to guide biological control efforts may prove useful. Our model suggests that targeting these highly productive sites would lead to the largest reduction in pathogen prevalence.

Classical biological control strategies have emphasized the use of specialist predators to maintain pest populations at low, stable equilibrium levels (Murdoch et al., 1985; Stiling and Cornelissen, 2005). Our model also suggests that it is not essential for the predator to extirpate the vector population in order to eradicate the pathogen. The minimum vector population threshold predicted by our model (N_T, equation (2.3)) provides a target for vector control. Biological control agents are often successful at reducing vector abundance, at least in the short term (see Legner 1995; Kumar and Hwang 2006; Ostfeld et al. 2006*a*; Walker and Lynch 2007; Chandra et al. 2008 for examples); although they will not eradicate the pathogen if the equilibrium vector density remains above N_T. For example, in three communities examined by Nam et al. (2005) in which predaceous copepods were used to control *Aedes* mosquitoes, dengue cases dropped to 0 in both 2002 and 2003 even though mosquitoes were still present at low densities. These results are consistent with our prediction that biological control can maintain vector density below N_T.

Even if predation intensity is not high enough to remove the pathogen from the host population, predation can still decrease disease prevalence in the host population to low levels, potentially delaying the onset of an epidemic. For human diseases, an increase in the time between the introduction of a pathogen and an outbreak would provide additional time for disease control efforts (such

as vaccination or quarantine) to be implemented (Anderson and May, 1991). In agricultural systems, farmers are often concerned about an economic threshold where crop losses become great enough to trigger economic losses (Kogan, 1998). In this case, the reduction in the rate of disease spread due to predation may be sufficient to allow crop harvest before an epidemic outbreak. For example, vector-transmitted plant pathogens such as the barley and cereal yellow dwarf viruses (BYDV/CYDV) can have detrimental effects on crop yields by causing stunted growth, reduced seed-set, or early senescence (Irwin and Thresh, 1990; D'Arcy and Burnett, 1995); therefore, reducing disease prevalence within the host population could limit crop losses to acceptable levels. Natural predators and biological control agents have been used in agricultural settings to reduce the abundance and slow the population growth of several different aphid species that transmit BYDV/CYDV (Chiverton, 1986; Brewer and Elliott, 2004), but the corresponding effects on BYDV/CYDV have not yet been investigated. Laboratory studies of aphid predators have found either no impact on BYDV infection rates or a transient reduction in spread of the virus (Christiansen-Weniger et al., 1998; Smyrnioudis et al., 2001). However, these studies were short term and did not continue long enough for the predator to regulate the aphid population, which is required to observe large reductions in pathogen prevalence in our model.

In the absence of predation, an increase in the vector mortality rate leads to a decline in disease prevalence. However, when a predator with a type I linear functional response is present, an increase in the vector mortality rate from factors other than predation does not change disease prevalence. Because the predator

regulates the vector population, an increase in non-predation mortality reduces predator, but not vector, abundance. The overall vector mortality rate stays the same because the increase in the background mortality rate is compensated by a decrease in mortality due to predation. If the predator has a type II saturating functional response, pathogen prevalence may decline with an increase in non-predation mortality if the predator's consumption rate is already saturated (see Appendix C for details). However, even with a type II response, once the vector density decreases to a level at which the predator consumption rate is no longer saturated, pathogen prevalence will level off despite further increases in non-predation mortality.

As a result, predator regulation of the vector population may have implications for the use of other vector control methods (such as pesticides) in conjunction with biological control. Biological control is often part of an integrated pest management (IPM) strategy that includes other vector control methods, such as spraying insecticides, environmental manipulation, or the application of larvicides to vector breeding sites (WHO, 2004). Ideally these integrated approaches will have synergistic effects, but our model suggests that predator regulation of the vector population could reduce or prevent the effectiveness of other control methods aimed at increasing vector mortality. Instead, these additional mortality factors may reduce predator abundance, limiting the regulatory effects of predation on the vector population as Chansang et al. (2004) and Snyder and Ives (2001) have observed in mosquitoes and aphids, respectively. Chansang et al. (2004) found that the application of *Bacillus thuringiensis* alone or in combina-

tion with *Mesocyclops thermocyclopoides* initially reduced *Aedes aegypti* densities more than a *Mesocyclops*-only treatment, but after 16 weeks the *Mesocyclops*-only treatment had higher *Mesocyclops* densities and lower *A. aegypti* densities than the combined treatment. This suggests that *B. thuringiensis* prevented *Mesocyclops* from strongly regulating the *A. aegypti* population. Other sources of density-independent vector mortality besides vector control efforts, such as the presence of other predators, can interfere with pathogen regulation by a specialist predator. Snyder and Ives (2001) found that specialist parasitoids introduced to control the pea aphid (*Acyrthosiphon pisum*), which transmits several crop viruses, were disrupted by generalist predators that fed on both the aphid and its parasitoid.

Previous work has explored how predation on a host population affects host-pathogen dynamics (Packer et al., 2003; Ostfeld and Holt, 2004; Duffy et al., 2005; Hall et al., 2005; Holt and Roy, 2007; Duffy and Hall, 2008; Caceres et al., 2009). Packer et al. (2003) detailed how predation often reduces the incidence of parasitic infections and increases the overall size of the prey population. Our model reveals that predation on a vector can similarly reduce pathogen prevalence in both the host and vector. In addition, when the pathogen regulates the host by increasing mortality or reducing fecundity, predation can weaken the pathogen's negative impact on the host, thereby increasing host abundance. When predation on immune individuals occurs predation can increase pathogen prevalence in a prey population (Holt and Roy, 2007). We found that including acquired immunity in the host does not alter the qualitative effects of predation

on pathogen prevalence (see Appendix C for details). Because our model does not include recovery or acquired immunity of infectious vectors, predation on the vector population cannot lead to an increase in pathogen prevalence in the host or vector; however, relaxing this assumption by incorporating predation on vectors resistant to infection could increase pathogen prevalence. This could affect disease control efforts; predation on mosquitoes that have been genetically modified to be incapable of transmitting malaria or other pathogens (Alphey et al., 2002; Scott et al., 2002) could limit the effectiveness of their introduction.

In addition to predator effects on the pathogen, predation may indirectly increase host abundance by reducing the negative impacts of infection. Indirect effects of predators on lower trophic levels, i.e. trophic cascades, are common in nature (Pace et al., 1999; Shurin et al., 2002), and are predicted to be stronger in highly productive systems (Oksanen et al. 1981; Polis 1999; but see Borer et al. 2005). In a system with direct predation on the host population, Hall et al. (2005) found that high ecosystem productivity (as measured by the carrying capacity of the host population) could facilitate invasion of a parasite. However, increasing the strength of predation in a highly productive environment destabilized parasite-host dynamics leading to extinction of both the parasite and its host. In our model, the predator, vector, and host populations form a tri-trophic system with both direct trophic interactions and indirect interactions mediated by the pathogen. The indirect effects of predation on pathogen prevalence and host abundance are predicted to be strongest when the vector population experiences high growth rates, as may be expected to occur in highly productive

environments. For vectors such as mosquitoes that complete different life stages in different environments, population growth rates often are influenced primarily by productivity in the larval environment rather than by host density (Southwood et al., 1972; Juliano, 2007), and therefore we would expect the strength of the indirect effects of predation to be related to larval vector productivity. However, the productivity of other vectors that remain in the same environment throughout their life cycle, such as many fleas, ticks or aphids, may be positively influenced by host density (Dixon, 1998).

Our model results suggest that predation on a vector can strongly influence pathogen prevalence and host abundance in both intuitive and non-intuitive ways. The introduction of biological control agents to control vector populations can reduce prevalence or eradicate the pathogen, particularly in productive environments where the vector population experiences a high turnover rate. In the absence of predation, these productive environments would be expected to have the highest infection rates. This predator-induced reversal in disease prevalence indicates that reductions in the abundance of natural predators due to invasive species, habitat modifications, or climate change may be partially responsible for the increased frequency of disease outbreaks caused by vector-borne pathogens (Gubler, 1998; Gratz, 1999; Daszak et al., 2000). The presence of a predator could also decrease the risk of zoonotic diseases such as Lyme disease and West Nile virus spilling over from reservoir hosts to humans (Bernard et al., 2001; Schmidt and Ostfeld, 2001; LoGiudice et al., 2003). With the emergence and re-emergence of many vector-borne diseases, determining the potential interactions

of the host(s) and pathogen with other species in the community is essential for predicting potential disease risks and guiding control efforts. Our model results suggest that empirical research into the role of native and introduced predators across a range of vector productivity and mortality will be essential to determining the influence of predators on vectored disease transmission.

2.6 Acknowledgements

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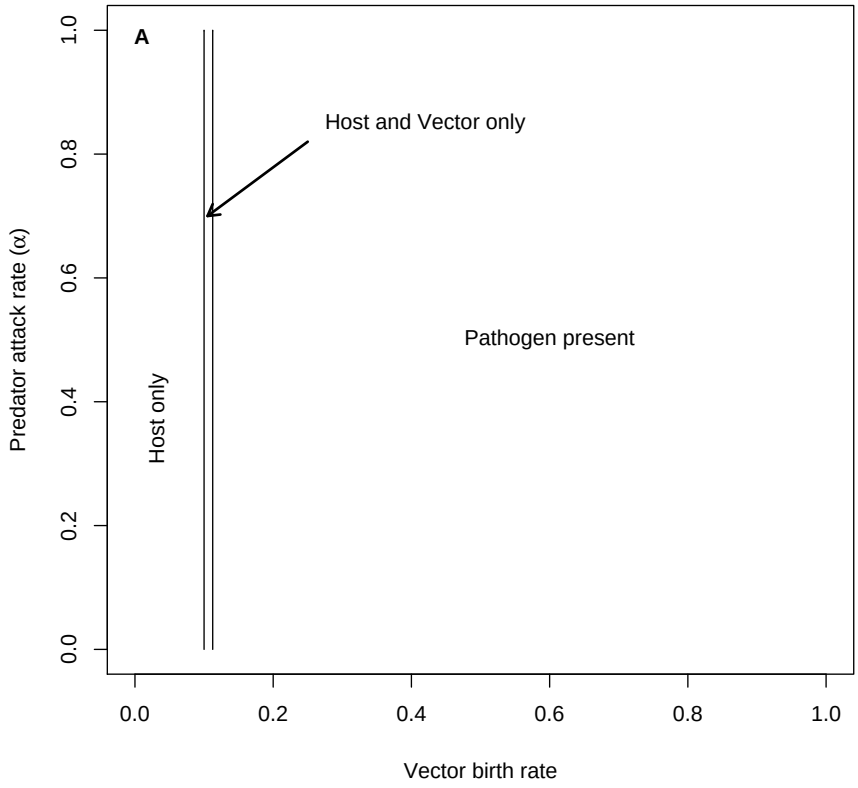
Table 2.1: Equilibrium equations for the vector-predator SI model with a constant host population. (Equilibria for the constant host population model described by equation 2.1. Because host density remains constant, the host population is present in each of these equilibria as long as the parameter $H > 0$. Equilibrium (i) is host (H) population only, in equilibrium (ii) only uninfected hosts and vectors (U) are present, (iii) the vector and predator equilibria in the absence of the pathogen (U^* and P^*) match those for a Lotka-Volterra predator-prey model with prey self-regulation, (iv) The pathogen is present in the host and vector populations but the predator is absent, and (v) all populations including the pathogen coexist at nonzero densities. Note: for equilibria (iii) and (v), we denote the population size of the vectors without the predators as K_V (equivalent to U^* in (ii)).)

Equilibrium	I^*	U^*	V^*	P^*
(i)	0	0	0	0
(ii)	0	$\frac{b_N - m_N}{d_N}$	0	0
(iii)	0	$\frac{m_P}{\epsilon\alpha}$	0	$\frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V})^a$
(iv)	$\frac{\beta_{VH}\beta_{HV}H(b_N - m_N) - b_N d_N \gamma}{\beta_{HV}(\beta_{VH}(b_N - m_N) + \gamma d_N)}$	$\frac{b_N(\beta_{VH}(b_N - m_N) - d_N\gamma)}{\beta_{VH}d_N(\beta_{HV}H + b_N)}$	$\frac{\beta_{VH}\beta_{HV}H(b_N - m_N) - b_N d_N \gamma}{\beta_{VH}d_N(\beta_{HV}H + b_N)}$	0
(v)	$\frac{\beta_{VH}\beta_{HV}Hm_P - \alpha\epsilon b_N\gamma}{\beta_{HV}(\beta_{VH}m_P + \epsilon\alpha\gamma)}$	$\frac{b_N(\beta_{VH}m_P - \epsilon\alpha\gamma)}{\epsilon\alpha\beta_{VH}(\beta_{HV}H + b_N)}$	$\frac{\beta_{VH}\beta_{HV}Hm_P - \alpha\epsilon b_N\gamma}{\epsilon\alpha\beta_{VH}(\beta_{HV}H + b_N)}$	$\frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V})$

[a] $K_V = \frac{b_N - m_N}{d_N}$


A
Host and Vector only
Pathogen present
Host only
Predator attack rate (α)
Vector birth rate
0.0
0.2
0.4
0.6
0.8
1.0

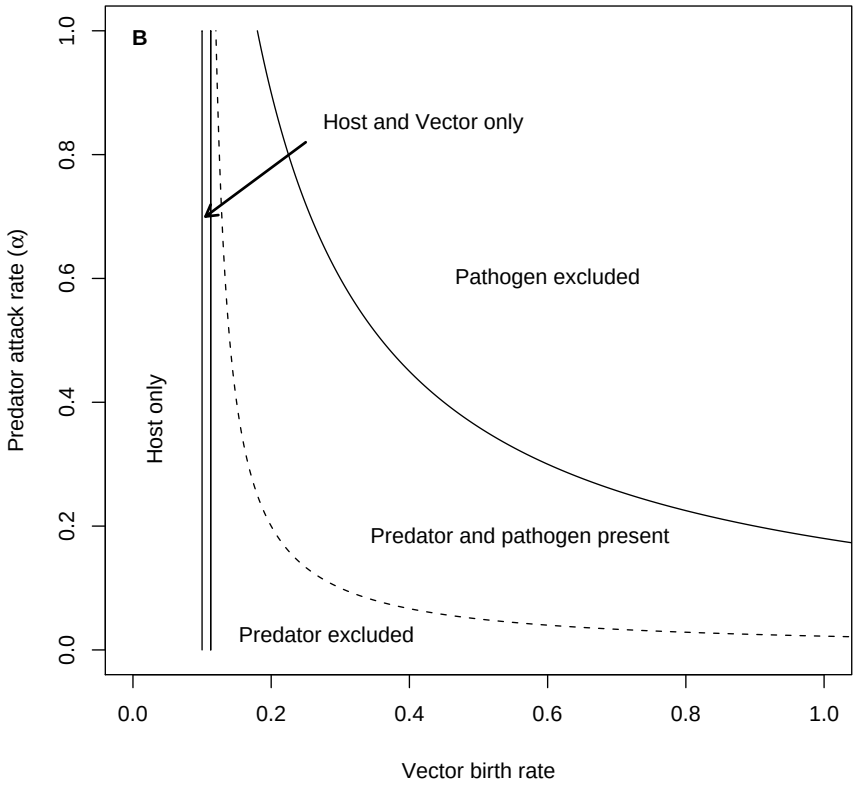


Figure 2.1: Regions of stability in parameter space for each of the system equilibria as a function of vector birth rate (b_N) and predator attack rate (α). (a) When there is no predator in the system, the pathogen reproduction number, R_0, and pathogen persistence are a function of vector birth rate. (b) When a predator is added the pathogen reproduction number and pathogen persistence depend on b_N and α. The solid line represents the $R_0 = 1$ isocline, and the dashed line represents the $P^* = 0$ isocline. The other model parameters values are $H = 1$, $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $\gamma = 0.05$, $m_N = 0.1$, $d_N = 0.05$, $\epsilon = 0.25$, $m_P = 0.1$.

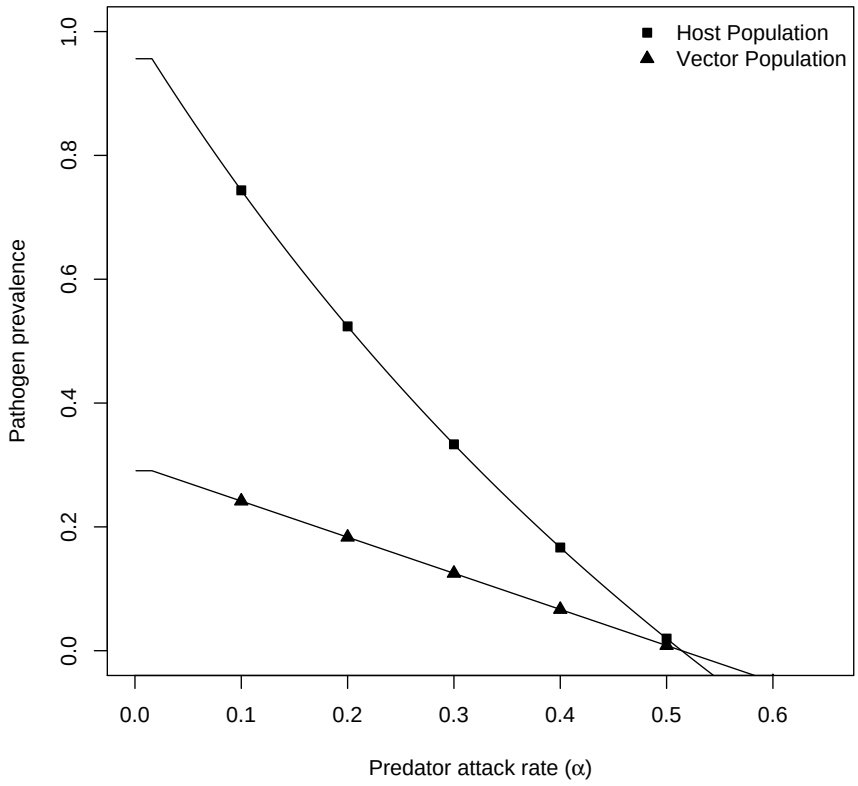


Figure 2.2: Pathogen prevalence in the host and vector populations as a function of the predator attack rate (α). Pathogen prevalence is measured as the proportion of infected hosts (I^*/H) and vectors (V^*/N^*) in their respective populations at equilibrium. The other model parameters values are $H = 1$, $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $\gamma = 0.05$, $b_N = 0.35$, $m_N = 0.1$, $d_N = 0.05$, $\epsilon = 0.25$, $m_P = 0.1$.

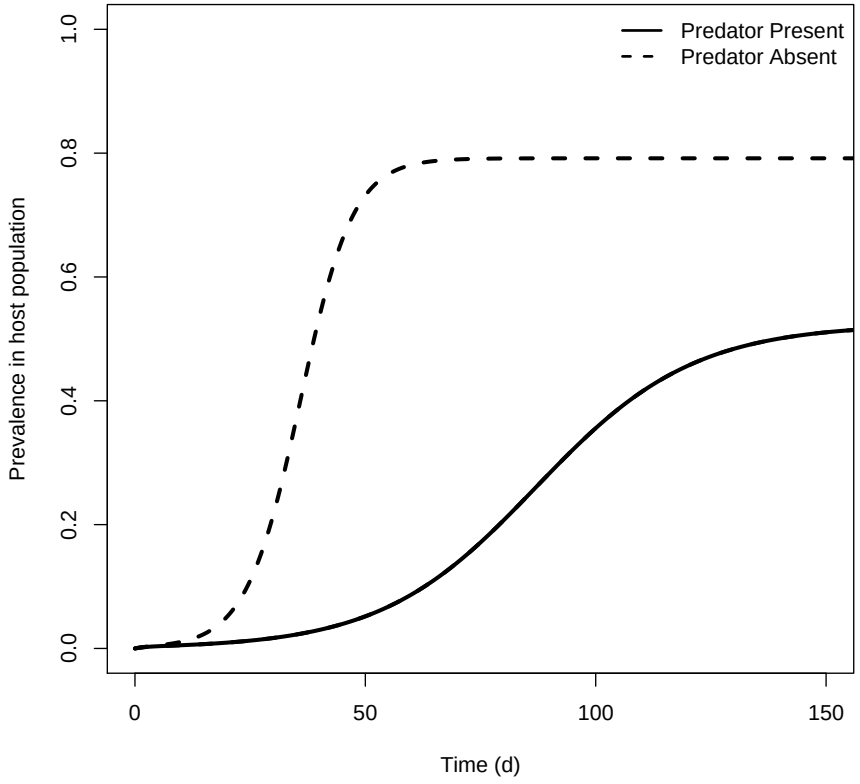
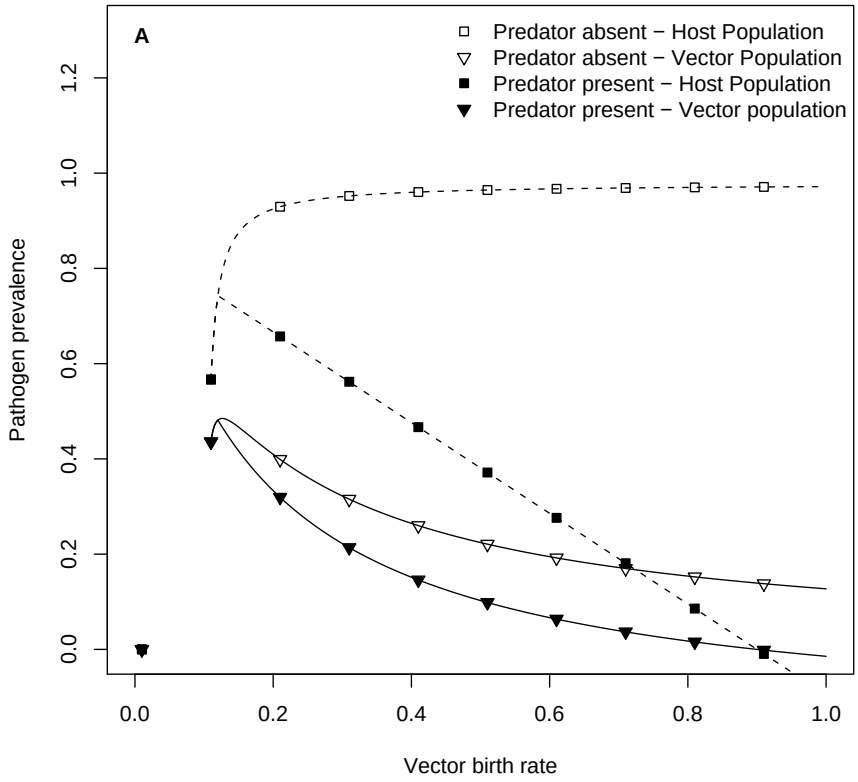


Figure 2.3: Model of an epidemic outbreak in the presence or absence of a predator. At $t = 0$, the host population is entirely susceptible and 1% of the vector population is infectious. Parameters values are $H = 1$, $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $\gamma = 0.05$, $b_N = 0.35$, $d_N = 0.05$, $m_N = 0.1$, $\alpha = 0.2$, $\epsilon = 0.25$, $m_P = 0.1$. $R_0 = 2.54$ when predator is absent, and $R_0 = 1.60$ when predator is present at its equilibrium density.


A
Predator absent − Host Population
Predator absent − Vector Population
Predator present − Host Population
Predator present − Vector population
Pathogen prevalence
0.0
0.2
0.4
0.6
0.8
1.0
1.2
Vector birth rate
0.0
0.2
0.4
0.6
0.8
1.0

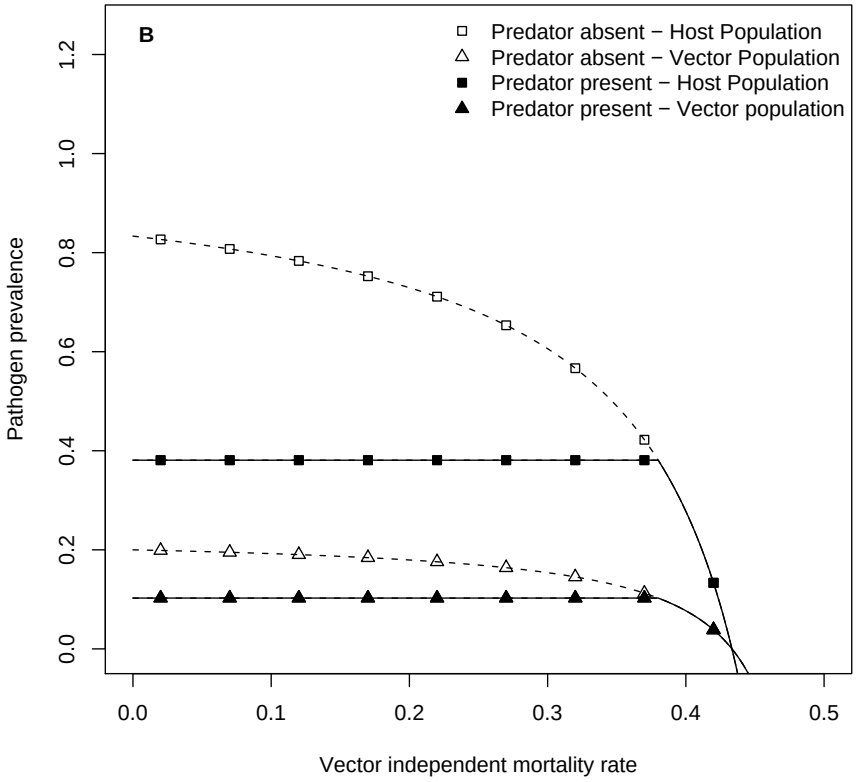
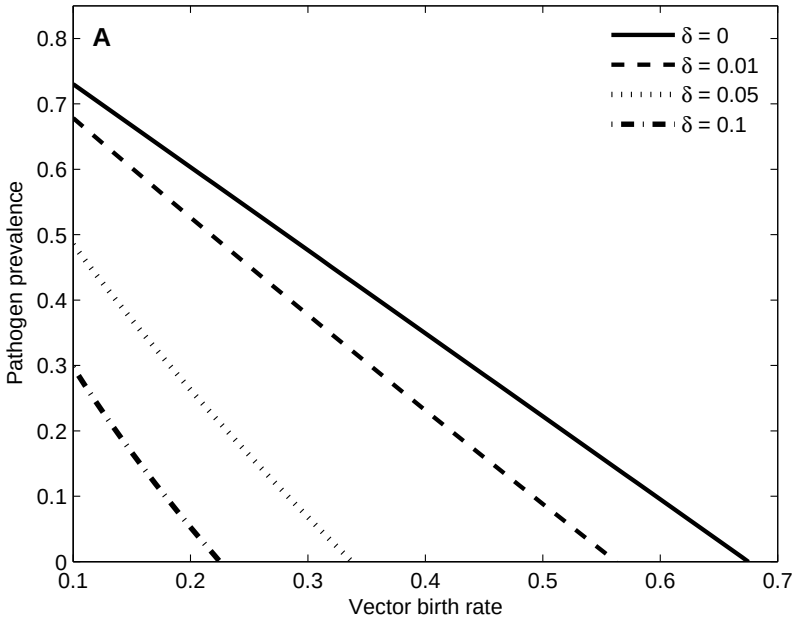


Figure 2.4: (a) Pathogen prevalence, represented as the proportion of the host and vector population that is infected, as a function of the vector birth rate (b_N) either in the absence of predation (open symbols), or with the predator present at its equilibrium density (closed symbols). When $b_N < m_N$ ($m_N = 0.1$), the vector population is absent at equilibrium, and by necessity the pathogen cannot persist. (b) Pathogen prevalence in the host and vector populations as a function of the non-predation vector mortality rate (m_N). In the absence of the predator an increase in the vector mortality rate leads to a decrease in pathogen prevalence, while pathogen prevalence does not respond to an increase in vector mortality when a predator is present. The other model parameters values are $H = 1$, $b_V = 0.5$ (b only), $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $\gamma = 0.05$, $d_N = 0.05$, $\alpha = 0.2$, $\epsilon = 0.25$, $m_P = 0.1$.


A
δ = 0
δ = 0.01
δ = 0.05
δ = 0.1
Pathogen prevalence
Vector birth rate
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.1
0.2
0.3
0.4
0.5
0.6
0.7

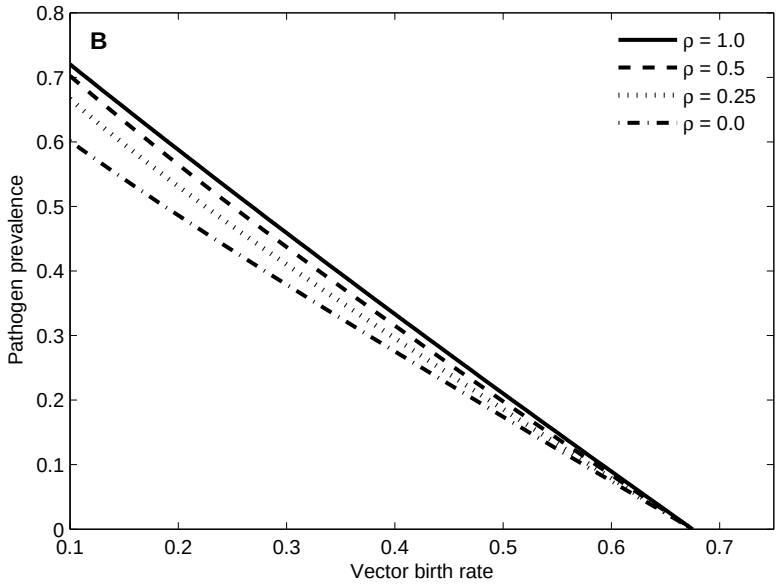


Figure 2.5: Disease prevalence as a function of vector productivity with varying rates of (a) disease-induced mortality and (b) reductions in host fecundity. The other model parameters values are $b_H = 0.20$, $m_H = 0.05$, $\phi = 0.2$, $\delta = 0$, $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $m_N = 0.1$, $d_N = 0.05$, $\alpha = 0.2$, $\epsilon = 0.25$, $m_P = 0.1$, $\rho = 1$ (a only), $\delta = 0$ (b only).

Climate change and sleeping sickness in Eastern and Southern Africa (*Trypanosoma brucei rhodesiense*): integrating epidemiology with parasite and vector biology

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Chapter 3 – Climate change and sleeping sickness (*Trypanosoma brucei rhodesiense*) in Eastern and Southern Africa: integrating epidemiology with parasite and vector biology

Abstract

Climate warming over the next century is expected to have a large impact on the interactions between pathogens and their animal and human hosts, and vector-borne diseases are particularly sensitive to warming because temperature changes can alter vector development rates and generation times, shift their geographical distribution, and alter transmission dynamics. Because the distribution of tsetse flies in Africa is strongly correlated with temperature and other climatic variables, trypanosomiasis (causative agent *Trypanosoma brucei rhodesiense*) was recently identified as one of the twelve wildlife or zoonotic diseases most likely to spread due to predicted climate changes during the 21st century. To examine the potential impacts of projected warming on trypanosomiasis epidemiology we constructed a model of disease transmission dynamics that incorporates the effect of temperature on several epidemiological parameters including tsetse feeding, mortality, and the parasite's incubation period. The model predicts that sleeping sickness epidemics are can occur between 20.7-26.1 °C. The predicted suitable range for *T. b. rhodesiense* in 2090 is predicted to be 85-112% of its current size depending on greenhouse gas emissions. Although we do not predict a large

expansion in the size of the suitable range, there is a large shift of as much as over 50% in the geographic extent of the range. The model also predicts that 46-77 million people who are not currently at risk of exposure live within the projected range for 2090 (including portions of South Africa, the Ethiopian highlands, and Rwanda). The modeling approach presented here provides a framework for using the climate-sensitive aspects of vector and pathogen biology to predict changes in disease prevalence and risk due to climate change.

3.1 Introduction

Global climate changes have been implicated in the emergence, reemergence, or range expansion of many wildlife and human diseases in recent years, such as cholera, West Nile virus, malaria, and amphibian chytridiomycosis (Daszak et al., 2000; Pascual et al., 2000; Hay et al., 2002; Pascual et al., 2006; Pounds et al., 2006). The global mean temperature has increased by 0.7 °C during the past 100 years and is predicted to increase by an additional 1.1 °C to 6.4 °C during the 21st century (IPCC, 2007). Additional warming is likely to affect the epidemiology of vector-borne diseases by altering pathogen and vector development rates and generation times, shifting the geographical distribution of vector or reservoir host populations, altering transmission dynamics, or modifying host susceptibility to infection (Patz et al., 2000; Gubler et al., 2001). Such changes could cause pathogen range expansions and host declines, or release hosts from

disease control by interfering with the precise conditions many parasites require for persistence (Harvell et al., 2002, 2009; Lafferty, 2009; Ostfeld, 2009*b*).

As the evidence for climate impacts on disease has increased, there has been a move towards incorporating climate effects into models of disease transmission and potential distributions of vectors (Rogers and Williams, 1993; Rogers and Randolph, 2006). Since climate changes affect multiple parameters involved in the epidemiology of a particular disease, often in different directions and with different intensities, predicting the impact of climate change on disease transmission and risk requires a framework that specifically incorporates the role of each climate-sensitive parameter. One such approach, as proposed by Rogers and Randolph (2006), focuses on understanding the effects of climatic changes on the basic reproductive number, R_0, of the parasite. R_0 provides a threshold quantity for predicting the pathogen's ability to persist, and also provides other valuable information regarding the nature of the epidemic (Anderson and May, 1979; May and Anderson, 1979; Heesterbeek, 2002). Here we use the approach of Rogers and Randolph (2006) to examine trypanosomiasis, which was recently identified by the Wildlife Conservation Society as one of twelve wildlife or zoonotic diseases that are likely to increase in incidence or expand their geographic range due to predicted climate changes during the 21st century.

An estimated 70,000 cases of Human African Trypanosomiasis (HAT), commonly known as sleeping sickness, occur each year, and 60 million people are currently estimated to be at risk of infection in sub-Saharan Africa (WHO, 2006; Fèvre et al., 2008). HAT infections are caused by the parasitic protozoa *Try-*

panosoma brucei gambiense in West and Central Africa and *T.b. rhodesiense* in East Africa, and can be transmitted to humans by over 20 species of *Glossina* tsetse flies (WHO, 1998; Rogers and Robinson, 2004). In Eastern and Southern Africa *G. morsitans morsitans* and *G. pallidipes*, along with other species and subspecies classified in the Morsitans subgroup are the major vectors of *T. b. rhodesiense* (Leak, 1999; Rogers and Robinson, 2004). These species are potential vectors for sleeping sickness because their distributions occur in areas with suitable climate conditions for trypanosome reproduction, and they prefer habitats, such as open savannah or riverine areas, that lead to potential interactions with humans (Leak, 1999).

In addition to differences between the identity of their major vector species, the two *Trypanosoma brucei* subspecies also differ epidemiologically. *T. b. gambiense* infections are chronic and may be asymptomatic for several months or years, while the progression of *T. b. rhodesiense* infections is typically much quicker, with symptoms developing within days and almost 80% of deaths occurring within 6 months of the onset of illness (WHO, 1998). Importantly, given the timelines and profiles of the diseases, it is presumed that humans may be a primary reservoir for chronic *T. b. gambiense* infections but not for acute *T. b. rhodesiense* infections, which likely require a wildlife or livestock reservoir to maintain the parasite between outbreaks (Welburn et al., 2001).

Since the Great Epidemic of the 1900s in eastern Africa that infected half a million people (Bruce, 1903; Christy, 1903; Hide et al., 1996), periodic sleeping sickness outbreaks have occurred throughout eastern and southern Africa

(Berrang-Ford et al., 2006). Outbreaks tend to occur at historical endemic foci where the parasite appears to persist at endemic levels in the reservoir populations between outbreaks (Welburn et al., 2001; Berrang-Ford et al., 2006). By the 1960s, new case loads had dropped due to prevention methods and medical assistance to these areas (WHO, 1998). However, since the 1960s there has been a resurgence in sleeping sickness cases in certain historic foci, as well as a spread of trypanosomiasis into several new areas (Fèvre et al., 2001; Picozzi et al., 2005), due to the discontinuation of control programs, civil disturbances, and economic problems (Stich et al., 2001). As a result, a recent epidemic of the Rhodesian form of sleeping sickness occurred in Uganda (Fèvre et al., 2005), and outbreaks of Gambian sleeping sickness have occurred in Angola, Sudan, Democratic Republic of Congo, Uganda, and Cameroon (Moore and Richer, 2001; van Nieuwenhove et al., 2001; Abel et al., 2004; Welburn et al., 2006; WHO, 2006). It is unclear what triggered these epidemics, but one hypothesis is that periodic tsetse range shifts expose naive animal and human populations (WHO, 1998). This possibility is relevant because projected changes to the regional climate regime are likely to cause changes in the distribution of certain tsetse species and alter the suitability of the environment for the parasite.

The distribution of different *Glossina* species throughout sub-Saharan Africa appears to be strongly correlated with climate variables (Rogers and Robinson, 2004). The strongest predictor of *Glossina morsitans* distribution in Zimbabwe was the maximum of the mean monthly temperature—correctly predicting the flies' presence/absence over 82% of the country (Rogers and Williams, 1993). *G.*

morsitans is also highly sensitive to changes in mean temperatures; the average temperature difference between areas of fly presence and absence may be less than 1°C (Rogers and Randolph, 1993; Rogers and Robinson, 2004). In West Africa, temperature was the most important variable for describing the distribution of 8 different species of *Glossina* (Rogers et al., 1996), and efforts to predict the distribution and abundance of various *Glossina* species using a combination of temperature, moisture, and vegetation variables derived from remote sensing satellite data typically achieve greater than 80% accuracy (Rogers and Williams, 1993; Rogers et al., 1996; Robinson et al., 1997*a*,*b*; Rogers and Robinson, 2004). The importance of meteorological variables, particularly temperature, in determining tsetse abundance and distribution suggests that climate change will likely alter the distribution of suitable tsetse habitat throughout much of sub-Saharan Africa.

In addition to influencing tsetse range distributions, temperature is also the main abiotic driver of tsetse population dynamics that influence trypanosomiasis epidemiology (Hargrove, 2004). The length of the pupal development period decreases with temperature, while larval production and both pupal and adult mortality increase with temperature above a certain threshold (Hargrove, 2004). Supporting this field-based evidence, laboratory studies of tsetse physiology have also shown that tsetse survival and metabolic rates are temperature-dependent (Terblanche et al., 2005; Terblanche and Chown, 2007; Terblanche et al., 2008). In addition to affecting tsetse distribution and population dynamics, temperature has been shown to influence other important aspects of trypanosomiasis epidemi-

ology, including reservoir host population dynamics and the development time of the trypanosome parasite (Desowitz and Fairbairn, 1955).

Here we focus on modeling R_0 for sleeping sickness, and incorporating the effect of mean annual temperature on the important epidemiological parameters in order to understand the likely impacts of climate change on the geographic range of *T. b. rhodesiense* in Southern and Eastern Africa. The predicted suitable temperature range for *T. b. rhodesiense* is then used to forecast changes to the parasite's range under several climate change scenarios. We assess the degree to which the current distribution of the Morsitans group of tsetse flies overlaps with both the current and future *T. b. rhodesiense* ranges predicted by the model. We also compare the model predictions with the current human population distribution in the region to determine how the human risk of exposure might shift during the 21st century.

3.2 Model

We model the dynamics of trypanosomiasis transmission and infection between the tsetse vector population and the human and animal host populations using an SIR framework (Anderson and May, 1991; Hethcote, 2000). The human and animal host populations consist of susceptible (S_H and S_A) and infected (I_H and I_A) individuals, while the tsetse vector population includes susceptible (S_V), exposed (E_V), and infectious (I_V) individuals. Humans and animals are born into their susceptible classes at per-capita rates b_H and b_A respectively, and we assume

that only uninfected humans and animals reproduce. Susceptible humans become infected with a force of infection, λ_H, and recover from infection and return to the susceptible class at rate, γ_H, which represents the rate of successful treatment of infected individuals. Humans are removed from the population with a per-capita mortality rate, d_H, and infected individuals are subject to an additional disease-induced mortality factor, κ_H. The animal host population demographics and transmission dynamics are identical to human dynamics, except that animal hosts recover from infection at rate, γ_A, and enter the recovered class (R_A), while successfully treated humans re-enter the susceptible class.

$$\begin{aligned}
\frac{dS_H}{dt} &= b_H\, N_H - d_H\, S_H - \beta_H\, S_H + \gamma_H\, I_H \\
\frac{dI_H}{dt} &= \lambda_H\, S_H - d_H\, I_H - \kappa_H\, I_H - \gamma_H\, I_H \\
\frac{dS_A}{dt} &= b_A\, N_A - d_A\, S_A - \beta_A\, S_A \\
\frac{dI_A}{dt} &= \lambda_A\, S_A - d_A\, I_A - \kappa_A\, I_A \\
\frac{dR_A}{dt} &= \gamma_A\, I_A - d_A\, R_A \\
\frac{dS_V}{dt} &= b_V\, N_V - d_V\, S_V - \beta_V\, S_V \\
\frac{dE_V}{dt} &= \lambda_V\, S_V - d_V\, E_V - \mu\, E_V \\
\frac{dI_V}{dt} &= \mu\, E_V - d_V\, I_V
\end{aligned} \tag{3.1}$$

Tsetse flies are born into the susceptible class at rate, b_V, and die from all classes at a rate of d_V. Susceptible tsetse flies are subject to a force of infection, λ_V. Once infected, tsetse flies move into the exposed class and become infectious

at a rate, μ_V, that depends on the parasite's development rate in the fly. Once infectious, we assume that tsetse flies remain in that state for the duration of their lifespan.

Trypanosomiasis transmission to humans occurs with a force of infection, λ_H, that depends on the proportion of susceptible human hosts in the total host population (N_H+N_A), the density of infected tsetse vectors (I_V), the vector biting rate (a), the probability of transmission from tsetse to humans upon contact ($\beta_{V\to H}$), and the relative preference of tsetse flies for human blood meals relative to blood meals from an animal host ($1-\rho$). The force of infection, λ_A, for animal hosts is similar to λ_H, except it depends on the proportion of susceptible animals rather than humans, the probability of transmission from tsetse to animals upon contact ($\beta_{V\to A}$), and the tsetse's preference for animal blood meals (ρ). The force of infection experienced by the tsetse population, λ_V, depends on their biting rate (a), their relative preference for animal and human blood meals (ρ and $(1-\rho)$), the proportions of susceptible human and animals in the total host population, and the probabilities of disease transmission from humans or animals to the tsetse when bitten ($\beta_{H\to V}$ and $\beta_{A\to V}$).

$$\lambda_H = a\,(1-\rho)(\frac{I_V}{N_H+N_A})\beta_{V\to H}$$
$$\lambda_A = a\,\rho\,(\frac{I_V}{N_H+N_A})\,\beta_{T\to A}$$
$$\lambda_V = a\,(1-\rho)(\frac{I_H}{N_H+N_A})\beta_{H\to V} + a\,\rho\,(\frac{I_A}{N_H+N_A})\,\beta_{A\to V}$$

3.2.1 Calculation of R_0 and parameter values

Using the next-generation method described by van den Driessche and Watmough (2002) to calculate the basic reproductive number, R_0, for the model described by equation (3.1), we arrive at the following formulation:

$$R_0 = \sqrt{\left[\frac{a^2\,(1-\rho)^2\,\mu\,N_H\,N_V\,\beta_{H\to V}\,\beta_{V\to H}}{(N_H+N_A)^2\,d_V\,(\mu+d_V)\,(d_H+\kappa_H+\gamma_H)}\right] + \left[\frac{a^2\,\rho^2\,\mu\,N_A\,N_V\,\beta_{A\to V}\,\beta_{V\to A}}{(N_H+N_A)^2\,d_V\,(\mu+d_V)\,(d_A+\kappa_A)}\right]} \tag{3.2}$$

From this formulation, R_0, can be separated into human and animal components:

$$\begin{aligned} R_0^H &= \frac{a^2\,(1-\rho)^2\,\mu\,N_H\,N_V\,\beta_{H\to V}\,\beta_{V\to H}}{(N_H+N_A)^2\,d_V\,(\mu+d_V)\,(d_H+\kappa_H+\gamma_H)} \\ R_0^A &= \frac{a^2\,\rho^2\,\mu\,N_A\,N_V\,\beta_{A\to V}\,\beta_{V\to A}}{(N_H+N_A)^2\,d_V\,(\mu+d_V)\,(d_A+\kappa_A)} \end{aligned} \tag{3.3}$$

Hence, $R_0 = \sqrt{R_0^H + R_0^A}$.

Parameter values were taken from field studies, lab experiments, and other trypanosomiasis models found in the literature (see Table 3.1 for parameter values and Appendix D for details on how these values were selected).

3.2.2 Effect of temperature-dependent parameters on R_0

The effects of climate change on trypanosomiasis (HAT) epidemiology can be determined by examining how climate affects the values of the variables and parameters in equation (3.2) (Rogers and Randolph, 2006). Because $R_0 = 1$

represents an important threshold for parasite invasion and persistence, any influence of climate on R_0 will influence the ability of the parasite to establish in a susceptible host community. Climate-induced changes to the parameters that determine R_0, such as the biting rate (a) or the vector latent period (μ), will have a corresponding effect on R_0. The sensitivity of R_0 to climate change can be examined by analyzing the effect of climate on each parameter value, coupled with the effect that such changes in each parameter value will have on R_0. We initially assume that the only influence of climate changes on HAT will occur due to changes in the mean annual temperature ($\bar{T}$). Tsetse flies are also susceptible to humidity levels (Hargrove, 2004), but the effect of changes in humidity are more difficult to quantify and sparsely documented in the literature. For our analysis, unless otherwise stated, we use the estimates presented in Table (3.1).

Evidence suggests that the vector biting rate (a), vector mortality rate (d_V), and parasite development rate in the vector (μ) are all sensitive to changes in temperature. In addition, the distribution and abundance of different tsetse species are highly sensitive to temperature (Rogers, 1979, 2000; Rogers and Robinson, 2004). Because vector density appears in equation (3.2), any changes to tsetse abundance will also alter R_0. Transmission rates from the vector to human ($\alpha_{V\to H}$) and animal ($\alpha_{V\to A}$) hosts, and from the hosts back to the vector ($\alpha_{A\to V}$, $\alpha_{A\to V}$) may also be affected by temperature, but the data needed to estimate such a relationship is lacking, so we will assume that all transmission rates are constant. The change in R_0 with a change in mean temperature can be determined by the sum of the effects of temperature on each temperature-sensitive

component of R_0 coupled with the corresponding change to R_0:

$$\frac{dR_0}{dT} = \frac{da}{dT}\frac{dR_0}{da} + \frac{dd_V}{dT}\frac{dR_0}{dd_V} + \frac{d\mu}{dT}\frac{dR_0}{d\mu} + \frac{dN_V}{dT}\frac{dR_0}{dN_V}. \tag{3.4}$$

The mathematical relationships between R_0 and the temperature-sensitive biological parameters are as follows:

$$\frac{dR_0}{da} = \frac{R_0}{a}, \tag{3.5}$$

$$\frac{dR_0}{d\mu} = \frac{d_V}{2\mu(\mu + d_V)}\, R_0. \tag{3.6}$$

$$\frac{dR_0}{dd_V} = \frac{-(\mu + 2d_V)}{2d_V(\mu + d_V)}\, R_0. \tag{3.7}$$

$$\frac{dR_0}{dN_V} = \frac{R_0}{\sqrt{N_V}} \tag{3.8}$$

Equations $(3.5 - 3.8)$ indicate that increases in a, μ, or N_V will all have a positive effect on R_0, while an increase in d_V will have a negative effect. However, the quantitative effect of temperature change on R_0 will depend on both the individual relationships of these parameters with temperature and their combined impact within the R_0 equation. While the relationship between R_0 and changes to its various components is relatively straight forward there is a greater deal of uncertainty in determining the relationship between temperature and the various model parameters, because these parameters often incorporate various aspects of the physiology, behavior, and ecology of tsetse flies and their hosts (Leak, 1999). In some cases, the directional effect of temperature can be predicted, but even

for these parameters an accurate quantitative relationship to temperature is typically not available. In the sub-sections that follow we describe the quantitative effects of temperature on several parameters for which plausible estimates can be derived, namely tsetse abundance (N_V), tsetse mortality rates, (d_V), biting rates (a) and the parasite development rate in tsetse (μ). These temperature equations can then be coupled with the appropriate equations ($3.5 - 3.8$) to examine how R_0 is influenced by parameter-specific temperature effects.

3.2.2.1 Tsetse mortality rate, d_V and temperature

Temperature has a nonlinear effect on the mortality rate of tsetse flies; mortality rates are high at both low and and high temperatures with optimal rates occurring at intermediate temperatures (Hargrove, 2004). The relationships between temperature and the mortality rates of *G. pallidipes* and *G. m. morsitans* were determined via a mark-recapture study on Antelope Island, Lake Kariba, Zimbabwe (Hargrove, 2001). Mean temperatures explained the majority of the variance in mortality rates, although the exact relationship between tsetse mortality rates and temperature depends on both the species and sex of the fly. Here we will use the general equation derived by Hargrove (2004):

$$d_V = \frac{e^{k_1 \bar{T} - k_2}}{100}. \tag{3.9}$$

The estimated parameter values were $k_1 = 0.071$ and $k_2 = 0.19$ for *G. m. morsitans* males, $k_1 = 0.083$ and $k_2 = 0.85$ for *G. m. morsitans* females, $k_1 = 0.181$ and $k_2 = 3.50$ for *G. pallidipes* males, and $k_1 = 0.106$ and $k_2 = 1.47$ for *G. pallidipes* females. For *G. pallidipes*, equation (3.9) only applies when $\bar{T} > 24\,^{\circ}\mathrm{C}$, when $\bar{T} \leq 24\,^{\circ}\mathrm{C}$ mortality is assumed to be a constant $d_V = 0.0286$ (Hargrove, 2004). We averaged the male and female estimates of k_1 and k_2 for each species to get species-specific parameter values (Figure 3.1a). The derivative of d_V with respect to temperature ($\bar{T}$) is therefore

$$\frac{dd_V}{d\bar{T}} = \frac{k_1(e^{k_1\bar{T}-k_2})}{100}. \tag{3.10}$$

3.2.2.2 Biting rate, a, and temperature

The biting rate, a, represents the frequency of feeding activity by tsetse flies. As ectotherms, tsetse internal rates of reaction, which affect growth and cellular differentiation, are particularly sensitive to environmental temperatures (Cossins and Bowler, 1987). In lab experiments, Terblanche et al. (2005); Terblanche and Chown (2007); Terblanche et al. (2008) found that the basal metabolic rates of several *Glossina* species increased log-linearly with temperature. Because adult tsetse flies tend to remain inactive in a resting location between blood meals, and only emerge to search for an appropriate host when hungry (Leak, 1999; Hargrove, 2004), we assume that their feeding rate will show the same rate-temperature response as their metabolic rate. Therefore, the slope for the biting

rate-temperature equation is the same as the slope of the relationship between temperature and log metabolic rate for *G. m. morsitans* and *G. pallidipes* over a range of 20 to 32 °C as experimentally determined by Terblanche and Chown (2007):

$$\begin{aligned} \log_{10}(a) &= b + c\bar{T} \\ \frac{da}{dT} &= c\,10^{(b+c\bar{T})}\log(10), \end{aligned}$$

where $c = 0.031$ for *G. pallidipes* and $c = 0.0329$ for *G. morsitans*. The y-intercept, b, is parameterized so that $a = 0.25$ at 21 °C for each species. Although the metabolic rate-temperature response is subject to a maximum tolerance threshold, above which rates can drop rapidly due to enzyme inactivity (van der Have and de Jong, 1996), the maximum temperature of 32 °C in this study is higher than the maximum temperature at which positive population growth rates occur for either species (see Section 3.2.2.4). Therefore, we can justify the assumption of a log-linear relationship between biting rate and temperature over the range of temperatures considered in this article (Figure 3.1b).

3.2.2.3 Parasite development rate, μ, and temperature

An early study by Kinghorn and Yorke (1912) found that the length of the *T. b. rhodesiense* development cycle in *G. morsitans* tended to be negatively correlated with ambient temperatures. A laboratory study by Desowitz and Fairbairn (1955)

found that the development period for *T. vivax* in *G. p. palpalis* decreased in a linear fashion as temperature increased from 21 to 30 °C. By assuming that the recruitment rate of tsetse flies into the infectious class (μ) is 1/(development period), we derive the following equations from Desowitz and Fairbairn (1955)'s experimental data:

$$\begin{aligned} \mu &= 0.00681\,\bar{T} - 0.2833, \\ \frac{d\mu}{dT} &= 0.00681. \end{aligned}$$

We have assumed that the development rate of *T. b. rhodesiense* will show the same quantitative relationship to temperature as *T. vivax* (Figure 3.1c). We also parameterized the y-intercept so that the development rate is $\mu = 0.056d^{-1}$ at 25 °C to match estimates from a laboratory study by Dale et al. (1995).

3.2.2.4 Tsetse density, N_V, and temperature

Mean temperature is one of the key influences on the distribution and abundance of several tsetse species (Rogers, 1979; Williams et al., 1990; Rogers, 2000; Hargrove, 2004; Rogers and Robinson, 2004). Tsetse reproductive, development, and mortality rates are all temperature-sensitive (Hargrove, 2004), so the population growth rate will be influenced by temperature. Here we calculate the population growth rate from these life-table parameters using the Euler-Lotka equation from

Williams et al. (1990):

$$\beta e^{[(\sigma_a - r)\tau_a + (\sigma_b - r)\tau_b + (\sigma_c - r)\tau_c]} = 1 - e^{(\sigma_c - r)\tau_c}. \quad (3.11)$$

The population growth rate, r, depends on the daily survivorship of pupae (σ_a), nulliparous adults (σ_b), and adult flies (σ_c), as well the number of days spent in each of these age classes, τ_a, τ_b, and τ_c respectively. The population growth rate also depends on the fecundity rate (β), which depends on the larval mortality rate, the length of the inter-larval period, and female adult mortality rate. A complete list of the parameters in equation (3.11), and the temperature-response rate of *G. morsitans* for each of these parameters, is included in Table (3.2). We assume that the equilibrium tsetse density is directly correlated to the average population growth rate, with the maximal equilibrium density occurring when the growth rate is maximized and a zero density if the population growth rate is negative for a given mean annual temperature. The density at other temperatures is calculated by scaling density proportional to the maximum density based on the growth rate relative to the maximum growth rate (Figure 3.1d).

3.2.3 Model analysis

The relationships between R_0 and temperature described in equations (3.5-3.11) were entered into equation (3.4) to calculate the temperature range where $R_0 > 1$ with either *G. m. morsitans* or *G. pallidipes* acting as the primary vector for *T.*

b. rhodesiense. Here we only examine the current range of *T. b. rhodesiense* in Eastern and Southern Africa (Hide et al., 1996; Hide, 1999; Welburn et al., 2001), excluding the range of *T. b. gambiense* in Central and Western Africa. Hide (1999) identified 14 specific areas (referred to as foci) in Southern and Eastern Africa where sleeping sickness outbreaks have occurred since 1900. To validate the results regarding the sensitivity of R_0 to temperature we examined whether the current mean annual temperatures at these known sleeping sickness foci fell within the predicted suitable range for *T. b. rhodesiense*. The annual mean temperature from 1950-2000 was taken for each historical foci from the appropriate 2.5 arc-minute grid in a dataset compiled by Hijmans et al. (2005). The 2.5 arc-minute spatial dataset of 1950-2000 mean annual temperatures was then used to create a map of the suitable range for *T. b. rhodesiense* in Eastern and Southern Africa. All spatial analyses were conducted using ArcGIS 9.3 (ESRI; San Diego, CA USA). Because the parasite has a slightly wider temperature range when vectored by *G. pallidipes* (see Results), all spatial predictions use the temperature range calculated with *G. pallidipes* as the vector.

The map of the predicted suitable range for *T. b. rhodesiense* was compared to a map of the predicted areas of suitability for the Morsitans group of tsetse flies created by Wint and Rogers (2000). The Morsitans group consists of tsetse species in the subgenus *Glossina* s.s.: *G. morsitans*, *G. pallidipes*, *G. austeni*, *G. longipalpis*, and *G. swynnertoni* (Jordan, 1993). The Morsitans dataset provides a map of the probability of occurrence rather than presence/absence, so for our analysis we used a probability of occurrence of 75% as a threshold for

presence/absence. We calculated the percentage of the current Morsitans range predicted to also be suitable for *T. b. rhodesiense*, as well as the proportion of tsetse habitat either too cold or too hot for the parasite.

Future climate conditions were recreated using results from two general circulation models (GCMs) included in Fourth Assessment Report of the IPCC (2007). For the GCMs developed by the Hadley Centre (HadCM3) and the National Center for Atmospheric Research (CCSM3) we examined two greenhouse gas emissions scenarios: a moderate scenario with intermediate population and economic growth estimates and modest emission controls leading to emissions peaking at mid-century (B1) and a more extreme scenario with high global population, slow economic growth, and slow technological changes (A2) (IPCC, 2007). For each GCM and emissions scenario we used the 20-year mean annual temperature for two periods: 2046-2065 and 2080-2099. The future climate datasets have a coarser spatial resolution (2.5 x 3.75 degrees for HadCM3 and 1.4 x 1.4 degrees for CCSM3) than the current climate dataset; therefore, we overlaid the future temperature anomalies over the current climate layer to create a future climate data layer with a spatial resolution of 2.5 arc-minutes. We then determined the predicted suitable geographic range for *T. b. rhodesiense* for the periods 2046-2065 and 2080-2099 under the A2 and B1 emissions scenarios by averaging the results from the HadCM3 and CCSM3 GCMs. We also examined the proportion of the current Morsitans range that will become too hot for the parasite under each of these scenarios. Because our model does not provide a prediction of how tsetse distributions will shift we present results regarding the parasite's range

expansion without making any assumptions about whether the vector will also shift its geographic distribution.

The number of people currently living within the suitable temperature range for *T. b. rhodesiense* was calculated using population estimates provided in the Gridded Population of the World (Balk et al., 2006). We have assumed here that the human population size and distribution will remain constant because future population estimates are not yet available at the spatial resolution of our model. Population counts at a spatial resolution of 2.5 arc-minutes were overlaid with current mean annual temperatures, and the future climate scenarios, in order to estimate the number of people currently at risk, the number of additional people who could be at risk under the projected warming scenarios, and the number of people living in regions that will likely become too hot for sustained HAT transmission under the various future climate projections.

3.3 Results

Based on the relationships between mean annual temperature and the four temperature-sensitive parameters in equation (3.4), the temperature range where $R_0 > 1$ for *T. b. rhodesiense* is predicted to be 20.7 - 26.1 °C with *G. pallidipes* as the primary vector species (Figure 3.2). The suitable temperature range for *G. morsitans* is similar but narrower, with $R_0 > 1$ when the mean annual temperature is 20.9 - 25.6 °C. A maximum R_0 of 1.51 occurs at 24.0 °C with *G. pallidipes*, and a maximum R_0 of 1.24 occurs at 23.6 °C with *G. morsitans*. Twelve of the

14 historical foci fall within the predicted current suitable range for *T. b. rhodesiense* (Figure 3.3). The two foci outside of the suitable range are in Gambela and Gilo, Ethiopia where the last major epidemics occurred in 1967 and 1970 respectively (Hide, 1999). The mean annual temperature at both of these foci is 27.6 °C, 1.5 degrees warmer than the predicted maximum suitable mean annual temperature of 26.1 °C. However, this region has already experienced an increase of > 1°C in mean annual temperatures since 1960, which may partially explain their exclusion from the suitable range.

Our model predicts an expansion in the suitable geographic range of *T. b. rhodesiense* for the 20-year period 2045-2064 of 10.4% (B1 emission scenario) or 11.5 % (A2 emissions scenario). Both of these predicted expansions are due to moderate shifts in the suitable geographic range (Figure 3.4a). Under the B1 scenario, 20.2% of the current suitable range will become too hot by 2055, while 27.7% of the future range is in areas currently too cold for the parasite. The range shift by 2055 is even larger under the A2 scenario, with a loss of 31.4% of the current range and 38.4% new habitat in 2055. The predicted suitable geographic range for *T. b. rhodesiense* shifts even further by 2080-2099. Under the B1 scenario, the geographic range in 2090 is an additional 1.3% larger than the 2055 range, an expansion of 11.8% from the current range. By 2090, 27.8% of the current range will be too hot for *T. b. rhodesiense* under the B1 scenario, and 35.4% of the 2090 range represents new habitat. The more severe A2 emissions scenario is predicted to lead to a decrease in the size of the suitable geographic range by 2090 (Figure 3.4b). The extent of the predicted range in 2090 is only

85.2% of the current suitable range size, a decrease of 23.6% from the predicted 2055 range. 68.5% of the current suitable range is predicted to be too hot by 2090 and 63.0% of the 2090 range under the A2 scenario is in areas that are currently predicted to be too cold to support an $R_0 > 1$ for *T. b. rhodesiense*.

84.2% of the predicted geographic distribution for the Morsitans group of *Glossina* also has a suitable temperature for sustained *T. b. rhodesiense* transmission. 10.4% of the Morsitans distribution is colder than the suitable temperature range for *T. b. rhodesiense*, and 5.4% is currently too hot. The percentage of the Morsitans distribution with annual mean temperatures suitable for *T. b. rhodesiense* decreases under both the B1 and A2 emissions scenarios, with larger declines occurring under the A2 scenario. Under the B1 scenario, the suitable proportion of the Morsitans distribution falls to 71.1% in 2055 and 64.6% by 2090. Under the A2 scenario, the suitable portion is 58.6% in 2055 and 29.7% in 2090, with over 70% of current Morsitans habitat becoming too hot for *T. b. rhodesiense* by 2090. Under both scenarios the portion of unsuitable habitat is almost entirely areas that will become too warm, only the B1 scenario in 2055 predicts that more than $> 1\%$ of the current Morsitans geographic range will still be too cold (1.5%) for *T. b. rhodesiense*.

None of the historical foci (besides the two in Ethiopia) are predicted to become too hot for *T. b. rhodesiense* by 2055 under the B1 emissions scenario, and only the South Luangwa Valley focus in Zambia is predicted to be too hot in 2055 under the A2 emissions scenario. The South Luangwa focus is also the only one of the foci predicted to be outside the 2090 range under the B1 scenario.

However, under the A2 emissions scenario as many as 10 of the 14 foci may become too hot for *T. b. rhodesiense* by 2090.

Although there isn't a large increase in the predicted geographic range of *T. b. rhodesiense* under the forecasted warming scenarios, the predicted range shift does correspond to a significant increase in the number of people potentially exposed to the parasite. 75.7 million people live within the current potential range of *T. b. rhodesiense*, but over 97.9 and 108.8 million people live within the projected range for 2055 under the B1 and A2 emissions scenarios respectively. In addition, over 105 million people live within the projected range for 2090 under both emissions scenarios. For 2090, this includes 46.4 (B1) to 76.7 (A2) million people within the expanded portion of the range who are not currently predicted to be at risk of infection according to our model.

3.4 Discussion

Climate change, particularly global warming, is already altering habitat quality, species distributions, biodiversity, and many essential ecosystem services (Parmesan and Yohe, 2003; Root et al., 2003; Parmesan, 2006). In the Northern hemisphere species distributions are shifting northward at a rate of 6.1km per decade and upwards in elevation by 6.1m per decade (Parmesan and Yohe, 2003). Climate warming over the next century is also expected to have a large impact on the interactions between pathogens and their animal and human hosts (Harvell et al., 2002; Pascual and Bouma, 2009). Our model results indicate that projected

increases in mean annual temperatures over the next 50-100 years are likely to significantly shift the distribution of *T. b. rhodesiense* in Eastern and Southern Africa. These shifts in distribution may lead to an increase in the number of people at risk of infection.

The suitable geographic range for *T. b. rhodesiense* based on mean annual temperatures is predicted to increase 10-11% by 2055. However, by the end of the century the extent of the suitable range is predicted to be 85-111% its current size depending on assumptions about future GHG emissions. The greatest amount of warming is predicted under the A2 emissions scenario (an increase of 3.4 °C in the global mean temperature by 2090; IPCC, 2007), which our model predicts will lead to a 15% decrease in the geographic extent of the suitable range by 2090. This occurs because 68.5% of the current suitable range becomes too hot for the parasite. Due to regional variation in the GCM predictions, some areas in southern Africa are actually predicted to go from being too cold at current temperatures (<20.7 °C), to being too hot by 2090 (>26.1 °C). The more modest temperature increases projected for 2055, or under the B1 emissions scenario through 2090, are predicted to result in small expansions in the size of the parasite's suitable geographic range. While our model does not predict a major expansion or contraction in the suitable range for *T. b. rhodesiense*, our results suggest that there may be a significant shift in the geographic areas at risk of HAT outbreaks.

Although many recent studies have predicted that the geographic ranges of vector-transmitted pathogens will expand due to global warming (e.g. Epstein,

2000), Lafferty (2009) suggests that shifts in the suitable range for pathogen transmission and persistence are more likely than large range expansions. The relationship between climate and habitat suitability for vector-transmitted pathogens is likely to be convex because important epidemiological parameters exhibit nonlinear, or contrasting, responses to changes in temperature or other climatic variables. For example, our model predicts that tsetse population growth rates and tsetse abundance show a unimodal response to temperature, with the highest growth rates occurring at intermediate temperatures (Figure 3.1). Our results in this study largely support Lafferty (2009)'s hypothesis as the model predicts a large shift in the geographic range of *T. b. rhodesiense* due to a considerable contraction of the existing range and a corresponding expansion into new areas. These results suggest that the modeling framework presented here could be an important tool used to predict whether the geographic distributions of other infectious diseases are likely to expand, contract, or undergo range shifts under different climate change scenarios.

Even if the size of the geographic range does not increase significantly, range shifts can lead to changes in the number of people at risk of exposure and disease incidence. For example, Pascual and Bouma (2009) point out that the highland plains in East Africa are the most densely populated region on the continent; therefore an upwards shift in the suitable elevation range for malaria would lead to a large increase in the number of people exposed to the disease. This parallels our finding that between 22-33 million additional people live in the projected future suitable range for *T. b. rhodesiense* as compared to its current suitable

range. This projected shift upwards in elevation for trypanosomiasis is of particular concern because the East African highlands have higher population densities partly because of their lower risk of infectious diseases such as malaria and trypanosomiasis that are more common in the lowlands. In addition, the expansion of trypanosomiasis into areas containing immunologically-naive wildlife and domestic animal populations could lead to increased transmission rates and a greater risk of spillover from animal reservoirs to humans (Dobson, 2009).

The projected suitable geographic ranges for *T. b. rhodesiense* presented here represent the broadest possible extent of the parasite's distribution, and not the predicted distribution, because the distribution of the parasite is dependent on abiotic and biotic factors other than the mean annual temperature. In particular, the parasite is obviously limited to regions where tsetse flies are present. Although mean temperatures are an important determinant of tsetse distributions (Rogers and Williams, 1993; Rogers and Robinson, 2004), tsetse abundance can also be influenced by many other environmental factors such as relative humidity, minimum and maximum temperatures, and vegetation (Rogers and Williams, 1993; Rogers et al., 1996; Robinson et al., 1997*a*; Wint and Rogers, 2000; Rogers and Robinson, 2004). Only 32.2% of *T. b. rhodesiense's* current suitable geographic range—as predicted by our model—is considered likely *Glossina* habitat (Wint and Rogers, 2000). However, we have presented the entire possible geographic range of the parasite for comparison to it's projected ranges in 2055 and 2090 because we do not have predictions of how tsetse distributions will shift in the future, and we do not want to limit our analysis to current tsetse distributions.

If tsetse distributions do not adjust to future climate conditions, then reductions in the potential geographic range of *T. b. rhodesiense* are likely to be significant. We predict that 27-41% of current tsetse habitat in Eastern and Southern Africa will be too hot to sustain the parasite by 2055, and 35-70% will be too hot by 2090. However, tsetse are unlikely to be limited by their dispersal ability (Hargrove, 2004), so it is likely that they will be able to shift the elevational and latitudinal extents of their range in regions with suitable climate and habitat conditions. The projected geographic ranges of *T. b. rhodesiense* presented here should be considered as preliminary risk maps, in areas of particular concern an assessment of the current and forecasted habitat conditions should be conducted to determine whether future environmental conditions are likely to support both the parasite and its vector(s).

In addition to the presence of at least one *Glossina* species, *T. b. rhodesiense* also requires the presence of animal reservoir hosts (Welburn et al., 2004). Because *T. b. rhodesiense* cannot be sustained solely by human-fly-human transmission, humans are only at risk if their is a sufficient abundance of potential reservoir hosts (Welburn et al., 2006). Therefore, the predicted suitable temperature range for the parasite will also be limited by reservoir host distributions. Wildlife hosts were traditionally assumed to be the major reservoir because many wildlife species were thought to be highly trypanotolerant (Murray et al., 1982; but see Onyango et al., 1966; Ford, 1971 for early counterexamples), but domestic livestock have also been implicated as reservoirs in several recent outbreaks of Rhodesian sleeping sickness (Wellde et al., 1989*a*; Hide et al., 1996; Hide,

1999; Waiswa et al., 2003; Picozzi et al., 2005). In rural areas where land use changes have led to increased contact rates between wildlife and domestic livestock, local populations of wildlife and livestock may jointly serve as reservoirs (Welburn et al., 2006). In addition to cattle, in some regions of East Africa such as south-eastern Uganda, pigs, goats, and sheep may also play a role in the epidemiology of Rhodesian sleeping sickness (Waiswa et al., 2003). The improved use of trypanocidal drugs and insecticides in regions such as Uganda has helped lead to an increase in the number of livestock, but caution needs to be taken as the suitable geographic range for *T. b. rhodesiense* shifts into currently trypanosomiasis-free regions. Rhodesian sleeping sickness outbreaks in Eastern and Southern Africa have historically been limited to rural areas (Hide, 1999); however, there have recently been several outbreaks of Gambian sleeping sickness in Central and West Africa in more densely populated areas, particularly in peri-urban areas surrounding Kinshasa, DRC (Simo et al., 2006). Although *T. b. rhodesiense* is more reliant on reservoir hosts for sustained transmission, the risk of transmission could increase in certain regions under future climate conditions. Our model predicts a shift towards regions with higher population densities in Southern Africa and the highlands of East Africa. If tsetse species can shift their distributions as conditions become favorable these more densely populated regions that also have large livestock populations may be at particular risk of Rhodesian sleeping sickness outbreaks.

One particular concern is that a shift in the distribution of Rhodesian sleeping sickness in East Africa could lead to an overlap in the ranges of *T. b. rhodesiense*

and *T. b. gambiense* (Picozzi et al., 2005). Although the geographic distribution of the two trypanosome subspecies are currently distinct, recent shifts in the range of *T. b. rhodesiense* in Uganda—likely due to the movement of infected livestock—have brought their ranges to within 150 km of each other (Picozzi et al., 2005). Convergence of the two forms of sleeping sickness would have important implications for the diagnosis and treatment of the disease, because the treatment of the diseases differs and current diagnostic methods may be insufficient to appropriately distinguish between them before treatment commences (Welburn et al., 2001; Picozzi et al., 2005). Our model indicates that the mean annual temperatures in the region between the two parasite subspecies is currently suitable for *T. b. rhodesiense*, indicating that current temperatures are not a barrier to the continued expansion of the parasite's geographic range. However, under the A2 emission scenario our model predicts that parts of central and western Uganda will be too hot by 2055, and almost the entire northern 2/3 of the country will be too hot by 2090. This may not prevent the persistence of *T. b. rhodesiense* in Uganda however, because our predictions are based only on transmission by tsetse flies in the Morsitans group. The northern shore of Lake Victoria in Uganda is one of the few areas in East Africa where *G. fuscipes fuscipes* of the Palpalis group is present, and this species may be able to adapt better to warmer mean annual temperatures (Wint and Rogers, 2000).

The effects of climate change on human African trypanosomiasis and other diseases are likely to occur on several fronts and vary in both degree and direction, often in a non-additive fashion (Rogers and Randolph, 2006). Using

parameters related to vector and parasite biology can help refine predictions of disease prevalence and risk due to climate change. This approach has the potential to not only identify regions of risk as we have done here, but also assess the levels of risk based on R_0 values. By formulating a model, one can provide a framework to explore the effects of the complex processes involved in parasite transmission and epidemiology in a systematic manner. Our results show that combining the effects of climate change on different parameters involved in human African trypanosomiasis epidemiology is essential to obtaining a more comprehensive understanding of the overall effect of climate change on disease risk. By incorporating the effects of temperature on several key parameters (tsetse density, mortality, and feeding activity, and trypanosome development rate in tsetse flies), we forecasted how trypanosomiasis epidemiology might respond to changes in mean annual temperature in Eastern and Southern Africa.

3.5 Acknowledgements

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Table 3.1: SIR Model variables, parameters and default estimates used to calculate R_0. All rates are day^{-1}. See text for parameter estimate sources.

Name	**Description**	**Estimate**
N_H	Total human population size	1000
N_V	Total animal population size	2000
N_A	Total tsetse population size	60000^a
b_H	Natural human birth rate	$1/(365 * 40)$
d_H	Natural human death rate	$1/(365 * 40)$
κ_H	Additional mortality rate of infected humans	$1/108$
γ_H	Recovery rate of infected humans	0
b_A	Natural birth rate of animal host	$1/(365 * 2)$
d_A	Natural death rate of animal host	$1/(365 * 2)$
κ_A	Additional mortality rate of infected animals	0.0008
γ_A	Recovery rate of infected animals	$1/120$
d_V	Natural death rate of tsetse	$0.041^{a,b}, 0.030^{a,c}$
μ_V	Parasite maturation rate in tsetse	$1/18^a$
ρ	Relative tsetse preference for animal hosts	25
a	Tsetse biting rate	0.25^a
$\alpha_{V\to H}$	Prob. of transmission upon contact from tsetse to human	0.0083
$\alpha_{V\to A}$	Prob. of transmission upon contact from tsetse to animal	0.0083
$\alpha_{H\to V}$	Prob. of transmission upon contact from human to tsetse	0.0355
$\alpha_{A\to V}$	Prob. of transmission upon contact from animal to tsetse	0.0355

[a]For parameters that are temperature-dependent, value in table is for a mean annual temperature of 25 °C. [b]*G. m. morsitans.* [c]*G. pallidipes.*

Table 3.2: Parameters used to calculate *Glossina morsitans* population growth rate and density as a function of the mean annual temperature ($\overline{T}$). Reference column includes references used to estimate parameter values and their sensitivities to temperature.

Param.	**Description**	**Temperature Response**	**Reference**
β	Fecundity rate	$\beta = e^{(-d_L * \tau_c)}$	Williams et al. (1990)
d_L	Larval mortality rate	$d_L = 0.01 * 10^{(-0.829+0.055*\bar{T})}$	Hargrove (2004)
σ_a	Pupal survival rate	$\sigma_a = 0.995$	Williams et al. (1990); Hargrove (2004)
σ_b	Nulliparous survival rate	$\sigma_b = 1 - .015 * e^{(.083*\bar{T}-0.85)}$	Hargrove (2004)
σ_c	Adult survival rate	$\sigma_c = 1 - (.01 * e^{(.083*\bar{T}-0.85)})/3$	Hargrove (2004)
τ_a	Length pupal period (d)	$\tau_a = (1 + e^{(4.88-0.216*\bar{T})})/0.05884$	Phelps and Burrows (1969), Hargrove and Williams (1998), Hargrove (2004)
τ_b	Nulliparous period (d)	$\tau_b = 1/(0.061 + (0.002 * (\bar{T} - 24)))$	Hargrove (1994, 2004)
τ_c	Length adult lifespan (d)	$\tau_c = 1/(0.105 + (0.0052 * (\bar{T} - 24)))$	Hargrove (1994, 2004)

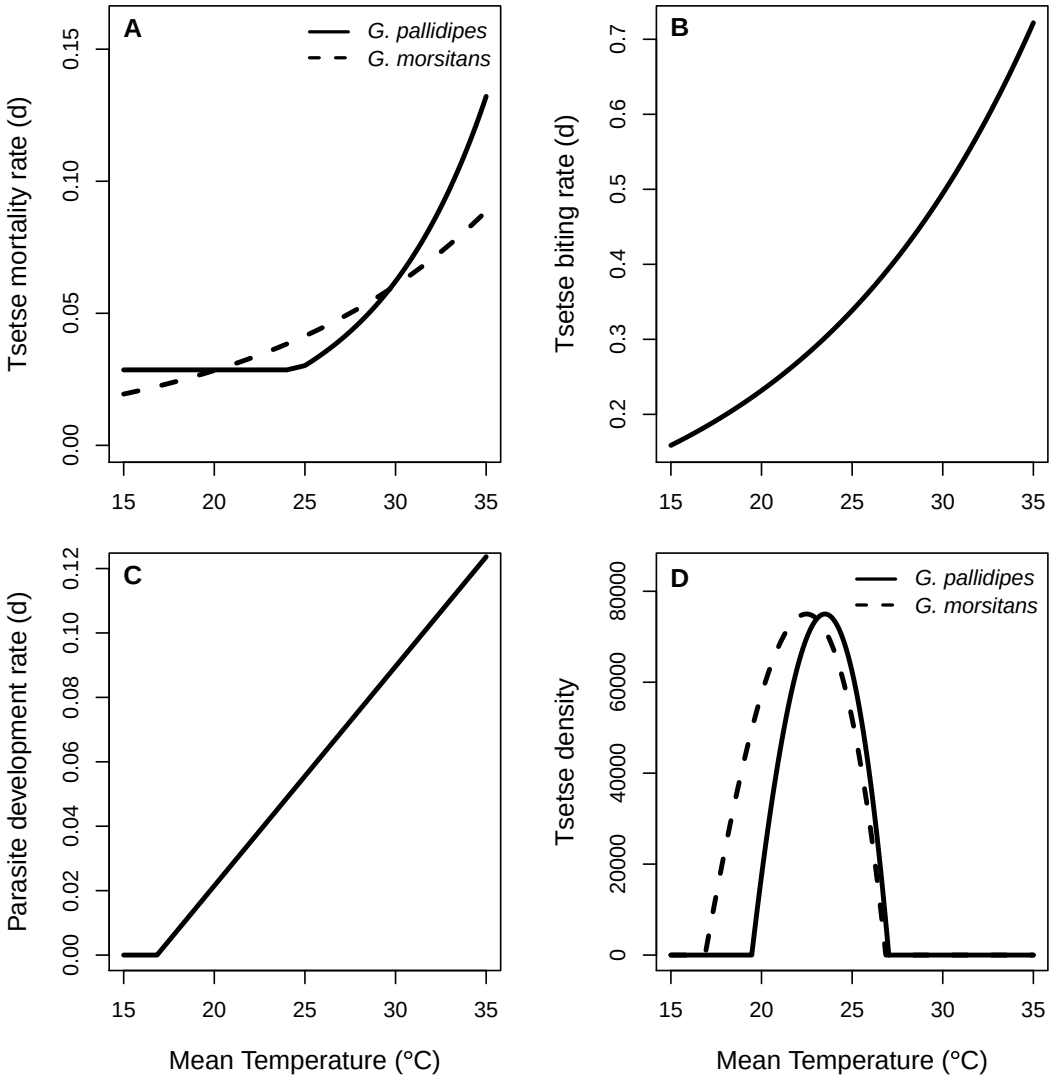

Figure 3.1: Relationship between temperature and four different parameters that influence R_0. The (A) daily mortality rate of *G. m. morsitans* and *G. pallidipes* (d_V), (B) tsetse daily feeding rate (a), (C) daily rate of parasite development in tsetse (μ), and (D) *G. m. morsitans* and *G. pallidipes* abundance (N_V) as a function of mean annual temperature.

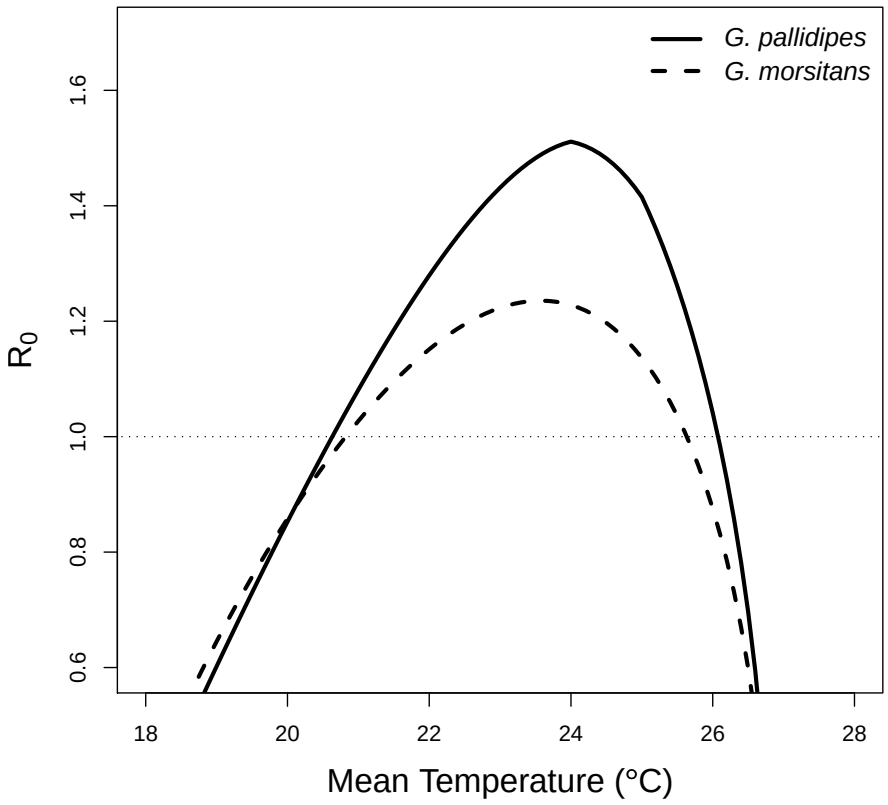

Figure 3.2: Relationship between temperature and R_0 when *T. b. rhodesiense* is vectored by *G. m. morsitans* or *G. pallidipes*. $R_0 = 1$ represents a threshold for the successful invasion or persistence of the parasite into a susceptible host community.

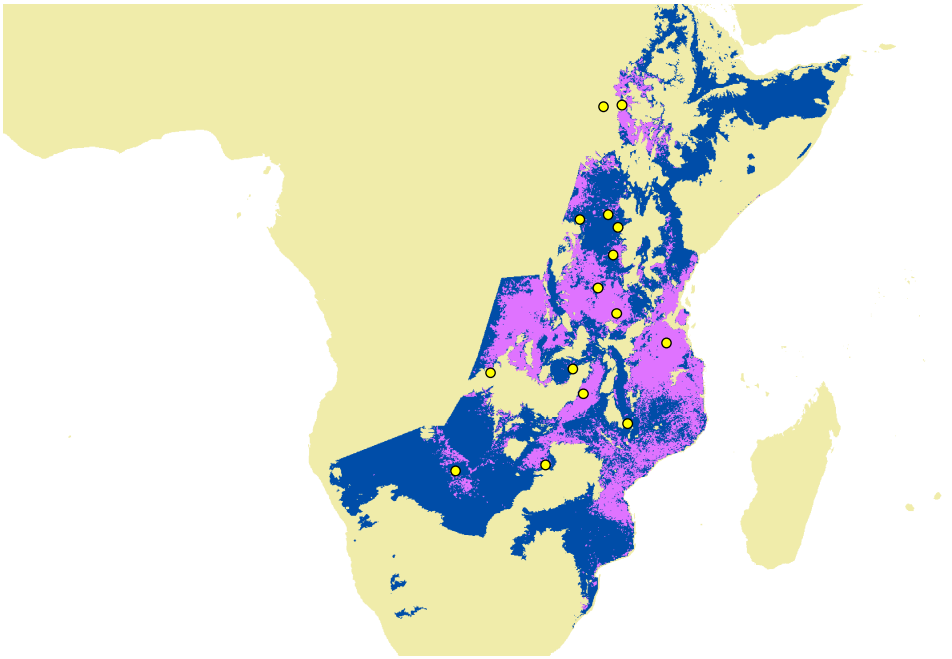

Figure 3.3: Suitable geographic range for *T. b. rhodesiense* transmission based on range where $R_0 > 1$ for *G. pallidipes*. The purple region represents the portion of the range also predicted to be ideal habitat for Morsitans group tsetse flies. Blue represents the portion of the suitable range currently believed to be unoccupied by Morsitans group tsetse flies. Yellow circles represent locations of previous HAT outbreaks in East Africa (see Hide (1999)).

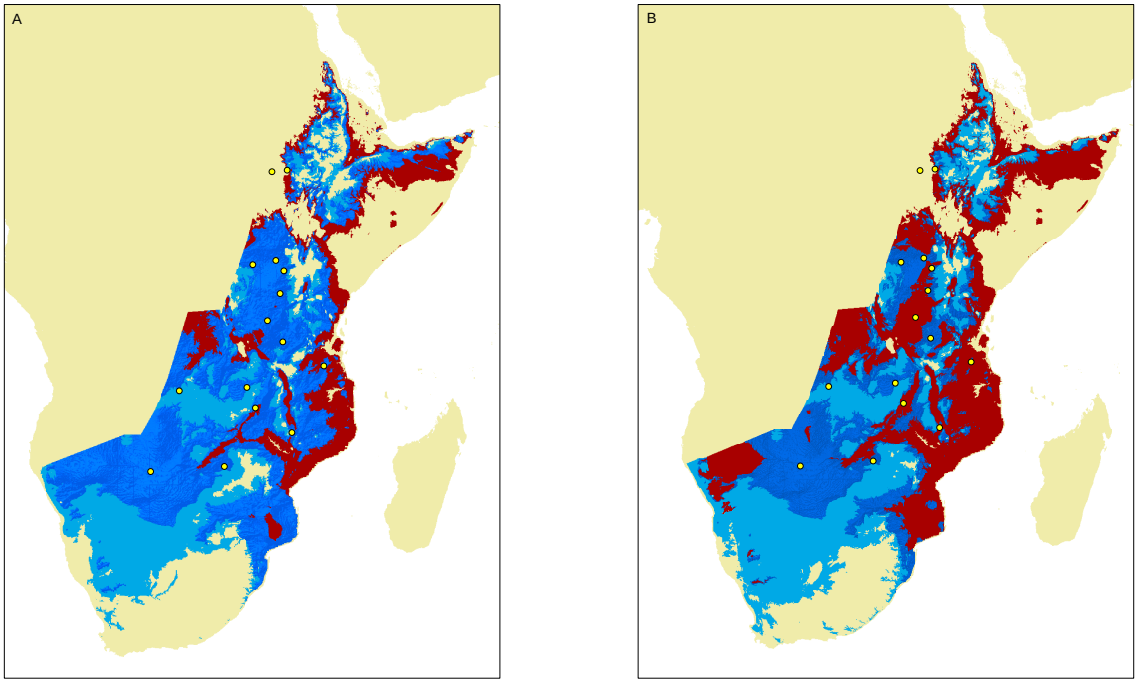

Figure 3.4: Suitable geographic range for *T. b. rhodesiense* transmission in (a) 2055 and (b) 2090 under the A2 emissions scenario using the CCSM3 global circulation model. The predicted range is colored blue, with light blue representing the newly expanded portion of the predicted range and dark blue representing the existing part of the range. Red areas on the map represent currently suitable areas predicted to be too hot under future conditions. Yellow circles represent locations of previous HAT outbreaks in East Africa (see Hide (1999)).

Habitat fragmentation and host composition control the spread of multi-host pathogens: synthesis of spatial heterogeneity and disease dynamics

Sean M. Moore

Chapter 4 – Habitat fragmentation and host composition control the spread of multi-host pathogens: synthesis of spatial heterogeneity and disease dynamics

Abstract

Landscape structure can affect the spread and persistence of pathogens in a variety of ways. Habitat fragmentation can lead to the aggregation of hosts into discrete patches or alter dispersal of infectious hosts or vectors between populations, which can dramatically affect the dynamics of infectious diseases. Heterogeneity in community composition and movement patterns of different host species among landscape fragments will also influence the spread and persistence of generalist pathogens that infect multiple host species. Here we develop a multi-host, multi-patch metapopulation disease model to identify the potential effects of landscape connectivity, patch heterogeneity, and host community composition on the initial spread, prevalence, and persistence of multi-host pathogens at the patch and regional scales. We review recent empirical findings for multi-host pathogens of animals and plants and use our model to examine ways in which spatial heterogeneity may influence disease dynamics in real communities. For example, habitat fragmentation generally changes host community composition, as well as the heterogeneity of habitat patches and connectivity patterns; these, in turn can influence the prevalence of zoonotic diseases such as Lyme disease, han-

tavirus, and West Nile virus in wildlife communities and, therefore, their spillover risk to human populations. We use our model to examine how the correlation of host traits associated with resistance to fragmentation, host quality and dispersal ability may affect the invasion and spread of multi-host pathogens in fragmented landscapes.

4.1 Introduction

Spatial patterns of disease spread and incidence are a frequently observed phenomenon in epidemiology and ecology (Grenfell et al., 2002; Ostfeld et al., 2005; Plantegenest et al., 2007). The simplest disease transmission models assume spatial homogeneity of the host population(s), with disease transmission determined by the mean contact rate between individuals in a population (Anderson and May, 1991). However, spatial heterogeneity in the distribution and movement patterns of the host population can lead to heterogeneity in disease transmission and prevalence. Host populations are often spatially structured, with frequent contact among individuals within a local population or subpopulation, and less frequent contact between individuals in different subpopulations (Grenfell and Harwood, 1997; Hess et al., 2002; Keeling et al., 2004). For multi-host pathogens, differential host species' responses to environmental heterogeneity and landscape structure, mediated by species interactions, will generate spatial heterogeneity in the presence and abundance of multiple species across a landscape. Therefore, the spread and persistence of pathogens that infect multiple host species also will

be influenced by heterogeneities in the community composition and movement patterns of different host species.

Pathogens capable of infecting multiple host species are quite common, including ~60% of known human pathogens and over 80% of the pathogens of domestic animals (Cleaveland et al., 2000; Taylor et al., 2001; Woolhouse and Gowtage-Sequeria, 2005). The majority of emerging diseases, including Lyme disease, West Nile Virus, Ebola, and Avian Influenza, are caused by zoonotic pathogens that infect both humans and wildlife or domestic animals (Taylor et al., 2001). Many pathogens of livestock also infect one or more wildlife species (Cleaveland et al., 2000), and many pathogens responsible for wildlife diseases can also infect multiple host species (Dobson and Foufopoulos, 2000). Infectious diseases that have been implicated in the decline or extinction of endangered species are typically multi-host pathogens that are maintained in a reservoir host(s) when the target population is too small (Gog et al., 2002; McCallum and Dobson, 2002; de Castro and Bolker, 2005; Smith et al., 2006). Recently a lot of attention has also been focused on how biodiversity can influence disease dynamics, witha particular emphasis on zoonotic pathogens such as Lyme disease and West Nile virus. Higher host diversity may cause a dilution effect, whereby increasing host species richness lowers prevalence and reduces the risk of spillover to humans (Ostfeld and Keesing, 2000; Keesing et al., 2006). Even in studies that have demonstrated an effect of species diversity, community composition is often a more important determinant of disease prevalence than species richness alone (Mitchell et al., 2002; LoGiudice et al., 2003; Keesing et al., 2006; Kilpatrick et al., 2006*b*). The

importance of community composition highlights the need to determine how different species traits influence the ecology and epidemiology of multi-host systems (Dobson, 2004; LoGiudice et al., 2008).

Traditional epidemiological models ignore the spatial dimension of disease transmission by assuming that every individual in a population is equally likely to contact every other individual resulting in a mean-field approximation or "mass effects" transmission term (homogeneous mixing; Anderson and May 1991; McCallum et al. 2001). However, the spread of infectious disease epidemics, as well as spatial patterns of disease incidence, are influenced by the spatial structure of host populations. Host distribution patterns are influenced by abiotic conditions and patterns of landscape connectivity, and many host species are spatially distributed in patches that influence disease spread and pathogen persistence (Hess et al., 2002). Metapopulation theory provides a framework for linking the dynamics of spatially separated populations of both pathogens and hosts at multiple spatial scales (Grenfell and Harwood, 1997; Hess et al., 2002; Keeling et al., 2004). The host metapopulation is divided into a set of smaller local populations located within a network of discrete patches with differing within-patch and between-patch disease transmission rates. This framework can be used to investigate the effects of local and regional-scale dynamics on host and pathogen populations, and the effects of patch isolation and coupling on disease epidemics and pathogen persistence (Keeling et al., 2004). Fragmented habitat, and particularly anthropogenic fragmentation, is an important source of heterogeneity for

host distribution and movement patterns that can influence disease transmission and persistence.

Epidemiological studies incorporating spatial dynamics and landscape heterogeneity have largely been limited to host-pathogen metapopulation models representing pathogens that are specialists on a single host (Grenfell and Harwood 1997; but see Keeling and Gilligan 2000; Rushton et al. 2000; Tompkins et al. 2003; Arino et al. 2005; Craft et al. 2008). The dynamics of generalist pathogens that can infect multiple host species will also depend on the relative spatial structure of the different host populations and cross-species transmission dynamics. Host species can differ in their susceptibility to a disease and their competency in transmitting the disease to other hosts. Host movement patterns due to foraging, dispersal, or migration will also vary, and respond differently to changes in the structure and composition of the landscape. Therefore the within-patch host community composition—as well as the relative abundances of the host populations and their spatial arrangement within a patch network—can influence the transmission and persistence of a pathogen. The presence of a highly susceptible host species can lead to a local epidemic with spillover to other host species, while the presence of a host with a low reservoir competency can lead to reduced disease prevalence (Grenfell and Harwood, 1997; LoGiudice et al., 2003; Keesing et al., 2006). If a generalist pathogen is vector-transmitted then host species may differ in their contact with, and effect on, the vector population, as well.

Here we review the potential effects of landscape structure/connectivity, patch heterogeneity, host community composition, and isolation on the spread and persistence of multi-host pathogens. First we develop a deterministic, patch-based spatial disease model to examine the factors related to spatial heterogeneity and host community composition that influence the initial invasion of pathogen, as well as its longer-term persistence. Using the model, we identify parameters and variables related to patch-level and regional-level host community composition, and between-patch connectivity, which determine pathogen prevalence and persistence at the patch and regional scales. Connectivity between patches of suitable habitat depends on the movement rates of different host and vector species, mediated by the effects of landscape structure and fragmentation on species' movement rates. We review recent research on various multi-host pathogens, and provide specific examples of how spatial heterogeneity influences dynamics in different disease systems.

4.2 Methods

4.2.1 Multi-patch, multi-host model

To examine several of the ways in which spatial heterogeneity can affect the persistence and prevalence of multi-host pathogens, we analyze a deterministic multi-species metapopulation model based on a model formulated by Arino et al. (2005).

Within-patch dynamics are represented using a set of susceptible-infected-recovered (SIR) equations for each patch, and patches are linked via host or vector movement among patches. A given system with h host and vector species and n patches can be represented by a set of $h \times n$ SIR equations:

$$\begin{aligned} \frac{dS_{ip}}{dt} &= b_i(N_{ip})N_{ip} - \beta_{ip}(N_i)S_{ip}I_p - d_iS_{ip} + M_i(S_i) \\ \frac{dI_{ip}}{dt} &= \beta_{ip}(N_{ip})S_{ip}I_p - (d_i + \delta_i + \gamma_i)I_{ip} + M_i(I_i) \\ \frac{dR_{ip}}{dt} &= \gamma I_{ip} - d_iR_{ip} + M_i(R_i). \end{aligned} \tag{4.1}$$

Here S_{ip} represents the density of susceptible individuals of species i in patch p. Likewise, I_{ip} and R_{ip} represent the density of infectious and recovered individuals of species i in patch p respectively. Therefore, the total density of species i in patch p is $N_{ip} = S_{ip} + I_{ip} + R_{ip}$, and the total density of species i across all n patches is $N_i = \sum_{p=1}^{n} N_{ip}$. Although within-patch transmission dynamics appear similar to the basic SIR model (Anderson and May, 1991; Hethcote, 2000), the presence of multiple hosts and patches necessitates additional complexities. Disease transmission is represented by the function $\beta(N_i)$, which encompasses both within- and between-species transmission, and $M_i(N_i)$ is a function representing the movement of species i among patches (see Appendix E for full details of the model).

4.2.2 Patch and regional-level invasion and persistence

Successful invasion and spread of a pathogen requires that the disease-free equilibrium (DFE) be locally unstable when a pathogen is introduced into a susceptible host population or community (Hethcote, 2000). This scenario is typically examined by determining the pathogen's basic reproductive number, R_0, defined as the number of secondary infections produced from an initial infectious individual in an otherwise susceptible population. If $R_0 < 1$, the number of secondary infections produced per infectious individual will be insufficient to sustain the continued propagation of the pathogen. In a multi-host, multi-patch system, R_0 is a function of host demographic parameters, the epidemiological parameters related to disease transmission and recovery, and host movement rates. Arino et al. (2005) derived the R_0 equation for a multi-host, multi-patch model similar to equation (4.1) using the next-generation matrix method (Diekmann et al., 1990; van den Driessche and Watmough, 2002). The large number of equations needed to describe even a moderate number of patches makes it difficult to display the R_0 equation in a succinct form. However, we know from the next-generation method that R_0 will be a function of the epidemiological and demographical parameters included in the disease transmission model described in equation (4.1). We examine how R_0 depends on host community composition, patch heterogeneity, and connectivity between patches.

Using the condition $R_0 < 1$, Arino et al. (2005) proved that if one patch is at a stable DFE, then all patches connected directly or indirectly will also be disease-

free. Similarly, if one patch is at endemic equilibrium, then all patches will be at a positive endemic equilibrium. Since the deterministic model requires that all connected patches are either disease-free or at a non-zero endemic equilibrium, it is appropriate for examining highly prevalent diseases (e.g. Lyme disease, West Nile virus) that tend to persist in local patches. However, isolated patches may remain disease free.

We focus on communities with two host types: reservoir hosts that can harbor persistent infections and efficiently transmit to other species, and spillover hosts in which infection does not persist without regular re-infection and transmission is less efficient. Reservoir hosts have an individual $R_0 > 1$, while spillover hosts have an individual $R_0 < 1$ and are incapable of sustaining a pathogen invasion in the absence of additional host species (Haydon et al., 2002).

4.3 Results and Discussion

4.3.1 Spatial heterogeneity in host community composition

Heterogeneous host composition among patches leads to disease spillover from high to low quality areas (quality is defined here in terms of the R_0 for the pathogen) via host movement from patches with higher proportions of competent reservoir hosts to patches with higher proportions of less competent spillover hosts (Figure 4.1). Thus, the regional context is a critical component of local disease incidence and prevalence levels. This is seen in Lyme disease where preva-

lence varies at the local, regional, and continental scales, with high variability among patches occurring even in endemic regions in the northeastern United States (Glavanakov et al., 2001; Chen et al., 2005; Killilea et al., 2008). This local-scale variation in prevalence is at least partially due to the effects of fine scale heterogeneity in habitat quality on host community composition, but host movement among habitat types may also play a role (Buskirk and Ostfeld, 1998).

In addition to Lyme disease, the risk of exposure to humans for many other zoonotic diseases—such as Chagas disease, leishmaniasis, African trypanosomiasis, hantavirus pulmonary syndrome, and West Nile virus—depends on the local and/or regional abundance of reservoir hosts (Ostfeld et al., 2005). Spatial heterogeneity in WNV incidence can be explained, in part, by the diversity and composition of the bird community (Ezenwa et al., 2006; Kilpatrick et al., 2006*b*; Ezenwa et al., 2007; Bradley et al., 2008; Swaddle and Calos, 2008; Allan et al., 2009), which is strongly associated with the composition of habitat types in the landscape (Ezenwa et al., 2007; Bradley et al., 2008). While local vector and host community composition appears to be an important determinant of WNV incidence, the ability of many avian host species to travel long distances suggests that larger scale factors are also likely to be important (Rappole et al., 2000; Peterson et al., 2003; Owen et al., 2006; Mundt et al., 2009).

A fungal pathogen, *Batrachochytrium dendrobatidis*, has recently spread rapidly to amphibian populations around the world causing the disease chytridiomycosis and leading to the extinction of several species (Berger et al., 1998; Lips et al., 2006; Skerratt et al., 2007; James et al., 2009). Amphibian species differ in their

susceptibility to infection (Blaustein et al., 2005), and the American bullfrog in particular has been implicated as a potential facilitator for the geographic spread of the fungus because of its wide distribution and apparent capacity to serve as a reservoir for the pathogen (Daszak et al., 2003). The distribution of infection within a region is not evenly distributed among ecological guilds, with stream-breeding species, and to a lesser extent pond-breeders, having the highest prevalence levels (Lips et al., 2003; Kriger and Hero, 2007). Our model highlights that local disease risk is likely to be a function of local host composition and regional landscape connectivity, and applied to the chytrid system could help determine whether prevalence patterns are driven by local host composition or patterns of connectivity between local communities.

Although plants are sessile, natural and cultivated plant communities exist in spatially heterogeneous landscapes and host species are often distributed in patches that influence pathogen persistence and disease spread, particularly via vector movement. Landscape composition—defined as the relative frequencies of different types of habitat (including different types of agriculture) patches—affects the global pathogen pressure experienced by hosts at the local scale (Plantegenest et al., 2007). In addition, landscape structure and heterogeneity also can influence the spatiotemporal dynamics of disease spread (Plantegenest et al., 2007). For example, Fabre et al. (2005) found that the proportion of infectious aphids that transmit barley and cereal yellow dwarf viruses (B/CYDV) to cereal crops increased with the ratio of crop land planted as small grains to maize within a 50 km radius surrounding a suction trap. In this study, regional host composition

was as important as local composition in determining local pathogen prevalence. The prevalence of B/CYDV is increased by the presence of long-lived perennial grasses that can serve as reservoir hosts for the pathogen (Henry and Dedryver, 1991; Borer et al., 2009). Host community composition is also important for B/CYDV prevalence in natural grassland communities as there are large differences in host competency and vector preference among hosts with different life history traits (Malmstrom et al., 2005; Borer et al., 2007). Another multi-host plant pathogen that has been shown to be influenced by landscape composition is bean dwarf mosaic virus (BMDV). BMDV is transmitted by whiteflies and can infect soybeans, but does not cause any symptoms, but causes a severe disease in common bean plants. An increase in soybean acreage in Argentina led to the emergence of BMDV that threatened local common bean production (Morales and Anderson, 2001). As predicted in Figure (4.1), the landscape-scale composition of the host community is an important determinant of both B/CYDV and BMDV prevalence in local patches when pathogen dispersal between patches occurs relatively frequently due to vector movement.

It is already appreciated that the spatial distributions of almost all infectious diseases are heterogeneous due to environmental or other factors (Ostfeld et al., 2005); however, these results suggest that it is important to consider heterogeneities at multiple scales when attempting to explain local prevalence patterns or predict disease risk at a fine scale. In particular, host or vector movement between habitats with different species compositions can substantially affect the

spread of disease among habitats and may determine the locally realized infection prevalence.

4.3.2 Connectivity patterns and host traits – Pathogen invasion (R_0)

The effect of host movement ($M_i(N_i)$) on pathogen invasion (R_0) depends on both the frequency of movement and the identity of the host with the highest movement rate. In particular, when the density of the reservoir host varies among patches, increasing its movement rate causes a decline in R_0 (Figure 4.2a). When emigration of infected individuals out of the largest (source) patch exceeds the return of infected individuals into the patch, there is a net loss of infection at the local scale, making it harder for the pathogen to succesfully initiate an epidemic. However, if the density of the less competent host is highly variable among patches, then increasing the movement rate of the spillover host can cause a larger reduction in R_0 than increasing the movement of either the reservoir host only or both hosts (Figure 2b). This will occur when the density of the less competent host is high enough in at least one patch to make its individual contribution to R_0 larger than the contribution from the reservoir host. This model component reflects important characteristics of a variety of pathogens.

One of the most important questions regarding *Yersinia pestis*—the plague bacterium—is how it spreads and persists at the landscape scale in different rodent communities around the globe (Gage and Kosoy, 2005). In the United States, plague epizootics occur irregularly in prairie dog colonies, but the mech-

anism(s) of spread among colonies and long-term persistence of the pathogen are still uncertain (Cully Jr. and Williams, 2001). Within a metapopulation framework, Stapp et al. (2004) found that the probability of an individual colony's extinction due to plague was related to the colony's size (with intermediate-sized colonies the most resistant to extinction) and the fate of adjacent colonies. The landscape structure surrounding host communities is also important, with roads, streams and lakes serving as barriers that slow the spread of plague among prairie dog colonies (Collinge et al., 2005), and low-lying drainages serving as dispersal corridors between colonies (Antolin et al., 2006). In a black-tailed prairie dog metapopulation in Montana, Snall et al. (2008) also found that larger colonies were more likely to be infected, but colony size did not influence its infectiousness to other colonies.

Interestingly, prairie dog movement does not appear to drive the spread of plague at the landscape scale (Snall et al., 2008), suggesting that alternative hosts are responsible for the maintenance and spread of the pathogen in prairie dog colonies. Recent evidence suggests that grasshopper mice may facilitate the spread of *Y. pestis* during plague epizootics, and the mice or other hosts may serve as vector and/or pathogen reservoirs between epizootics (Stapp, 2007; Stapp et al., 2009), although a metapopulation model questions the need for an additional reservoir species (George and Webb, *In review*). The dynamics of plague in prairie dogs suggests the importance of interactions among potential host species on its spread and persistence as a function of landscape connectivity, patch heterogeneity, and host composition. Prairie dog population sizes vary

among colonies, so according to Figure (4.2a), regional plague epidemics are more likely to occur if pathogen dispersal occurs via the movement of host species that are less competent than the highly susceptible prairie dogs.

The spread of the foot and mouth disease (FMD) within wildlife and between domestic animals and wildlife is also influenced by the distribution and movement patterns of the various potential host species (Thomson et al., 2003). African buffalo in South Africa are believed to be a reservoir for FMD virus, and contact patterns between buffalo and impala and the subsequent movements of impala have influenced the spread of multiple FMD epidemics in impala populations (Bastos et al., 2000). Contact patterns between domestic livestock and Saiga antelope are also an important determinant of FMD dynamics in Central Asia (Morgan et al., 2006). Although the antelope doesn't appear to be a permanent reservoir for FMD, its long-distance migration may spread the virus to poorly- or un-vaccinated livestock populations in the region. Figure (4.2a) suggests that pathogen invasion and persistence is actually more likely when movement between patches is by a non-reservoir species, such as the Saiga antelope, rather than by the more competent host species. Even though the spread of FMD among farms in the UK is not dependent on host dispersal patterns of infection, the geographic spread of FMD during the 2001 UK epidemic was dependent on the spatial distribution, size and species composition of individual farms because sheep and cattle differ in their susceptibility and ability to transmit the virus (Keeling et al., 2001).

4.3.3 Connectivity patterns and host traits – Local and regional prevalence

While increasing host movement rates tends to decrease R_0, the effect of host movement on local and regional pathogen prevalence is more complex. Host movement always increases prevalence in sink patches (where $R_0 < 1$), while the impact of host movement on prevalence in high quality (source) patches depends on the identity of the host species responsible for the majority of movement between patches. In a situation with a source and sink patch coupled by host movement, increasing the movement rate of all hosts will lead to a decrease in regional prevalence (Figure 4.3). Increasing the movement rate of the spillover host will lead to an increase in regional prevalence, while increasing the reservoir host's movement rate first decreases, but then increases, prevalence. Figure (4.3) shows that the decrease in regional prevalence when both hosts move is caused by a small increase in prevalence in the sink patch but a large decrease in prevalence in the source patch. Movement by the spillover host increases regional prevalence because it increases prevalence in both patches. Movement by the reservoir host increases prevalence in the sink patch while decreasing prevalence in the source patch, with the effect of movement on regional prevalence determined by the relative strengths of these two effects.

Observational and experimental studies of Lyme disease incidence in humans and infection prevalence in the blacklegged tick, *Ixodes scapularis*, (the primary vector in eastern North America) have highlighted the importance of habitat distribution and connectivity for Lyme disease (LD) dynamics. Buskirk and Ostfeld

(1998) observed that habitats with high densities of adult ticks relative to earlier nymphal densities had higher LD prevalence levels in adult ticks. According to Figure (4.3), this could occur because hosts are dispersing out of high quality (source) patches. Tick abundances are positively correlated with connectivity to high quality habitat (Estrada-Peña, 2002), suggesting that host movement patterns are important determinants of tick distribution, and potentially the transmission of Lyme disease and other tick-borne pathogens. In New York State, Lyme disease incidence rates are spatially autocorrelated at distances up to 120 km (Glavanakov et al., 2001). Coupled with studies showing variation in tick densities and infection prevalence between local habitats (Buskirk and Ostfeld, 1998; Allan et al., 2003; LoGiudice et al., 2003; LoGiudice et al., 2008), this spatial autocorrelation suggests an important role for host movement and habitat connectivity in determining tick abundances and human disease risk. Habitat fragmentation also plays an important role in the Lyme disease system (see Section 4.3.5 on Habitat fragmentation).

Host movement patterns are also an important determinant of regional-scale patterns of prevalence for many ungulate diseases because host species often have large home ranges or migrate seasonally. The risk of cross-species transmission of brucellosis in Montana and Wyoming between wildlife and livestock appears to depend on the movement patterns of both bison and elk (e.g. seasonal movement of bison out of park, elk migratory behaviors). Local heterogeneity in the risk of spillover from bison, the reservoirs in this case, to livestock, the spillover hosts, in the Greater Yellowstone area depends on environmental factors and bison

densities (Dobson and Meagher, 1996; Kilpatrick et al., 2009). Near Yellowstone NP, in the National Elk Refuge in Wyoming, patterns of elk aggregation due to seasonal movements and supplemental feeding are the predominant determinants of seroprevalence in elk (Cross et al., 2007*a*, 2010). This increase in prevalence in areas of high elk density (source patches) could lead to increasing levels of prevalence in areas of low elk density (sink patches) as occurs in Figure (4.3).

Patterns of bovine tuberculosis infection in southern Africa are influenced by the distribution and movement patterns of buffalo, antelope, and other ungulate species (Renwick et al., 2007). In regions with stronger control efforts in domestic cattle, such as Europe and New Zealand, there has been considerable controversy over whether certain wildlife species serve as reservoir hosts for *Mycobacterium bovis*. In the UK, badgers are believed to be a reservoir for *M. bovis* (Krebs, 1997); however, badger culling operations have not successfully controlled the spread of bovine TB (Donnelly et al., 2003; Woodroffe et al., 2005). Although badger culling has had some success in reducing bovine TB cases in cattle at the local level, it also increases the home range sizes of badgers, thus increasing contact rates between badgers and cattle, and contributing to the continued spread of the pathogen (Tuyttens et al., 2000; Donnelly et al., 2006; Woodroffe et al., 2006). This is similar to the increase in prevalence that occurs in sink patches with high densities of spillover hosts when the movement rate of reservoir hosts out of source patches is increased. The social structure and movements of badgers also are important for the prevalence and spread of bovine TB within badger populations in a region not subject to culling (Vicente et al., 2007).

Patterns of host distribution and movement are also likely to be important determinants of the prevalence of transmissible spongiform encephalopathies (prion diseases), such as chronic wasting disease (in deer, elk, and moose), bovine spongiform encephalopathy (cattle), and scrapie (sheep and goats). Because CWD prions shed from an infected animal's saliva can persist in the environment for extended periods (Miller et al., 2004; Johnson et al., 2006), cross-species transmission may occur where host species distributions overlap. In addition, the long incubation and infectious periods of CWD may also facilitate spread via host movement. Several studies have examined the spatiotemporal dynamics of CWD in mule deer (Conner and Miller, 2004; Farnsworth et al., 2005; Miller and Conner, 2005; Farnsworth et al., 2006) and white-tailed deer (Joly et al., 2006; Osnas et al., 2009). Miller and Conner (2005) established that CWD prevalence was increasing at multiple spatial scales in Northern Colorado. In addition, Farnsworth et al. (2006) found evidence that the spatial distribution of prevalence was best explained by fine scale mixing of individual mule deer rather than larger-scale seasonal movement patterns. Although prevalence in this area appears to be primarily influenced by local-scale interactions, Conner and Miller (2004) did find that mule deer movement patterns appeared to explain prevalence differences between population units. Identifying which host species is more likely to spread the pathogen via dispersal or migration could help explain infection patterns because our model indicates that the identity of the host species primarily responsible for spreading a pathogen has important implications for regional- and local-scale prevalence.

4.3.4 Connectivity patterns and host traits – Rates of spread

Higher movement rates by host species will also tend to increase the rate of disease spread in a patchy system. If highly competent hosts have the highest movement rates, then the disease will spread faster than if low competency hosts have higher movement rates (Figure 4.4). Knowing the absolute and relative movement rates of different host species can be important for forecasting the spread of a pathogen when it is introduced into a new area or an area with a large number of susceptible hosts.

The spread and prevalence of rabies in different carnivore species is a well-documented example of the effect of spatial heterogeneity and landscape connectivity on disease transmission (Childs et al., 2000; Real and Biek, 2007). Local heterogeneities in landscape structure and connectivity (e.g. rivers, mountains, highways, forest) affect the movement patterns of rabies hosts, and can help inform control strategies (Murray et al., 1986; Lucey et al., 2002; Smith et al., 2002, 2005; Russell et al., 2005, 2006). Although spillover to other host species occurs during epidemics, it does not appear that these spillover hosts play a large role in determining the patterns of spread and prevalence of raccoon or fox rabies in the US or Europe. Our model indicates that spillover host movement rates would have to be considerably faster than reservoir movement rates to influence the spread of rabies (Figure 4.4), and this does not appear to be the case in the US. However in Africa, the spillover of rabies from domestic dogs into various wildlife hosts can cause outbreaks, with potential implications for conservation and ecosystem health (Cleaveland et al., 2007; Lembo et al., 2008). These re-

sults suggest that the movement patterns of alternative hosts, as well as spatial heterogeneity in host community composition, are important for the spread and spillover dynamics of rabies in this region. Spillover dynamics may also influence the long-term maintenance of the disease, which is particularly significant for the development of control strategies in the reservoir or threatened populations. In Ethiopia, Haydon et al. (2006) used knowledge of the movement patterns among Ethiopian wolf subpopulations to design a rabies vaccination strategy to protect this endangered species against rabies epidemics following a spillover event.

Canine distemper virus (CDV) is another multi-host pathogen that is believed to have spilled over from domestic animals into wildlife populations in Africa and elsewhere, leading to several epidemics (Deem et al., 2000). The spread of CDV through African lion prides in Serengeti National Park in the 1990s likely occurred due to the movement patterns of hyenas and jackals that also carry the disease (Craft et al., 2008, 2009). In addition, like rabies, the epidemic is believed to have originated from domestic dog populations outside the park, making it critical to understand connectivity patterns between wildlife populations and the human settlements surrounding the park. The spread and persistence of CDV in the Greater Yellowstone Ecosystem also depends on interspecific transmission and the spatial connectivity among host populations (Almberg et al., 2010). Craft et al. (2008) found that introducing high interspecific transmission rates always increased the velocity of the CDV spread rate, but when interspecific coupling was weak, the pathogen could actually spread slower than it would with a single host. Similar to the predictions from our model, spread rates were highest when

hyenas and jackals were included because they have higher between-population transmission rates (equivalent to between-patch transmission) than lions. presence of jackals or lions

The spatial distribution of host populations, and movement patterns among these populations, also played an important role in several recent outbreaks of phocine distemper virus (PDV) and canine distemper virus (CDV) in marine mammals (Swinton et al., 2002). Swinton et al. (1998) showed that the rapid spread of PDV during a 1988 epidemic in harbor seals, and its subsequent fadeout, was partially a function of the spatial structure and strength of coupling between subpopulations of harbor seals at haul-out sites. PDV outbreaks in harbor seals may also depend on the rate of cross-species transmission with harp or grey seals, which is a function of the movement and contact patterns of each seal species (Duignan et al., 1995; Harkonen et al., 2006). In addition, recent declines in Arctic sea ice coverage may have increased the movement of seals in the Arctic, leading to the transmission of PDV to Alaskan sea otters, which threaten to introduce the pathogen into immunologically naive seal and sea lion populations in the Pacific (Goldstein et al., 2009). Our model suggests that the pattern of spread for future PDV epidemics will depend on which host species has the highest movement rate between populations or haul-out sites; therefore it is important to determine whether potential reservoir hosts could also act as rapid spreaders in a spatial context.

The geographic spread of Ebola virus outbreaks in human populations has been influenced by landscape structure, with rivers altering the direction of spread

(Walsh et al., 2005). Connectivity patterns between separate social groups of different ape species are important for transmission (Bermejo et al., 2006). Geographic spread among primates appears to be based on seasonal feeding patterns that lead to close contact between con-specific individuals from different social groups, and potentially other species as well (Caillaud et al., 2006; Walsh et al., 2007). Ebola virus does not persist in human or ape populations following outbreaks, and several species of fruit bats are believed to serve as reservoirs for the virus (Leroy et al., 2005). Little is currently known about contact patterns between these bat species and other susceptible species, and whether the recent geographic spread of Ebola is due to the movement of bats or other wildlife species is also unknown. Multi-host models incorporating host-specific movement patterns could provide additional insights into the potential mechanisms of cross-species transmission within the reservoir host community and between the reservoir hosts and species of concern such as gorillas, chimpanzees, and humans. Our model suggests that the presence of a reservoir species, such as fruit bats, with high movement rates can increase the rate at which the disease spreads geographically.

The spread of multi-host pathogens can also influence the interactions among host species, potentially altering their geographic distributions. A parapox virus is believed to have facilitated the invasion of the North American grey squirrels and replacement of native red squirrels in the UK (Rushton et al., 2000; Tompkins et al., 2003). The virus is highly pathogenic in red squirrels, but the presence of antibodies and a lack of symptoms in grey squirrels suggest they may serve

as a reservoir host for the virus (Sainsbury et al., 2000; Tompkins et al., 2002*b*). Simulations by Rushton et al. (2000) showed that the probability of extinction for red squirrel populations in Norfolk, UK was significantly related to the rate of grey squirrel expansion via dispersal. The effect of host identity on the spread rate of a multi-host pathogen in Figure (4.4) suggests that it is also important to examine which host species is more likely to spread the pathogen via dispersal or migration.

At a global scale, the spread of avian influenza has been influenced by both the poultry trade and migratory birds (Kilpatrick et al., 2006*a*). Kilpatrick et al. (2006*a*) determined that migratory birds were responsible for spreading H5N1 to most European countries, but imported poultry was likely responsible for introducing the pathogen from Southeast Asia to the Western hemisphere, with subsequent spread within North America occurring via a mixture of the poultry trade and the migration of wild birds. They suggest that in areas with high risk for spillover of H5N1 from migratory birds, control efforts should be directed towards preventing contact between local poultry and migratory birds (in affect altering local host composition and contact rates). Host identity is also important for the spread of H5N1; mallards in particular have been identified as a potential long-distance vector of the pathogen due to a combination of their dispersal ability and role as carriers of the virus (Keawcharoen et al., 2008).

Peterson et al. (2003) used information on the known winter and summer distributions of over 100 migratory bird species to look at the potential spread of West Nile virus over large geographic areas. Although studies conducted over

large spatial scales have found evidence of a dilution effect arising from host species diversity (Ezenwa et al., 2006; Allan et al., 2009), a finer scale study conducted in Chicago, Illinois found no effect of species richness on WNV prevalence (Loss et al., 2009). Figure (4.4) suggests that an examination of the correspondence between smaller-scale movement patterns of mosquitoes or particular host species with annual spread of WNV at local or regional levels could be a fruitful future direction.

Determining how the distribution and movement of host species influence the transmission of multi-host pathogens is also a critical concern in marine systems (Harvell et al., 2004). Identifying mechanisms of pathogen dispersal and connectivity patterns between populations is especially important because the spatial spread of disease in aquatic systems can be very rapid (McCallum et al., 2003). For example, the salmonid sea louse, *Lepeophtheirus salmonis*, is currently threatening many wild salmon populations due to the spillover of high parasite levels from farmed salmon populations (Krkosek, 2010). Host movement patterns are critical to transmission dynamics of these parasites, as the vulnerable juveniles of wild anadromous populations usually do not encounter large numbers of parasites until parasitized adults return to spawn (Krkosek et al., 2007*b*). However in areas with salmon farms, juveniles may encounter farmed species with high parasite burdens earlier in development; early parasitism may decrease juvenile survival leading to population declines (Krkosek et al., 2007*a*).

Two other marine systems that are likely to be patchy are coral reefs and marine reserve systems. McCallum et al. (2005) showed that the effect of a marine

reserve on host and pathogen populations depends on host movement between the reserve and the rest of the population. The role of host movement is likely to be even more important when multiple marine protected areas are combined into a reserve network. While the movement of infected hosts is typically not relevant for coral diseases, the spatial structure of reef systems and composition of the susceptible coral community are important for pathogen spread and persistence. For example, an outbreak of white plague, which infects a range of hard coral species, exhibited metapopulation dynamics in the Florida Keys, with pathogen colonizations and fadeouts occurring regularly at a number of sites within the region (Sokolow et al., 2009).

4.3.5 Habitat fragmentation

If fragmentation increases the number of available patches without decreasing the average host population size in each patch, then fragmentation will not affect R_0 when there is no host movement between patches (Figure 4.5a). However, increasing the host movement rates will lead to a decline in R_0, with a minimum value set by the R_0 in a single patch with a host population size equal to the mean size. If the total regional population size of each host is fixed, then increasing the number of patches via fragmentation will lead to progressively smaller local patch host population sizes. Under this scenario, R_0 will remain constant as fragmentation increases if within-patch disease transmission is frequency-dependent, but decline if it is density-dependent (Figure 4.5b).

As fragmentation of a habitat occurs, the species richness in that habitat is often reduced (Fahrig, 2003). For a host community where species richness declines from five to one as the habitat is fragmented from one continuous patch into 10 separate patches, the effect on the pathogen's R_0 depends on whether the species loss is random with respect to both host quality (as measured by the individual R_0 for that host) and dispersal ability (Figure 4.6). The reduction in R_0 due to fragmentation is much greater when species are lost randomly with respect to their quality as hosts as compared to when higher quality species are the most resistant to fragmentation. In addition, R_0 declines the fastest when the species resistant to fragmentation also have the highest movement rates. R_0 declines the least when hosts that are resistant to fragmentation have the lowest movement rates. Note that R_0 always declines with species loss because we have assumed that there is no effect of different host species on the density or encounter rates of other host species. If we assume that removing one host species leads to an increase in the encounter rates or density of the remaining species (Keesing et al., 2006), then R_0 may increase with increasing fragmentation, particularly for the scenarios where the most competent hosts are also resistant to fragmentation (cf. Ostfeld and LoGiudice, 2003).

Habitat fragmentation, in conjunction with habitat loss, is believed to be the leading cause of species declines and extinction (Stein et al., 2000). Habitat fragmentation is likely to have a particularly strong effect on multi-host pathogens because of changes in the regional and local host community composition in addition to changes in connectivity. As species are extirpated from the local

community due to fragmentation, multi-host pathogens are likely to experience a shift in the composition of available hosts (McCallum and Dobson, 2006). The loss of less competent host species from a community may lead to a reversal of the dilution effect. Because the loss of species due to fragmentation is often nonrandom, species' traits related to their dispersal ability or quality as hosts may correlate with their resistance to fragmentation.

One of the clearest and best studied examples of the effect of habitat fragmentation on disease risk is for Lyme disease in the Northeast United States (Buskirk and Ostfeld, 1998; Allan et al., 2003; Brownstein et al., 2005; LoGiudice et al., 2008; Killilea et al., 2008; Ostfeld, 2009*a*). Allan et al. (2003) found that the size of forest fragments was inversely correlated with both nymphal tick density and nymphal infection prevalence (NIP). These results occurred due to host community composition shifts that occur in highly fragmented forests. Small forest fragments have increased densities of the most competent reservoir, the white-footed mouse, and fewer less-competent host species to dilute prevalence in the vector (LoGiudice et al., 2008). Because NIP is a key indicator of human infection risk, these studies suggest that highly fragmented landscapes will have higher prevalence in the wildlife reservoir community and an increased spillover risk to humans. In a study in suburban Connecticut, Brownstein et al. (2005) also found a positive correlation between fragmentation and both tick density and infection prevalence in ticks. However, they also found a significant negative relationship between the human incidence of Lyme disease and mean patch isolation distance, and a positive relationship between human incidence and mean

patch size. Although more fragmented landscapes had higher entomological risk (as measured by NIP), this doesn't necessarily translate to increased incidence in humans.

Extinction risk due to fragmentation in the potential host community for Lyme disease is non-random Ostfeld and LoGiudice (2003); LoGiudice et al. (2008). The most highly-competent hosts—white-footed mice, eastern chipmunks, and short-tailed shrews—are all widespread species in the region and abundant in fragmented habitat, while less-competent hosts tend to be the first species lost from the community when fragmentation or another disturbance occurs LoGiudice et al. (2003); LoGiudice et al. (2008). Models that calculate NIP based on the composition of the local host community and the LD competency of each host in the community have been able to predict observed NIP values with a reasonable accuracy LoGiudice et al. (2008). However, there is still more variability in the observed data than would be predicted based on local community composition suggesting that landscape configuration and host movement between sites may influence prevalence. For example, Buskirk and Ostfeld (1998) showed that dispersal via host movement could influence the spatial heterogeneity of tick density and NIP. In addition to differing in their competency and resistance to fragmentation, LD host species will also have different movement rates in a fragmented landscape. It is possible that species that are less competent hosts for LD than the white-footed mouse, such as chipmunks, squirrels or birds, might enhance the spread of LD between forest fragments due to their movement pat-

terns. Figure (4.6) suggests that the movement of these less competent hosts could actually enhance LD risk in a fragmented landscape.

Habitat fragmentation may also alter hantavirus dynamics in both North and South America. Both the percentage of suitable habitat and the amount of habitat fragmentation were shown to influence the prevalence of Sin Nombre virus in deer mice populations in Canada (Langlois et al., 2001). In Panama and South America, Suzán et al. (2008) found that habitat fragmentation affected rodent species diversity, and that the two rodent species that are highly competent reservoirs for the hantavirus were more abundant in fragmented habitat. Habitat fragmentation was implicated as a potential cause of an outbreak of hantavirus pulmonary syndrome in Panama (Ruedas et al., 2004). Ruedas et al. (2004) found that species diversity was lower in these fragmented areas, and observational studies in other regions have also found that higher rodent diversity is associated with lower prevalence of hantaviruses in the reservoir host population or community (Suzán et al., 2008; Tersago et al., 2008; Dizney and Ruedas, 2009). In addition, Suzán et al. (2009) experimentally reduced rodent diversity in Panama and found that less diverse communities containing reservoir hosts were associated with higher hantavirus prevalence. Although Suzán et al. (2009) collected data on various landscape characteristics to compare control and manipulated sites, they do not mention whether any of these characteristics influenced hantavirus prevalence. In addition, to our knowledge studies have not looked at whether differential host movement rates between patches in fragmented habitat influence prevalence patterns.

Habitat fragmentation and deforestation has led to increased incidence of Chagas disease (causative agent, *Trypanosoma cruzi*) in humans in some regions of South America (Patz et al., 2000). Recent research has found that small mammal diversity is lower in fragmented habitats, while the abundance of marsupials that serve as reservoirs is higher (Vaz et al., 2007). Because many of the small mammals are inferior hosts for *T. cruzi* compared to opossums, fragmentation may reduce the dilution potential provided by host diversity (Roque et al., 2008). Indeed, Vaz et al. (2007) found higher seroprevalence in the wildlife host community of the Atlantic rainforest of Brazil within fragmented habitat as compared to continuous forest. Spatial heterogeneity and fragmentation are also important determinants of the distribution and abundance of *Triatoma infestans*, which serves as the primary vector for *T. cruzi* in peridomestic areas. Spraying efforts to control *T. infestans* populations at the local scale have failed because the vector can rapidly recolonize from unsprayed areas (Cecere et al., 2006; Kitron et al., 2006). Our model suggests that it would be useful to relate the spread of the pathogen following control efforts in villages based on their connectivity, patch heterogeneity, and host community composition in the surrounding area. Such efforts might also be important in determining the risk associated with African trypanosomiasis, another multi-host pathogen where local vector control efforts have failed due to vector reinvasion following control efforts in several countries in Africa (Hargrove, 2000).

Habitat fragmentation does not always lead to smaller local population sizes or a reduction in movement between habitat patches. Urbanization of flying fox

habitat in Australia has led to changes in their dispersal and roosting habits, with species that are reservoirs for Hendra virus tending to roost in fewer, larger colonies (Markus and Hall, 2004) and more frequent co-roosting occurring among multiple species (Plowright, 2007). Instead of fragmentation leading to a decrease in the local richness of host species, it has instead led to an increase in roosting densities and potentially more frequent contact between different species (Plowright, 2007). This shift from many small roosting colonies into fewer, larger colonies appears to have altered host community composition within colonies at the local scale and increased the connectivity between different populations (McCallum and Dobson, 2006). It is still not clear whether the increased spillover of Hendra virus from bats to humans and horses is the result of increased contact rates or changes in prevalence in the reservoir community due to changes in their network structure and movement patterns.

Landscape fragmentation can also influence the spread, prevalence, and severity of plant diseases (Kelly and Meentemeyer, 2002; Holdenrieder et al., 2004). The probability of *Phytophtora ramorum*, a water mold that is the causative agent of sudden oak death (SOD) in several oak species, spreading into new habitat patches was determined to be a function of environmental factors (temperature and precipitation in the wet season), community composition (abundance of bay laurel, an amplifying host), and distance to surrounding inoculum sources (Meentemeyer et al., 2008*a*). In addition, at the regional scale disease presence was associated with human densities and access to forest habitat (public vs. private lands), suggesting that humans are acting as important dispersal agents for the

pathogen (Cushman and Meentemeyer, 2008). Kelly and Meentemeyer (2002) found that proximity to forest edge increased the risk of mortality due to sudden oak death (SOD). However, a spatial analysis by Condeso and Meentemeyer (2007) revealed that disease severity was highest in continuous forest understory and that both the landscape configuration and composition played a role in disease severity. In addition, the highest pathogen loads were found in areas of oak forest that have expanded in the past 50 years, suggesting that changes in host community composition may be as important as current composition in determining pathogen dynamics (Meentemeyer et al., 2008*b*). In an observational study of the spread of the fusiform rust (*Cronarrtium quercuum*) among plantations of three pine species (all potential hosts of *C. quercuum* of varying susceptibility) and naturally seeded stands of mixed oak (the alternate host for *C. quercuum*) forest, Perkins and Matlack (2002) found that the degree of fragmentation was the main explanatory variable for rate of spread of the pathogen. Stands in pine plantations were closer together, increasing connectivity via wind dispersal of the fungal spores.

In addition to fragmentation's effect on pathogen dynamics within the remaining suitable habitat patches, it may also provide increased opportunities for pathogen spillover to novel hosts. Of particular interest are zoonotic diseases, because fragmentation may increase the number of contacts between wildlife reservoirs and humans or domestic livestock (Daszak et al., 2000; Patz et al., 2004). For example, spillover of Hendra virus from bats to humans may be occurring due to increased contact rates and the outbreaks of Ebola and other emerging

pathogens are often attributed to humans moving into previously undisturbed habitat. In addition, the risk of spillover of brucellosis from bison to domestic cattle is related to interspecific contact where their ranges overlap (Kilpatrick et al., 2009), as is the spillover of rabies and CDV from domestic dogs to wildlife in Africa. The risk of spillover is likely to be the result of an interplay between the effect of fragmentation on within-patch prevalence, the movement rates of hosts between patches, and relative contact rates in habitat patches versus the surrounding matrix. Although we have shown that R_0 will be reduced when the higher quality hosts also have the highest movement rates, a higher movement rate of infected individuals between patches could increase the opportunity for spillover to humans or other hosts outside of the patch.

4.4 Conclusions

Host species respond differently to the various environmental and biological factors, shaping their spatial distributions, which in turn determines the local and regional host community composition. In addition, the movement patterns of different host and vector populations are influenced by landscape structure, which determines the connectivity between suitable habitats. Heterogeneity in the geographical distribution and movement patterns of host species will lead to variation in the local community composition across a landscape. The model results presented here demonstrate that this variability in composition can lead to very different patterns of pathogen spread and incidence then would be predicted based

solely on the local host composition, as regional factors alter the influence of the local community.

Many of the examples presented here highlight the importance of identifying the role of interspecific contact and movement patterns in the spillover and spread of multi-host pathogens in wildlife populations. Our model shows how the invasion, spread, and prevalence of multi-host pathogens can be affected by spatial heterogeneity in host community composition. However, because the model is deterministic it doesn't address questions related to the persistence of a pathogen in a patchy system where local patches are below the pathogen's critical community size for persistence. The deterministic nature of the model prevents pathogen extinction at the local level as long as $R_0 > 1$ at the regional level, so either all patches eventually reach an endemic equilibrium or are disease-free in the absence of external forcing. This is unrepresentative for systems where local populations are small and local fadeouts are likely due to the depletion of susceptibles or demographic stochasticity (Cross et al., 2005). In these cases a stochastic model which permits local fadeouts is more appropriate (e.g. Craft et al., 2008). Integrating the mathematical theory behind the deterministic multi-host approach of Arino et al. (2005, 2007) into a stochastic metapopulation framework would permit the extension of existing theory of stochastic metapopulation dynamics to a system with multiple hosts. Research has already shown how spatial coupling between populations can lead to asynchronous dynamics at the metapopulation scale promoting regional persistence of a pathogen in the host metapopulation (Bolker and Grenfell, 1995; Keeling, 2000; Keeling and Rohani, 2002; Park et al.,

2002; Hagenaars et al., 2004). In addition, the relative timescales of the infectious period and host movement are critical for pathogen spread and persistence in structured populations (Cross et al., 2005, 2007*b*). Extending this research to a system containing multiple host species with differing movement rates and infectious periods would be challenging, but potentially rewarding given the ubiquity of multi-host pathogens.

A stochastic framework may also be appropriate if the question of interest relates to whether there is threat of pathogen-mediated extinction of one or more of the host species (Hess, 1996; Gog et al., 2002; McCallum and Dobson, 2002; de Castro and Bolker, 2005). While earlier theoretical work suggested that corridors between separate populations could promote the spread of disease and increase the risk of extinction risk for threatened populations (Hess, 1996), subsequent analyses including a reservoir species concluded that the effect of connectivity on host extinction was less straight-forward (Gog et al., 2002; McCallum and Dobson, 2002). The fate of the endangered host species depends on the relative colonization and extinction rates of the two species, as well as cross-species transmission rates and the probability of pathogen fadeout in local populations (McCallum and Dobson, 2002). While we examined the effect of increasing fragmentation on the ability of a pathogen to invade a multi-host community, it may also be appropriate to examine how the combination of increasing fragmentation and infectious disease is likely to affect particular populations of concern.

The effects of fragmentation on multi-host pathogens under different modeling scenarios of community disassembly point to the need to investigate whether host

traits related to migration or dispersal are associated with resistance to fragmentation. Hosts with high dispersal rates may be more resistant to fragmentation because they can move into the remaining suitable habitat areas as fragmentation occurs. On the other hand, anthropogenic fragmentation may create barriers to dispersal that lead to the extirpation of species when dispersal or migration is a necessary part of their life cycle. Home range size may also influence a species resistance to fragmentation, with species with large home ranges unable to persist in small patches when their habitat becomes fragmented. It is possible that species with smaller range sizes that can persist in smaller habitat fragments will have lower movement rates between patches, which will influence the ability of their pathogen's to spread and persist at the landscape scale. Relating these traits to epidemiological traits related to host competence is also critical, because the order in which species are lost from a community due to fragmentation can have a large impact on pathogen prevalence and persistence (Ostfeld and LoGiudice, 2003). Fragmentation may also alter the structure of the community beyond the host species, leading to changes in food web dynamics that could have important implications for host-pathogen interactions. For example, fragmentation can lead to the loss of large predators from the system, which will potentially impact the abundance of one or more host species (Ostfeld and Holt, 2004).

Landscape structure will affect habitat connectivity and therefore influence the ability of host movement to connect patchy populations and spread pathogens (Ostfeld et al., 2005; Real and Biek, 2007). Understanding the spatial patterns of spread for multi-host pathogen therefore requires consideration of the ecology of

each host species. For example, while rivers slow the geographic spread of rabies by raccoons (Smith et al., 2002), they can serve as corridors for the migration and dispersal of some species and therefore facilitate the spread of other pathogens (Russell et al., 2004; Real and Biek, 2007). Multi-host, multi-patch models like the one presented here can be used to examine the importance of movement by different host species for pathogen invasion and persistence in heterogeneous landscapes.

Geographical and statistical tools are often used to analyze the distribution of vectors or hosts in order to create explanatory maps of incidence or predictive risk maps (Ostfeld et al., 2005). However these approaches typically do not incorporate the potential influences of landscape composition and structure on the distribution of host species or the connectivity between different populations in a heterogeneous landscape. Multi-host models that incorporate knowledge of host movement patterns could be integrated with research on the correlation between environmental factors and host distributions to examine the relative importance of local community composition and landscape heterogeneity for determining patterns of pathogen distribution and prevalence. We still need to understand more about how host distributions are influenced by heterogeneity, and how differences in species' responses to environmental factors will alter community composition. Multi-host pathogens are also likely to have effects on community structure via apparent competition between hosts or more complex multispecies interactions (Hatcher et al., 2006). Recognizing that pathogens can influence host distributions is important when considering how overlapping host species distributions

influence cross-species transmission. Community composition and overlapping distributions are especially important for pathogens that require alternate hosts (e.g. plant fungal pathogens, parasites with complex life stages that require intermediate hosts such as flukes). In addition, the movement abilities of alternate hosts are likely to influence contact rates and therefore the probability of cross-species transmission.

Climate change is expected to alter the global distribution and prevalence of infectious diseases, particularly those involving ectothermic hosts or arthropod vectors (Harvell et al., 2002). In a recent analysis of the existing evidence for climate impacts on disease dynamics, Lafferty (2009) concluded that range shifts in disease distributions are more likely than large increases in the geographic range. However even if their range only shifts rather than expands, the community composition experienced by multi-host pathogens is likely to be different in their new range. Because species richness is lower in temperate regions than in the tropics, if pathogen and/or vector distributions shift towards the poles the host community in their new geographic ranges may contain fewer species reducing the potential for a dilution effect (Dobson, 2009). Shifting host or vector distributions may also lead to disease transmission to previously unexposed host species, which can have important implications for host-pathogen dynamics if the pathogen is highly virulent in naïve populations (Harvell et al., 2009). The spatiotemporal dynamics of multi-host pathogens might also be altered due to changes in the movement patterns of hosts as species shift their geographic ranges or alter their migratory patterns due to changes in seasonal climate patterns.

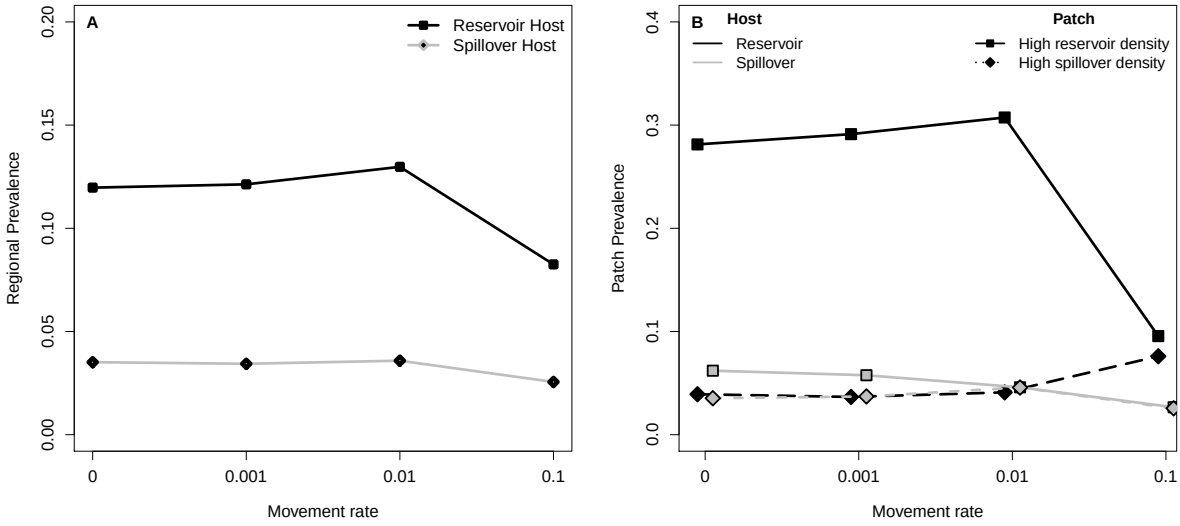

Figure 4.1: Equilibrium infection prevalence in a reservoir host and a spillover host at the (a) regional and (b) local scales across a connectivity (as determined by the host movement rates). The regional prevalence does not change significantly with changes in the host movement rate, but the difference between local prevalence in source (high reservoir density) and sink (low reservoir density) patches is reduced as host movement rates increase.

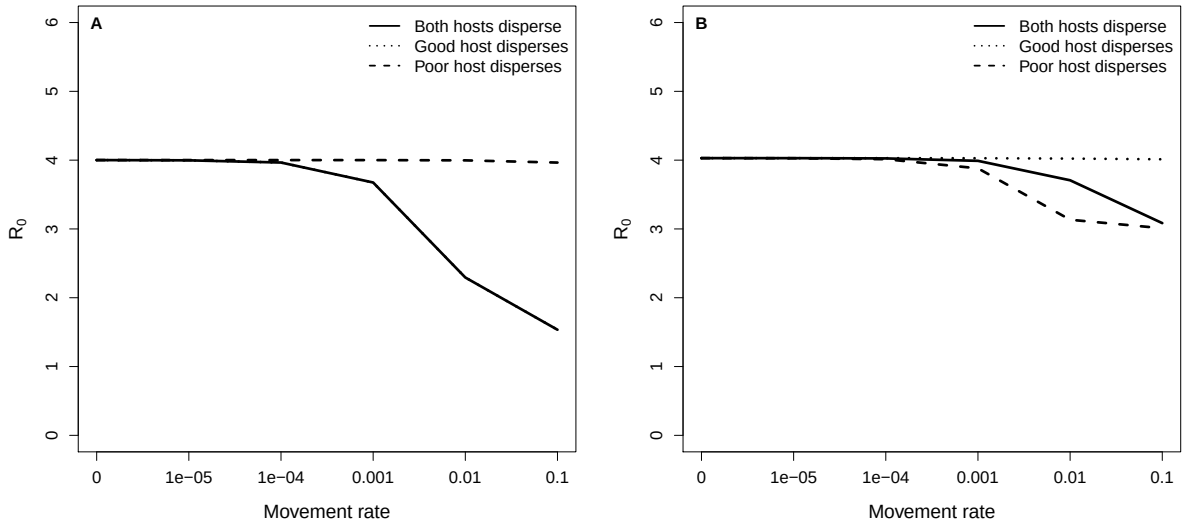

Figure 4.2: R_0 as a function of host movement rate when the density of (a) good hosts, or (b) poor hosts varies between patches. In (a) the solid line represents movement by both hosts and the dashed line represents movement of the poor (spillover) host. The dotted line representing movement of the good (reservoir) host only is not visible because it is identical to the solid line representing both hosts. In (b) the solid line represents movement by both hosts while the dotted and dashed lines represent movement by the good and poor hosts respectively.

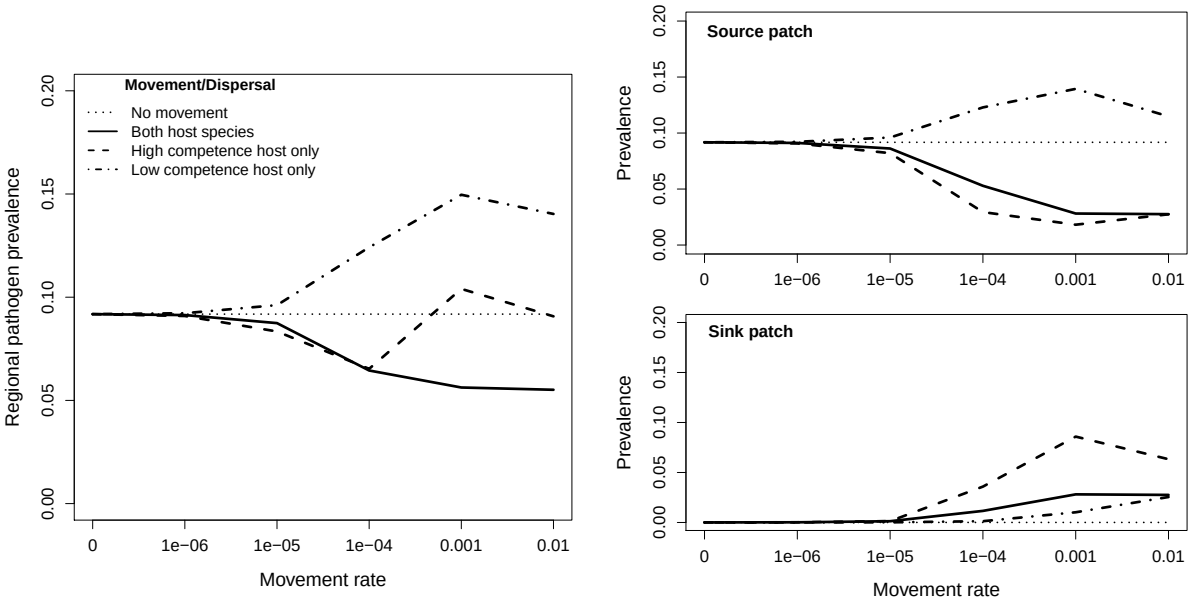

Figure 4.3: Pathogen prevalence at the regional and local scales in a two patch (source-sink) system where coupling between patches occurs via movement by either the good host (dashed line), poor host (dot-dashed line), or both (solid line). Figure on left is regional prevalence averaged across the two patches, while figures on right are prevalence in the source (top) and sink (bottom) patches.Without movement $R_0 = 1.4$ in the source patch and 0.7 in the sink patch.

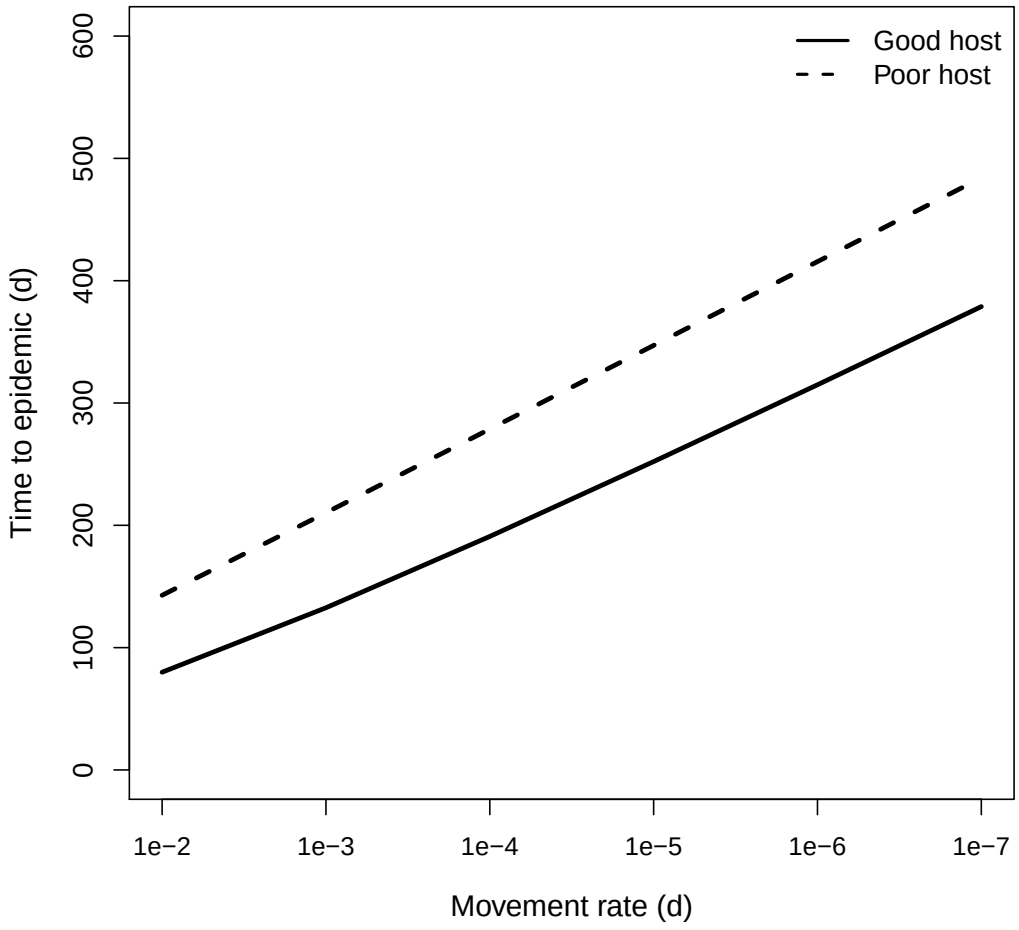

Figure 4.4: Spread rate of the pathogen as a function of the host movement rate when movement between patches is by either the good (reservoir) or poor (spillover) host. Spread rate is measured as the time to the peak of the epidemic in the patch furthest from the initial source of infection.

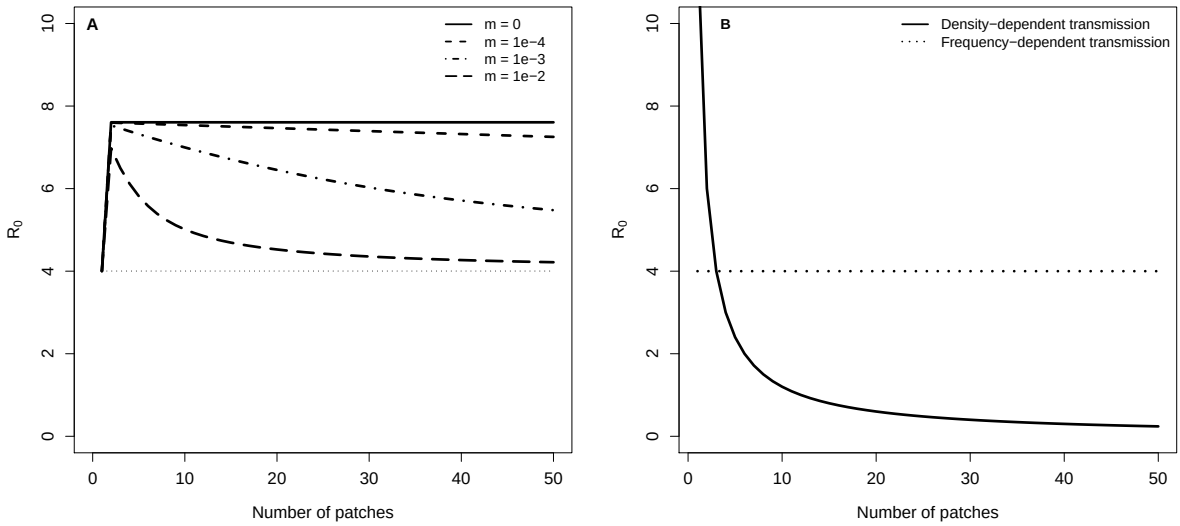

Figure 4.5: R_0 as a function of the number of patches when (a) the average patch population size remains constant as the number of patches increases, or (b) the regional population size remains constant, but the average patch population size decreases, as the number of patches increases. Results in (a) are all for density-dependent transmission at different movement rates with an average patch population size of 100 individuals and a range in patch population sizes of 10 to 200. The shaded, dotted line represents a metapopulation where each patch population size = 100 individuals. The value of R_0 with frequency-dependent transmission would be identical to the value for a constant host population size regardless of movement rate. Results in (b) are for frequency- vs. density-dependent transmission.

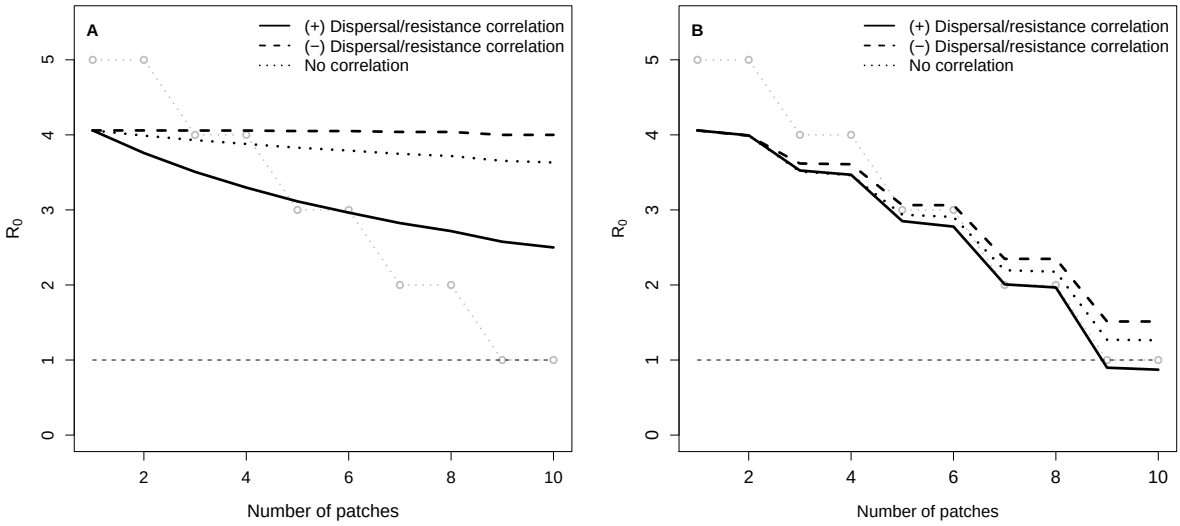

Figure 4.6: R_0 as a function of increasing fragmentation of a habitat where host species richness declines from 5 to 1 as fragmentation increases. In (A) host resistance to fragmentation and host quality/compentency are positively correlated, and in (B) host resistance and competency are uncorrelated. Solid lines represent a positive covariance between host dispersal ability and resistance to fragmentation, dashed lines a negative covariance, and dotted lines no covariance. The grey line is the number of species per patch (scale is the same as for R_0). Individual R_0 values for the 5 hosts are 4, 2, 1.1, 0.7, and 0.5.

The influence of host diversity and composition on epidemiological patterns at multiple spatial scales: Barley yellow dwarf viruses in a Cascades meadow system

Sean M. Moore, Elizabeth T. Borer

Chapter 5 – The influence of host diversity and composition on epidemiological patterns at multiple spatial scales: Barley and cereal yellow dwarf viruses in a Cascades meadow system

Abstract

Spatial patterns of pathogen prevalence are determined by ecological processes acting across multiple spatial scales. Host-pathogen interactions are influenced by environmental factors, landscape structure and the local community composition. Here we investigate the role of local community interactions and the effects of landscape structure and regional processes on the dynamics of barley and cereal yellow dwarf viruses (B/CYDV) in the open meadows of the Cascade Mountains of Oregon. We used variance components analysis and model selection techniques to partition the sources of variation in B/CYDV prevalence and determine which abiotic and biotic factors influence host-pathogen interactions in a Cascades meadow system. B/CYDV prevalence in Cascades meadows varied by host species identity, with a significantly higher proportion of infected *Festuca idahoensis* individuals than *Elymus glaucus* or *Bromus carinatus*. While there was significant variation in prevalence among host species and among meadows in the same meadow complex, there was no evidence of any significant variation in prevalence among different meadow complexes at a larger spatial scale. Variation in prevalence among meadows was primarily associated with the local community

context—host identity, the relative abundance of different host species, and host species richness—and the physical landscape attributes of the meadow. These results highlight the importance of local host community composition, mediated by landscape characteristics such as meadow aspect, as a determinant of the spatial pattern of infection of a multi-host pathogen.

5.1 Introduction

Like other species interactions in ecological systems, host-pathogen interactions are influenced by environmental factors, landscape characteristics and the broader community context (Guernier et al., 2004; Collinge and Ray, 2006; Keesing et al., 2006; Ostfeld et al., 2006*b*; Borer et al., 2010). Spatiotemporal patterns of infection in host communities may be driven by climate variables such as temperature and precipitation (Pascual et al., 2000; Harvell et al., 2002; Zhou et al., 2004; Garrett et al., 2006; Snall et al., 2008; Seabloom et al., 2010), which can vary in a spatially consistent manner based on the topography of a landscape. For vector-transmitted, multi-host pathogens, differential vector and host species' responses to environmental heterogeneity and landscape structure—mediated by species interactions—will generate spatial heterogeneity in the composition and abundance of the vector and host communities across the landscape. Because these processes that drive host-pathogen interactions can act at a broad range of spatial scales (Smith et al., 2003; Fabre et al., 2005; Borer et al., 2010; Duffy et al., 2010; Seabloom et al., 2010), it is necessary to examine the relative im-

portance of these different processes to both local- and larger-scale patterns of infection.

At a local scale, the diversity and composition of the ecological community can affect the prevalence of infectious diseases (Keesing et al., 2006). Increasing host species richness can lead to a reduction in prevalence by reducing the abundance of highly competent hosts or decreasing the rate of transmission between hosts (Ostfeld and Keesing, 2000; Ezenwa et al., 2006; Keesing et al., 2006; Dizney and Ruedas, 2009). The composition of multi-host communities can also affect prevalence, because interspecific variation in host competency (a function of host susceptibility, recovery, and infectiousness) can lead to the dilution or amplification of prevalence at the community level (Power and Mitchell, 2004; LoGiudice et al., 2008). In the case of vector-borne diseases, the composition of the local community (including both host and non-host species) may also influence the abundance and composition of the vector community, vector preference for different host species, or transmission rates between vector and host species (Power and Mitchell, 2004; Malmstrom et al., 2005; Borer et al., 2009). However, the composition and configuration of the host community at larger spatial scales may mediate the effect of local-scale influences (Plantegenest et al., 2007). For vector or wind-dispersed pathogens, local-scale disease incidence or prevalence can be influenced by the regional abundance of highly competent hosts (Fabre et al., 2005) or the proximity to neighboring host populations (Ericson et al., 1999; Smith et al., 2003).

The local context for infection also includes the role of local abiotic conditions that can influence host-pathogen or vector-host interactions. Local nutrient supplies can affect vector abundance (Pope et al., 2005; Borer et al., 2009) and increase pathogen prevalence and disease incidence (Strengbom et al., 2002; Borer et al., 2010). Other abiotic factors that affect community productivity and composition, such as temperature and soil moisture availability, may also influence infection patterns. Environmental conditions also affect patterns of infection at larger spatial scales because they are important determinants of transmission dynamics and the distribution of host and vector communities (Gubler et al., 2001; Ostfeld et al., 2005; Stenseth et al., 2006; Seabloom et al., 2010).

In complex disease systems with multiple host, vector, and pathogen or parasite species, each of these species may be influenced by different abiotic factors or processes at different spatial scales, making it difficult to predict patterns of infection (Ostfeld et al., 2005). Landscape structure can influence ecological interactions and processes, leading to spatial heterogeneity in the presence or abundance of organisms, including host-pathogen communities (Turner, 1989). The physical attributes of a landscape are particularly important determinants of pathogen dispersal, which affects the spread, prevalence, and persistence of infectious diseases (Hess et al., 2002; Holdenrieder et al., 2004; Plantegenest et al., 2007; Real and Biek, 2007). The degree of connectivity between host populations has influenced the patterns of infection and spread of rabies (Smith et al., 2002; Russell et al., 2005; Smith et al., 2005), hantaviruses (Langlois et al., 2001), and plague (Collinge et al., 2005) in wildlife populations. The size and degree

of connectivity between local host populations are also important determinants of persistence and prevalence for plant pathogens (Park et al., 2001; Ericson et al., 1999; Smith et al., 2003; Laine and Hanski, 2006). For vector-dispersed pathogens, topographic features and landscape structure can influence vector dispersal and landing patterns (Plantegenest et al., 2007).

The goal of our observational study was to assess the effect of landscape structure and local and regional processes on the distribution and prevalence of a vector-transmitted, multi-host pathogen. We examined the role of local plant community interactions and the effects of environmental conditions, landscape structure, and regional processes on the prevalence of barley and cereal yellow dwarf viruses (B/CYDV) in the open meadows of the Cascades mountain range in Oregon. We collected B/CYDV infection data for several host grass species, along with a set of abiotic and biotic factors that have the potential to influence infection prevalence at multiple spatial scales. The first objective of our study was determine whether variation in B/CYDV prevalence occurs primarily among host species at a local within-meadow scale, among adjacent meadows, or among groups of meadows at a larger spatial scale. Second, we used model selection techniques that have recently been advocated for ecological data (Johnson and Omland, 2004; Whittingham et al., 2006; Bolker et al., 2009) to determine which abiotic and biotic factors were important predictors of local prevalence. Potential explanatory factors were grouped into categories of factors or processes that could potentially influence host-pathogen interactions in this system. These categories were then used to construct a set of candidate models from which we

quantified the relative importance of the different factors for explaining variation in B/CYDV prevalence.

5.2 Methods

5.2.1 Study system

The barley and cereal yellow dwarf viruses are a group of generalist, aphid-vectored plant viruses that infect over 100 grass species in both agricultural and natural systems (D'Arcy and Burnett, 1995). B/CYDV is one of the most economically important diseases of grain crops worldwide (Irwin and Thresh, 1990), and has been widely studied for over 50 years (D'Arcy and Burnett, 1995). The virus has a short latency period in both its host plants and the aphid vector; however, once infected a vector is potentially infective for life and individual hosts typically do not recover from a B/CYDV infection. Host susceptibility to B/CYDV varies, with some species suffering increased mortality and reduced fecundity when infected and other species experiencing little change in their overall fitness (Irwin and Thresh, 1990). Studies have also shown that the presence of highly competent reservoir species can increase the prevalence of B/CYDV in local host communities (Power and Mitchell, 2004). Host-aphid interactions also vary by host, with aphids showing preference for and experiencing higher fitness on certain host species (Borer et al., 2009). While the effect of these host community differences have been investigated at the local level, their importance

for regional patterns of B/CYDV spread and persistence has only recently been explored (Borer et al., 2010; Seabloom et al., 2010). Both local, within-field movements and long-distance dispersal by aphids are important for B/CYDV transmission (Irwin et al., 1988; McElhany et al., 1995), and host-vector interactions at multiple spatial scales may influence local and regional disease dynamics (Borer et al., 2010). This complexity of B/CYDV epidemiology makes it an ideal study system for the exploration of spatial community dynamics and disease ecology.

5.2.2 Sampling design

Field observations were conducted in the summer of 2008 in the montane meadow system within the H.J. Andrews Experimental Forest and adjacent areas of the McKenzie River drainage in Oregon's central-western Cascade Mountains. Meadows in this region are typically found at elevations ranging from 1000-1620 m and are most common on drier, steeper slopes with southern aspects and near ridge lines (Takaoka and Swanson, 2008). These open meadows are patchily distributed within a forested landscape among the higher-elevation forest where environmental conditions are more stressful for trees and rock outcrops are more common (Franklin and Halpern, 2000). Sampling occurred in 20 meadows from four separate, small, meadow systems—here referred to as meadow complexes—that contain at least five meadows of varying size (ranging from ~600 m^2 to 9 ha in size). Meadows within a complex are typically located within a kilometer or two of the

other meadows in the complex, while each of the separate meadow complexes is located at least several kilometers and one mountain ridge away from the other meadow complexes. The four different meadow complexes were selected to cover the range of different abiotic conditions (soil moisture, elevation, slope, aspect, etc.) typical of Cascade meadows, and to examine the effect of complex (regional) scale measurements, such as average meadow size and meadow isolation, on the spatial patterns of plant community composition and B/CYDV prevalence.

In each of the 20 meadows, cover data of each plant species was measured in eight 1 m^2 quadrats. Quadrats were established at 10 m intervals along a transect across the center of a meadow, expect for in the largest four meadows where quadrats were established at 25 m intervals along a similar transect. The mean percent cover across the eight quadrats was then calculated to represent the abundance for each species found in a meadow. Biomass data was also collected from a $0.1\,m^2$ strip in each quadrat, and sorted by plant functional group (except grasses, which were sorted to the species level). Soil moisture in each quadrat was measured using a portable TDR probe, and the percent cover of moss, rocks, leaf litter, woody debris (ranging from fallen branches to decaying logs), gopher mounds and bare ground were also recorded. Because dispersing aphids may select their feeding habitat partly based on the ratio of plant cover to exposed ground in a meadow (Irwin et al., 2007), the amount of each plot covered by gopher mounds, bare ground, and exposed rock was recorded as a composite variable.

In addition to plant species composition data, the mean elevation, slope, aspect, size, and isolation were calculated for each meadow. Slope and aspect data for each meadow were derived from a 30 m digital elevation map of the area in ArcGIS 9.3 (ESRI, San Diego, CA USA). Aspect data was sine and cosine transformed from the 360 ° orientation to create two aspect variables representing the east-west and north-south orientations of each meadow. These transformed variables both vary from -1 to +1. Meadow isolation was calculated as either the distance to the nearest meadow or as the average distance between a meadow and all of the other meadows within the same meadow complex. Both isolation metrics yielded comparable results, so analyses using nearest neighbor distance are presented here.

Three of the most common grass species in the study area are the native perennials *Elymus glaucus*, *Bromus carinatus* and *Festuca idahoensis*. Twenty samples of *E. glaucus* were collected from each meadow in order to estimate site-level viral prevalence. In addition, 20 samples of *B. carinatus* and *F. idahoensis* were collected from each meadow that contained at least 20 individuals of each species respectively. In total, *E. glaucus* was collected from each of the 20 meadows, *B. carinatus* from 18 of 20, and *F. idahoensis* from 12 of 20, for a total of 1000 samples. Grass tissue samples were air dried and then assayed for infection with three species in the B/CYDV complex (BYDV-PAV, BYDV-MAV, and CYDV-RPV) via enzyme-linked immunosorbent assay (ELISA; antibodies from Agdia, Elkhart, IN USA).

5.2.3 Statistical analysis

Host-species specific pathogen prevalence was modeled as the proportion of infected host individuals within a meadow. B/CYDV prevalence data were initially analyzed using a generalized linear mixed-effects regression model (GLMM) with binomial errors and a logit link (using the lme4 package in R v. 2.9.2). Meadow complex, meadow, and host species within a meadow were treated as nested random effects in order to provide an estimate of the variance associated with each factor after accounting for variance at the other hierarchical levels (variance components analysis; Crawley, 2007). Partitioning the variance among host species, meadow, and meadow complex provides an estimate of the relative importance of the different processes influencing infection patterns in this system (Borer et al., 2010; Duffy et al., 2010). Because the meadow-complex spatial scale was not a significant source of variance after accounting for the variation among meadows within each complex (see Results), subsequent analyses were conducted using general linear models (GLMs) with fixed effects only. There was significant variance among species within a site, therefore species identity was treated as a fixed effect in subsequent analyses. All statistical analyses were conducted using R version 2.9.1 (R Development Core Team 2009).

5.2.3.1 Statistical Modeling

The relationship between B/CYDV prevalence data and potential explanatory factors was analyzed by developing a set of candidate models with different groups

of explanatory variables. Each model of prevalence was examined using a GLM assuming a binomial error distribution and logit link (logistic regression). A goodness-of-fit test of the full model including all possible explanatory variables indicated that data dispersion did not match the assumptions of the binomial distribution (Venables and Ripley, 2002). However, a full model using mean meadow-level prevalence averaged across all host species as the response variable provided an adequate fit to the data without overdispersion (χ_4=1.96; p=0.74). Therefore, we used meadow-level prevalence averaged across all host species as the response variable for regression model selection purposes.

The set of candidate models were compared using an information theoretic approach in order to generate a confidence set of models for further analysis and multi-model inference (Burnham and Anderson, 2002). The candidate set of models was generated by grouping the explanatory variables into categories of factors or processes that could potentially influence host-pathogen interactions in this system. The groups chosen were: physical landscape attributes, landscape structure attributes, meadow productivity, meadow community composition, host abundance, host richness, and host community composition. The host community composition category was divided into four different factors representing the relative abundances of *F. idahoensis, E. glaucus, B. carinatus,* and all other grasses. This resulted in 10 single factor models. We then explored all possible subsets of these 10 single factors as candidate models for a total candidate set of 1024 models.

5.2.3.2 Physical landscape attributes

The variables included in this category were elevation, slope, and aspect. Aspect was divided into two variables according to a meadow's orientation along an east-west axis and a north-south axis. Each of these physical landscape attributes may influence infection through their influence on the phenology of the host grasses, the phenology and population dynamics of aphids, or meadow productivity and richness. In particular, elevation affects the length of the growing season and may also affect the timing of aphid dispersal. Meadow aspect may also influence local aphid abundance and the timing of aphid population dynamics, because regional aphid migration in the spring and early summer typically occurs from west to east and upwards in elevation (S. Moore, personal observation). Physical landscape attributes are also likely to influence the arrival of aphids because they are weak fliers and therefore their dispersal ability is often limited by the direction of the prevailing winds (Irwin et al., 2007).

Because elevation and slope were highly correlated (r=0.79), and elevation, slope, and E-W aspect were all moderately correlated, we conducted principal components analysis (PCA) to reduce the dimensionality of the data. The first two principal components explained 86% of the variance (59% by PC1 and 27% by PC2) and were used for further statistical analyses. The loadings of the first principal component suggest that PC1 represents a positive influence of elevation (0.62) and slope (0.56) and a negative influence of N-S aspect (-0.44). The second

principal component (PC2) represents a positive influence of E-W aspect (0.80) and a negative influence of N-S aspect (-0.49).

5.2.3.3 Landscape structure attributes

The two landscape structure attributes were log-transformed meadow area and meadow isolation. Both the size and isolation of a meadow may influence the richness and composition of the local host community. In addition, the size and isolation of a meadow may affect the likelihood of aphids dispersing to the meadow (Traore et al., 2005; Irwin et al., 2007).

5.2.3.4 Site productivity attributes

The site productivity category includes plant species richness, total plant biomass, litter biomass, soil moisture percentage, and the ground variable which represents the amount of meadow area covered by gopher mounds, rocks, woody debris, or bare ground. Local-level plant community productivity and richness have been shown to be correlated with the prevalence and severity of some plant pathogens (Mitchell et al., 2002). In addition, site productivity may correlate with nutrient availability, which can influence B/CYDV prevalence (Borer et al., 2010). The amount of standing biomass and the relative amount of bare ground in a meadow can also influence the landing behavior of aphids during dispersal (Irwin et al., 2007).

As with the physical landscape attributes, we used PCA to reduce the dimensionality of the site productivity category. The first 3 of 5 principal components contained 43%, 23%, and 18% of the variation (84% combined) and were used to represent site productivity for model selection purposes. The first productivity principal component is positively associated with the ground variable (0.53), and negatively associated with soil moisture (-0.50), plant species richness (-0.47), and litter abundance (-0.41). The second principal component is negatively associated with litter abundance (-0.65) and positively associated with plant species richness (0.49) and soil moisture (0.45). The third principal component is negatively associated with total plant biomass (-0.95).

5.2.3.5 Meadow community composition

Meadow community composition was represented by the relative abundance of forbs, legumes, and sedges. While the composition of the plant community may not directly impact B/CYDV, plant community composition varied significantly among meadows in our study (S. Moore, *unpublished*), and may co-vary with B/CYDV prevalence.

5.2.3.6 Host abundance

Host abundance was represented by either total grass biomass or the amount of grass biomass relative to total plant biomass. If B/CYDV transmission is

density-dependent, then prevalence would be expected to increase as a function of host density—as represented by total grass biomass—in a meadow. However, the relative amount of grass biomass in a meadow may be more important for transmission and prevalence if dispersing aphids respond to the relative abundance of potential host species when selecting where to feed. Candidate sets of models were constructed with either total or relative grass biomass to determine which measurement is more important for B/CYDV prevalence. Total grass biomass was included as a significant explanatory variable more frequently than relative grass biomass, so results from the candidate set of models including total grass biomass are presented here. However, results regarding the significance of the other explanatory variables did not differ between the two candidate model sets.

5.2.3.7 Host richness

Host species richness was included as a potential explanatory variable because host diversity is often an important determinant of infection prevalence in multi-host communities (Ostfeld and Keesing, 2000). Several studies have shown that species diversity causes a dilution effect, with prevalence decreasing as diversity increases (Ostfeld and Keesing, 2000; LoGiudice et al., 2003; Ezenwa et al., 2006; Keesing et al., 2006; Allan et al., 2009; Dizney and Ruedas, 2009). There are several plausible mechanisms that could lead to the dilution of prevalence in our system with an increase in host species richness including: (a) encounter reduction

between vector species and highly competent hosts, (b) vector regulation by poor hosts, (c) a reduction in the probability of transmission, or (d) susceptible host regulation (Keesing et al., 2006).

5.2.3.8 Host community composition

For multi-host pathogens such as B/CYDV, the composition of the host community may be a more important determinant of prevalence than either host richness or total host abundance (Mitchell et al., 2002; Power and Mitchell, 2004; Keesing et al., 2006; Kilpatrick et al., 2006*b*; LoGiudice et al., 2008). Therefore, in addition to examining the importance of total host abundance and host species richness, we also examined the importance of the abundance of different host species for B/CYDV prevalence. Analyses were conducted using either the total or relative abundances of each grass species as explanatory variables. Relative abundance consistently explained more of the variance than total abundance, so relative abundance was used to construct the set of candidate models presented here. Because infection data was collected from *F. idahoensis*, *E. glaucus*, and *B. carinatus* we treated the meadow-level abundance of each of these three species as potential explanatory variables in separate single factor models, and in conjunction with other variables in the multiple factor models within the candidate model set. In addition to these three species, we also considered the combined abundance of the remaining grass species in a meadow as a potential explanatory variable. In addition to the three focal host species, 19 other grass species were

found in at least one meadow. Although none of these species were as common or abundant as the three focal species, the most common of these additional grasses were *Agropyron repens, Danthonia intermedius, Stipa occidentalis, Calamagrostis canadensis,* and several *Agrostis spp.*

5.2.3.9 Model selection criteria

Models were selected from the candidate set of models using bias-adjusted Akaike's information criterion (AICc) (see Appendix F for details). AICc adjusts for bias when the ratio of the number of observations (N) to the number of parameters (K) is below 40 (Burnham and Anderson, 2002). The best model is the one with the smallest AICc ($AICc_{min}$), and all other models are then compared to the best model by calculating their AICc difference $\Delta_i = AICc_i - AICc_{min}$, which represents the loss of information for model g_i compared to the g_{min}. Models with Δ_i values of less than 2 are considered to have substantial support, while models with $\Delta_i > 10$ are considered to have almost no support (Burnham and Anderson, 2002). The AICc differences can also be used for model comparison and multi-model inference by using them to calculate Akaike weights, w_i, for each model (Burnham and Anderson, 2002). The Akaike weights, w_i, sum to 1 for all R candidate models and represent the probability that model g_i is the best model (from an information theoretic standpoint) among the candidate set of models. A 95% confidence set of models is then chosen from the candidate set of models by selecting the smallest subset of models that have a sum of $w_i \geq 0.95$.

An assessment of the relative importance of the various explanatory variables was conducted using the confidence set of models. Rather than infer the significance of a variable from a single "best" model, the importance of each potential explanatory variable, x, can be calculated based on how frequently the variable was included as a parameter in the confidence set of models (Johnson and Omland, 2004; Whittingham et al., 2006). The Akaike weights are summed for all models from the confidence set containing the variable in order to calculate a term (predictor) weight, ς_x, for each variable. The 95% confidence set of models was also used to calculate model-averaged parameter estimates and their 95% confidence intervals (see Appendix F for details).

5.3 Results

B/CYDV prevalence was largely determined by factors at the local, meadow-scale rather than at the scale of the regional meadow complex. 29% of the variation in infection occurred among meadows within a meadow complex, and $< 1\%$ of the remaining variation in prevalence was explained by differences among meadow complexes. Host species identity within a meadow explained an additional 6% of the variation in prevalence. The remaining 65% of variance in infection occurred at the within-species level. Total BYDV prevalence was significantly higher in *F. idahoensis* (12.9%) than *B. carinatus* (7.2%) or *E. glaucus* (8.2%) (p=0.016; Figure 5.1). In addition, *F. idahoensis* had a higher prevalence of BYDV-MAV and CYDV-RPV than *E. glaucus*, and a higher prevalence of BYDV-PAV than

B. carinatus. CYDV-RPV prevalence in *E. glaucus* was significantly lower than in either of the other two species.

54 models out of the 1024 candidate models were identified as plausible models of site-level BYDV prevalence based on their AICc values, making up a 95% confidence set of models (Table 5.1). None of the single factor models were included in the 95% confidence set of models, suggesting that infection is driven by multiple factors. The best fit model included host species richness, the relative abundance of grass species other than *F. idahoensis*, *B. carinatus,* or *E. glaucus*, and the two physical landscape principal components as explanatory variables. The second best model was the only model with $\Delta_i < 2$, and included only host species richness and the relative abundance of other grass species as explanatory variables. These top two models had Akaike weights of 0.22 and 0.17, while the third best model had an Akaike weight of 0.07. Because inferences should be based on a single best model only if $w_i \geq 0.90$ (Burnham and Anderson, 2002), we determined the relative importance of the different explanatory variables and their parameter estimates using the model-averaged estimates from the 95% confidence set of models.

The relative abundance of other grass species appeared as an explanatory variable in 53 of the 54 models in the confidence set, and had the highest predictor weight of $\varsigma_x = 0.93$ (Table 5.2). Host species richness had the next highest predictor weight (0.84), followed by physical landscape attributes (0.38) and total grass (host) abundance (0.22). Host species richness and total host abundance were highly correlated (r=0.88). This may explain why total host abundance was

the best fitting single factor model ($\Delta_i = 10.6$, Table 5.1), but was not included in most of the models in the 95% confidence set (Figure 5.3a). The set of variables representing plant community composition (relative abundance of forbs, legumes, and sedges) did not appear as explanatory variables in any of the models within the 95% confidence set.

Host species richness and the relative abundance of other grass species were the only two explanatory variables with 95% confidence intervals not encompassing zero (Table 5.2). Based on $\hat{\hat{\beta}} = -0.33$ for host species richness, the odds of infection increase by a factor of 1.39 for each decrease by one in host species richness (95% CI: 1.06-1.85; Figure 5.2). Likewise, each 10% increase in the relative abundance of other grass species besides *F. idahoensis, B. carinatus* or *E. glaucus* increases the odds of infection by 1.25 (95% CI: 1.08-1.48; Figure 5.3b). The relative abundance of other grass species is not significantly correlated with prevalence (Figure 5.3b); however, it is correlated with host species richness (r=0.67) and after accounting for variation in host species richness the partial correlation of prevalence and the relative abundance of grass species is $r_{partial} = 0.45$.

The third most important explanatory factor was physical landscape attributes, with a predictor weight of $\varsigma_x = 0.38$. The parameter estimates for the physical landscape variables PC1 and PC2 were $\hat{\hat{\beta}} = 0.007$ and $\hat{\hat{\beta}} = -0.135$ respectively. The parameter estimate near zero for PC1 suggests that only the PC2 variable was responsible for the inclusion of these two physical landscape variables in the 95% confidence set of models. To determine whether PC2 might be a significant

explanatory variable, we re-conducted the model selection process with only PC2, instead of both PC1 and PC2, serving as a potential explanatory variable. The updated model selection exercise produced very similar results to those presented in Tables (5.1) and (5.2), except that the predictor weight for physical landscape attributes increased from 0.38 to 0.80. The relative abundance of other grass species and host species richness sill had the highest predictor weights of 0.94 and 0.91 respectively. The best fit model had a model weight of $w_i = 0.39$ and included three significant variables: host species richness, the relative abundance of other grasses, and PC2. Although the predictor weight for the physical landscape attributes increased, the 95% confidence interval for the model-averaged parameter estimate of the PC2 variable still included zero ($\hat{\bar{\beta}} = -0.281$; 95% CI: -0.607 – 0.045).

5.4 Discussion

Spatial patterns of pathogen prevalence are determined by ecological processes acting across multiple spatial scales. Here we used variance components analysis and model selection techniques to partition the sources of variation in B/CYDV prevalence and determine which abiotic and biotic factors influence host-pathogen interactions in a Cascades meadow system. B/CYDV prevalence in Cascades meadows varied by host species identity, with a significantly higher proportion of infected *F. idahoensis* individuals than *E. glaucus* or *B. carinatus*. While there was significant variation in prevalence among host species and among meadows

in the same meadow complex, there was no evidence of any significant variation in prevalence among different meadow complexes. Variation in prevalence among meadows was primarily associated with the local community context—host identity, the relative abundance of different host species, and host species richness—and the physical landscape attributes of the meadow.

B/CYDV prevalence was negatively correlated with the number of host species in a meadow, suggesting that increasing species richness may cause a dilution effect in this system. The co-variation of host richness and B/CYDV prevalence was not due to prevalence patterns in a single host species. Species diversity is negatively correlated with the incidence and prevalence of a number of different infectious diseases including Lyme disease (Ostfeld and Keesing, 2000; LoGiudice et al., 2003), West Nile virus (Ezenwa et al., 2006; Allan et al., 2009), hantaviruses (Dizney and Ruedas, 2009), rust fungi (Mitchell et al., 2002), and bartonellosis (Telfer et al., 2006). In some cases the biodiversity of the entire ecological community can lead to a reduction in pathogen prevalence by regulating susceptible host populations or reducing the contact rate between the pathogen and its hosts (Ostfeld and Holt, 2004; Dobson et al., 2006). However, we found no association between the diversity of the entire plant community and prevalence in a meadow. Because this was an observational study we cannot assign a causal role for the effect of host species richness on B/CYDV infection patterns. Determining a possible mechanism for the relationship between host richness and prevalence is difficult for two additional reasons: (1) the high degree of correlation between host

species richness and total host abundance, and (2) the significant co-variation of host community composition, host species richness, and prevalence.

The correlation between the abundance of grasses (hosts) and the number of grass species in a meadow makes it difficult to distinguish between the effects of host diversity and host abundance on pathogen prevalence. Although total host abundance is significantly correlated with B/CYDV prevalence when analyzed with a univariate regression model and the host abundance model had the lowest AICc value of any single factor model, it was not a significant explanatory factor when the entire candidate set of models was considered. Although not significant, there was a negative correlation between total host abundance and B/CYDV prevalence. A negative correlation between prevalence and host abundance is a pattern typically seen for vector-transmitted pathogens with frequency-dependent transmission, where an increase in host abundance reduces the contact rate between the vector and infected hosts, leading to a lower prevalence at equilibrium (Anderson and May, 1991; Antonovics et al., 1995; McCallum et al., 2001). While vector-borne diseases may exhibit frequency-dependent transmission when the density of the vector population is independent of host abundance, aphid abundance is at least partially coupled to host abundance (Malmstrom et al., 2005; Borer et al., 2009). Therefore, increasing the the total abundance of grasses will increase the abundance of aphids, and total host abundance and transmission will not necessarily be negatively correlated as would be expected with frequency-dependent transmission (Hosseini et al., *In prep*).

The most important explanatory variable for B/CYDV prevalence was the relative abundance of grass species other than *E. glaucus, B. carinatus,* or *F. idahoensis*. An increase in the relative abundance of 'other' grasses was positively related to prevalence after accounting for the effect of host species richness. Even in studies that have demonstrated an effect of species diversity on infection, community composition is often a more important determinant of disease prevalence than species richness alone (Mitchell et al., 2002; LoGiudice et al., 2003; Keesing et al., 2006; Kilpatrick et al., 2006*b*; LoGiudice et al., 2008). The presence of a host species that is a highly competent reservoir can amplify infection (e.g. *Avena fatua* and B/CYDV, Power and Mitchell, 2004; or the white-footed mouse, *Peromyscus leucopus*, and Lyme disease, LoGiudice et al., 2003), while increasing the relative abundance of less competent hosts can lead to the dilution effect (e.g. non-passerine bird species and West Nile virus, Ezenwa et al., 2006). In our study it is not possible to identify one particular species that could be amplifying prevalence because the composition of 'other' grass species varies among meadows. Interestingly, a univariate regression model indicated that there is a significant negative relationship between the relative abundance of *F. idahoensis* (the host species with the highest proportion of infected individuals) and the mean B/CYDV prevalence in a meadow. However, *F. idahoensis* abundance was not identified as an important explanatory variable via model selection.

The composition of the host community also co-varied with host species richness. One reason host composition and diversity can co-vary is that species richness in a community may be nested, with species that are highly competent reser-

voir hosts occurring in both species-depauperate and species-rich communities, but less competent hosts occurring only in more diverse communities (LoGiudice et al., 2003; Ostfeld and LoGiudice, 2003; LoGiudice et al., 2008). Although host species richness wasn't strictly nested in the Cascade meadows included in our study, host community composition did vary based on host richness. The relative abundances of the two most common host species, *E. glaucus* and *B. carinatus*, were negatively correlated with host species richness, and both the relative and total abundance of 'other' grass species increased with increasing host species richness. However, there is no evidence that *E. glaucus* or *B. carinatus* is acting as a reservoir host in this system. Both species had lower levels of infection than *F. idahoensis*, and mean prevalence was not correlated with the abundance of either species. While several studies have identified a particular focal host species responsible for the amplification and spillover of infection to other species (see examples above from Power and Mitchell, 2004 and LoGiudice et al., 2003), our results suggest that the different grass species present in these meadows vary in their transmission properties, without a single species driving infection patterns.

The third most important explanatory factor based on term weights was the physical landscape attributes. Although their model-averaged parameter estimates were not significant, the two principal component variables were included in the "best-fit" model with the lowest AICc value. The first principal component (PC1) had a parameter estimate of 0.007 (95% CI: -0.07 – 0.08), and the second principal component (PC2) had a parameter estimate of -0.135 (95% CI: -0.47 – 0.21) when both variables were considered simultaneously and an estimate of

-0.281 (95% CI: -0.61 – 0.04) when only PC2 was considered. The parameter estimate for PC1 is very close to zero, suggesting that this variable is not associated with prevalence. PC2 is positively correlated with both east- and south-facing aspects and negatively correlated with west- and north-facing aspects. Therefore, a (non-statistically significant) negative relationship between PC2 and prevalence indicates that prevalence is lower in meadows with S, E, or SE aspects and higher in meadows with N, W, and NW aspects. In a study of two species of planthoppers that transmit rice viruses in Japan, Noda and Kiritani (1989) found that the insects landed favorably in windward-facing valleys or on the side of hills facing away from the wind. The long-distance dispersal of cereal aphid species that vector B/CYDV is primarily guided by prevailing air currents above the atmospheric boundary layer, so topographic features that influence meteorological conditions or are situated favorably may experience higher landing rates by dispersing aphids (Irwin et al., 2007). One potential explanation for the association of north- and west-facing slopes with higher prevalence is that these sites experience higher rates of aphid immigration, although meadow aspect could also affect prevalence indirectly via its affect on the composition of the plant community. B/CYDV infection patterns can vary latitudinally, possibly in conjunction with precipitation and host community composition (Seabloom et al., 2010), but we did not see any relationship between infection and elevation across an elevation range from 1201-1558 m. It is possible that the dispersal ability of the aphid species that transmit B/CYDV supersedes the amount of variation in elevation

and landscape connectivity observed in the fragmented habitat of the Oregon Cascades included in this study.

Unlike in several recent studies of plant pathogens, landscape structure did not affect the prevalence of B/CYDV in Cascade meadows. The incidence or prevalence of several wind-dispersed fungal plant pathogens has been related to the size of local populations and their degree of connectivity in fragmented landscapes (Ericson et al., 1999; Smith et al., 2003; Laine and Hanski, 2006). Landscape structure also affects the spread and persistence of several animal pathogens; for example, habitat fragmentation and Lyme disease prevalence are positively correlated in the eastern US (Allan et al., 2003; Brownstein et al., 2005), and increasing landscape connectivity increases the likelihood of plague outbreaks in prairie dog colonies in the western US (Collinge et al., 2005; Snall et al., 2008). However, here meadow size and isolation did not explain a significant portion of the variation in prevalence. B/CYDV is vector- not wind-dispersed, so this suggests that aphid dispersal is not limited by the range of distances examined in this study. The minimum distance to the nearest meadow ranged from 120-752 m and the average distance to other meadows within a complex ranged from 310-914 m. Because several of the aphid species that transmit B/CYDV are capable of dispersing several hundred kilometers in short periods of time (Irwin et al., 1988), the distances among meadows in this study were probably not large enough for the viruses to be dispersal-limited. In addition, almost all of the grasses in this system are perennial, which means that B/CYDV does not have to recolonize each meadow annually.

The covariation among host species richness, total host abundance, and community composition makes it difficult to determine which factors are the main drivers of prevalence. However, our results clearly suggest that biotic factors are an important determinant of B/CYDV prevalence, because the two most important explanatory variables were host species richness and the relative abundance of 'other' grass species. Host species richness and the total abundance of hosts in a meadow community were likely correlated because environmental conditions favorable to grasses positively affect both the abundance and richness of grasses. Although observational studies cannot determine the mechanistic causes of the relationship between infection and various abiotic and biotic factors, our study does allow us to examine whether theoretical predictions about the role of host diversity and composition (Keesing et al., 2006) are still applicable in a natural system where other environmental factors have the potential to overshadow their importance. Even though meadows varied in their size, isolation, elevation, and primary productivity, local host composition was still an important determinant of prevalence.

A growing number of studies have demonstrated the importance of host diversity and composition on disease risk and prevalence (Keesing et al., 2006; LoGiudice et al., 2008; Allan et al., 2009; Dizney and Ruedas, 2009). Here we demonstrated that local context—host composition, richness, and meadow aspect—was a more important predictor of prevalence patterns than landscape structure or regional-scale environmental conditions. The use of multi-model inference and model averaging techniques permitted a comparison of the various potential ex-

planatory factors in a complex natural system. These methods largely avoid the problems, such as model over-fitting or unsupported reliance on a single "best fit" model, associated with traditional statistical techniques, particularly when there are significant correlations between the different potential explanatory variables. Determining whether host diversity or the presence of a particular set of host species is responsible for the correlation between host composition and prevalence will require experimental manipulation of the host community. Further research is also required in order to identify the causal mechanism behind the relationship between physical landscape attributes (particularly meadow aspect) and B/CYDV prevalence. The local and regional-scale population dynamics and dispersal behavior of aphid vector species are likely important determinants of spatial patterns of B/CYDV prevalence. Therefore, manipulating the vector and host communities in a complex landscape could provide insight into the general roles of vector behavior and population dynamics for the transmission dynamics of vector-transmitted pathogens.

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Table 5.1: The single factor candidate models and first the 10 models from the 95% confidence set of models for meadow-level prevalence. Model factors are the explanatory variables included in each model. The table indicates the number of parameters (k), AICc, $\Delta_i$values (difference between the AICc for a given model and the best fitting model), and the model Akaike weights (w_i). Number of model parameters includes intercept parameter.

Model Factors	k	AICc	Δ_i	w_i
(b) Single factor models				
Total grass abundance	2	111.4	10.6	0.0011
Host richness	2	114.0	13.2	<0.001
F. idahoensis relative abundance	2	116.0	15.2	<0.001
B. carinatus relative abundance	2	118.8	18.0	<0.001
Meadow composition attributes	4	119.0	18.2	<0.001
Relative abundance of other grasses	2	121.7	20.9	<0.001
Landscape structure attributes	3	122.3	21.5	<0.001
E. glaucus relative abundance	2	122.7	21.9	<0.001
Physical landscape attributes	3	123.8	23.0	<0.001
Meadow productivity attributes	4	127.0	26.2	<0.001
(a) Ten best models of the 54 total models in the 95% confidence set				
Host rich, other grass abund, phys land attr	5	100.8	0	0.220
Host rich, other grass abund	3	101.3	0.5	0.168
Host rich, other grass abund, *B. c.* abund	4	103.2	2.4	0.066
Host rich, other grass abund, total grass abund	4	104.1	3.3	0.042
Host rich, other grass abund, *F. i.* abund	4	104.1	3.3	0.041
Host rich, other grass abund, *E. g.* abund	4	104.2	3.4	0.040
Host rich, other grass ab, *E. g.* abund, phys land attr	6	104.5	3.7	0.034
Total grass abund., other grass abund	3	104.7	3.9	0.031
Host rich, other grass ab, *B. c.* abund, phys land attr	6	104.8	4.0	0.030
Host rich, other grass ab, tot grass ab, phys land attr	6	104.8	4.0	0.029

Table 5.2: Potential explanatory variables for site-level infection prevalence. Term weights (ς) are calculated by summing the Akaike weights (w_i) for all models in the 95% confidence set containing the explanatory variable. Parameter estimates are the model-averaged estimates ($\hat{\bar{\beta}}$) (see Methods section for details). 95% Confidence Intervals are calculated using the unconditional SE($\hat{\bar{\beta}}$) which incorporates a variance component arising from model selection uncertainty. Bold values are significantly different from 0 at the 95% confidence level.

Variable	Term wt (ς)	Param est ($\hat{\bar{\beta}}$)	95% CI
Host richness	**0.844**	**-0.330**	**-0.61 – -0.06**
Total host abundance	0.225	-0.0041	-0.02 – 0.01
F. idahoensis relative abundance	0.150	-0.067	-0.38 – 0.24
B. carinatus relative abundance	0.196	0.029	-0.29 – 0.35
E. glaucus relative abundance	0.160	-0.090	-0.46 – 0.28
Rel abundance of other grasses	**0.929**	**2.220**	**0.73 – 3.70**
Physical landscape attributes PC1	0.384	0.007	-0.07 – 0.08
Physical landscape attributes PC2	0.384	-0.135	-0.47 – 0.21
Meadow area	0.054	0.004	-0.03 – 0.04
Meadow isolation	0.054	5.63e-5	-1e-4 – 3e-4
Meadow productivity PC1	0.011	0.003	-0.01 – 0.01
Meadow productivity PC2	0.011	-0.004	-0.02 – 0.01
Meadow productivity PC3	0.011	-0.002	-0.01 – 0.01
Relative forb abundance	0	0	–
Relative legume abundance	0	0	–
Relative sedge abundance	0	0	–

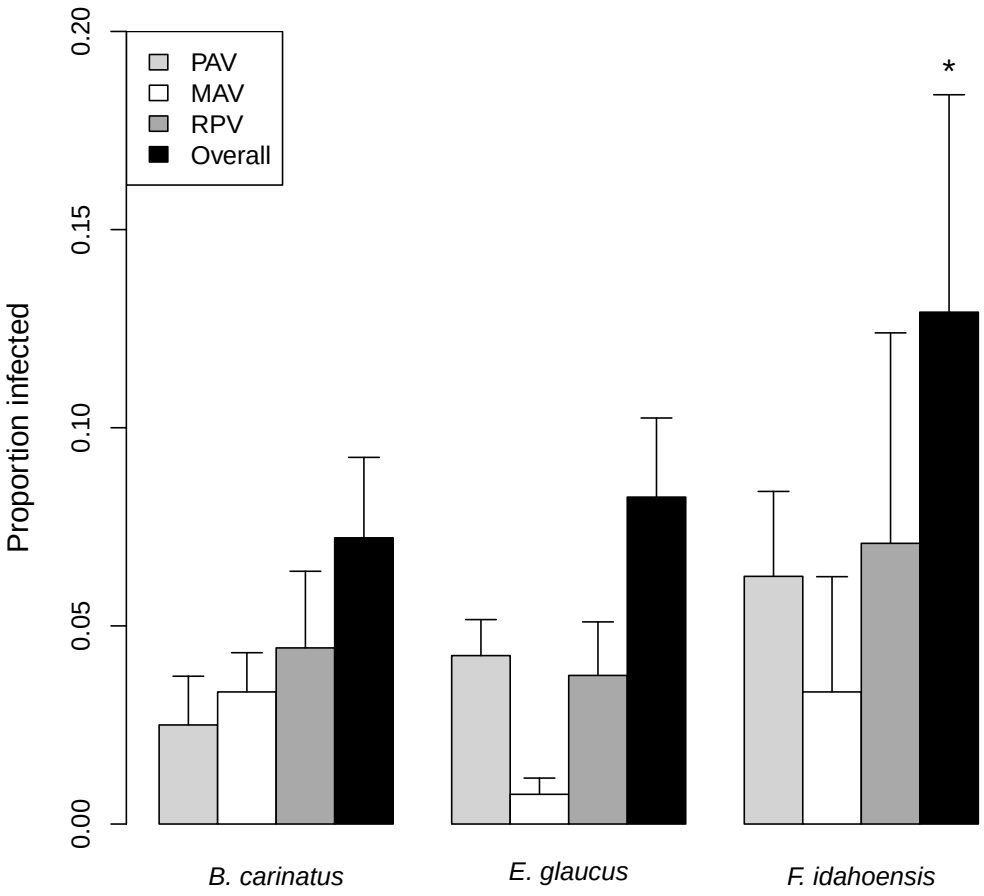

Figure 5.1: Proportion of infected individuals of three grass species: *Bromus carinatus*, *Elymus glaucus*, and *Festuca idahoensis*. PAV, MAV, RPV, and total prevalence of all strains combined. (*) Overall prevalence of *F. idahoensis* is significantly higher than overall prevalence in *B. carinatus* or *E. glaucus* (p=0.016). Error bars represent +1 SE.

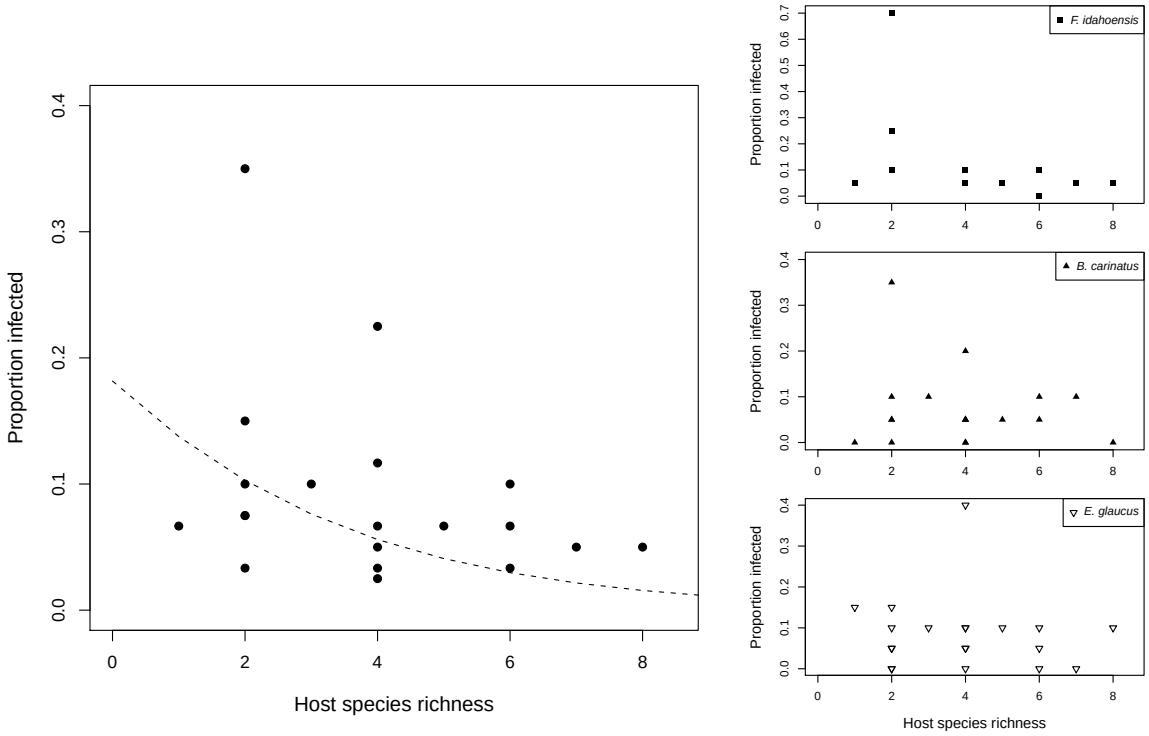

Figure 5.2: Association of the proportion of infected hosts in a meadow with host species richness. Left side of figure is mean prevalence averaged across all host species. Right side of figure is proportion of infected individuals of each of the three host species (*F. idahoensis, B. carinatus,* and *E. glaucus*). Dashed line represents the logistic regression $logit(y) = \hat{\bar{\beta}}_0 + \hat{\bar{\beta}}_1 rich$ where $\hat{\bar{\beta}}_0 = -1.51$ and $\hat{\bar{\beta}}_1 = -0.33$ are the model-averaged parameter estimates for the y-intercept and the host species richness variable.

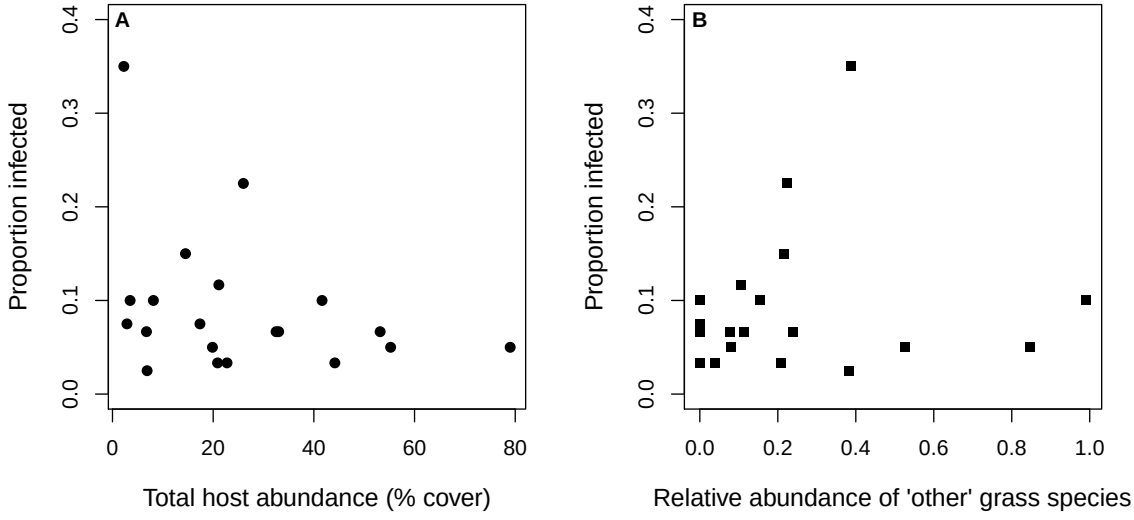

Figure 5.3: BYDV prevalence as a function of (a) total host abundance and (b) the relative abundance of grass species other than *F. idahoensis*, *B. carinatus*, and *E. glaucus*

Chapter 6 – Conclusion

Pathogens are an important component in ecological communities, often regulating host populations and influencing community structure (Collinge and Ray, 2006; Hatcher et al., 2006). Like other species interactions in ecological systems, host-pathogen interactions are influenced by environmental factors, landscape characteristics and the broader community context (Guernier et al., 2004; Keesing et al., 2006; Ostfeld et al., 2006*b*; Borer et al., 2010). In recent years there has been an increasing appreciation of the importance of studying diseases within the context of the larger ecological community, but research has largely been focused on a limited set of interactions. My thesis explores the potential influences of food-web interactions (Chapter 2), climate change (Chapter 3), landscape structure and host movement patterns (Chapter 4), and the combined influences of local community context and regional processes (Chapter 5) on host-pathogen interactions.

Host-pathogen interactions of infectious diseases transmitted by vectors depend on the population dynamics of the vector species as well as its interactions with other species within the community. In Chapter 2, I presented a theoretical model integrating predator-prey and host-pathogen theory that examines the effect of predator-vector interactions on vector-transmitted infectious diseases. The model predicts that predation on a vector may drastically slow the initial

spread of a pathogen and decrease the proportion of hosts infected at equilibrium. The presence of the predator can also increase host abundance indirectly by reducing or eliminating infection in the host population. In the absence of predation, pathogen prevalence and vector fecundity are positively correlated, but the introduction of a predator leads to a negative relationship between prevalence and vector fecundity, with the pathogen being driven out of the system at high rates of predation or vector fecundity. These results highlight the importance of studying interactions that—within the broader community—may alter our predictions when studying disease dynamics. It also suggests that the introduction of biological control agents to control vector populations can reduce prevalence or even eradicate a pathogen, particularly in productive environments where the vector population experiences a high turnover rate.

In Chapter 3 I examined how temperature influences the biology of a parasite, *Trypanosoma brucei rhodesiense,* and its tsetse fly vector in order to examine the potential effects of global warming on sleeping sickness in Eastern and Southern Africa. Model results indicate that projected warming over the next 50-100 years is likely to significantly shift the distribution of sleeping sickness in this region and these shifts in distribution may lead to an increase in the number of people at risk of infection. The modeling approach presented in Chapter 3 provides a framework for using the climate-sensitive aspects of vector and pathogen biology to predict disease prevalence and risk due to climate change. Chapter 3 focuses on looking at large scale changes in the geographic distribution of the disease, but this approach could also be used to explore likely changes in the risk of exposure

at the local level as well. Because the model examines the sensitivity of the pathogen reproductive number (R_0) to temperature, the potential intensity of an epidemic or equilibrium prevalence could also be examined.

The spread of infectious disease epidemics and spatial patterns of disease prevalence are influenced by landscape structure and the spatial structure of host populations (Hess et al., 2002; Plantegenest et al., 2007; Real and Biek, 2007). In Chapter 4, I developed a multi-host, multi-patch metapopulation disease model to identify the potential effects of landscape connectivity, patch heterogeneity, and host community composition on the initial spread, prevalence, and persistence of multi-host pathogens at the patch and regional scales. In addition, I also examined how the correlation of host traits associated with resistance to fragmentation, host quality and dispersal ability can affect the invasion and spread of multi-host pathogens in a fragmented landscape.

Spatial patterns of pathogen prevalence are determined by ecological processes acting across multiple spatial scales (Borer et al., 2010; Duffy et al., 2010). Host-pathogen interactions are influenced by the composition of the local community, mediated by larger-scale environmental conditions and landscape structure (Guernier et al., 2004; Collinge and Ray, 2006; Keesing et al., 2006; Ostfeld et al., 2006*b*; Borer et al., 2010). In Chapter 5 I investigated the role of local community interactions and the effects of landscape structure and regional processes on the dynamics of barley and cereal yellow dwarf viruses (B/CYDV) in the open meadows of the Cascade Mountains of Oregon by using variance components analysis to partition the sources of variation in B/CYDV prevalence. In addition

I used nd model selection techniques to determine which abiotic and biotic factors influence host-pathogen interactions in a Cascades meadow system. Prevalence varied by host species identity, with a significantly higher proportion of infected *Festuca idahoensis* individuals than *Elymus glaucus* or *Bromus carinatus*. While there was significant variation in prevalence between host species and between meadows in the same meadow complex, there was no evidence of any significant variation in prevalence between different meadow complexes at a larger spatial scale. Variation in prevalence between meadows was primarily associated with the local community context—host identity, the relative abundance of different host species, and host species richness—and the physical landscape attributes of the meadow. These results highlight the importance of local host community composition, mediated by landscape characteristics such as meadow aspect, as a determinant of the spatial patterns of infection of a multi-host pathogen.

Until recently only the outcome of direct interactions between a single host and pathogen had received much attention in ecology, despite the extensive role pathogens can play in natural communities (Collinge and Ray, 2006). Results from my dissertation highlight the importance of considering host-pathogen interactions within a broader community context and at multiple spatial scales. The local prevalence of B/CYDV in Cascade meadows is influenced by the diversity and composition of the host community, a phenomenon that occurs in many other disease systems (LoGiudice et al., 2003; Power and Mitchell, 2004; Keesing et al., 2006; LoGiudice et al., 2008; Allan et al., 2009; Dizney and Ruedas, 2009). Local B/CYDV prevalence also depended on the orientation of the meadow within a

larger landscape, and in Chapter 4 I also demonstrated how landscape connectivity can influence the spread and prevalence of a broad range of multi-host pathogens. In the case of vector-borne pathogens, vector population dynamics will influence host-pathogen interactions. Using mathematical models I demonstrated that predator-vector interactions can influence both pathogen persistence and host abundance, and that geographic patterns of disease risk are influenced by the responses of both vector and parasite biology to changing environmental conditions.

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APPENDICES

Appendix A – Dynamic host population model equilibria

The model incorporating host population demographics represented by equation (2.4) has eight biologically relevant equilibria. Equilibria (i-vi) are all disease-free equilibria with different combinations of the host, vector, and predator populations present at equilibrium. Because the vector population does not depend on the host as a resource, the vector and predator populations can persist in the absence of the host. Equilibrium (vii) represents an endemic disease equilibrium in the host and vector populations in the absence of the predator; while the host, vector, predator, and pathogen populations are all present in equilibrium (viii). The equilibrium equations for the total host density (H^*) when the pathogen is present are too complex to display succinctly. However, the equilibrium values for the other populations can be solved as a function of H^*. Note that $K_H = \frac{(b_H - m_H)}{b_H \phi}$ represents the carrying capacity of the host population in the absence of infection.

Equilbrium (i):

$I^* = 0,\ H^* = 0,\ U^* = 0,\ V^* = 0,\ P^* = 0.$

Equilibrium (ii):

$I^* = 0,\ H^* = K_H,\ U^* = 0,\ V^* = 0,\ P^* = 0.$

Equilibrium (iii):

$I^* = 0,\ H^* = 0,\ U^* = (b_N - m_N)/d_N,\ V^* = 0,\ P^* = 0.$

Equilibrium (iv):

$I^* = 0,\ H^* = K_H,\ U^* = (b_N - m_N)/d_N,\ V^* = 0,\ P^* = 0.$

Equilibrium (v):

$I^* = 0,\ H^* = 0,\ U^* = m_P/\epsilon\alpha,\ V^* = 0,\ P^* = \frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V}).$

Equilibrium (vi):

$I^* = 0,\ H^* = K_H,\ U^* = m_P/\epsilon\alpha,\ V^* = 0,\ P^* = \frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V}).$

Equilibrium (vii):

$I^* = \frac{\beta_{VH}\beta_{HV}H^*(b_N - m_N) - b_N d_N \gamma}{\beta_{HV}(\beta_{VH}(b_N - m_N) + \gamma d_N)},$

$H^* = H^*,$

$U^* = \frac{b_N(\beta_{VH}(b_N - m_N) - d_N\gamma)}{\beta_{VH} d_N(\beta_{HV}H^* + b_N)},$

$V^* = \frac{\beta_{VH}\beta_{HV}H^*(b_N - m_N) - b_N d_N \gamma}{\beta_{VH} d_N(\beta_{HV}H^* + b_N)},$

$P^* = 0.$

Equilibrium (viii):

$I^* = \frac{\beta_{VH}\beta_{HV}H^* m_P - \alpha\epsilon b_N \gamma}{\beta_{HV}(\beta_{VH} m_P + \epsilon\alpha\gamma)},$

$H^* = H^*,$

$U^* = \frac{b_N(\beta_{VH} m_P - \epsilon\alpha\gamma)}{\epsilon\alpha\beta_{VH}(\beta_{HV}H^* + b_N)},$

$V^* = \frac{\beta_{VH}\beta_{HV}H^* m_P - \alpha\epsilon b_N \gamma}{\epsilon\alpha\beta_{VH}(\beta_{HV}H^* + b_N)},$

$P^* = \frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V}).$

Appendix B – Frequency-dependent model formulation

The constant host population model with frequency-dependent transmission is:

$$\begin{aligned}
\frac{dI}{dt} &= \beta_{VH} V(H-I)/H - \gamma I, \\
\frac{dU}{dt} &= b_N(U+V) - \beta_{HV} UI/H - (m_N + d_N(U+V))U - \alpha UP, \\
\frac{dV}{dt} &= \beta_{HV} UI/H - (m_N + d_N(U+V))V - \alpha VP, \\
\frac{dP}{dt} &= \epsilon\alpha(U+V)P - m_P P.
\end{aligned} \tag{B.1}$$

The vector and predator population dynamics are identical to the density-dependent model described in equation (2.1). The only alteration to the system equations is the alteration of the disease transmission terms from $\beta_{VH} SV$ and $\beta_{HV} IU$, to $\beta_{VH} SV/H$ and $\beta_{HV} IU/H$. Because disease transmission depends on the frequency of infection in the host population as opposed to the density of the host population, the pathogen reproduction rate, R_0, differs between the two models. The equation for R_0 with frequency-dependent disease transmission is:

$$R_0 = \sqrt{N/H}\frac{\sqrt{\beta_{VH}\beta_{HV}}}{\sqrt{\gamma(m_N + d_N N + \alpha P)}}. \tag{B.2}$$

The equilibrium values for the total vector population (N) and the predator population (P) are the same whether disease transmission is density or frequency dependent. The equilibrium densities of infected hosts (I) and infectious vectors

(V) differ from the equilbrium densities in the density-dependent model as follows:

Equilbrium (i):

$I^* = 0,\ U^* = 0,\ V^* = 0,\ P^* = 0.$

Equilibrium (ii):

$I^* = 0,\ U^* = (b_N - m_N)/d_N,\ V^* = 0,\ P^* = 0.$

Equilibrium (iii):

$I^* = 0,\ U^* = m_P/\epsilon\alpha,\ V^* = 0,\ P^* = \frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V}).$

Equilibrium (iv):

$I^* = \frac{H(\beta_{VH}\beta_{HV}H(b_N - m_N) - b_N d_N \gamma H)}{\beta_{HV}(\beta_{VH}(b_N - m_N) + \gamma d_N H)},$

$U^* = \frac{b_N(\beta_{VH}(b_N - m_N) - d_N\gamma H)}{\beta_{VH}d_N(\beta_{HV} + b_N)},$

$V^* = \frac{\beta_{VH}\beta_{HV}(b_N - m_N) - b_N d_N \gamma H)}{\beta_{VH}d_N(\beta_{HV} + b_N)},$

$P^* = 0.$

Equilibrium (v):

$I^* = \frac{H(\beta_{VH}\beta_{HV}m_P - \alpha\epsilon b_N\gamma H)}{\beta_{HV}(\beta_{VH}m_P + \epsilon\alpha\gamma H)},$

$U^* = \frac{b_N(\beta_{VH}m_P - \epsilon\alpha\gamma H)}{\epsilon\alpha\beta_{VH}(\beta_{HV} + b_N)},$

$V^* = \frac{\beta_{VH}\beta_{HV}m_P - \alpha\epsilon b_N\gamma H}{\epsilon\alpha\beta_{VH}(\beta_{HV} + b_N)},$

$P^* = \frac{(b_N - m_N)}{\alpha}(1 - \frac{m_P}{\epsilon\alpha K_V}).$

Appendix C – Additional model extensions

C.1 Acquired host immunity

The addition of a recovered class (R) with acquired immunity in the host population does not change the qualitative effects of predation on pathogen prevalence or persistence. The constant host population model with host immunity is:

$$\begin{aligned}
\frac{dS}{dt} &= m_H(S+I+R) - \beta_{VH}SV - m_H S \\
\frac{dI}{dt} &= \beta_{VH}SV - \gamma I - m_H I, \\
\frac{dR}{dt} &= \gamma I - m_H R, \\
\frac{dU}{dt} &= b_N(U+V) - \beta_{HV}IU - (m_N + d_N(U+V))U - \alpha UP, \\
\frac{dV}{dt} &= \beta_{HV}IU - (m_N + d_N(U+V))V - \alpha VP, \\
\frac{dP}{dt} &= \epsilon\alpha(U+V)P - m_P P.
\end{aligned} \tag{C.1}$$

The equations representing the predator (P) and vector (U and V) populations are indentical to the basic model (Equation 2.1). Infected host individuals recover at a rate γ, and then remain immune to reinfection for life. The modified pathogen reproduction number with host immunity is:

$$R_0 = \sqrt{NH}\frac{\sqrt{\beta_{VH}\beta_{HV}}}{\sqrt{(\gamma + m_H)(m_N + d_N N + \alpha P)}}. \tag{C.2}$$

The rate at which infected hosts recover and become immune (γ) appears in the denominator of R_0, indicating that acquired host immunity lowers the pathogen reproduction number, and lowers the threshold at which predation can eliminate the pathogen from the system (Figure C.1). Figure (C.1) shows that predation decreases pathogen prevalence in the host population whether or not hosts are immune to infection, and an increase in the recovery rate decreases pathogen prevalence.

C.2 Vector latency period

For many diseases, vectors experience a latent period between their initial exposure to a pathogen and when they become infectious (Anderson and May, 1991). For some diseases, such as malaria, the length of this latent period relative to the lifespan of the vector is an important factor in determining pathogen persistence (Macdonald, 1957). In the malaria model originally developed by Ross (1910), extending the latent period decreases the basic pathogen reproduction number, R_0, and reduces equilibrium prevalence. Similarly, our basic model can be extended by adding an exposed vector class, E, to equation (2.1):

$$\frac{dE}{dt} = \beta_{HV} IU - \eta E - (m_N + d_N(U+V))E - \alpha EP. \tag{C.3}$$

When the pathogen is transmitted to an uninfected vector, the vector now enters the exposed class and then becomes infectious at a rate, η. Because vectors in

the exposed class may be killed by the predator before they become infectious, adding a vector latency period raises the minimum vector threshold density, N_T, for pathogen persistence, and further lowers pathogen prevalence at equilibrium. The adjusted pathogen reproduction number with vector latency is

$$R_0 = \sqrt{NH}\frac{\sqrt{\beta_{VH}\beta_{HV}\eta}}{\sqrt{(m_H)(\eta + m_N + d_N N + \alpha P)(m_N + d_N N + \alpha P)}}. \tag{C.4}$$

Increasing the length of this latent period (reducing η) decreases R_0 and increases N_T, increasing the chance that predation will be sufficient to eradicate the pathogen by driving $R_0 < 1$.

C.3 Predator functional response

We initially assumed that the predator has a Holling type I linear functional response to vector abundance—as vector density increases, per capita predation scales linearly at the rate αN. However, this assumption becomes biologically unrealistic at high vector densities as the individual predator attack rate becomes limited by the time required to handle and digest each prey item. This saturating predator functional response can be represented by a Holling type II functional response (Holling, 1959):

$$\begin{aligned}
\frac{dI}{dt} &= \beta_{VH}(H-I)V - \gamma I, \\
\frac{dU}{dt} &= b_N N - \beta_{HV} IU - (m_N + d_N N)U - \frac{\alpha' U}{f+N}P, \\
\frac{dV}{dt} &= \beta_{HV} IU - (m_N + d_N N)V - \frac{\alpha' V}{f+N}P, \\
\frac{dP}{dt} &= \epsilon \frac{\alpha' N}{f+N}P - m_P P.
\end{aligned} \tag{C.5}$$

The adjusted pathogen reproduction number is:

$$R_0 = \sqrt{NH}\frac{\sqrt{\beta_{VH}\beta_{HV}}}{\sqrt{\gamma(m_N + d_N N + \frac{\alpha'}{f+N}P)}}. \tag{C.6}$$

Introducing a type II functional response does not change the qualitative effect of predation on pathogen prevalence and persistence. The presence of a predator still lowers pathogen prevalence, and increasing the strength of predation leads to a decline in pathogen prevalence. With a type I functional response the proportion of infected hosts always reachs a stable equilibrium. In contrast, increasing predation strength with a type II functional response leads to cycles in pathogen prevalence in the host (Figure C.2). These cycles occur because predator and vector densities oscillate, leading to oscillation in the force of infection experienced by the host population. Despite these oscillations, predation can still eliminate the pathogen from the system while vector densities are > 0.

When the predator has a type I functional response, increasing the vector birth rate leads to a decline in pathogen prevalence. With a type II functional

response, increasing the vector birth rate initially leads to a decline in prevalence. However, at higher vector birth rates the predator's per capita consumption rate becomes saturated and further increases in the birth rate do not reduce the mean pathogen prevalence (Figure C.3a). The relationship between the vector's non-predation mortality rate (m_N) and pathogen prevalence also depends on the predator's functional response. With a type I response, increasing m_N does not affect pathogen prevalence in the host population as long as the predator is present (Figure 2.4b). If the predator has a type II response, increasing m_N leads to a decrease in pathogen prevalence when m_N is low enough that the predator's per capita consumption rate is saturated (Figure C.3b). Once m_N is high enough that the predator's per capita consumption rate is no longer saturated, further increases in m_N do not affect pathogen prevalence.

C.4 Predator selectivity

The capacity of predators to selectively prey on infectious or non-infectious vectors could also alter the quantitative effect of predation on pathogen prevalence. For example, East African jumping spiders (*Evarcha culicivora*) preferentially prey on female *Anopheles* mosquitoes carrying blood meals, and therefore are more likely to be carrying the malarial parasite (Nelson and Jackson, 2006). Our model predicts that if the predator preferentially preys on susceptible vectors, the negative effect of predation on pathogen prevalence is weakened, but predation never increases prevalence. Preferential predation on exposed or infectious

vectors enhances the negative effects of predation on prevalence, and lowers the threshold for disease eradication. Predation consistently reduces pathogen prevalence in the host and vector populations under different assumptions about host demographics or immunity, latency, and predator selectivity.

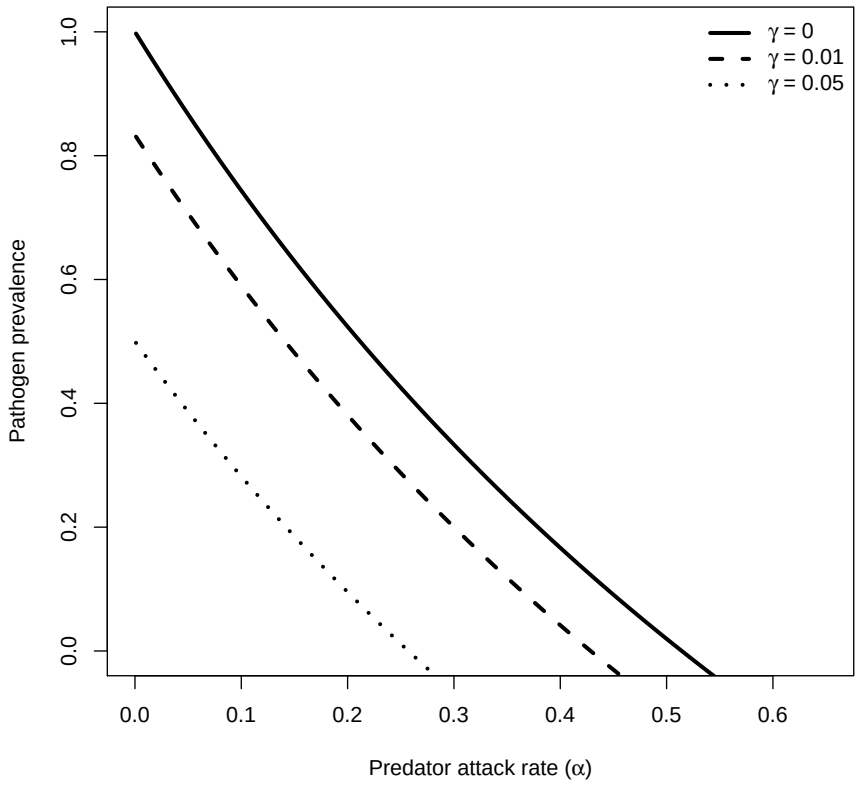


Figure C.1: Disease prevalence in the host population as a function of predator attack rate (α) for three different host recovery rates (γ) with lifelong immunity for recovered individuals. The other model parameters values are $H = 1$, $\beta_{VH} = 0.2$, $\beta_{HV} = 0.2$, $\gamma = 0.05$, $b_N = 0.35$, $m_N = 0.1$, $d_N = 0.05$, $\epsilon = 0.25$, $m_P = 0.1$.

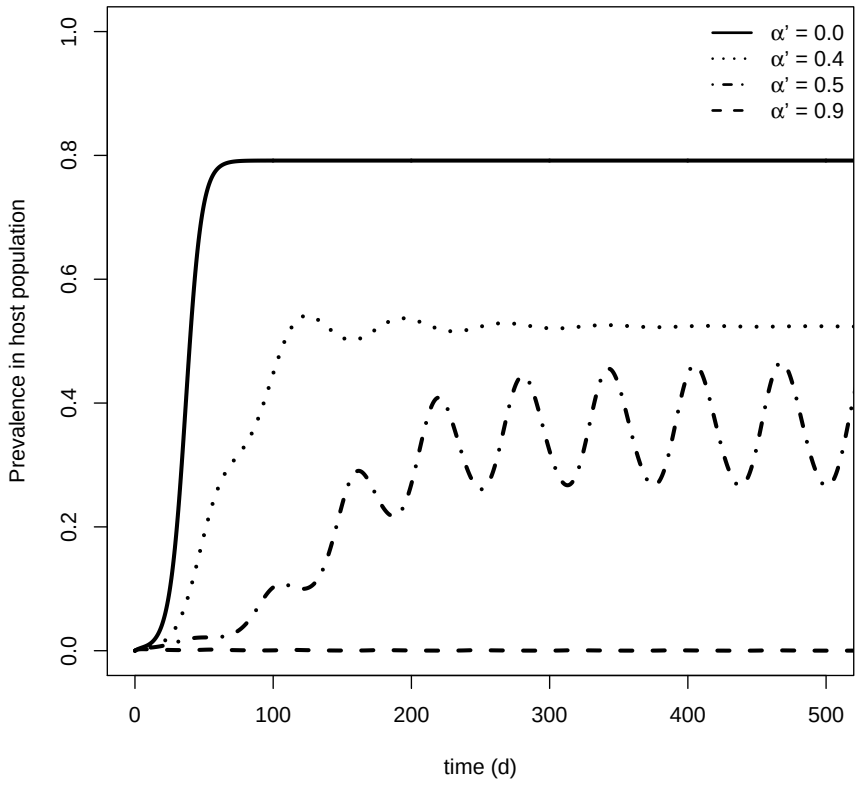
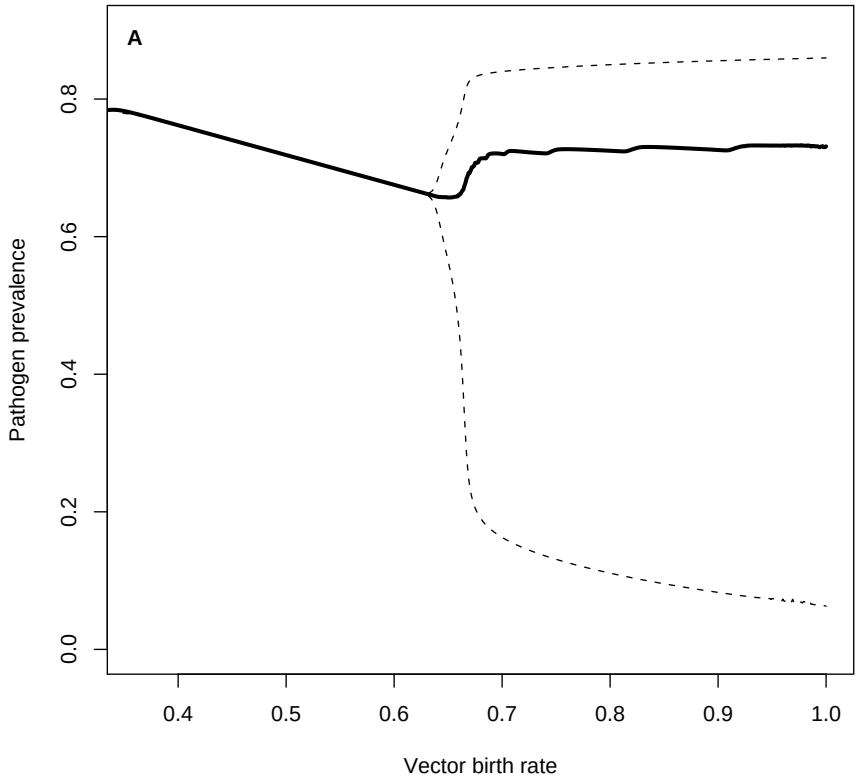


Figure C.2: Model of an epidemic outbreak for different values of $\alpha^{'}$ for a predator with a type II functional response. At $t = 0$, the host population is entirely susceptible and 1% of the vector population is infectious. Parameters values are $H = 1$, $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $\gamma = 0.05$, $b_N = 0.35$, $d_N = 0.05$, $m_N = 0.1$, $\epsilon = 0.25$, $m_P = 0.1$, $f = 1$.


A
Pathogen prevalence
0.0
0.2
0.4
0.6
0.8
0.4
0.5
0.6
0.7
0.8
0.9
1.0
Vector birth rate

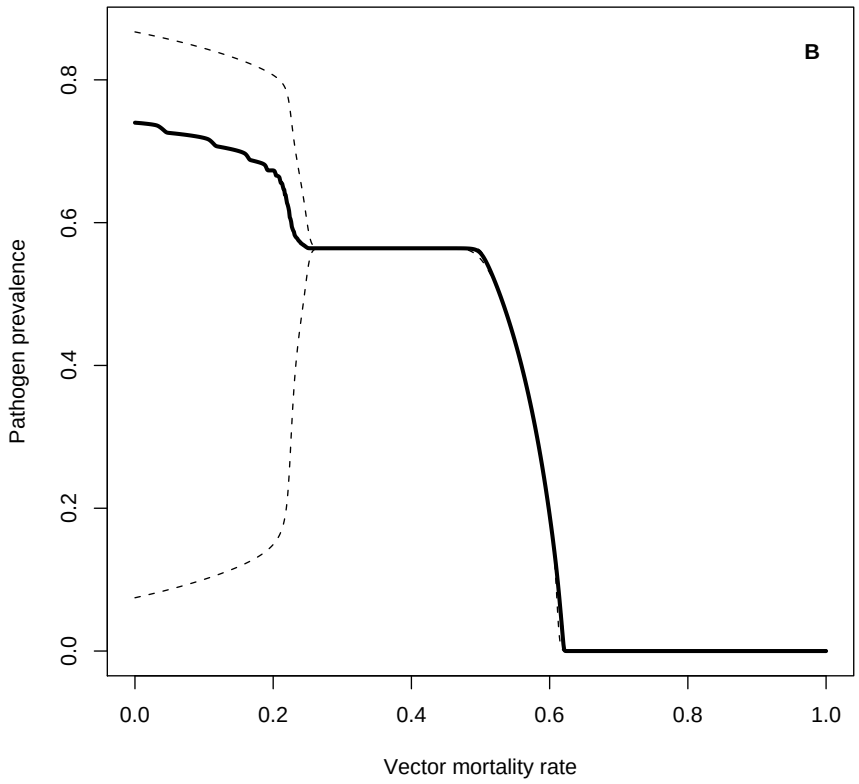


Figure C.3: (a) Pathogen prevalence, represented as the proportion of the host population that is infected, as a function of the vector birth rate (b_N) when the predator has a type II functional response. (b) Pathogen prevalence in the host population as a function of the non-predation vector mortality rate (m_N). Solid lines represent mean prevalence and dashed lines represent the minimum and maximum prevalence values when prevalence is cyclical. Parameters values are $H = 1$, $\beta_{VH} = 0.15$, $\beta_{HV} = 0.15$, $\gamma = 0.05$, $b_N = 0.7$ (b only), $d_N = 0.05$, $m_N = 0.1$ (a only), $\alpha^{'} = 0.5$, $\epsilon = 0.25$, $m_P = 0.1$, $f = 1$.

Appendix D – Trypanosomiasis parameter values

Trypanosoma brucei rhodesiense infections in humans typically reach the central nervous system within 2 months of infection and most ($> 80\%$) untreated individuals die within 6 months of infection (Odiit et al., 1997). The average duration from onset of symptoms to death during one epidemic in Uganda was 108 days in the absence of treatment (Odiit et al., 1997, 2005), so we assume that the daily instantaneous mortality rate due to infection is $\kappa_H = 0.0093d^{-1}$. This rate is only an approximation because it ignores the incubation period prior to the onset of symptoms, as well as additional mortality in treated individuals that can be as high as 10%. Determining a recovery rate in humans is difficult because recovery is only possible through medical treatment of an infection, but the number of undetected cases per detected case may be fairly high (Odiit et al., 2005). Odiit et al. (2005) found that during the 1988-1990 sleeping sickness outbreak in Tororo, Uganda an estimated 39% of the cases went undetected and untreated (presumably leading to death), 20% were reported during the early stages of illness, and 42% did not present until the later stages. Based on these percentages, and average times from the onset of symptoms to treatment of 45 days and 94 days for early and late cases respectively (Odiit et al., 2005), we have calculated a recovery rate of $\gamma_H = 0.009d^{-1}$ for humans.

Many domestic livestock and wildlife species can be infected by *T. b. rhodesiense* (Hide et al., 1996; Waiswa et al., 2003; Welburn et al., 2004), and these species show a wide range in their resistance or tolerance to infection (Murray et al., 1982). The relative importance of wildlife species versus domestic livestock as a reservoir for *T. b. rhodesiense* depends on their local densities and proximity to humans and tsetse habitat, but in many regions of East Africa cattle are increasingly becoming an important reservoir species due to land use changes that reduce the abundance of potential wildlife hosts in areas of moderate or heavy human habitation (Welburn et al., 2006). Following an outbreak of Rhodesian sleeping sickness in the Lambwe Valley of Kenya in the early 1980s, Wellde et al. (1989*a*) found that the local breeds of Zebu cattle had high levels of *T. b. rhodesiense* infection and several showed signs of illness. A subsequent study with several local cattle breeds found that close to 50% of experimentally infected cattle eventually died from the illness, with the time to death ranging from 85-1613 days (Wellde et al., 1989*b*). Based on the results of this study we have calculated a disease-induced mortality rate for animal hosts of $\kappa_A = 0.0008d^{-1}$. All of the cattle in the study by Wellde et al. (1989*b*) became infected and parasitemia levels in the blood typically remained high enough to infect tsetse flies for 3-5 months. Therefore we assume that the recovery rate of infected reservoir hosts is $\gamma_A = 0.0083d^{-1}$.

Dale et al. (1995) found that the average development period for *T. b. rhodesiense* in *G. m. morsitans* was 18 days under laboratory conditions at 25 °C, resulting a parasite development rate of $\mu = 0.056d^{-1}$. The mortality rate of adult

tsetse is species-, sex-, and temperature-dependent (Hargrove, 2004); therefore, the estimate of tsetse mortality is discussed in more detail in subsection (3.2.2.1) describing the relationship between tsetse mortality and temperature. A preference of tsetse for non-human over humans hosts of $\rho = 25$ was estimated from tsetse blood meal data collected in 3 districts of south-eastern Uganda (Waiswa et al., 2006), and human and livestock population estimates for each of these 3 districts from the 2002 national census and the 2006 livestock census. This strong preference of *Glossina* for non-human hosts has been observed in other studies of tsetse feeding preferences (Weitz, 1963; Clausen et al., 1998).

Field-derived estimates of the probability of infectious tsetse flies transmitting *T. brucei* are extremely limited. Although previous studies have assumed that the efficiency of transmission from tsetse to competent host species is relatively high, Baylis (1997) found that the probabilities of transmission from *G. pallidipes* and *G. longipennis* to cattle for *T. vivax* and *T. congolense* were only 0.84% and 2.36% respectively. Because the development of *T. brucei* in tsetse flies is more similar to that of *T. congolense* than *T. vivax* (Leak, 1999), we have assumed that the probability of transmission of *T. b. rhodesiense* from tsetse to animals or humans is comparable to the *T. congolense* transmission efficiency of 0.0236. We could not find any accurate estimates of the average probability of tsetse flies acquiring *T.b. rhodesiense* from an infected host during a blood meal. However, Baylis (1997) found that the susceptibility of *G. palpalis* to infection with *T. b. gambiense* was 3.55%, so we assume a transmission probability from either human or animal hosts to tsetse of 0.0355.

Initial human, animal, and tsetse abundances are 1000, 2000, and 60,000 respectively. These values represent abundances for a small village near prime tsetse habitat.

Appendix E – Further details for multi-host, multi-patch model

E.1 Transmission terms

The introduction of new susceptibles of species i occurs at a rate determined by the function $b_i(N_i) = b_i(1 - N_{ip}/K_{ip})$. New individuals of each species are born into the susceptible class at a species-specific birth rate, b_i, that is also dependent on K_{ip}, the carrying capacity for species i in patch p. Density-independent mortality occurs from all classes at a species-specific mortality rate, d_i. In addition, infected individuals may suffer additional mortality at a species-specific rate, δ_i. Infectious individuals of each species recover and enter the recovered class at a species-specific rate, γ_i.

Susceptible individuals of species i in each patch can become infected as a result of either intra- or interspecific transmission within the patch. Disease transmission to species i in patch p is determined by the function,

$$\beta(N_{ip}) = \sum_{j=1}^{s} \beta_{ij}(N_j) S_{ip} I_{jp}. \tag{E.1}$$

Within-species (intraspecific) transmission occurs when $i = j$, and between-species (interspecific) transmission from species j to species i occurs when $i \neq j$. The transmission term is $\beta_{ij}(N_j) = \beta_{ij}/N_j$ for frequency-dependent transmission, and $\beta_{ij}(N_j) = \beta_{ij}$ for density-dependent transmission. The transmission function,

$\beta(N_{ip})$, for each patch can also be represented via a "who acquires infection from whom" (WAIFW) matrix (Dobson, 2004). Here we have assumed that the within- and between-species transmission rates are species-specific, but do not vary among patches; therefore, $\beta(N_{ip}) = \beta(N_i)$ in each patch.

E.2 Migration terms

The movement of species i in and out of patch p is determined by the function,

$$M_i(N_i) = \sum_{q=1}^{n} m_{ipq} N_{iq} - \sum_{q=1}^{n} m_{iqp} N_{ip} \tag{E.2}$$

Equation (E.2) represents the movement of all individuals of species i, replacing N with S, I, or R represents movement of individuals of the susceptible, infected, and recovered classes respectively. The movement (i.e. migration or dispersal) rate for species i to patch p from patch q is m_{ipq}. Therefore, in equation (E.2) the first summation term, represents the combined movement of individuals of species i into patch p from all other patches $q = 1, ..., n$; and the second summation term, represents the movement of species i out of patch p to patches $q = 1, ..., n$. We assume that migration does not depend on infection status, although this assumption can be relaxed for diseases such as rabies that can increase movement rates, or other diseases that result in morbidity and thus decrease the movement of infectious or recovered individuals.

E.3 Full Model

By incorporating the detailed descriptions of the birth, transmission, and migration terms into our model we obtain the full version of equation (4.1):

$$\begin{aligned}
\frac{dS_{ip}}{dt} &= b_i(1 - N_{ip}/K_{ip})N_{ip} - d_i S_{ip} - \sum_{j=1}^{s} \beta_{ij}(N_j) S_{ip} I_{jp} + \sum_{q=1}^{n} m_{ipq} S_{iq} - \sum_{q=1}^{n} m_{iqp} S_{ip} \\
\frac{dI_{ip}}{dt} &= \sum_{j=1}^{s} \beta_{ij}(N_j) S_{ip} I_{jp} - (d_i + \delta_i) I_{ip} - \gamma_i I_{ip} + \sum_{q=1}^{n} m_{ipq} I_{iq} - \sum_{q=1}^{n} m_{iqp} I_{ip} \qquad \text{(E.3)} \\
\frac{dR_{ip}}{dt} &= \gamma_i I_{ip} - d_i R_{ip} + \sum_{q=1}^{n} m_{ipq} R_{iq} - \sum_{q=1}^{n} m_{iqp} R_{ip}
\end{aligned}$$

Appendix F – Model selection criteria for B/CYDV prevalence data

Models were selected from the candidate set of models using bias-adjusted Akaike's information criterion (AICc). AICc adjusts for bias when the ratio of the number of observations (N) to the number of parameters (K) is below 40 (Burnham and Anderson, 2002). In our case, $N/K = 20/16 = 1.25$, which is well below 40. AICc is defined as

$$AICc = -2L(\hat{\theta}_i|data) + 2K + 2K * (K+1)/(N-K-1), \qquad \text{(F.1)}$$

where L is the log likelihood of the model parameters, $\hat{\theta}_i$, given the data. The first half of the equation represents the traditional AIC formula and the second half is the bias adjustment for small sample size. Therefore, AICc represents the likelihood of the data given the model and a penalty for the number of parameters in the model, with an extra penalty for additional parameters that becomes steeper as the ratio of N/K decreases. The individual AICc values for each model are not meaningful, rather they are used for comparison purposes with the other candidate models. The best model is the one with the smallest AICc ($AICc_{min}$). All other models are then compared to the best model by calculating their AICc difference (Δ_i):

$$\Delta_i = AICc_i - AICc_{min}, \qquad \text{(F.2)}$$

which represents the loss of information for model g_i compared to the g_{min}. Models with Δ_i values of less than 2 are considered to have substantial support, while models with $\Delta_i > 10$ are considered to have almost no support (Burnham and Anderson, 2002). The AICc differences can also be used for model comparison and multi-model inference by using them to calculate Akaike weights for each model (Burnham and Anderson, 2002):

$$w_i = \frac{\exp(-\frac{1}{2}\Delta_i)}{\sum_{r=1}^{R} \exp(-\frac{1}{2}\Delta_r)}. \tag{F.3}$$

The Akaike weights, w_i, sum to 1 for all R candidate models and represent the probability that model g_i is the best model (from an information theoretic standpoint) among the candidate set of models. A confidence set of models is then chosen from the candidate set of models by selecting the smallest subset of models that have a sum of $w_i \geq 0.95$. The confidence set represents a set of models for which we have a 95% confidence that the set contains the best approximation of the true model from among the candidate models.

An assessment of the relative importance of the various explanatory variables was conducted using the confidence set of models. Rather than infer the significance of a variable from a single "best" model, the importance of each potential explanatory variable, x, can be calculated based on how frequently the variable was included as a parameter in the confidence set of models (Johnson and Omland, 2004; Whittingham et al., 2006). The Akaike weights are summed for all models from the confidence set containing the variable in order to calculate a

term (predictor) weight, ς_x, for each variable. The term weight is the probability that variable x is in the best approximating model, and provides a measure of the explanatory importance of each variable (Burnham and Anderson, 2002). The confidence set of models (C) was also used to calculate model-averaged parameter estimates. The weighted average for parameter β_k across all models in the confidence set is:

$$\hat{\bar{\beta}}_k = \sum_{i=1}^{C} w_i \hat{\beta}^{+}_{k,i}. \tag{F.4}$$

$\hat{\beta}^{+}_{k,i}$is the estimate of $\beta_k$when the variable x_k is included in model i; otherwise $\hat{\beta}^{+}_{k,i} = 0$. Because model-averaged parameter estimates are not conditional on a single model, there is an additional variance component due to model selection uncertainty that needs to be incorporated into the precision (standard error) of parameter estimates (Burnham and Anderson, 2002). The unconditional standard error of $\hat{\bar{\beta}}$ is

$$SE(\hat{\bar{\beta}}) = \sum_{i=1}^{R} w_i \sqrt{\hat{var}(\hat{\beta}_i|g_i) + (\hat{\beta}_i - \hat{\bar{\beta}})^2}, \tag{F.5}$$

where $\hat{var}(\hat{\beta}_i|g_i)$ represents the variance of the estimate$\hat{\beta}_i$ conditional on model g_i, and $(\hat{\beta}_i - \hat{\bar{\beta}})^2$ is an additional variance component representing model uncertainty. As with the term weights and parameter estimates, the variance is summed across all models weighted by w_i. The unconditional standard errors were used to calculate 95% confidence intervals for each model-averaged parameter estimate. Model averaging can reduce bias and increase precision compared to analysis based on a single best model. Burnham and Anderson (2002) used Monte

Carlo simulations to show that confidence interval coverages for model-averaged estimates approached the nominal level and were less biased than estimates from single models selected from large candidate sets.