

Modelling Bluetongue and Malaria

Bluetongue

- Bluetongue is a viral infection of ruminants, including cattle and sheep, spread by midges of the *Culicoides* family.
- bluetongue has long been present in most tropical and sub-tropical countries, but since 1999 has expanded northwards across Europe
- vector-borne disease (midges as vectors, cattle and sheep as hosts).
- linear stability analysis leads to identification of a threshold that determines if the disease introduced at a low level dies out or persists.
- effects of seasonality are important - midges are not active all year round. This complicates the mathematics (Hayley O'Farrell's PhD).

- Bluetongue generally does not cause death in cattle, so assume the total number of cattle is a constant N_c
- Bluetongue does cause death in sheep, but mild cases usually recover rapidly and completely
- Assume that only susceptible sheep have viable offspring, since bluetongue virus tends to cause abortion and congenital anomalies in sheep
- Incubation period for sheep is around 4 to 6 days. For simplest model, include only the longer incubation time for midges (often around 2 weeks, varying from 4 days at 30°C to 26 days at 15°C).
- $f(\xi) d\xi$ is the probability that the incubation period for midges lasts between ξ and $\xi + d\xi$ days. We have $\int_0^\infty f(\xi) d\xi = 1$.

$I_c(t)$ = infectious cattle at time t

$S_c(t)$ = susceptible cattle at time t ($I_c + S_c = N_c$ for simplest model)

$I_s(t)$ = infectious sheep at time t

$S_s(t)$ = susceptible sheep at time t

$S_m(t)$ = susceptible midges at time t

$E_m(t)$ = exposed midges at time t

$I_m(t)$ = infectious midges at time t

Simple bluetongue model

$$I'_c(t) = \frac{\beta_{mc}S_c(t)I_m(t)}{I_s(t) + S_s(t) + N_c} - \mu_c I_c(t),$$

$$S'_s(t) = b_s(S_s(t)) - \frac{\beta_{ms}S_s(t)I_m(t)}{I_s(t) + S_s(t) + N_c} + \gamma I_s(t) - \mu_s S_s(t),$$

$$I'_s(t) = \frac{\beta_{ms}S_s(t)I_m(t)}{I_s(t) + S_s(t) + N_c} - \gamma I_s(t) - \mu_{is} I_s(t),$$

$$S'_m(t) = e^{-\mu_l \tau} b_m(S_m(t - \tau)) - \mu_m S_m(t)$$

$$- \frac{\beta_{cm}S_m(t)I_c(t)}{I_s(t) + S_s(t) + N_c} - \frac{\beta_{sm}S_m(t)I_s(t)}{I_s(t) + S_s(t) + N_c},$$

$$E'_m(t) = -\mu_{em}E_m(t) + \frac{\beta_{cm}S_m(t)I_c(t)}{I_s(t) + S_s(t) + N_c} + \frac{\beta_{sm}S_m(t)I_s(t)}{I_s(t) + S_s(t) + N_c}$$

$$- \int_{-\infty}^t \left(\frac{\beta_{cm}S_m(\eta)I_c(\eta)}{I_s(\eta) + S_s(\eta) + N_c} + \frac{\beta_{sm}S_m(\eta)I_s(\eta)}{I_s(\eta) + S_s(\eta) + N_c} \right) e^{-\mu_{em}(t-\eta)} f(t - \eta) d\eta,$$

$$I'_m(t) = -\mu_{im}I_m(t)$$

$$+ \int_{-\infty}^t \left(\frac{\beta_{cm}S_m(\eta)I_c(\eta)}{I_s(\eta) + S_s(\eta) + N_c} + \frac{\beta_{sm}S_m(\eta)I_s(\eta)}{I_s(\eta) + S_s(\eta) + N_c} \right) e^{-\mu_{em}(t-\eta)} f(t - \eta) d\eta$$

Situation with no bluetongue disease

Without disease, there are N_c susceptible cattle and the numbers $S_s(t)$ and $S_m(t)$ of susceptible sheep and susceptible midges evolve according to

$$S'_s(t) = b_s(S_s(t)) - \mu_s S_s(t)$$

$$S'_m(t) = e^{-\mu_l \tau} b_m(S_m(t - \tau)) - \mu_m S_m(t)$$

Assume that, when disease is absent, numbers of susceptible sheep and midges evolve to constants as $t \rightarrow \infty$. These constants are S_s^0 and S_m^0 , satisfying

$$b_s(S_s^0) = \mu_s S_s^0, \quad e^{-\mu_l \tau} b_m(S_m^0) = \mu_m S_m^0.$$

If various conditions hold, including

$$\mu_m > e^{-\mu_l \tau} |b'_m(S_m^0)|$$

then this state is stable if no disease is introduced.

Linear stability of the bluetongue-free equilibrium

If

$$\frac{S_m^0}{(S_s^0 + N_c)^2} \{ \beta_{cm} \beta_{mc} N_c (\gamma + \mu_{is}) + \beta_{sm} \beta_{ms} S_s^0 \mu_c \} \int_0^\infty f(\eta) e^{-\mu_{em} \eta} d\eta$$
$$< \mu_c \mu_{im} (\gamma + \mu_{is})$$

then the bluetongue-free equilibrium $(I_c, S_s, I_s, S_m, E_m, I_m) = (0, S_s^0, 0, S_m^0, 0, 0)$ is locally asymptotically stable.

Persistence of solutions

Mathematicians concept of persistence: there exists (for midges) some constant $\eta > 0$, which is independent of the initial conditions, such that

$$\liminf_{t \rightarrow \infty} I_m(t) \geq \eta$$

If various technical conditions hold, and

$$\begin{aligned} & \frac{S_m^0}{(S_s^0 + N_c)^2} \left\{ \beta_{cm} \beta_{mc} N_c (\gamma + \mu_{is}) + \beta_{sm} \beta_{ms} S_s^0 \mu_c \right\} \int_0^\infty f(\eta) e^{-\mu_{em} \eta} d\eta \\ & > \mu_c \mu_{im} (\gamma + \mu_{is}) \end{aligned}$$

then bluetongue is uniformly strongly persistent in the sense that there exists $\eta > 0$ such that $\liminf_{t \rightarrow \infty} I_m(t) \geq \eta$ for all solutions. Moreover, for the same η ,

$$\liminf_{t \rightarrow \infty} I_c(t) \geq \frac{\eta \beta_{mc} N_c}{\mu_c (b_s^{\text{sup}} / \mu_s + N_c) + \eta \beta_{mc}}$$

Larviciding mosquito populations, resistance and implications for malaria control

- 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. But larvicide-resistant mutants may have shorter adult longevity, and this is good for malaria control.

Simple larvicide-resistance model

- Adult mosquitoes classed as V (vulnerable) or R (resistant) to larvicides.
- Larvicide-resistant strains may:
 - live less long as adults. This is good for malaria control.
 - have lower biting rates
 - malaria parasites may develop more slowly in them

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

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

where δ is the effect of the larvicide.

If an equilibrium $(V, R) = (0, R^*)$ exists and

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

and

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

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

Malaria Disease Dynamics and Mosquito Larviciding

- *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,

If (certain conditions hold) 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.

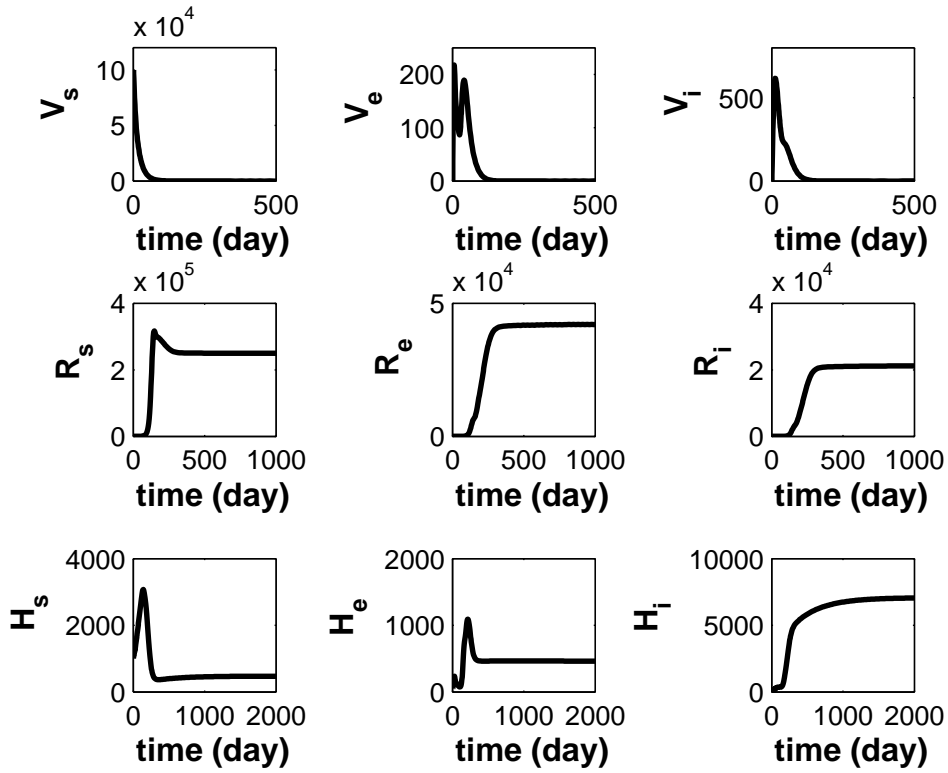


Figure 1: Situation where mosquitoes pay a low cost for acquiring resistance to larvicide. Malaria remains endemic and resistant mosquito strain dominates.

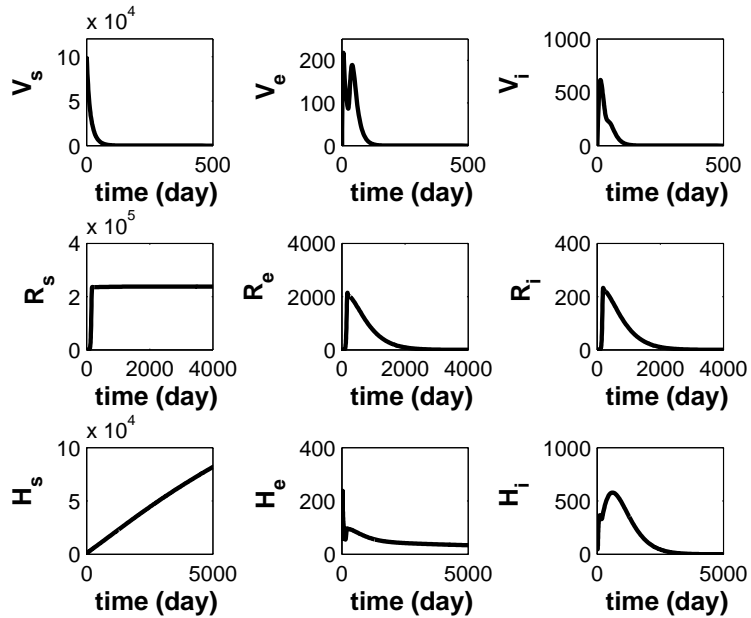


Figure 2: Greatly increased costs of resistance. Malaria has been eradicated.

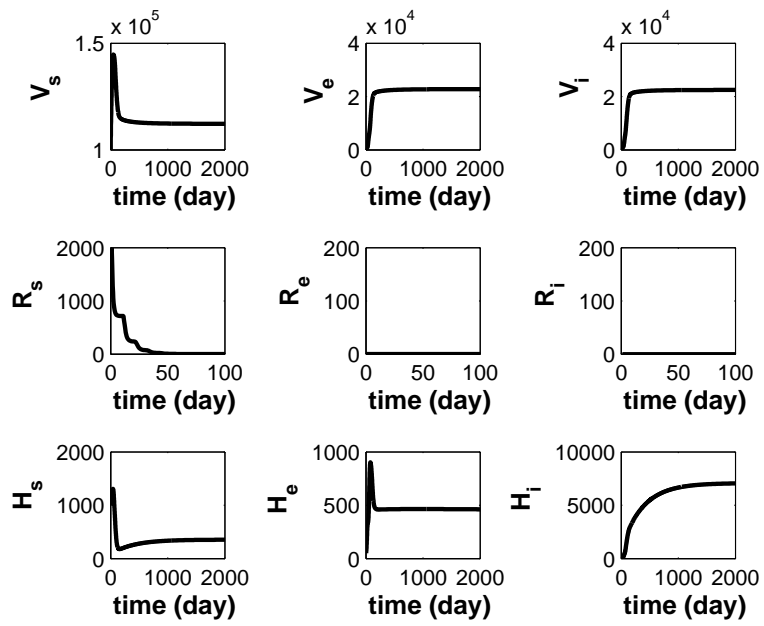


Figure 3: Costs of resistance are so high that the larvicide-resistant strain is driven to extinction. As a result the vulnerable strain dominates and malaria is once again endemic.