MODELLING A NOVEL METHOD TO CONTROL HUMAN MALARIA: INSECTICIDE TREATED LIVESTOCK

Ana Franco*

Los Alamos National Laboratory

Centre for Nonlinear Studies

Los Alamos, NM 87545, U.S.A

August 2003

Abstract

Malaria, a re-emergent vector-borne disease, has always had a deep impact on the health and economy of a large percentage of the world population. In areas where malaria vectors also feed on animals, the presence of livestock impacts the risk of disease transmission to humans. Treatment of livestock, with insecticides that are fatal to the vector, has been proposed as a novel approach in malaria control. Promising results have been observed from trials in Pakistan. However, several factors underlying the effectiveness of insecticide treated livestock remain poorly understood. This study looks at the relevance of some of these factors including coverage treatment levels and vector preference. We expand on the Ross-Macdonald framework through the incorporation of vector feeding behaviours. The main focus of this research is to understand the circumstances under which a policy that involves the systematic use of insecticides on livestock will decrease the prevalence of human malaria.

1. INTRODUCTION

According to the World Health Organization (WHO), at least 300 million new cases of clinical malaria are reported every year, causing more than 1 million deaths (one death every 30 seconds). Over 40% of the world's population lives in areas where malaria is transmitted (e.g. parts of Africa, Asia, Middle East, Central and South America, Hispaniola, and Oceania). Human malaria is caused by infection with one or more of four species of the *Plasmodium* parasite: *P. falciparum* (tropics), *P. vivax* (tropical and

* Disease Control and Vector Biology Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1 7HT, UK. Ana.Franco@lshtm.ac.uk

temperate zones), *P. ovale*, and *P. malariae*). The first two are the main causes of disease, with most deaths being due to infection with *P. falciparum*. Animals can also contract malaria, but animal malaria cannot spread to humans, nor can human malaria spread to animals. The rare exceptions occur with *P. malariae,* which may also infect the higher primates (chimpanzes) and with simian malaria, which can be transmitted to humans. The life cycle of the malaria parasite involves both a vertebrate host and an insect vector. The parasite is transmitted to humans by the bite of a blood feeding female mosquito of the genus *Anopheles,* infected with sporozoites. Only female mosquitoes are involved in transmission, as the males do not feed on blood. Following infection of the human host, the parasite undergoes two multiplication phases. After multiplying in the liver, *Plasmodium* spp. invades the red blood cells, where it develops into gametocytes (gametogony) which are the infective form for the mosquito. Within the mosquito, the parasite must also go through a developmental phase (sporogony), taking around 10 - 14 days before sporozoites are formed and the mosquito becomes infectious to other human.

The traditional malaria control and prevention measures include case management, with antimalarial drugs, and vector control. Different strategies have been used to control the anopheline population, such as: use of insecticide treated personal protection materials (e.g. bednets), spraying houses with residual insecticides, larviciding and environmental management (to reduce the mosquito breeding sites). At the present, the majority of malaria cases occur in developing countries: i.e. regions where people can less afford to pay for prevention, and treatment of disease (at least 90% of deaths from malaria occur in sub-Saharan Africa). Consequently, one of the major challenges faced is the demand for alternative and sustainable prevention strategies. This is one of the priorities for health research recently established by the WHO.

There are 60 species of Anopheline mosquito involved in malaria transmission (amongst these, 30 species are of major importance) [1]. More importantly, distinct behaviours can be exhibited both between and within anopheline species. Namely, in terms of host feeding preference: some mosquitoes prefer to blood-feed on humans, (the so called antropophily), while others feed preferentially on non-human hosts, such as livestock (zoophily). Mosquitoes can also show preference for the place where the blood meal is taken: the vector can be classified as endophagic - i.e. feed inside the house -, vs. exophagic - feed outdoors. Regarding the resting habits after having taken a blood meal: some prefer to rest indoors (endophilic), while others rest mostly outdoors (exophilic). For example: the main vector of malaria in sub-Saharan Africa (*Anopheles gambiae* ss) feeds exclusively on humans. (~100% antropophily) and rests mostly indoors (endophilic); another important vector in semi-arid areas of Sub-Saharan Africa (*An. arabiensis* in Ethiopia, Zimbabwe and Tanzania), presents a substantial degree of zoophily and exophily; and finally, one of the main vectors of malaria in South Asia (*An. stephensis*) feeds preferentially on domestic animals (99% zoophilic), but commonly bites humans as well, and rests mostly indoors (endophilic). Such diversity on vector behaviour has major implications on malaria transmission dynamics and design of vector control programs. On one hand, it contributes to the high complexity of the disease transmission dynamics. On the other hand, it opens up the possibility of applying diverse control strategies; namely, it enables the implementation of strategies targeted at the nonhuman host of the mosquito.

In areas where the vector for human malaria also feed on animals, the presence of livestock impacts the risk of disease transmission to people. Although livestock is not susceptible to malaria infection, it may act as a readily accessible source of blood meal to the host-seeking mosquitoes, thereby increasing vector population densities. Treatment of livestock with insecticides (a widely used and effective strategy to control ectoparasites, flies and the diseases they transmit to livestock), has recently started to be evaluated as a novel method to control human malaria. Promising results have been observed from recent field trials in Pakistan. The treatment of livestock with pyrethroid insecticides that are fatal to the vector, decreased the incidence of malaria with a similar efficacy to the traditional indoor

insecticide spraying but with much lower costs. Moreover, significant improvements in livestock productivity were obtained, enhancing communities uptake of the programme [2]. Additional studies are being conducted in sub-Saharan Africa (Ethiopia, Zimbabwe and Tanzania). However, several factors underlying the effectiveness of insecticide treated livestock remain poorly understood. In this study, we develop an epidemiological framework to quantitatively address the relevance of some of these factors: namely, vector host-feeding preference and livestock coverage treatment levels. These questions are investigated by building and analysing a deterministic model of malaria transmission.

Figure 1. Sponging cattle with insecticide in a Pakistan field trial [2].

2. MALARIA MODEL WITH INSECTICIDE TREATED CATTLE

In this section, we develop a mathematical model for the transmission dynamics of malaria based on the seminal theoretical work of Ross and Macdonald (reviewed in [3]), which have remained a cornerstone for existing epidemiological studies. The Ross-Macdonald framework is a deterministic SEIS type model with human hosts and mosquito vectors divided into epidemiological compartments according to whether they are Susceptible (uninfected and not immune), Exposed/latent (have been infected but are not yet infectious) or Infectious. In this paper, we present an extension of the Ross-Macdonald model, which discriminates the feeding behaviour of the vector on its alternative hosts: livestock and human populations, and incorporates the treatment of livestock with insecticide as a *novel* method to control human malaria.

A number of assumptions are made, to simplify the structure of the model and the subsequent analysis (a diagrammatic flow chart of the model is presented in Figure 2, and the parameters are specified in Table 1).

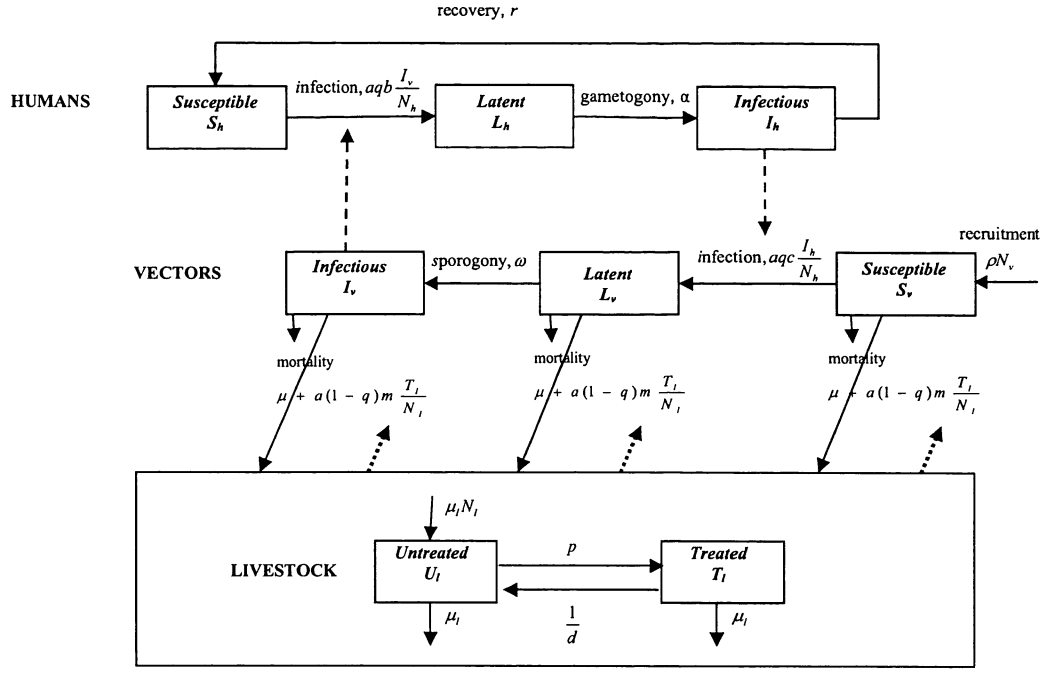

Figure 2. A schematic representation of the malaria model. Horizontal solid lines denote transitions between epidemiological states, and dashed lines represent transmission of infection between human hosts and mosquito vectors. Diagonal solid lines denote vectors feeding on livestock, and dotted lines represent the effect of insecticide treated livestock on vectors mortality.

Table 1. Parameters used in the malaria model with insecticide treated livestock.

Parameter	Description
N_v / N_h	Number of female mosquitoes per human host
a	Vector daily biting rate on any host (average interval between blood meals = duration of gonotrophic cycle = 1/a)
q	Proportion of vector bites on humans. The remaining, 1-q, are bites on livestock.
b	Proportion of humans which become infected following the bite of an infectious vector.
c	Proportion of vectors which become infected after biting an infectious human
α	Daily rate at which latent humans become infectious (duration of latent period in humans = $1/\alpha$)
ω	Daily rate at which latent mosquitoes become infectious (duration of latent period in surviving vectors = $1/\omega$)
r	Human daily recovery rate from infectiousness (duration of infectious period = 1/r)
ρ	Vector (adult female mosquito) recruitment rate
μ	Vector daily natural mortality rate (life expectancy = $1/\mu$)
m	Increased vector mortality rate due to biting/trying to bite on insecticide treated livestock
p	Proportion of livestock population treated with insecticide, in each intervention.
d	Duration of insecticide residual effect
μ_l	Livestock recruitment rate = Livestock removal rate

Throughout the paper, the human, vector and livestock populations will be referred to with the subscripts h, v and l, respectively.

First, let us consider the dynamics of infection in the human population, which is modelled by the following set of ordinary differential equations (ODE):

$$\begin{aligned}
\frac{dS_h}{dt} &= -\left(aqb\frac{I_v}{N_h}\right)S_h + rI_h, \\
\frac{dL_h}{dt} &= \left(aqb\frac{I_v}{N_h}\right)S_h - \alpha L_h, \qquad (1) \\
\frac{dI_h}{dt} &= \alpha L_h - rI_h,
\end{aligned}$$

where $N_h = S_h+L_h+I_h$ (total human population size).

Transmission of infection from vectors to humans depends on the number of infected vectors per human, I_v/N_h, the vector blood feeding rate a, the proportion q of feeds taken on humans (antropophily); the probability b that a human will become infected following the bite of an infected vector; and the number of susceptible hosts (S_h). Infected latent (L_h) become infectious after a period for development of infective gametocytes (latent period = $1/\alpha$). Infectious individuals (I_h) recover from infection at a rate r, becoming fully susceptible to re-infection (the average duration of infectiousness is $1/r$). It is therefore assumed no boosting immunity due to frequent infections. In our model, the natural human demography (mortality and reproduction) are ignored, since humans have a long life expectancy relative to all other time periods in the model (such as infectious period and vector life span). Moreover, we assume no disease-induced death and therefore, the human population size remains constant.

The disease dynamics in the vector population may be similarly described by the following system of ODEs:

$$\begin{aligned}
\frac{dS_v}{dt} &= \rho N_v - \left(aqc\frac{I_h}{N_h} + a(1-q)m\frac{T_l}{N_l} + \mu\right)S_v, \\
\frac{dL_v}{dt} &= \left(aqc\frac{I_h}{N_h}\right)S_v - \left(\omega + \mu + a(1-q)m\frac{T_l}{N_l}\right)L_v, \qquad (2) \\
\frac{dI_v}{dt} &= \omega L_v - \left(\mu + a(1-q)m\frac{T_l}{N_l}\right)I_v,
\end{aligned}$$

where $N_v = S_v+L_v+I_v$ (total vector population size).

We assume that transovarial transmission does not occur in the malaria vector, thus all the emergent adult mosquitoes are considered susceptible to infection. Transmission of infection from humans to vectors depends on the proportion of infectious humans, I_h/N_h, the vector feeding rate on humans, aq, and the probability c that a vector will become infected after biting an infectious human. Infected latent mosquitoes (L_v) become infectious following a period for sporozoites maturation (latent period = $1/\omega$). For mathematical simplicity, we assume that latent hosts and vectors become infectious at a constant rate, as opposed to the fixed time-delay used in the Ross-Macdonald model. Anophelines usually remain infectious throughout their life, not recovering from infection. Infection is assumed to have no impact on vector reproduction or mortality.

The vector life expectancy is short relatively to other time periods in the model. Consequently, vector demography must be incorporated. In the absence of any control intervention, the abundance of vectors is limited only by their natural mortality rate, μ (assumed to be age independent, such that average life-span = $1/\mu$). We assume perfect and intrinsic density dependence compensation of the vector population, by setting the average vector mortality rate equal to the recruitment rate, ρ , of newly emerged female adults entering the susceptible class. Therefore, the total population size, N_v, remains constant.

The vector population comprises only adult female Anopheline mosquitoes, since males do not feed on blood. As in previous malaria models, we assume that vectors take one blood meal per gonotrophic cycle, and therefore, the interval between blood meals corresponds to the length of the gonotrophic cycle. Female mosquitoes are assumed to have a homogenous feeding behaviour, and feed with a fix preference on humans and animals. Data on the proportion of vector bites on humans, the so-called human blood index (HBI), is easier to obtain than the proportion of bites on a given animal species. Therefore, we assume that the proportion of bites on livestock can be approximated by the value (1-*q*) although, in reality, this figure corresponds to the proportion of vector bites on non-human hosts (livestock and other animals). This means that in a scenario where the HBI is 0.10 (e.g. in regions of South Asia), at any given point in time 90% of the mosquitoes will be feeding on livestock and 10% will be feeding on humans. Additionally, we assume that vectors have no preference for a particular animal species (e.g. cows vs. goats).

When mosquitoes feed or try to feed on insecticide treated livestock, their mortality rate will be increased by the factor

$$a(1-q)m\frac{T_l}{N_l},$$

which is a function of the vector biting rate on livestock, *a(1-q),* the proportion of insecticide treated livestock, T_l / N_l, and the vector additional mortality due to insecticide, *m*. The increased mortality can be either due to direct insecticidal effect or due to indirect behavioural effect: either mosquito repellence or masking the host odour - since odour is one of the clues that help mosquitoes to find their host, the process of searching for a host may take longer, reducing the probability of vector survival.

The final section of the model is the livestock population, modelled by U_l and T_l, the number of untreated and treated livestock, respectively. The equations are given by:

$$\frac{dU_l}{dt} = \mu_l N_l - pU_l + \frac{1}{d}T_l - \mu_l U_l, \qquad (3A)$$

$$\frac{dT_l}{dt} = pU_l - \frac{1}{d}T_l - \mu_l T_l,$$

where $N_l = U_l + T_l$ (total livestock population size).

Notice that since the malaria parasite is not infective to livestock, this system is linear, as opposed to the human and vector systems. We consider the case where the livestock recruitment rate (μ_l) equals the rate at which animals are removed from the livestock population (μ_l), giving a constant population size. In the absence of any control intervention, all recruited animals remain in the untreated class (U_l), until their removal by death or sold. At each pulse intervention, a proportion *p* of the livestock population is treated with insecticide, thus moving into the treated class (T_l). The insecticide effect is assumed to be maximum on the day of the intervention and is subject to exponential decay, with average duration *d*. The value of *d* will depend mainly on the type of insecticide

formulation used, as well as on the method of application (e.g. 'spot-on' *vs.* sponging) and area of the animal covered by the insecticide. Keeping animals under shelter during the raining periods might also impact on d (in the case of formulations where insecticide washes off, the insecticide effect will last longer on sheltered than on grazing animals [4]. Performing simulations with various d values may provide insights into the election of the most cost-effective insecticide.

3. THRESHOLD DYNAMICS

The average number of secondary cases generated by a typical infectious individual introduced in a population of fully susceptible individuals, is known as the basic reproduction number, denoted by R_0 [3]. This threshold quantity expresses the maximum transmission potential of an infectious disease and must exceed unity for the infection to be maintained in the population. Here, we determine the threshold conditions required for persistence of malaria, by analyzing the equilibriums of the model represented by Systems (1) - (3).

R_0 is easily derived by linearization around the disease free equilibrium (DFE), using the next generation approach [5, 6]. The DFE for the malaria model with insecticide treated livestock is

$$\text{DFE} = (S_h^*, L_h^*, I_h^*, S_v^*, L_v^*, I_v^*) = (N_h, 0, 0, N_v, 0, 0),$$

where the entire population consists of susceptible humans and vectors, and

$$R_o = \sqrt{\frac{N_v}{N_h}\frac{(aq)^2 bc}{r}\frac{\omega}{\left(\mu + a(1-q)m\frac{T_l}{N_l}\right)\left((\omega+\mu) + a(1-q)m\frac{T_l}{N_l}\right)}}.$$

The mathematical details for deriving R_0 are in Appendix A1. It is also possible to derive the R_0 for malaria heuristically [3]. To illustrate this simpler derivation, consider one infectious human coming into a population where everyone is susceptible (e.g. an individual with malaria infection, immigrating to an isolated area in the USA). The human host will remain infectious for the period $1/r$, during which time he will suffer an average of $(N_v/N_h)aq$ bites by susceptible mosquitoes. Of these bites, a fraction c will lead to infection in the vector, producing a total of $(N_v/N_h)aqc/r$ infected mosquitoes. A proportion $\omega/(\omega+\mu+a(1-q)mT_l/N_l)$ of these will survive the latent period and become infectious. These mosquitoes will survive, on average, $1/(\mu+a(1-q)mT_l/N_l)$ days and bite on humans at a rate aq during this period. A fraction b of these bites will lead to infection of susceptible humans. When no animal is treated with insecticide ($T_l/N_l=0$) or when the vector is strictly antropophilic (i.e. feeding exclusively on humans, q=1), R_0 reduces to

$$R_o = \frac{N_v}{N_h}\frac{(aq)^2 bc}{r\mu}\left(\frac{\omega}{\omega+\mu}\right).$$

It is easily seen from R_0 that, in this scenario, the insecticide treatment of livestock has no impact on the disease transmission dynamics. This expression for R_0 is similar to the classical Ross-Macdonald R_0 for a model with no control intervention

$$R_o = \frac{ma^2 bc}{r\mu}\exp^{-\mu\tau},$$

(where $m=N_v/N_h$ and $a=aq$), with the exception that the term $\omega/(\omega+\mu)$, where latency is modelled with a constant rate ω, replaces the Ross-Macdonald's term $\exp^{-\mu\tau}$, where latency is modelled with a fixed time delay τ.

If R_0 is greater than 1, the DFE is unstable and we are in the presence of an endemic equilibrium, where the disease can invade and persist (Figure 3A). However, if R_0 is smaller than 1, then the DFE is stable, and the disease dies out (Figure 3B).

Small changes in vector life expectancy, $1/\mu$, and interval between blood meals, $1/a$, may originate a drastic shift in disease dynamics. For instance, decreasing $1/\mu$ by one day, while increasing $1/a$ by the same amount, can produce a reduction in R_0 to <1, thereby shifting the disease dynamics from persistence to extinction (see Figure 3).

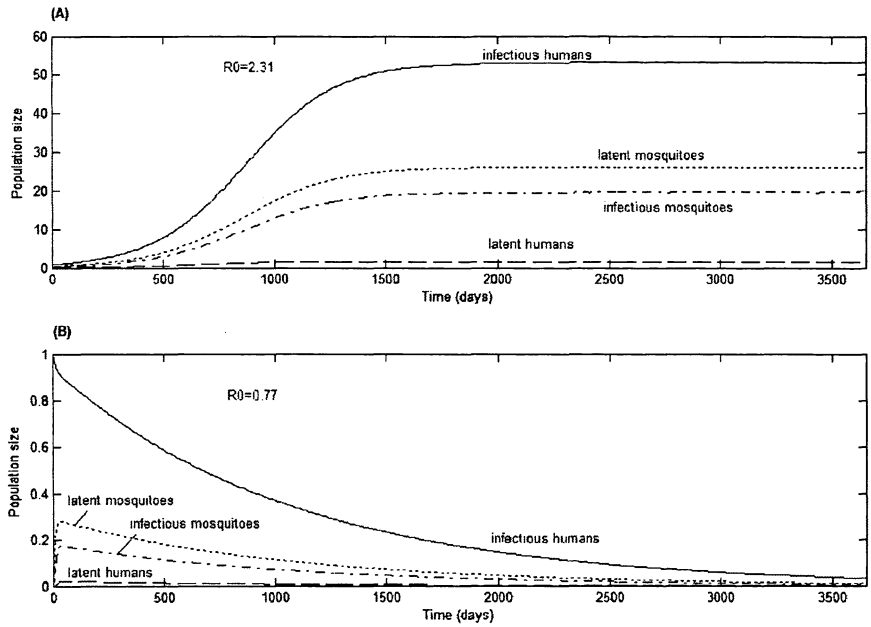

Figure 3. The general behaviour of the malaria model prior to a control intervention. **(A)** Scenario where $R_0>1$, ($R_0=2.31$), and therefore the disease persists ($N_v/N_h=10$, $a=1/2$, $q=0.05$, $b=1$, $c=0.6$, $\alpha=1/7$, $r=1/240$, $\mu=\rho=1/6$, $\omega=1/8$). **(B)** Scenario where $R_0<1$ ($R_0=0.77$), and thus the disease dies out (all parameters are kept fixed as in (A) except for $a=1/3$ and $\mu=\rho=1/5$).

For illustration, the initial conditions in the number of individuals in each class were set to simulate the situation where one infected human is introduced into a fully susceptible population of humans and vectors ($S_h=99$, $I_h=1$, $S_v=1000$, $L_h=L_v=I_v=0$). The model was run for different sets of initial data and the final results were qualitatively the same.

4. SENSITIVITY OF MALARIA R_0 TO PARAMETER VALUES

The R_0 for malaria is determined by several parameters, and here, we investigate the sensitivity of $(R_0)^2$ to each parameter. The sensitivity S of $(R_0)^2$ to a parameter P is defined conventionally as:

$$S_{(P)} = \frac{P}{(R_0)^2}\frac{\partial(R_0)^2}{\partial P}$$

The definition shows that the sensitivity measures the proportional change in R_0, for a small proportional change in the parameter P. When R_0 changes linearly as the parameter alters, the sensitivity S is equal to (+ or -) unity [7].

Table 2. Sensitivity analysis of $(R_0)^2$ in malaria model with and without insecticide treatment of livestock.

Parameter	Without Treatment				
	$S=\frac{P}{(R_0)^2}\frac{\partial(R_0)^2}{\partial P}$	$\lvert S\rvert$	$S=\frac{P}{(R_0)^2}\frac{\partial(R_0)^2}{\partial P}$	$\lvert S\rvert$	
aq	2	$=2$	$\frac{2\mu(\mu+\omega)+am\frac{T_I}{N_I}(2-q)(2\mu+\omega)+2(am\frac{T_I}{N_I})^2(1-q)}{(\mu+\omega+am\frac{T_I}{N_I}(1-q))(\mu+am\frac{T_I}{N_I}(1-q))}\geq 2$		>=2 If $T_I/N_I=0$, then =2
μ	$-2<-\frac{2\mu+\omega}{\mu+\omega}<0$	<2	$-2<-\frac{\mu(2\mu+\omega+2am\frac{T_I}{N_I}(1-q))}{(\mu+\omega+am\frac{T_I}{N_I}(1-q))(\mu+am\frac{T_I}{N_I}(1-q))}<0$		<2
$\frac{N_v}{N_h}=b=c$	1	$=1$	1		$=1$
r	-1	$=1$	-1		$=1$
ω	$0<\frac{\mu}{\mu+\omega}<1$	<1	$0<\frac{\mu+am\frac{T_I}{N_I}(1-q)}{\mu+am\frac{T_I}{N_I}(1-q)+\omega}<1$		<1
$\frac{T_I}{N_I}=m$	---	---	$\frac{ma\frac{T_I}{N_I}(1-q)\left(2\mu+\omega+2am\frac{T_I}{N_I}(1-q)\right)}{\left(\mu+\omega+am\frac{T_I}{N_I}(1-q)\right)\left(\mu+am\frac{T_I}{N_I}(1-q)\right)}\geq 0$		>1 or <1, depending on parameter values

The sensitivity analysis (Table 2) shows that the parameters that have a greater impact on R_0 are the mosquito biting rate on humans, aq, and the mosquito natural mortality rate, μ. These findings are in accordance with the insights provided by the classical Ross-Macdonald model, which have been the rational behind control strategies to increase the vector mortality rate (e.g. insecticides), or decrease the human biting rate (e.g. use of bed nets, screens or repellents). Not surprisingly, the treatment of livestock with insecticide further increases the sensitivity of R_0 to the human biting rate.

4. CONTROLLING HUMAN MALARIA

In this section we investigate the impact of treating livestock with insecticide on malaria transmission potential (R_0), for different scenarios of vector host feeding preference and livestock treatment coverage.

As illustrated in Figure 4, for a given level of effectively treated livestock (T_I/N_I), increases in vector antropophily (q) lead to increase in R_0. The smaller the coverage, the steeper the increase in R_0, and vice-versa. Conversely, for a given antropophily, increases in coverage generate a decrease in R_0. These results are in accordance with the sensitivity analysis.

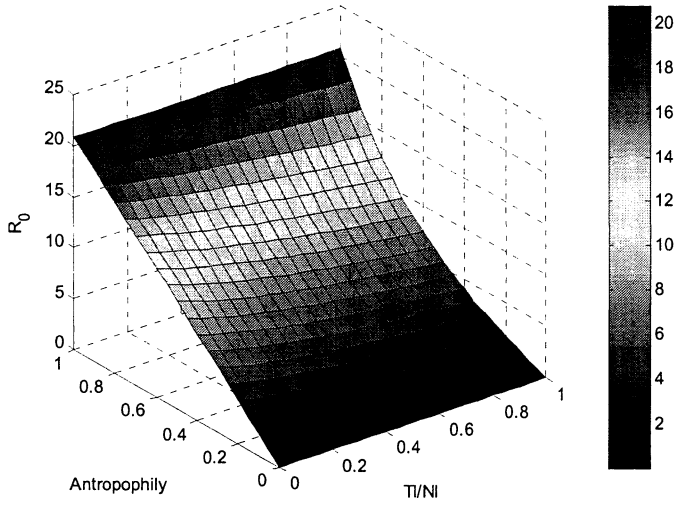

Figure 4. The basic reproductive number with respect to vector feeding preference for humans (antropophily, *q)* and proportion of livestock with residual insecticide (T_l/N_l). (N_v/N_h=15, a=1/2, b=1, c=1, r=1/45, ω=1/8, μ=1/6, m=0.73); a, ω, μ and m were estimated from Pakistan data [8, 9]; N_v/N_h, b, c, are difficult to measure, and therefore, conservative values were chosen.

We proceed to analyse the critical proportion $(T_l/N_l)^*$ of livestock population that must be effectively treated with insecticide in order to decrease R_0 below 1. The critical proportion is easily derived by setting R_0=1 and solving for T_l/N_l, through algebraic manipulation:

$$(T_l/N_l)^* = \frac{1}{2}\frac{\sqrt{r\,\omega\left(4\frac{Nv\,a^2\,q^2\,b\,c}{Nh}+r\,\omega\right)}-r\,(\omega+2\,\mu)}{r\,a\,(1-q)\,m}$$

The results presented in Figure 5. suggest that in areas where malaria vectors feed predominantly on non-human hosts (low antropophily & strong zoophily, as in South East Asia), a constant coverage of livestock with effective insecticide can potentially reduce R_0 <1 and therefore, promote the control of this most important tropical disease.

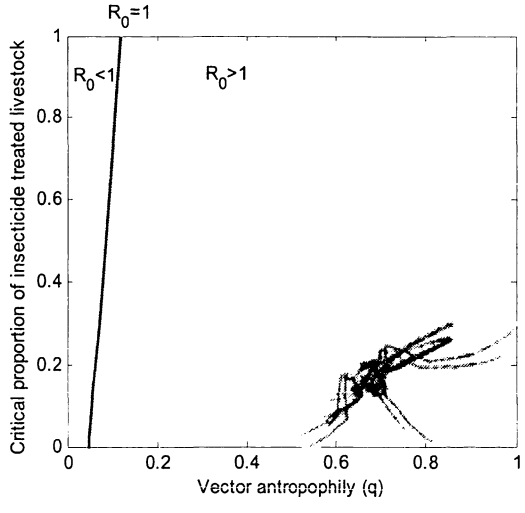

Figure 5. Critical proportion of livestock effectively treated with insecticide $(T_l/N_l)^*$, as a function of vector antropohily (*q*). The red line depicts the proportion of livestock effectively treated with insecticide, above which R_0 will be decreased below 1, for a given vector antropophily. (Parameter values were kept fix as in Figure 4).

Finally, we explore the impact of the intervention on R_0 ratio, which is defined as the ratio between the R_0 under a constant coverage level of insecticide treated livestock (T_l/N_l) and the R_0 pre-intervention (see Figure 6). The proportionate reduction on the pre-intervention R_0 is given by 1- (R_0 ratio). In scenarios where the malaria vector has strong zoophily, high levels of livestock treatment coverage could produce a reduction of up to 60% on the pre-intervention R_0. Interestingly, even in settings where the vector has a stronger preference for human blood-meals (stronger antropophily, as in Africa) the intervention has the potential to achieve a considerable decrease on R_0, and thereby decrease malaria transmission and infection.

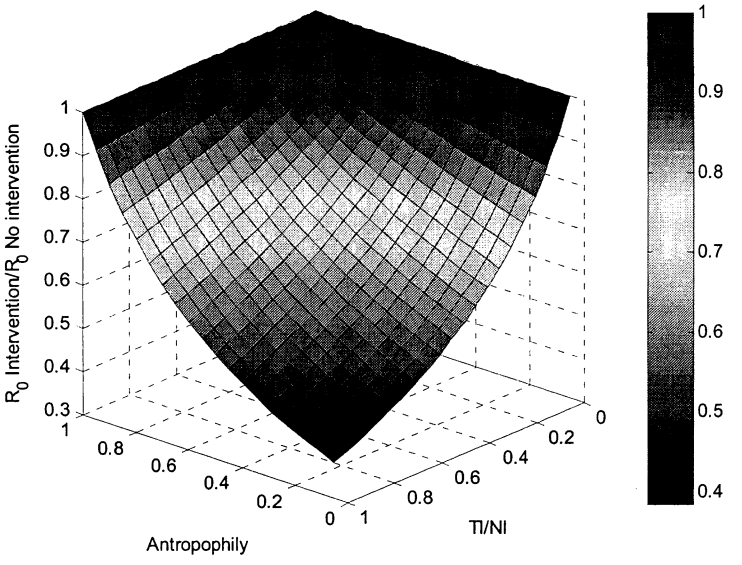

Figure 6. Effect of insecticide treated livestock on the R_0 ratio, with respect to vector antropophily (q) and proportion of livestock with residual insecticide (T_l/N_l). (Parameter values were kept fix as in Figure 4).

5. DISCUSSION

The main focus of this research is to understand the circumstances under which a policy that involves the systematic use of insecticides on livestock will decrease the burden of human malaria. We addressed this question by expanding the classical Ross Macdonald model to incorporate vector feeding behaviour on livestock and human populations, and treatment of livestock with insecticide. One of the strengths in a modelling approach is that it enables the evaluation of the control strategy under a different set of conditions and scenarios, requiring much less time and financial effort than experimental field trials. Moreover, it can provide valuable insights towards the identification of critical parameters for the intervention success, thereby informing data collection in experimental trials. By their nature, epidemiological models do not consider all the biological complexities, but can still be useful in understanding the disease dynamics and the impact of control interventions. Accordingly, our model framework does not reflect the whole of the complexity of malaria transmission and infection, to allow us to focus on malaria control via insecticide treated livestock. Namely, we have explored the relevance of vector host-feeding preferences and livestock treatment coverage.

The results presented in this paper are still preliminary, and further work is being conducted such as numerical simulations to assess the impact of the intervention on malaria cumulative prevalence and incidence. The treatment frequency and duration of insecticide residual activity are also being considered. Vector feeding preference is likely

to depend on the number of animals nearby the household, as well on the distance from the animal shelters to the place where humans sleep. Therefore, future goals aim at investigating the effect of heterogeneities on vector host-feeding behaviour. Climatic factors are also known to influence key parameter of malaria transmission. Namely, warm temperatures, heavy rainfall and high humidity may decrease both the duration of the parasite sporogonic cycle and the time for development of the larval instars of the vector, while increase vector longevity. Moreover, temperature also reduces the anopheline blood-feeding intervals [1]. Therefore, the incorporation of seasonality into the malaria model is likely to provide useful insights into the best timing for a single annual insecticide application.
Such comprehensive understanding will be a major contribution to the optimization of this control strategy in a given setting. Most importantly, it will enable the impact of the strategy in different settings to be estimated. The quantitative framework developed in our study is an important step towards this direction.

6. ACKNOWLEDGMENTS

A special thanks to Prof. Carlos Castillo-Chavez for making possible the unique opportunity to participate in MTBI and for his helpful advices. We would also like to thank the entire MTBI faculty, for sharing their expertise and teaching the course that introduced techniques critical to the development of this paper. Namely, we acknowledge Prof. Aziz Yakubu, for tutoring, Dr. Elmer de la Pava, for the mathematical advice provided with so much joy, as well as Gerardo Chowell, Dr. Steve Wirkus and Dr. Erika Camacho for the precious help with the Matlab code. A special appreciation is extended to the following staff at the London School of Hygiene and Tropical Medicine (UK): Dr. Paul Coleman, for supervision, Mark Rowland, for providing data from a Pakistan trial, Dr. Clive Davies and Prof. Chris Curtis (LSHTM, UK) for advices, as well as to Dr. Gabriela Gomes (Gulbenkian Institute of Science, Portugal) for technical and personal support. This research has been partially supported by grants given by the Portuguese National Science Foundation (FCT) and the USA National Science Foundation, National Security Agency, and the Sloan Foundation (through Cornell - Sloan National Pipeline Program in the Mathematical Sciences). Substantial financial and moral support was also provided by the T Division of Los Alamos National Lab (LANL), CNLS at LANL, Office of the Provost of Cornell University, and the Dept. of Biological Statistics & Computational Biology. The authors are solely responsible for the views and opinions expressed in this research; it does not necessarily reflect the ideas and/opinions of the funding agencies, Cornell University, and/or LANL.

7. APPENDIX:

APPENDIX A1.

To implement the Next Generation Operator (NGO) approach [5, 6] we only consider the equations for the infectious human host and mosquito vector. The Jacobian for this reduced system at the DFE is

$$J(DFE) = \begin{bmatrix} -r & abq \\ \frac{N_v}{N_h}\frac{\omega a q c}{((\omega+\mu)+a(1-q)m\frac{T_l}{N_l})} & -(\mu + a(1-q)m\frac{T_l}{N_l}) \end{bmatrix}$$

Let $J(DFE) = M\text{-}D$, where M is the non-negative matrix

$$M = \begin{bmatrix} 0 & abq \\ \frac{N_v}{N_h}\frac{\omega a q c}{((\omega+\mu)+a(1-q)m\frac{T_l}{N_l})} & 0 \end{bmatrix}$$

and D is the positive diagonal matrix

$$D = \begin{bmatrix} r & 0 \\ 0 & \mu + a(1-q)m\frac{T_l}{N_l} \end{bmatrix}$$

The basic reproduction number is given by the dominant eigenvalue λ of the matrix MD^{-1}, i.e., the eigenvalue that is larger in absolute value than all other eigenvalues of MD^{-1}

$$MD^{-1} = \begin{bmatrix} 0 & ab\frac{q}{\mu+a(1-q)m\frac{T_l}{N_l}} \\ \frac{N_v}{N_h}\omega a q \frac{c}{\left(\omega+\mu+a(1-q)m\frac{T_l}{N_l}\right)r} & 0 \end{bmatrix}.$$

The eigenvalues of MD^{-1} are given by the solutions of $| MD^{-1} - \lambda I | = 0$, and we therefore obtain

$$R_o = \sqrt{\frac{N_v}{N_h}\frac{(aq)^2 bc}{r}\frac{\omega}{\left(\mu + a(1-q)m\frac{T_l}{N_l}\right)\left((\omega+\mu)+a(1-q)m\frac{T_l}{N_l}\right)}}$$

where the square-root reflects the biological requisite in the vector-human host system for the parasite to pass through two types of individuals to complete its life cycle [10]. Note that all the terms that characterize R_0 are >=0, and consequently, R_0 >=0.

Note:

The majority of previous malaria models present a formula for R_0 that does not include a square route. However, using the NGO approach, we obtain a squared expression. The NGO approach is known to generate a more accurate expression for R_0 than other methods, such as linearization around the disease free equilibrium, which would give the same expression but without the square rout. At first sight, it might seem more difficult to interpret R_0 with a square root. An interesting paper by Lord *et al.* [10], presents the biological explanation stated above.

In practice, the relevance of the square route in the R_0 expression depends on the question being addressed. When investigating the threshold conditions for R_0 to be smaller or higher than 1, the square route could be ignored, since for any number λ>1 if and only if λ^2>1. Therefore, we can define $R_0 = \lambda^2$ = (the dominant eigenvalue of M) squared [10]

$$R_o = \frac{N_v}{N_h}\frac{(aq)^2 bc}{r}\frac{\omega}{\left(\mu + a(1-q)m\frac{T_l}{N_l}\right)\left((\omega+\mu) + a(1-q)m\frac{T_l}{N_l}\right)}$$

However, when estimating the level of disease control efforts, the insights can be significantly different if the square route is omitted. For instance, a higher effort is required to control disease transmission in a scenario where $R_o = 16$, than in a scenario where $R_o = \sqrt{16} = 4$.

Therefore, for mathematical accuracy, the analysis and simulations throughout the paper refer to

$$R_o = \sqrt{\frac{N_v}{N_h}\frac{(aq)^2 bc}{r}\frac{\omega}{\left(\mu + a(1-q)m\frac{T_l}{N_l}\right)\left((\omega+\mu) + a(1-q)m\frac{T_l}{N_l}\right)}}$$

except in the sensitivity analysis, wherein $(R_0)^2$ is referred.

8. REFERENCES

1. Gilles, H.M. and D.A. Warrel, *Bruce-Chwatt's Essential Malariology.* 3rd Edition ed. 1997, London: Arnold. 340.
2. Rowland, M., et al., *Control of malaria in Pakistan by applying deltamethrin insecticide to cattle: a community-randomised trial.* Lancet, 2001. **357**(9271): p. 1837-41.
3. Anderson, R.M. and R.M. May, *Infectious Diseases of Humans: Dynamics and Control.* 1991, Oxford: Oxford University Press.
4. Hewitt, S. and M. Rowland, *Control of zoophilic malaria vectors by applying pyrethroid insecticides to cattle.* Trop Med Int Health, 1999. **4**(7): p. 481-6.
5. Diekmann, O., J.A. Heesterbeek, and J.A. Metz, *On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations.* J Math Biol, 1990. **28**(4): p. 365-82.
6. van den Driessche, P. and J. Watmough, *Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission.* Math Biosci, 2002. **180**: p. 29-48.
7. Ariola, L. and J. Hyman, *Theory of Application of Sensitivity Analysis*: (In preparation).
8. Mahmood, F. and W.K. Reisen, *Duration of the gonotrophic cycles of Anopheles culicifacies Giles and An. stephensi Liston, with observations onreproductiveactivity and survivorship during winter.* Mosquito News, 1981. **41**: p. 22 - 30.
9. Reisen, W.K. and P.F. Boreham, *Estimates of malaria vectorial capacity for Anopheles culicifacies and Anopheles stephensi in rural Punjab province Pakistan.* J Med Entomol, 1982. **19**(1): p. 98-103.
10. Lord, C.C., M.E.J. Woolhouse, and J.A.P. Heesterbeek, *Vector-borne diseases and the basic reproduction number: a case study of African horse sickness.* Medical and Veterinary Entomology, 1996. **10**: p. 19-28.