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

Michael P. Atkinson[†], Zheng Su[†], Nina Alphey[‡§], Luke S. Alphey[‡§], Paul G. Coleman[§¶], and Lawrence M. Wein[‖††]

[†]Institute for Computational and Mathematical Engineering and [‖]Graduate School of Business, Stanford University, Stanford, CA 94305; [‡]Department of Zoology, University of Oxford, South Parks Road, Oxford OX1 3PS, United Kingdom; [§]Oxitec, Limited, 71 Milton Park, Abingdon, Oxford OX14 4RX, United Kingdom; and [¶]Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Edited by Simon A. Levin, Princeton University, Princeton, NJ, and approved April 14, 2007 (received for review December 1, 2006)

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 ≈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 provided 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, γ be the human recovery rate, and for $i = \{H,$

Author contributions: P.G.C. and L.M.W. designed research; M.P.A., Z.S., and L.M.W. performed research; M.P.A., Z.S., N.A., L.S.A., P.G.C., and L.M.W. analyzed data; and M.P.A., N.A., L.S.A., P.G.C., and L.M.W. wrote the paper.

Conflict of interest statement: N.A., L.S.A., and P.G.C. are or were employees or collaborative students of Oxitec, Limited, which therefore provided salary and other support for the research program. Also, N.A., L.S.A., and P.G.C. have shares or share options in Oxitec, Limited. Both Oxitec, Limited, and Oxford University have one or more patents or patent applications related to the subject of this paper. All other authors declare no conflict of interest.

This article is a PNAS Direct Submission.

Freely available online through the PNAS open access option.

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

[††]To whom correspondence should be addressed. E-mail: lwein@stanford.edu.

This article contains supporting information online at www.pnas.org/cgi/content/full/0610685104/DC1.

$V\}$, let μ_i be the death rate and τ_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 λ 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 μ_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 τ_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

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

where $L(t)$ is the larval female population at time t, $\tilde{K}$ is the carrying capacity of the larvae population (15), τ_1^b is the time lag between the beginning of larval competition and adulthood, and τ_1^e is the delay between the end of larval competition and adulthood. For simplicity, we approximate

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

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 τ_1^b and τ_e. Thus we set our density-dependent factor to $D(t) = [\tilde{K} - \beta(\tau_l^b - \tau_l^e)N_V(t - \tau_e)]/\tilde{K} = [K - N_V(t - \tau_e)]/K$, where $K = \tilde{K}/\beta(\tau_l^b - \tau_l^e)$, 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

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

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
γ	Human recovery rate	0.25 per day	23
μ_H	Human death rate	$\frac{1}{60}$ per year	
μ_V	Adult female mosquito death rate	0.12 per day	14, 16
λ	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	
τ_H	Human incubation period	7 days	12, 24, 25
τ_V	Mosquito incubation period	9 days	20, 24, 25
τ_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*

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

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 θ, the system is unstable, and θ^* 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 θ^* 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,

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

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.

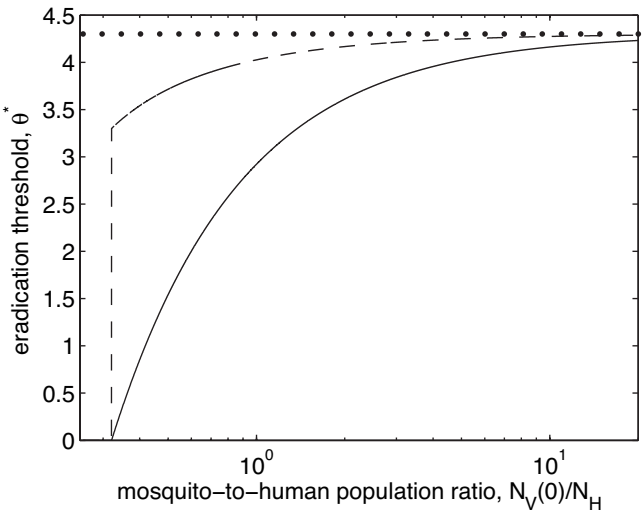

Fig. 1. The RIDL eradication threshold (θ^*) for the proportional policy vs. the logarithm of the pretreatment mosquito-to-human population ratio ($N_V(0)/N_H$), which is generated by varying the population parameter K, for late-lethal (—), early-lethal (- -), and the asymptotic {as $N_V(0)/N_H \to \infty$}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

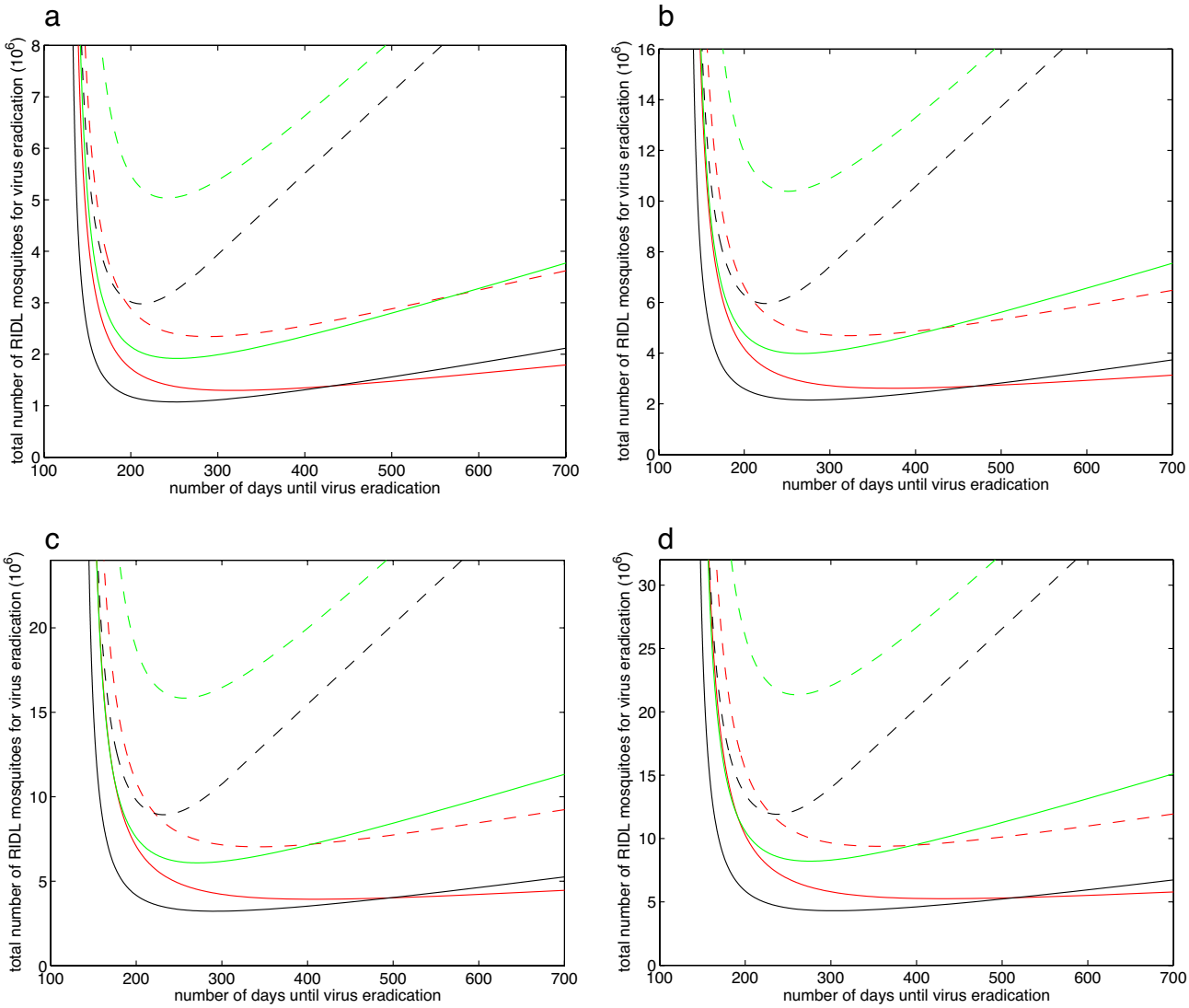

Fig. 2. The number of RIDL mosquitoes required for eradication in Eq. **8** vs. the number of days until eradication t^* [i.e., $I_V(t^*) \leq 0.1$] for both late-lethal (—) and early-lethal (- -) for all three policies: the proportional policy (red), the constant policy (green), and the trajectory policy (black). These curves are generated by varying the free parameter (θ, C, and ϕ, 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)

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

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., θ 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 θ that minimizes M in Fig. 2 is 6.0 for late-and 8.3 for early-lethal. Eradication can take several years for θ values close to the critical θ^*, but for values closer to the M-minimizing θ 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 θ 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

mosquitoes required for eradication by the constant policy is very sensitive to the value of C (SI Fig. 3), which makes it a less robust policy than the proportional policy. Although the M-minimizing constant policy requires significantly more mosquitoes to achieve eradication than the M-minimizing proportional policy, it does achieve eradication in less time (Fig. 2).

The Trajectory Policy. Our final policy is reverse-engineered in an attempt to maintain an exponential decline in the total number of infected female mosquitoes [$I_V(t)$]. Analytically, we construct the trajectory policy so it achieves an exponential decay in the total number of female mosquitoes [$N_V(t)$] in the late-lethal version of Eq. **5** in the absence of time lags (i.e., setting $\tau_e = 0$). This calculation (see *SI Appendix*, Section 2) yields the trajectory policy,

$$R(t) = \phi \frac{N_V(t)(K - N_V(t))}{K} - N_V(t), \qquad [9]$$

where θ is a free parameter that dictates the rate of exponential decay. Under this policy, the RIDL-to-female ratio is

$$\frac{R(t)}{N_V(t)} = (\phi - 1) - \frac{\phi N_V(t)}{K},$$

which equals $(\phi\mu_V)/r - 1$ at time 0 and (for practical values of θ) steadily increases (SI Fig. 5, which provides a detailed comparison of the dynamics of all three policies) as the female mosquito population decreases, eventually approaching $\theta - 1$ as eradication nears. This behavior suggests that the trajectory policy can be viewed in more general terms as a variable proportional policy, where the proportion of RIDL mosquitoes increases as the female mosquito population decreases. Under late-lethal (which is what the trajectory policy was constructed for), at the M-minimizing value of θ, the trajectory policy requires slightly fewer mosquitoes for eradication than the M-minimizing proportional policy. However, when the two policies both release the minimum number of mosquitoes required under the proportional policy, eradication occurs nearly twice as fast for the trajectory policy (Fig. 2).

Overall, late-dominates early-lethal for all three policies, and the trajectory policy outperforms the other two policies. The trajectory policy slightly dominates the proportional policy if the main performance measure is the total number of RIDL mosquitoes required for eradication and significantly dominates the proportional policy if the primary measure is the time until eradication. The proportional policy significantly outperforms the constant policy if the main performance measure is the number of mosquitoes required for eradication. A third performance measure not shown in Fig. 2 is the peak release quantity, which in general is the initial deployment when $R(0)$ RIDL mosquitoes are released into the system (the only situation where the peak release is not at $t = 0$ is the trajectory policy for $R(0)/N_V(0) < 0.2$). This value is higher for the proportional policy than the other two policies (SI Fig. 3). However, if production capacity is limited, factories could stockpile male mosquitoes before the start of a program, when the peak release occurs.

Analytical Approximations for *M*. In *SI Appendix*, Section 4, we derive the following approximation for the number of released mosquitoes in **8** under the proportional policy, denoted by $\tilde{M}$, assuming the adult female mosquito population is in its pretreatment steady-state at time 0:

$$\tilde{M} = \begin{cases} \mu_V\tau_e\theta N_V(0) - (1+\theta)\dfrac{\mu_V\theta}{r}K\ln\left(1 - \dfrac{r-\mu_V}{\mu_V\theta}\right) \\ \qquad \text{for late-lethal;} \\ \mu_V\tau_e\theta N_V(0) - (1+\theta)^2\dfrac{\mu_V\theta}{r} \\ \qquad K\ln\left(1 - \dfrac{r-\mu_V}{\theta(\mu_V(1+\theta) - (r-\mu_V))}\right) \\ \qquad \text{for early-lethal.} \end{cases} \qquad [10]$$

This approximation is valid only if $\theta > (r/\mu_V) - 1$, because this is a necessary and sufficient condition for $N_V(\infty) = 0$ (see *SI Appendix*, Section 1). Although it is possible to eradicate the virus for $\theta < (r/\mu_V) - 1$, the quantity M in Eq. **8** is a convex function of θ and achieves a unique minimum in the region $\theta > (r/\mu_V) - 1$, where approximation **10** is valid (SI Fig. 3). The expression $\tilde{M}$ in Eq. **10** is sufficiently accurate to provide a useful ballpark approximation for the number of mosquitoes required for eradication (SI Fig. 6). The values of θ that minimize $\tilde{M}$ in Eq. **10** are 5.2 for late- and 6.4 for early-lethal, which are smaller than the values 6.0 and 8.3 that minimize M in SI Fig. 3. Finally, in *SI Appendix*, Section 5 and SI Fig. 7, we derive and assess somewhat cruder (i.e., less accurate than Eq. **10**) approximations for M that act as lower bounds for the total number of mosquitoes required for eradication for all three release policies.

Discussion

Although Eq. **5** captures the important features of the RIDL policy, the epidemic model in Eqs. **1**–**4** lacks the fidelity to accurately predict the outcome of an epidemic. In the case of dengue fever, the inclusion of four serotypes with serotype-specific immunity rates (27), age-dependent susceptibility and disease severity, seasonality (28), and spatial aspects would be required. In addition, the model does not allow for the immigration of infected humans or vectors, which could lead to some secondary infections even if eradication is ultimately achieved. Nonetheless, the susceptible–exposed–infectious–susceptible human-vector epidemic model and its variants (in the absence of RIDL intervention) have a long history of capturing the salient characteristics of a variety of mosquito-based disease outbreaks (ref. 12, chapter 14), including dengue fever (20, 26, 28). Similarly, the density dependence modeled in Eq. **5** is consistent with data for a variety of insects, including the *A. aegypti* mosquito (13). Consequently, our model should suffice for an order-of-magnitude assessment of the effectiveness and practicality of the RIDL strategy, as well as providing a relative comparison of six reasonable and applicable control strategies.

Proposition 1 and the identity $r = \lambda\mu_V/2$ suggest that eradication of the virus requires the RIDL population to be maintained at a population $\approx(\lambda/2) - 1$ times larger than the adult female mosquito population in the proportional policy, where λ is the number of progeny per adult female mosquito. For *A. aegypti* in our dengue fever example, this value is 4.3. Although eradication can be achieved at some smaller values (Fig. 1), to minimize the number of RIDL mosquitoes required for eradication, it is optimal to maintain a somewhat higher ratio ($\approx$6); at the optimal ratio, eradication takes $\approx$13 months. Under the proportional policy, the total number of mosquitoes required for eradication is $\approx$45% less for late-than for early-lethal, because of the strong density-dependent competition during the larval stage. Hence, late-lethal RIDL offers another benefit, beyond improved fitness, relative to SIT, which kills before the larval stage. By Eq. **10** and $r = \lambda\mu_V/2$, the total number of mosquitoes required for eradication in the late-lethal case of the proportional policy can be approximated by

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

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 $\approx 25.9 N_V(0)$ for *A. aegypti* when using the *M*-minimizing θ. 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 3×10^5 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 ≈ 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 5×10^8 per day (4), rearing insects on this scale is not infeasible (i.e., 200 days of production at 5×10^8 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 θ (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 θ to some value $\hat{\theta}$ (and perhaps decrease θ 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., $R(t) = \hat{\theta}\hat{N}_V(t)$].

We thank an anonymous reviewer for proposing the trajectory policy. This research was supported by an Abbott Laboratories Stanford Graduate Fellowship (to M.P.A.), the U.K. Biotechnology and Biological Sciences Research Council (N.A.), and the Center for Social Innovation, Graduate School of Business, Stanford University (L.M.W.).

1. Gubler DJ (2002) *Arch Med Res* 33:330–342.
2. Rigau JG, Clark GG, Gubler DJ, Reiter P, Sanders EJ, Vorndam AV (1998) *Lancet* 352:971–977.
3. Krafsur E (1998) *J Agr Entomol* 15:303–317.
4. Dyck V, Hendrichs J, Robinson A, eds (2005) *Sterile Insect Technique: Principles and Practice in Area-Wide Integrated Pest Management* (Springer, Dordrecht, The Netherlands).
5. Benedict M, Robinson A (2003) *Trends Parasitol* 19:349–355.
6. Andreasen M, Curtis CF (2005) *Med Vet Entomol* 19:238–244.
7. Helinski M, Parker A, Knols BGJ (2006) *Malaria J* 5:41–50.
8. Thomas DD, Donnelly CA, Wood RJ, Alphey LS (2000) *Science* 287:2474–2476.
9. Alphey L, Andreasen M (2002) *Mol Biochem Parasitol* 121:173–178.
10. Slosek J (1986) *Soc Sci Med* 23:249–257.
11. Gubler DJ (1998) *Clin Microbiol Rev* 11:480–496.
12. Anderson RM, May RM (1991) *Infectious Diseases of Humans* (Oxford Univ Press, Oxford).
13. Hassell MP, Lawton JH, May RM (1975) *J Anim Ecol* 45:471–486.
14. Dye C (1984) *J Anim Ecol* 53:247–268.
15. Crow JF, Kimura M (1970) *An Introduction to Population Genetics Theory* (Harper & Row, New York).
16. Sheppard PM, MacDonald WW, Tonn RJ, Grab B (1969) *J Anim Ecol* 38:661–697.
17. Moreira L, Wang J, Collins F, Jacobs-Lorena M (2004) *Genetics* 166:1337–1341.
18. Marrelli M, Moreira C, Kelly D, Alphey L, Jacobs-Lorena M (2006) *Trends Parasitol* 22:197–202.
19. Macdonald WW (1956) *Ann Trop Med Parasitol* 50:399–414.
20. Newton EAC, Reiter P (1992) *Am J Trop Med Hyg* 47:709–720.
21. Canyon DV, Hii JLK, Muller R (1999) *Bull Entomol Res* 89:35–39.
22. Watts DM, Burke DS, Harrison BA, Whitmire RE, Nisalak A (1987) *Am J Trop Med Hyg* 36:143–152.
23. Gubler DJ, Suharyono W, Tan R, Abidin M, Sie A (1981) *Bull World Health Org* 59:623–630.
24. Siler JF, Hall MW, Hitchens AP (1926) *Phillip J Sci* 29:1–304.
25. Callisher CH (2005) *Emerg Infect Dis* 11:738–739.
26. Focks DA, Brenner RJ, Hayes J, Daniels E (2000) *Am J Trop Med Hyg* 62:11–18.
27. Ferguson N, Anderson R, Gupta S (1999) *Proc Natl Acad Sci USA* 96:790–794.
28. Bartley LM, Donnelly CA, Garnett GP (2002) *Trans R Soc Trop Med Hyg* 96:387–397.
29. Grover KK, Curtis CF, Sharma VP, Singh KRP, Dietz K, Agarwal HV, Razdan RK, Vaidyanathan Y (1976) *Bull Entomol Res* 66:469–480.
30. Klassen W, Curtis CF (2005) in *Sterile Insect Technique: Principles and Practice in Area-Wide Integrated Pest Management*, eds Dyck VA, Hendrichs J, Robinson AS (Springer, Dordrecht, The Netherlands), pp 3–36.
31. Seawright J, Kaiser P, Dame D, Lofgren C (1978) *Science* 200:1303–1304.
32. World Health Organization (2002) *Fact Sheet No 117* (World Health Organization, Geneva).
33. Pates H, Curtis C (2005) *Annu Rev Entomol* 50:53–70.
34. Harrington LC, Scott TW, Lerdthusnee K, Coleman RC, Costero A, Clark GC, Jones JJ, Kitthawee S, Kittayapong P, Sithiprasasna R, *et al.* (2005) *Am J Trop Med Hyg* 72:209–220.