Attacking the mosquito on multiple fronts: Insights on integrated vector management from a mathematical model

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3 April 2016

1 Introduction

Here, we extend a previous-published elaborated feeding cycle model (REF) to incorporate interventions that target mosquitoes both indoors and outdoors and at all stages of the mosquito life cycle and feeding cycle.

2 Method

In this section, we present ordinary differential equation models describing the mosquito life & feeding cycles and interaction with its human & non-human hosts. We also present several interventions (i.e., Larvaciding, ATSB, swarm spraying, LLINs, IRS, house modification, and treating livestock with endectocides) that can affect various stages of mosquito life & feeding cycles.

2.1 Mosquito Life Cycle

We present the compartment model describing the interaction between human and malaria vectors. The classical SIR compartmental model (REF) divides a population of hosts into three classes: susceptible (S_h), infected (I_h), and recovered (R_h) humans and that of vectors into five classes: Early Instar (E), Late Instar (L), Pupal (P) stages, Susceptible, (S_v), Latent (L_v), and Infectious (I_v) vectors. The mosquito life and feeding cycles have been previously described in details (REF) as well as interactions with with human hosts (REF). In summary (see Fig 1), 1) each female mosquito lays β eggs on average per day that hatch into early instar E; 2) E may undergo a density-dependent daily mortality at a rate μ_E or progress into late instar larvae L after d_E days (or at a rate $r_E = 1/d_E$) ; 3) L may undergo density-dependent daily mortality at a rate μ_L or progress into pupal (P) stage after d_L days; 4) P may undergo independent mortality at a rate μ_P or progress into susceptible (S_v) vectors after d_P days.

The mosquito life cycle can thus be described by the following set of continuous ordinary differential equations (V is total number of vectors, K is the carrying capacity, and γ is a factor allowing for the differential effects of density-dependent mortality on late instar larvae compared to early instar larvae.):

$$\frac{d}{dt}(E) = \beta V - \mu_E \left[1 + \frac{(E+L)}{K}\right] E - r_E E \tag{1}$$

$$\frac{d}{dt}(L) = r_E E - \mu_L \left[1 + \gamma\frac{(E+L)}{K}\right] L - r_L L \tag{2}$$

$$\frac{d}{dt}(P) = r_L L - \mu_P P - r_P P \tag{3}$$

$$\frac{d}{dt}(V_s) = r_P P - r_{V_s} V_s - \mu_v V_s \tag{4}$$

Where, the environmental carrying-capacity (K) is calculated as follows; (REF):

$$K = \frac{2V_{eq}\mu_V d_L(1+\mu_P d_P)\gamma(\omega+1)}{\frac{\omega}{\mu_L d_E} - \frac{1}{\mu_L d_L} - 1} \tag{5}$$

and ω is given by (REF);

$$\omega = \frac{-\beta_\omega}{2} + \sqrt{\frac{\beta_\omega^2}{4} + \frac{\gamma\beta\mu_L d_E}{2\mu_E\mu_M d_L(1+\mu_P d_P)}}, \tag{6}$$

and β_ω is given by (REF),

$$\beta_\omega = \gamma\frac{\mu_L}{\mu_E} - \frac{d_L}{d_E} + (\gamma-1)\mu_L d_E. \tag{7}$$

2.2 Female Mosquito Feeding Cycle

The feeding cycle starts with female (assumed to be half of all adult mosquitoes (REF)) emerging mosquito searching for sugar and blood-meals. Equation (4) is extended to account for the proportion of bites (b_v) by which one female susceptible mosquito becomes infected (but not infectious) and moves to latent vector (V_L) stage after biting a proportion (H_i/H) of humans (H) that is infectious (H_i) at a rate a (i.e., $r_{V_s} = ab_vH_i/H$ same as force of infection in mosquitoes at equilibrium and $H_{i,eq} = H_i/H$ same as malaria prevalence in humans at equilibrium), thus,

$$\frac{d}{dt}(V_S) = 0.5r_P P - aQ_0 b_v H_{i,eq} V_S - \mu_v V_S. \tag{8}$$

Where, Q_0 is the proportion of blood-meals obtained from human by a mosquito in the absence of an intervention.

For the latent vectors, we need to capture the proportion of vectors becoming infective (assuming the latent period τ is fixed with constant mortality μ_v) by

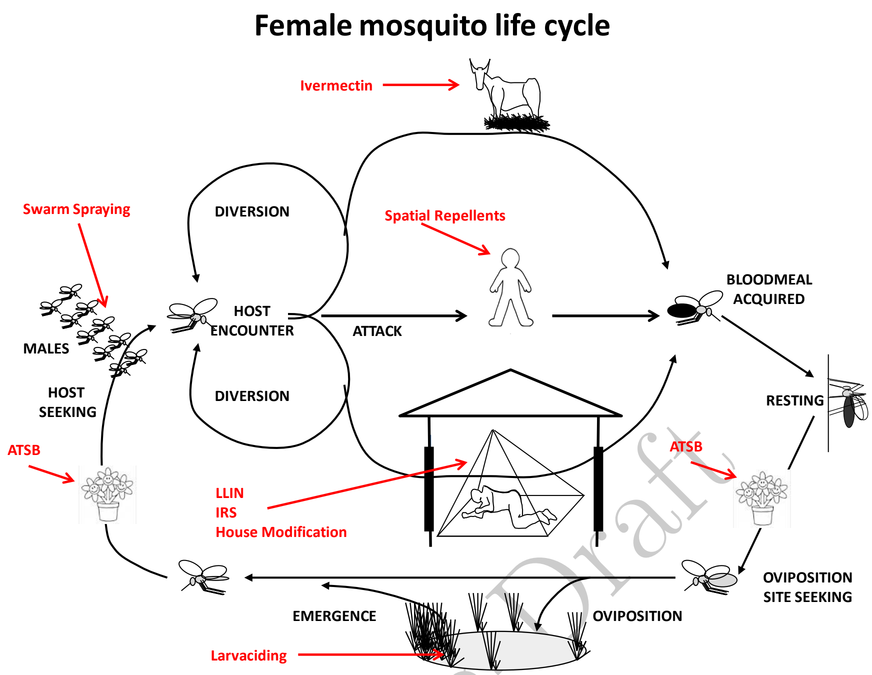

Figure 1: Elaborated Feeding Cycle.

A schematic illustration of potential interventions targeting mosquito life and feeding cycles

adjusting V_S by $(t-\tau)e^{-\mu_v \tau}$ and also the proportion of mosquitoes surviving the extrinsic incubation period after time t (i.e., adjusting $H_{i,eq}$ by t-τ), thus,

$$\frac{d}{dt}V_L(t) = aQ_0 b_v H_{i,eq} V_S - aQ_0 b_v \left[H_{i,eq}(t-\tau)\right] V_S(t-\tau)e^{-\mu_v \tau} - \mu_v V_L(t). \quad (9)$$

After completing the latent period τ, a vector becomes infectious (V_I), Thus,

$$\frac{d}{dt}V_I(t) = ab_v \left[H_{i,eq}(t-\tau)\right] V_S(t-\tau)e^{-\mu_v \tau} - \mu_v V_I(t). \quad (10)$$

The assumption is made such that mosquitoes undergo constant daily mortality rate μ_v at each of the three adult mosquito stages (REF).

2.3 The Impact of Vector Control Interventions

We now extend the model to incorporate interventions that target mosquitoes both indoors and outdoors and at all stages of the mosquito life cycle and feeding cycle. The mathematics of the model follows from the schematic shown in Figure (FIGURE 1), highlighting opportunities for vector control. Upon emergence from eggs, female mosquitoes mate and sugar feed, life processes which may be targeted by spraying of male swarms (REF) and ATSBs (REFs), respectively. The mosquito gonotrophic cycle then follows, in which female mosquitoes alternate between blood-feeding in order to support egg production and egg-laying. There are multiple options that female mosquitoes may pursue to obtain a blood meal - biting livestock (REF), which can be mitigated by treating livestock with endectocides or spraying with insecticides (REF); biting humans outdoors (REF), against which humans can protect themselves with spatial repellents (REF); and biting humans indoors (REF), for which LLINs (REF), IRS (REF) and housing modifications (REF) are protective. After taking a blood-meal, female mosquitoes then produce eggs and oviposit (lay eggs) in water; larviciding is thus an effective measure since it kills immature mosquitoes in aqueous habitats (REF).

All of these interventions can be modeled by the effects they have on diverting mosquitoes, which can increase the amount of time it takes for a mosquito to find a blood meal, and the effects they have on the mosquito death rate, which can reduce the mosquito population size. Another effect that can be modeled is the effect of these interventions on entomological inoculation rate (EIR) (i.e. the number of infectious mosquito bites per human per unit time) (REF), which is relevant for malaria transmission from both mosquito to human and from human to mosquito.

The parameters mosquito density (V), biting rate (a) and mosquito mortality rate (μ_v) are important in assessing the impact of vector control interventions.

2.4 Model Parameters Values

Symbol	Definition	Value (Literature)	Value (*from specific site)*
a	Human biting rate	0.01-0.5 day^{-1}	
b_h	Proportion of bites that produce infection in human	$0.2 - 0.5$	
b_v	Proportion of bites by which one susceptible mosquito becomes infected	0.5	
V_i	Infected vectors		
V_s	Susceptible vectors		
L_v	Latent vectors		
μ_v	Per capita rate of mosquito mortality	0.05- 0.5 day^{-1}	
τ	Latent period of mosquito	5 - 15 days	
C_{ITN}	Proportion coverage of ITN		
C	Vectorial capacity		
EIR	Entomological inoculation rate		

Table **1** Notations and associated values- place holder for now - to be completed

2.5 The Impact of interventions on mosquito population parameters

We first provide the equations describing the mosquito population parameters in absence of interventions:

The time to complete one feeding cycle

After emergence, a mosquito host-seeking process takes $\tau_1(0)$ days and survives this process with a probability $p_1 0$) in the absence of an intervention. Following a successfully fed, a mosquito rest, find larval habitat and oviposits during τ_1 days, surviving this process with a probability p_2. Thus, the average time to complete one feeding cycle, $f(0)$, in the absence of an intervention is given by the inverse of gonotrophic cycle as follows;

$$f(0) = \frac{1}{\tau_1(0) + \tau_2} \tag{11}$$

Probability of surviving one feeding cycle

Let μ_v represents the natural death rate of mosquito specie v, then, the probabilities of feeding p_1 and resting p_2 in the absence of an intervention is given by $p_1 = \exp^{-\mu_v t_1(0)}$ and $p_1 = \exp^{-\mu_v t_2}$ respectively. Thus, the probability $p(0)$ of surviving one feeding cycle in the absence of an intervention is given by:

$$p(0) = [p_1(0)p_2]_0^f \tag{12}$$

Number of Eggs per oviposition per mosquito

The number of eggs per oviposition per mosquito N_E in the absence of an intervention is given by

$$N_E = \beta \frac{\exp^{\frac{\mu_V}{f(0)-1}}}{\mu_V} \tag{13}$$

Where, β is the number of eggs laid per day by female mosquito and μ_V is the adult mosquito daily natural mortality

The Human blood index

The proportion of blood meals that are taken on human in the absence of an intervention is $(Q_{h,0})$ is given by

$$Q_{h,0} = \frac{Z_{h,0}}{Z_{h,0} + Z_c} = \frac{\epsilon_h p_{1,0} N_h}{\epsilon_h p_{1,0} N_h + \epsilon_c p_c N_c} \tag{14}$$

Where, $Z_{h,0}$ and Z_c are the availability of blood from human and cattle respectively, ϵ_h and ϵ_c are the rate at which individual vectors encounter human and cattle respectively, N_h and N_c are number of humans and cattle respectively, and p_c is the feeding probability upon cattle.

2.5.1 The impact of IRS, LLINs, and House Modification

The following assumptions will need to be relaxed/revisted 1) mosquito survives after successfully feeding in the presence of an intervention - The impact of mosquito dying after successful feeding/biting on human isn't considered at this time - this will have an impact on malaria transmission/EIR, 2) House modification is considered to contain treated eaves, etc, hence, having an ability to kill mosquito (as well as repelling them).

Probability of a mosquito being repelled from an ITN or IRS treated house or due to House Modification (HM)

Let $C_{ITN,t}$,$C_{IRS,t}$, $C_{HM,t}$ represent ITNs, IRS, and HM proportion coverage when in use respectively, then, proportion coverage from ITNs, IRS, and HM only is given by C_{ITN}, C_{IRS}, and C_{HM} respectively as follows:

$$\begin{aligned} C_{ITN} &= C_{ITN,t} - C_{ITN,t}C_{IRS,t} - C_{ITN,t}C_{HM,t} - C_{IRS,t}C_{HM,t}, \\ C_{IRS} &= C_{IRS,t} - C_{ITN,t}C_{IRS,t} - C_{IRS,t}C_{HM,t} - C_{ITN,t}C_{HM,t}, \\ C_{HM} &= C_{HM,t} - C_{HM,t}C_{ITN,t} - C_{HM,t}C_{IRS,t} - C_{ITN,t}C_{IRS,t}. \end{aligned} \tag{15}$$

Thus, the combined proportion coverage ($C_{ITN,IRS,HM}$) from the three interventions is given by

$$C_{ITN,IRS,HM} = C_{ITN,t}C_{IRS,t}C_{HM,t} \tag{16}$$

Thus, unprotected proportion (C_0) is given by;

$$\begin{aligned} C_0 = 1 - C_{ITN,t} - C_{IRS,t} - C_{HM,t} + \\ C_{ITN,t}C_{IRS,t} + C_{ITN,t}C_{HM,t} + C_{IRS,t}C_{HM,t} - C_{ITN,t}C_{IRS,t}C_{HM,t}. \end{aligned} \tag{17}$$

Now, let r_{ITN},r_{IRS}, and r_{HM} be a probability of mosquito repeating a feeding attempt due to ITNs, IRS, and HM respectively, then, a probability of repellency due to ITN, IRS and HM (insert a simple diagram to illustrate this scenario) is given by

$$r_c = r_{HM} + (1 - r_{HM})(r_{IRS} + (1 - r_{IRS})r_{ITN}). \tag{18}$$

If we let ϕ_b and ϕ_i be a proportion of mosquito bites on a person while they are in bed and indoors respectively, then, a probability of a mosquito being repelled from an ITN and IRS treated house is given by

$$\begin{aligned} p_r = Q_{h,0}C_{HM}\phi_b r_{HM} + (1 - Q_{h,0}C_{HM}(\phi_b + \phi_i)r_{HM})(Q_{h,0}C_{ITN}\phi_b r_{ITN} + \\ Q_{h,0}C_{IRS}\phi_i r_{IRS} + Q_{h,0}C_{ITN,IRS}(\phi_i - \phi_b)r_{IRS} + Q_{h,0}C_{ITN,IRS}\phi_b r_c) \end{aligned} \tag{19}$$

The time to complete one feeding cycle in the presence of ITN or IRS or HM

Given that a mosquito resets and begins a new search with probability p_r, then, the time to complete one feeding cycle in presence of ITNs or IRS or HM $f(\theta)$ is given by

$$f_\theta = \frac{1}{\frac{\tau_1(0)}{1-P_r} + \tau_2} \tag{20}$$

Probability of surviving one feeding cycle in the presence of ITN or IRS or HM

A mosquito successfully feeds by finding and feeding on a cattle or an unprotected human or a protected human. Thus, a probability of surviving one feeding cycle in presence of ITNs or IRS or HM is given by:

$$\begin{aligned} p_{f,\theta} = 1 - Q_{h,0} + Q_{h,0}C_0 + Q_{h,0}C_{HM}(\phi_b + \phi_i)S_{HM} + (1 - Q_{h,0}C_{HM}(\phi_b + \phi_i)S_{HM}) \\ (Q_{h,0}C_{ITN}(1 - \phi_b + \phi_b S_{ITN}) + Q_{h,0}C_{IRS}(1 - \phi_i + \phi_i S_{IRS}) + \\ Q_{h,0}C_{ITN,IRS}((\phi_i - \phi_b)S_{IRS} + 1 - \phi_i + \phi_b S_{ITN,IRS})) \end{aligned} \tag{21}$$

Where, S_{ITN}, S_{IRS}, and S_{HM} is the probability of mosquito feeding and surviving in presence of ITNs, IRS, and HM respectively.

Computing female mosquito death rate in presence of ITN or IRS treated house or HM

The probability of surviving feeding period, $p_{1,\theta}$, (p_2 is unchanged) in presence of an intervention is given by

$$p_{1,\theta} = \frac{p_1 p_{f,\theta}}{1 - p_r p_{f,\theta}} \tag{22}$$

So, probability of surviving one feeding cycle in presence of ITN, IRS, and HM is

$$p_\theta = p_{1,\theta} p_2^{(f_\theta)} \tag{23}$$

Mosquito death rate due to an intervention can be computed as follows (Sam remember to add mosq density using lambda);

$$\mu_{V,\theta} = -log(p_\theta) \tag{24}$$

Calculating the number of eggs laid per day per a female mosquito in the presence of interventions The number of eggs per oviposition per mosquito ($N_(E,\theta)$) in the presence of ITN, IRS, and HM is given by;

$$N_(E,\theta) = \beta \frac{e^{\frac{\mu_{V,\theta}}{f_\theta}} - 1}{\mu_{V,\theta}}. \tag{25}$$

Therefore, the number of eggs laid per day per female mosquito in presence of these interventions is given by;

$$\beta_\theta = \frac{N_{E,\theta}\mu_{V,\theta}}{e^{\frac{\mu_{V,\theta}}{f_\theta}} - 1}. \tag{26}$$

Proportion of blood meals obtained from human in the presence of an intervention

The human blood index is the proportion of all blood meals obtained from both protected and unprotected humans, thus,

$$Q_{h,\theta} = \frac{Z_{h,\theta} + Z_{h,0}}{Z_{h,\theta} + Z_{h,0} + Z_c} = \frac{\epsilon_h p_{1,\theta} N_h + \epsilon_h p_{1,0} N_h}{\epsilon_h p_{1,\theta} N_h + \epsilon_h p_{1,0} N_h + \epsilon_c p_c N_c} \tag{27}$$

Where, $Z_{h,\theta}$ is the availability of blood from protected humans.

2.5.2 Incorporating endocticides-treated cattle into the model

Several experiments have indicated that endocticides-treated cattle can reduce malaria transmission in humans (REFs). We explore the impact of ivermectin-treated cattle in increasing mosquito mortality rate associated with ivermectin contact during blood-feeding from cattle in areas where 1) LLINs only and 2) LLINs and IRS 3) LLINs, IRS, HM are already in use.

Given that a mosquito successfully feeds by finding a non-human host or by finding a protected or unprotected humans, we can then modify Equation 21 to incorporate the impact of endocticide-treated cattle (e.g., ivermectin)as follows:

$$\begin{aligned} p_{f,\theta} = &(1 - Q_{h,0})(1 - C_c S_c) + Q_{h,0}C_0 + Q_{h,0}C_{HM}(\phi_b + \phi_i)S_{HM} \\ &+ [1 - Q_{h,0}C_{HM}(\phi_b + \phi_i)S_{HM}][Q_{h,0}C_{ITN}(1 - \phi_b + \phi_b S_{ITN}) \\ &+ Q_{h,0}C_{IRS}(1 - \phi_i + \phi_i S_{IRS}) + Q_{h,0}C_{ITN,IRS}((\phi_i - \phi_b)S_{IRS} \\ &+ 1 - \phi_i + \phi_b S_{ITN,IRS})] \end{aligned} \tag{28}$$

Where, C_c is the proportion coverage of ivermectin-treated cattle and S_c is the probability of mosquito feeding on ivermectin-treated cattle and surviving. Therefore, by substituting Equation 28 into Equation 22, then updated Equations 22 into Equation 23 and updated Equation 23 into 24, then the updated mosquito death $\mu_{V,\theta}$ is computed by incorporating the impact of ivermectin-treated cattle.

Similarly, the impact of ivermectin-treated cattle on the number of eggs laid per mosquito per oviposition and per day can be computed by replacing $\mu_{V,\theta}$ with the updated $\mu_{V,\theta}$ into Equation 25 and Equation 26 respectively.

2.5.3 Incorporating spatial repellents into the model

Note: I need to re-work the ability for spatial repellents to repel mosquito either to protected humans and/or to non-human host.

We can incorporate the impact of spatial repellents by targeting the proportion of humans ($Q_{h,0}C_0$) that is not protected by LLINs, IRS, or HM. Thus, Equation 28 can be modified to incorporate the impact of spatial repellents in preventing mosquito bites as follows;

$$\begin{aligned} p_{f,\theta} = &(1 - Q_{h,0})(1 - C_c S_c) + Q_{h,0}C_0(1 - C_{SR}S_{SR}) + Q_{h,0}C_{HM}(\phi_b + \phi_i)S_{HM} \\ &+ [1 - Q_{h,0}C_{HM}(\phi_b + \phi_i)S_{HM}][Q_{h,0}C_{ITN}(1 - \phi_b + \phi_b S_{ITN}) \\ &+ Q_{h,0}C_{IRS}(1 - \phi_i + \phi_i S_{IRS}) + Q_{h,0}C_{ITN,IRS}((\phi_i - \phi_b)S_{IRS} \\ &+ 1 - \phi_i + \phi_b S_{ITN,IRS})] \end{aligned} \tag{29}$$

Where, C_{SR} is the proportion coverage of an area by spatial repellents and S_{SR} is the probability of mosquito feeding in presence of spatial repellents.

Again, by substituting Equation 29 into Equation 22, then updated Equation 22 into Equation 23 and updated Equation 23 into 24, then the updated mosquito death $\mu_{V,\theta}$ is computed by incorporating the impact of spatial repellents.

Similarly, the impact of spatial repellents on the number of eggs laid per mosquito per oviposition and per day can be computed by replacing $\mu_{V,\theta}$ with the updated $\mu_{V,\theta}$ into Equation 25 and Equation 26 respectively.

2.5.4 Incorporating Larvaciding into the model

I'll include existing equations/explanations

2.5.5 Incorporating ATSB into the model

I'll include existing equations/explanations

2.5.6 Incorporating swarm spraying into IVM model

I'll work with Sean to add this intervention. Initial thinking is to consider the 1) impact of number of eggs laid as a result of this intervention, 2) reduction in number of female mosquito searching for host N_v, 3)etc

2.5.7 Model simulations and Data

3 Model Results

The impact of these interventions in reducing mosquito density and EIR will be assessed against three primary malaria vectors. In addition, a plot against Qh,0 will be provided to help map various mosquito species

4 Discussion