

*Biocide resistance and diverse fitness cost mechanisms in optimal malaria vector control*

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**One sentence summary**

The mechanisms of fitness costs—and not just their magnitude—can be critical in determining optimal policies to manage biocide resistance, as shown by this bioeconomic model of optimally controlled insecticide resistance in malaria vector management.

**Abstract**

Biological theory and evidence have pointed to the existence of fitness tradeoffs associated with organisms' evolution of resistance to many biocides (e.g. insecticides and antibiotics). We use a simple model of malaria transmission, insecticide spraying impacts, and evolution of insecticide resistance coupled with an optimality criterion to develop intuition about how different types of fitness costs in malaria vectors impact economic insecticide policies for disease reduction. We show that large economic losses from short- and long-term malaria burden due to qualitative differences in management strategies can be incurred through misinformed assumptions about sources of evolutionary fitness costs in vectors.

Evolution of resistance among pathogens, disease-causing vectors, agricultural pests, and invasive species to the biocides used to limit their spread provides one of the clearest examples of the economic relevance of evolutionary dynamics. However, accurate economic analysis and control of these dynamics requires understanding the relative fitness of organisms which have evolved resistance to biocides. By definition, resistance confers a selective advantage in the presence of biocide exposure, and biologists have theorized that organisms must face a tradeoff in evolutionary terms in order to acquire this advantage (1). Such fitness costs have been confirmed in antibiotic-resistant bacteria (2), mosquito disease vectors (3), and arthropod pests (4).

Economic models of the optimal management of biocide resistance in arthropods usually allow for fitness costs only through increased adult mortality (5-8). In economic models of microbial infections and antibiotic resistance, fitness costs typically consist of higher recovery rates among hosts infected with an antibiotic-resistant strain of the microbe relative to an antibiotic-susceptible strain *in the absence of treatment* (9, 10). In both cases, theoretical economic modeling has shown that the magnitude of fitness costs in the pest/pathogen strain which is resistant to a biocide is decisive in constructing an optimal policy for biocide use (5-10).

Yet different types of fitness costs have different economic implications: Some types of fitness costs, such as increased adult mortality in the case of insecticide resistance for disease vector control, have direct economic benefits (higher mortality means lower vector abundance and decreased disease transmission), as well as indirect effects (slower evolution of resistance to the insecticide at the population level). Other types of fitness costs, such as decreased sexual competitiveness or fecundity, have a similar indirect benefit but a reduced or nonexistent direct economic benefit (11).

Here we address the question of whether and how different mechanisms for evolutionary fitness costs can affect economic policies which seek to optimally manage biocide resistance to maximize the benefits of biocide use over time. We use a simple conceptual model of malaria vector control using insecticides, in which a selection dynamic for insecticide resistance is coupled with a simple epidemiological model. This is a relevant example for our research question, because decreases in adult mosquito survival are in theory more beneficial for malaria control reduction than decreases in larval or pupal survival (12). Mutations conferring vector resistance to the major classes of insecticides—organochlorides (e.g. DDT), pyrethroids, organophosphates, and carbamates—have been confirmed in a variety of malaria-endemic countries in Africa and Asia (13-17). A growing literature has found evidence for and against the existence and diversity of fitness costs associated with these mutations (3, 18-24). See this article's online supplement for details (25).

Our conceptual model consists of 3 equations: 2 differential equations—one for vectored transmission of malaria in the human population and another selection for insecticide resistance in the vector population—and a third equation which links levels of insecticide control and resistance to impacts on population level vector mortality, which controls malaria transmission. The online supplement provides references and a detailed construction of the model (25). Malaria transmission was characterized by compartmentalizing the human population into susceptible and infected groups. By assuming a constant human population and a Macdonald-Ross transmission term, we can write the differential equation for the fraction  $\gamma \in [0,1]$  of humans infected with malaria:

$$\frac{d\gamma}{dt} = r \left[ R_0 \frac{e^{-\tau_S(\mu - \mu_0)}}{\left(\frac{\mu}{\mu_0}\right)^2} \frac{\mu}{\mu + h\gamma} (1 - \gamma) - 1 \right] \gamma \quad (1)$$

where the rate of recovery from malaria is  $r$ , the basic reproductive number for the disease in the baseline case is  $R_0 > 0$ , the incubation time of the pathogen in the vector is  $\tau_S > 0$ , the baseline vector mortality rate is  $\mu_0 > 0$ , and the population-level vector mortality under the insecticide control regime is  $\mu \geq \mu_0$ , and  $h > 0$  is a scaling factor determined by a suite of vector ecology parameters (25).

Selection for insecticide resistance was based on a replicator dynamic (26), assuming that resistance was conferred by an allele at a single locus. For simplicity, the resistant and the susceptible genes were characterized as equally dominant in heterozygotes (27). The differential equation for the fraction  $s \in [0,1]$  of the vector population that has at least one copy of the allele conferring insecticide susceptibility is:

$$\frac{ds}{dt} = \varepsilon(f - Cg)s(1 - s) \quad (2)$$

where  $\varepsilon$  is a parameter controlling the timescale on which insecticide resistance evolves relative to disease transmission,  $f$  is the relative evolutionary fitness cost for vectors which are resistant to the insecticide, and  $g$  is the excess mortality induced by insecticide exposure of the homozygote-susceptible genotypes.

The equation linking the transmission and selection dynamics in equations (1) and (2), uses the Hardy-Weinberg formulae for the genotype frequencies, and expresses population-level vector mortality as a function of the insecticide coverage level  $C \in [0,1]$  among the human population and  $s$ :

$$\mu(s, C) = \mu_0 + \mu_r + (Cg - \mu_r)s \quad (3)$$

where  $\mu_0$  is the baseline vector mortality level in the absence of insecticide exposure and  $\mu_r$  is the portion of fitness costs  $f$  which are attributable to adult mortality. In general,  $\mu_r \leq f$ . We let  $\alpha \equiv \mu_r/f \in [0,1]$  denote the fraction of fitness costs which are attributable to an adult mortality mechanism. The primary innovation of our model is to allow other fitness cost mechanisms, making the inequality hold strictly with  $\alpha < 1$ .

The economic criterion was to minimize discounted present value costs of malaria infections and spraying. We assumed a constant cost per malaria case based on published studies (28), spread evenly over the average length of infection, and a nominal cost per person-year for the spray program (29). A time-varying schedule of insecticide coverage levels  $C^*(t)$  satisfying the economic criterion was found using standard optimal control and dynamic programming methods (25).

We examine optimal policies and minimized costs under different fitness cost mechanisms. In Figure 1, we show optimal economic policies given 2 different biological scenarios which change the parameter  $\alpha$ , as well as a third policy scenario in which there is no selection for resistance. Allowing for the evolution of insecticide resistance and different fitness cost mechanisms strongly affects the computed optimal policies. As anticipated, the gap between the policy assuming no evolution and the other two is due to a sizable cost associated with insecticide use and efficacy in the short-run versus the long-run. More insightfully, changing the mechanism of fitness costs by varying  $\alpha$  strongly affects optimal policies. When fitness costs can be attributed to sources other than adult vector mortality  $\alpha = .55$ , then at low initial levels of susceptibility [ $s(0) = .1$ ] insecticide usage is lower in the short-run and higher in the long-run, implying lower short-run insecticide susceptibility. At high levels of vector

susceptibility [ $s(0) = .9$ ], the cost-effective spray regimes under the different modeling assumptions begin to converge, as suggested by theory (25).

We then matched cost-effective spray regimes displayed in Figure 1 with the “wrong” biological model—i.e. one based on different assumptions regarding evolution and fitness cost mechanisms. The goal of this procedure was to calculate relative economic losses from incorrect assumptions used to compute a cost-effective policy. Comparisons of the relative costs from implementing correct versus incorrect policies indicate there are significant cost increases associated with basing policy on incorrect assumptions (Fig. 2). In the case where the policy was optimized based on the assumption that fitness costs were mortality-specific ( $\alpha_{POLICY} = 1$ ) but the biological model assumed multiple fitness cost mechanisms ( $\alpha_{BIOLOGY} = 0.55$ ) as in (Fig. 2A), the costs of the wrong assumption are severe at high initial levels of vector susceptibility, up to 200% in excess of the costs of the correct policy. When the situation is reversed (Fig. 2B), economic losses are highest—up to 400% above the optimum—at low initial levels of vector susceptibility.

These economic losses result from suboptimal management of the tradeoff between reducing malaria infection in the short-run versus maintaining insecticide efficacy to manage infections in the long-run. In particular, optimal insecticide policies in this model manipulate the transmission and selection dynamics to different long-run steady states of insecticide resistance and malaria prevalence depending on the types of fitness cost mechanisms which are assumed. Figure 3 shows a bifurcation diagram which plots the stable and unstable steady states of the optimally controlled system given different mixes of fitness cost mechanisms. The bifurcation along the dotted line of the figure represents a boundary between one basin of attraction, in which an optimal policy allows insecticide susceptibility to re-charge to full capacity in the long-

run [ $s(\infty) = 1$ ], and another basin of attraction, which sacrifices long-run efficacy for immediate disease reductions [ $s(\infty) \ll 1$ ]. Increasing the proportion  $\alpha$  of fitness costs attributable to adult mortality pushes the bifurcation point—the unstable equilibrium separating these two basins of attraction—lower. When fitness costs are completely attributable to adult mortality ( $\alpha = 1$ ), the bifurcation vanishes, a result which is shown to hold in general (25). Recall that fitness costs associated with adult mosquito mortality should have direct economic benefits since higher vector mortality reduces disease transmission. Thus, when fitness costs convey fewer direct economic benefits, the cost-benefit calculus embodied in the economic optimization values short-run disease reductions over long-run insecticide efficacy for a wider range of initial insecticide resistance levels.

This brings us back to the basic insight from this analysis, which is that the mechanisms—and not simply the magnitude—of fitness costs associated with insecticide resistance can affect the consequences of a given policy seeking to manage evolutionary dynamics. Our results indicate, in this case, that incorporating more realistic fitness landscapes in optimal control models of malaria vector resistance to insecticides can have a dramatic impact on scientifically-based policy prescriptions.

## Figure Legends

**Figure 1.** *Optimal insecticide policies over time under different model assumptions.* These policies were generated using a numerical algorithm for dynamic economic optimization (25), which is an approximation of a partial differential equation with a nested unidimensional optimization problem. The policies shown correspond to initial malaria prevalence in the human population of 76%. Policies for other initial infection levels were similar. Policies generated through this method were then tested in simulations of the biological model to evaluate the potential economic gains from implementing the approximation of the optimal policy under the correct assumptions about the evolutionary dynamics of insecticide resistance (Fig. 2). Simulations were computed using differential equation solvers in MATLAB®.

**Figure 2.** *Percentage increases in discounted present value costs from implementing optimized insecticide policies, by initial malaria prevalence and insecticide resistance levels: (a) a policy assuming  $\alpha = 1$  in a biological model simulated with  $\alpha = 0.55$ , (b) a policy assuming  $\alpha = 0.55$  in a biological model with  $\alpha = 1$ , (c) a policy assuming no evolution of resistance in a biological model with  $\alpha = 0.55$ , (d) a policy assuming no evolution of resistance in a biological model with  $\alpha = 1$ .*

**Figure 3.** *Bifurcation diagram for  $\alpha$  of steady-state insecticide susceptibility in optimally controlled system. Arrows indicate basins of attraction.*

**Fig14**

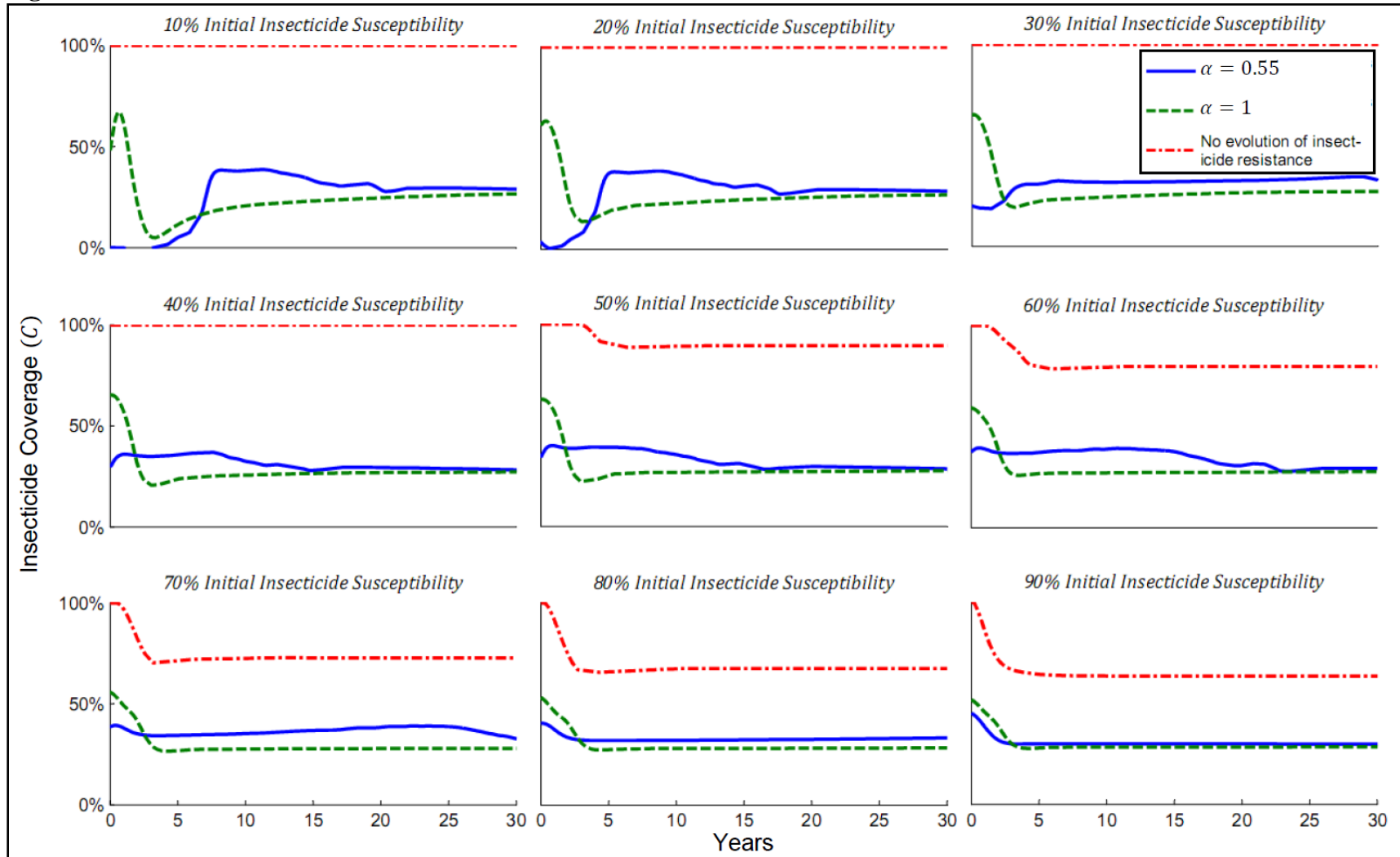
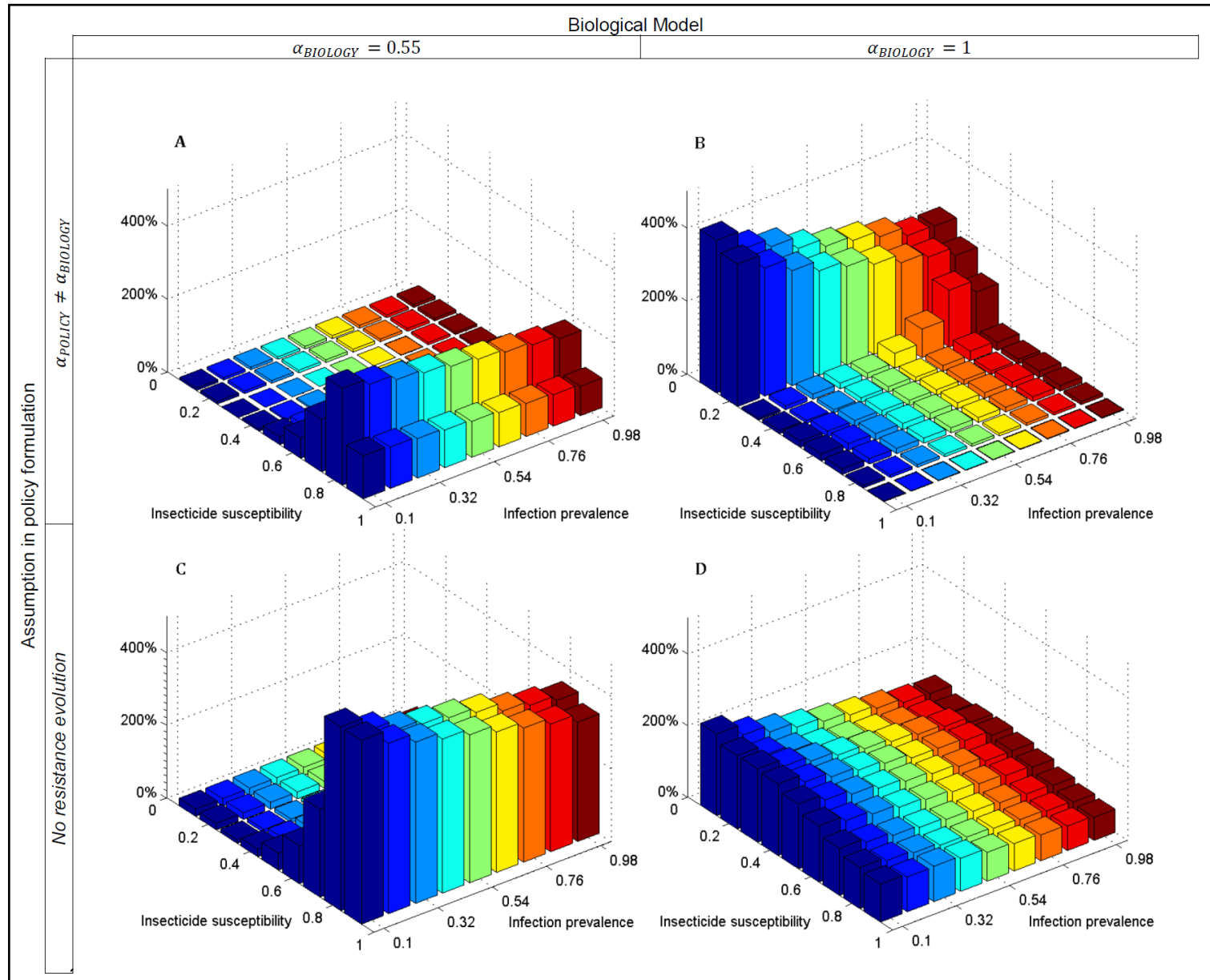
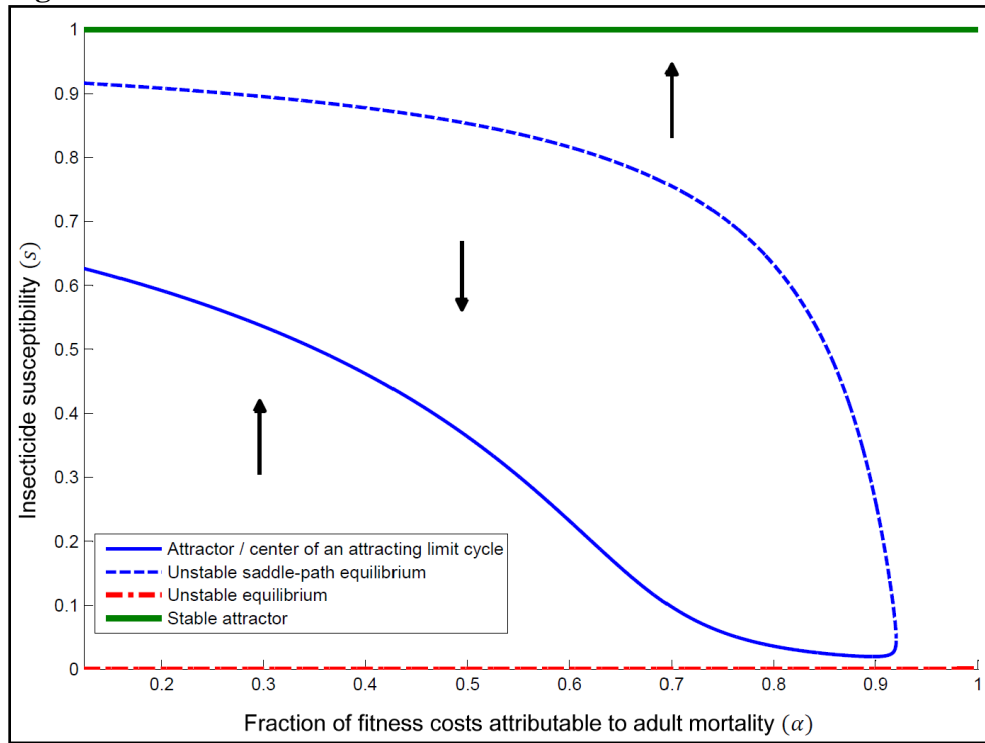


Fig2



**Fig3**



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## **Supporting Online Material**

This document contains more detailed information about field studies of insecticide resistance in disease vectors, and the “Materials and Methods” section of the paper. The sections of this document, which are hyperlinked, are organized as follows:

### **Background on insecticide resistance mutations in mosquitoes**

#### **Materials and Methods**

*[The epidemiological model](#)*

*[Fast vector dynamics](#)*

*[Population-level vector mortality and the evolution of insecticide resistance](#)*

*[Economic objective](#)*

*[Mathematical analysis of the steady states of the model](#)*

*[Parameterization of fitness costs and the speed of evolution](#)*

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#### **Supporting Tables**

#### **Supporting Figures**

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## **Background on insecticide resistance mutations in mosquitoes**

At least two “knockdown resistance” (kdr) mutations, kdr-w (or L1014F) and kdr-e (or L1014S), are known to impart simultaneous vector resistance to DDT and pyrethroids by blocking these insecticides’ interference with voltage-gated sodium channels in synapses (1, 2). The *ace-1*-G119S (or *ace-1<sup>R</sup>*) mutation in the vector *Anopheles gambiae* confers resistance to both carbamates and organophosphates through a modification of acetylcholinesterase, which is the synapse-regulating enzyme targeted by these insecticides (3).

Recent studies have examined the fitness costs associated with these mutations. For the kdr mutations, Okoye et al (4), in a laboratory study, found no statistical evidence that pyrethroid resistance in the southern African malaria vector *Anopheles funestus* was associated with developmental, reproductive, or survival related fitness costs. In other malaria vectors, researchers have found direct and indirect evidence consistent with the existence of substantial fitness costs (5-8). Djogbénou et al. (2) found substantially lower pupal survival rates among *Anopheles gambiae* mosquitoes possessing the *ace-1*-G119S mutation. Sarita, Anita et al (9) found large reproductive differences between pyrethroid susceptible and resistant types of the dengue vector *Aedes aegypti*. In the West Nile vector *Culex pipiens*, thirty years of data on organophosphate resistance have shown substantial fitness costs in terms of survival and reproductivity associated with the G119S mutation (10).

Because only adult *Anopheles* mosquitoes are capable of transmitting malaria and because an incubation time of approximately 2 weeks is required before an infected mosquito can become infectious to humans, any decreased fitness associated with adult mosquito mortality is especially important in terms of reducing malaria transmission.

## Materials and Methods

### *The epidemiological model*

The principle cost that insecticide spraying aims to limit is that incurred by disease spread by arthropod vectors. We consider a setting in which the disease is highly endemic in a human population, and which the disease does not have a noticeable effect on human mortality levels.

The dynamic evolution of the disease is specified using a MacDonald-Ross compartmental vector-borne disease model, in which human hosts are either infected or susceptible:

$$\frac{d\gamma}{dt} = r \left[ R_0 \frac{e^{-\tau_S(\mu - \mu_0)}}{\left(\frac{\mu}{\mu_0}\right)^2} \frac{\mu}{\mu + h\gamma} (1 - \gamma) - 1 \right] \gamma \quad (1)$$

where  $\gamma(t) \in (0,1]$  is the fraction of the human population infected with the disease at time  $t$ ,

the rate of recovery is  $r$ , the basic reproductive number for the disease in the baseline case is

$R_0 > 0$ , the incubation time of the pathogen in the vector is  $\tau_S > 0$ , the baseline vector mortality

rate is  $\mu_0 > 0$ , and the population-level vector mortality under the insecticide control regime is

$\mu \geq \mu_0$ , and  $h > 0$  is a scaling factor determined by various vector ecology parameters. The

interpretation of this equation is that susceptible individuals move to the infected compartment at

a rate of  $rR_0 \frac{e^{-\tau_S(\mu - \mu_0)}}{\left(\frac{\mu}{\mu_0}\right)^2} \frac{\gamma\mu}{\mu + h\gamma}$  and recover, returning to susceptible status, at rate  $r$ . For interested

readers, we provide the standard derivation of the Macdonald-Ross transmission rate beginning

from a compartmental model of malaria transmission within the vector population, assuming fast

dynamics of the vector relative to the human population.

This presentation of the standard MacDonald-Ross model is rather unusual, because we

write the equation of motion in terms of  $R_0$  rather than in terms of specific vector-ecology

parameters, and the relative densities of hosts and vectors. This presentation, while equivalent to

the standard one, eases economic interpretation of our results:  $R_0$  is an ecological threshold determining growth or decay of the disease. In the baseline case, when there is no control and vector mortality is at its natural rate  $\mu = \mu_0$ , then  $R_0 > 1$  implies that disease prevalence becomes endemic in the human population, with  $\gamma(t) \rightarrow \frac{(R_0-1)\mu}{h+R_0\mu}$  as  $t \rightarrow \infty$ . Furthermore, whereas specific vector ecology parameters are often unavailable in the literature,  $R_0$  is a frequently reported statistic for a variety of infectious diseases, including malaria, which is the disease focused on in the numerical analysis. In the following, we assume that the disease is endemic in the absence of any control so that  $R_0 > 1$ .

In this paper, we only consider the control of the disease through increases in vector mortality  $\mu$  above the baseline  $\mu_0$ . In considering how changes in vector mortality impact the change in disease levels, it is convenient to define the function:

$$z(\mu, \gamma) \equiv \frac{e^{-\tau_S(\mu-\mu_0)} \mu}{\left(\frac{\mu}{\mu_0}\right)^2 \mu + h\gamma} \quad (2)$$

This allows us to write the differential equation (1) more compactly as  $\frac{d\gamma}{dt} = r[R_0 z(\mu, \gamma)(1 - \gamma) - 1]\gamma$ . The function  $z$  can be interpreted as the proportion of basic reproductive number ( $R_0$ ) remaining after reducing vector mortality level from  $\mu_0$  to  $\mu$ . It is easy to verify that  $z(\mu_0, 0) = 1$ ,  $z(\infty, 0) = 0$ , and  $z$  is strictly decreasing and convex in  $\mu$  and  $\gamma$ . For fixed  $\mu$ , the basic reproductive number and steady state endemic infection levels become respectively:

$$\begin{aligned} R(\mu) &\equiv R_0 z(\mu, 0) \\ \gamma^\infty(\mu) &\equiv \frac{(R(\mu)-1)\mu}{h+R(\mu)\mu} \quad \text{when } R(\mu) > 1 \text{ and } 0 \text{ otherwise} \end{aligned} \quad (3)$$

Given this formulation, a relevant epidemiological quantity is that vector mortality level above which the disease can be extinguished. Given our definitions, and the fact that  $z$  is strictly

decreasing in  $\mu$ , we can define this vector mortality threshold  $\mu^e$  by the inversion of equation (3):<sup>1</sup>

$$\mu^e \equiv R^{-1}(1) \tag{4}$$

The next section specifies how  $\mu$  is to be controlled through insecticide spraying, and how resistance evolves in response to spraying.

### *Fast vector dynamics*

For interested readers, this section presents the basic derivation of the Macdonald-Ross transmission rate used in the epidemiological dynamic in equation (1). The standard assumption used to derive the formula is that the disease dynamics with respect to mosquitoes are much faster than the disease dynamics with respect to humans. To derive the above formula, we follow (11); we need to introduce some additional free parameters, in order to clarify the exposition. We also omit equation numbers here, as this section is somewhat tangential to the main paper. As with the human population, we start by assuming that mosquitoes may be compartmentalized into a susceptible group of  $X$  individuals, a group of  $Y$  individuals harboring incubating malaria parasites, and an infectious group of  $Z$  individuals. Keeping the time argument  $t$  explicit, the dynamics of the three subpopulations of mosquitoes take the following form:

$$\frac{dX(t)}{dt} = \Xi - b\rho_{hm}\gamma X(t) - \mu X(t)$$

$$\frac{dY(t)}{dt} = b\rho_{hm}\gamma X(t) - e^{-\tau_s\mu} b\rho_{hm}\gamma X(t - \tau_s) - \mu Y(t)$$

$$\frac{dZ(t)}{dt} = e^{-\tau_s\mu} b\rho_{hm}\gamma X(t - \tau_s) - \mu Z(t)$$

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<sup>1</sup> Note that  $\mu^e$  is guaranteed to exist in this context because of the mathematical properties of the function  $z$ .

where  $\Xi$  is the density-independent recruitment rate of female, adult mosquitoes,  $b$  is the human biting rate,  $\rho_{hm}$  is the probability that a bite on an infectious human will lead to infection of a mosquito, and as before  $\mu$  is the population-level vector mortality rate and  $\tau_S$  is the incubation time of malaria in mosquito vectors. Note that this formulation assumes that all incubating vectors become infectious exactly when  $\tau_S$  time elapses, i.e. there is no randomness in the incubation time in vectors. This assumption necessitates the use of delay differential equations. An alternative formulation, avoiding the use of time delay equations, would assume that incubating vectors become infectious at rate  $1/\tau_S$  so that the *expected* incubation time is  $\tau_S$ .

The general infection malaria dynamics in the human population consist of the subpopulations of susceptible individuals  $S$  and infected individuals  $I$ :

$$\frac{dS}{dt} = -b\rho_{mh}ZS + rI$$

$$\frac{dI}{dt} = b\rho_{mh}ZS - rI$$

where  $\rho_{mh}$  is the probability that a bite from an infectious mosquito will lead to infection of a human. Because the total human population is constant, we can convert the above system to a single differential equation for fraction  $\gamma$  of humans who are infected:

$$\frac{d\gamma}{dt} = b\rho_{mh}Z(1 - \gamma) - r\gamma$$

It is then apparent that the transmission rate facing humans is  $b\rho_{mh}Z$ , and it is left to show that this is equivalent to the above formulation under the stated assumptions.

Imposing the assumption that the vector dynamics are at equilibrium—i.e. fast relative to the human population—and defining  $h = b\rho_{hm}$  we can calculate the equilibrium value of  $Z^*$ :

$$Z^* = \frac{h\Xi e^{-\tau_S\mu}}{\mu(h\gamma + \mu)}$$

Finally, defining  $R_0 := r^{-1} b \rho_{mh} Z^* |_{\mu_0} = r^{-1} b \rho_{mh} \frac{h \Xi e^{-\tau_S \mu_0}}{\mu(h\gamma + \mu_0)}$  yields the equivalence between the two transmission rates. That is:

$$b \rho_{mh} Z^* = r R_0 \frac{e^{-\tau_S(\mu - \mu_0)}}{\left(\frac{\mu}{\mu_0}\right)^2} \frac{\gamma \mu}{\mu + h\gamma}$$

The right-hand-side of this equation has the convenient interpretation that  $R_0$  is the threshold determining whether the malaria epidemic grows or decay within the human population, if vector mortality is set to its baseline level, i.e.  $\mu = \mu_0$ .

#### *Population-level vector mortality and the evolution of insecticide resistance*

At the population level, average adult vector mortality is the weighted average of vector mortality from adult vectors which are exposed to the insecticide and ones which are not.

Furthermore, among those vectors which are exposed to the insecticide, the overall mortality rate is an average of those vectors which are resistant to the insecticide and those which are not.

We assume that vectors reproduce sexually and so possess two chromosomes, and that insecticide resistance is characterized by the presence or absence of a single polymorphism on each chromosome. Thus, each chromosome has either a susceptible (S) or resistant (R) copy of a certain gene, so that each vector can be classified as a homozygote-resistant (RR), a heterozygote (RS), or a homozygote-susceptible (SS). Let  $\mu_\theta^E$  and  $\mu_\theta^U$  be the mortality rates for vectors of genotype  $\theta \in [RR, RS, SS]$  which are exposed (E) and unexposed (U) to the insecticide respectively. We assume initially that the resistant and susceptible copies of the gene are equally dominant in heterozygotes. We then define the individual-level mortality rates as:

$$\mu_{RR}^E \equiv \mu_0 + \mu_r \qquad \mu_{RR}^U \equiv \mu_0 + \mu_r \qquad (5)$$

$$\mu_{SS}^E \equiv \mu_0 + g$$

$$\mu_{SS}^U \equiv \mu_0$$

$$\mu_{RS}^E \equiv \frac{1}{2}(\mu_{RR}^E + \mu_{RR}^E)$$

$$\mu_{RS}^U \equiv \frac{1}{2}(\mu_{RR}^U + \mu_{RR}^U)$$

where  $\mu_r \geq 0$  is the potential excess mortality rate associated with possession of the resistant genes regardless of insecticide exposure, and  $g > \mu_r$  is the excess mortality induced by exposure of the SS types to the insecticide. The parameter  $\mu_r$  is one possible component in the evolutionary fitness costs associated with insecticide resistance, which are discussed further below.

To obtain population-level mortality rates, define  $s(t) \in [0,1]$  as the fraction of vectors at time  $t$  which have at least one chromosome with a susceptible copy of the gene. We make the simplifying assumption that genotypes mix homogeneously and mate randomly, whether or not they are exposed to the insecticide and whether or not the females are infected with malaria; this admits the use of Hardy-Weinberg equations to calculate the frequencies of each genotype. The average mortalities  $\mu^E$  and  $\mu^U$  among exposed and unexposed vector subpopulations are then:

$$\mu^E = (1-s)^2 \mu_{RR}^E + 2s(1-s) \mu_{RS}^E + s^2 \mu_{SS}^E \quad (6)$$

$$\mu^U = (1-s)^2 \mu_{RR}^U + 2s(1-s) \mu_{RS}^U + s^2 \mu_{SS}^U$$

Now let  $C(t) \in [0,1]$  be the fraction of the human population which is protected at time  $t$ . The average mortality rate among the vector population is then:

$$\mu = C\mu^E + (1-C)\mu^U \quad (7)$$

Combining the equations in (5), (6), and (7), we obtain a simple expression for average vector mortality as a function of the prevalence of the susceptible gene in the vector population and the fraction of the human population protected by insecticide spraying:

$$\mu(s, C) = \mu_0 + \mu_r + (Cg - \mu_r)s \quad (8)$$

This last equation is to be used in the epidemiological dynamic specified in equation (1).

The overall level of insecticide exposure in the vector population is assumed to drive the selection for genetic resistance in the vector population. We use replicator dynamics to model the selection for the three different genotypes, in conjunction with the Hardy-Weinberg equations for the genotype frequencies. These dynamics express the rates of change of the genotype frequencies as functions of the evolutionary fitness of each genotype. These replicator dynamics can be reduced to a single differential equation for  $s$ . This differential equation is:

$$\frac{ds}{dt} = \varepsilon(f - Cg)s(1 - s) \quad (9)$$

where  $\varepsilon$  is an exogenous parameter controlling the timescale on which insecticide resistance evolves relative to disease transmission, and  $f$  is the relative evolutionary fitness cost for vectors which are resistant to the insecticide (12).

The fitness cost  $f$  is an aggregate term that includes the mortality-specific cost  $\mu_r$  so that  $f \geq \mu_r$ . It can consist of a variety of other components, including differences in reproductive cycle length, fecundity, as well as larval and pupal survival rates between the RR and SS genotypes. Allowing for  $f > \mu_r$  is the main innovation of this model. With this dynamic,  $s$  exhibits logistic growth to unity or decay to zero of insecticide resistance when  $C < \frac{f}{g}$  and  $C > \frac{f}{g}$ , respectively. By definition resistance confers a selective advantage: Relative fitness costs are less than the insecticide-induced mortality rate among SS genotypes, i.e.  $f < g$ .

Before turning to the economic analysis of these dynamics, we discuss the properties of the coupled epidemiological and evolutionary system defined by equations (1), (8), and (9). The phase space for this bidimensional system is depicted in **Figure S1**. The nullclines for the dynamic variables  $\gamma$  and  $s$  are plotted for a variety of constant levels of insecticide coverage  $C$ . Note that the nullclines for  $s$  are constant over different levels of  $C$ ; it is only the stability of

these nullclines that changes with different insecticide coverage levels. The system exhibits three potentially stable types of steady states defined as follows:

$$\begin{aligned}
SS_1^\infty &\equiv [\gamma_1^\infty, s_1^\infty] \equiv [\max\{\gamma^\infty[\mu_0 + gC], 0\}, 1] \\
SS_2^\infty &\equiv [\gamma_2^\infty, s_2^\infty] \equiv [\max\{\gamma^\infty[\mu_0 + \mu_r], 0\}, 0] \\
SS_3^\infty &\equiv [\gamma_3^\infty, s_3^\infty] \equiv [\max\{\gamma^\infty[\mu_0 + \mu_r + (f - \mu_r)s_3^\infty], s_3^\infty\}, 0] \text{ such that } s_3^\infty \in [0,1]
\end{aligned} \tag{10}$$

For fixed  $C$ , one—and only one—of these three types of steady states obtains, i.e. exists and is stable. Which obtains depends on whether the insecticide-induced mortality in the susceptible vector population exceeds the relative fitness costs associated with resistance. If  $C < f/g$ , then  $SS_1^\infty$  obtains;  $SS_2^\infty$  obtains if  $C > f/g$ . The somewhat pathological case  $SS_3^\infty$  obtains when  $C = f/g$ , and plays an important role in the economic analysis in subsequent sections.

Lastly, observe from the equations in (10) and (4) that whether or not the disease can be extinguished in the long-run depends on the three quantities  $\mu^e$ ,  $\mu_0$ , and  $f$ . Specifically, if and only if  $\mu^e < \mu_0 + f$  then the disease can be eliminated using insecticide spraying. The interpretation of this condition is that the threshold vector mortality  $\mu^e$  which eliminates the disease must be low relative to the overall fitness cost in the resistant vector population.

### *Economic objective*

Here we consider the net social welfare gain from insecticide spraying in per capita terms.<sup>2</sup> Two costs are considered in this model, the cost of infection and the cost of insecticide spraying. Let  $q_\gamma$  be the total cost per unit time incurred while a single individual is infected. Let  $q_C$  be the total cost per unit time of protecting a single person with the insecticide spraying program. Total costs per person in period  $t$  are thus:

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<sup>2</sup> Since we assume population is constant, per capita welfare is equivalent to population-level welfare and precludes the introduction of an unnecessary parameter for population size.

$$k(t) \equiv q_Y \gamma(t) + q_C C(t) \quad (11)$$

The economic objective is to maximize present value net benefits—equivalent to minimizing present value costs—using the control  $C$ :

$$\max_{c(t) \in [0,1]} \int_0^{\infty} -[q_Y \gamma(t) + q_C C(t)] e^{-\delta t} dt \quad (12)$$

where  $\delta > 0$  is a constant rate of discount which determines the relative weight given to current and future costs.

It is possible to consider a formulation of costs which is nonlinear in the states or control. From a social welfare perspective, the cost of infection embodies the cost of care, the costs of pain and suffering, as well as the cost of mortality risks while infected, any one of which, at a societal level, could exhibit either increasing marginal costs (e.g. through saturation of the health system) or decreasing marginal costs (e.g. through economies of scale) in terms of disease prevalence. In this paper we restrict ourselves to constant marginal infection costs in order to keep the number of parameters in the model manageable, and to keep our attention on the effects of insecticide resistance. The cost of the insecticide spray programs involves purchases of insecticides, transport, wages for the sprayers, administration costs, as well as the purchase of durable inputs such as vehicles, spray tanks, and protective garments for the workers (13). These latter items involve an important startup cost of spray programs, introducing potentially complex dynamics such as investment irreversibility into the economic decision model. We circumvent these complications by considering spray programs which are already under way. That is, the purpose of this analysis is to shed light on how insecticide resistance could be factored into economic decision-making about existing vector control programs.

Before applying optimal control theory to the problem, we first use a change of variables for the level of insecticide resistance which allows a more tractable representation of the control problem. Define the new variable  $\omega(s) \equiv \ln s - \ln(1 - s)$ , whose differential equation is:

$$\frac{d\omega}{dt} \equiv \varepsilon(f - gC) \quad (13)$$

After applying optimal control theory, we will also need to change back from this variable using the inverse of  $\omega(\cdot)$ . The inverse of  $\omega(s)$  is  $\check{s}(\omega) \equiv \frac{1}{1+e^{-\omega}}$ , which is the logistic function.

Given the objective in (12) and the epidemiological and evolutionary constraints in equations (1), (8), and (9), the optimal control  $C$  maximizes the current value Hamiltonian for the problem:

$$H \equiv -q_\gamma \gamma - q_C C + \lambda r [R_0 z \{ \mu [\check{s}(\omega), C], \gamma \} (1 - \gamma) - 1] \gamma + \eta \varepsilon (f - gC) \quad (14)$$

where  $\lambda$  and  $\eta$  are the shadow prices/costs on the infection level and insecticide resistance level, respectively. The shadow prices evolve according to the following differential equations:

$$\begin{aligned} \frac{d\lambda}{dt} - \delta\lambda &= q_\gamma - \lambda r \left[ R_0 z (1 - 2\gamma) + R_0 \frac{dz}{d\gamma} \gamma (1 - \gamma) - 1 \right] \\ \frac{d\eta}{dt} - \delta\eta &= -\lambda r \left[ R_0 \frac{dz}{d\mu} (1 - \gamma) \gamma \right] (gC - \mu_r) s (1 - s) \end{aligned} \quad (15)$$

where we have suppressed arguments for the functions  $z$ ,  $\frac{dz}{d\gamma}$ ,  $\frac{dz}{d\mu}$ , and  $\frac{d\mu}{ds}$  to keep presentation concise. In deriving (15), we first use the state variable  $\omega$  in place of  $s$  to derive the Hamiltonian and co-state equations, and then substitute  $s$  back into the problem using  $\omega(s)$  and  $\frac{ds}{d\omega} = s(1 - s)$ .

At a moment in time, the marginal net benefit of increasing insecticide coverage is composed of three parts:

$$\frac{\partial H}{\partial C} \equiv \underbrace{\lambda r \left[ R_0 \frac{dz}{d\mu} s(1 - \gamma) - 1 \right] \gamma}_{\text{dynamic marginal benefit from spraying}} - \underbrace{q_C}_{\text{static marginal cost of spraying}} - \underbrace{g\eta\varepsilon}_{\text{dynamic marginal cost of insecticide resistance}} \quad (16)$$

Because  $z$  is convex in  $\mu$ , the marginal net benefit is decreasing in the control  $C$ , as long as the shadow price  $\lambda$  of infections is negative (infections are costly). Thus, solving for  $C$  such that marginal net benefits are zero provides a global maximum for  $H$ . If the solution to this first-order condition does not fall in the interval  $[0,1]$ , then one of the boundary constraints binds. We study the steady states of the optimized system first, before analyzing the transition dynamics of the socially optimal insecticide-based control policy.

#### *Mathematical analysis of the steady states of the model*

We approach analysis of the optimally controlled steady states by considering whether long-run vector susceptibility is in turn full, partial, or nonexistent. Our mathematical findings are summarized as propositions. A steady state is a solution to the system of equations formed by setting the left-hand-sides of (1), (9), and (15) to zero, and verifying that (16) is maximized with respect to  $C$ . A solution is denoted as  $(\gamma^*, s^*, C^*)$ .

*Proposition I: A steady state with full vector susceptibility is identical to the long-run optimum which is unconstrained by insecticide resistance. If the vector population is fully susceptible to insecticides in the long-run, with  $s^* = 1$ , then  $C^* \leq f/g$ . Moreover, the steady state of the optimally controlled system is identical to that which would obtain if only the epidemiological dynamic (1) were optimally controlled, ignoring insecticide resistance—i.e. taking  $s \equiv 1$  and ignoring the dynamic in (9). If a positive level of*

control is optimal in the long-run ( $C^* > 0$ ) in such a situation, the steady state level of control in this case satisfies the following equations:

$$0 = \frac{\partial H}{\partial C} = -q_c + \frac{gq_\gamma \left( \tau_s + \frac{1}{\mu^*} + \frac{1}{\mu^* + w\gamma^*} \right)}{\left[ \frac{1}{1 - \gamma^*} + \frac{w}{\mu^* + w\gamma^*} \right] + \frac{\delta}{r\gamma^*}} \quad (17)$$

$$\gamma^* = \gamma^\infty(\mu_0 + gC^*)$$

$$\mu^* = \mu_0 + gC^*$$

*Proposition II: Partial vector susceptibility requires a control at a unique fitness threshold.* If the vector population is *partially* susceptible to insecticides in the long-run, with  $s^* \in (0,1)$ , then  $C^* = f/g$  and  $s^* \in [0,1]$  satisfies the following system of equations:

$$0 = \frac{\partial H}{\partial C} = -q_c + \frac{gq_\gamma \left( \tau_s + \frac{1}{\mu^*} + \frac{1}{\mu^* + w\gamma^*} \right)}{\left[ \frac{1}{1 - \gamma^*} + \frac{w}{\mu^* + w\gamma^*} \right] + \frac{\delta}{r\gamma^*}} \left[ s^* - \frac{\varepsilon(f - \mu_r)s^*(1 - s^*)}{\delta} \right] \quad (18)$$

$$\gamma^* = \text{Max}\{ \gamma^\infty(\mu^*), 0 \}$$

$$\mu^* = \mu_0 + \mu_r + (f - \mu_r)s^*$$

The proof for Propositions I and II consists of direct calculation. The steady states in (17) and (18) cannot in general be solved explicitly for the steady state level of spray coverage  $C^*$  or susceptibility  $s^*$ , respectively. This is because of the transcendental nature of the function  $z$ , which is in turn due to the pathogen's incubation time  $\tau_s > 0$  in the vector. Of principle concern in characterizing the optimal states is to determine if multiple stable steady states can coexist, and if so which ones are stable. A closer inspection of the system in (18) reveals the importance of the qualitative properties of the fitness costs associated with insecticide resistance in

answering this question. In particular, we consider the case with  $f = \mu_r$ . In this case, the equations in (18) reduce to a linear equation in  $s^*$ , which possesses at most a single solution:

*Proposition III: The properties of fitness costs determine the number of interior steady states. If  $f = \mu_r$  then any solution to (18) is unique. If in addition eradication is feasible, with  $\mu_0 + \mu_r \geq \mu^e$ , then there is no solution to (18). When eradication is not feasible, the unique interior steady state (if it exists) in terms of the model's parameters is:*

$$\gamma^* = \gamma^\infty(\mu_0 + \mu_r)$$

$$s^* = \frac{q_c}{gq_\gamma} \times \frac{\left( \frac{1}{1-\gamma^*} + \frac{w}{\mu_0 + \mu_r + w\gamma^*} \right) + \frac{\delta}{r\gamma^*}}{\tau_s + \frac{1}{\mu_0 + \mu_r} + \frac{1}{\mu_0 + \mu_r + w\gamma^*}} \quad (19)$$

*Proof of Proposition III*

Suppose fitness costs are simple with  $f = \mu_r$ , and say  $C^* \leq f/g$ . Then  $\mu_0 + \mu_r \geq \mu_0 + gC^*$ . If eradication feasible then (an interior)  $s^*$  does not exist (the slope coefficient is zero since  $\gamma^\infty(\mu_0 + \mu_r) < 0$ ). If eradication is not feasible, the slope coefficient is a positive constant over  $s$ , and the  $s^* = 0$  value is negative since  $q_\gamma > 0$ , so that there is at most a unique  $s^*$  solving (18).

It may seem strange that  $\delta$  unambiguously increases  $s^*$  in (19). This is due to two facts: First, the steady state marginal shadow cost of infection  $\lambda^*$  decreases with an increasing discount rate, *ceteris paribus*. This is because the higher the discount rate the less the present-value cost associated with a long-run level of disease. Second, the steady state shadow cost of resistance is zero when fitness costs are totally mortality-specific and when the steady state is interior. Thus,

a higher discount rate places less weight on future infection costs, decreasing the dynamic benefits from insecticide spraying and leaving resistance costs unchanged. This implies a less intensive spray program and hence a higher stock of insecticide susceptibility in the vector population. Similarly, the cost ratio  $\frac{q_c}{gq_\gamma}$  has a positive impact on  $s^*$ , so that, for instance, a higher direct marginal cost of infection  $q_\gamma$  implies a lower steady state stock of insecticide susceptibility.

When fitness costs are complex ( $f > \mu_r$ ), the steady state level of vector susceptibility becomes difficult to analyze symbolically, and we turn to numerical methods. Before doing so, numeric values for the model's parameters must be selected.

#### *Parameterization of fitness costs and the speed of evolution*

**Table S1** shows the parameters used for the three scenarios considered in the paper. Of principal importance, the aggregate measure of fitness costs  $f$  should be kept in the same units as mortality, for use in equation (9). In general, empirical studies of fitness costs report relative fitness costs, which are dimensionless (14). In keeping with our strategy of selecting representative—not precisely estimated—parameter values from the literature, we first detail a way of producing an aggregate fitness cost per unit time from previously published studies of insecticide fitness costs.

The formula we derive for aggregate fitness costs of resistance assumes that genetic fitness can be specified as the natural logarithm of the expected number of viable offspring produced at the end of a given length of time, allowing for differences in adult mortality, number of eggs laid, survivability of pupa and larva, and reproductive cycle length. Using this assumption and the Hardy-Weinberg equations for genotype frequencies, and assuming equal

dominance between the resistant and susceptible copies of the gene, the aggregate fitness cost can be written as:

$$f = \left( \frac{\tau_G^{RR}}{\tau_G^{SS}} - 1 \right) \mu_0 + \frac{\tau_G^{RR}}{\tau_G^{SS}} \mu_r + \frac{1}{\tau_G^{SS}} \log \frac{G_{SS}}{G_{RR}} \quad (20)$$

where  $\tau_G^\theta$  and  $G_\theta$  are respectively the average gonotrophic cycle length (i.e. time between egg-laying) and average number of offspring which survive to adulthood for homozygous genotype  $\theta \in \{RR, SS\}$ .

This formula is applicable to a wide variety of published findings on insecticide fitness costs. For example, applying this formula to findings from (2) about differential pupal survivability between *A. gambiae* strains with and without the *ace-1*-G119S mutation, we retrieve measures for  $f$ , ranging from 0.01 to 0.4 per day, depending on food availability and assuming a gonotrophic cycle of 3 days for both genotypes. Applying this formula to findings from (9) about differential hatchability and pupal survivability between *Aedes aegypti* mosquitoes (non-malaria vectors) with and without a *kdr* mutation yields a rough estimate of 0.21 per day, assuming a gonotrophic cycle length of 3 days for homozygous susceptible genotypes. Since our aims are principally illustrative in this paper, we arbitrarily select a value from within this reasonable range of 0.26 per day (Table 1).

We then are left to determine the timescale of evolution which is captured through the parameter  $\varepsilon$  in equation (9), which we calibrate by defining an initial level of susceptibility  $s(0)$ , and length of time  $T$ , and a terminal level of susceptibility  $s(T)$ , assuming full insecticide coverage  $C = 1$ . The parameter  $\varepsilon$  is chosen to satisfy this outcome. In this paper, we choose  $\varepsilon$  such that insecticide susceptibility declines to 5% after 15 years of full coverage of the population by a spray program, starting from an initial value of 99%. This is consistent with what little is known about the speed of evolution of insecticide resistance in malaria vectors (15).

Lastly, the discount rate used for the economic simulations is set at 10%, which factors in both a deterministic rate of discount and an uncertain but finite time horizon for the policy. For example, a 10% discount rate could be derived assuming (a) the WHO standard discount rate of 3%, (b) an expected planning horizon of 14.28 years, and (b) a constant hazard rate (of 7%) that the planning horizon randomly ends. In malaria control programs, a planning horizon of 5 to 20 years is reasonable, given the uncertain arrival of “game changing” interventions, such as vaccines.

### *Numerical methods*

To compute the optimal policies in the numerical experiments, we used dynamic programming techniques, implemented using the CompEcon Toolbox by Miranda and Fackler (16) in MATLAB®. These methods interpolate the following partial differential equation in the value function  $v(\gamma, \omega)$ :

$$\delta v(\gamma, \omega) = \max_{C \in [0,1]} \left\{ -q_\gamma \gamma - q_C C + v_\gamma r [R_0 z \{ \mu[\tilde{s}(\omega), C], \gamma \} (1 - \gamma) - 1] \gamma + v_\omega \varepsilon (f - gC) \right\} \quad (21)$$

Numerical approximations  $\hat{v}$  to this equation were then validated by re-constructing the optimal feedback insecticide policy implied by  $\hat{v}$  and then using differential equation solvers in MATLAB to simulate the optimally controlled system. The simulated equilibria of the system were then verified to match the theoretical equilibria in Propositions I-III above. The stability properties of these equilibria were then validated by comparing the stability of equilibria in the simulations (e.g. whether the equilibria are stable, saddle-path stable, unstable limit cycle nodes, or simply unstable) and verified to match results from a numerical stability analysis of the optimal control system, using reverse-shooting methods (17). **Figure S2** shows the results of this reverse shooting analysis.

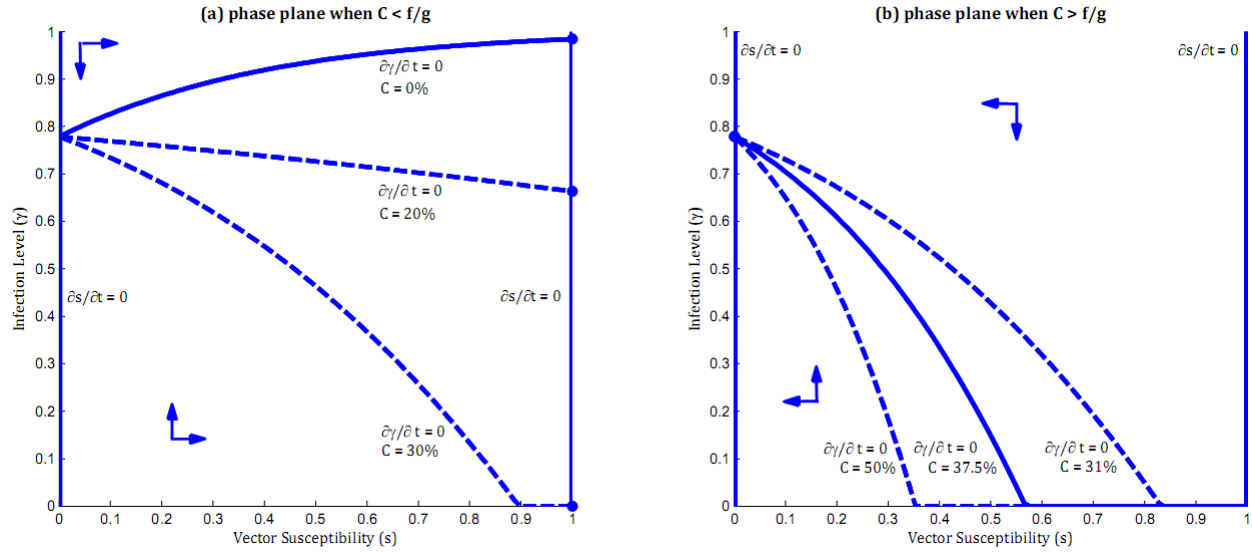
It is important to emphasize that these numerical methods only approximate cost-minimizing policies. Often, the more complex the model, the poorer the approximation. However, in addition to implementing the validation procedures described above, we also evaluated the economic costs of each policy through ex-post simulation (as opposed to direct evaluation of the value function approximation in equation 21). As shown in Figure 2 of the paper, these approximations of the optimal policies perform well in the simulations, based on the original economic criterion in equation (12). Figure S3 shows some example trajectories of the optimally controlled system calculated using these numerical methods.

**Table S1.** Simulation parameters used in the model and economic optimization, by scenario. Parameters which vary by scenario are in bold. Parameters were selected to be broadly representative of the literature, and to characterize a plausible malaria transmission context in a setting of endemic transmission.

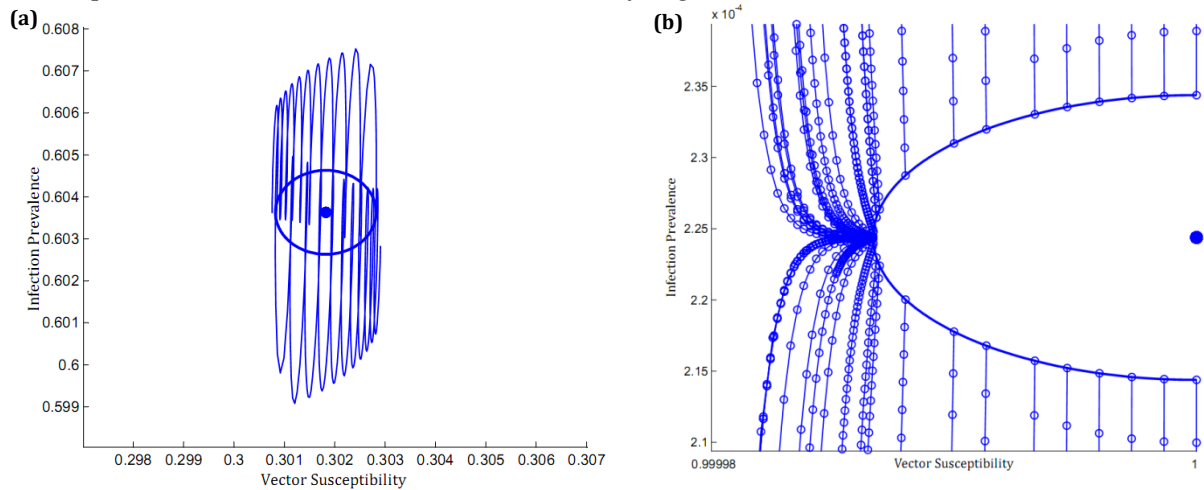
	Basic Reproductive number of malaria (18) (# secondary per primary case)	Recovery rate of malaria-infected individuals (19-21) (per day)	Incubation time of malaria in mosquitoes (22) (days)	Mass-action saturation factor (23) (dimensionless)	Baseline vector mortality (24, 25) (per day)	Insecticide-induced mortality (24, 25) (per day)	Total fitness cost (9, 24, 26) (per day)	<b>Mortality-specific fitness cost (% of total)</b>	Economic cost of a single infection (27) (USD per case)	Spray cost per person (28) (USD per person-year)	Risk-adjusted discount rate (% per year)	<b>Exogenous speed of resistance evolution (per year)</b>
Scenario I: Mortality-specific fitness costs	100	0.01	14	61	0.27	0.83	0.26	<b>100%</b>	\$10	\$1.21	10%	<b>15<sup>-1</sup></b>
Scenario II: Diverse fitness costs	100	0.01	14	61	0.27	0.83	0.26	<b>55%</b>	\$10	\$1.21	10%	<b>15<sup>-1</sup></b>
Scenario III: No evolution of resistance	100	0.01	14	61	0.27	0.83	0.26	<b>100%</b>	\$10	\$1.21	10%	<b>0</b>

## Supporting Figures

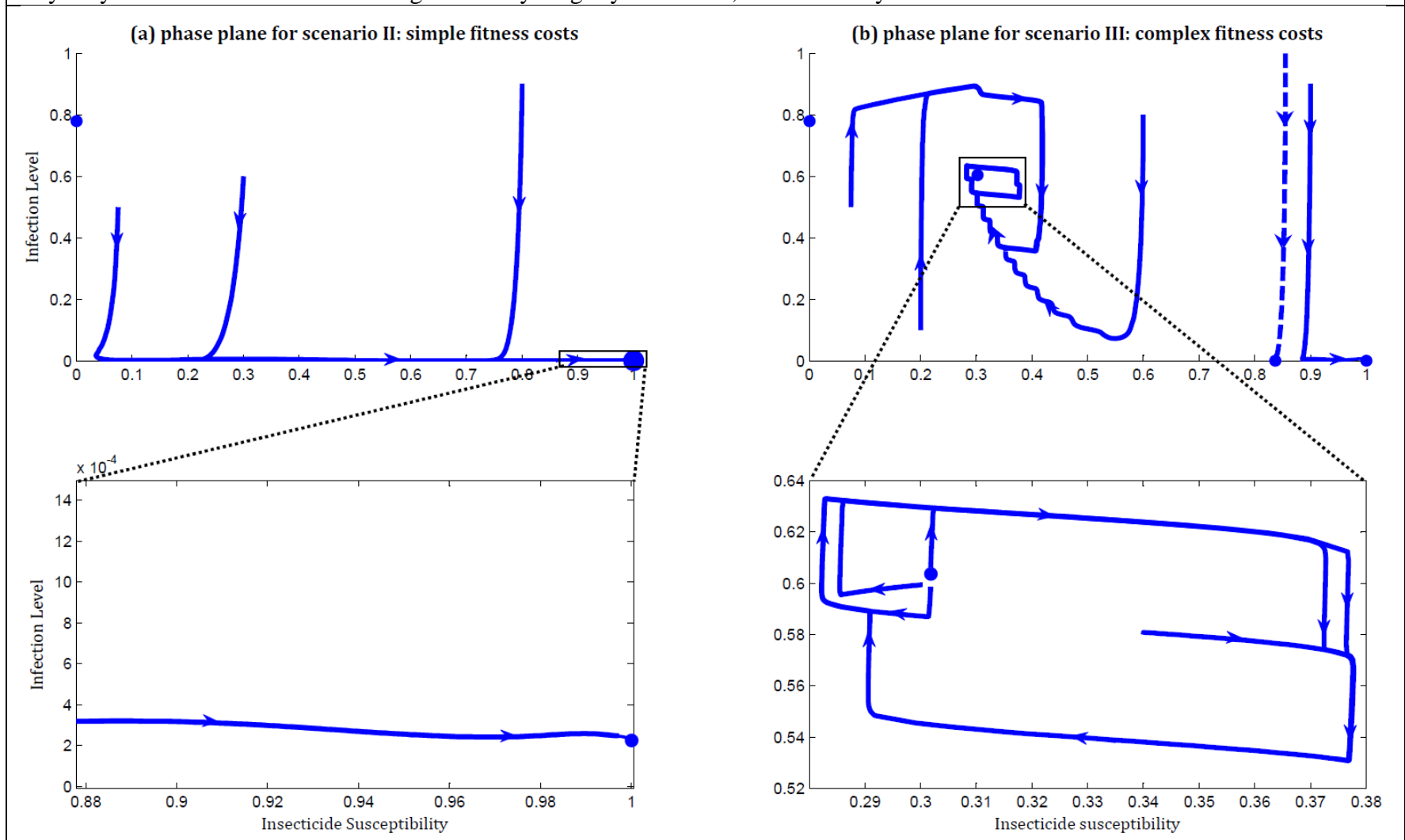
**Figure S1: Phase planes for the biological system given a fixed control.** Insecticide spray coverage is (a) less than the fitness threshold leading to full insecticide susceptibility, and (b) greater than the fitness threshold leading to full insecticide resistance.



**Figure S2: Reverse shooting stability analysis of steady states.** Reverse shooting draws a small circle around a given steady state and simulates the optimal control dynamic system backwards in time using the steady state co-state values as the corresponding initial conditions for the co-states. When the simulated trajectories radiate away from the steady state (as in panel b), it is stable. When the trajectories collapse in on themselves, back to the steady state (as in panel a), then the steady state is unstable. Panel (a) corresponds to point  $z$  in Figure 3 of the main paper. Panel (b) corresponds to point  $x$  of Figure 3.



**Figure S3:** Simulations of malaria prevalence and insecticide resistance with the implementation of an economic insecticide policy: (a) Trajectories corresponding to Scenario I (Table S1). Zoomed in portion that optimal steady-state does not eliminate malaria, but reduces prevalence to an extremely low level. (b) Trajectories corresponding to Scenario II. Zoomed in portion shows that in this scenario the optimal control induces a limit cycle in the long-run. Thus, the interior steady state of the optimally controlled system may only be stable in the sense of being orbited by a tightly controlled, stable limit cycle.



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