

Resistance to larvicides in mosquito populations and how it could benefit malaria control

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joint work with

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Mosquito insecticides

- Effects of insecticide use on mosquito evolution, insecticide resistance, implications of costs of resistance — hot topics in mosquito control.
- Insecticides such as DDT are cheap and effective in short term, but mosquitoes quickly become resistant in areas of intensive use.
- 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.
- Mosquitoes tend to develop resistance to both adulticides and larvicides. Resistance comes at a cost. Is there a way we can exploit this?

Simple Insecticide-Resistance 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) *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 $[-\tau_i, 0]$.

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

$$V'(t) = -\mu_v V(t) + e^{-(\mu_i + \delta)\tau_i} \frac{V(t - \tau_i)}{M(t - \tau_i)} B_m(M(t - \tau_i)),$$

$$R'(t) = -\mu_r R(t) + e^{-\mu_i \tau_i} \frac{R(t - \tau_i)}{M(t - \tau_i)} B_m(M(t - \tau_i)).$$

- 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 2 *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 2 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 3 Suppose that $\delta > 0$ and the hypotheses of Theorem 2 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

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

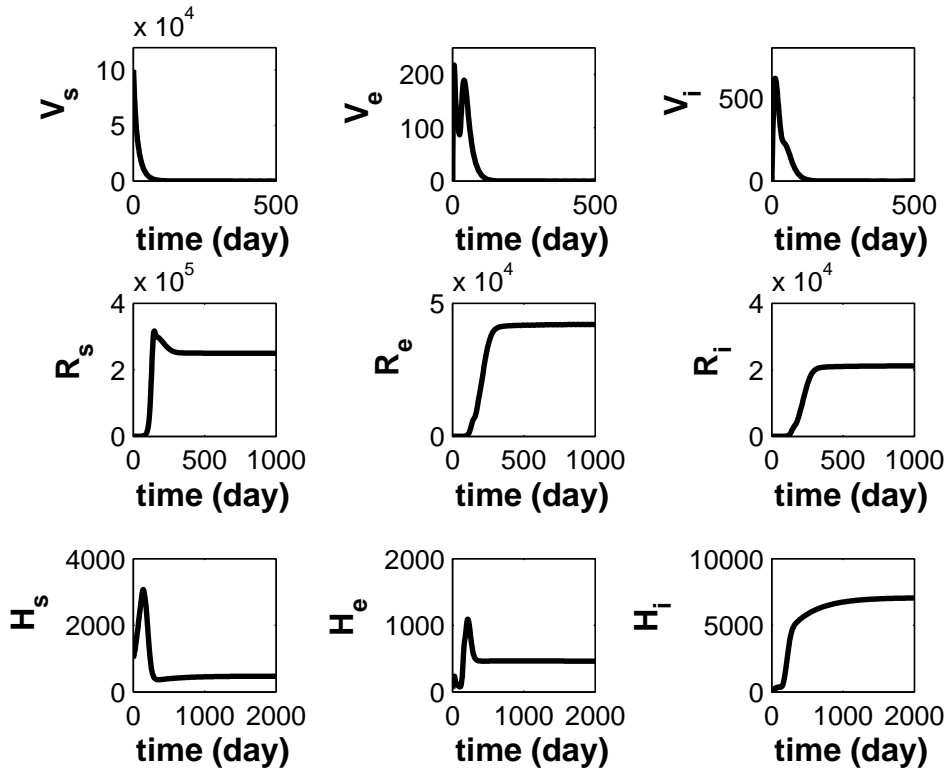


Figure 1: Situation where mosquitoes pay a low cost for acquiring resistance to larvicide. Malaria remains endemic and resistant mosquito strain dominates.

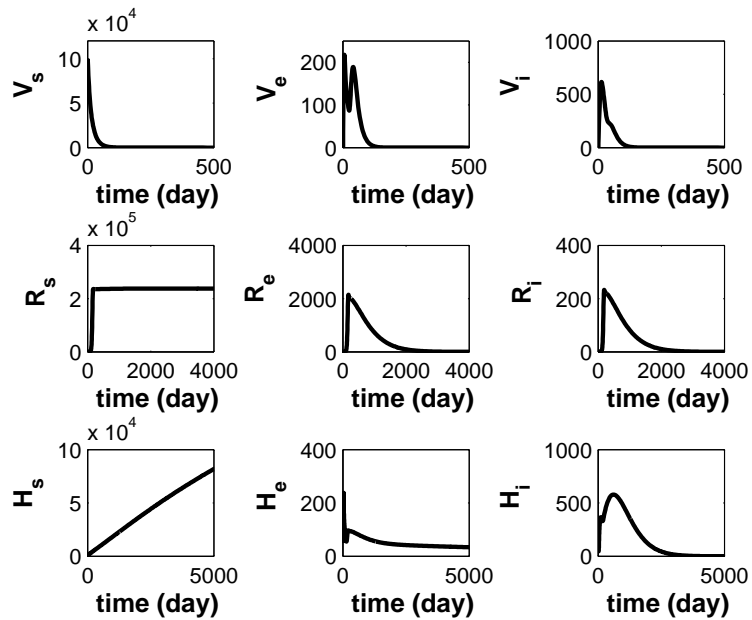


Figure 2: Greatly increased costs of resistance. Malaria has been eradicated.

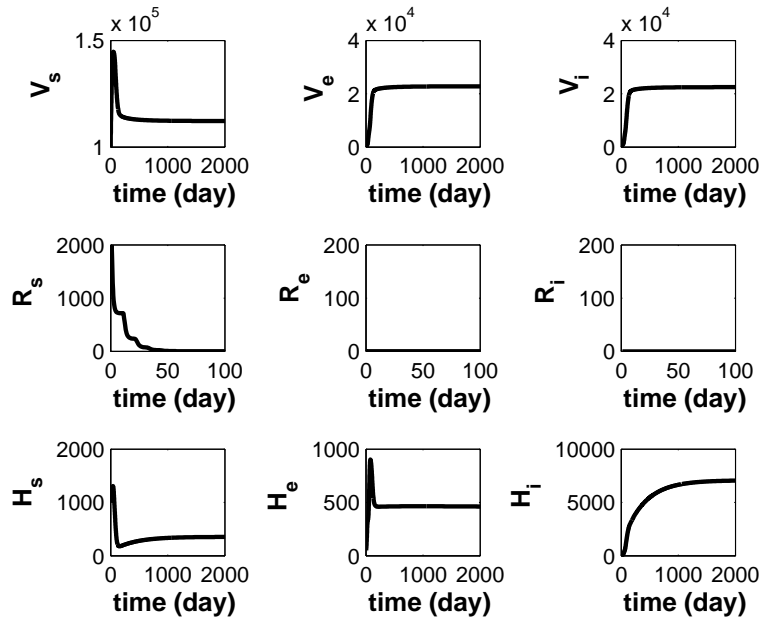


Figure 3: Costs of resistance are so high that the larvicide-resistant strain is driven to extinction. As a result the vulnerable strain dominates and malaria is once again endemic.

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.