

Modeling Malaria as a Complex Adaptive System

Abstract As the resistance of the malaria parasite to antimalarial drugs continues to increase, as does that of the malarial mosquito to insecticides, the efficacy of efforts to control malaria in many tropical countries is diminishing. This trend, together with the projected consequences of climate change, may prove to exacerbate substantially the significance of malaria in the coming decades.

In this article we introduce the use of an evolutionary modeling approach to simulate the adaptation of mosquitoes and parasites to the available pesticides and drugs. By coupling genetic algorithms with a dynamic malaria-epidemiological model, we derive a complex adaptive system capable of simulating adapting and evolving processes within both the mosquito and the parasite populations.

This approach is used to analyze malaria management strategies appropriate to regions of higher and lower degrees of endemicity. The results suggest that adequate use of insecticides and drugs may reduce the occurrence of malaria in regions of low endemicity, although increased efforts would be necessary in the event of a climate change. However, our model indicates that in regions of high endemicity the use of insecticides and drugs may lead to an increase in incidence due to enhanced resistance development. Projected climate change, on the other hand, may lead to a limited reduction of the occurrence of malaria due to the presence of a higher percentage of immune persons in the older age class.

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1 Introduction

Malaria is one of the world's most important vector-borne diseases; there are few infectious diseases that have as great an impact on the social and economic development of societies. Of a world population of approximately 5.3 billion people in 1990, some 2.2 billion were regarded as being at risk of contracting malaria, while some 270 million people were actually infected with the malaria parasite. At present, the distribution of malaria is mainly restricted to the tropics and subtropics, although before the Second World War malaria was a relatively common disease in many temperate areas of the world.

Although the effective use of DDT and other insecticides after 1945 led to a significant global decrease in the prevalence of malaria and to its eradication or near-eradication in temperate zones and in some tropical areas, the rate of decrease has now slowed down considerably, and a resurgence of malaria has occurred in several countries [22, 46]. The

development of resistance to insecticides is considered to be one of the main obstacles in using insecticides for vector control in any strategy of malaria control/eradication. Resistance to insecticides is most pronounced in regions of Africa, Central America and West and Southeast Asia [36].

A further obstacle is the development of resistance to antimalarial drugs in *Plasmodium falciparum*, the malaria parasite responsible for most deaths. For many centuries, malaria has been treated with an extract from the bark of the cinchona tree, namely quinine, while a new (synthetic) drug, chloroquine, which became available at the end of World War II, was found capable of preventing and curing malaria, especially because it was less toxic and effective in less frequent doses. By the 1960s, however, plasmodia resistant to chloroquine had emerged, and *P. falciparum* that are resistant to the drug are currently found throughout extensive regions of Africa, Southeast Asia and South America [7, 38, 45]. The increased selection and progressive dispersal of parasites resistant to antimalarial drugs is mainly caused by the fact that these preparations are increasingly being used as prophylactics and for self-medication, usually in insufficient doses. The problem of drug resistance has become particularly alarming in Africa, and its continual exacerbation hampers efforts to provide adequate treatment of the disease [35].

It is evident that malaria patterns have, hitherto, depended to a large extent on the effectiveness of control efforts, together with socioeconomic development. Although new drugs are being developed and work is progressing on various potential malaria vaccines, given the increasing resistance of the malaria mosquito to insecticides, on one hand, and of its parasite to antimalarial drugs, on the other, the treatment of malaria seems likely to be more problematic in the future. A further factor that may influence future malaria trends, and to which attention has only recently been paid, is the projected effect of a human-induced climate change on the transmission dynamics of malaria [6, 27–30]. Anthropogenic climate change may directly affect both the behavior and geographical distribution of the malaria mosquito and the life cycle of the parasite and, thus, may have implications for the incidence of the disease.

There are many mathematical modeling approaches to malaria, the first of which was Ross's [39]. After Ross, the models evolved and many important processes were included. Although these models are not intended to include all components of a real system, they do prove useful in studying the population dynamics of this infectious disease [2]. Furthermore, modeling experience leads to the formulation of hypotheses that may inspire experimental research, an example of which would be the model-based hypothesis that inbreeding may accelerate the buildup of drug resistance, which has recently been confirmed empirically in Papua, New Guinea [37]. Over and above enhancing scientific understanding, an important role of malaria models is to support decision making in the management of malaria control operations. A well-known example of a malaria model used for the planning of malaria control was developed during the Garki project [32]. However, in this model, resistance development, although acknowledged as a potential important effect, was not explicitly taken into account. Because the ability of organisms to develop resistance to human interventions has become an important issue in managing malaria, current modeling efforts incorporate the adaptation process by adopting either a deterministic or a stochastic approach (e.g., [1, 8, 34]).

Although the above techniques have been useful, new mathematical tools based on evolutionary processes have appeared during the last decade that are eminently suitable for modeling adaptation. According to Levins [24], it has become apparent that the classic deterministic approach is incapable of confronting the rapid and unexpected changes on the horizon. In assessing the impact of both global and local changes, the modeling of adaptation to changes and modeling of evolutionary processes themselves

provide a crucial tool with which to scan the future [20]. The aim of this article is to discuss the deployment of evolutionary modeling tools in scanning future risks of the occurrence of malaria and assessing possible means of controlling those risks.

A model designed to enhance quantitative projections of climate-related changes in the potential distribution of malaria has been developed by Martens et al. [27, 28]. Although this model does take account of how climate change directly affects the mosquito population, that is, mosquito development, feeding-frequency, longevity of the mosquito, and the climatic effect on the incubation period of the malarial parasite inside the mosquito, it does not address artificial interventions by humans and how this may affect the increased malaria risk associated with climate changes. To allow for both antimalarial control measures *and* the adaptation of mosquitoes and parasites to such malaria control policies, the simulation model created by Martens et al. (which describes the transmission dynamics between human and mosquito populations) is combined with genetic algorithms. The latter involves a general and robust evolutionary modeling approach based on the mechanics of the survival of the fittest, whereby the inclusion of the notion of variability within the population renders the genetic algorithm a suitable tool for simulating the adaptive behavior of a population within a changing environment [15, 17, 18, 21]. In this article, a simplistic, idealized model of the resistance cycles associated with insecticide and drug use in malaria control programs is presented, together with the impact of climate changes. Although this approach is adopted solely for heuristic purposes, it nevertheless succeeds in elucidating the mechanism of resistance development, interactions associated with climate change, and consequences for the implementation of strategies in malaria management.

2 The Model

2.1 Introduction

The model described in this article is an extension of the systems approach previously adopted by Martens et al. [27, 28] and addresses two general malaria control options, namely: the use of insecticides to decrease mosquito densities, and the use of drugs to suppress the viability of parasites. While Martens et al. intended to create a global model of the effects of an anthropogenically induced climate change on malaria risk, the model presented here aims at incorporating local dynamics, to derive a generic local model that takes account of human intervention in terms of insecticide and drug use and the development of resistance to these control measures.

The interaction between the human population and the mosquito population determines the transition rates among susceptible, infected, and immune populations, respectively. To this end, the mosquito system is denoted by state variable $x(t)$ and the human system by state variable $\mathbf{y}(t) \in \mathbb{R}^7$. The potential of the mosquito population to transmit *P. falciparum*¹ is in the model assumed to be influenced by temperature, $T(t)$, and by the use of insecticides, $u_1(t)$. The dynamics within the human population are affected by the transmission potential of the mosquitoes and by the use of antimalarial drugs, $u_2(t)$.

$$\begin{aligned} x(t) &= f(T, u_1) \\ \frac{d\mathbf{y}(t)}{dt} &= g(\mathbf{y}, x, u_2) \end{aligned} \tag{1}$$

¹ We have focused on the transmission dynamics of *P. falciparum* because it is the most lethal malaria parasite and is exhibiting worldwide development of resistance to antimalarial drugs.

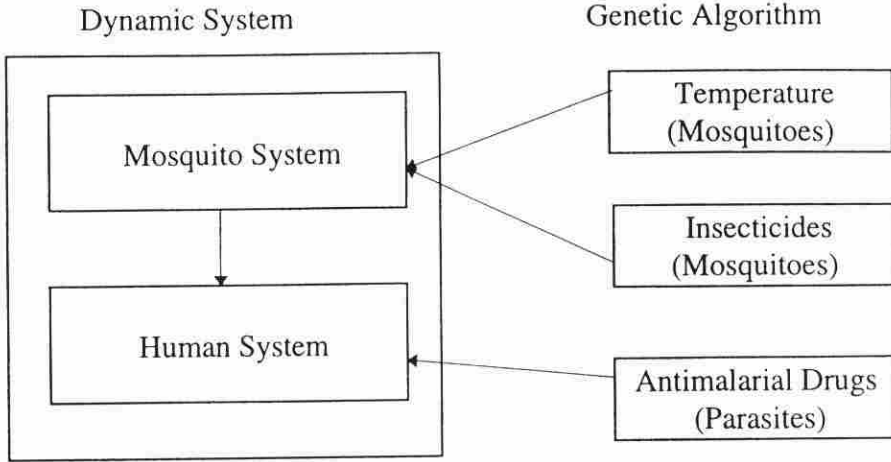


Figure 1. Simplified scheme of the integration of a system dynamic model with genetic algorithms.

To incorporate adaptation to antimalarial drugs and insecticides, this dynamic system is coupled to genetic algorithms that enable the genetic variety within the mosquito population and the parasite population (Figure 1). The genetic algorithms determine parameters that, in turn, determine the resistance of the mosquitoes and parasites and the optimum temperature for mosquito survival. The system can, therefore, be reformulated as

$$\begin{aligned}
 x(t) &= f(T^a, u_1^a, T, u_1) \\
 \frac{d\mathbf{y}(t)}{dt} &= g(\mathbf{y}, x, u_2^a, u_2)
 \end{aligned}
 \tag{2}$$

where T^a , u_1^a and u_2^a represent fixed parameters in system (Equation 1). T^a represent the change of the optimal temperature with respect to the reference value, u_1^a and u_2^a represent the degree of resistance (see Section 2.3). Now that they are simulated by genetic algorithms, they are subject to adaptations if the temperature changes or if insecticides and antimalarial drugs are used. In Sections 2.2, this original model representation (Equation 2) will be described, and in Section 2.3 the implications of the incorporation of the genetic algorithms are discussed.

2.2 A Dynamic Malaria-Epidemiological Model

2.2.1 The Mosquito Population

The (infection-related) dynamics of the mosquito population proceed much more rapidly than do human population dynamics, so that the mosquito system can be considered as being in equilibrium with respect to changes in the human population. Therefore, the description of the mosquitoes is given in terms of an equilibrium instead of in a set of differential equations. Following Garrett-Jones [13], the entire mosquito population is incorporated in a single state variable, namely: vectorial capacity. The formulation of vectorial capacity used by Martens et al. [27, 28] is multiplied by the relative fitness of mosquitoes to insecticides, F^m (see Section 2.3.1), resulting in a formulation of an adaptive vectorial capacity that includes the impact of the use of insecticides. Furthermore, an adaptive representation of survival probability can be used to describe the

adaptation of a mosquito population to a change in temperature (see Section 2.3.1):

$$x = \frac{\beta_1 \cdot z_1^2 \cdot z_2^{z_3}}{-\ln(z_2)} \cdot F^m(u_1) \quad (3)$$

where x is the adaptive vectorial capacity; β_1 incorporates variables assumed to be temperature independent (including the efficiency with which a mosquito infects a susceptible human; the propensity of the mosquito population to feed on humans; and the density of the mosquito population in relation to man). The term z_1 represents the man-biting habit (number of blood meals taken from humans per mosquito per day); z_2 is the daily survival probability of the mosquito; and z_3 is the incubation period of the parasite in the vector (in days).

The man-biting habit depends on the frequency with which one vector takes a blood-meal and the total number of these blood-meals being taken from man. The frequency of feeding depends mainly on the rapidity of digestion of a blood-meal, a rate that increases as temperature rises so that at the optimum temperature, one meal is taken every 48 hours [33]. The relation between temperature and the rapidity of blood digestion is given in [11]. The resulting equation for the man-biting habit (per day) is

$$z_1 = \frac{T - \beta_3}{\beta_2} \quad (4)$$

where β_2 is the number of “degree-days” required for the digestion of a portion of ingested blood, (36.5 degree-days at relative humidity 70–90%), β_3 is the minimum temperature required for the digestion of the blood meal (9.9°C) and T is the actual average temperature (in °C).

The vector’s longevity determines its ability to transmit a parasite, because the female mosquito has to live long enough for the parasite to complete its development. There is presumably an optimum temperature and an optimum humidity for each species of mosquito, and it is apparent that, between certain limits, longevity decreases as temperature rises, and increases as relative humidity rises [5, 31]. Data reported by Boyd [5] and Horsfall [19] on mosquito longevity indicate an optimum temperature of about 20–25°C and an optimum relative humidity of 60–90%, and the assumption about the relation between the longevity of the *Anopheles* mosquito and temperature is based on these data. The maximum mean longevity is assumed to be 10 days ($z_2 = 0.9$) at temperatures of about 20°C. The assumed (nonadaptive) relationship between temperature and daily survival probability of the adult mosquito is written as follows [21] (see Section 2.3.1 for an adaptive representation):

$$z_2 = \exp\left(\frac{-1}{-4.4 + 1.31 \cdot T - 0.03 \cdot T^2}\right) \quad (5)$$

The incubation period (duration of sporogony) in the vector must have elapsed before the infected vector can transmit the parasite. The duration of this latent period depends on two critical factors: species of parasite and ambient temperature. The parasites develop in the vector only within a certain temperature range, and whereas the minimum temperature for parasite development lies between 16 and 19°C in the case of *P. falciparum*, the proportion of parasites surviving decreases rapidly at temperatures over 32–34°C [11, 19, 26]. The relation between the incubation period and temperature (if

higher than 16°C) can be expressed in the following equation [26]:

$$z_3 = \frac{\beta_4}{T - \beta_5} \tag{6}$$

where z_3 is the incubation period of the parasite inside the vector (in days), β_4 the number of "degree-days" required for the development of the parasite (= 111 degree-days for *P. falciparum* [11]), T the actual average temperature (between β_5 and a maximum temperature of about 40°C; in °C), and β_5 the minimum temperature required for parasite development (16°C for *P. falciparum*).

2.2.2 The Human Population

The model used to describe the transition between the reservoirs of the human population at risk is based on a microparasite-epidemiological model as described in [1, 3, 4, 23]. The human population subject to a risk of malaria is divided into three categories for each of two different age classes ($i = 1$: children younger than 5; and $i = 2$: people of 5 years and older). The three categories are susceptible persons (y_1^i), infected persons (y_2^i), and immune persons (y_3^i). The latent reservoir is omitted, because the duration of a stay in this reservoir is usually very short in comparison to the residence time in the other reservoirs. The total population is represented by y_4 .

The number of susceptible persons may change over time, as they become members of the infected class at a rate r_1 . Infected individuals either die from infection at a rate $\mu_1^{(i)}$ or recover to join the immune category (at a rate r_2). Immune persons lose their immunity at a rate r_3 , and those who have lost their immunity return to the reservoir of susceptible persons. All newborn babies are assumed to be members of the category of susceptibles; as they grow older, they graduate from the younger age class to the older (at a rate λ_a). People die from other causes at a rate μ .

The dynamic behavior of the human system can be described thus (see also Figure 2)

$$dy/dt = \mathbf{M} \cdot \mathbf{y}$$

with $\mathbf{y} = [y_1^{(1)}, y_1^{(2)}, y_2^{(1)}, y_2^{(2)}, y_3^{(1)}, y_3^{(2)}, y_4]$ (7)

and

$$\mathbf{M} = \begin{bmatrix} -r_1 - \mu - \lambda_3 & 0 & 0 & 0 & r_3 & 0 & \lambda \\ \lambda_3 & -r_1 - \mu & 0 & 0 & 0 & r_3 & 0 \\ r_1 & 0 & -\mu - \mu_1^{(1)} - \lambda_a - r_2 & 0 & 0 & 0 & 0 \\ 0 & r_1 & \lambda_a & -\mu - \mu_1^{(2)} - r_2 & 0 & 0 & 0 \\ 0 & 0 & r_2 & 0 & -r_3 - \mu - \lambda_a & 0 & 0 \\ 0 & 0 & 0 & r_2 & \lambda_a & -r_3 - \mu & 0 \\ 1 & 1 & 1 & 1 & 1 & 1 & 0 \end{bmatrix}$$

where r_1 is the rate of infection, r_2 the rate of loss of infection, and r_3 the rate of loss of immunity.

The rate at which individuals become infected (r_1) depends on the adaptive vectorial capacity (x) that represents the transmission potential of the mosquito population, the proportion of infected people in the human population, the amount of drug use, and the sensitivity of malarial parasites to such drugs (i.e., the fitness of the parasites). $F^P(u_2)$ represents a maximum fitness that may decrease in the event of antimalarial drug use, depending on the degree of resistance (see Section 2.3). The use of drugs, thus, leads to a decrease in the infection rate and, consequently, an increase in the rate

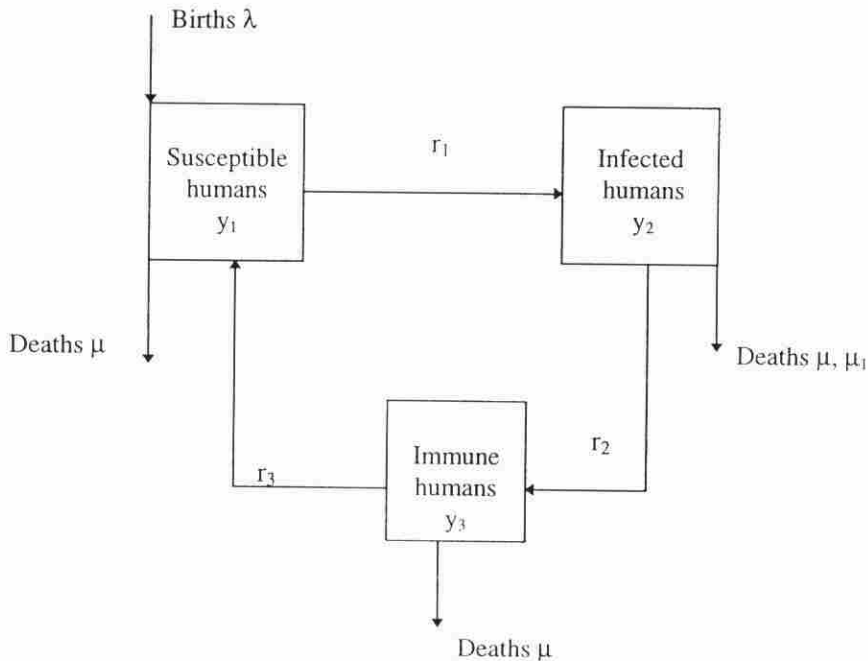


Figure 2. Scheme of the dynamics within the human system.

of losing immunity and in the rate of losing infection (formulas 9 and 10).

$$r_1 = x \cdot \frac{y_2^{(1)} + y_2^{(2)}}{y_4} \cdot F^p(u_2) \tag{8}$$

Rates of recovery from infection appear to increase with the increased longevity of living people in endemic areas. Assuming that reexposure does not occur, states of infection and immunity endure for fixed periods of time. However, if a person is further exposed before such a period has elapsed, both infection and immunity are prolonged. The basic rate of loss of infection, b_1 , is defined as the reciprocal of the average duration of infectiousness (average one year for *P. falciparum*). The basic loss rate of immunity b_2 is 0.67/year, corresponding with a mean duration of immunity of 1.5 years [3]. If infection occurs at a per capita rate r_1 , the average per capita rate of loss of infection (r_2) and loss of immunity (r_3) as a function of r_1 can be expressed as follows:

$$\text{if } r_1 = 0 \text{ then } r_2 = b_1 \text{ else } r_2 = r_1 / (e^{r_1/b_1} - 1) \tag{9}$$

$$\text{if } r_1 = 0 \text{ then } r_3 = 1/b_2 \text{ else } r_3 = r_1 / (e^{r_1/b_2} - 1) \tag{10}$$

2.3 Adaptation Modeling

Now the application of genetic algorithms to simulate the adaptation of the mosquito and the parasite population can be described. For each subject of adaptation (temperature change, use of insecticides, and use of drugs) a genetic algorithm is employed in modeling the transmission of genetic information by means of sexual reproduction. In the following sections, one of the most crucial aspects of the genetic algorithm

is discussed, namely its fitness function, as used to simulate the fitness of individual mosquitoes and parasites.

The output generated by each genetic algorithm is a set of individual parameter values of $u_{1,i}^a$, $u_{2,i}^a$ and T_i^a . In conformance with the system dynamic framework as described in Section 2.1, the averages of these parameter values are used (u_1^a , u_2^a , T^a).

If genetic algorithms are to be used to simulate the dynamics of malaria, the validity of a number of assumptions must first be considered:

- The values adopted for crossover probability (p_c) and mutation probability (p_m) are imaginary numbers and cannot be validated by empirical research. Although the selected numbers are at best educated guesses, they have no significant influence on the main conclusions, as is shown in [21].
- There is a lack of knowledge about the various shapes of the fitness functions, and those discussed in the following subsections, although mimicking observed patterns (e.g., [10, 40]), are therefore rather subjective and should be regarded as being of illustrative value only.
- There is a question as to which population size is adequate for simulating the variety within a population. Too large a population would detract from the model's usefulness as an interactive learning tool. After testing various numbers, we decided that a population of 100 individuals (mosquitoes/ parasites) would be appropriate. Although we realized that the "real" population of mosquitoes or parasites cannot be accurately simulated by reference to such a group, nevertheless, a simulation of the aggregate adaptive behavior of a representative heterogeneous group of mosquitoes and parasites can be made.

These problems are by no means unfamiliar within the modeling community. Taylor [43] discussed the lack of experimental data with which one could validate the modeling approach to the issue of resistance development.

2.3.1 The Mosquito

With the help of the genetic algorithm, sexual reproduction is implemented using the two genetic parameters, namely the crossover probability (p_c) and the mutation probability (p_m). To simulate the adaptation of mosquitoes, a crossover probability of 0.4 and a mutation rate of 0.001 were assumed. These values are consistent with those generally used in genetic algorithm applications, and the results are not sensitive to this assumption [21].

The fitness of a (biological) population is related to the chance of its members begetting descendants [16]. The expected lifetime of a mosquito is assumed to be a measure of individual fitness, since life expectancy might be related to the production of offspring. Having adopted this approach, we distinguish two pressures on the mosquito population, namely temperature change and insecticide use. We assume that adaptation to temperature change and to insecticides are independent of each other.

Adaptation to Temperature Change For every mosquito, a temperature level is assumed at which its expected lifetime would be maximized (Figure 3), but within the mosquito population there is variation of these optima among individuals. If the temperature increases over a longer period (say various years), mosquitoes for which the optimum is higher than average exhibit greater fitness. Due to the mechanisms associated with the "survival of the fittest," the average optimum temperature for longevity

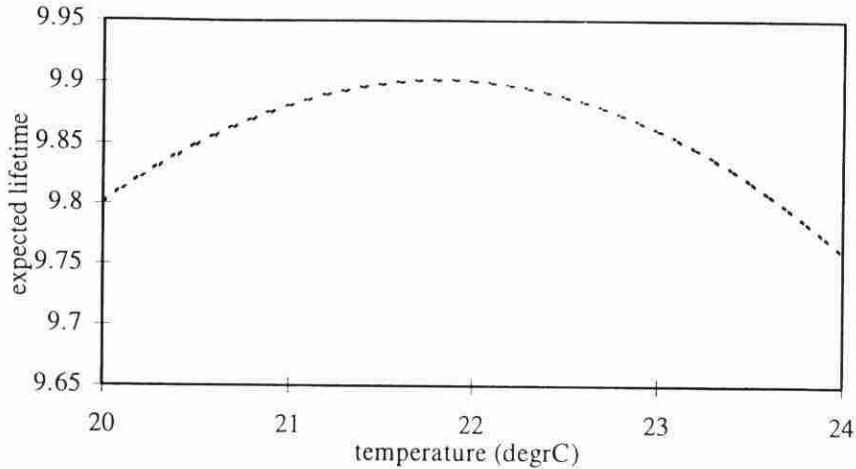


Figure 3. Life expectancy (in days) as a function of temperature (Equation 5).

will, therefore, rise.² The implementation of this process by means of a genetic algorithm proceeds as follows. Within the mosquito system, the daily probability of survival is a function of temperature (see Equation 5). Within the population, individual temperature optima are scattered around the mean temperature. For simplicity, no distinction is made in seasonal temperature changes. The daily survival probability can, therefore, be treated as a function of the *local mean temperature*, whereupon the variable T_i^a is introduced, representing the individual adaptation to temperature. This results in a daily survival probability so that the fitness function of mosquito i becomes

$$F_{T,i} = -4.4 + 1.31 \cdot (T - T_i^a) - 0.03 \cdot (T - T_i^a)^2 \quad (11)$$

If temperature T changes, the value of T_i^a will also change, since the “survival of the fittest” keeps the mosquitoes in the optimum temperature zone.

Furthermore, the daily survival probability of the adult mosquito becomes

$$z_2 = \exp\left(\frac{-1}{-4.4 + 1.31 \cdot (T - T^a) - 0.03 \cdot (T - T^a)^2}\right) \quad (12)$$

where T^a is the mean of T_i^a .

Adaptation to Insecticides An important human-induced pressure on the mosquito population is the use of insecticides. Several models have been developed to enable us to understand and manage the evolution of insecticide resistance, and nearly all of them assume that resistance is controlled by two alleles at one locus [1, 43]. However, the fitness function is based on the studies published by Schapira [40] and Tabashnik [41], although our modeling framework forces us to make subjective interpretations.

In our simulations, we distinguish three kinds of mosquitoes, namely, susceptibles, moderately-resistant, and resistant individuals, taking them as three classes of individual sensitivity to insecticides. The assumption is that a certain dose of insecticide reduces fitness in the manner depicted in Figure 4, whereby it is assumed that the same dose would have a more pronounced impact on susceptible mosquitoes than on (moderately)

² We recognize that this account of adaptation to unfavorable temperatures is just one of the possibilities. Another would be the migration of mosquitoes to microhabitats where temperatures are more suitable.

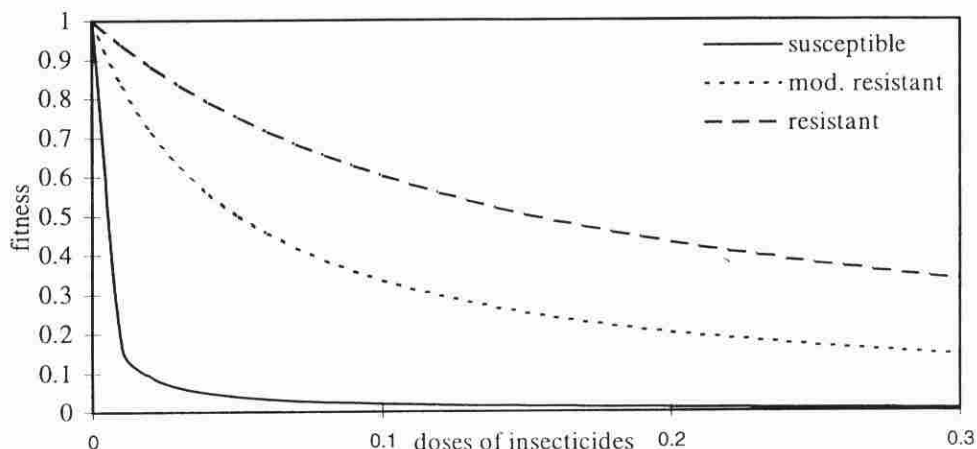


Figure 4. Relative fitness of mosquitoes related to the use of insecticides. A certain dose of insecticides leads to a reduction in fitness that is more severe in the case of susceptible than resistant individuals.

Table 1. Fitness of mosquitoes.

	$u_{1,i}$	$F_{\text{bio}}^m()$	$F_{\text{ins}}^m()$
susceptible	[0.0, 0.99)	1.0	$1 - u_1/(0.002 + u_1)$
moderately resistant	[0.99, 0.999)	0.95	$1 - u_1/(0.05 + u_1)$
resistant	[0.999, 1.0]	0.9	$1 - u_1/(0.15 + u_1)$

$F_{\text{bio}}^m()$ is relative biotic fitness. $F_{\text{ins}}^m()$ is relative fitness under insecticides.

resistant ones. The fitness function expresses the notion that the fitness of the three classes drops in a decreasing rate for a higher dose of insecticides [10, 40]. Obviously, if alternative insecticides are applied that affect the three categories differently for some reason, for example, by being more effective, the results and conclusions may differ.

In addition, the simulation incorporates a "biotic fitness" component that represents the relative fitness of the mosquito, in the event of no insecticides being used at all. A lower value for the biotic fitness of the more resistant genes explains the lower density of these genes in an insecticide-free environment. Given an initial random distribution, Table 1 is derived for the fitness of mosquitoes to which a certain dose of insecticides u_1 is applied, whereby we assume that 99% of the mosquitoes are susceptible, 0.9% are moderately resistant, and 0.1% resistant in the initial situation.

The fitness function for a mosquito $F^m(u_1)_i$ is the product of the "biotic" and "insecticide" fitness; the average fitness of the mosquito population, $F^m(u_1)$, is used in the equation for the adaptive vectorial capacity x .

2.3.2 The Parasite

The dynamics of the gene pool in parasites differ from those in the mosquitoes. Because the population of parasites is spread among the human population and the mosquito population, the transmission of resistant parasites through a vector population to other human hosts limits the efficacy of adaptation in the parasite population at large. Note that a single gene pool for parasites is assumed, although several local clusters do exist (in the hosts). In view of the lack of relevant data, we have been obliged to use the same crossover and mutation probabilities as for the mosquitoes in the reference runs.

Table 2. Fitness of parasites.

	$u_{2,i}$	F_{bio}^p	F_{dr}^p
susceptible	[0.0, 0.99)	1.0	$1 - u_2/(0.002 + u_2)$
moderately resistant	[0.99, 0.999)	0.95	$1 - u_2/(0.05 + u_2)$
resistant	[0.999, 1.0]	0.9	$1 - u_2/(0.15 + u_2)$

F_{bio}^p is relative biotic fitness. F_{dr}^p is relative fitness under drugs.

Adaptation to Drugs Having established the modeling approach to the resistance among mosquitoes to the use of insecticides, the adaptation of parasites to the use of antimalarial drugs is modeled in a similar manner. Thus, a three-phenotype model is simulated by distinguishing three kinds of parasites, namely, susceptibles, moderately resistant, and resistant individuals, and these are taken as three classes of individual sensitivity to the drugs involved. Given an initial random distribution, Table 2 is derived for the fitness of parasites to which a certain dose of drugs u_2 is applied, whereby it is assumed that 99% of the population is susceptible, 0.9% is moderately resistant, and 0.1% resistant in the initial situation.

Similarly, the fitness function for a parasite $F^p(u_2)_i$ is the product of the “biotic” and “drugs” fitness; the average fitness of the individual parasites, $F^p(u_2)$, is used to determine the impact of resistance on the transmission dynamics within the human population in Equation 8. It should be noted, however, that in some places biological advantage of chloroquine-resistant *P. falciparum* has been observed (discussed by Wernsdorfer [44]). This would imply that resistance development would proceed more rapidly than under the assumption discussed above.

2.3.3 Migration and Refugees Among Mosquitoes and Parasites

Georghiou and Taylor [14] argued that the migration of insects tends to delay the rate of evolution of resistance. In addition, the percentage of mosquitoes or parasites not reached by the antimalarial treatment (the so-called refugees) will inevitably influence resistance development. The complex adaptive systems approach takes account of both of these processes in the development of resistance, among mosquitoes as well as among parasites.

It would seem self-evident that, depending on landscape and infrastructure, mosquitoes are more or less able to migrate from place to place, and that mosquitoes susceptible to insecticides may, thus, enter a treated area. Moreover, parasites susceptible to antimalarial drugs can also migrate, whether they are carried by mosquitoes or humans. Migration is modeled by assuming that during each time step a fraction of the new population is bred under the initial conditions, that is, not yet adapted to the changed conditions.

Insecticides are sprayed on specific areas so that 100% coverage is seldom achieved. Drugs are not taken (sufficiently) by all humans, so that a fraction of the parasites escape from it. This phenomenon of refugees is modeled by assuming that during each time step, a part of the population, the size of which is randomly selected, has not been treated despite the control programs that have been implemented.

3 Results and Discussion

3.1 Introduction

The experiments deal with the consequences of the use of insecticides and antimalarial drugs, together with a temperature change, on the occurrence of malaria for a time horizon of one decade, using time steps of 0.1 year. Although malaria situations are

extremely heterogeneous with respect to resistance to change, the two types of regions distinguished are a region of low endemicity and a region of high endemicity. Although the real generational longevity among the parasites and mosquitoes is not specified, the time horizon is based on observed time elapsed in acquiring resistance [21]. Furthermore, we assume that the initial force of infection (r_1) is 2.0 per annum in highly endemic regions and 0.1 in areas of lower endemicity [28]. These values were chosen because they lie within the range of the values reported in several studies on the pristine force of infection among young children. The initial settings for these systems are given in Table 3. Areas of lower endemicity can be characterized as exhibiting low vectorial capacity resulting in a high percentage of susceptible persons ($\approx 80\%$), and low percentages of infected ($\approx 8\%$) and immune persons ($\approx 12\%$). Areas of low endemicity vis-à-vis *P. falciparum* can be found in Southeast Asia and South America. Regions of high endemicity are characterized by a relatively high vectorial capacity. In the initial situation there is a high percentage of immune ($\approx 68\%$) and infected persons ($\approx 27\%$). The younger age class especially suffers from a high percentage of infected ($\approx 45\%$). Highly endemic regions are mainly found in tropical Africa.

We now propose to report a set of results that we have derived using the complex adaptive systems approach. In the starting year, the situation is assumed to be near equilibrium. This assumption about an equilibrium state is made for analytical purposes, namely, to render the impact of control policies and temperature change on the occurrence of malaria transparent, thereby including the adaptation of mosquitoes and parasites. Therefore, we have assumed a steady-state situation in demographic, social, and economic development, although we recognize that these factors may influence future developments of malaria.

The results are presented as time series covering a period of 10 years. In view of the stochastic elements of the model, we elected to use a large number of runs (100) and determine the mean and the extremes of important indicators.³ This procedure yields ranges of uncertainty, whereby the uncertainty does not lie in the different parameter values of the model, but rather in the stochastic characteristics and the complexity of the system.

In the interest of analytical lucidity, two broad control levels for both insecticides and antimalarial drugs are distinguished, namely, the low and the high dose. In the case of a low dose, we adopt a value of u_i equal to 0.002, which represents a 50% deterioration in the fitness of susceptible mosquitoes or parasites. The high dose u_i is assumed to be equal to 0.05, such that the fitness of the moderately resistant mosquito or parasite decreases by 50%.

A typical outcome is shown in Figure 5, which shows the impact of using a low dose of insecticides. Although the input variables are the same for the 100 runs, there is a large spread in the optimal temperature for the mosquitoes, the adaptive vectorial capacity, and the incidence of malaria. Although on average the use of a low dose of insecticides leads to an increase in the incidence of malaria in the long run, it might also lead to a slow decrease of the incidence if evolutionary adaptation among mosquitoes proceeds very slowly. To envisage the trends for the various sensitivity tests we will confine ourselves to depicting the average scores in the following subsections.

3.2 Impact of Control Programs

If we consider the case in which mosquitoes and parasites do not adapt to the use of insecticides and drugs, we are able to calculate the new equilibrium given that constant levels of insecticides and/or drugs are used. Because the impact of both control programs is modeled in a similar manner, they have identical effects. The control

³ Experiments showed that a higher number of runs would not affect the mean values significantly.

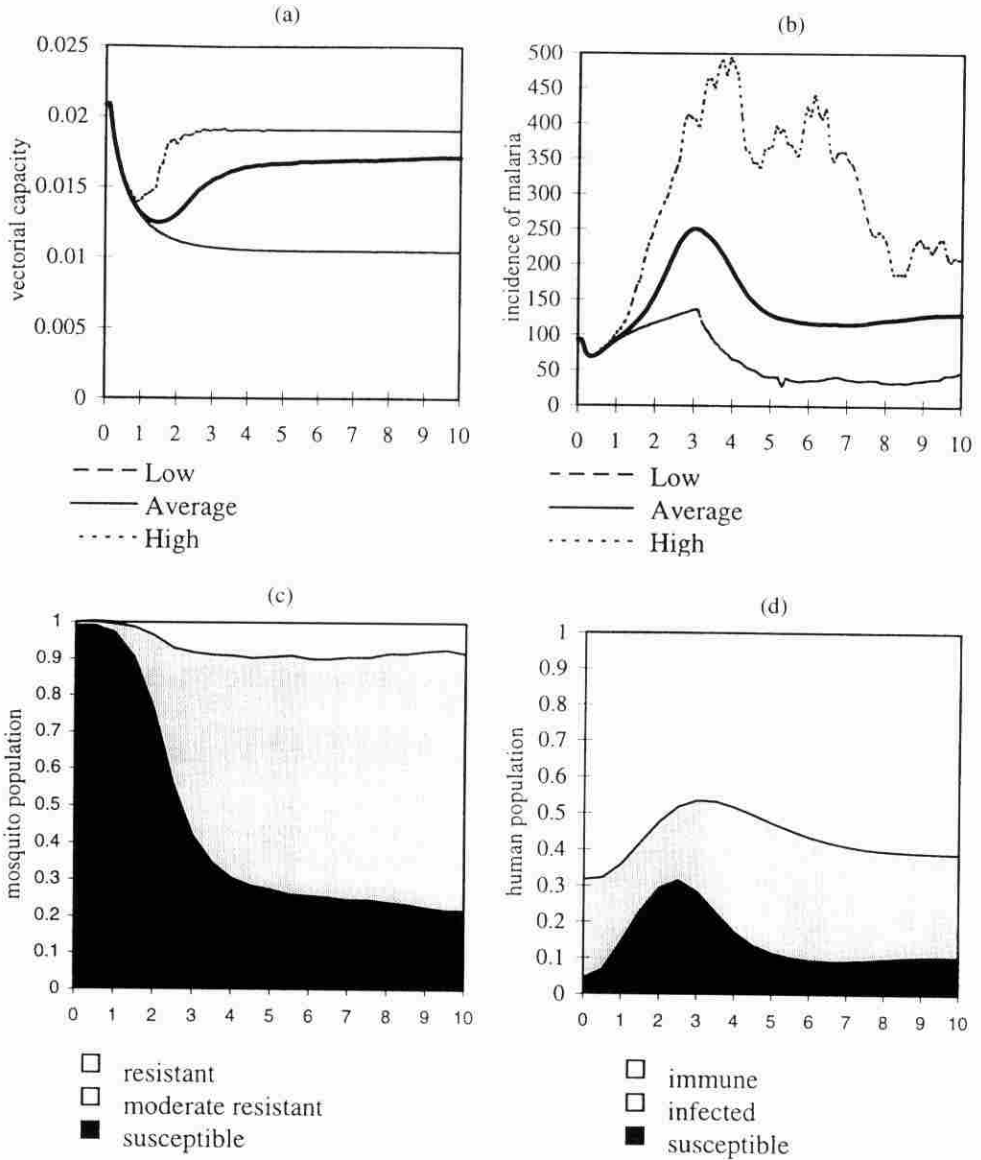


Figure 5. An example of an experiment in a region of high endemicity. Depicted are the average and extremes (a) and (b); and fraction of resistant, moderately resistant, and susceptible mosquitoes (c), and average fraction of immune and susceptible people (d), for a sample of 100 runs.

Table 3. The initial situations were arrived at as follows: For highly endemic regions an infection rate, r_1 , of 2.0 is assumed, and for regions of lower endemicity an infection rate of 0.1. The birth rate is assumed to be equal to the natural death rate, although the additional death rates due to malaria imply a slightly declining population. The initial values for β_1 , $y_1^{(0)}$, $y_2^{(0)}$, and $y_3^{(0)}$ reflect an equilibrium situation in the case of malaria-related deaths not being included.

	Low endemicity	High endemicity	Description
β_1	0.02226	0.13445	temperature-independent parameter
β_2		36.5	degree days blood digestion
β_3		9.9	minimum temperature
β_4		111	degree days development parasites
β_5		16.0	minimum temperature development parasites
T		21.88	initial local mean temperature
x	0.00335	0.02018	adaptive vectorial capacity
λ		0.02	birth rate
λ_a		0.2	aging children
μ		0.02	natural death rate
$\mu_1^{(1)}$		0.04	fatality rate (0-5)
$\mu_1^{(2)}$		0.01	fatality rate (>5)
b_1		1	basic loss rate infection
b_2		1.5	basic duration immunity
$y_1^1(0)$	0.077	0.011	susceptible persons (0-5)
$y_1^2(0)$	0.718	0.034	susceptible persons (>5)
$y_2^1(0)$	0.007	0.041	infected persons (0-5)
$y_2^2(0)$	0.076	0.231	infected persons (>5)
$y_3^1(0)$	0.008	0.039	immune persons (0-5)
$y_3^2(0)$	0.115	0.644	immune persons (>5)

program will lower the rate of infection as a result of (a) rendering the mosquitoes and/or parasites less fit, and (b) the decrease in the percentage of infected persons. The percentage of immune persons will likewise decrease, resulting in an increase in the size of the fraction of susceptible humans.

As expected, the incidence of malaria will decrease in regions of low endemicity, as a consequence of the control programs (Figure 6a). In regions of high endemicity an increase of malaria may occur if the control programs are not stringent enough, the effect being a steeper increase in susceptible humans (immune persons lose their immunity) relative to the decrease in the infection rate (Figure 6b).

As a result of the ability of vector and parasite to adapt to the control programs, such programs' effectiveness decreases in such a manner that the new equilibria are located nearer to those obtained in the absence of control programs. Not unexpectedly, adaptation may eventually lead to higher incidence rates than those obtained in the absence of adaptation. A notable exception is the case of low doses in regions of high endemicity, since adaptation will then result in a less-pronounced increase in susceptibles that will exceed the reduced decrease in the infection rate, leading to lower incidence rates.

In Figure 7 we have depicted the averaged values over time for different levels of control programs. In regions of low endemicity the adaptive vectorial capacity first decreases, but due to adaptation among mosquitoes, subsequently increases, albeit to a level that lies somewhat below the initial level. The result is a similar pattern in the incidence of malaria, although the level continues to fall (gradually). It is, thus, evident that a combination of both drugs and insecticides at low levels is more efficient than

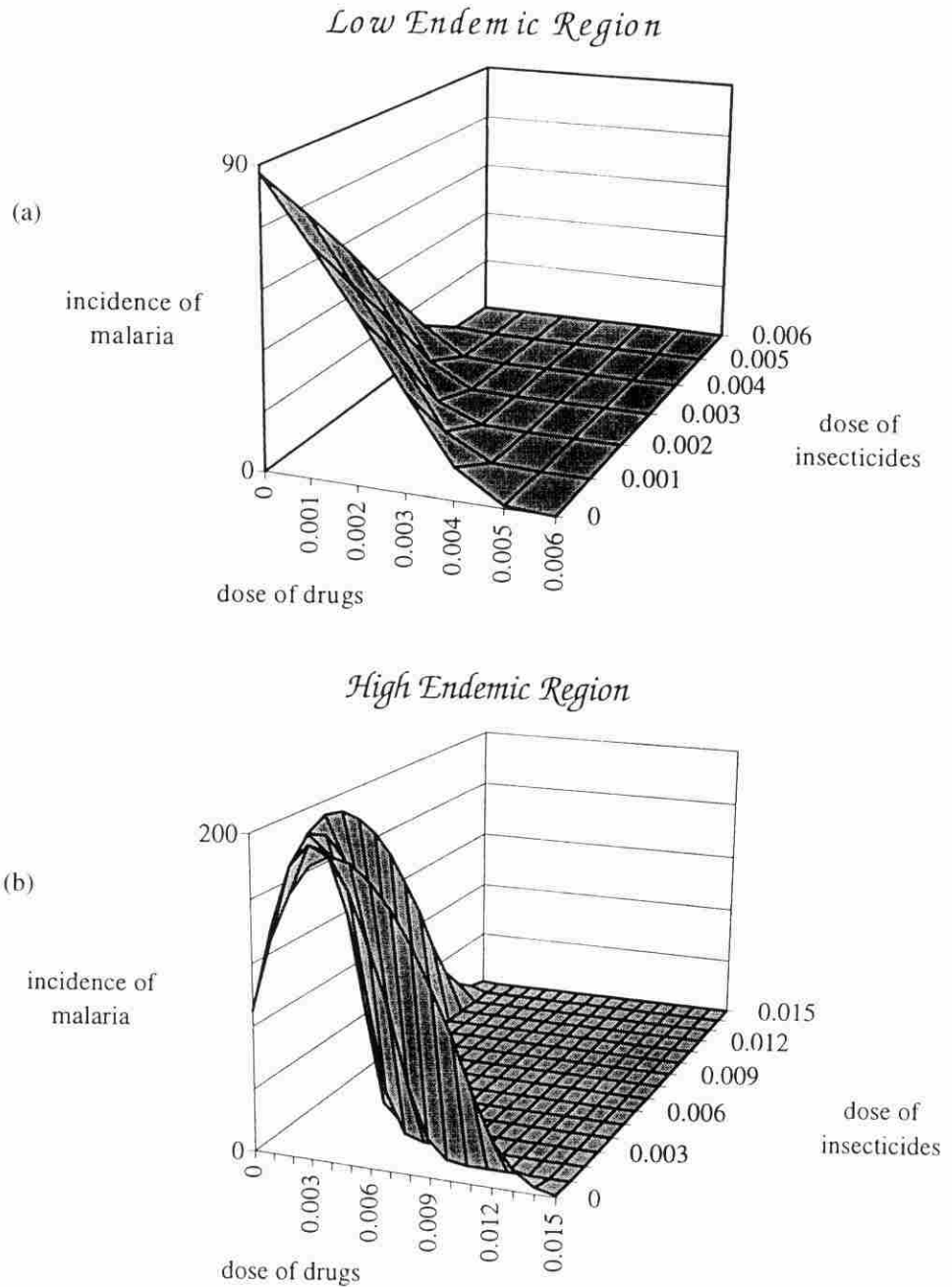


Figure 6. Incidence of malaria for different levels of control in the case of no adaptation (high and low endemic regions).

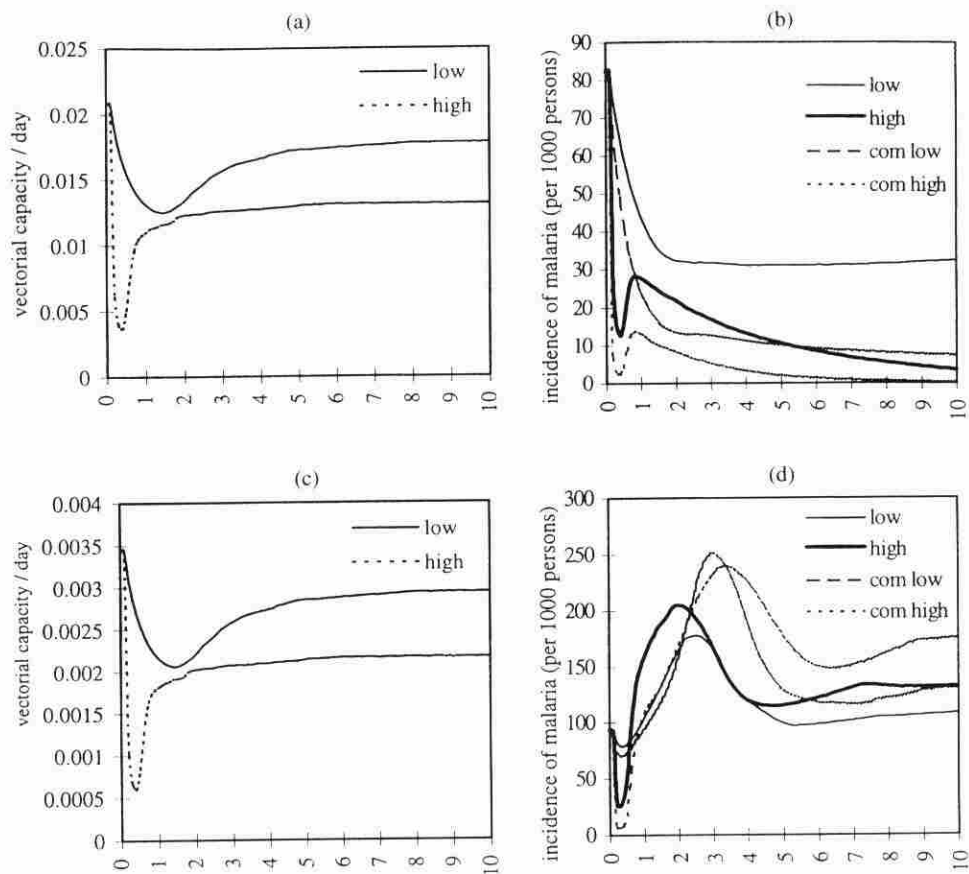


Figure 7. Adapted vectorial capacity and incidence of malaria for different levels of control in a region of low endemicity (a and b) and high endemicity (c and d). Scenarios *low* and *high* depict the results of a low or high dose of insecticides. For the scenario *com low*, low doses of insecticides as well as drugs are combined. This also holds for *com high*.

high level use of only one of the two, a finding that reflects the enhanced development of resistance at higher doses.

In regions of high endemicity, the decrease in adaptive vectorial capacity exhibits a similar pattern to that obtained in regions of low endemicity. (We would expect that resistance development would differ in the two regions due to a difference in the gene pool. Nevertheless, for simplicity's sake we have used the same fixed population size within the genetic algorithm and therefore have arrived at similar results. An improvement of the model might be the coupling of adaptive vectorial capacity and the population size of the genetic algorithm.) Due to the difference in the profiles of the populations, the patterns of incidence of malaria are quite dissimilar. Following a reduction in incidence at the outset of the control programs, incidence subsequently shows an increase due to the lower effectiveness of the control measures. Due to the high fraction of susceptible humans after a successful period of control, again as a result of the flow of immune persons due to the increased rate of immunity loss, incidence may even rise to surpass the initial level. In the long run, a combination of two low levels of control does not achieve a better performance than control by a single method. Indeed, incidence peaks at a level even higher than the initial (precontrol) level due to the higher number of susceptible humans who become reinfected.

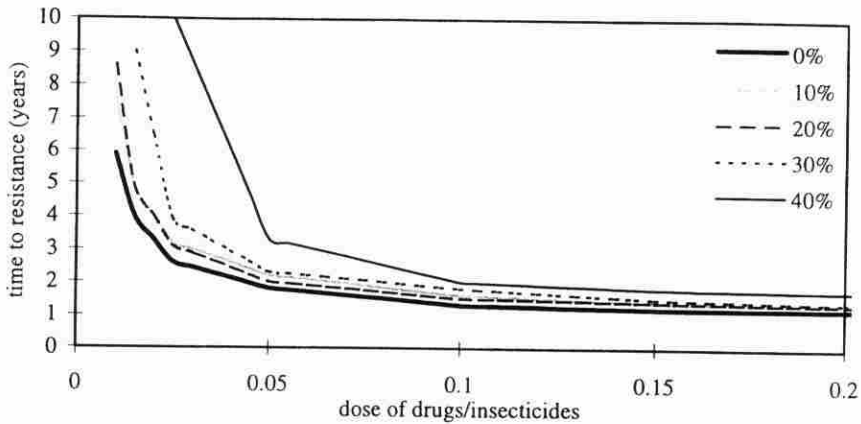


Figure 8. Effect of dose on the rate of evolution of resistance featuring various percentages of migrants per time step.

3.3 Sensitivity of Malaria Incidence to Migration

Migration of mosquitoes and parasites can influence the development of resistance. Comins [9], for example, showed that the migration of insects may greatly retard the development of insecticide resistance, and recent observations in Papua, New Guinea, and Tanzania support such model-based hypotheses [37]. Various studies (e.g., [9, 42]) found two distinct phases in the time required to develop resistance. At low doses, resistance develops more rapidly as the dose increased, paralleling the case in which migration is absent, this in contrast to the case of high doses in which resistance develops more slowly as the dose increases. In the absence of migration, the rate of resistance development is determined primarily by the rate at which susceptible genes are removed from the population. As the dose increases, susceptible genes are removed more rapidly, and resistance consequently develops apace. At low doses in the presence of migration the pattern is similar. Where migration is present and doses are high enough to kill heterozygotes (which are intermediate between the susceptible and resistant genes, comparable with moderately resistant in this article), however, mosquito mortality due to insecticides also removes resistant genes from the population. As the dose increases in this range, more heterozygotes are killed, leaving relatively few resistant mosquitoes. The resistant survivors are effectively swamped by the susceptible immigrants, thereby retarding resistance development.

We analyzed the impact of mosquito migration on insecticide resistance development by postulating various levels of insecticide application and various percentages of migration and subsequently calculating the number of time steps required for 50% of the genes to achieve resistance. The results are depicted in Figure 8 and show, as expected, that the migration of susceptible mosquitoes impedes the development of resistance. Furthermore, at high levels of migration (>40% inflow of susceptible mosquitoes) the development of insecticides resistance among the mosquitoes will be entirely blocked.

That the results do not show the two distinct phases that were found in [9] and [42] is a consequence of our different fitness function⁴ for the various genes. The relative

⁴ Commins [9] and Tabashnik and Croft [42] do not actually employ the term "fitness function," but in our interpretation it is equivalent to their "dose-mortality lines."

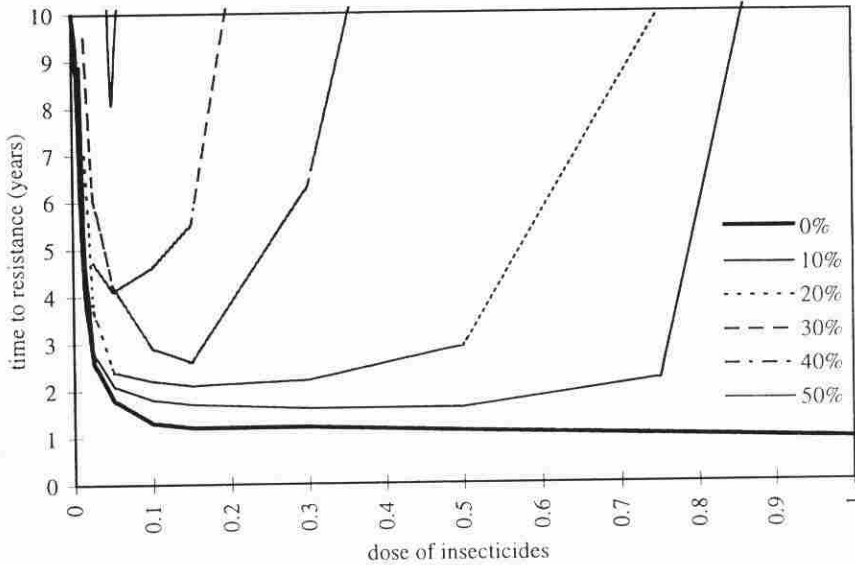


Figure 9. Effects of dose on the rate of evolution of resistance featuring various percentages of refugees per time step.

fitness among the various gene combinations remains rather the same along the line of increasing doses of insecticides. This is not the case for models such as the one adopted by Tabashnik and Croft [42], since heterozygotes are not killed at low doses, but only at high ones. In fact, in such models there is a kind of threshold value in the fitness function (survival rates for the different types of genes), while in our model a more gradual decrease of the fitness function is assumed. There is no field data that is known to the authors at the time of writing that would favor either of these approaches.

3.4 Sensitivity of Malaria Incidence to the Coverage Rate

In the absence of refugees from control programs (i.e., 100% coverage), rates of insecticide resistance increase with increasing doses. If, however, a fraction of the mosquito population evades treatment by becoming "refugees," the development of resistance is expected to be impeded. Tabashnik [41], for example, shows that if 10% of the mosquitoes are refugees evading exposure to insecticides, this may significantly impede the development of resistance.

We explored the impact of the coverage rate for the different doses applied in various control programs, and our results are depicted in Figure 9. For each time step a certain fraction of the mosquito population is not reached by the control measures, and two distinct phases in the time required to develop resistance were found. In the case of low doses and low percentages of refugees, the results are about the same as in the case of zero refugees. However, when higher doses are applied, the time period required to develop resistance rapidly lengthens. The doses of control that mark the two distinct phases are different for each of the various fractions of refugees. Where higher percentages of refugees are concerned, the period of time required to develop resistance starts to become greater at an earlier juncture. Among more than 50% of the refugees, resistance will not develop at all. The rate of evolution of resistance by *P. falciparum* could be retarded by selective treatment of those people with high parasitaemias.

An explanation for the existence of these two distinct phases, which are also found by Tabashnik [41], is the fact that during the period in which the mosquito evades treatment, the benefits of being resistant do not hold. In other words, mosquitoes will not benefit from being resistant in periods during which they are not being sprayed with insecticides. On the contrary, during such periods, susceptible mosquitoes enjoy a higher biotic fitness than resistant mosquitoes. By the same token, in the periods during which the mosquito population is reached by insecticides, a resistant mosquito enjoys the benefits of higher fitness. In the case of higher doses, the difference in fitness in the two cases (reached or not reached by a control program) becomes greater, resulting in the time required to develop resistance becoming longer. Furthermore, the presence of a higher fraction of refugees decreases the average time during which the population in general profits from the availability of resistant genes, consequently impeding the development of resistance.

3.5 Adaptive Malaria Management

In this subsection we analyze the impact of the combined effects of climate change and resistance development among mosquitoes and parasites on the prevalence of malaria. This analysis is performed using an adaptive management style, that is, one that relates the level of control programs according to the observed state of the system. Because in our model the resistance development dynamics are implemented in an identical manner for both mosquitoes and parasites, we need only consider one of the two in the analysis, and the mosquitoes are selected for this purpose.

The use of insecticides is related to the observed incidence of malaria, and there are two levels of application: a zero dose and a high dose. We assume that if the incidence of malaria fell below 20 per 1,000 persons, the use of insecticides would be stopped, while if malaria once more exceeded this level, it would be reintroduced again (at high dose levels). Furthermore, if the incidence of malaria exceeded the level of 100 per 1,000 persons, which is above the initial level, the use of insecticides would be stopped as not being effective.

The results set out in Figure 10 illustrate that in areas of low endemicity the use of insecticides leads to a successful control of malaria occurrence. However, if the temperature was to increase by some 0.5°C within a single decade, the efforts to control malaria would have to be intensified significantly. In areas of high endemicity the control of malaria fluctuates during the decade while the incidence would continue to fluctuate around the level of 100 per 1,000 persons regardless of any temperature increase.

This modeling exercise thus shows that it would not be possible to eradicate malaria in regions of high endemicity using the assumed (i.e., adaptive) management style. However, in regions of low endemicity malaria could be reduced significantly using adaptive management, although increased efforts would be needed in the event of climate change.

4 Conclusions

Models can be useful, especially if the opportunity to perform experiments in laboratories or in the field is limited. This is certainly the case where the growing problem of resistance development among malaria vectors as well as malaria parasites to control programs is concerned, and much remains to be elucidated. Most malaria modeling approaches, however, do not explicitly address the evolutionary character of the development of resistance. The malaria assessment model presented in this article is neither comprehensive nor predictive, but rather intended to include evolutionary processes of resistance development to provide insights into this complex adaptive system and thus

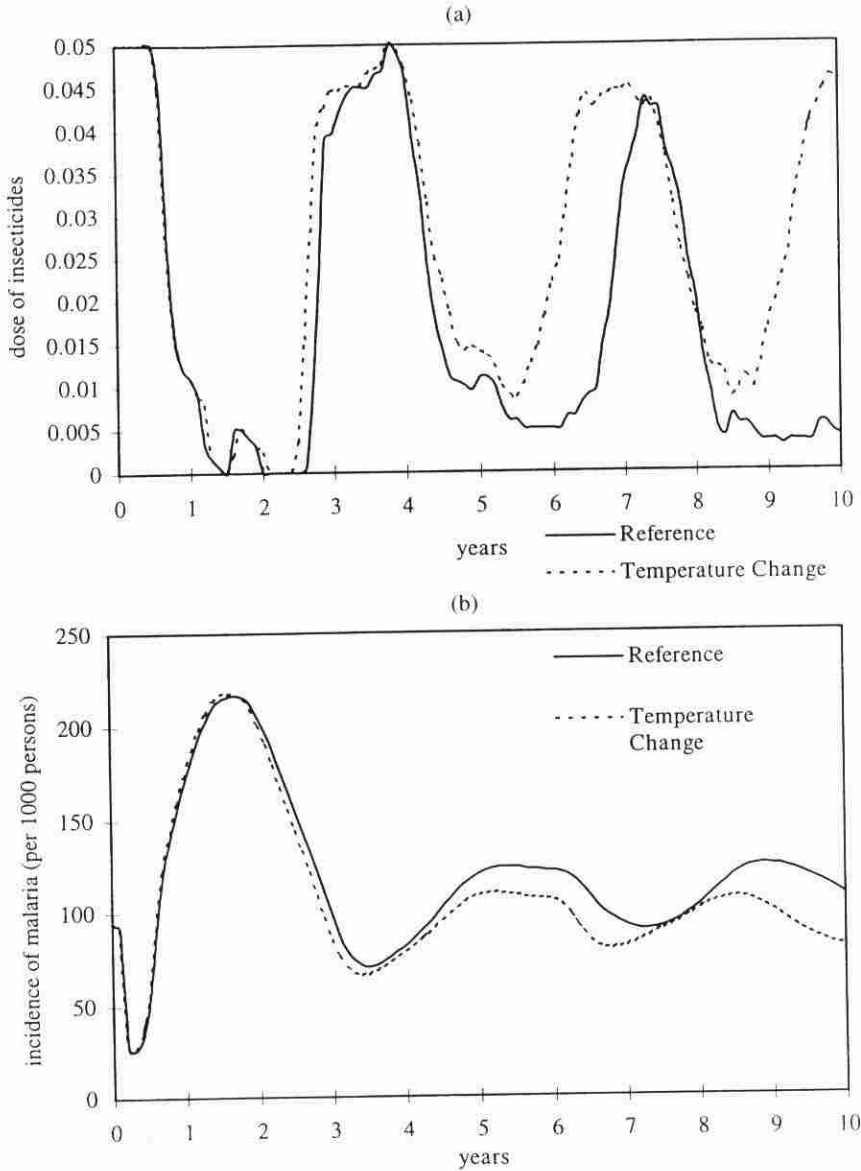


Figure 10. Control patterns and malaria incidence for a region of high endemicity (a and b) and low endemicity (c and d) in the event of an adaptive management style being adopted. The different lines show the impact of a projected climate change of the adaptive control programs.

help us to arrive at a better understanding of the possible effects of control programs. The analysis distinguishes between two exemplary malaria regions, although malaria situations are extremely heterogeneous with respect to resistance to change. The results for the two situations described in this article suggest that *adequate* use of insecticides and drugs may reduce the occurrence of malaria in regions of low endemicity, although increased efforts would be necessary in the event of a climate change. However, the model indicates that in regions of high endemicity the use of insecticides and drugs may

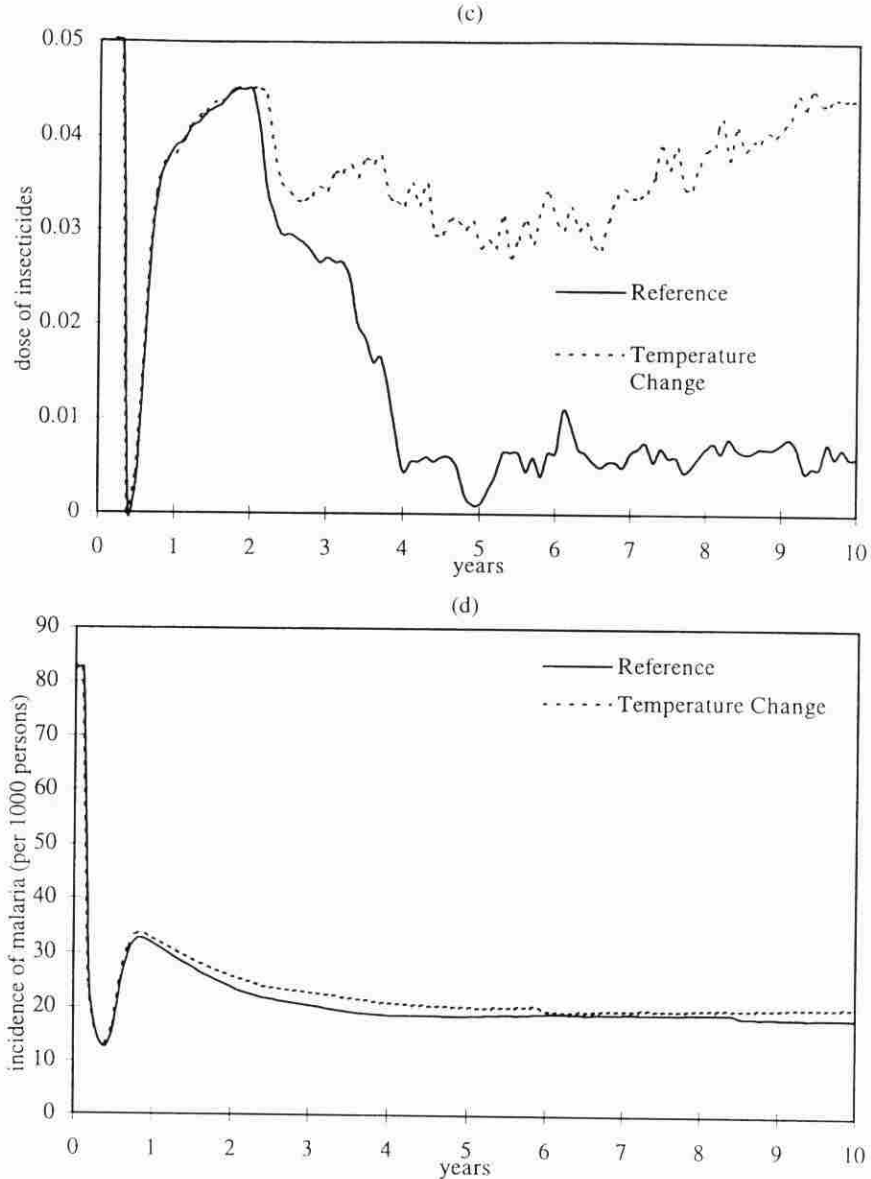


Figure 10. Continued.

lead to an increase in incidence due to enhanced resistance development. Projected climate change, on the other hand, may lead to a limited reduction of the occurrence of malaria due to the presence of a higher percentage of immune persons in the older age class. Given this observation, to retard the evolution of resistance, a combination of methods or drugs should be used, combined with a selective high dosage rate for those people or areas most vulnerable. Elements of a sustainable antimalarial policy in regions of high endemicity will furthermore need to rely upon a stimulation of socio-economic development and provision of vector-proof housing. However, given the multiplicity of ecological and biological elements and of the natural, adaptive defence

mechanisms of the malaria parasite/vector complex, control or eradication must be planned with consideration of prevailing local conditions.

The modeling approach presented here fits in well with the qualitative attention currently being paid to the importance of evolutionary principles (e.g., [12, 25]). However, a great deal of empirical research is needed to improve the modeling approach. In the specific case of malaria, it is especially important that more insights into the possible shapes of the fitness functions of the parasites and the mosquitoes are acquired. This need is illustrated by the results of the impact of migration on the development of resistance at high doses, since they differ from the results of previous studies as a result of different assumptions regarding the fitness functions. Nevertheless, the fact remains that development of integrated assessment models that are based on the evolutionary and local dynamics of ecological systems may prove essential in assessing future developments in these complex adaptive systems.

The present version of the model simulates the incidence of malaria based on the use of insecticides and medication together with temperature change. Additional factors would need to be included before one could speak of an integrated approach to the malaria problem, whereby the inclusion of environmental management would be of particular importance. The effects of land use changes, water management, housing, and so forth on malaria transmission would therefore need to be incorporated. As a means of accommodating such spatial differentiation, the use of geographical information systems (GIS) might be considered. In fact, the present model simulates the dynamics of a single area, whereas in a spatial model it would be connected to changes in other areas.

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