

Combining zooprophylaxis and insecticide spraying: a malaria-control strategy limiting the development of insecticide resistance in vector mosquitoes

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Strategies to eradicate the vector-borne infectious diseases (e.g. malaria and Japanese encephalitis) are often directed at controlling vectors with insecticides. Spraying insecticide, however, opens the way for the development of insecticide resistance in vectors, which may lead to the failure of disease control. In this paper, we examine whether the combined use of insecticide spray and zooprophylaxis can limit the development of insecticide resistance in mosquitoes. Zooprophylaxis refers to the control of vector-borne diseases by attracting vectors to domestic animals in which the pathogen cannot amplify (a dead-end host). The human malaria parasite *Plasmodium* spp. has a closed transmission cycle between humans and mosquitoes, and hence cattle can serve as a dead-end host. Our model reveals that, by a suitable choice of insecticide spraying rate and cattle density and location, malaria can, in some situations, be controlled without mosquitoes developing insecticide resistance.

Keywords: malaria control; zooprophylaxis; vector mosquito; insecticide resistance

1. INTRODUCTION

Human malaria parasites, four species of *Plasmodium*, have a closed infection cycle between humans and anopheline mosquitoes. As in other vector-borne infectious diseases, a principal strategy for controlling malaria is to use insecticides to eradicate the vectors. Spraying too much insecticide, however, has triggered the development of insecticide resistance in mosquitoes, resulting in a failure of disease control (Brodgton & McAllister 1998; WHO 2000). Control strategies that do not rely heavily on insecticides are therefore required. Zooprophylaxis is one such strategy, which intends to control vector-borne infectious diseases by attracting vectors to domestic animals that can act as dead-end or decoy hosts (Sota & Mogi 1989; Mogi & Sota 1991; Habtewold *et al.* 2001; Killeen *et al.* 2002; Seyoum *et al.* 2002). In malaria, for example, cattle can serve as a dead-end host, because human malaria parasites cannot amplify in cattle. Zooprophylaxis with cattle as a dead-end host can indeed be an effective strategy for controlling malaria (Sota & Mogi 1989). In zoophilic vectors, however, a condition arises in which the introduction of domestic animals may increase mosquito density, thereby enhancing, rather than reducing, malaria transmission (as has been shown theoretically by Sota & Mogi (1989) and supported empirically by Bouma & Rowland (1995)). Furthermore, the livestock density necessary for the successful control of malaria would exceed a manageable level in practice. In this paper, we therefore extend the previous models to combine zooprophylaxis with mosquito control by insecticides. Our objective here is to examine whether combining these two methods will have synergistic or adverse effects on malaria control, with particular reference to the development of

insecticide-resistant mosquitoes. We also highlight the different intervention outcomes when the vector mosquitoes are zoophilic or anthropophilic and when human and cattle populations live separately or are mixed.

The morbidity and mortality of an infectious disease can be measured in terms of the basic reproductive ratio, R_0 , of the parasite, which in the case of vector-borne diseases is the product of two factors: the total number of secondary infections in a human population caused by one infectious mosquito during its lifetime; and in a mosquito population caused by an infectious human before it dies or recovers. From the perspective of parameter estimation, a different decomposition of R_0 would be useful. For example, Killeen *et al.* (2000a) proposed separating the entomologic inoculation rate (EIR), the extent to which a human is exposed to the malaria parasite via mosquitoes, from the post-inoculation factors of the basic reproductive ratio, which depend on immunity, age, health, access to an anti-malarial drug and the genetic background of the host. In other words, the EIR is a component of the basic reproductive ratio that is related only to vector activity.

More realistic models for malaria-vector-mediated infection dynamics, including those by Graves *et al.* (1990) and Saul *et al.* (1990), have been proposed recently, which take into account the cyclic blood-feeding behaviour of mosquitoes in more detail than previous models. We, however, adopt a classical epidemiological model for the blood-feeding process, as our focus is on a control strategy using complex evolutionary processes such as the combined use of zooprophylaxis and insecticide spraying, and the development of insecticide resistance.

Unlike standard models for malaria infection, we consider not only the epidemiological dynamics of malaria in human and mosquito populations but also the demographic dynamics of mosquitoes, because it is necessary to evaluate the effects of livestock and insecticide spraying on the vector population density. We derive conditions

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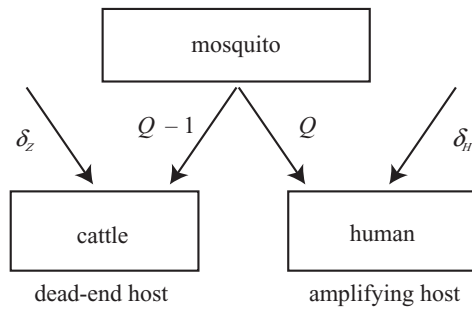


Figure 1. The structure of the model. Mosquitoes in a single breeding population visit the human and the cattle sites with probabilities Q and $1 - Q$, which are functions of human and cattle densities, H and Z (see § 2a). The insecticide can be sprayed in each site with rates δ_H and δ_Z . Humans are an amplifying host of malaria parasites but cattle are a dead-end host (malaria parasites cannot grow in cattle). By increasing the density of the dead-end host, the vector insects are more attracted to it, making the control of an infectious disease easier (zooprophylaxis).

for malaria control and for the development of insecticide resistance in the mosquito. We assume that human and cattle areas are separated from each other by a distance greater than the mosquito’s daily blood-searching distance, and that mosquitoes in a single mating pool will visit either of these sites with a rate that depends on densities and host preferences (the mosquito is attracted more to the site with larger density if the host preferences for humans and cattle are equal). By changing the cattle density, the rate at which the mosquito visits the dead-end host (cattle) rather than the amplifying host (human) can be modulated (figure 1). We then ask, by adjusting the insecticide spraying rate and the cattle density, whether we can control malaria without allowing the development of insecticide resistance in mosquitoes.

2. THE MODEL

We here model the demographics of the mosquito and the epidemiological dynamics of the malaria parasite in humans and mosquitoes, assuming that there are human dwellings and cattle sites, both of which the mosquitoes from a single mating pool can visit in their daily activity (figure 1).

(a) Blood feeding and mosquito demography

Let us define the human visitation rate Q of the mosquito

$$Q = \frac{a_H H}{a_H H + a_Z Z} = \frac{1}{1 + (a_Z/a_H)(Z/H)} \equiv \frac{1}{1 + k\rho} \tag{2.1}$$

as the probability that the mosquito visits the human dwelling rather than the cattle site, where a_H and a_Z are the mosquito feeding preferences for the humans and the cattle, respectively, and H and Z are the numbers of humans and cattle in each site, respectively. The human visitation rate Q depends only on the ratio of mosquito feeding preference for cattle to that for humans $k = a_Z/a_H$ and the ratio of the number of cattle to the number of humans $\rho = Z/H$. We assume that the number of mosquito bites per night in each site is proportional to the host density, with constant coefficient b . The total number of bites B per night in either the human or the cattle site is then

$$B = b[QH + (1 - Q)Z]. \tag{2.2}$$

The human blood index, HBI, is the fraction of human-fed mosquitoes among randomly sampled blood-fed mosquitoes. In the present model, in which the human and the cattle sites are clearly separated (figure 1), the HBI depends on the ratios of the blood-feeding preferences $k = a_Z/a_H$ and the relative densities $\rho = Z/H$, i.e.

$$HBI = \frac{bQH}{b[QH + (1 - Q)Z]} = \frac{a_H H^2}{a_H H^2 + a_Z Z^2} = \frac{1}{1 + k\rho^2}. \tag{2.3a}$$

If, alternatively, humans and cattle are living in the same area (i.e. within the mosquito’s daily blood-searching range), the feeding preferences a_H and a_Z refer to the likelihood that humans or cattle attract a mosquito. The HBI in this mixed situation is then

$$HBI' = \frac{ba_H H}{b[a_H H + a_Z Z]} = \frac{1}{1 + k\rho}. \tag{2.3b}$$

Though we focus here on the case where the human and cattle sites are separated, we also obtain the result for the mixed case, and compare the two results.

We denote the mortalities resulting from the insecticide, δ_H and δ_Z , as the probabilities that the mosquito visiting the human and the cattle sites, respectively, is killed by the insecticide. The total daily mortality resulting from insecticide spray is then

$$D = Q\delta_H + (1 - Q)\delta_Z. \tag{2.4}$$

Assuming that the intrinsic growth rate of the mosquito density M is proportional to the daily biting rate B and the fecundity

$$F = \frac{\text{the number of eggs per oviposition}}{\text{gonotrophic period}},$$

the mosquito density would change as

$$\dot{M} = \left[BF \left(1 - \frac{M}{K} \right) - u \right] M, \tag{2.5}$$

where the dot denotes differentiation with respect to time (d/dt), $u = u_0 + D$ is the adult mosquito mortality, with u_0 being the natural mortality, and K is the carrying capacity resulting from the density-dependent competition between larva. We assume that the human and cattle densities, H and Z , are constant, because the lifetimes of humans and cattle are much longer than those of the mosquito and the malaria parasite.

The typical values for these parameters are listed in table 1. The blood-feeding preference for cattle relative to humans, $k = a_Z/a_H$, is calculated from the data of Killeen *et al.* (2001). We used equation (2.3b) and the data on HBI' and the ratio of Z (cattle) to H (humans) in African villages reported by White *et al.* (1972) and Lindsay *et al.* (1993). According to these estimates, *Anopheles funestus* and *A. gambiae s. s.* in Segera, Tanzania are strongly anthropophilic ($k = 0.0011$ and 0.021 , respectively), whereas *A. arabiensis* in Segera and *A. gambiae s. l.* in The Gambia are zoophilic ($k = 1.61$ and 1.61 , respectively). As we will show in § 2f, optimal malaria control by the mixed use of insecticide and zooprophylaxis strongly depends on whether the vector is zoophilic or anthropophilic.

(b) Malaria dynamics

We now consider the epidemiological dynamics of malaria in human and mosquito populations. Note again the fact that cattle is the dead-end host of malaria, and hence we can ignore malaria in cattle.

Let X and Y be the numbers of malaria-infected humans and mosquitoes, respectively. The numbers of uninfected susceptible humans and mosquitoes are $H - X$ and $M - Y$, respectively. Noting that only mosquitoes that visit human sites may transmit or become infected with the malaria parasite, the numbers of the malaria-infected humans and mosquitoes then change according to

$$\dot{X} = \beta b Q (H - X) Y - v X, \quad (2.6a)$$

$$\dot{Y} = \beta' b Q (M - Y) X - u Y, \quad (2.6b)$$

where v is the recovery rate from malaria infection, and β and β' are the per-bite transmission rates from an infected mosquito to a susceptible human and from an infected human to a susceptible mosquito, respectively. The recovered host becomes susceptible to malaria (the Ross–Macdonald model or SIS model—see Macdonald 1957; Aron & May 1982; Bailey 1982).

The frequencies $x = X/H$ of infected humans and $y = Y/M$ of infected mosquitoes then change as follows:

$$\dot{x} = \frac{\dot{X}}{H} = \beta b Q M (1 - x) y - v x, \quad (2.7)$$

$$\dot{y} = \frac{\dot{Y}}{M} - y \frac{\dot{M}}{M} = \beta' b Q H x (1 - y) - B F \left(1 - \frac{M}{K}\right) y. \quad (2.8)$$

After the mosquito density M reaches a demographic equilibrium $\hat{M} = K(1 - u/BF)$ (derived from equation (2.5)), the malaria infection dynamics of equations (2.7) and (2.8) can be simplified to

$$\dot{x} = \beta b Q \hat{M} (1 - x) y - v x, \quad (2.9a)$$

$$\dot{y} = \beta' b Q H x (1 - y) - u y. \quad (2.9b)$$

We then derive the condition for malaria control by examining the local stability of the disease-free equilibrium of the epidemiological dynamics (equations (2.9)).

(c) Condition for malaria control

The local stability of the malaria-free equilibrium, $x = y = 0$ is determined from the Jacobian matrix

$$\mathcal{J}_0 = \begin{pmatrix} -v & \beta b Q \hat{M} \\ \beta' b Q H & -u \end{pmatrix}. \quad (2.10)$$

The equilibrium is locally stable if the determinant of \mathcal{J} is positive, i.e. $uv - \beta\beta'b^2Q^2H\hat{M} > 0$, or if the basic reproductive ratio of the malaria parasite is less than 1 (Anderson & May 1991), i.e.

$$R_0 = \frac{\beta\beta'b^2Q^2H\hat{M}}{uv} < 1. \quad (2.11)$$

If $R_0 > 1$, alternatively, the equilibrium where malaria is endemic is locally stable. The equilibrium frequencies of malaria-infected humans and mosquitoes in the endemic equilibrium are

$$\hat{x} = \left(1 - \frac{1}{R_0}\right) \left/ \left(1 + \frac{v}{\beta b Q \hat{M}}\right)\right., \quad (2.12a)$$

$$\hat{y} = \left(1 - \frac{1}{R_0}\right) \left/ \left(\frac{\beta \hat{M}}{\beta' H} + \frac{u}{\beta' b Q H}\right)\right.. \quad (2.12b)$$

The condition for malaria eradication (2.11) can be rewritten as

$$\frac{u}{u_0} = \frac{u_0 + D}{u_0} > \frac{1}{G(\rho)}, \quad (2.13)$$

where

$$G(\rho) = \frac{(1 + k\rho)^2}{r_0} + \frac{1}{\lambda_0} \frac{(1 + k\rho)}{1 + k\rho^2}, \quad (2.14a)$$

$$r_0 = \frac{\beta\beta'b^2HK}{u_0v}, \quad (2.14b)$$

$$\lambda_0 = \frac{bFH}{u_0}. \quad (2.14c)$$

We define r_0 as the basic reproductive ratio of the malaria parasite under the following conditions:

- (i) no insecticide is sprayed;
- (ii) no livestock are present; and
- (iii) the mosquito density is at carrying capacity.

Further, λ_0 is the reproductive value of a mosquito under the same conditions as (i), (ii) and (iii) the mosquito density is low enough that the density-dependent regulation can be ignored. Using equations (2.13) and (2.14) we can examine the effect of zoonophylaxis, by increasing the cattle density Z , and the effect of insecticide spray on malaria control.

Only the left-hand side of equation (2.13) depends on the mortality, $D = Q\delta_H + (1 - Q)\delta_Z$, caused by the insecticide spray. Malaria can be eradicated by setting the insecticide spraying rate larger than the threshold given by equation (2.13). However, spraying the insecticide would open the way for the evolution of insecticide-resistant mosquitoes, and malaria control would fail. Therefore we next examine the condition for the spread of insecticide resistance in the mosquito population.

(d) Conditions for the development of insecticide resistance in the mosquito

The insecticide-resistant mosquitoes, when introduced into the mosquito population, would have a lower mortality rate, u_0 , than that of the wild-type mosquitoes, $u = u_0 + D$, but would also have a lower fecundity, F' , than that of the wild-type mosquitoes (F) owing to the resistance cost. The density m of the insecticide-resistant mosquitoes then changes, when rare, as

$$\dot{m} = B F' \left(1 - \frac{\hat{M}}{K}\right) m - u_0 m, \quad (2.15)$$

where B is the total number of bites per night defined already, and \hat{M} is the equilibrium density of mosquitoes before the introduction of the insecticide-resistant mutant. Substituting $\hat{M} = K(1 - u/BF)$ into equation (2.15), we have

$$\dot{m} = \left[\frac{uF'}{F} - u_0\right] m. \quad (2.16)$$

Noting that $u = u_0 + D$, the condition for the development of insecticide resistance in the mosquito population is therefore

Table 1. Symbols and parameters used in the model. (NWFP, Northwest Frontier Province.)

symbol	definition	values	reference
mosquito			
$b \times H$	biting rate per female mosquito (estimated from the mean gonotrophic cycle, $T = 2-5$ days ($b \times H = 1/T$))	0.2–0.5 (day^{-1})	Gilles & Warrell (1993); Rajagopalan <i>et al.</i> (1977)
F	fecundity of susceptible mosquito	80–90 (eggs)	Brown (1983), in <i>Culicidae</i> (note that this is not a malaria vector)
F'	fecundity of insecticide-resistant mosquito	20–30 (eggs)	Brown (1983), in <i>Culicidae</i> (note that this is not a malaria vector); Brown & Pal (1971)
u	adult mortality	0.2 (day^{-1})	Gilles & Warrell (1993); Rajagopalan <i>et al.</i> (1977)
K	carrying capacity	10^5 (ha^{-1})	
H, Z	human and cattle densities (constant) used in deriving the main result shown in figure 2	100–500 (ha^{-1})	
a_H, a_Z	blood-feeding preference for humans and cattle		
	<i>A. funestus</i>	$a_Z/a_H = 0.0011$	Killeen <i>et al.</i> (2001)
	<i>A. gambiae s.s.</i>	$a_Z/a_H = 0.021$	Killeen <i>et al.</i> (2001)
	<i>A. gambiae s.l.</i>	$a_Z/a_H = 1.61$	Killeen <i>et al.</i> (2001)
	<i>A. arabiensis</i>	$a_Z/a_H = 1.61$	Killeen <i>et al.</i> (2001)
HBI'	human blood index when humans and livestock live together		
	<i>A. stephensi</i> (NWFP in Pakistan)	0.01%	Hewitt & Rowland (1999)
	<i>A. culicifacies</i> (NWFP in Pakistan)	0.05%	Hewitt & Rowland (1999)
	<i>A. arabiensis</i> (Kankiya in Nigeria)	0.75%	Killeen <i>et al.</i> (2000a)
	<i>A. gambiae s.l.</i> (Kaduna in Nigeria and Namawala in Tanzania)	0.90–0.95%	Killeen <i>et al.</i> (2000a)
δ_H, δ_Z	insecticide-spraying rate at human and cattle sites (δ_i/u : the mosquito mortality caused by the insecticide spray, relative to the natural mortality, at each site $i = H, Z$)		
malaria parasite			
β (β')	malaria transmission rate from mosquito to human (from human to mosquito)	<i>ca.</i> 0.1 (bite^{-1})	
ν	recovery rate of malaria-infected human	0.01 (day^{-1})	Gilles & Warrell (1993)
M	density of adult female mosquitoes		
X	density of malaria-infected humans		
Y	density of malaria-infected mosquitoes		

$$\frac{D}{u_0} > \frac{\Delta F}{F'}, \text{ with } \Delta F = F - F'. \quad (2.17)$$

Thus, if mortality resulting from the insecticide spray $D = Q\delta_H + (1 - Q)\delta_Z$ relative to the natural mortality, u_0 , is larger than the threshold (the right-hand side of equation (2.17)), the insecticide-resistant genotype spreads in the mosquito population. The left-hand side of equation (2.17) represents one advantage of insecticide resistance (the mortality reduction in resistant mosquitoes in the insecticide environment), and the right-hand side represents the cost of resistance. Thus, equation (2.17) simply implies that resistance evolves when the benefit of escaping the insecticide exceeds the cost of resistance.

We now combine these two analyses to obtain conditions for robust malaria control that does not allow for the development of insecticide resistance.

(e) *Malaria control free from the development of insecticide resistance in mosquitoes*

Combining the condition for malaria eradication (equation (2.13)) with that for the prevention of the development of insecticide resistance (equation (2.17)), we see

that malaria can be eradicated without the development of insecticide resistance in the vector if the following condition is met:

$$\frac{1}{G(\rho)} < \frac{u}{u_0} = \frac{u_0 + D}{u_0} < \frac{F}{F'}, \quad (2.18)$$

where $G(\rho)$ is defined in equation (2.14a).

We now examine this condition in terms of the mortality resulting from the insecticide spraying (δ_H and δ_Z) and the cattle density (Z), which we choose as the control parameters because they are relatively easy to control in practice. Throughout the analysis we set the human density H to be constant, and then the dependence of the cattle density Z is only through $\rho = Z/H$. By changing the cattle density, the probability that the mosquitoes visit the site of the dead-end host (cattle) rather than that of the amplifying host (human) of the malaria parasite is changed, thereby influencing the ease of malaria control. The cattle density also influences the total mortality resulting from the insecticide spray, because it changes the mosquito visiting rate of the human and cattle sites where the insecticide can be sprayed at different rates. We first

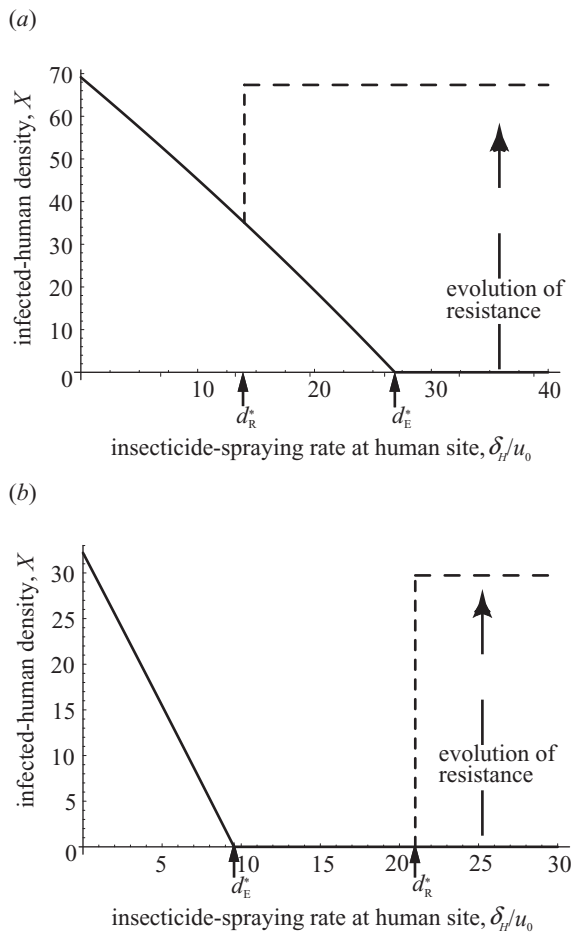


Figure 2. The equilibrium density of malaria-infected humans as a function of the insecticide-spraying rate at the human site. In each panel, the solid line indicates the malaria-infected human density at equilibrium before the evolution of insecticide resistance (obtained from equations (2.5) and (2.6)), and the dashed line indicates that after the spread of insecticide resistance in mosquitoes (obtained from the same equations but replacing F by F' and u by u_0 in equation (2.5)). (a) When the cattle density is low, malaria control fails because of the evolution of insecticide resistance. In the absence of insecticide resistance (solid line), malaria is eradicated if the insecticide-spraying rate is larger than the threshold d_E^* . However, insecticide resistance evolves if the spraying rate is larger than d_R^* . (b) If the cattle density is sufficiently large, however, evolution-free eradication is possible. The two threshold spraying rates exist as in (a), but now the reverse inequality $d_E^* < d_R^*$ holds. Hence, if the spraying rate is in the range $d_E^* < \delta_H/u_0 < d_R^*$, malaria can be eradicated without allowing the development of insecticide resistance in mosquitoes. The parameters are $K = 1.5 \times 10^5$, $H = 100$, $F = 100$, $F' = 50$, $b = 0.003$, $u_0 = 0.2$, $\beta = 0.1$, $\beta' = 0.1$, $\nu = 0.01$, $a_Z/a_H = 10$ and $\delta_Z = 0$. The cattle density Z is (a) 130 and (b) 180. See table 1 for the definition of parameters.

examine the case where the insecticide is sprayed only at the human site ($\delta_H > 0$ and $\delta_Z = 0$); we will consider the case where it is sprayed at either site ($\delta_H > 0$ and $\delta_Z > 0$) later.

If the insecticide is sprayed only at the human site ($\delta_H > 0$ and $\delta_Z = 0$), then the total mortality resulting from the insecticide is $D = Q\delta_H$. If the insecticide spraying rate at the human site is varied, there are two thresholds for

δ_H/u_0 : one for the eradication of the malaria parasite (d_E^*), and the other for the development of insecticide resistance in mosquitoes (d_R^*). The condition for malaria eradication (equation (2.13)) is

$$\frac{1}{G(\rho)} < \frac{u_0 + \delta_H Q}{u_0}, \quad (2.19)$$

with $Q = 1/(1 + k\rho)$. This yields

$$\frac{\delta_H}{u_0} > d_E^* \equiv (1 + k\rho) \left(\frac{1}{G(\rho)} - 1 \right). \quad (2.20)$$

The condition (equation (2.17)) for the prevention of the development of insecticide resistance is rewritten as $(u_0 + Q\delta_H)/u_0 < F/F'$ or

$$\frac{\delta_H}{u_0} < d_R^* \equiv (1 + k\rho) \left(\frac{F}{F'} - 1 \right). \quad (2.21)$$

Figure 2a illustrates the malaria-infected human density at equilibrium when the cattle density is relatively low. Along the horizontal axis, the mosquito mortality from the insecticide spray δ_H at the human site relative to the natural mortality u_0 is varied. The malaria-infected human density decreases as the insecticide-spraying rate increases (solid line), and malaria is eradicated when the relative mortality caused by the insecticide exceeds the threshold d_E^* . However, if the relative mortality caused by the insecticide exceeds d_R^* then the mosquitoes can spread. Once insecticide resistance has developed in the mosquito population, the malaria-infected human density rises again (dashed line in figure 2a). We found that the insecticide-spraying rate necessary for malaria eradication is greater than the rate allowing the development of insecticide resistance ($d_E^* > d_R^*$). If this is the case, there is no hope for evolution-free control of malaria when cattle density is low—when the spraying rate is low malaria is endemic and when it is high insecticide-resistant mosquitoes emerge, leading again to the endemism of malaria.

However, the situation drastically changes when we increase cattle density (figure 2b). The threshold spraying rate for malaria control is now lower than the threshold for the spread of insecticide resistance, i.e. $d_E^* < d_R^*$. Thus, the parameter space is divided into three regions: if the spraying rate is too low ($\delta_H/u_0 < d_E^*$), malaria persists as expected; if the spraying rate is too high ($\delta_H/u_0 > d_R^*$), insecticide resistance spreads in the mosquito population and malaria control fails; but if the spraying rate is in between the two thresholds ($d_E^* < \delta_H/u_0 < d_R^*$), malaria is eradicated without the development of insecticide resistance in mosquitoes.

(f) *Anthropophilic and zoophilic mosquitoes*

In discussing the effects of insecticide spraying and zoophylaxis, we have so far focused on zoophilic mosquitoes ($k > 1$), which are rather common in Asian malaria vectors. Here, we consider the situation where mosquitoes are anthropophilic ($k < 1$), as is often the case in the African malaria vectors. Figure 3 plots the threshold δ_H/u_0 for malaria eradication when the vector is zoophilic ($k = 10$; figure 3a) and when it is anthropophilic ($k = 0.05$; figure 3b). Compared with the case of zoophilic mosquitoes discussed so far, the effect of livestock on the malaria control becomes a little more complicated if the

mosquito is anthropophilic. The introduction of cattle at a low density, while keeping the same insecticide-spraying rate, would make malaria control difficult. In this region, increasing cattle density increases the threshold insecticide-spraying rate necessary for eradicating malaria. By increasing the cattle density further, however, malaria control becomes possible again (figure 3*b*). This is in sharp contrast to the results for zoophilic mosquitoes, in which increasing cattle density always makes malaria control easier (figure 3*a*).

There is an apparent discrepancy between these results and those of Sota & Mogi (1989). In the model of Sota & Mogi (1989), introduction of the cattle makes the situation worse if the mosquito is zoophilic. Sota & Mogi assumed that the cattle and humans live in the same compound (i.e. within the range of mosquito daily feeding activity); whereas our model assumed that cattle and humans are sufficiently separated. In § 2h we analyse the mixed-habitat model, corresponding to the situation assumed in the model of Sota & Mogi (1989), and show how these differences have various implications for malaria control.

(g) Insecticide spraying at the cattle site

In § 2e,f we varied the insecticide-spraying rate only at the human site, keeping the spraying rate at the cattle site at zero. We here examine the case where the insecticide-spraying rates at both sites can be varied. As is clear from the definition of total mosquito mortality resulting from the insecticide (equation (2.4)) and the conditions (equation (2.18)) for malaria control and the development of insecticide resistance in mosquitoes, the threshold spraying rates constitute two parallel lines in the $\delta_H - \delta_Z$ plane (figure 4). Therefore our conclusion from the analysis with $\delta_Z = 0$ remains qualitatively the same if we vary both δ_H and δ_Z . However, as a result of the differences in the human and cattle densities and the differences in mosquito preference for humans and cattle as a blood meal, the efficiency of the insecticide would be greatly influenced by the location where it is sprayed. If mosquitoes are anthropophilic, more mosquitoes visit a human site than a cattle site ($Q > 1/2$), and thus spraying the same amount of insecticide at the human site would kill more mosquitoes than if it is sprayed at the cattle site. The reverse is true if $Q < 1/2$.

(h) Mixed habitat: cattle living at a human dwelling

Next we consider the case where humans and cattle live within the mosquito daily blood-searching range. In the northwestern part of Pakistan, for example, most households with domestic animals live together with their animals in a high-walled compound (Hewitt *et al.* 1994; Bouma & Rowland 1995). In this mixed situation, we focus on the difference in the b_H and b_Z rates at which a mosquito bites humans and cattle, respectively. The total mosquito biting rate \tilde{B} in a population with H humans and Z cattle is then

$$\tilde{B} = b_H H + b_Z Z. \tag{2.22}$$

The mosquito-density dynamics are the same as those given by equation (2.5) with B replaced by \tilde{B} . The malaria dynamics are given by equations (2.6) by simply replacing Q by b_H and $(1 - Q)$ by b_Z . The condition for successful malaria control, corresponding to equation (2.18) is then

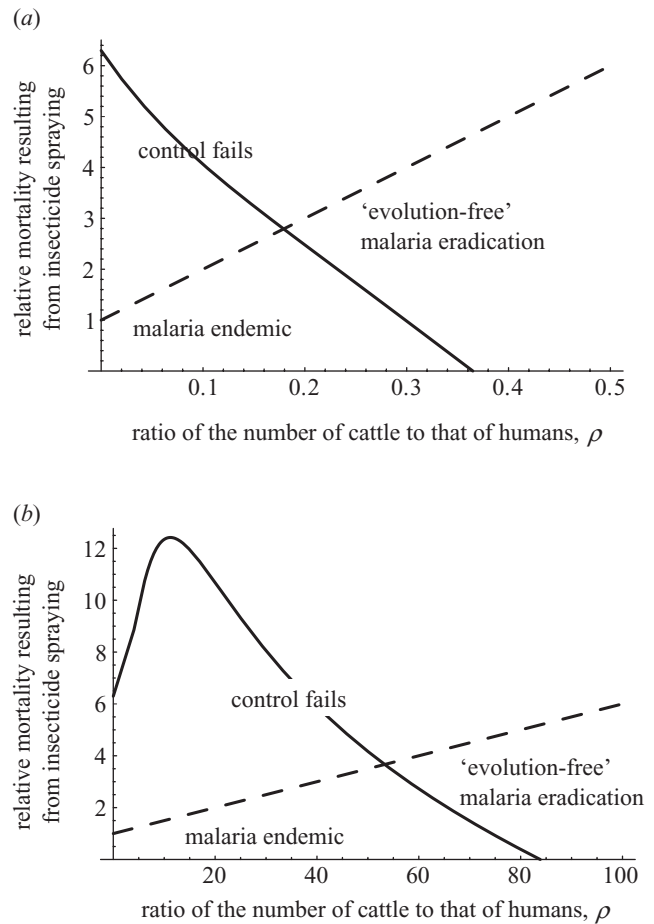


Figure 3. The threshold relative mortality d_E^* resulting from spraying insecticide for malaria eradication, equation (2.20), as a function of the ratio of the number of humans to that of cattle, ρ . Along the horizontal axis, representing $\rho = Z/H$, the cattle density Z is varied relative to a fixed human density H . If we spray the insecticide more intensely than this threshold, d_E^* (solid line), we can eradicate malaria. If, however, the relative mortality resulting from spraying insecticide is above another threshold d_R^* (dashed line), then insecticide resistance evolves in the mosquito population, thereby leading to the failure of malaria control. If the insecticide-spraying intensity is kept in the range $d_E^* < \delta_H/u_0 < d_R^*$ (the region labelled ‘evolution-free’ malaria eradication), malaria can be eradicated without allowing for the development of insecticide resistance. (a) When the mosquito is highly zoophilic ($k > 1$), introduction of the cattle always reduces the threshold for malaria eradication. (b) However, when the mosquito is anthropophilic ($k < 1$), the situation will be worse if we introduce small numbers of cattle. The parameters are the basic reproductive ratio, equation (2.14*b*), $r_0 = 27$, and the mosquito growth rate, equation (2.14*c*), $\lambda_0 = 10$. The ratio of the mosquito-feeding preference for humans over cattle is (a) $k = 0.10$ and (b) $k = 0.05$.

$$\frac{1}{\tilde{G}(\rho)} < \frac{u}{u_0} < \frac{F}{F'} \tag{2.23}$$

where

$$\tilde{G}(\rho) = \frac{1}{\tilde{r}_0} + \frac{1}{\tilde{\lambda}_0} \frac{1}{1 + k\rho} \tag{2.24a}$$

$$\tilde{r}_0 = \frac{\beta\beta'(b_H)^2HK}{u_0v} \tag{2.24b}$$

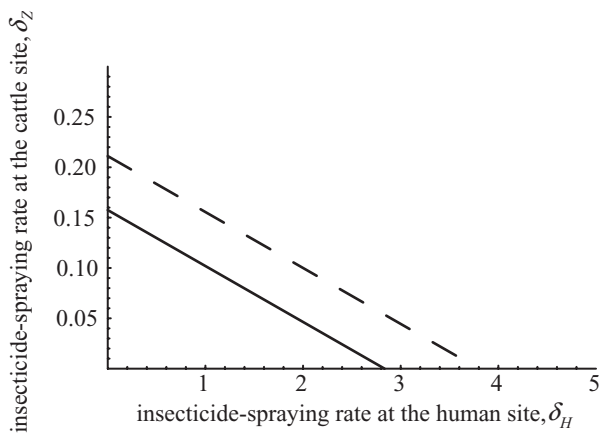


Figure 4. The effect of spraying insecticide at both the human and the cattle sites. Axes show the insecticide spraying rates δ_H at the human site and δ_Z at the cattle site. There are two parallel lines that correspond to the condition (equation (2.13)) for malaria eradication (solid line), and the condition (equation (2.17)) for the spread of insecticide resistance (dashed line). If $Z > H$, as shown in this figure ($Z = 180$ and $H = 100$), spraying insecticide at the cattle site is more efficient (i.e. the eradication can be achieved with less spraying) than spraying at the human site. The reverse is true if $Z < H$ (not shown). The parameters other than the spraying rates are the same as in figure 2.

$$\tilde{\lambda}_0 = \frac{b_H F H}{u_0}, \quad (2.24c)$$

with $\tilde{k} = b_Z/b_H$ and $\rho = Z/H$; \tilde{r}_0 and $\tilde{\lambda}_0$ have the same meanings as before, i.e. they give the base values for the basic reproductive ratio of the malaria parasite and the reproductive value of the mosquito when we examine the effect of introducing livestock and insecticide.

In the mixed situation, inserting livestock always acts against malaria control (see figure 5). The results are therefore quite different from those of the model in § 2e where the human and cattle sites are sufficiently separated relative to the mosquito daily blood-searching range. This has a very important implication: for zooprophyllactic control to be successful, the separation of human and livestock sites is critically important. Another important point is the difference between our result for the mixed habitat and that of the model of Sota & Mogi (1989), in which they also assume a mixed habitat of humans and livestock but showed that malaria can be controlled by zooprophyllaxis. This difference is caused by their inclusion of the satiation effect in blood feeding, which we discuss in greater detail in § 3.

3. DISCUSSION

Dichlorodiphenyltrichloroethane (DDT) has been one of the major insecticides used to control malaria all over the world. The morbidity of malaria was reduced by the DDT spraying campaign in the 1960s and 1970s (Roberts *et al.* 1997). However, DDT-resistant mosquitoes evolved and spread following this worldwide campaign (WHO 1992). Owing to this counter-evolution in mosquitoes and the reported detrimental effects of DDT on wildlife, the use of DDT has been banned in many countries. The

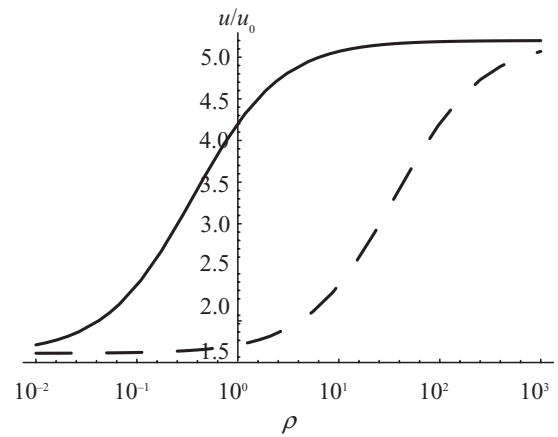


Figure 5. The threshold for malaria eradication when humans and cattle cannot be separated. The horizontal axis and the vertical axis are the same as in figure 3. The solid line is the situation where the mosquito is zoophilic, and the dashed line is the situation where the mosquito is anthropophilic. If we cannot separate the human and cattle sites, the introduction of cattle makes malaria eradication difficult regardless of whether the mosquito is zoophilic or anthropophilic. The parameters are $\tilde{r}_0 = 5.2$, $\tilde{\lambda}_0 = 2$. The ratio of blood-feeding preference is $k = 10$ for the solid line and $k = 0.1$ for the dashed line.

WHO currently recommends pyrethroid-(insecticide) treated materials, such as insecticide-impregnated bednets, instead of DDT (WHO 2000). The development of pyrethroid resistance and cross-resistance against both DDT and pyrethroid have been reported (Brodgon & McAllister 1998; WHO 2000). This again emphasizes the importance of a control strategy that takes into account the development of resistance. Our model suggests that the combined use of livestock and insecticide (either DDT or pyrethroid) will enable us to control malaria without the evolution of insecticide resistance. This is in sharp contrast to the combined use of different insecticides (e.g. DDT and pyrethroid), which is likely to fail owing to the development of multiple resistance (e.g. knockdown resistance conferring a cross-resistance to DDT and a wide range of pyrethroids; WHO (2000)).

Bouma & Rowland (1995) found that malaria prevalence is higher in households with livestock than in households without livestock in the Northwest Frontier province of Pakistan. The malarian vectors (*A. culicifacies* and *A. stephensi*) are highly zoophilic, and the ratio of livestock density to human density is high. In this region, the domestic animals are kept close to human domestic sites, which corresponds to the mixed-habitat case of our model. Our mixed-habitat model predicts that placing livestock among humans leads only to a higher malaria prevalence. As we have shown, habitat separation is primarily important for zooprophyllaxis to work.

An apparently contradicting result was obtained by Sota & Mogi (1989), who also assumed a mixed habitat of humans and livestock, but showed that malaria can be controlled by zooprophyllaxis. This apparent discrepancy is caused by different assumptions in the models with respect to the blood-feeding process: our model and the model of Sota & Mogi (1989) become consistent with each other if the blood-feeding rate is far below the satiation level.

Sota & Mogi (1989) incorporated a satiation effect for mosquito blood feeding as a function of blood-host density. With this assumption, increasing livestock density can attract mosquitoes to dead-end hosts without greatly increasing the total blood-feeding rate, leading to successful malaria control. Comparing this with the result of our mixed-habitat model, which ignores blood-host satiation, we see that blood satiation is an essential factor for the success of zooprophylaxis in the mixed-habitat case.

As shown above, if the blood-host density is far below the satiation level of blood feeding, then the model of Sota & Mogi (1989) approaches our mixed-habitat model, and therefore zooprophylaxis will unconditionally fail. This is what Bouma & Rowland (1995) suggested in interpreting their results in northwest Pakistan in the context of the model of Sota & Mogi (1989)—they argued that the finding that malaria prevalence is higher in households with livestock than in those without livestock can be explained by assuming that blood feeding is not satiated. Our model then states that even in such areas malaria can be controlled by placing livestock ‘sufficiently’ far from the human dwelling, where a ‘sufficient’ distance is roughly given by the mosquito daily blood-searching distance. We expect that if we take both blood-feeding satiation and site separation into account, then malaria control would become easier, which we will examine in a separate forthcoming paper (I. Kawaguchi and A. Sasaki, unpublished data).

One may think that another counter-evolution in mosquitoes would prevent the successful control of malaria through zooprophylaxis. In zooprophylaxis, the mosquitoes are attracted to newly placed livestock. We should note, however, that this modulation *increases* mosquito fitness by supplying more blood, while surely reducing the basic reproductive ratio of the malaria parasite (because their vectors are attracted more to dead-end than to amplifying hosts). Hence, no counter-evolution, or evolutionary change that acts against malaria control, would be expected in the mosquito population, because avoiding visits to cattle sites is maladaptive for mosquitoes. If, however, the insecticide is sprayed mostly at one site, then mosquitoes would avoid visiting this site and this creates an advantage because by doing so the mosquito can reduce the risk of mortality. Alternatively, mosquitoes that are more resistant to the insecticide would have an advantage over other mosquitoes (Killeen *et al.* 2002). If this altered preference is heritable, mosquitoes will be attracted more to the site where the insecticide is not sprayed. If we wish to preclude the failure of control by the spread of an altered site preference, it is necessary to spray the insecticide at the site of the amplifying host (i.e. humans). If we spray the insecticide at a human dwelling thoroughly, then mosquitoes will avoid visiting this site owing to the repellent effect of the insecticide. Counter-evolution in mosquitoes then makes the control of malaria via zooprophylaxis easier, rather than harder (Killeen *et al.* 2000b).

Strategies similar to the one proposed for malaria eradication in this paper would also apply to the control of other vector-borne infectious diseases. Japanese encephalitis is one of the major infectious diseases in Southeast Asia and India (WHO 1995), in which swine rather than humans are the major amplifying host (Mogi & Sota 1991). Hence, the presence of swine in the vicinity of a

human dwelling is a risk factor for Japanese encephalitis, but cattle can again serve as the dead-end host livestock (Mogi & Sota 1991). It is then possible to design an eradication strategy for Japanese encephalitis by placing the cattle sites near the swine site (amplifying host) thereby preventing insecticide resistance from spreading in the mosquitoes. The presence of cattle (i.e. a dead-end host) alone is not enough to prevent epidemics—the relative local densities of the amplifying and dead-end hosts, together with their spatial configuration relative to human dwellings must satisfy a condition for zooprophylaxis to take effect (Mogi & Kamimura 2000). It is again preferable to spray insecticide at the site of the amplifying host (swine), to preclude any failure of disease eradication as a result of the evolution of mosquitoes that avoid visiting the site where the insecticide is sprayed.

The present model has a number of potential limitations. We have ignored the explicit spatial structure in our model. The degree to which mosquitoes are attracted to livestock and the effect of insecticide should, however, depend on the spatial arrangement of livestock (e.g. uniform versus clumped) and the distance to the human dwellings. If the livestock site is too far from the human site, the mosquito population tends to be divided into those visiting humans and those visiting livestock, reducing the effect of zooprophylaxis. As we have shown in our mixed-habitat model, placing livestock too close to the human site (relative to the mosquito’s daily blood-searching range) again reduces the efficiency of zooprophylaxis. Studies on the genetic variation of mosquitoes with respect to site preference are critically important to the practical problems raised in this paper. The cost of insecticide resistance is assumed to be relatively large. In spite of some supporting evidence listed in table 1, a thorough understanding of resistance, cross-resistance and the costs involved is still needed and these factors are presently under intensive study.

The implications of the results derived in this paper can be summarized, in terms of the relative mosquito mortality u/u_0 of the insecticide, as follows.

- (i) Excess use of insecticide leads to the failure of malaria control, equation (2.17). For example, if the fecundity of insecticide-resistant mosquitoes is half that of insecticide-sensitive mosquitoes ($\Delta F/F' = 1$), intense insecticide spraying (i.e. causing more than 50% of total mosquito deaths, $D/u_0 > 1$) leads to the development of resistant mosquitoes, which in turn leads to the re-emergence of malaria. However, the insecticide-spraying rate must be larger than a certain threshold (equation (2.13)) to eradicate malaria. To eradicate malaria, we need to spray thoroughly with insecticide so that most mosquito mortality is caused by this insecticide. Under such an intensive spraying regime, the development of insecticide resistance is inevitable even if the cost of resistance is fairly large.
- (ii) This evolutionary dilemma can be resolved if one can reduce the basic reproductive ratio, R_0 , of the malaria parasite by attracting mosquitoes to the dead-end hosts of the parasite. We can then make the threshold spraying rate for the development of

insecticide resistance, δ_R^* , higher than the threshold δ_E^* for malaria eradication.

- (iii) If the mosquito is zoophilic, using dead-end livestock always acts in favour of malaria control. We found, however, that using livestock would make malaria control more difficult if the mosquito is anthropophilic—the effect of raising the biting rate by placing livestock is greater than the effect of increasing the fraction of dead-end bites. Increasing the number of cattle further, it is again possible to control malaria successfully even with an anthropophilic vector mosquito (see figure 3*b*).
- (iv) If we cannot separate the human dwelling from the cattle, the introduction of cattle always acts against malaria control. Separating humans and cattle is thus very important in control via zooprophyllaxis.

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REFERENCES

- Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control*. Oxford University Press.
- Aron, J. L. & May, R. M. 1982 The population dynamics of malaria. In *Population dynamics of infectious disease* (ed. R. Anderson), pp. 129–179. New York: Chapman & Hall.
- Bailey, T. J. 1982 *The biomathematics of malaria*. London: Griffin.
- Bouma, M. & Rowland, M. 1995 Failure of passive zooprophyllaxis: cattle ownership in Pakistan is associated with a higher prevalence of malaria. *Trans. R. Soc. Trop. Med. Hyg.* **89**, 351–354.
- Brodgon, W. G. & McAllister, J. C. 1998 Insecticide resistance and vector control. *Emerging Infect. Dis.* **4**, 605–613.
- Brown, A. W. A. 1983 Insecticide resistance in culicidae. In *Integrated mosquito control methodologies. 1. Experience and components from conventional chemical control* (ed. M. Laird & J. Miles), pp. 161–235. New York: Academic.
- Brown, A. W. A. & Pal, R. 1971 *Insecticide resistance in arthropods*. Geneva: WHO.
- Gilles, H. M. & Warrell, D. A. 1993 *Bruce-Chwatt's essential malariaology*, 3rd edn. New York: Oxford University Press.
- Graves, P. M., Burkot, T. R., Saul, A. J., Hayes, R. J. & Carter, R. 1990 Estimation of anopheline survival rate. Vectorial capacity and mosquito infection probability from malaria vector infection rates in villages near Madang, Papua New Guinea. *J. Appl. Ecol.* **27**, 134–147.
- Habtewold, T., Walker, A., Curtis, C. F., Osir, E. & Thapa, N. 2001 The feeding behaviour and plasmodium infection of anopheles mosquitoes in southern Ethiopia in relation to the use of insecticide-treated livestock for malaria control. *Trans. R. Soc. Trop. Med. Hyg.* **95**, 584–586.
- Hewitt, S. & Rowland, M. 1999 Control of zoophilic malaria vectors by applying pyrethroid insecticides to cattle. *Trop. Med. Int. Hlth* **4**, 481–486.
- Hewitt, S., Kamal, M., Muhammad, N. & Rowland, M. 1994 An entomological investigation of the likely impact of cattle ownership on malaria in an Afghan refugee camp in the North West Frontier Province of Pakistan. *Med. Vet. Entomol.* **8**, 160–164.
- Killeen, G. F., McKenzie, F. E., Foy, B. D., Schieffelin, C., Billingsley, P. F. & Beier, J. C. 2000*a* A simplified model for predicting malaria entomologic inoculation rates based on entomologic and parasitologic parameters relevant to control. *Am. J. Trop. Med. Hyg.* **62**, 535–544.
- Killeen, G. F., McKenzie, F. E., Foy, B. D., Schieffelin, C., Billingsley, P. F. & Beier, J. C. 2000*b* The potential impact of integrated malaria transmission control on entomologic inoculation rate in highly endemic areas. *Am. J. Trop. Med. Hyg.* **62**, 545–551.
- Killeen, G. F., McKenzie, F. E., Foy, B. D., Bøgh, C. & Beier, J. C. 2001 The availability of potential hosts as determinant of feeding behaviours and malaria transmission by African mosquito populations. *Trans. R. Soc. Trop. Med. Hyg.* **95**, 469–476.
- Killeen, G. F., Fillinger, U. & Knols, B. 2002 Advantages of larval control for African malaria vectors: low mobility and behavioural responsiveness of immature mosquito stages allow high effective coverage. *Malaria J.* **1**, 8–15.
- Lindsay, S. W., Alonso, P. L., Armstrong-Schellenberg, J. R. M., Hemingway, J., Adiamah, J. H., Shenton, F. C., Jawa, M. & Greenwood, B. M. 1993 A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 7. Impact of permethrin-impregnated bed nets on malaria vectors. *Trans. R. Soc. Trop. Med. Hyg.* **87**(Suppl. 2), 45–51.
- Macdonald, G. 1957 *The epidemiology and control of malaria*. Oxford University Press.
- Mogi, M. & Kamimura, K. 2000 Japanese encephalitis: Japanese experiences. In *Mosquitoes and mosquito-borne diseases* (ed. F. S. P. Ng & H. S. Yong), pp. 137–148. Kuala Lumpur: Academy of Sciences Malaysia.
- Mogi, M. & Sota, T. 1991 Towards integrated control of mosquitoes and mosquito borne diseases in ricelands. In *Advances in disease vector research*, vol. 8 (ed. K. Harris), pp. 47–75. New York: Springer.
- Rajagopalan, P. K., Menon, P. K. B. & Brooks, G. D. 1977 A study on some aspects of *Culex pipiens fatigans* population in an urban area, Faridabad, northern India. *Indian J. Med. Res.* **65**, 65–76.
- Roberts, D. R., Laughlin, L. L., Hsheuh, P. & Legeters, L. 1997 DDT, global strategies and a malaria control crisis in South America. *Emerging Infect. Dis.* **3**, 295–302.
- Saul, A. J., Graves, P. M. & Kay, B. H. 1990 A cyclical feeding model for pathogen transmission and its application to determine vectorial capacity from vector infection rates. *J. Appl. Ecol.* **27**, 123–133.
- Seyoum, A., Balcha, F., Balkew, M., Ali, A. & Gebre-Michael, T. 2002 Impact of cattle keeping on human biting rate of anopheline mosquitoes and malaria transmission around Ziway, Ethiopia. *East Afr. Med. J.* **79**, 485–490.
- Sota, T. & Mogi, M. 1989 Effectiveness of zooprophyllaxis in malaria control: a theoretical inquiry, with a model for mosquito populations with two bloodmeal hosts. *Med. Vet. Entomol.* **3**, 337–345.
- White, G. B., Magayuka, S. A. & Boreham, P. F. L. 1972 Comparative studies on sibling species of the *Anopheles gambiae* Giles complex (Dipt., Culicidae): bionomics and vectorial activity of A and species B at Segera, Tanzania. *Bull. Entomol. Res.* **62**, 295–317.
- WHO 1992 *Vector resistance to pesticides*. WHO technical report series, 818. Geneva: WHO.
- WHO 1995 *Vector control for malaria and other mosquito-borne diseases*. WHO technical report series, 857. Geneva: WHO.
- WHO 2000 *WHO expert committee on malaria*. WHO technical report series, 892. Geneva: WHO.

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