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Can antibodies against flies alter malaria transmission in birds by changing vector behavior?

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HIGHLIGHTS

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- Change vector behavior.
- Affect disease prevalence.

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ABSTRACT

Transmission of insect-borne diseases is shaped by the interactions among parasites, vectors, and hosts. Any factor that alters movement of infected vectors from infected to uninfeced hosts will in turn alter pathogen spread. In this paper, we study one such pathogen–vector–host system, avian malaria in pigeons transmitted by fly ectoparasites, where both two-way and three-way interactions play a key role in shaping disease spread. Bird immune defenses against flies can decrease malaria prevalence by reducing fly residence time on infected birds or increase disease prevalence by enhancing fly movement and thus infection transmission. We develop a mathematical model that illustrates how these changes in vector behavior influence pathogen transmission and show that malaria prevalence is maximized at an intermediate level of defense avoidance by the flies. Understanding how host immune defenses indirectly alter disease transmission by influencing vector behavior has implications for reducing the transmission of human malaria and other vectored pathogens.

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1. Introduction

Species interactions in ecological communities create the network of influences that different species have on one another (Abrams, 1987). The population dynamics and behavior of any one species can directly or indirectly affect the community as a whole. Most simply, we can think of a community as a set of two-way interactions between species that directly affect each other. However, these direct pairwise interactions can be modified by the presence or density of other species (Adler and Morris, 1994), generating three-way or even higher-order interactions (Dungan, 1986; Billick and Case, 1994; Wootton, 1994). These interactions define the role that species play within communities and create the potentially complex chains by which they positively or negatively affect the species around them.

Although pathogens are necessarily involved in a pairwise interaction with their hosts, those with multiple hosts can find themselves embedded in complex of higher-order interactions. Among the most widespread of these are pathogens transmitted by arthropod vectors in wildlife, agricultural, and human communities. The full suite of interactions that regulate host–vector–pathogen dynamics shape vector-borne disease transmission, and thus pathogen prevalence, in the host community. This transmission involves a triangle (Fig. 1) of pairwise interactions between parasites or pathogens, vectors, and vertebrate hosts. Movement of infected vectors from infected to uninfected hosts plays a central role in pathogen spread, and any factor that affects this movement has the potential to generate a higher-order interaction.

In this paper, we study one such pathogen–vector–host system where complex three-way interactions play key roles in controlling disease spread. Many species of haemosporidian parasites infect birds, including *Plasmodium* and related genera which are

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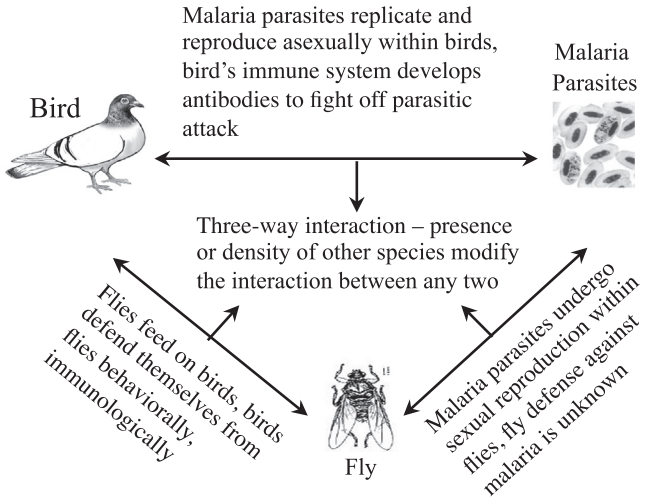

Fig. 1. Interactions between bird, fly and malaria parasites.

often collectively called avian malaria parasites and are transmitted by biting flies (Martinsen et al., 2008). We focus on interactions among rock pigeons (*Columba livia*), the malaria parasite (*Haemoproteus columbae*) that infects them, and the ectoparasitic hippoboscid fly (*Pseudolynchia canariensis*) that vectors the malaria parasite. Each pair of these species interacts strongly, and some of these pairwise interactions are modified by behaviors or responses of the third species (Fig. 1). Our models aim to quantify the importance of these three-way interactions for the prevalence of both the vector and the parasite.

In the bird–fly interaction, flies are rarely found away from their hosts, feed entirely on blood (Corbet, 1956), and harm birds by transmitting the pathogen. Defensive reactions by the bird against blood-sucking flies include a complex of adaptations to prevent attack, reduce fly reproduction, or directly kill flies (Waite et al., 2012a). Behavioral responses include mechanical removal of ectoparasites, such as by preening (Waite et al., 2012a). In addition, pigeons develop antibodies against the salivary antigens of flies after being bitten (Waite et al., 2014). These immune defenses might be effective against feeding flies in several ways (Owen et al., 2010). Tissue swelling at the feeding site can force the ectoparasite's mouthparts away from capillaries, neutralize salivary compounds that inhibit host immune responses, or directly damage ectoparasite tissues with toxins (Wikel, 1996; Owen et al., 2009). Such responses affect ectoparasites by decreasing the quality and size of blood meals and interfering with digestion. These effects together may reduce ectoparasite fecundity, inhibit molting, or even cause death (Wikel, 1996; Owen et al., 2009; Dusbabek and Skarkova-Spakova, 1988).

Just as the flies are obligate ectoparasites of the pigeons, the malaria parasite depends entirely on flies for reproduction and transmission. The two-way interaction between the fly and the malaria parasite begins with the need for the malaria parasite to undergo sexual reproduction in the fly to complete its life cycle. As far as we know, behavioral and physiological responses of the fly have little effect on the parasite and little is known about the fly's immune system. Theory predicts that parasites should not reduce vector life span as this will reduce the window of opportunity for transmission (Dye and Williams, 1995; Frank and Schmid-Hempel, 2008). However, the parasite must use some of the vector's limited resources, creating an unavoidable physiological cost that can reduce vector fitness (Smith, 2007). Some studies of vectors (sandflies and mosquitoes) point to decreased female reproduction (Ferguson and Read, 2002; Hurd et al., 2005; Schall, 2011) and one study in this bird–fly system (Waite et al., 2012b) shows that female insects suffer decreased survival and the surviving females also have reduced fecundity while male fly survival is not affected.

The malaria parasite increases its population through asexual reproduction in the endothelial lung tissues of its avian host the pigeon. Once these stages leave the lung tissues and enter the peripheral blood they mature into the non-replicating sexual stages (the gametocytes) that are transmitted to the flies (Valkiunas, 2005). The pairwise interaction between the avian host and the malaria parasite is thus characterized by adaptations of the parasite that enable it to optimize exploitation of the host to reach high numbers, while the cost of infection is minimized by the host, presumably through some sort of immunological control as in other host species infected with malaria parasites. There is presumably an energetic cost to both the host for immune protection and to the parasite for evasion (Tsakonas et al., 2003).

This system includes several forms of behavioral manipulation that can create higher-order interactions. The malaria parasite can affect the physiology of the fly vectors in transmitting the disease (Waite et al., 2012b). The flies can alter the bird's immune system through the release of salivary antigens that induce the birds' immune system to produce antibodies specific to *P. canariensis* (Waite et al., 2014). In this paper, we focus on the effects of antifly antibodies on fly movement. Because antibodies reduce fly survival and offspring size we expect that flies should leave protected birds if they can detect antibodies. Anecdotal evidence suggests that flies prefer nestling pigeons over adults, perhaps in part because they are less well defended (Bishopp, 1929). Establishing the generality of this response, however, is difficult for these fast-moving and evasive flies in a field setting (Corbet, 1956). This change in behavior could reduce transmission by reducing fly residence time on infected birds or could increase transmission by inducing infected flies to move more or prefer attacking uninfected birds.

Mathematical models remain the main tool for the epidemiological and ecological analysis of infectious diseases with the complex interactions that characterize malaria. Theoretical work on malaria began with the classic "Ross Model" (Ross, 1915) which explained the relationship between the number of mosquitoes and incidence of malaria in humans by incorporating the complexities of host–vector–parasite interactions. Subsequent models extend the basic Ross model to include a latent period of infection in mosquitoes and humans (Macdonald, 1957; Anderson and May, 1991), age-related differential susceptibility to malaria (Anderson and May, 1991; Aron and May, 1982; Dietz, 1988), acquired immunity (Aron and May, 1982; Aron, 1988; Filipe et al., 2007), drug sensitivity (Koella and Antia, 2003), and heterogeneity of host and parasite (Hasibeder and Dey, 1988; Gupta et al., 1994; Gupta and Hill, 1995) in the context of human malaria research.

Other theoretical work has focused on arthropod-borne plant diseases where the movement and feeding preferences of insect vectors affect rates of disease spread (Real et al., 1992; Roche, 1993; McElhany et al., 1995; Antonovics et al., 1995). Only a few studies have considered avian infectious disease, with work focusing on the impact of deforestation (Sehgal, 2010), the effects of global warming and predation on the vector population (Hobbelen et al., 2013) and the influence of biotic and abiotic factors on the intensity of malaria transmission among birds (Samuel et al., 2011).

Models and empirical tests of how vector behavior can affect the three-way interaction among hosts, vectors and parasites to reduce or increase the rate of transmission, remain few. In this study we develop a compartmental ODE model that illustrates how vector behavior can influence pathogen transmission dynamics in a natural avian disease system. Bird immune defenses can decrease malaria prevalence by reducing fly residence time on infected birds,

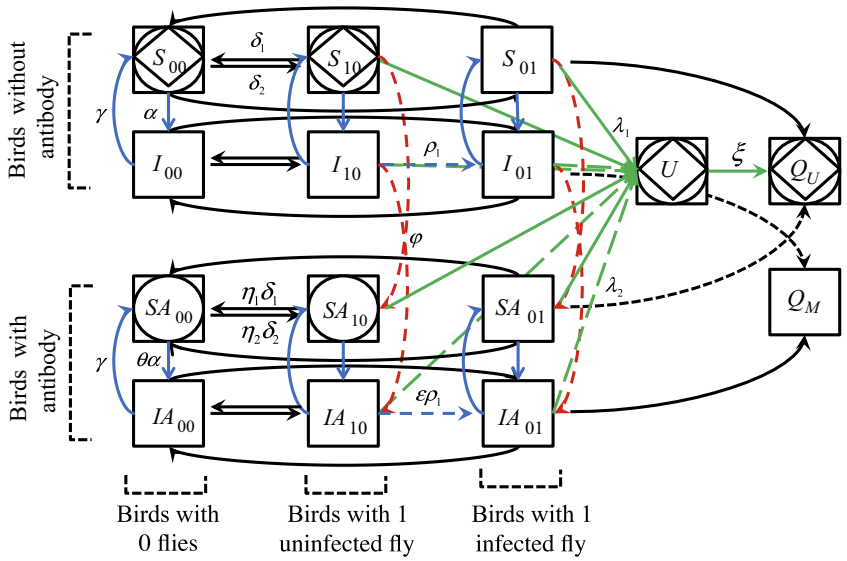

Fig. 2. Schematic diagram of *SI* compartmental model of the pigeon–fly–malaria system. Black arrows (solid and dashed) represent fly movement among different classes of birds, blue solid arrows represent transmission of disease to birds, blue dashed arrows represent infection of flies, green solid arrows represent reproduction of flies feeding on susceptible birds and eclosion from pupae, green dashed arrows represent reproduction of flies feeding on infected birds, and red arrows represent antibody acquisition by birds. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

or increase malaria prevalence by enhancing the fly movement that transmits the infection. Our models address the question of which of these competing forces dominates, and when defense against flies has the greatest positive or negative effect on the parasite that the flies transmit.

2. The model

Here we develop the bird–fly–malaria model by building from smaller modules to a complete system with the three-way interaction.

2.1. B–F model

We first consider a basic bird fly (*B–F*) two-way interaction model (Fig. 2, using only variables are enclosed by diamonds) We first model only one fly per pigeon. Unlike the mosquitoes that transmit human and other avian malarias, both fly sexes can transmit malaria between birds. Although male and female flies are typically found in equal sex ratios, we consider only the female flies to simplify the model. Female flies store sperm (Bequaert, 1953) and so fly population growth is limited by the number of females and their access to food resources on the birds. Thus the larval production from a single fly is assumed to depend on the number of infested hosts. In the basic bird–fly interaction (*B–F*) model, the variables S_0, S_1 represent susceptible birds with 0 and 1 fly per host respectively, and U and Q_U represent fly pupae and uninfected searching adult fly respectively.

$$\frac{dS_0}{dt} = \mu_b(N - S_0) + \delta_1 S_1 - \delta_2 S_0 Q_U \tag{2.1.1}$$

$$\frac{dS_1}{dt} = -\mu_b S_1 - \delta_1 S_1 + \delta_2 S_0 Q_U \tag{2.1.2}$$

$$\frac{dU}{dt} = -\mu_f U + \lambda S_1 - \xi U \tag{2.1.3}$$

$$\frac{dQ_U}{dt} = -\mu_f' Q_U + \xi U + \delta_1 S_1 - \delta_2 S_0 Q_U \tag{2.1.4}$$

The demographic parameters are μ_b, the birth and death rates of birds that are set equal to maintain a constant population size N, λ, the reproduction rate of flies, μ_f and μ_f', the death rates of fly pupae and searching adult flies respectively, and ξ, the maturation rate of fly pupae. Fly behavior is described by the departure rate δ_1 and the per bird discovery rate δ_2.

2.2. BA–F model

This model adds classes of birds (Fig. 2 using the variables enclosed by circles) to include the antibodies against the salivary antigens of flies that develop after birds have been bitten by flies. We divide the bird population into two categories: birds with and without antibodies. We extend our model to track antibody acquisition and the resulting increased departure and decreased colonization by flies. In the *BA–F* model the new variables SA_0, SA_1 represent birds with antibody and with zero and one fly per host respectively.

$$\frac{dS_0}{dt} = \mu_b(N - S_0) + \delta_1 S_1 - \delta_2 S_0 Q_U \tag{2.2.5}$$

$$\frac{dS_1}{dt} = -\mu_b S_1 - \delta_1 S_1 + \delta_2 S_0 Q_U - \phi S_1 \tag{2.2.6}$$

$$\frac{dSA_0}{dt} = -\mu_b SA_0 + \eta_1\delta_1 SA_1 - \eta_2\delta_2 SA_0 Q_U \tag{2.2.7}$$

$$\frac{dSA_1}{dt} = -\mu_b SA_1 - \eta_1\delta_1 SA_1 + \eta_2\delta_2 SA_0 Q_U + \phi S_1 \tag{2.2.8}$$

$$\frac{dU}{dt} = -\mu_f U + \lambda(S_1 + SA_1) - \xi U \tag{2.2.9}$$

$$\frac{dQ_U}{dt} = -\mu_f' Q_U + \xi U + \delta_1(S_1 + \eta_1 SA_1) - \delta_2(S_0 + \eta_2 SA_0) Q_U \tag{2.2.10}$$

The new parameters in this model are ϕ, the rate of antibody acquisition, η_1, the relative increase in the fly departure rate from birds with antibody, and η_2, the decrease in colonization of birds with antibody.

2.3. BA–F–M model

We next introduce the malaria parasite as a third species to create *BA–F–M* model that includes a three-way interaction (Fig. 2 with variables enclosed by squares). We divide birds into susceptible – latent – infected – chronic ($S-L-I-C$) categories, each split into birds with and without antibodies and break adult flies into infected and uninfected classes. For simplicity only one infected class is presented in the schematic (Fig. 2). Pathogen transmission occurs through the interaction between infected birds and uninfected flies or between infected flies and uninfected birds. The equations for flies and infected birds without antibody for a simple $S-I$ model are shown here, with the full equations in the Supplementary Material. New variables are Q_M, infected searching adult flies; I_{00}, I_{10} and I_{01}, infected birds with no flies, one uninfected fly and one infected fly respectively,

$$\frac{dU}{dt} = -\mu_f U + \lambda_1(S_{10}+S_{01}+SA_{10}+SA_{01}) + \lambda_2(I_{10}+I_{01}+IA_{10}+IA_{01}) - \xi U \quad (2.3.11)$$

$$\frac{dQ_U}{dt} = -\mu_f' Q_U + \xi U + \delta_1(S_{10}+I_{10}) + \eta_1\delta_1(SA_{10}+IA_{10}) - \delta_2((S_{00}+I_{00})+\eta_2(SA_{00}+IA_{00}))Q_U \quad (2.3.12)$$

$$\frac{dQ_M}{dt} = -\mu_f' Q_M + \delta_1(S_{01}+I_{01}) + \eta_1\delta_1(SA_{01}+IA_{01}) - \delta_2((S_{00}+I_{00})+\eta_2(SA_{00}+IA_{00}))Q_M \quad (2.3.13)$$

$$\frac{dI_{00}}{dt} = -\mu_b I_{00} + \delta_1(I_{10}+I_{01}) - \delta_2 I_{00}(Q_U+Q_M) + \beta S_{00} - \gamma I_{00} \quad (2.3.14)$$

$$\frac{dI_{10}}{dt} = -\mu_b I_{10} - \delta_1 I_{10} + \delta_2 I_{00} Q_U - \phi I_{10} + \beta S_{10} - \gamma I_{10} - \rho_1 I_{10} \quad (2.3.15)$$

$$\frac{dI_{01}}{dt} = -\mu_b I_{01} - \delta_1 I_{01} + \delta_2 I_{00} Q_M - \phi I_{01} + \beta S_{01} - \gamma I_{01} + \rho_1 I_{10} \quad (2.3.16)$$

Key new parameters are β, the transition rate from the susceptible stage to the infectious stage; γ, the recovery rate from the infectious stage, and ρ_1, the rate of fly infection on infected birds without antibodies.

We represent the effect of bird antibodies on transmission with two key parameters: θ, the relative change in susceptibility of birds and ϵ, the relative change in susceptibility of flies. The equations for the complete *BA–F–M* model with multiple infectious classes and birds with and without antibodies are provided in the Supplementary Material.

2.4. BA–F*–M model

The final model extension tracks multiple flies per bird. We assume that flies leave independently but arrive and stay on the birds only if space is available. Flies infect independently with equal probability but multiple flies do not change the rate of antibody induction. To reduce the dimension of this *BA–F*–M* model, we consider only one infected class (I) and adjust the recovery rate parameter value γ to capture the average time to traverse all three stages of infection – latent, acute and chronic.

The corresponding equations for birds with antibodies are obtained as in the one fly per host model. The complete *BA–F*–M* models with two and three flies per host are given in Supplementary Material. All parameters with values used for simulation are described in Table 1.

3. Results

Using the parameter values in Table 1, we solve the model numerically and find a unique stable equilibrium in every case, starting with initial conditions with 20 searching adult free flies among which one fly is infected with malaria. Here we present and compare the results of the four models *B–F* (the bird–fly interaction in the absence of antibody production), *BA–F* (the bird–fly interaction in the presence of antibody production), *BA–F–M* (bird–fly–malaria interaction when fly behavior is induced by antibody assuming one fly per host), and *BA–F*–M* (the extension of the previous model by introducing more than one fly per host).

3.1. Comparison of B–F, BA–F and BA–F–M models

The fly population cannot persist when its birth rate, encounter rate or residence time on birds is too low (Fig. 3, left panel). As these parameters increase, the fly population persists at a stable positive equilibrium leading the bird population to develop antibodies. With our parameters, the disease persists in the system only when there are enough flies to induce a majority of birds to have antibodies (Fig. 3).

3.2. Results from BA–F–M model in the absence of antibody

The equilibrium malaria prevalence in birds and the equilibrium population size of uninfected and infected free flies in the absence of antibody production is shown in Fig. 4. This provides a baseline for understanding the effects of immune defense on vector behavior and parasite transmission dynamics.

3.3. Results from BA–F–M model

Behavioral changes induced by antibodies do alter pathogen transmission and prevalence. Malaria prevalence in birds reaches a maximum at an intermediate value of the effect of antibodies on the fly departure rate, η_1 (Fig. 5a). Although the number of uninfected flies decreases monotonically with the effect of antibodies (Fig. 5b), the number of infected flies reaches a maximum at an intermediate value (Fig. 5c). Decreased colonization due to antibodies (η_2) has a simpler effect on malaria prevalence, decreasing the prevalence of infection in both birds and flies. Although almost all the birds have antibodies at equilibrium, the increase in the fly departure rate reduces the equilibrium population of birds with antibodies (results not shown), creating feedbacks in the fly population and malaria prevalence.

3.4. Comparison of BA–F–M and BA–F*–M models

The value of η_1 that produces the maximum prevalence depends on the mean time flies spend on birds without antibodies ($1/\delta_1$). When fly residence time is long, accelerated departure is better for the malaria. With one fly per bird and a residence time of 40 days on birds, malaria prevalence is maximized by an antibody-induced speed up of departure by 3 to 8 times, compared to the residence time of 7 days that maximizes prevalence (Fig. 6a). With two flies per bird the departure rate needs to increase less to maximize malaria prevalence (Fig. 6b).

Increased departure rate acts differently in transmitting the malaria if we consider multiple flies (2 or 3) per individual bird host. Malaria prevalence reaches its maximum with a smaller increase from the baseline departure rate ($\eta_1 = 3$ for two flies and $\eta_1 \approx 1.5$ for three flies per host) and then decreases as departure rate increases (Fig. 7a – left panel). Including more flies per bird does not create a significant difference in malaria prevalence when fly departure rate increases (comparing Fig. 7a top and bottom).

Table 1
Parameter values for simulations of the *BA–F–M* model.

Species	Parameters	Description	Probable values	Source	Reference
Host	N	Total population size of birds	100	Scaled for convenience	
	μ_b	Birth (and death) rate of birds	0.34/365 day^{-1}	Life tables for adult uninfected pigeons	Johnston and Janiga (1995)
Vector	μ_f	Death rate of fly pupae	0.05/25 day^{-1}	Lab experiment	
	μ_f'	Death rate of adult female fly	1/4.29 day^{-1}	Lab experiment and literature	Waite et al. (2012b), Klei (1971)
	λ_1	Fly birth rate when feeding on uninfected birds	2.3/7 day^{-1}	Literature	Waite et al. (2012b)
	λ_2	Fly birth rate when feeding on infected birds	2/7 day^{-1}	Literature	Waite et al. (2012b)
	ξ	Rate of eclosion from pupae to adult fly	1/27 day^{-1}	Lab experiment and estimated from literature	Herath (1966)
	δ_1	Departure rate of flies from birds	1/28 day^{-1}	Extrapolated from data from shed experiment, a minimum estimate for movement based on different numbers of flies found on birds over 2 week intervals	Harbison
	δ_2	Colonization rate of flies on birds	1/2.8 day^{-1} fly^{-1}	Extrapolated from shed experiment data (above)	Harbison
	η_1	Increase in departure rate due to antibodies	variable (1–15)	Assumption	
	η_2	Reduction in colonization rate due to antibodies	variable (0–1)	Assumption	
	ϕ	Rate of antibody acquisition of birds	1/12 day^{-1}	Lab experiment and estimated from references	Dusbabek et al. (1989), Dusbabek et al. (1990)
Parasite	α	Infection rate of susceptible birds with one infected fly	1 day^{-1}	Typically the day the bird is bitten	Waite et al. (2014)
	β	Transition rate from latent stage of infection	1/21 day^{-1}	Lab experiment and estimated from reference	Waite et al. (2014), Ahmed and Mohammed (1978)
	γ	Transition rate to chronic stage of infection	1/20 day^{-1}	Lab experiment and estimated from reference	Waite et al. (2014), Ahmed and Mohammed (1978)
	κ	Transition from chronic to susceptible class	1/60 day^{-1}	Lab experiment and estimated from literatures	Waite et al. (2014), Ahmed and Mohammed (1978)
	θ	Reduction in bird's susceptibility due to antibodies	0.5	Assumption: based on data in other malaria vector systems	Alger et al. (1972), Titus et al. (2006)
	ρ_1	Rate of fly infection on an infected bird without antibodies	4 day^{-1}	Extrapolated from mouse models	Ferguson et al. (2003)
	ρ_2	Rate of fly infection on chronic bird without antibodies	2 day^{-1}	Extrapolated from mouse models	Ferguson et al. (2003)
	ϵ	Reduction in fly infection rate due to antibodies	0.5	Assumption	

In the multiple fly system the adult uninfected fly population decreases as departure rate increases (Fig. 7b) but the infected fly population reaches a maximum at some intermediate value of η_1 ($\eta_1 = 5$) (Fig. 7c), similar to the results of modeling a single fly per individual bird. An increase in the infected fly population at some intermediate value of η_1 does not change the prevalence of malaria in birds in the case of multiple flies.

4. Discussion

We have developed a mathematical model to study the three-way interactions among pathogen, vector and host to measure how the bird's immune defense against the vector could alter pathogen transmission. As a relatively simple model system, we study feral rock pigeons as hosts which are infected with the malaria parasite *H. columbae* as vectored by the ectoparasitic hippoboscid fly *P. canariensis*. The malaria parasite depends on both hosts to complete its life cycle, and female flies require blood from the birds for survival and reproduction. A network of defense is overlaid upon this network of dependence, and we focus on bird defenses against flies. Antibodies and specifically sensitized cells may react with tissues and saliva to disrupt blood meal acquisition, impair physiological responses, and even kill flies (Wikel, 1996, 1982). Effective defenses can diminish fly population size and directly reduce disease transmission, but fly behavioral responses to defense can create equally large indirect effects. If flies avoid defended birds they will be less likely to bite infected birds, while if they are more likely to leave defended birds they might be less likely to acquire infection but more likely to transmit any infection they acquire. Our models examine how these processes shape infection prevalence and fly population size.

We focus on two important parameters that describe the preference flies have for colonizing undefended birds and their increased departure rate from defended birds. Our key result is that increased preference for undefended hosts decreases fly population size and thus disease prevalence. Although an increased departure rate from defended hosts also decreases fly population size by increasing fly mortality while searching, disease prevalence is maximized at an intermediate level of increased preference. At this level, flies remain on birds long enough to acquire infection but leave quickly enough to spread it to other birds. The strength of this effect depends of course on the parameters of the model. Our basic model allows only a single fly per bird consistent with the low observed numbers of flies on birds in nature. Because the flies must mate, and because their numbers do increase seasonally, we extended the model to track two or three flies per bird, which increases the efficiency of transmission and decreases the effect of fly behavioral adjustment.

Our model considers a host immune response that alters vector behavior. Although consistent with observations, many questions remain about the mechanism by which host immune responses

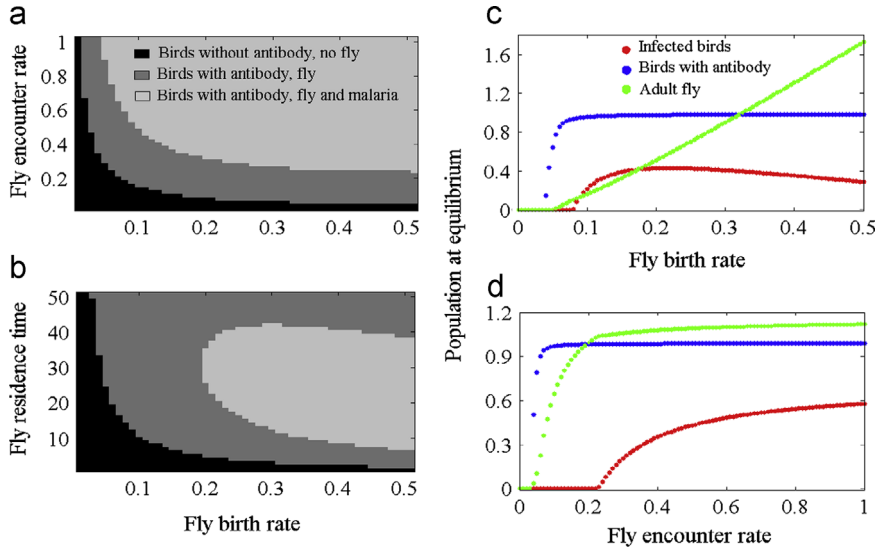

Fig. 3. Regions of fly and antibody persistence as a function of (a) the fly birth rate (λ) and encounter rate (δ_2), (b) the fly birth rate and the mean residence time ($1/\delta_1$), and equilibrium population size as functions of (c) the fly birth rate (λ) and (d) the fly encounter rate (δ_2). Parameter values come from Table 1.

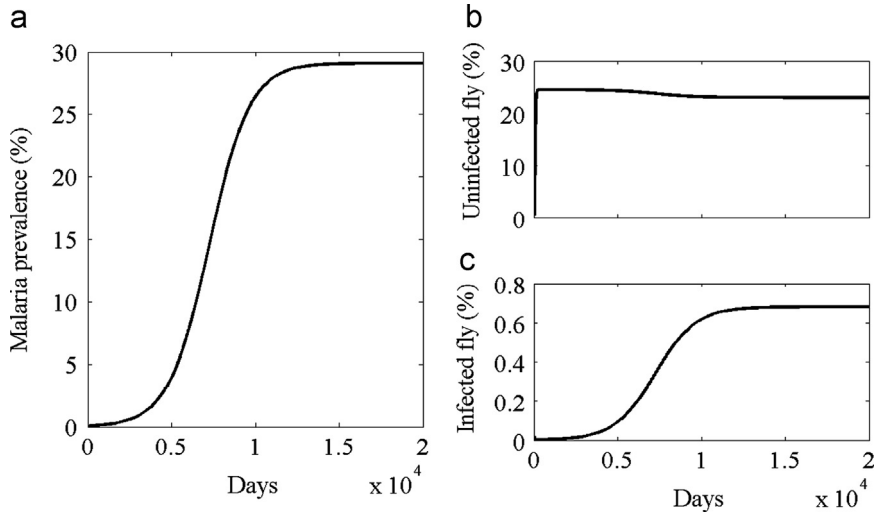

Fig. 4. (a) Equilibrium malaria prevalence in birds in the absence of antibody production. (b) Equilibrium population size of uninfected adult free flies and (c) equilibrium population size of infected adult free flies in the absence of antibody production by birds.

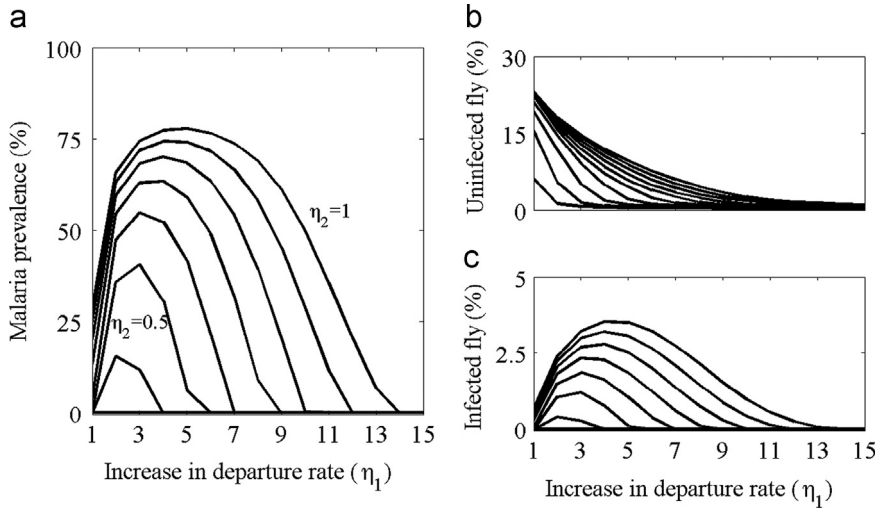

Fig. 5. From *BA–F–M* model (a) disease prevalence in birds (b) uninfected and (c) infected adult fly populations at equilibrium as a function in the increase of fly departure rate (η_1) induced by antibodies. The effect of reduced colonization (η_2) is shown along the curves from top to bottom.

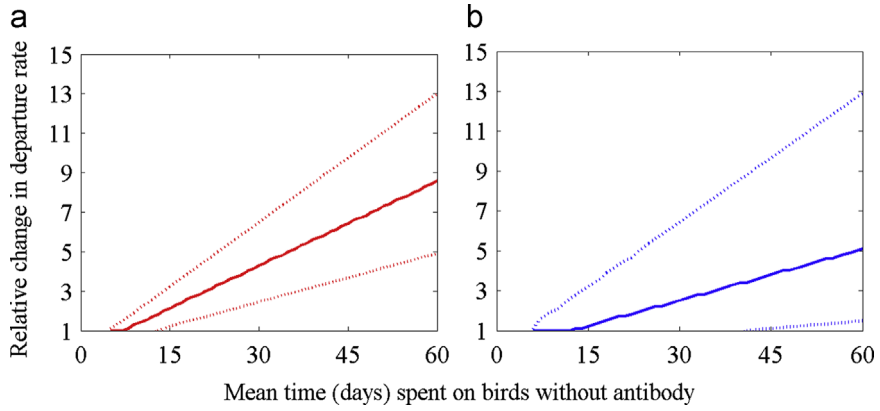

Fig. 6. Relative change in departure rate of flies from birds with antibodies which leads to maximum disease prevalence as a function of the mean time spent on the birds without antibodies with (a) one and (b) two flies per bird. Solid lines show the value that maximizes disease prevalence, and dashed lines where prevalence is 90% of the maximum.

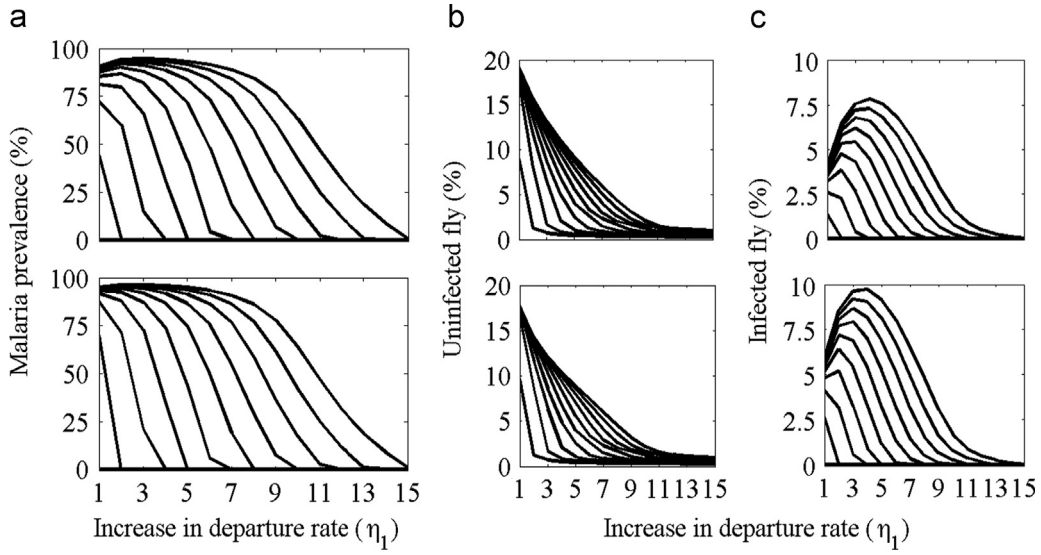

Fig. 7. (a) Disease prevalence in birds with two (top) and three (bottom) flies per bird, from BA–F^*–M model, with the effect of reduced colonization η_2 shown along the curves from top to bottom. (b) Adult uninfected and (c) infected fly population with two (top) and three (bottom) flies per bird respectively.

affect the physiology and behavior of ectoparasitic arthropods. Data on the role of immune responses of hosts on blood-feeding arthropods are limited, particularly for repeated exposures of hosts to arthropods as the immune system changes over time (Donovan et al., 2007). Due to this incomplete knowledge, we have assumed that the rate of antibody acquisition in the multiple fly model system is the same as for the single fly model. If the likelihood of antibody acquisition depends on the number of exposures, rather than only on the number of flies as we have assumed, then the results could change. Immune responses are integrated with a variety of other physiological responses to blood-feeding arthropod saliva. Some arthropods produce compounds in their saliva known to counteract host haemostatic defenses to facilitate feeding and modulate host immunity at the bite site (through local edema or histological responses) and such changes can facilitate pathogen transmission (Titus et al., 2006; Billingsley et al., 2006; Brossard and Wikel, 2004). Inhibition of the host immune response can alter the disease dynamics observed in our model. Additional host influences, such as defensive grooming behavior, can also influence vector movement and alter fly reproductive success. Vector responses to behavioral defenses could be modeled in ways similar to those described here for host immune responses.

Our results suggest that a host's defense against an ectoparasitic vector can significantly affect malaria parasite transmission by modifying vector behavior, as found in studies of infectious diseases of plants (Real et al., 1992; Roche, 1993; McElhany et al., 1995; Antonovics et al., 1995). In the aphid barley yellow dwarf virus system, vector preference for diseased plants alters the probability of disease spread, but with an interesting dependence on disease prevalence. With a high frequency of diseased plants, disease spread is favored by vectors that prefer healthy plants, but with a low frequency of diseased plants, disease spread is favored by vectors that prefer diseased plants (McElhany et al., 1995). A simple spatially explicit model (Sisterson, 2008) based on McElhany et al. (1995) illustrates how the feeding preference and orientation preference of insect vectors affect pathogen spread differently, emphasizing the importance of explaining the mechanisms that control vector preference for healthy versus infected plants. Vector behavior and host defensive traits also control parasite aggregation in a system that consists of the leafless holoparasitic mistletoe, its cactus host and a bird vector (Medel et al., 2004). Other studies have found that vectors preferentially visit healthy flowers, but the strength of this preference is lower for vectors with prior exposure to diseased flowers (Roche, 1993; Shykoff and Bucheli, 1995; Altizer et al., 1998). Studies that determine the impact of defensive behavior of vertebrate hosts on the movement of vectors remain few. Our demonstration that a preference of flies for birds without

antibodies would significantly affect disease spread is, to our knowledge, the first to test of the effect of immune defense of an avian host on pathogen transmission.

Here we present a detailed mathematical model to investigate the interactions between a host, a vector towards which the host exhibits immune defense, and a parasite, focusing on how malaria transmission and prevalence is influenced by host immune defense and vector avoidance of these defenses. In a large range of parameter space, we find that parasite prevalence is maximized at intermediate levels of behavioral evasion by flies of birds with antibodies. These results suggest that changes in vector foraging either by reduced residency times on birds with antibodies or by preferential colonization on birds without antibodies, can impact malaria in complicated ways. To the extent that the model appropriately captures the relevant biology, the results provide some useful insight into how modifications of vector foraging behavior will impact vector abundance and disease prevalence in this particular system. Our models can be expanded to exploit vector behavior against hosts' physical as well as immunological defenses. Defenses that induce increased vector movement can alter the disease transmission in a complex way. Implementation of preventive measures to reduce host–vector contact in diseases like human malaria or dengue will maximize the effect of interventions if based on the knowledge of vector behavior and its impact on disease dynamics. Thus the behavioral factors which alter transmission of infectious agents have implications for the design of control programs. Our study may provide a foundation for understanding how these behavioral changes in vectors could determine the success of control strategies and shape our thinking about innovative alternatives.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2014.05.020.

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