

Insecticide resistance and its implications for mosquito and malaria control

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joint work with

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Evolution-proof insecticides?

- Evolution-proof insecticides — hot topic in mosquito control. Potential to slow or halt the evolution of insecticide-resistance in mosquitoes.
- Insecticides such as DDT are cheap and effective in short term, but mosquitoes quickly become resistant in areas of intensive use.
- Current insecticides kill young adult insects rapidly on contact, but this leads to intense selection for resistance because they kill young female adults.
- Want to enhance the useful lifespan of an insecticide by the way we use it.
- Most mosquitoes don't live long enough to transmit malaria, due to long latency stage (10 to 14 days, almost a lifetime to a mosquito). Majority of egg laying done before mosquito can transmit malaria.

- Biologist Andrew Read et al (Penn State) suggest that an insecticide should target only old mosquitoes. They call it a late-life-acting (LLA) insecticide. Idea: insecticide should start to take effect on a female mosquito after she has laid most of her eggs but before she can start to transmit malaria. Result: much weaker selection for resistance.
- Possibilities:
 - insecticide could take effect not on initial contact but some time later (eg. fungal pesticides that kill 7 to 14 days after contact).
 - insecticide could take effect only on older insects by exploiting physiological changes and weaknesses associated with aging.

Conventional Insecticide Model

$$V'(t) = -(\mu_a + \delta)V(t) + e^{-\mu_i \tau_i} \frac{V(t - \tau_i)}{V(t - \tau_i) + R(t - \tau_i)} b(V(t - \tau_i) + R(t - \tau_i))$$
$$R'(t) = -\mu_a R(t) + e^{-\mu_i \tau_i} \frac{R(t - \tau_i)}{V(t - \tau_i) + R(t - \tau_i)} b(V(t - \tau_i) + R(t - \tau_i))$$

where δ is the effect of the insecticide.

- Adult mosquitoes classed as V (vulnerable) or R (resistant) to insecticide.
- Mosquitoes come into contact with insecticide on maturation and the insecticide is effective immediately.
- Resistance arises via a genetic mutation that occurs once, at time $t = 0$, and generates a small non-zero initial value for $R(t)$. The mutation increases resistance to insecticide but has no other effect (in particular, no effect on fecundity).
- Overall egg laying rate at time t is therefore taken to be a function $b(V(t) + R(t))$ of the total number of adult mosquitoes, with $b(0) = 0$. Reasonable possibility: $b(M) = pM e^{-qM}$.
- Model has no coexistence equilibrium.
- An equilibrium $(V, R) = (0, R^*)$ can exist with $\mu_a R^* = e^{-\mu_i \tau_i} b(R^*)$.
- An equilibrium $(V^*, 0)$ will then also exist if δ is sufficiently small but not if δ is large (i.e. insecticide is very effective).
- δ small is a reasonable assumption because a single mutation would have a small effect.

Theorem 1 (Linear stability, conventional insecticide) *Suppose that $\delta > 0$ and $\mu_a > e^{-\mu_i \tau_i} b'(R^*) > 0$. Then the equilibrium $(V, R) = (0, R^*)$ is locally asymptotically stable.*

Global stability of $(0, R^*)$ holds as well, if $b(\cdot)$ has the classic hump shape with the equilibrium on the increasing side, for all solutions with non-negative initial data such that $R(\theta) \not\equiv 0$ on $[-\tau_i, 0]$.

LLA (Late-Life-Acting) Insecticide Model

Assumptions:

- Mosquito goes through a larval stage (all pre-adult stages of egg, larva and pupa) — total duration τ_i
- mosquito immediately exposed to insecticide on maturation (through contact with bed-nets, for example).
- then there is an *adult* stage of duration τ_a , during which the LLA insecticide is not effective yet
- this is followed by the *old age* stage when the LLA insecticide is taking effect. Old mosquitoes have ages exceeding $\tau_i + \tau_a$.
- we are interested in the decay rate λ_{all} which indicates how fast the solutions evolve to the equilibrium $(0, R^*)$ for the *conventional* insecticide model in which *all* adult mosquitoes are targeted. Time to reach equilibrium is of order $|\lambda_{\text{all}}|^{-1}$. Want to compare this with the corresponding decay rate λ_{old} , for the *LLA* insecticide model in which only *old* mosquitoes are targeted.

Table 1: Parameter values, mainly for the malarial *Anopheles* genus.

Parameter	Definition
μ_i	per-capita death rate for mosquito larvae
μ_a	per-capita death rate for adult mosquitoes
μ_o	per-capita death rate for old mosquitoes
δ	insecticide-induced death rate for vulnerable mosquitoes
τ_i	duration of larval stage
τ_a	duration of adult stage
$b(M)$	birth function: $b(M) = pMe^{-qM}$
p	maximum possible per capita female egg production rate
$1/q$	population size at which the population as a whole achieves maximum reproductive success

LLA insecticide model:

$$V'_a(t) = -\mu_a V_a(t) + e^{-\mu_i \tau_i} b(M_a(t - \tau_i) + M_o(t - \tau_i)) \left(\frac{V_a(t - \tau_i) + V_o(t - \tau_i)}{M_a(t - \tau_i) + M_o(t - \tau_i)} \right) \\ - e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} b(M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)) \left(\frac{V_a(t - \tau_i - \tau_a) + V_o(t - \tau_i - \tau_a)}{M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)} \right)$$

$$V'_o(t) = -(\mu_o + \delta)V_o(t) +$$

$$e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} b(M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)) \left(\frac{V_a(t - \tau_i - \tau_a) + V_o(t - \tau_i - \tau_a)}{M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)} \right)$$

$$R'_a(t) = -\mu_a R_a(t) + e^{-\mu_i \tau_i} b(M_a(t - \tau_i) + M_o(t - \tau_i)) \left(\frac{R_a(t - \tau_i) + R_o(t - \tau_i)}{M_a(t - \tau_i) + M_o(t - \tau_i)} \right) \\ - e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} b(M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)) \left(\frac{R_a(t - \tau_i - \tau_a) + R_o(t - \tau_i - \tau_a)}{M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)} \right)$$

$$R'_o(t) = -\mu_o R_o(t) +$$

$$e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} b(M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)) \left(\frac{R_a(t - \tau_i - \tau_a) + R_o(t - \tau_i - \tau_a)}{M_a(t - \tau_i - \tau_a) + M_o(t - \tau_i - \tau_a)} \right)$$

where $M_a(t) = V_a(t) + R_a(t)$, etc. Note δ (insecticide induced death) appears only in the equation for *old* vulnerable mosquitoes.

The V_a equation can be replaced by the integral equation

$$V_a(t) = e^{-\mu_i \tau_i} \int_{t-\tau_a}^t e^{-\mu_a(t-s)} b(M_a(s - \tau_i) + M_o(s - \tau_i)) \frac{V_a(s - \tau_i) + V_o(s - \tau_i)}{M_a(s - \tau_i) + M_o(s - \tau_i)} ds$$

(Similar integral equation for R_a).

Interested in linear stability of the equilibrium in which vulnerables are extinct but resistant mosquitoes are not. At equilibrium, $V_a = V_o = 0$ and $R_a = R_a^*$, $R_o = R_o^*$ where

$$\begin{aligned}\mu_a R_a^* &= (1 - e^{-\mu_a \tau_a}) e^{-\mu_i \tau_i} b(R_a^* + R_o^*), \\ \mu_o R_o^* &= e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} b(R_a^* + R_o^*).\end{aligned}$$

Alternatively, $R_a^* = (1 - e^{-\mu_a \tau_a}) e^{\mu_a \tau_a} \mu_o R_o^* / \mu_a$ and

$$\mu_o R_o^* = e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} b(R_o^* + (e^{\mu_a \tau_a} - 1) \mu_o R_o^* / \mu_a).$$

Theorem 2 (Linear stability, LLA insecticide) *Suppose that*

$$\mu_o > e^{-\mu_a \tau_a} e^{-\mu_i \tau_i} \left(1 + \frac{\mu_o}{\mu_a} (e^{\mu_a \tau_a} - 1) \right) b'(R_a^* + R_o^*) > 0.$$

Then, for any $\delta > 0$, the equilibrium $(V_a, V_o, R_a, R_o) = (0, 0, R_a^, R_o^*)$ is locally asymptotically stable.*

- In both models the resistant strain takes over but ...
- in the LLA insecticide model resistance develops more slowly.

Theorem 3 *Suppose that $\mu_o = \mu_a$ and $\delta > 0$. Then the convergence of solutions to the equilibrium $(0, 0, R_a^*, R_o^*)$ of the LLA insecticide model occurs more slowly than the convergence of solutions of the conventional insecticide model to its equilibrium $(0, R^*)$. More precisely, if λ_{old} and λ_{all} are respectively the dominant real eigenvalues of the linearisations of those models then*

$$\lambda_{\text{all}} < \lambda_{\text{old}} < 0.$$

Simulations

- Egg laying rate chosen as $b(M) = pMe^{-qM}$.
- For conventional insecticide model, vulnerables go extinct more quickly than in the LLA insecticide model.
- Increasing δ (potency of insecticide) shortens the time taken for the resistant strain to take over. This effect is many times more dramatic in the conventional insecticide model than in the case where only older mosquitoes are targeted (LLA model).
- If $p = 50$ vulnerables die out and resistant mosquitoes still become dominant, but evolve to an oscillatory state rather than an equilibrium.
- Increasing the delay τ_a before the insecticide takes effect dramatically increases the time for the resistant strain to take over.

Other points

- Evolution of resistance to an LLA insecticide could be slowed down even more if the insecticide could be made to act only on malaria-infected mosquitoes, because in this way one further relaxes selection for resistance without any loss of control. Moreover there would be increased selection pressure favouring mosquitoes that are resistant to malaria.
- The strategy of killing only old mosquitoes emphasizes **disease control, not insect control**. Killing mosquitoes of all ages is popular with the public but increases selection pressure favouring resistance.
There is therefore a trade off between effective prevention of malaria transmission, and having to live with mosquito bites involving no malarial transmission.

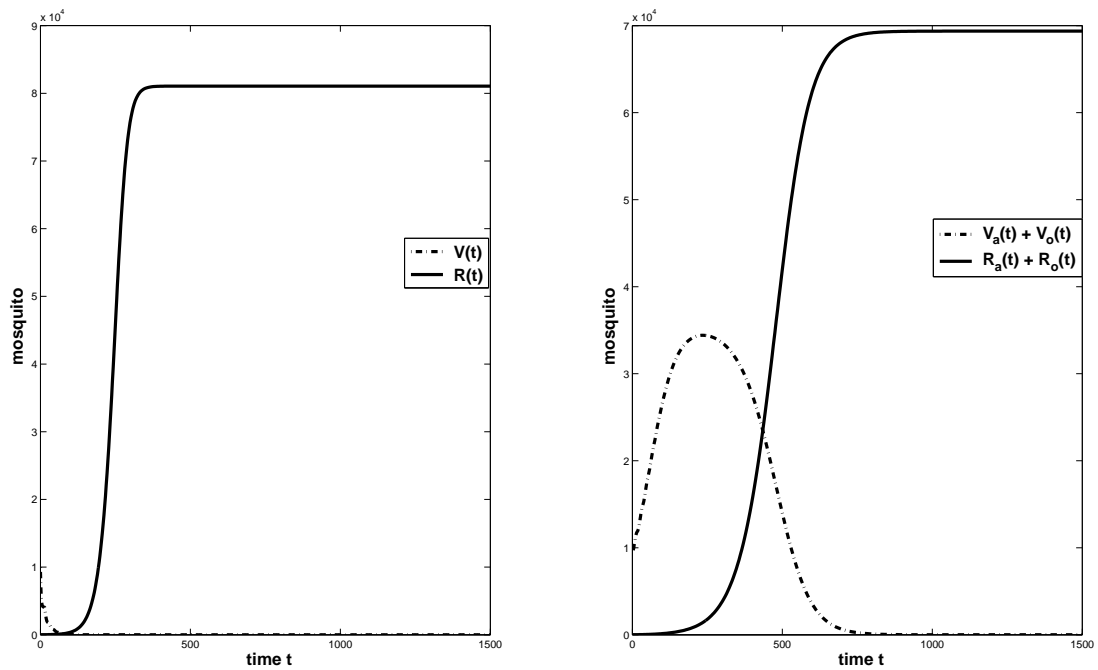


Figure 1: In this figure, $p = 15$.

Left panel — conventional insecticide model. Vulnerables die out and resistant strain rapidly takes over.

Right panel — LLA insecticide model. Vulnerables again driven to extinction by the resistant strain, but on a much longer timescale ~ 700 days.

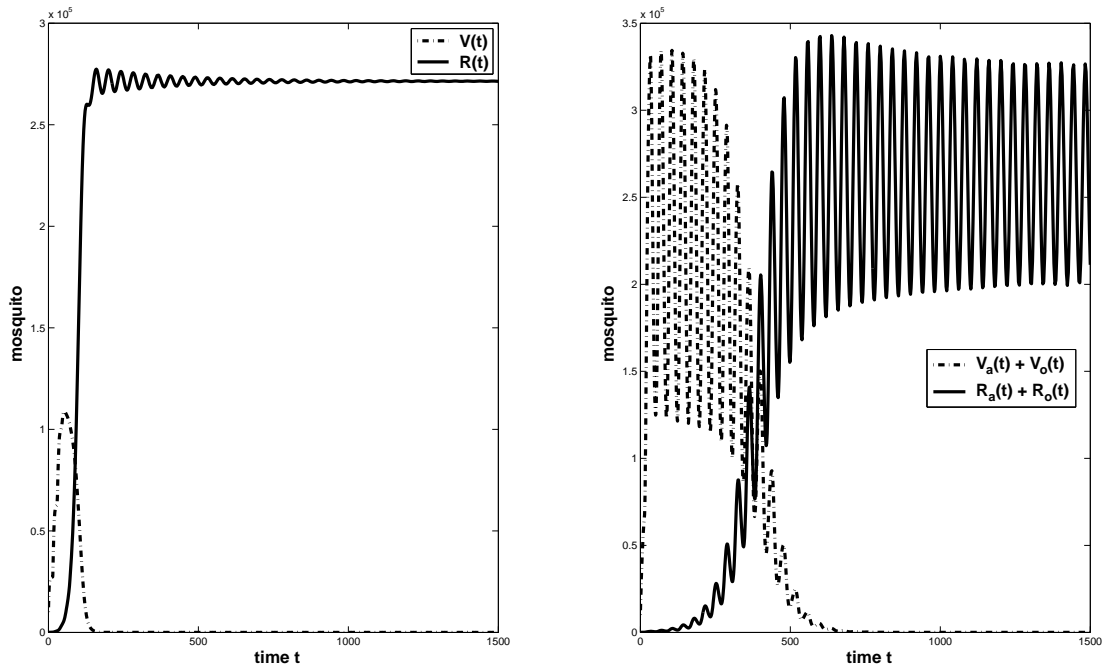


Figure 2: In this figure p has been increased to $p = 50$.

Left panel — conventional insecticide model: vulnerables die out and resistant strain takes over.

Right panel — LLA insecticide model. Resistant strain takes over much more slowly, and they evolve to a limit cycle rather than an equilibrium.

Late-Life-Acting Insecticide Model with Malaria

$S_{va}(t)$ = number of susceptible vulnerable adult mosquitoes

$S_{vo}(t)$ = number of susceptible vulnerable old mosquitoes

$E_{va}(t)$ = number of exposed vulnerable adult mosquitoes

$E_{vo}(t)$ = number of exposed vulnerable old mosquitoes

$I_{va}(t)$ = number of infectious vulnerable adult mosquitoes

$I_{vo}(t)$ = number of infectious vulnerable old mosquitoes

$(S_{ra}(t) = \text{number of susceptible } \underline{\text{resistant}} \text{ adult mosquitoes, etc})$

$$\begin{aligned}
 S'_{va}(t) &= \frac{T_v(t - \tau_i)}{T_v(t - \tau_i) + T_r(t - \tau_i)} b(T_v(t - \tau_i) + T_r(t - \tau_i)) e^{-\mu_i \tau_i} \\
 &- e^{-\mu_i \tau_i} e^{-\mu_{va} \tau_a} \exp \left(- \int_{\tau_i}^{\tau_i + \tau_a} b_{va} \beta_{hva} \frac{I_h(\eta + t - \tau_i - \tau_a)}{T_h(\eta + t - \tau_i - \tau_a)} d\eta \right) \\
 &\times \frac{T_v(t - \tau_i - \tau_a)}{T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)} b(T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)) \\
 &- \mu_{va} S_{va}(t) - b_{va} \beta_{hva} S_{va}(t) \frac{I_h(t)}{T_h(t)}.
 \end{aligned}$$

$$\begin{aligned}
 S'_{vo}(t) &= e^{-\mu_i \tau_i} e^{-\mu_{va} \tau_a} \exp \left(- \int_{\tau_i}^{\tau_i + \tau_a} b_{va} \beta_{hva} \frac{I_h(\eta + t - \tau_i - \tau_a)}{T_h(\eta + t - \tau_i - \tau_a)} d\eta \right) \\
 &\times \frac{T_v(t - \tau_i - \tau_a)}{T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)} b(T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)) \\
 &- (\mu_{vo} + \delta_o) S_{vo}(t) - b_{vo} \beta_{hvo} S_{vo}(t) \frac{I_h(t)}{T_h(t)}
 \end{aligned}$$

$$\begin{aligned}
 E'_{va}(t) &= -(\mu_{va} + \gamma_{va}) E_{va}(t) + b_{va} \beta_{hva} S_{va}(t) \frac{I_h(t)}{T_h(t)} \\
 &- \frac{T_v(t - \tau_i - \tau_a)}{T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)} b(T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)) e^{-\mu_i \tau_i} \\
 &\times \int_{\tau_i}^{\tau_i + \tau_a} e^{-(\mu_{va} + \gamma_{va})(\tau_i + \tau_a - \eta)} \exp \left(- \int_{\tau_i}^{\eta} \left\{ \mu_{va} + b_{va} \beta_{hva} \frac{I_h(\bar{\eta} + t - \tau_i - \tau_a)}{T_h(\bar{\eta} + t - \tau_i - \tau_a)} \right\} d\bar{\eta} \right) \\
 &\times b_{va} \beta_{hva} \frac{I_h(\eta + t - \tau_i - \tau_a)}{T_h(\eta + t - \tau_i - \tau_a)} d\eta.
 \end{aligned}$$

$$\begin{aligned}
E'_{vo}(t) &= -(\mu_{vo} + \gamma_{vo} + \delta_o)E_{vo}(t) + b_{vo}\beta_{hvo}S_{vo}(t)\frac{I_h(t)}{T_h(t)} \\
&+ \frac{T_v(t - \tau_i - \tau_a)}{T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)}b(T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a))e^{-\mu_i\tau_i} \\
&\times \int_{\tau_i}^{\tau_i+\tau_a} e^{-(\mu_{va}+\gamma_{va})(\tau_i+\tau_a-\eta)} \exp\left(-\int_{\tau_i}^{\eta} \left\{ \mu_{va} + b_{va}\beta_{hva}\frac{I_h(\bar{\eta} + t - \tau_i - \tau_a)}{T_h(\bar{\eta} + t - \tau_i - \tau_a)} \right\} d\bar{\eta}\right) \\
&\quad \times b_{va}\beta_{hva}\frac{I_h(\eta + t - \tau_i - \tau_a)}{T_h(\eta + t - \tau_i - \tau_a)} d\eta.
\end{aligned}$$

$$\begin{aligned}
I'_{va}(t) &= \gamma_{va}E_{va}(t) - \mu_{va}I_{va}(t) \\
&- \frac{T_v(t - \tau_i - \tau_a)}{T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)}b(T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a))e^{-\mu_i\tau_i} \\
&\times \gamma_{va} \int_{\tau_i}^{\tau_i+\tau_a} e^{-\mu_{va}(\tau_i+\tau_a-\eta)} \left[\int_{\tau_i}^{\eta} e^{-(\mu_{va}+\gamma_{va})(\eta-\psi)} b_{va}\beta_{hva}\frac{I_h(\psi + t - \tau_i - \tau_a)}{T_h(\psi + t - \tau_i - \tau_a)} \right. \\
&\quad \left. \times \exp\left(-\int_{\tau_i}^{\psi} \left\{ \mu_{va} + b_{va}\beta_{hva}\frac{I_h(\bar{\eta} + t - \tau_i - \tau_a)}{T_h(\bar{\eta} + t - \tau_i - \tau_a)} \right\} d\bar{\eta}\right) d\psi \right] d\eta.
\end{aligned}$$

$$\begin{aligned}
I'_{vo}(t) &= \gamma_{vo}E_{vo}(t) - (\mu_{vo} + \delta_o)I_{vo}(t) \\
&+ \frac{T_v(t - \tau_i - \tau_a)}{T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a)}b(T_v(t - \tau_i - \tau_a) + T_r(t - \tau_i - \tau_a))e^{-\mu_i\tau_i} \\
&\times \gamma_{va} \int_{\tau_i}^{\tau_i+\tau_a} e^{-\mu_{va}(\tau_i+\tau_a-\eta)} \left[\int_{\tau_i}^{\eta} e^{-(\mu_{va}+\gamma_{va})(\eta-\psi)} b_{va}\beta_{hva}\frac{I_h(\psi + t - \tau_i - \tau_a)}{T_h(\psi + t - \tau_i - \tau_a)} \right. \\
&\quad \left. \times \exp\left(-\int_{\tau_i}^{\psi} \left\{ \mu_{va} + b_{va}\beta_{hva}\frac{I_h(\bar{\eta} + t - \tau_i - \tau_a)}{T_h(\bar{\eta} + t - \tau_i - \tau_a)} \right\} d\bar{\eta}\right) d\psi \right] d\eta.
\end{aligned}$$

(plus 6 similar equations for resistant mosquitoes, and 3 for susceptible, exposed and infectious humans. So 15 equations in all).

Theorem 4 (Linear stability, LLA insecticide with malaria) *If*

$$\begin{aligned} & \frac{(\mu_h + \zeta)(\mu_h + \gamma_h)\mu_{ra}\mu_{ro}}{\gamma_h} > \frac{S_{ra}^* \gamma_{ra} \mu_{ro} b_{ra}^2 \beta_{hra} \beta_{rah}}{S_h^* (\mu_{ra} + \gamma_{ra})} \\ & + \frac{S_{ro}^*}{S_h^*} \left\{ \mu_{ro} b_{ra} \beta_{hra} \tau_a (1 - g(\gamma_{ra} \tau_a)) [\mu_{ra} b_{ro} \beta_{roh} - \mu_{ro} b_{ra} \beta_{rah}] \right. \\ & \left. + \frac{\gamma_{ro} \mu_{ra} b_{ro} \beta_{roh}}{\mu_{ro} + \gamma_{ro}} [b_{ro} \beta_{hro} + \mu_{ro} b_{ra} \beta_{hra} \tau_a g(\gamma_{ra} \tau_a)] - \frac{\gamma_{ra} \mu_{ro}^2 b_{ra}^2 \beta_{hra} \beta_{rah}}{\mu_{ra} + \gamma_{ra}} \tau_a g(\gamma_{ra} \tau_a) \right\} \end{aligned}$$

where $g(x) = (1 - e^{-x})/x$, then the malaria-free equilibrium in which $S_{ra}^* > 0$, $S_{ro}^* > 0$ and $S_h^* > 0$, and all other variables are zero, is locally asymptotically stable.

Malaria Disease Dynamics and Mosquito Larviciding

- Larviciding means killing mosquito larvae using larvicides.
- Mosquitoes can become resistant to larvicides. In fact since larvicides kill larvae before they mature, selection pressure favouring resistance is strong.
- However, resistance to mosquito larvicides may actually benefit malaria control.
- Idea: exploit the evolutionary costs of resistance to larvicides, which are:
 - reduced adult longevity for resistant mutants
 - malaria parasites may develop more slowly in resistant mutants
 - biting rate may be lower in resistant mutants

Larviciding without malaria

$$\begin{aligned}
 V'(t) &= -\mu_v V(t) + e^{-(\mu_i + \delta)\tau_i} \frac{V(t - \tau_i)}{M(t - \tau_i)} B_m(M(t - \tau_i)), \\
 R'(t) &= -\mu_r R(t) + e^{-\mu_i \tau_i} \frac{R(t - \tau_i)}{M(t - \tau_i)} B_m(M(t - \tau_i)).
 \end{aligned}$$

- Usually assume $\mu_r > \mu_v$ (because resistant live less long as adults)
- a coexistence equilibrium (one with $V^* > 0$ and $R^* > 0$) cannot exist generically
- two boundary equilibria $(V, R) = (0, R^*)$ and $(V^*, 0)$
- particularly interested in the equilibrium $(V, R) = (0, R^*)$, because we want the mosquito population to acquire resistance to the larvicide, so that we can exploit the costs of this.

Theorem 5 *Suppose an equilibrium $(V, R) = (0, R^*)$ exists and $\delta > 0$, and that*

$$\mu_v < \mu_r < \mu_v e^{\delta \tau_i} \tag{1}$$

and

$$-\mu_r \leq e^{-\mu_i \tau_i} B'_m(R^*) < \mu_r. \tag{2}$$

Then $(V, R) = (0, R^)$ is locally asymptotically stable.*

- (1) will hold if δ is large enough (i.e. larvicide needs to have a minimum strength if the resistant strain is to win). Otherwise, vulnerables could win due to their increased longevity as adults.
- Can prove a theorem like Theorem 5 relating to the equilibrium $(V^*, 0)$. Stability conditions include the requirement that $\mu_r > \mu_v e^{\delta \tau_i}$, which holds if δ is sufficiently small (i.e. the larvicide is weak), since we always assume $\mu_r > \mu_v$.

Larviciding with malaria

- *Vulnerable* means vulnerable to *insecticide*. *Susceptible* means susceptible to *malaria*.
- V_s, V_e and V_i : susceptible, exposed and infectious vulnerable adult mosquitoes
- R_s, R_e and R_i : susceptible, exposed and infectious resistant adult mosquitoes
- H_s, H_e and H_i : susceptible, exposed and infectious humans.
- $V(t) = V_s(t) + V_e(t) + V_i(t)$, $R(t) = R_s(t) + R_e(t) + R_i(t)$
- No transovarial transmission (vertical transmission) of malaria in mosquito, so newborn insects are susceptible (and remain so throughout larval development).

For vulnerable adult mosquitoes (i.e. vulnerable to insecticide as larvae)

$$V'_s(t) = \frac{V(t - \tau_i)}{V(t - \tau_i) + R(t - \tau_i)} B_m (V(t - \tau_i) + R(t - \tau_i)) e^{-(\mu_i + \delta)\tau_i} - \mu_v V_s(t) - \frac{b_v \beta_{hv} V_s(t) H_i(t)}{H_s(t) + H_e(t) + H_i(t)}$$

b_v is the biting rate for vulnerable mosquitoes

$$V_e(t) = \int_{t-l_v}^t \frac{b_v \beta_{hv} V_s(\xi) H_i(\xi)}{H_s(\xi) + H_e(\xi) + H_i(\xi)} e^{-\mu_v(t-\xi)} d\xi$$

l_v is the latency period of the parasite in vulnerable mosquitoes

$$V'_e(t) = -\mu_v V_e(t) + \frac{b_v \beta_{hv} V_s(t) H_i(t)}{H_s(t) + H_e(t) + H_i(t)} - \frac{e^{-\mu_v l_v} b_v \beta_{hv} V_s(t - l_v) H_i(t - l_v)}{H_s(t - l_v) + H_e(t - l_v) + H_i(t - l_v)}$$

$$V_i'(t) = \frac{e^{-\mu_v l_v} b_v \beta_{hv} V_s(t - l_v) H_i(t - l_v)}{H_s(t - l_v) + H_e(t - l_v) + H_i(t - l_v)} - \mu_v V_i(t)$$

For resistant adult mosquitoes (i.e. resistant to insecticide as larvae)

$$R_s'(t) = \frac{R(t - \tau_i)}{V(t - \tau_i) + R(t - \tau_i)} B_m (V(t - \tau_i) + R(t - \tau_i)) e^{-\mu_i \tau_i} - \mu_r R_s(t) - \frac{b_r \beta_{hr} R_s(t) H_i(t)}{H_s(t) + H_e(t) + H_i(t)}$$

b_r is the biting rate for resistant mosquitoes

$$R_e(t) = \int_{t-l_r}^t \frac{b_r \beta_{hr} R_s(\xi) H_i(\xi)}{H_s(\xi) + H_e(\xi) + H_i(\xi)} e^{-\mu_r(t-\xi)} d\xi$$

where l_r is the latency period of the parasite in resistant mosquitoes,

$$R_e'(t) = -\mu_r R_e(t) + \frac{b_r \beta_{hr} R_s(t) H_i(t)}{H_s(t) + H_e(t) + H_i(t)} - \frac{e^{-\mu_r l_r} b_r \beta_{hr} R_s(t - l_r) H_i(t - l_r)}{H_s(t - l_r) + H_e(t - l_r) + H_i(t - l_r)}$$

$$R_i'(t) = \frac{e^{-\mu_r l_r} b_r \beta_{hr} R_s(t - l_r) H_i(t - l_r)}{H_s(t - l_r) + H_e(t - l_r) + H_i(t - l_r)} - \mu_r R_i(t)$$

For humans

$$H_s'(t) = B_h (H_s(t) + H_e(t) + H_i(t)) - \mu_h H_s(t) - \frac{b_v \beta_{vh} H_s(t) V_i(t)}{H_s(t) + H_e(t) + H_i(t)} - \frac{b_r \beta_{rh} H_s(t) R_i(t)}{H_s(t) + H_e(t) + H_i(t)}$$

$$H_e(t) = \int_{t-l_h}^t \left[\frac{b_v \beta_{vh} H_s(\xi) V_i(\xi)}{H_s(\xi) + H_e(\xi) + H_i(\xi)} + \frac{b_r \beta_{rh} H_s(\xi) R_i(\xi)}{H_s(\xi) + H_e(\xi) + H_i(\xi)} \right] e^{-\mu_h(t-\xi)} d\xi$$

l_h is the latency period for malaria in a human

$$H'_e(t) = -\mu_h H_e(t) + \frac{[b_v \beta_{vh} V_i(t) + b_r \beta_{rh} R_i(t)] H_s(t)}{H_s(t) + H_e(t) + H_i(t)} - \frac{e^{-\mu_h l_h} [b_v \beta_{vh} V_i(t - l_h) + b_r \beta_{rh} R_i(t - l_h)] H_s(t - l_h)}{H_s(t - l_h) + H_e(t - l_h) + H_i(t - l_h)}$$

$$H'_i(t) = -(\mu_h + \zeta) H_i(t) + \frac{e^{-\mu_h l_h} [b_v \beta_{vh} V_i(t - l_h) + b_r \beta_{rh} R_i(t - l_h)] H_s(t - l_h)}{H_s(t - l_h) + H_e(t - l_h) + H_i(t - l_h)}$$

ζ is the per-capita human mortality due to malaria,

Theorem 6 *Suppose that $\delta > 0$ and the hypotheses of Theorem 5 hold (with R_s^* in place of R^*) together with*

$$B'_h(H_s^*) < \mu_h$$

and

$$\mu_r(\mu_h + \zeta) > \frac{b_r^2 \beta_{hr} \beta_{rh} R_s^* e^{-\mu_r l_r} e^{-\mu_h l_h}}{H_s^*}.$$

Then the malaria-free equilibrium in which $(V_s, R_s, H_s) = (0, R_s^, H_s^*)$, and the other components are all zero, is locally asymptotically stable.*

Basic reproduction number

$$R_0 = \frac{b_r^2 \beta_{hr} \beta_{rh} e^{-\mu_r l_r} e^{-\mu_h l_h} R_s^*}{\mu_r(\mu_h + \zeta) H_s^*}$$

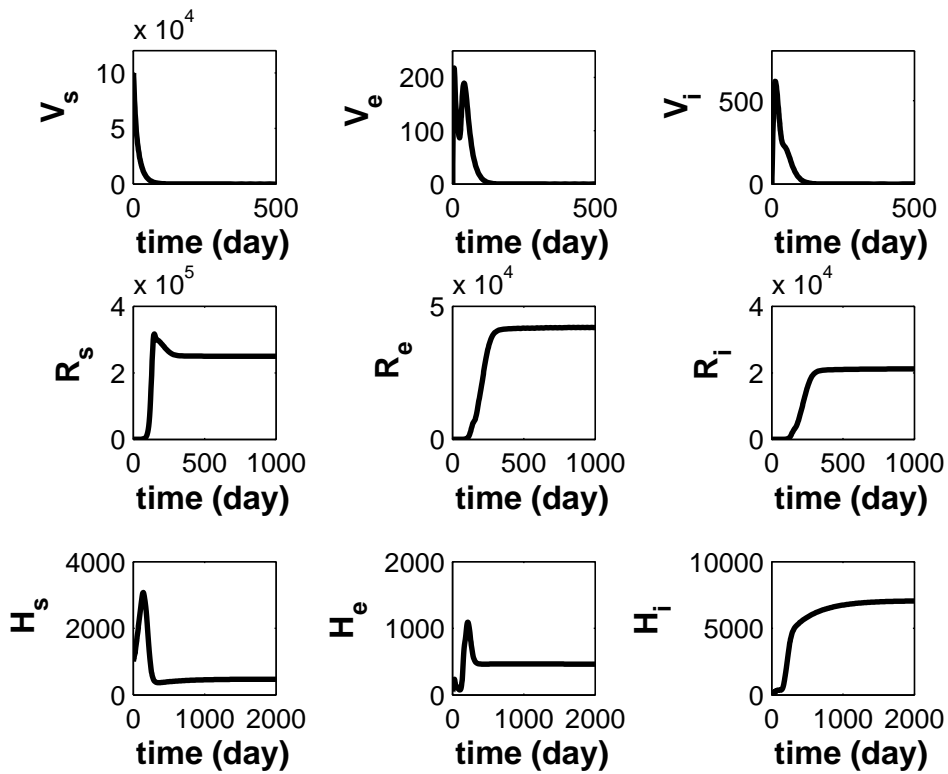


Figure 3: Situation where mosquitoes pay a low cost for acquiring resistance to larvicide. Malaria remains endemic and resistant mosquito strain dominates.

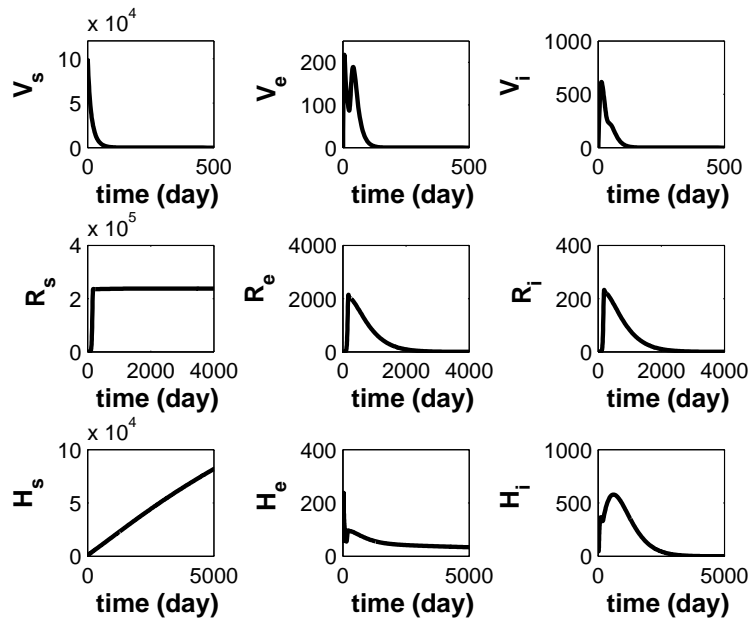


Figure 4: Greatly increased costs of resistance. Malaria has been eradicated.

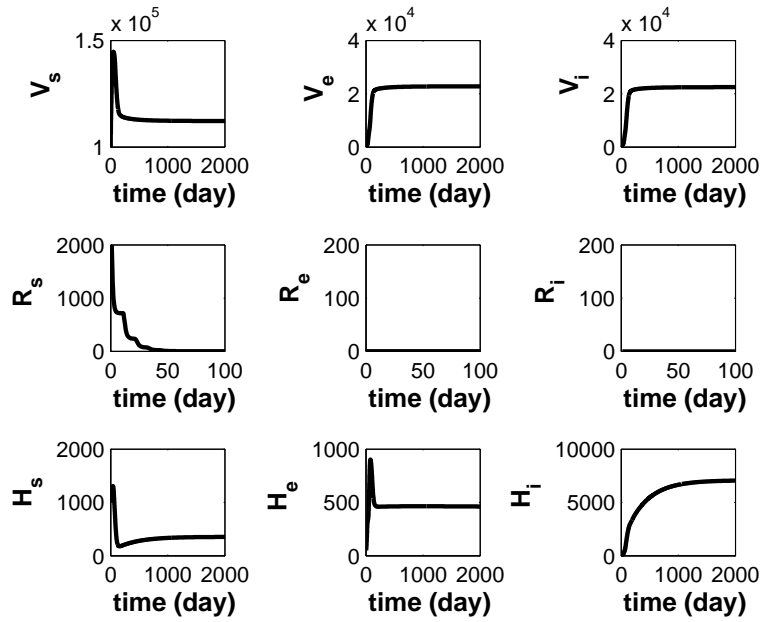


Figure 5: Costs of resistance are so high that the larvicide-resistant strain is driven to extinction. As a result the vulnerable strain dominates and malaria is once again endemic.

Concluding remarks

- Larviciding has not always been popular. Simple models suggest that its effect is a simple linear decrease in the number of adult mosquitoes ...
- ... but costs of resistance to larvicides imply the effect is not so simple.
- R_0 expressions from Ross-Macdonald type models have suggested that it is better to target adult mosquitoes and aim to reduce the biting rate or adult longevity. This has led to an emphasis on adult control ...
- ... but in reality adults are more mobile than larvae and can avoid intervention measures like bed nets.
- The analysis of our model is most sensitive to μ_r (per-capita death rate of adult resistant mosquitoes). Increasing this parameter dramatically reduces R_0 ...
- ... but increasing μ_r too much causes the wild type to outcompete the resistant mutants and the control strategy fails.
- Exploitation of costs of resistance to larvicides thus offers a possible malaria control measure if the larvicide is sufficiently potent and costs of resistance are neither too great nor too small.