Supplementary material to accompany

Insecticide resistance and malaria vector control: The importance of fitness cost mechanisms in determining economically optimal control trajectories.

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CONTENTS

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 (Djogbénou et al., 2010; Reimer et al., 2008). The *ace-1*-G119S (or *ace-1*^{R}) 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 (Nauen, 2007).

Recent studies have examined the fitness costs associated with these mutations. For the kdr mutations, Okoye et al (2007), 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 (Agnew et al., 2004; Rowland, 1991a, b; Stump et al., 2004). Djogbénou et al. (2010) found substantially lower pupal survival rates among *Anopheles gambiae* mosquitoes possessing the *ace-1*-G119S mutation. Sarita, Anita et al (2009) 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 (Raymond et al., 2001).

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.

Reparameterizing epidemiological dynamics from the Macdonald-Ross Model

Here, we present the formulation of a 2 equation model of the evolution of insecticide resistance and malaria transmission. We use a textbook compartmental model of vector-borne transmission of malaria (Anderson and May, 1991; Keeling and Rohani, 2008): Humans are either susceptible or harboring blood-stage malaria parasites. Ordinary differential equations are used to represent the flows of individuals to and from the susceptible (S) and infected (I) compartments:

$$\frac{dS}{dt} = bN - \rho_{mh}\beta Z_t\left(\frac{S_t}{N}\right) + \xi I_t - bS_t$$
$$\frac{dI}{dt} = \rho_{mh}\beta Z_t\left(\frac{S_t}{N}\right) - \xi I_t - bI_t \quad \text{(A.1)}$$

This system depicts a process in which infected mosquitoes Z bite humans at rate β, that each bite lands on an uninfected human with probability equal to the proportion of susceptibles in the population (S_t/N), and infects that human with conditional probability $\rho_{mh} \in [0,1]$. Infected humans recover at rate ξ. Meanwhile, humans are born and die at rate b (the human population N is held constant). This system can be reduced to a single differential equation for the prevalence of malaria in the human population:

$$\frac{d\gamma}{dt} = \rho_{mh}\beta\frac{Z_t}{N}(1-\gamma_t) - (\xi + b)\gamma_t \quad \text{(A.2)}$$

where $\gamma \equiv I/N$ is malaria prevalence. We can see from the above that for the present analysis, we can safely combine the malaria recovery rate and the birth/death rate in one "demographically

adjusted" recovery rate $r \equiv \xi + b$ (the recovery rate in general is much larger than the human birth/death rate, since the duration of malaria infection is much shorter than a human lifespan).

The number of infectious vectors Z is determined by a separate set of dynamic equations. A compartmental disease model is again assumed to apply, with vectors being either susceptible (X), incubating malaria parasites (Y), or infectious (Z):

$$\begin{aligned} \frac{dX}{dt} &= V - \rho_{hm}\beta\gamma_t X_t - \mu X_t \\ \frac{dY}{dt} &= \rho_{hm}\beta\gamma_t X_t - e^{-\tau_s\mu}\rho_{hm}\beta\gamma_{t-\tau_s}X_{t-\tau_s} - \mu Y_t \\ \frac{dZ}{dt} &= e^{-\tau_s\mu}\rho_{hm}\beta\gamma_{t-\tau_s}X_{t-\tau_s} - \mu Z_t \end{aligned} \quad \text{(A.3)}$$

These equations represent a process in which a given mosquito bite lands on an infected human with probability $\gamma \equiv I/N$, is subsequently infected with probability ρ_{hm}, and meanwhile dies at rate μ. Infected mosquitoes incubate malaria parasites for a fixed time interval τ ($\approx$ 2 weeks), during which mosquitoes continue to die at rate μ. At the end of this interval, a proportion $e^{-\tau\mu}$ of a given cohort is remaining and able to infect humans. These mosquitoes also die at rate μ. Finally, a constant number of V vectors are assumed to emerge per unit time. This model of mosquito population and transmission dynamics is used by Kawaguchi, Sasaki et al. (2004). We invoke a common assumption in the malaria modeling literature (see above references in this section) that the system depicting mosquito dynamics is always near equilibrium $(X_\infty, Y_\infty, Z_\infty)$, satisfying $dX/dt = dY/dt = dZ/dt = 0$:

$$\begin{aligned} X_\infty &= \frac{V}{\rho_{hm}\beta\gamma + \mu} \\ Y_\infty &= \frac{\rho_{hm}\beta\gamma(1 - e^{-\tau_s\mu})}{\mu} X_\infty = \frac{V\rho_{hm}\beta\gamma(1 - e^{-\tau_s\mu})}{\mu(\rho_{hm}\beta\gamma + \mu)} \end{aligned} \quad \text{(A.4)}$$

$$Z_\infty = \frac{v\rho_{hm}\beta e^{-\tau_s \mu}\gamma}{\mu(\rho_{hm}\beta\gamma + \mu)}$$

Substituting (A.4) into (A.2) reduces the disease dynamics to a single ordinary differential equation:

$$\frac{d\gamma_t}{dt} = \frac{v\rho_{mh}\rho_{hm}\beta^2 e^{-\tau\mu}}{\mu(\rho_{hm}\beta\gamma_t + \mu)}\gamma_t(1-\gamma_t) - (r+b)\gamma_t \qquad \text{(A.5)}$$

where $v \equiv V/N$ is the number of newly emerged vectors per person per unit time. We make one more transformation of the equation to obtain a form which is more policy relevant and less notationally cumbersome: The intuition behind this transformation is that we are most interested in analyzing disease dynamics in terms of how they are affected by insecticide spraying, which operates through decreases in vector mortality μ. We therefore define μ_0 as the baseline vector mortality rate in the absence of insecticide control, $R_0 \equiv \frac{v\rho_{mh}\beta h}{r+b} \times \frac{e^{-\tau\mu_0}}{\mu_0^2}$ as the "basic reproductive number" of malaria, and $h \equiv \rho_{hm}\beta$. The quantity R_0 determines whether malaria prevalence converges to a positive level in the absence of spraying, and h determines how much the marginal change in malaria transmission decreases as prevalence increases. Then (A.5) can be rewritten as in equation (1) of the main text.

Phase Plane Analysis of the Biological System with a Fixed Control

The types of steady states enumerated in equation (10) of the paper can be visualized using plane analysis. In Figure A1

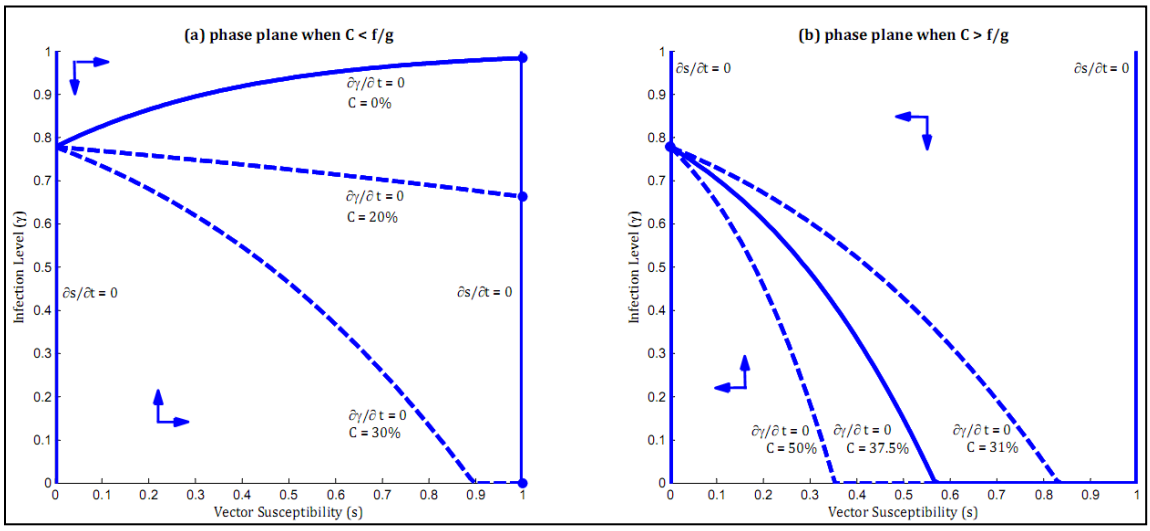

Figure A1 below, the nullclines of the biological system in equation (10) are plotted for different levels of a fixed amount of IRS. When IRS is below a level which selects for resistance, then insecticide resistance drains out of the system in te long-run due to fitness costs, and long-run malaria prevalence continuously caries with the level of IRS. When IRS selects for resistance, any reduction in long-run malaria prevalence is due to the existence of fitness costs.

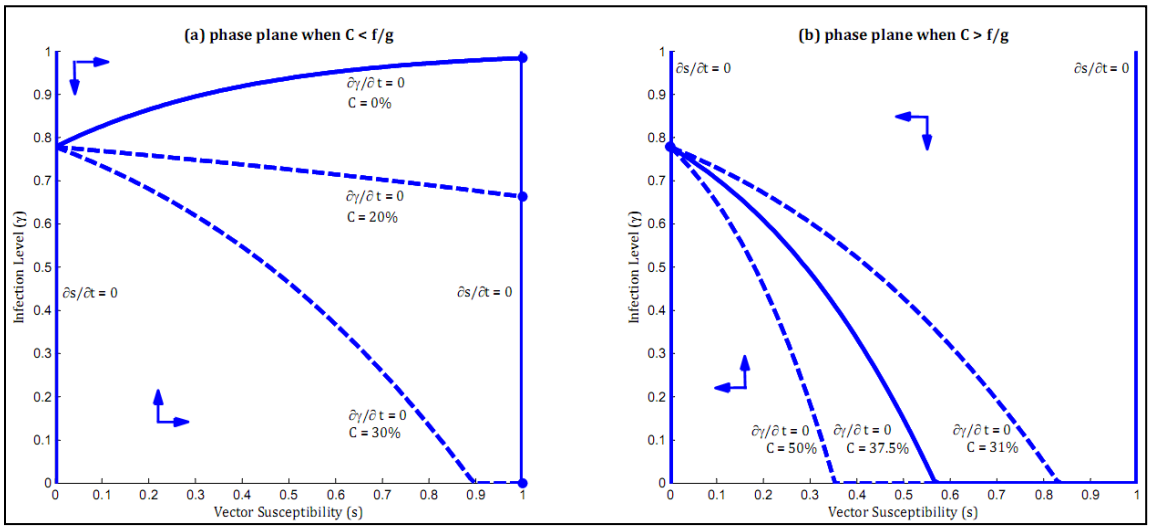

Figure A1: Phase plane and nullclines of the biological system for fixed C. ***(a) Control C does not select for resistance, (b) Control C selects for resistance.***

Steady States of the Optimally Controlled System: Analytic Results

In addition to Proposition 1, some other qualitative observations can be drawn from inspection of the steady state equations of the optimally controlled biological system.

Proposition A.1: 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 $s_\infty = 1$, then $C_\infty \leq f/g$. 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 ds/dt equation in (10). If a positive level of control is optimal in the long-run ($C_\infty > 0$) in such a situation, the steady state level of control in this case satisfies the following equations:

$$0 = \frac{\partial H}{\partial C} = -q_C + \frac{g q_\gamma \left(\tau_S + \frac{1}{\mu} + \frac{1}{\mu + h\gamma_\infty}\right)}{\left[\frac{1}{1-\gamma_\infty} + \frac{h}{\mu + h\gamma_\infty}\right] + \frac{\delta}{r\gamma_\infty}} \qquad \text{(A.6)}$$

$$\gamma_\infty = 1 - R(\mu_0 + gC_\infty)^{-1}$$

$$\mu = \mu_0 + gC_\infty$$

Proposition A.2: 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 $s_\infty \in (0,1)$, then $C_\infty = f/g$ and $s_\infty \in [0,1]$ satisfies the following system of equations:

$$q_C = \frac{g q_\gamma \left(\tau_S + \frac{1}{\mu} + \frac{1}{\mu + h\gamma_\infty}\right)}{\left[\frac{1}{1-\gamma_\infty} + \frac{h}{\mu + h\gamma_\infty}\right] + \frac{\delta}{r\gamma_\infty}} \left[s_\infty - \frac{\varepsilon f (1-\phi) s_\infty (1 - s_\infty)}{\delta}\right] \qquad \text{(A.7)}$$

$$\gamma_\infty = \text{Max}\{1 - R(\mu)^{-1},\ 0\}$$

$$\mu = \mu_0 + \phi f + (1 - \phi) f s_\infty$$

The proofs of the above 2 propositions follow from direct calculation.

Proof of Proposition 1

Suppose $\phi = 1$. For an interior solution to hold it must be that $C_\infty \leq f/g$, and it can be verified that the first line of (A.7) above still applies. Then $\mu_0 + f \geq \mu_0 + gC_\infty$. With $\phi = 1$, the quadratic term in s_∞ drops out of the expression in which case s_∞ solves a linear equation. Now, if elimination is feasible ($R(\mu_0 + f) < 1$), then an interior $s_\infty \in (0,1)$ solving this linear equation does not exist, since the slope coefficient on s_∞ becomes zero. If elimination is not feasible ($R(\mu_0 + f) \geq 1$), then nonetheless $\mu = \mu_0 + f$ so that the slope coefficient reduces to a constant which can be expressed in terms of the parameters. Thus, there is at most a single interior s_∞ solving the first line of (A.7) when $\phi = 1$.

Parameter References

References for the parameter used in the numerical simulations are provided in the table below:

Table A1: Parameter references for numerical solutions to the optimal control model.

Parameter	*Symbol*	*Sources*
Basic Reproductive number of malaria *(# secondary per primary case)*	R_0	Smith et al. (2007)
Recovery rate of malaria-infected individuals *(per day)*	r	Sama et al. (2004) Zongo et al. (2007) Sowunmi et al. (2000)
Incubation time of malaria in mosquitoes *(days)*	τ_S	Teklehaimanot et al. (2004)
Mass-action saturation factor *(dimensionless)*	h	Smith and McKenzie (2004)
Baseline vector mortality *(per day)*	μ_0	Kawaguchi et al. (2004) Worrall et al. (2007)
Insecticide-induced mortality *(per day)*	g	Kawaguchi et al. (2004) Worrall et al., (2007)
Total fitness cost *(per day)*	f	See Appendix references.
Mortality-specific fitness cost *(% of total)*	ϕ	See Appendix references.
Economic cost of a single infection *(USD per case per unit time)*	q_γ	Whittington et al. (2003) Russell (2004)
Spray cost per person *(USD per person-year)*	q_C	Sine and Doherty (2008)
Risk-adjusted discount rate *(% per year)*	δ	This spudy: assumem a 3% base-rate with expected time horizon of 15 years
Speed of resistance evolution *(per year)*	ε	See Read et al. (2009)

Dynamic Programming Methods

To compute the optimal policies in the numerical experiments, we used dynamic programming techniques, implemented using the CompEcon Toolbox by Miranda and Fackler (Miranda and Fackler, 2002) in MATLAB®. These methods interpolate the following partial differential equation in the value function $v(\gamma, \omega)$:

$$\delta v(\gamma,\psi) = \max_{C\in[0,1]}\{-q_\gamma\gamma - q_C C + v_\gamma r[R_0 z\{\mu[s(\psi), C], \gamma\}(1-\gamma) - 1]\gamma + v_\psi \varepsilon(f - gC)\} \quad \text{(A.8)}$$

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 the analytic equations for equilibria of the optimally controlled system.

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 (Atolia and Buffie, 2009). Figure A2 shows the results of this reverse-shooting analysis.

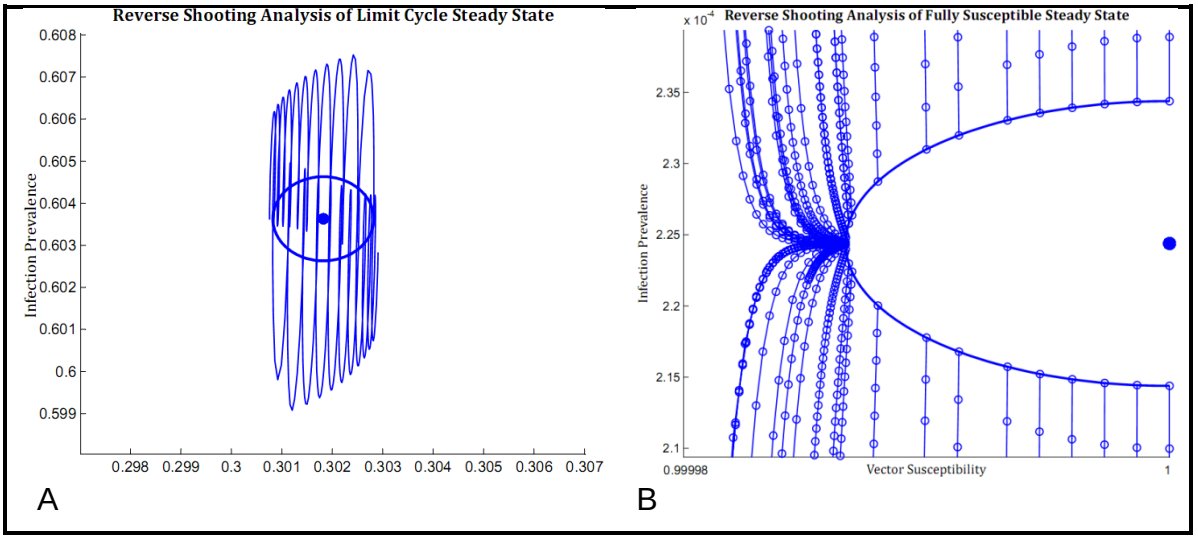

Figure A2: Reverse shooting stability analysis of steady states. *The reverse shooting method draws a small circle around a given steady state and simulates the optimal control dynamic system backwards in time using the steady state co-state values as the corresponding initial conditions for the co-states. 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.*

It is important to emphasize that these numerical methods only approximate cost-minimizing policies. Often, the more complex the model, the poorer the approximation,for a given method. 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 (A.8).

The policies that were computed using dynamic programming to solve the optimal control problem in (12) are shown in Figure A3. The policies in this figure were used to generate the cost comparisons in Figure 1. Not surprisingly, the optimal control policy when there is no evolution of insecticide resistance (the red lines in the figure) dictates much higher IRS use than when

evolution is accounted for. The optimal policies when multiple fitness cost mechanisms are present (solid blue lines) or only an adult mortality mechanism (dotted green lines) appear similar, though their seemingly small differences turn out to be quite important because the levels of control in the 2 scenarios are quite close to the fitness threshold determining whether or not insecticide resistance is selected for.

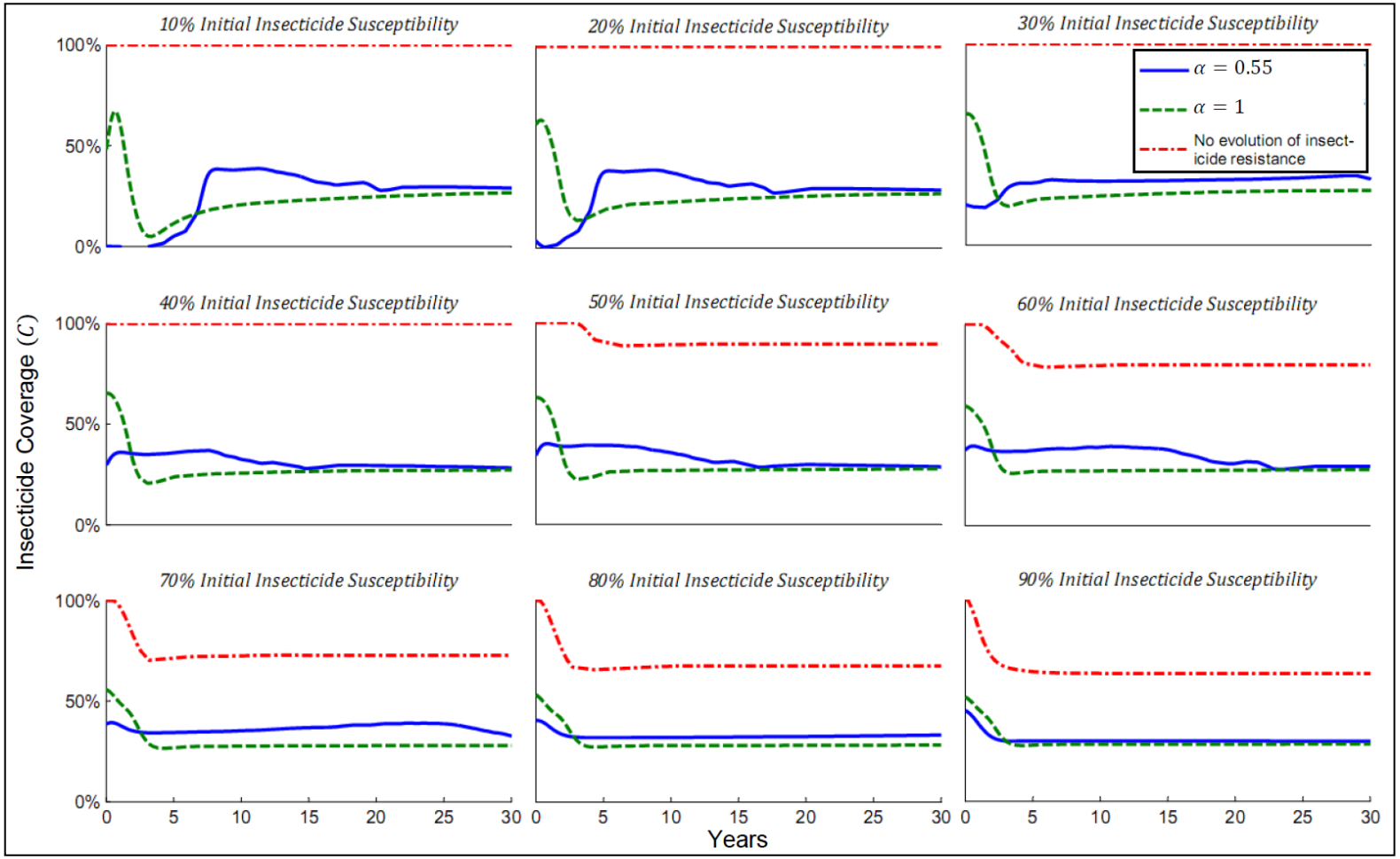

Figure A3: Optimal insecticide usage trajectories for different initial conditions.

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