

# Analyzing the control of mosquito-borne diseases by a dominant lethal genetic system

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Motivated by the failure of current methods to control dengue fever, we formulate a mathematical model to assess the impact on the spread of a mosquito-borne viral disease of a strategy that releases adult male insects homozygous for a dominant, repressible, lethal genetic trait. A dynamic model for the female adult mosquito population, which incorporates the competition for female mating between released mosquitoes and wild mosquitoes, density-dependent competition during the larval stage, and realization of the lethal trait either before or after the larval stage, is embedded into a susceptible–exposed–infectious–susceptible human–vector epidemic model for the spread of the disease. For the special case in which the number of released mosquitoes is maintained in a fixed proportion to the number of adult female mosquitoes at each point in time, we derive mathematical formulas for the disease eradication condition and the approximate number of released mosquitoes necessary for eradication. Numerical results using data for dengue fever suggest that the proportional policy outperforms a release policy in which the released mosquito population is held constant, and that eradication in  $\approx 1$  year is feasible for affected human populations on the order of  $10^5$  to  $10^6$ , although the logistical considerations are daunting. We also construct a policy that achieves an exponential decay in the female mosquito population; this policy releases approximately the same number of mosquitoes as the proportional policy but achieves eradication nearly twice as fast.

dengue fever | genetically modified mosquitoes | mathematical epidemiology

Worldwide morbidity and mortality from mosquito-borne viral diseases are substantial and on the rise (1). No licensed vaccine exists for the most important of these viruses, the dengue virus, which each year causes 50–100 million cases of dengue fever and 250,000–500,000 cases of the potentially fatal dengue hemorrhagic fever (2). The *Aedes aegypti* mosquito (also known as *Stegomyia aegypti*), which is the main vector for dengue fever and yellow fever, is endemic in the southeastern U.S., and the West Nile virus spread easily through the U.S. in recent years, suggesting the U.S. could be vulnerable in coming years to both natural and deliberate outbreaks of mosquito-borne viral diseases. Given the failure of current methods to control the spread of these diseases, considerable effort has gone into novel population-suppression strategies. The sterile insect technique (SIT), which releases sterile (irradiated) male insects that mate with wild females, resulting in no progeny, has been used successfully for  $>50$  years for control and eradication of several pests and disease vectors (3, 4). However, irradiated mosquitoes have difficulty competing with wild males for wild females (5–7) and there are no large-scale SIT mosquito programs currently in operation. A proposed alternative approach that is also environmentally benign is the release of insects carrying a dominant lethal (RIDL) strategy. In this approach, which would operationally resemble SIT, the released male mosquitoes would be homozygous for a repressible dominant lethal gene or genetic system. The repressor would be something that could be pro-

vided during mass-rearing but is not found in the wild, for example, a chemical dietary additive. These RIDL male mosquitoes would mate with wild females and produce heterozygous progeny that die under predetermined conditions (8, 9).

We develop a mathematical model for a RIDL strategy and derive analytical expressions for disease eradication conditions and the approximate number of released mosquitoes necessary for eradication. We illustrate this using data for dengue fever, which appears to be a particularly suitable target for RIDL, because it is specific to humans (i.e., it has no significant animal reservoirs) and (unlike malaria) has a single dominant vector, and area-wide programs have previously proven to be effective in controlling this disease (10).

## Results

**The Model.** The dengue virus has four major serotypes, and a person who recovers from an infection and is immune to one serotype may become secondarily infected (and appears to be more susceptible to dengue hemorrhagic fever) with a virus from a different serotype (11). For simplicity, we consider a single-serotype model and, to be conservative (i.e., overestimating the number of infections), we consider a susceptible–exposed–infectious–susceptible model in which all recovered people are susceptible to another infection. Let the subscripts  $H$  and  $V$  represent human and (adult female) vectors, respectively. For  $i = \{H, V\}$ , let  $I_i(t)$  be the number of infecteds at time  $t$ ,  $E_i(t)$  be the number of exposed (but not infectious), and  $N_i(t)$  be the total population size at time  $t$ , so that the total number of susceptibles at time  $t$  is  $N_i(t) - I_i(t) - E_i(t)$ . We assume that the human population is constant at  $N_H$  and define a model for the adult female vector population  $N_V(t)$  after describing the susceptible–exposed–infectious–susceptible human–vector epidemic model.

Following traditional notation, let  $a$  be the biting rate (number of bites per unit time),  $b$  be the probability that a bite from an infected mosquito will infect a susceptible human,  $c$  be the probability that a susceptible mosquito is infected from biting an infected human,  $\gamma$  be the human recovery rate, and for  $i = \{H,$

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Abbreviations: SIT, sterile insect technique; RIDL, release of insects carrying a dominant lethal.

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$V\}$ , let  $\mu_i$  be the death rate and  $\tau_i$  be the deterministic incubation (or latency) period. Then our epidemic model, which is similar to that in section 14.4.1 of ref. 12, is given by

$$\begin{aligned} \dot{E}_H(t) = & \frac{ab}{N_H} N_V(t)[N_H - E_H(t) - I_H(t)] \frac{I_V(t)}{N_V(t)} \\ & - e^{-\mu_H \tau_H} \frac{ab}{N_H} N_V(t - \tau_H) \\ & \cdot [N_H - E_H(t - \tau_H) - I_H(t - \tau_H)] \frac{I_V(t - \tau_H)}{N_V(t - \tau_H)} \\ & - \mu_H E_H(t), \end{aligned} \quad [1]$$

$$\begin{aligned} \dot{I}_H(t) = & e^{-\mu_H \tau_H} \frac{ab}{N_H} N_V(t - \tau_H) \\ & \cdot [N_H - E_H(t - \tau_H) - I_H(t - \tau_H)] \frac{I_V(t - \tau_H)}{N_V(t - \tau_H)} - (\gamma + \mu_H) I_H(t), \end{aligned} \quad [2]$$

$$\begin{aligned} \dot{E}_V(t) = & ac[N_V(t) - E_V(t) - I_V(t)] \frac{I_H(t)}{N_H} - e^{-\mu_V \tau_V} ac[N_V(t - \tau_V) \\ & - E_V(t - \tau_V) - I_V(t - \tau_V)] \frac{I_H(t - \tau_V)}{N_H} - \mu_V E_V(t), \end{aligned} \quad [3]$$

$$\begin{aligned} \dot{I}_V(t) = & e^{-\mu_V \tau_V} ac[N_V(t - \tau_V) - E_V(t - \tau_V) \\ & - I_V(t - \tau_V)] \frac{I_H(t - \tau_V)}{N_H} - \mu_V I_V(t). \end{aligned} \quad [4]$$

The temporal behavior of  $N_V(t)$  is dictated by growth, density dependence, RIDL control, and death. *A. aegypti* reproduce continuously (13), and we assume each adult female mosquito has  $\lambda$  progeny, half female and half male, that survive to adulthood if there is no density-dependent mortality. The dengue infection does not affect the life expectancy of adult female mosquitoes, and so adult females die at rate  $\mu_V$ . We assume the exponential adult female mosquito “birth” rate (i.e., the rate of emergence as adults) in the absence of density dependence is  $r = (\lambda\mu_V)/2$ . If there were no density-dependent mortality, we would have  $\dot{N}_V(t) = rN_V(t - \tau_e) - \mu_V N_V(t)$ , where  $\tau_e$  is the deterministic time lag between reproduction and adulthood. In our model, density-dependent mortality occurs in the larval stage and thus affects only the birth term, yielding  $\dot{N}_V(t) = rN_V(t - \tau_e)D(t) - \mu_V N_V(t)$ , where  $D(t)$  is the density-dependent factor. Because larval competition occurs over several days (14), the simplest form of our density-dependent factor is

$$D(t) = \frac{\bar{K} - \int_{\tau_1^e}^{\tau_1^b} L(t - \tau) d\tau}{\bar{K}},$$

where  $L(t)$  is the larval female population at time  $t$ ,  $\bar{K}$  is the carrying capacity of the larvae population (15),  $\tau_1^b$  is the time lag between the beginning of larval competition and adulthood, and  $\tau_1^e$  is the delay between the end of larval competition and adulthood. For simplicity, we approximate

$$\int_{\tau_1^b}^{\tau_1^e} L(t - \tau) d\tau$$

by  $L(t - \tau_1^b)(\tau_1^b - \tau_1^e)$ , and for further analytic tractability, we assume that  $L(t - \tau_1^b)$  is proportional to  $N_V(t - \tau_e)$ , i.e.,  $L(t - \tau_1^b) = \beta N_V(t - \tau_e)$ , which is natural in light of the definitions of  $\tau_1^b$  and  $\tau_e$ . Thus we set our density-dependent factor to  $D(t) = [\bar{K} - \beta(\tau_1^b - \tau_1^e)N_V(t - \tau_e)]/\bar{K} = [K - N_V(t - \tau_e)]/K$ , where  $K = \bar{K}/\beta(\tau_1^b - \tau_1^e)$ , and hence  $K$  is a population parameter related to the carrying capacity of the larval population. The number of adult female mosquitoes at time  $t$  in the absence of control is

$$\dot{N}_V(t) = rN_V(t - \tau_e) \frac{K - N_V(t - \tau_e)}{K} - \mu_V N_V(t).$$

The released adult male mosquitoes with the dominant lethal, which we refer to as the RIDL mosquitoes, can be engineered to have offspring that die either before or after the larval stage, which is where density-dependent competition occurs (e.g., for nutrients, space, or other limited resources). We refer to these two approaches as early- and late-lethal, respectively. In the absence of control, we assume there are equal numbers of wild-type adult male and female mosquitoes (14, 16). The control is modeled by  $R(t)$ , which is the number of RIDL adult male mosquitoes present at time  $t$ . In our analysis below, we consider six control strategies in total, which are early- and late-lethal versions of three classes of control strategies referred to as the proportional, constant, and trajectory policies. We assume RIDL male mosquitoes compete just as well as wild-type males for the adult females [because the dominant lethal trait, unlike irradiation, need not significantly reduce fitness (17, 18)], the fraction of progeny born at time  $t$  that have a wild-type father is

$$\frac{N_V(t)}{N_V(t) + R(t)}.$$

Taken together, our model for the number of adult female mosquitoes is

$$\begin{aligned} \dot{N}_V(t) = & \begin{cases} rN_V(t - \tau_e) \left( \frac{N_V(t - \tau_e)}{N_V(t - \tau_e) + R(t - \tau_e)} \right) \\ \quad \left( \frac{K - N_V(t - \tau_e)}{K} \right) - \mu_V N_V(t) \\ \quad \text{for late-lethal;} \\ rN_V(t - \tau_e) \left( \frac{N_V(t - \tau_e)}{N_V(t - \tau_e) + R(t - \tau_e)} \right) \\ \quad \left( \frac{K - \frac{N_V(t - \tau_e)}{N_V(t - \tau_e) + R(t - \tau_e)} N_V(t - \tau_e)}{K} \right) \\ \quad - \mu_V N_V(t) \\ \quad \text{for early-lethal} \end{cases}, \end{aligned} \quad [5]$$

and our entire model consists of Eqs. 1–5.

**The Proportional Policy.** Our main analytical result is the necessary condition for disease eradication [i.e.,  $I_H(\infty) = I_V(\infty) = 0$ , and hence the virus, not the vector, is being eradicated] for the proportional policy, where the RIDL mosquito population is maintained in a fixed proportion to the adult female mosquito population, i.e.,

$$R(t) = \theta N_V(t). \quad [6]$$

The proof of Proposition 1 is in [supporting information \(SI\) Appendix](#), Section 1.

**Table 1. Base-case parameter values**

Parameter	Description	Value	Ref.
$N_H$	Human population	10,000	
$N_V(0)$	No. of adult female mosquitoes at time 0 [= $K(1 - \mu_V/r)$ ]	0.811K	—
$a$	Biting rate (number of bites per day)	0.7 per day	19–21
$b$	Probability that a bite infects a susceptible human	0.75	20, 22
$c$	Probability that a bite infects a susceptible mosquito	0.75	20, 22
$\gamma$	Human recovery rate	0.25 per day	23
$\mu_H$	Human death rate	$\frac{1}{60}$ per year	
$\mu_V$	Adult female mosquito death rate	0.12 per day	14, 16
$\lambda$	Number of progeny per adult female mosquito	10.6	13, 14
$r$	Female mosquito birth rate (= $\lambda\mu_V/2$ )	0.636 per day	13, 14
$K$	Population parameter	Varies	
$\tau_H$	Human incubation period	7 days	12, 24, 25
$\tau_V$	Mosquito incubation period	9 days	20, 24, 25
$\tau_e$	Delay between reproduction and adulthood	18.84 days	14

The initial vector population  $N_V(0)$  equals the nontrivial pretreatment steady-state solution in Eq. 5, and we vary  $K$  to achieve different  $N_V(0)/N_H$  ratios in Figs. 1 and 2.

**Proposition 1.** If  $\mu_V > r$ , then eradication occurs in the absence of RIDL control. If  $\mu_V < r$ , eradication in the absence of RIDL control occurs only if  $\mu_V >$

$$\frac{a^2bcK(r - \mu_V)e^{-\mu_H\tau_H - \mu_V\tau_V}}{(\gamma + \mu_H)rN_H}$$

$$\text{If } \mu_V < \min\left\{r, \frac{a^2bcK(r - \mu_V)e^{-\mu_H\tau_H - \mu_V\tau_V}}{(\gamma + \mu_H)rN_H}\right\},$$

then the proportional RIDL strategy in Eq. 6 achieves eradication only if  $\theta > \theta^*$ , where

$$\theta^* = \begin{cases} \left(1 - \frac{(\mu_H + \gamma)N_H\mu_V e^{\mu_H\tau_H + \mu_V\tau_V}}{a^2bcK}\right) \frac{r}{\mu_V} - 1 & \text{for late-lethal;} \\ \left(1 + \frac{\sqrt{1 - \frac{4\mu_V^2 N_H(\gamma + \mu_H)e^{\mu_H\tau_H + \mu_V\tau_V}}{a^2bcKr}}}{2}\right) \frac{r}{\mu_V} - 1 & \text{for early-lethal.} \end{cases} \quad [7]$$

The right side of Eq. 7 is smaller for late-lethal, and hence late-lethal dominates early-lethal in the sense that it requires a smaller proportion of RIDL mosquitoes to wild-type female mosquitoes than early-lethal to achieve eradication.

Throughout this study, we use numerical values representative of dengue fever (Table 1) for a small urban population of 10,000 humans, which should not egregiously violate our homogeneous-mixing nonspatial model (14). We also set the adult female mosquito population at time 0 to  $K[1 - \mu_V/r]$ , which is its steady-state value in Eq. 5 in the absence of treatment, and vary  $K$  to obtain different values of the mosquito-to-human population ratio,  $N_V(0)/N_H$ . For the parameter values in Table 1, eradication in the absence of control occurs only if  $N_V(0)/N_H < 0.32$ , whereas  $N_V(0)/N_H$  values for dengue fever range from 2 upward (20, 26), although there will be considerable variation in this value depending on the specific setting.

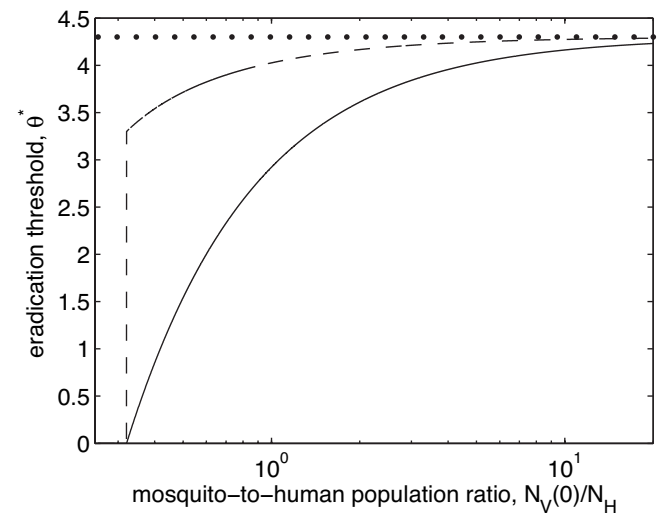
For the parameter values in Table 1, necessary condition [7] is also a sufficient condition for eradication for early but not for late-lethal. This is because, for small values of  $\theta$ , the system is unstable, and  $\theta^*$  is sufficiently bounded away from zero for early but not late-lethal (see *SI Appendix, Section 1*, and Fig. 1). However, for the examples analyzed in this paper, the instability

is not an issue, because  $\theta^*$  in these cases is much greater than the value required for stability (the system stabilizes for  $\theta \geq 0.55$ ). The mosquito population in the absence of control (i.e.,  $\theta = 0$ ) is unstable. This is not inconsistent with a mosquito population model with one density-dependent factor (which is what our model has) in ref. 14 that can have stability issues depending on the parameter values. Our focus, however, is on the controlled system, and we analyze only the uncontrolled population to determine the initial conditions.

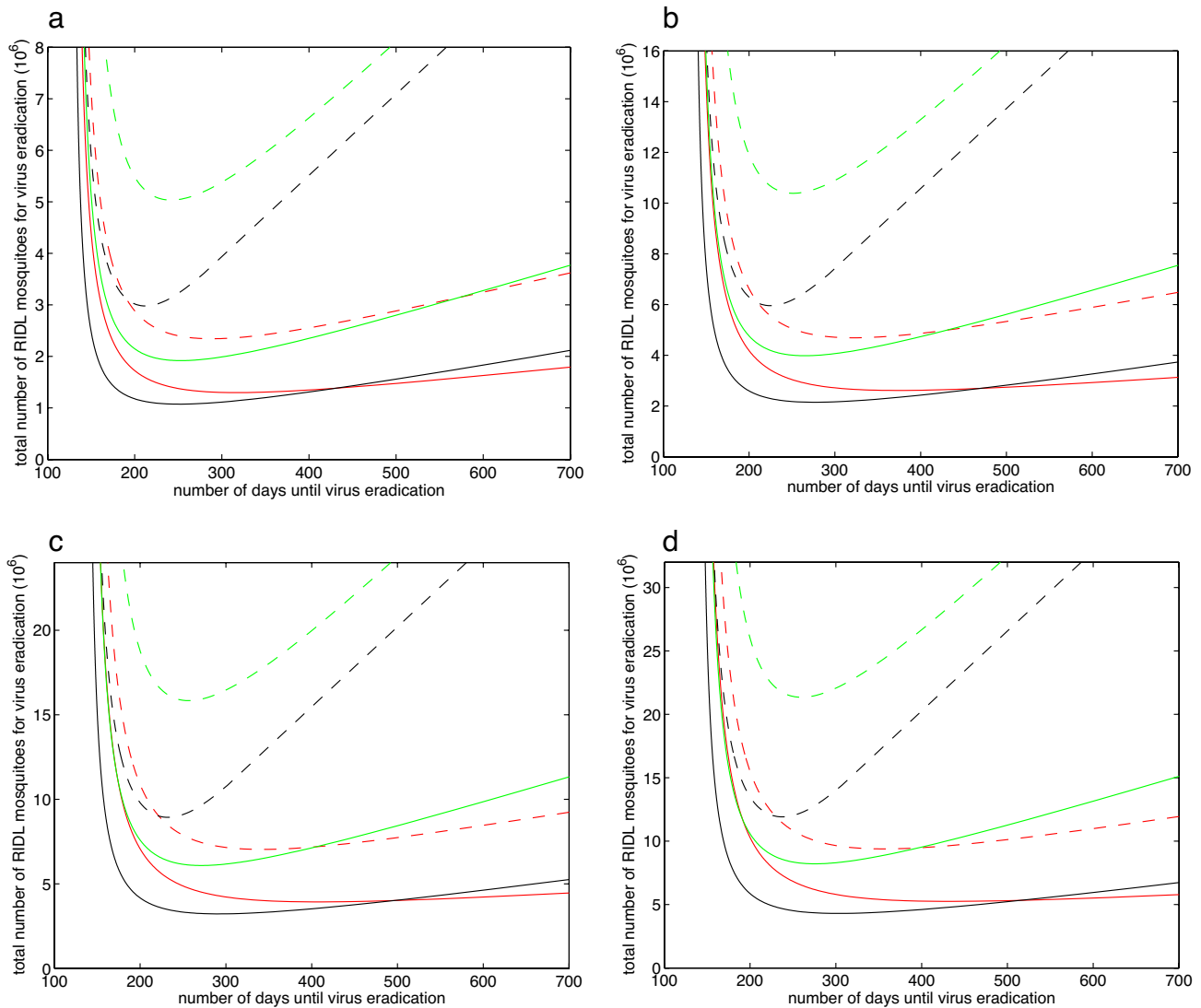
The two eradication thresholds in Eq. 7 are increasing and convex in the mosquito-to-human population ratio (Fig. 1) and converge to the asymptotic limit,

$$\lim_{\frac{N_V(0)}{N_H} \rightarrow \infty} \theta^* = \frac{r}{\mu_V} - 1 = 4.30,$$

which is the threshold where  $N_V(\infty)$  switches from positive to zero. The late-lethal threshold converges more slowly than the early-lethal threshold and hence there is a significant difference between the two thresholds for moderate (i.e.,  $< 5$ ) population ratios.



**Fig. 1.** The RIDL eradication threshold ( $\theta^*$ ) for the proportional policy vs. the logarithm of the pretreatment mosquito-to-human population ratio ( $N_V(0)/N_H$ ), which is generated by varying the population parameter  $K$ , for late-lethal (—), early-lethal (---), and the asymptotic (as  $N_V(0)/N_H \rightarrow \infty$ ) limit (⋯).



**Fig. 2.** The number of RIDL mosquitoes required for eradication in Eq. 8 vs. the number of days until eradication  $t^*$  [i.e.,  $I_V(t^*) \leq 0.1$ ] for both late-lethal (—) and early-lethal (---) for all three policies: the proportional policy (red), the constant policy (green), and the trajectory policy (black). These curves are generated by varying the free parameter ( $\theta$ ,  $C$ , and  $\phi$ , respectively) in the three policies (the curves are in the upper-left portion of the graphs for larger values of the free parameters) and numerically computing Eqs. 1–5 with the initial state variables set at their nontrivial pretreatment steady-state values (see *SI Appendix*, Section 1). We consider four values of  $N_V(0)/N_H$ . (a) 4, (b) 8, (c) 12, and (d) 16.

From a practical point of view, it is also important to understand how many RIDL mosquitoes are required for eradication, and how long it takes to eradicate the virus. In the case where  $\theta > \theta^*$ , we consider eradication to be achieved when  $I_V(t) \leq 0.1$ , and let  $t^*$  denote the eradication time; i.e.,  $t^*$  is the minimum  $t$  such that  $I_V(t) = 0.1$ . The number of RIDL mosquitoes required for eradication is (see *SI Appendix*, Section 2, for a derivation)

$$M = R(t^*) + \mu_V \int_0^{t^*} R(t) dt. \quad [8]$$

For each of the three policies, Fig. 2 displays the tradeoff between these two performance measures, and *SI Figs. 3 and 4* show how these two measures vary with the parameters of the three policies; although we refer to the curves in Fig. 2 as tradeoff curves, both performance measures simultaneously increase as the free policy parameter (e.g.,  $\theta$  for the proportional policy) is reduced to near its eradication threshold value. Fig. 2 reveals that

late-lethal offers a 44% reduction in the number of RIDL mosquitoes required for eradication relative to early-lethal. For the four cases in Fig. 2 ( $N_V(0)/N_H = 4, 8, 12, 16$ ),  $\approx 10^6$  RIDL mosquitoes are required to eradicate the virus. The value of  $\theta$  that minimizes  $M$  in Fig. 2 is 6.0 for late- and 8.3 for early-lethal. Eradication can take several years for  $\theta$  values close to the critical  $\theta^*$ , but for values closer to the  $M$ -minimizing  $\theta$  eradication takes between 10 and 15 months (Fig. 2). Given the nature of the curves in Fig. 2, the inherent uncertainty in some of the parameter values, and the difficulty of achieving uniform spatial dispersion of mosquitoes, it would be prudent in practice to choose a somewhat larger value of  $\theta$  than the  $M$ -minimizing value.

**The Constant Policy.** The constant policy,  $R(t) = C$ , maintains a constant number of RIDL mosquitoes in circulation. Compared with the proportional policy in Eq. 6, the constant policy requires  $\approx 1.5$ -fold more mosquitoes to achieve eradication for late- and 2.2-fold more for early-lethal (Fig. 2). Moreover, the number of



$$\left( \mu_V \tau_e \theta - \frac{(1 + \theta)}{\delta} \ln(1 - \delta) \right) N_V(0),$$

where the megaparameter

$$\delta = \frac{1}{\theta} \left( \frac{\lambda}{2} - 1 \right).$$

In particular, this equation shows that the number of RIDL mosquitoes required for eradication is approximately linear in the initial number of adult female mosquitoes,  $N_V(0)$  (see also Fig. 2) and is  $\approx 25.9N_V(0)$  for *A. aegypti* when using the  $M$ -minimizing  $\theta$ . Although our main analytical results are for the proportional policy, the trajectory policy is the best policy under late-lethal RIDL; the  $M$ -minimizing trajectory policy requires roughly the same number of RIDL mosquitoes for eradication as the  $M$ -minimizing proportional policy, but by being more aggressive when the infected female mosquito population gets small (SI Fig. 5), it is able to achieve faster eradication than the proportional policy.

Given that eggs can be stored for up to 2 years and that *A. aegypti* mosquitoes are easy to breed,  $10^8$ - $10^9$  could be stockpiled for a given project [*Culex quinquefasciatus* mosquitoes have been released at  $3 \times 10^5$  per day (29, 30), and *Anopheles albimanus* mosquitoes have been released at  $10^6$  per day (30, 31)], and given the female mosquito-to-human population ratio in endemic areas is  $\approx 10$  (20, 26), it would appear that the RIDL strategy is capable of eradicating dengue fever for millions of people worldwide. The worldwide population in areas where dengue fever is endemic is  $\approx 10^9$  (32), suggesting that the number of adult

female mosquitoes in these regions is  $\approx 10^{10}$ , and the total number of RIDL mosquitoes required for worldwide eradication is  $\approx 10^{11}$ . Given that production facilities for Mediterranean fruit flies exist with a capacity in excess of  $5 \times 10^8$  per day (4), rearing insects on this scale is not infeasible (i.e., 200 days of production at  $5 \times 10^8$  per day is  $10^{11}$  insects). The biggest logistical challenge is not breeding but distribution; *A. aegypti* mosquitoes disperse only up to one-half mile (33, 34), although there is some uncertainty in this value, and hence distribution would likely need to be performed on a household basis, at least in rural areas.

We do not believe that our model is sufficiently detailed to solely and reliably determine a release schedule that would result in disease eradication. Rather, for implementation purposes and using the proportional policy as an example, we envision starting with a conservative estimate of  $\theta$  (i.e., a value somewhat higher than derived by our analysis) and then to sample over time to obtain estimates of the number of RIDL mosquitoes [ $\hat{R}(t)$ ], the number of adult female mosquitoes [ $\hat{N}_V(t)$ ], and the number of infected adult female mosquitoes [ $\hat{I}_V(t)$ ]. If the sampled fraction infected  $\{[\hat{I}_V(t)]/\hat{N}_V(t)\}$  is greater than the value of  $[I_V(t)]/N_V(t)$  predicted by our model, then we increase  $\theta$  to some value  $\hat{\theta}$  (and perhaps decrease  $\theta$  if  $[\hat{I}_V(t)]/\hat{N}_V(t)$  is less than predicted by our model). Our release schedule would be altered so that Eq. 5 is satisfied with our new values [i.e.,  $R(t) = \hat{\theta}\hat{N}_V(t)$ ].

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# Appendix

## 1. Proof of Proposition 1

In this proof, we analyze the stability properties necessary to eradicate the virus for the proportional control policy. To determine the steady-state solutions of this system, which is given by equations (1)-(5) of the main text, we set these equations to zero and ignore the time lags. Because equation (5) decouples, we can solve for the steady-state solutions of equations (1)-(4) separately from equation (5). The possible steady-state solutions of equations (1)-(4) are  $(E_H, I_H, E_V, I_V) = (0, 0, 0, 0)$  and

$$I_V = \frac{ac\mu_H e^{-\mu_V \tau_V}}{ac\mu_H + ((\mu_H + \gamma)e^{\mu_H \tau_H} - \gamma)\mu_V} \left( N_V - \frac{(\mu_H + \gamma)\mu_V N_H e^{\mu_H \tau_H + \mu_V \tau_V}}{a^2 bc} \right), \quad (\text{A.1})$$

$$I_H = \frac{\mu_V I_V}{\frac{ac}{N_H} e^{-\mu_V \tau_V} [N_V - I_V e^{\mu_V \tau_V}]}, \quad (\text{A.2})$$

$$E_H = \frac{(\mu_H + \gamma)(e^{\mu_H \tau_H} - 1)}{\mu_H} I_H, \quad (\text{A.3})$$

$$E_V = (e^{\mu_V \tau_V} - 1) I_V, \quad (\text{A.4})$$

and the possible steady-state solutions of equation (5) are  $N_V = 0$  and

$$N_V = \begin{cases} K \left( 1 - \frac{(1+\theta)\mu_V}{r} \right) & \text{for late - lethal;} \\ (1 + \theta) K \left( 1 - \frac{(1+\theta)\mu_V}{r} \right) & \text{for early - lethal.} \end{cases} \quad (\text{A.5})$$

Although there are four possible steady-state solutions, we are only interested in the two solutions that achieve eradication of the virus (i.e.,  $I_V = I_H = 0$ ):

$$(E_H, I_H, E_V, I_V, N_V) = (0, 0, 0, 0, 0), \quad (\text{A.6})$$

$$(E_H, I_H, E_V, I_V, N_V) = \begin{cases} \left( 0, 0, 0, 0, K \left( 1 - \frac{(1+\theta)\mu_V}{r} \right) \right) & \text{for late - lethal;} \\ \left( 0, 0, 0, 0, (1 + \theta) K \left( 1 - \frac{(1+\theta)\mu_V}{r} \right) \right) & \text{for early - lethal.} \end{cases} \quad (\text{A.7})$$

In the remainder of this section, we analyze the stability properties of solutions (A.6)-(A.7). These solutions are stable if all of the roots of the characteristic equations have negative real part.

Because we are dealing with a system of delay differential equations, the characteristic equation has an infinite number of roots and is given by [1]

$$\det(\mathbf{J} + e^{-\eta\tau_H} \mathbf{J}_{\tau_H} + e^{-\eta\tau_V} \mathbf{J}_{\tau_V} + e^{-\eta\tau_e} \mathbf{J}_{\tau_e} - \eta \mathbf{I}) = 0,$$

where  $\mathbf{I}$  is the identity matrix and the matrices  $\mathbf{J}$ ,  $\mathbf{J}_{\tau_H}$ ,  $\mathbf{J}_{\tau_V}$ , and  $\mathbf{J}_{\tau_e}$  have entries that are the partial derivatives of the right sides of (1)-(5) in the main text with respect to, respectively,

$(E_H(t), I_H(t), E_V(t), I_V(t), N_V(t))$ ,  $(E_H(t-\tau_H), I_H(t-\tau_H), E_V(t-\tau_H), I_V(t-\tau_H), N_V(t-\tau_H))$ ,  $(E_H(t-\tau_V), I_H(t-\tau_V), E_V(t-\tau_V), I_V(t-\tau_V), N_V(t-\tau_V))$ , and  $(E_H(t-\tau_e), I_H(t-\tau_e), E_V(t-\tau_e), I_V(t-\tau_e), N_V(t-\tau_e))$ . These matrices are given by

$$\mathbf{J} = \begin{pmatrix} -\frac{ab}{N_H} I_V - \mu_H & -\frac{ab}{N_H} I_V & 0 & \frac{ab}{N_H} [N_H - E_H - I_H] & 0 \\ 0 & -(\mu_H + \gamma) & 0 & 0 & 0 \\ 0 & \frac{ac}{N_H} [N_V - E_V - I_V] & -\frac{ac}{N_H} I_H - \mu_V & -\frac{ac}{N_H} I_H & \frac{ac}{N_H} I_H \\ 0 & 0 & 0 & -\mu_V & 0 \\ 0 & 0 & 0 & 0 & -\mu_V \end{pmatrix}, \quad (\text{A.8})$$

$$\mathbf{J}_{\tau_H} = \begin{pmatrix} e^{-\mu_H\tau_H} \frac{ab}{N_H} I_V & e^{-\mu_H\tau_H} \frac{ab}{N_H} I_V & 0 & -e^{-\mu_H\tau_H} \frac{ab}{N_H} [N_H - E_H - I_H] & 0 \\ -e^{-\mu_H\tau_H} \frac{ab}{N_H} I_V & -e^{-\mu_H\tau_H} \frac{ab}{N_H} I_V & 0 & e^{-\mu_H\tau_H} \frac{ab}{N_H} [N_H - E_H - I_H] & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad (\text{A.9})$$

$$\mathbf{J}_{\tau_V} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & -e^{-\mu_V\tau_V} \frac{ac}{N_H} [N_V - E_V - I_V] & e^{-\mu_V\tau_V} \frac{ac}{N_H} I_H & e^{-\mu_V\tau_V} \frac{ac}{N_H} I_H & -e^{-\mu_V\tau_V} \frac{ac}{N_H} I_H \\ 0 & e^{-\mu_V\tau_V} \frac{ac}{N_H} [N_V - E_V - I_V] & -e^{-\mu_V\tau_V} \frac{ac}{N_H} I_H & -e^{-\mu_V\tau_V} \frac{ac}{N_H} I_H & e^{-\mu_V\tau_V} \frac{ac}{N_H} I_H \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad (\text{A.10})$$

$$\mathbf{J}_{\tau_e} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\partial \dot{N}_V(t)}{\partial N_V(t-\tau_e)} \end{pmatrix}. \quad (\text{A.11})$$

The matrices  $\mathbf{J}$ ,  $\mathbf{J}_{\tau_V}$ , and  $\mathbf{J}_{\tau_e}$  depend on whether the late-lethal or early-lethal policy is used.

Beginning with solution (A.6), we find that the characteristic equation is the same for both



late-lethal and early-lethal, and reduces to

$$\det \begin{pmatrix} -\mu_H - \eta & 0 & 0 & ab(1 - e^{-\mu_H \tau_H} e^{-\eta \tau_H}) & 0 \\ 0 & -(\mu_H + \gamma) - \eta & 0 & abe^{-\mu_H \tau_H} e^{-\eta \tau_H} & 0 \\ 0 & 0 & -\mu_V - \eta & 0 & 0 \\ 0 & 0 & 0 & -\mu_V - \eta & 0 \\ 0 & 0 & 0 & 0 & \frac{r}{1+\theta} e^{-\eta \tau_e} - \mu_V - \eta \end{pmatrix} = 0. \quad (\text{A.12})$$

Therefore, we need to analyze the roots of

$$\frac{r}{1+\theta} e^{-\eta \tau_e} - \mu_V - \eta = 0. \quad (\text{A.13})$$

The left side of (A.13) is a decreasing function of  $\eta$ , and so we need to ensure that the function is less than zero at  $\eta = 0$ . Thus, we have the necessary requirement

$$\frac{r}{1+\theta} < \mu_V. \quad (\text{A.14})$$

We now need to check that (A.14) is a sufficient condition for all complex roots of (A.13) to have a negative real part. Setting  $\eta = \kappa + i\omega$  in (A.13) gives us two equations, corresponding to the real and imaginary components

$$\begin{aligned} e^{-\kappa \tau_e} \cos \omega \tau_e &= \frac{1+\theta}{r} (\mu_V + \kappa), \\ e^{-\kappa \tau_e} \sin \omega \tau_e &= -\frac{1+\theta}{r} \omega. \end{aligned} \quad (\text{A.15})$$

We want to show that all solutions are such that  $\kappa < 0$ . If we assume that there exists a solution such that  $\kappa \geq 0$ , then equation (A.15) implies that

$$\kappa \leq \frac{r}{1+\theta} - \mu_V. \quad (\text{A.16})$$

However, expressions (A.14) and (A.16) imply that  $\kappa < 0$ , and thus we have arrived at a contradiction. Therefore, the steady-state solution (0,0,0,0,0) is stable for both the early-lethal and late-lethal policies if and only if  $\mu_V > \frac{r}{1+\theta}$ .

Turning to solution (A.7),  $(E_H, I_H, E_V, I_V, N_V) = (0, 0, 0, 0, N_V)$ , with  $N_V > 0$  given by equation (A.5), we derive the characteristic equation (this depends on the policy since  $N_V$  is a parameter)

$$\det \begin{pmatrix} -\mu_H - \eta & 0 & 0 & ab(1 - e^{-\mu_H \tau_H} e^{-\eta \tau_H}) & 0 \\ 0 & -(\mu_H + \gamma) - \eta & 0 & abe^{-\mu_H \tau_H} e^{-\eta \tau_H} & 0 \\ 0 & \frac{ac}{N_H} N_V (1 - e^{-\mu_V \tau_V} e^{-\eta \tau_V}) & -\mu_V - \eta & 0 & 0 \\ 0 & \frac{ac}{N_H} N_V e^{-\mu_V \tau_V} e^{-\eta \tau_V} & 0 & -\mu_V - \eta & 0 \\ 0 & 0 & 0 & 0 & -\mu_V + (2\mu_V - \frac{r}{1+\theta}) e^{-\eta \tau_e} - \eta \end{pmatrix} = 0, \quad (\text{A.17})$$

which reduces to

$$\begin{aligned} & \left( -\mu_V + \left( 2\mu_V - \frac{r}{1+\theta} \right) e^{-\eta\tau_e} - \eta \right) \\ & \times \left( (\mu_V + \eta)^2 (\mu_H + \eta) (\mu_H + \gamma + \eta) - \frac{ac}{N_H} N_V e^{-\mu_V\tau_V} e^{-\eta\tau_V} (\mu_V + \eta) (\mu_H + \eta) a b e^{-\mu_H\tau_H} e^{-\eta\tau_H} \right) = 0. \end{aligned} \quad (\text{A.18})$$

At least one of the two terms in (A.18) needs to be zero in order for this equation to be satisfied. Simplifying the second term (noting that two roots,  $-\mu_V$  and  $-\mu_H$ , are always negative and real), we write the two factors of interest as

$$-\mu_V + \left( 2\mu_V - \frac{r}{1+\theta} \right) e^{-\eta\tau_e} - \eta, \quad (\text{A.19})$$

$$(\mu_V + \eta) (\mu_H + \gamma + \eta) - \frac{a^2 bc}{N_H} N_V e^{-\mu_H\tau_H - \mu_V\tau_V} e^{-\eta(\tau_V + \tau_H)}. \quad (\text{A.20})$$

Expression (A.19) tends to  $-\infty$  as  $\eta \rightarrow \infty$ . Thus, requiring expression (A.19) to be less than zero at  $\eta = 0$  yields the necessary condition

$$\mu_V < \frac{r}{1+\theta}. \quad (\text{A.21})$$

Expression (A.20) tends to  $\infty$  as  $\eta \rightarrow \infty$ , and consequently expression (A.20) must be greater than zero at  $\eta = 0$ . Substituting the value of  $N_V$  from (A.5) into expression (A.20) gives the necessary condition

$$\begin{aligned} \mu_V &> \frac{a^2 bc K (r - (1+\theta)\mu_V)}{(\mu_H + \gamma) N_H r} e^{-\mu_H\tau_H - \mu_V\tau_V} && \text{for late - lethal;} \\ \mu_V &> \frac{a^2 bc K (r - (1+\theta)\mu_V)(1+\theta)}{(\mu_H + \gamma) N_H r} e^{-\mu_H\tau_H - \mu_V\tau_V} && \text{for early - lethal.} \end{aligned} \quad (\text{A.22})$$

Taken together, inequalities (A.21) and (A.22) give us a necessary condition on  $\theta$  for the roots of equation (A.18) to have negative real part:

$$\begin{aligned} & \left( 1 - \frac{(\mu_H + \gamma) N_H \mu_V e^{\mu_H\tau_H + \mu_V\tau_V}}{a^2 bc K} \right) \frac{r}{\mu_V} - 1 < \theta < \frac{r}{\mu_V} - 1 && \text{for late - lethal;} \\ & \left( \frac{1 + \sqrt{1 - \frac{4\mu_V^2 N_H (\gamma + \mu_H) e^{\mu_H\tau_H + \mu_V\tau_V}}{a^2 bc K r}}}{2} \right) \frac{r}{\mu_V} - 1 < \theta < \frac{r}{\mu_V} - 1 && \text{for early - lethal.} \end{aligned} \quad (\text{A.23})$$

Now we investigate whether condition (A.23) is also sufficient for the roots of equation (A.18) to have negative real part. First, we assume all roots of both expressions (A.19) and (A.20) are real,

then we can show that condition (A.23) is sufficient for these roots to be negative. If  $2\mu_V > \frac{r}{1+\theta}$  then expression (A.19) is decreasing in  $\eta$  for  $\eta > 0$ , and if  $2\mu_V \leq \frac{r}{1+\theta}$  then expression (A.19) is less than zero for  $\eta > 0$ ; in either case, condition (A.21) prevents any roots of (A.19) from being positive. Condition (A.23) is also sufficient for the roots of (A.20) to be negative, because then expression (A.20) is increasing for  $\eta > 0$ .

We now drop the assumption that the roots of (A.19)-(A.20) are real, and explore whether condition (A.23) is sufficient for all complex roots of expressions (A.19)-(A.20) to have negative real parts, starting with (A.20). Introducing the positive constants  $A$ ,  $B$ ,  $D$ , and  $\tau$  we express equation (A.20) as

$$(A + \eta)(B + \eta) - De^{-\eta\tau} = 0. \quad (\text{A.24})$$

Substituting  $\eta = \kappa + i\omega$  into (A.24) gives us equations for the real and imaginary components,

$$\begin{aligned} De^{-\kappa\tau} \cos \omega\tau &= \kappa^2 - \omega^2 + (A + B)\kappa + AB, \\ De^{-\kappa\tau} \sin \omega\tau &= -2\kappa\omega - (A + B)\omega. \end{aligned} \quad (\text{A.25})$$

If  $(\kappa, \omega)$  is a solution to these two equations then so is  $(\kappa, -\omega)$  and thus we can assume  $\omega > 0$ . We want to show that  $\kappa < 0$ . If we assume  $\kappa \geq 0$  then the right side of equation (A.25) is negative, and hence  $\omega\tau \pmod{2\pi} \in (\pi, 2\pi)$ . Therefore, equation (A.25) gives two conditions,

$$\omega > \frac{\pi}{\tau} = \frac{\pi}{\tau_H + \tau_V}, \quad (\text{A.26})$$

$$\omega < \frac{D}{2a + A + B} \leq \frac{D}{A + B}. \quad (\text{A.27})$$

Substituting for  $A$ ,  $B$ , and  $D$  into (A.27) gives

$$\omega \leq \frac{D}{A + B} = \frac{a^2bcN_V}{N_H} e^{-\mu_H\tau_H - \mu_V\tau_V} \frac{1}{\mu_V + \mu_H + \gamma}. \quad (\text{A.28})$$

But by condition (A.22), inequality (A.28) simplifies to

$$\omega \leq \frac{(\mu_H + \gamma)\mu_V}{\mu_V + \mu_H + \gamma} < \mu_V. \quad (\text{A.29})$$

If  $\mu_V(\tau_H + \tau_V) < \pi$ , as it is using the parameter values in Table 1 of the main text, then conditions (A.26) and (A.29) lead to a contradiction, implying that  $\kappa \not\geq 0$ . Therefore, if  $\mu_V(\tau_H + \tau_V) < \pi$  then condition (A.23) is sufficient for the roots of expression (A.20) to have negative real components.

Unfortunately, condition (A.23) for late-lethal is not sufficient for the roots of (A.19) to have negative real parts, and thus it is possible to have instabilities in the system. Expression (A.19) can be analyzed in terms of the Lambert W function [2],  $W(x) = \{w : x = we^w\}$ . Rearranging (A.19) yields

$$\eta = \frac{W\left(\tau_e e^{\mu_V \tau_e} \left(2\mu_V - \frac{r}{1+\theta}\right)\right)}{\tau_e} - \mu_V. \quad (\text{A.30})$$

For the parameter values in Table 1 of the main text, the  $\eta$  given by equation (A.30) can have a positive real component for  $\theta \leq 0.55$  and thus the system only stabilizes for  $\theta > 0.55$ . For all examples in the main text,  $\theta^*$  is much greater than 0.55 and thus stability is not an issue. It should be noted that  $\theta = 0$  corresponds to the system in the absence of control and thus the natural mosquito population is unstable in our model. Other mosquito population models can also exhibit instabilities [3]. However we are studying the effects of the RIDL program and thus only need the natural population to set the initial conditions of the the controlled system.

However, condition (A.23) for early-lethal is sufficient for the roots of (A.19) to have negative real component because the early-lethal lower bound in (A.23) sufficiently bounds  $\theta$  away from 0, and thus prevents the instability that occurs for small values of  $\theta$  in the late-lethal case. Substituting  $\eta = \kappa + i\omega$  into expression (A.19) gives two equations for the real and imaginary component,

$$\begin{aligned} e^{-\kappa\tau_e} \cos \omega\tau_e &= \frac{1 + \theta}{2\mu_V(1 + \theta) - r} (\mu_V + \kappa), \\ e^{-\kappa\tau_e} \sin \omega\tau_e &= -\frac{1 + \theta}{2\mu_V(1 + \theta) - r} \omega. \end{aligned} \quad (\text{A.31})$$

Condition (A.23) for early-lethal implies  $2\mu_V(1 + \theta) - r > 0$ , which is not the case for late-lethal.

Using this inequality, equation (A.31), and assuming  $\kappa \geq 0$  implies that

$$\kappa \leq \mu_V - \frac{r}{1 + \theta}. \quad (\text{A.32})$$

However, expressions (A.21) and (A.32) imply that  $\kappa < 0$  and hence a contradiction. Therefore, the steady-state solution  $(0, 0, 0, 0, N_V)$ ,  $N_V > 0$ , is stable for early-lethal if and only if condition (A.23) holds. However for late-lethal we can only claim equation (A.23) is a necessary condition for stability.

Finally, it can be shown that the two non-eradicating steady-state solutions (i.e., using equations (A.1)-(A.4)) are not stable in the range of  $\theta$  we are interested in (i.e., equations (A.14) and (A.23)). Therefore, conditions (A.14) and (A.23) are necessary for eradication.

## 2. Derivation of the Trajectory Policy

Our goal is to find a function  $R(t)$  that leads to an exponential decay of  $N_V(t)$  in the late-lethal policy if we ignore the time lag (i.e., set  $\tau_e = 0$  in equation (5) of the main text). Substituting  $R(t) = \phi \frac{N_V(t)(K - N_V(t))}{K} - N_V(t)$  into the late-lethal version of equation (5) of the main text gives

$$\dot{N}_V(t) = rN_V(t - \tau_e) \left( \frac{N_V(t - \tau_e)}{N_V(t - \tau_e) + \phi \frac{N_V(t - \tau_e)(K - N_V(t - \tau_e))}{K}} - N_V(t - \tau_e) \right) \left( \frac{K - N_V(t - \tau_e)}{K} \right) - \mu_V N_V(t), \quad (\text{A.33})$$

$$= \frac{r}{\phi} N_V(t - \tau_e) - \mu_V N_V(t). \quad (\text{A.34})$$

Setting  $\tau_e = 0$  in (A.34) and solving gives  $N_V(t) = N_V(0)e^{\left(\frac{r}{\phi} - \mu_V\right)t}$ , as desired.

## 3. Derivation of M in Equation (8)

Before deriving equation (8) in the main text, we note that a practical control policy must satisfy two constraints on the function  $R(t)$ , which are  $R(t) \geq 0$  and

$$R'(t) + \mu_V R(t) \geq 0. \quad (\text{A.35})$$

Condition (A.35) follows because RIDL mosquitoes can only be added, and not removed, from the system, and because the RIDL population evolves according to  $R'(t) = -\mu_V R(t)$  in the absence of new releases.

The constant control policy,  $R(t) = C$ , satisfies condition (A.35). By equation (5) in the main text, the proportional policy,  $R(t) = \theta N_V(t)$ , leads to

$$R'(t) + \mu_V R(t) = \begin{cases} \theta r N_V(t - \tau_e) \left( \frac{1}{1+\theta} \right) \left( \frac{K - N_V(t - \tau_e)}{K} \right) & \text{for late - lethal;} \\ \theta r N_V(t - \tau_e) \left( \frac{1}{1+\theta} \right) \left( \frac{K - \frac{1}{1+\theta} N_V(t - \tau_e)}{K} \right) & \text{for early - lethal,} \end{cases} \quad (\text{A.36})$$

and hence to satisfy (A.35) we require

$$\begin{aligned} K &\geq N_V(t) && \text{for late - lethal;} \\ (1 + \theta)K &\geq N_V(t) && \text{for early - lethal.} \end{aligned} \quad (\text{A.37})$$

Both the initial condition  $N_V(0) = K(1 - \frac{\mu_V}{r})$  and the final steady state (either 0 or equation (A.5)) satisfy condition (A.37). For the range of  $\theta$  we investigate,  $N_V(t)$  evolves over time from the initial state to its steady state in a monotone or slightly oscillatory manner, and thus condition (A.37) is satisfied. However for small values of  $\theta$  where the system can destabilize, it is possible for condition (A.37) and hence (A.36) to fail. There is no straightforward analytical condition to verify (A.35) for the trajectory policy, however numerical and analytic investigations reveal that for  $\phi$  in the range of interest in this paper, condition (A.35) is satisfied.

To derive equation (8) in the main text, we sum the initial release,  $R(0)$ , and the number of mosquitoes we must add to the system to maintain the RIDL population at  $R(t)$ . The number of mosquitoes released in the small time interval  $[t, t + \Delta t)$  is  $R(t + \Delta t) - R(t)e^{-\mu_V \Delta t}$ ; condition (A.35) ensures that this quantity is nonnegative. Letting  $\Delta t \rightarrow 0$ , noting that  $e^{-\mu_V \Delta t} \rightarrow 1 - \mu_V \Delta t$ , and integrating from time 0 to  $t$  yields the total number of RIDL mosquitoes released into the system up to time  $t$ ,

$$M(t) = R(t) + \mu_V \int_0^t R(s) ds. \quad (\text{A.38})$$

Setting  $t = t^*$  in (A.38) and defining  $M = M(t^*)$  yields equation (8) in the main text.

For any control policy that depends only upon the value of  $N_V(t)$  (such as the proportional and trajectory policies), the lag between birth and adulthood (see equation (5) in the main text) implies that  $R(t) = R(0)$  for all  $t \leq \tau_e$ . In this case, we can write equation (8) in the main text as

$$M = R(t^*) + \mu_V \tau_e R(0) + \mu_V \int_{\tau_e}^{t^*} R(t) dt. \quad (\text{A.39})$$

#### 4. Derivation of $\tilde{M}$ in Equation (10)

By equations (A.39) and (6) and (8) in the main text, the total number of RIDL mosquitoes required for eradication using the proportional control policy is

$$M = \theta N_V(t^*) + \mu_V \tau_e \theta N_V(0) + \mu_V \theta \int_{\tau_e}^{t^*} N_V(t) dt. \quad (\text{A.40})$$

We have been unable to find a closed-form solution to equation (5) in the main text for  $R(t) = \theta N_V(t)$ . In an attempt to derive a closed-form expression that approximates  $M$  in equation (A.40), we ignore the time lags in equation (5) in the main text, so that  $N_V(t)$  satisfies

$$\dot{N}_V(t) = \begin{cases} r N_V(t) \left( \frac{1}{1+\theta} \right) \left( \frac{K - N_V(t)}{K} \right) - \mu_V N_V(t) & \text{for late - lethal;} \\ r N_V(t) \left( \frac{1}{1+\theta} \right) \left( \frac{K - \left( \frac{1}{1+\theta} \right) N_V(t)}{K} \right) - \mu_V N_V(t) & \text{for early - lethal,} \end{cases} \quad (\text{A.41})$$

Equation (A.41) can be solved using straightforward ODE techniques. Denoting the solution to equation (A.41) by  $\tilde{N}_V(t)$ , we have (our initial time being  $\tau_e$  and  $N_V(\tau_e) = N_V(0)$ )

$$\tilde{N}_V(t) = \begin{cases} \frac{\frac{[r - \mu_V(1+\theta)] K N_V(0)}{[r - \mu_V(1+\theta)] K - r N_V(0)}}{e^{-\left( \frac{r}{1+\theta} - \mu_V \right) (t - \tau_e)} + \frac{r N_V(0)}{[r - \mu_V(1+\theta)] K - r N_V(0)}} & \text{for late - lethal;} \\ \frac{\frac{[r - \mu_V(1+\theta)] (1+\theta) K N_V(0)}{[r - \mu_V(1+\theta)] (1+\theta) K - r N_V(0)}}{e^{-\left( \frac{r}{1+\theta} - \mu_V \right) (t - \tau_e)} + \frac{r N_V(0)}{[r - \mu_V(1+\theta)] (1+\theta) K - r N_V(0)}} & \text{for early - lethal.} \end{cases} \quad (\text{A.42})$$

Modifying equation (A.40) gives an estimate,  $\tilde{M}$ , for  $M$ :

$$\tilde{M} = \theta \tilde{N}_V(t^*) + \mu_V \tau_e \theta N_V(0) + \mu_V \theta \int_{\tau_e}^{t^*} \tilde{N}_V(t) dt. \quad (\text{A.43})$$

Substituting (A.42) into (A.43) and recalling that  $N_V(t)$  starts in its pre-treatment steady state (i.e.,

$N_V(0) = K(1 - \frac{\mu_V}{r})$ ) yields

$$\tilde{M} = \begin{cases} \theta \tilde{N}_V(t^*) + \mu_V \tau_e \theta N_V(0) + \frac{(1+\theta)}{r} \mu_V \theta K \ln\left(\frac{\mu_V \theta - (r - \mu_V) e^{\frac{r}{1+\theta} - \mu_V}(t^* - \tau_e)}}{\mu_V \theta - (r - \mu_V)}\right) & \text{for late - lethal;} \\ \theta \tilde{N}_V(t^*) + \mu_V \tau_e \theta N_V(0) + (1 + \theta)^2 \frac{\mu_V \theta}{r} K \ln\left(\frac{1 - \frac{(r - \mu_V)}{\theta(\mu_V(1+\theta) - (r - \mu_V))} e^{\frac{r}{1+\theta} - \mu_V}(t^* - \tau_e)}}{1 - \frac{(r - \mu_V)}{\theta(\mu_V(1+\theta) - (r - \mu_V))}}\right) & \text{for early - lethal.} \end{cases} \quad (\text{A.44})$$

Equation (A.44) still requires an estimate of the eradication time  $t^*$  to complete the approximation.

The simplest approach is to let  $t^* \rightarrow \infty$ . However, from equation (A.44), this is only valid for

$\frac{r}{\mu_V} - 1 < \theta$ , which also implies that  $N_V(t) \rightarrow 0$  by (A.14). Assuming  $\frac{r}{\mu_V} - 1 < \theta$  and letting

$t^* \rightarrow \infty$  simplifies expression (A.44) to

$$\tilde{M} = \begin{cases} \mu_V \tau_e \theta N_V(0) - \frac{(1+\theta)}{r} \mu_V \theta K \ln\left(1 - \frac{r - \mu_V}{\mu_V \theta}\right) & \text{for late - lethal;} \\ \mu_V \tau_e \theta N_V(0) - (1 + \theta)^2 \frac{\mu_V \theta}{r} K \ln\left(1 - \frac{r - \mu_V}{\theta(\mu_V(1+\theta) - (r - \mu_V))}\right) & \text{for early - lethal,} \end{cases} \quad (\text{A.45})$$

which is equation (10) in the main text. As expected, the argument of the logarithm is positive if

and only if  $\frac{r}{\mu_V} - 1 < \theta$ . Fig. 4 compares the approximation in (A.45) to their exact values. This

approximation performs well for late-lethal.

## 5. Crude Approximations for $M$ for all Three Policies

In this section, we derive crude approximations for  $M$  that act as lower bounds for practical versions of all three policies. The crux of this approximation is to assume that the RIDL control prevents all future births, which reduces equation (5) in the main text to  $\dot{N}_V(t) = -\mu_V N_V(t)$ .

For the constant policy,  $R(t) = C$ , we assume eradication occurs when  $N_V(t^*) = 0.1$  (rather than  $I_V(t^*) = 0.1$ ), i.e., at time  $\tau_e + \frac{\ln(10N_V(0))}{\mu_V}$ . Hence, by equation (8) in the main text, the number of mosquitoes required for eradication for the constant policy is

$$\hat{M}_{\text{constant}} = [1 + \mu_V \tau_e + \ln(10N_V(0))]C. \quad (\text{A.46})$$

For the proportional and trajectory policies, we substitute the solution of  $\dot{N}_V(t) = -\mu_V N_V(t)$  into equation (A.39), and assume  $t^* = \infty$  and  $R(t^*) = 0$  to obtain our approximations. For the



proportional policy ( $R(t) = \theta N_V(t)$ ), we have

$$\hat{M}_{\text{proportional}} = \mu_V \tau_e \theta N_V(0) + \mu_V \theta \int_{\tau_e}^{\infty} N_V(t) dt, \quad (\text{A.47})$$

$$= \mu_V \tau_e \theta N_V(0) + \mu_V \theta N_V(\tau_e) \int_{\tau_e}^{\infty} e^{-\mu_V(t-\tau_e)} dt, \quad (\text{A.48})$$

$$= (\mu_V \tau_e + 1) \theta N_V(0) \quad \text{because } N_V(\tau_e) = N_V(0). \quad (\text{A.49})$$

A similar calculation for the trajectory policy ( $R(t) = \phi \frac{N_V(t)(K-N_V(t))}{K} - N_V(t)$ ) yields

$$\hat{M}_{\text{trajectory}} = \left( \frac{\phi}{r} (\mu_V^2 \tau_e + \frac{r + \mu_V}{2}) - \mu_V \tau_e - 1 \right) N_V(0). \quad (\text{A.50})$$

Fig. 5 compares these three approximations to their exact values in the special case where  $N_V(0) = 8 \times 10^4$  and for late-lethal. Except when the policy parameters are very close to their threshold values, these approximations provide useful lower bounds for the number of mosquitoes required for eradication.

## References

- [1] Dugard L, Veriest EI (1998) *Stability and Control of Time-delay Systems* (Springer, New York).
- [2] Corless RM, Gonnet GH , Hare DEG, Jeffrey DJ, Knuth DE (1996) *Advances in Computational Mathematics* 5:329-359.
- [3] Dye C (1984) *Journal of Animal Ecology* 53:247-268.

## FIGURE LEGENDS

Figure 3. The number of RIDL mosquitoes required for eradication in equation (8) of the main text vs. the initial RIDL-to-female ratio,  $\frac{R(0)}{N_V(0)}$ , for both late-lethal (- -) and early-lethal (—) for all three policies: the proportional policy (red), the constant policy (green), and the trajectory policy (black). The ratio  $\frac{R(0)}{N_V(0)}$  equals  $\theta$ ,  $\frac{C}{N_V(0)}$ , and  $\phi \frac{\mu_V}{r} - 1$ , respectively, for the three policies. When computing equations (1)-(5) in the main text, we set the initial state variables to their nontrivial pre-treatment steady-state values. We consider four values of  $\frac{N_V(0)}{N_H}$ : **(a)** 4, **(b)** 8, **(c)** 12, **(d)** 16.

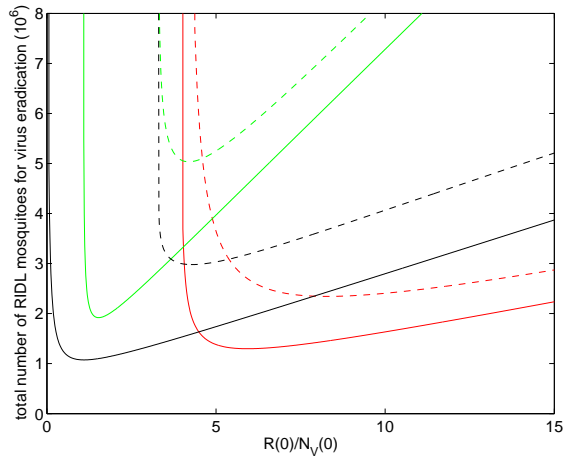
Figure 4. The number of days until eradication  $t^*$  (i.e.,  $I_V(t^*) \leq 0.1$ ) vs. the initial RIDL-to-female ratio,  $\frac{R(0)}{N_V(0)}$ , for both late-lethal (- -) and early-lethal (—) for all three policies: the proportional policy (red), the constant policy (green), and the trajectory policy (black). The ratio  $\frac{R(0)}{N_V(0)}$  equals  $\theta$ ,  $\frac{C}{N_V(0)}$ , and  $\phi \frac{\mu_V}{r} - 1$ , respectively, for the three policies. When computing equations (1)-(5) in the main text, we set the initial state variables to their nontrivial pre-treatment steady-state values. We consider four values of  $\frac{N_V(0)}{N_H}$ : **(a)** 4, **(b)** 8, **(c)** 12, **(d)** 16.

Figure 5. The system dynamics using late-lethal RIDL for the proportional policy (red), the constant control (green), and the trajectory policy (black) using the  $M$ -minimizing values of the free parameters ( $\theta = 6$ ,  $C = 1.5N_V(0)$ , and  $\phi = 11$ ), and for  $\frac{N_V(0)}{N_H} = 8$ . **(a)** The number of infected mosquitoes,  $I_V(t)$ , **(b)** the wild female population,  $N_V(t)$ , **(c)** the RIDL population,  $R(t)$ , **(d)** the total number of RIDL mosquitoes added to the system,  $M(t)$  from equation (A.38), **(e)**  $M'(t)$ , and **(f)**  $\frac{R(t)}{N_V(t)}$ .

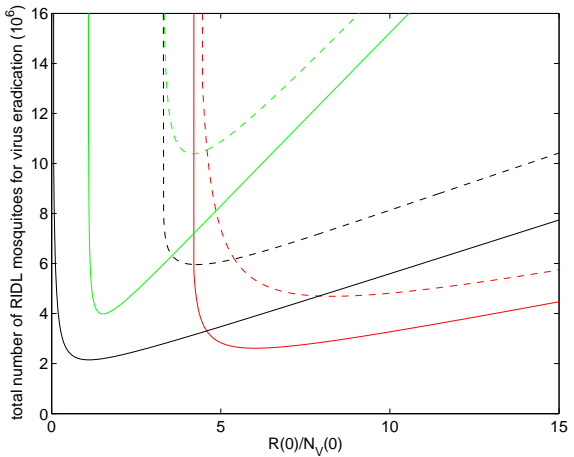
Figure 6. The exact (red) and approximate (black) number of RIDL mosquitoes required for eradication vs. the initial RIDL-to-female ratio,  $\frac{R(0)}{N_V(0)}$ , for both late-lethal (- -) and early-lethal (—) using the proportional policy. The exact value,  $M$ , is given by equation (8) of the main text and the approximation,  $\tilde{M}$ , is equation (10) in the main text. When computing equations (1)-(5) in the main text, we set the initial state variables to their nontrivial pre-treatment steady-state values. We

consider four values of  $\frac{N_V(0)}{N_H}$ : **(a)** 4, **(b)** 8, **(c)** 12, **(d)** 16.

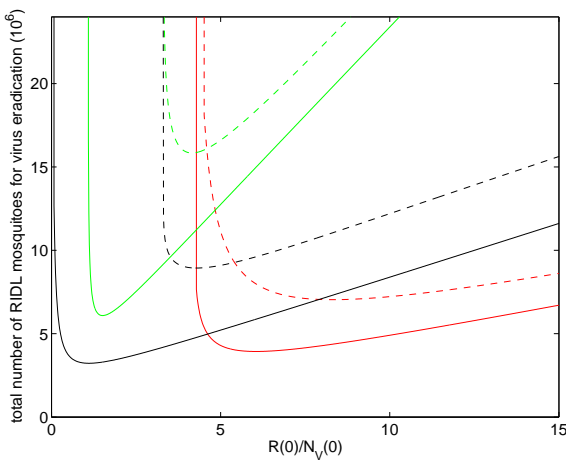
Figure 7. The exact (—) and approximate (- -) number of RIDL mosquitoes required for eradication using late-lethal control policies and  $\frac{N_V(0)}{N_H} = 8$ . The exact value,  $M$ , is given by equation (8) of the main text and the approximations are derived in §5. When computing equations (1)-(5) in the main text, we set the initial state variables to their nontrivial pre-treatment steady-state values. **(a)** Proportional policy, **(b)** constant policy, and **(c)** trajectory policy.



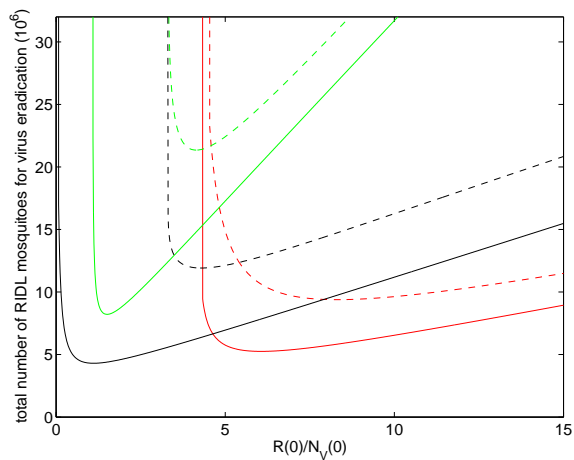
(a)  $N_V(0)/N_H = 4$



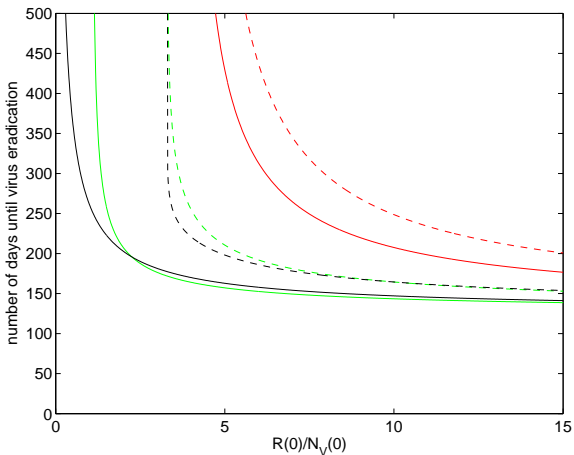
(b)  $N_V(0)/N_H = 8$



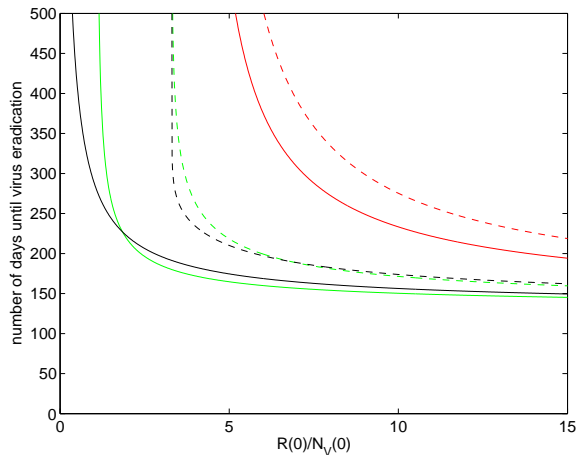
(c)  $N_V(0)/N_H = 12$



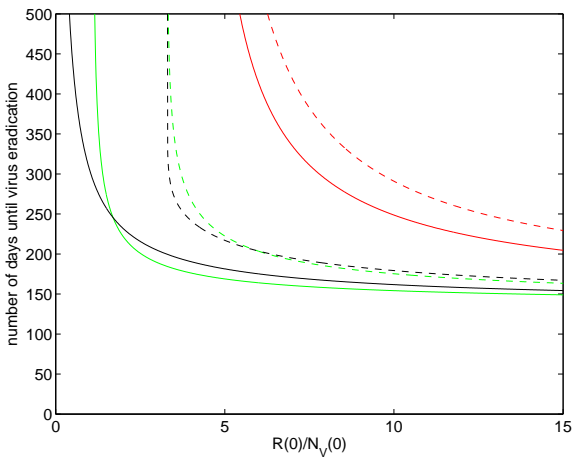
(d)  $N_V(0)/N_H = 16$



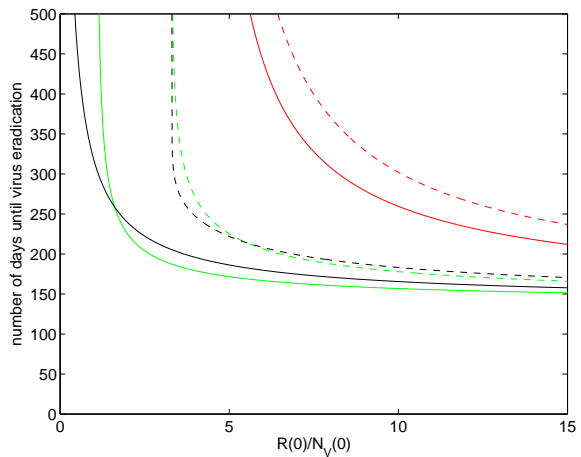
(a)  $N_V(0)/N_H = 4$



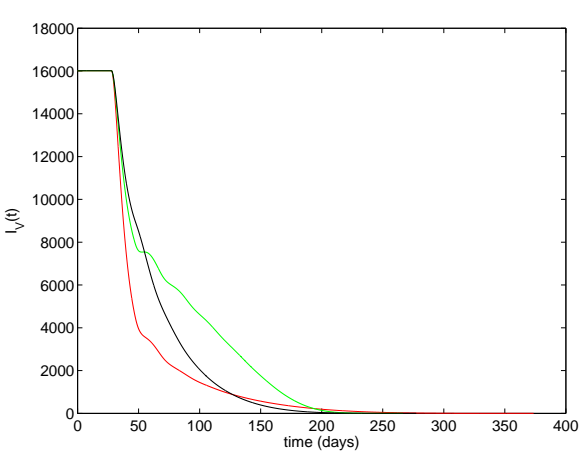
(b)  $N_V(0)/N_H = 8$



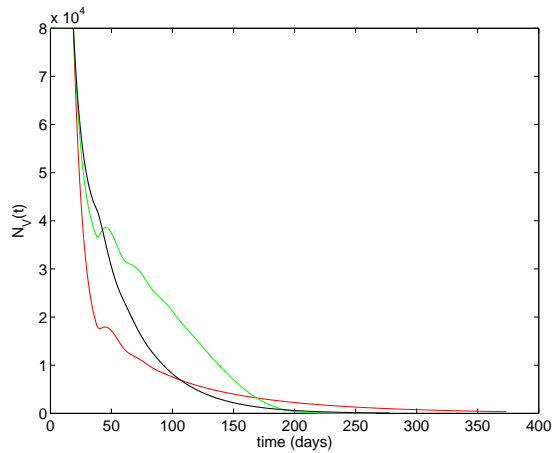
(c)  $N_V(0)/N_H = 12$



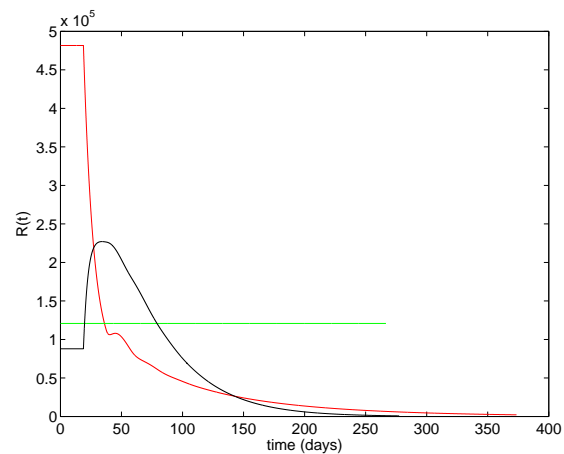
(d)  $N_V(0)/N_H = 16$



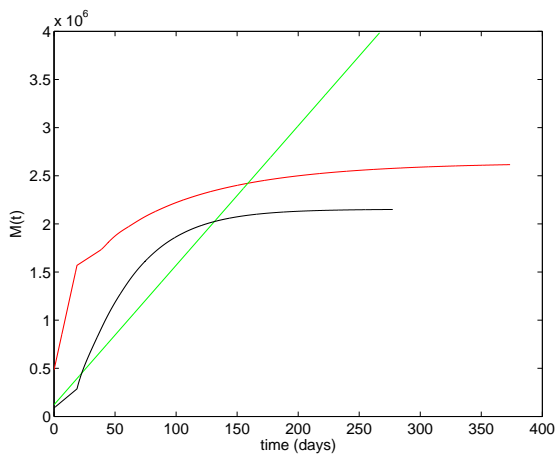
(a)  $I_V(t)$



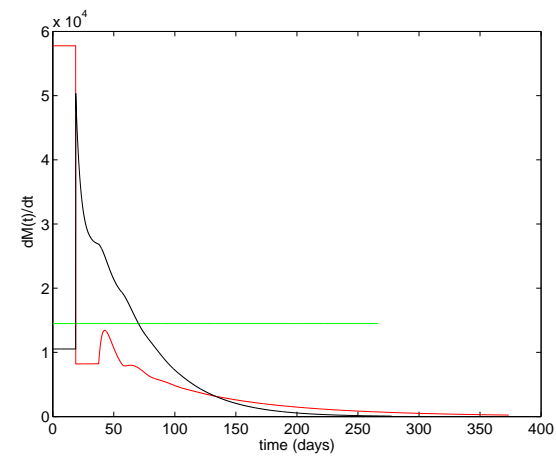
(b)  $N_V(t)$



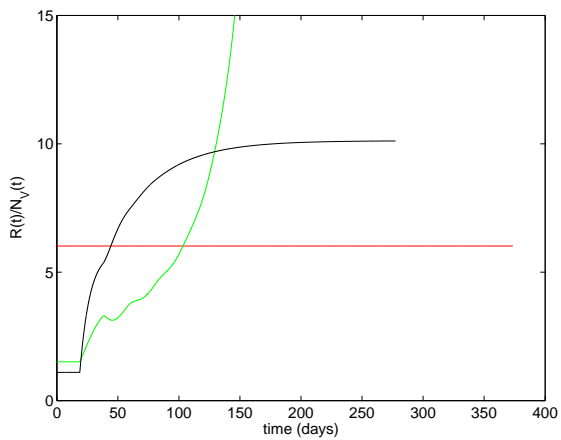
(c)  $R(t)$



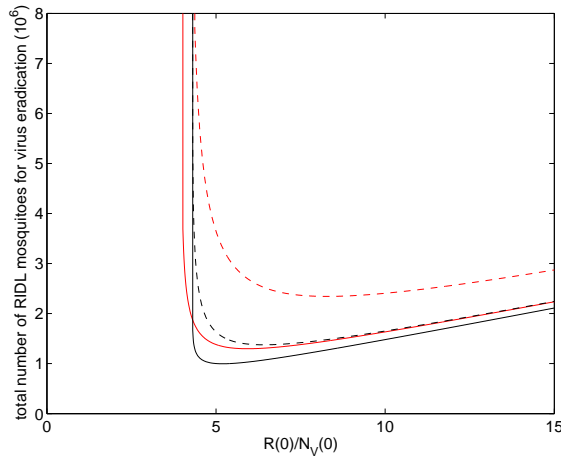
(d)  $M(t)$



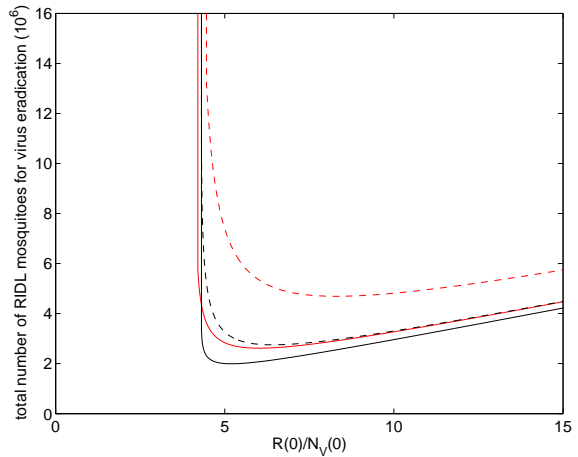
(e)  $M'(t)$



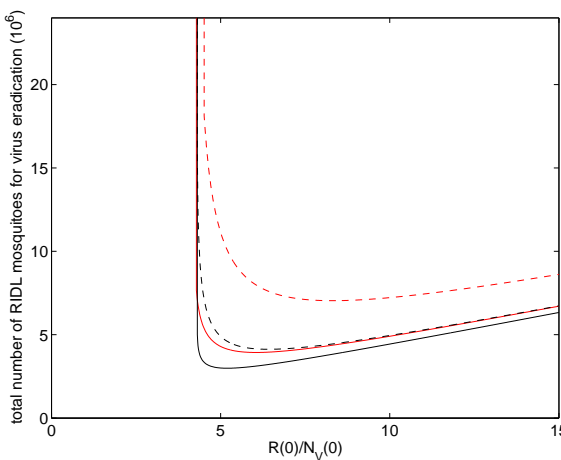
(f)  $R(t)/N_V(t)$



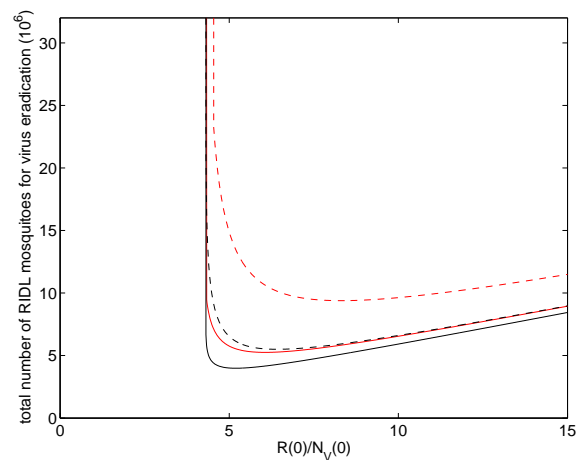
(a)  $N_V(0)/N_H = 4$



(b)  $N_V(0)/N_H = 8$

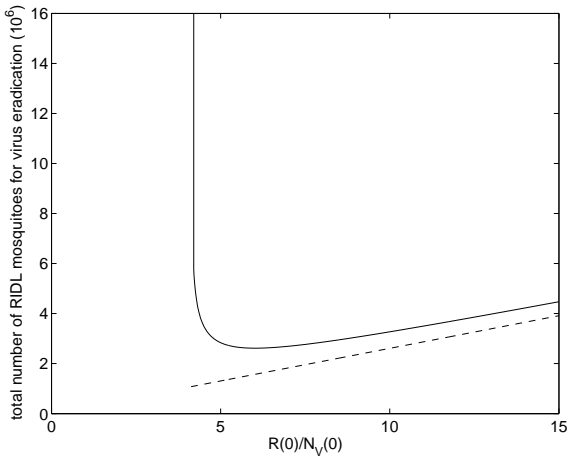


(c)  $N_V(0)/N_H = 12$

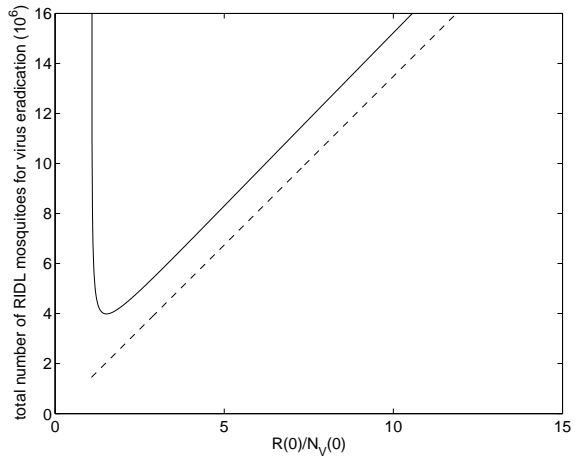


(d)  $N_V(0)/N_H = 16$

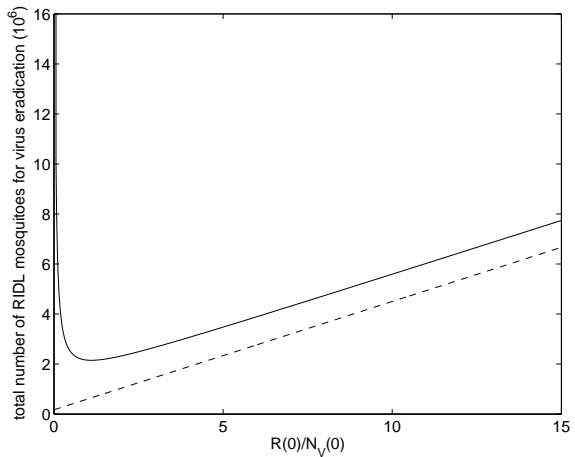




(a) proportional policy



(b) constant policy



(c) trajectory policy