Appendix A Evolution maximizes R_0

The dynamics of the frequencies of mosquitoes which are infected but not yet infectious, v and inefectious, w, are given by

$$\frac{\mathrm{d}v}{\mathrm{d}t} = aby(1-v-w) - ab\hat{y}\,(1-\hat{v}-\hat{w})\,e^{-\mu T} - \mu v \tag{A.1}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = ab\hat{y}\,(1-\hat{v}-\hat{w})\,e^{-\mu T} - \mu w \tag{A.2}$$

where a is the biting rate, b is the transmission rate from infected humans to susceptible mosquitoes, μ is the death rate of mosquitoes, T is the incubation period of malaria parasites in the vector, and y is the frequency of infected human host. Variables with a hat, $\hat{y}$, $\hat{v}$, and $\hat{w}$, denote proportions at time t-T.

The dynamics of the frequencies of susceptible humans, x, and infected humans, y, are given by

$$\frac{\mathrm{d}x}{\mathrm{d}t} = d - dx - hx + ry \tag{A.3}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = hx - ry - dy \tag{A.4}$$

where r is the recovery rate from infection, h is the inoculation rate, d represents the rate of host death, and a constant population size is assumed, so deaths are balanced by births into the susceptible class. The inoculation rate is given by

$$h = mapw \tag{A.5}$$

where m is the per human mosquito density and p is the transmission rate from infected mosquitoes to susceptible human hosts. Assuming the mosquito population is at equilibrium with respect to changes in human dynamics, the quasi-equilibrium density of infected mosquitoes, w^* is

$$w^* = \frac{abe^{-\mu T}y}{aby+\mu}. \tag{A.6}$$

The inoculation rate from equation A.5 can then be rewritten as

$$h = \frac{ma^2bpe^{-\mu T}y}{aby+\mu}. \tag{A.7}$$

Substituting equation A.7 into equations A.3 and A.4, and solving for equilibrium proportions of infected humans, y^*, and susceptible humans x^*, we find the only non-zero equilibrium occurs where

$$y^* = \frac{ma^2bpe^{-\mu T} - \mu(r+d)}{ma^2bpe^{-\mu T} + ab(r+d)} \tag{A.8}$$

$$x^* = 1 - y^*. \tag{A.9}$$

It can be shown that this equilibrium is stable when the 'infection growth' rate outweighs the 'infection loss' rate, or

$$ma^2bpe^{-\mu T} > \mu(r+d). \tag{A.10}$$

This condition must be true in order for infections to persist in the population, so for an endemic disease we can assume this condition is satisfied.

We can now imagine adding a mutant parasite, denoted with the subscript i, which differs in its transmission rates and causes different rates of mosquito mortality, host mortality and host recovery. System (A.1-A.2) is altered and the dynamics in the mosquito population are now described by

$$\frac{dv}{dt} = aby(1 - v - v_i - w - w_i) - ab\hat{y}\,(1 - \hat{v} - \hat{v}_i - \hat{w} - \hat{w}_i)\,e^{-\mu T} - \mu v \tag{A.11}$$

$$\frac{dv_i}{dt} = ab_i y_i(1 - v - v_i - w - w_i) - ab_i\hat{y}_i\,(1 - \hat{v} - \hat{v}_i - \hat{w} - \hat{w}_i)\,e^{-\mu_i T} - \mu_i v_i \tag{A.12}$$

$$\frac{dw}{dt} = ab\hat{y}\,(1 - \hat{v} - \hat{v}_i - \hat{w} - \hat{w}_i)\,e^{-\mu T} - \mu w \tag{A.13}$$

$$\frac{dw_i}{dt} = ab_i\hat{y}_i\,(1 - \hat{v} - \hat{v}_i - \hat{w} - \hat{w}_i)\,e^{-\mu T} - \mu_i w_i. \tag{A.14}$$

The equilibrium densities of mosquitoes infected with the resident strain, w^*, and with the mutant strain, w_i^* are

$$w^* = \frac{abe^{-\mu T} y\mu_i}{aby\mu_i + ab_i y_i\mu + \mu\mu_i} \tag{A.15}$$

$$w_i^* = \frac{ab_i e^{-\mu_i T} y_i\mu}{aby\mu_i + ab_i y_i\mu + \mu\mu_i}. \tag{A.16}$$

The human population is now described by the following set of equations

$$\frac{\mathrm{d}x}{\mathrm{d}t} = d - dx - hx - h_i x + ry + r_i y_i \tag{A.17}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = hx - (r+d)y \tag{A.18}$$

$$\frac{\mathrm{d}y_i}{\mathrm{d}t} = h_i x - (r_i + d)y_i \tag{A.19}$$

where

$$h = \frac{ma^2 bpe^{-\mu T} y\mu_i}{aby\mu_i + ab_i y_i \mu + \mu\mu_i} \tag{A.20}$$

$$h_i = \frac{ma^2 b_i pe^{-\mu_i T} y_i \mu_i}{aby\mu_i + ab_i y_i \mu + \mu\mu_i}. \tag{A.21}$$

To determine if the mutant can invade, we look at the stability matrix of the equilibrium with the mutant absent (i.e. y_i^*=0) described by A.8 and A.9. A mutant will be able to invade a population when this equilibrium is unstable (i.e. when at least one of the eigenvalues of the stability matrix is positive). This analysis results in a stability matrix of the following form

$$\begin{pmatrix} \mathbf{J_{res}} & \mathbf{v} \\ \mathbf{0} & \mathbf{J_{mut}} \end{pmatrix} \tag{A.22}$$

where $\mathbf{J_{res}}$ describes the stability of the equilibrium in the absence of the mutant strategy and

$$\mathbf{J_{mut}} = \frac{ma^2 b_i p_i e^{-\mu_i T} x^* \mu}{(aby^* + \mu)\mu_i} - (r_i + d). \tag{A.23}$$

We have already shown that the eigenvalues of $\mathbf{J_{res}}$ are negative because of inequality A.10. So, a mutant will be able to invade when $\mathbf{J_{mut}}>0$. Substituting in the equilibrium values y^* and x^* (from A.8 and A.9) and simplifying we find that a mutant can invade when

$$\frac{ma^2 b_i p_i e^{-\mu_i T}}{(r_i + d)\mu_i} > \frac{ma^2 bpe^{-\mu T}}{(r_i + d)\mu}. \tag{A.24}$$

Since

$$R_0 = \frac{ma^2 bpe^{-\mu T}}{(r+d)\mu}, \tag{A.25}$$

a mutant can invade only if a single host infected with the mutant, in a wholly susceptible population, leads to more secondary infections than a host infected with the non-mutant.

Appendix B Within-host model of infection

We present a simplified model of the dynamics of malaria infection within a host, assuming there is no immunity. Assuming a mass action infection rate of RBCs, the dynamics of RBCs, S, and two coinfecting parasite populations (tracking their merozoite, M, and gametocyte, G, densities) in the bloodstream is

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \theta - \beta_1 S M_1 - \beta_2 S M_2 - \eta S \tag{B.1}$$

$$\frac{\mathrm{d}M_1}{\mathrm{d}t} = \omega\,(1-\epsilon_1)\,\beta_1 S M_1 - \delta_1 M_1 \tag{B.2}$$

$$\frac{\mathrm{d}M_2}{\mathrm{d}t} = \omega\,(1-\epsilon_2)\,\beta_2 S M_2 - \delta_2 M_2 \tag{B.3}$$

$$\frac{\mathrm{d}G_1}{\mathrm{d}t} = \epsilon_1 \beta_1 S M_1 - \zeta_1 G_1 \tag{B.4}$$

$$\frac{\mathrm{d}G_2}{\mathrm{d}t} = \epsilon_2 \beta_2 S M_2 - \zeta_2 G_2 \tag{B.5}$$

where β is the strain-specific invasion rate of RBCs, ω is the number of merozoites produced by an infected RBC and δ and ζ are the strain-specific merozoite and gametocyte death rates in the bloodstream. This model is different from previous ones incorporating gametocytogenesis (e.g., Hellriegel 1992) since we assume that infected RBCs burst immediately (so we do not need to track densities of infected RBCS). This is clearly not the case in real malaria infections, but we are interested in the number of RBCs that are infected over the entire course of infection and the number of gametocytes that are produced, rather than the details of transient within-host dynamics. Our simplification should not qualitatively affect our results as long as different parasite strains take the same amount of time to mature within RBCs.

At steady state it is easy to show that the strain that can reduce the RBC number, S, to the lowest value will competitively exclude the other. The winning strain thus has the highest value of $\omega\beta(1-\epsilon)/\delta$.

At steady state, a strain produces

$$\frac{\epsilon}{\zeta}\left(\frac{\phi(1-\epsilon)\theta - \eta}{\phi(1-\epsilon)}\right) \tag{B.6}$$

gametocytes, where $\phi{=}\frac{\omega\beta}{\delta}$. This expression is used to generate Figure 1 and is incorporated into the model of superinfection (Appendix C) to generate Figure 2.

Similar qualitative results are obtained with a model displaying nonequilibrium within-host dynamics, as is typical of real malaria infections. In particular, malaria infections are characterized by multiple waves of parasitemia, with the first peak of parasitemia occuring before any significant

immune responses have built up against the parasite. We can model this by assuming there is some fixed pool of RBCs available for invasion, and their abundance governs the dynamics of infection at this early stage. In this case, we can use a variant of the above within-host model, with θ=0 and η=0. We can then ask how the total number of gametocytes produced during this wave of parasitemia changes with our traits of interest, and we obtain results qualitatively identical to those in Figure 1. This model also allows one to explore the evolutionary consequences of coinfection (as opposed to superinfection) as well. Again, the qualitative results are similar to those presented in Section 3.4.

References

Hellriegel, B. (1992) Modeling the immune response to malaria with ecological concepts - short-term behavior against long-term equilibrium. *Proc. Roy. Soc. B* **250**, 249–256.

Appendix C Ross-Macdonald and superinfection

Under superinfection, the mosquito equations are unchanged from the two strain model presented in Appendix A (except instead of having a resident and a mutant, which was denoted by the subscript *i*, we have two strains denoted by the subscripts 1 and 2). Equilibrium values of w_1 and w_2 are equivalent to those in equations A.15 and A.16,

$$w_1^* = \frac{ab_1 e^{-\mu_1 T} y_1 \mu_2}{ab_1 y_1 \mu_2 + ab_2 y_2 \mu_1 + \mu_1 \mu_2} \tag{C.1}$$

$$w_2^* = \frac{ab_2 e^{-\mu_2 T} y_2 \mu_1}{ab_1 y_1 \mu_2 + ab_2 y_2 \mu_1 + \mu_1 \mu_2}. \tag{C.2}$$

The human population is described by the following set of equations

$$\frac{\mathrm{d}x}{\mathrm{d}t} = d - dx - h_1 x - h_2 x + r_1 y_1 + r_2 y_2 \tag{C.3}$$

$$\frac{\mathrm{d}y_1}{\mathrm{d}t} = h_1 x + h_1 \sigma \left(R_1 - R_2\right) y_2 - \left(r_1 + d + h_2 \sigma \left(R_2 - R_2\right)\right) y_1 \tag{C.4}$$

$$\frac{\mathrm{d}y_2}{\mathrm{d}t} = h_2 x + h_2 \sigma \left(R_2 - R_1\right) y_1 - \left(r_2 + d + h_1 \sigma \left(R_1 - R_2\right)\right) y_2 \tag{C.5}$$

where h_j=*map*w_j^* and σ represents the 'dominance' (Bonhoeffer and Nowak 1994) of an introduced strain over one that is established within a host which depends on the difference in the values of κ for the two strains.

In the absence of superinfection, this model reduces to the one presented in equations A.3-A.4. To arrive at an expression for R_0 in this system we perform an invasion analysis similar to that in Appendix A. Here,

$$\mathbf{J_{mut}} = \frac{ma^2 b_2 p e^{-\mu_2 T} x^* \mu_1}{\left(ab_1 y^* + \mu_1\right) \mu_2} + \frac{ma^2 b_2 p e^{-\mu_2 T} y_1^* \sigma \left(\kappa_2 - \kappa_1\right) \mu_1}{\left(ab_1 y^* + \mu_1\right) \mu_2} - \left(h_1^* \sigma \left(\kappa_1 - \kappa_2\right) + r_2 + d\right) \tag{C.6}$$

The mutant can increase in frequency if $\mathbf{J_{mut}}>0$, which can be rearranged to give the mutant fitness expression of the text.

References

Bonhoeffer, S. and Nowak, M. A. (1994) Mutation and the evolution of virulence. *Proc. Roy. Soc. B* **258**, 133–140. (DOI: 10.1098/rspb.1994.0153.)