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Review

On the use of mathematical models of malaria transmission

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The key conclusions of several mathematical models of malaria are reviewed with emphasis on their relevance for control. The Ross-Macdonald model of malaria transmission has had major influence on malaria control. One of its main conclusions is that endemicity of malaria is most sensitive to changes in mosquito imago survival rate. Thus malaria can be controlled more efficiently with imagicides than with larvicides. An extension of this model shows that the amount of variability in transmission parameters strongly affects the outcome of control measures and that predictions of the outcome can be misleading. Models that describe the immune response and simulate vaccination programs suggest that one of the most important determinants of the outcome of a vaccine campaign is the duration of vaccine efficacy. Apparently malaria can be controlled only if the duration of efficacy is in the order of a human life-span. The models further predict that asexual stage vaccines are more efficient than transmission-blocking vaccines. Directions for further applications of mathematical models are discussed.

Key words: Malaria; Transmission; Mathematical models; Vaccine

Introduction

The epidemiology of malaria deals with the reasons for the prevalence of disease and the nature and causes of its variation. Its aim is to understand the dynamics of malaria transmission well enough to manage control programs efficiently. Biological studies in the field and the laboratory have greatly increased our knowledge of the life cycle of the malaria parasite and its interactions with its mosquito vector and its final host. However, since the beginnings of malaria research (Ross, 1911; Macdonald, 1957), it has been clear that even the most detailed biological knowledge of the parasite's life-cycle cannot lead to a complete understanding of what causes such radical differences in malaria patterns in different parts of the world. Such understanding can only be reached by synthesizing the many factors controlling transmission, integrating detailed biological information into one coherent picture.

This integration is the aim of mathematical epidemiology. As Macdonald (1957, p. 4) writes:

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> '[Mathematical epidemiology] gives a sense of proportion, relating the various factors of the transmission cycle to each other and to relevant biological characteristics of the mosquito. It can show the scale of changes in infection rates to be expected following changes in one of the transmission factors, and why this scale should differ greatly under different conditions. It can supply the principle which connects happenings in two countries and explain the detail of happenings in any individual country.'

The integration of the complex interactions between parasites and hosts leads to non-linear terms in the description of malaria transmission. The importance of such nonlinearities, both for an understanding of the dynamics of the system and for the interpretation of observed patterns of interactions between the malaria parasite, the mosquito vector, and the human host has been made clear by Anderson et al. (1989). But grasping the effect of nonlinearities is impossible without the help of a mathematical model.

Despite the early recognition by Ross and Macdonald of the importance of a quantitative description of malaria transmission, mathematical epidemiology has encountered many difficulties in gaining general acceptance by epidemiologists and public health workers. One of the reasons for this lack of acceptance may lie in the increasing complexity of the models published in the 1960's and 70's (reviewed by Bailey, 1977). These models are not only difficult for non-mathematicians to understand, but the interpretation of their results may actually be misleading. On the one hand, the more variables included in a model, the closer the predictions of the model often agree with observations, simply because more degrees of freedom are involved. However, a close agreement between prediction and observation does not necessarily imply an agreement between the structure of the model and the biological processes. Therefore the qualitative predictions of simple models may be more biologically meaningful than the precise quantitative predictions of complex models involving many parameters. On the other hand, more detailed models do not necessarily result in greater predictive power. In fact, the results of more complex models may be less reliable than those of simple ones (Lee, 1973; O'Neill, 1973). As one includes more detail into a model, the number of assumptions about interactions increases exponentially. Therefore, the probability of making a wrong and critical assumption increases rapidly, and it has been found that the predictive power of a model usually declines after some level of detail has been exceeded.

In this review, emphasis is placed on simple mathematical models and on their qualitative predictions. This is not a complete review of malaria models, which can be found in Aron and May (1982), Bailey (1982), Nåsell (1985), Nedelmann (1985) or Dietz (1988). My aim is to review the key conclusions of those mathematical models that have enhanced our understanding of malaria and that could help to plan control strategies. So that such conclusions can be seen clearly, some of the models presented are modifications of published models.

All of the models presented here are based on the life-cycle of malaria parasites outlined in Fig. 1, and basically describe changes of infection in the human host and the mosquito vector. Infection can be expressed in three ways. *Prevalence* of infection, or parasite rate, describes the proportion of the population harboring malaria parasites. *Parasitaemia* describes the density of parasites within a host, and is thought to be an important factor determining the severity of disease in humans (Trape et al., 1985). *Intensity* of infection describes the number of separate infections received by a host. Because different strains of parasites differ in their antigenic properties

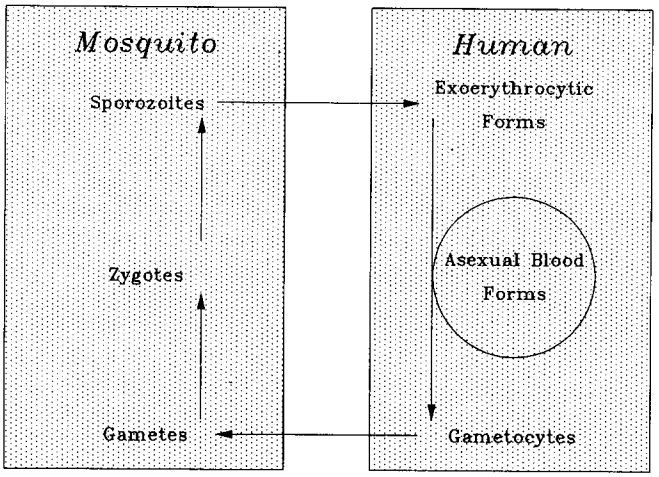


Fig. 1. Schematic life-cycle of the malaria parasite.

(Forsyth et al., 1989), intensity is certainly important in determining the level of acquired immunity. It might also contribute to severity of disease (Snow et al., 1988), possibly by determining the probability of a human becoming infected with a virulent parasite strain.

A basic model

The first model of malaria transmission was developed by Ross (1909, 1911) and later extended by Macdonald (1957). This so-called Ross-Macdonald model is the best-known and most widely used model. Despite its simple structure (Fig. 2), it allows a comparison and interpretation of broad epidemiological patterns. The model

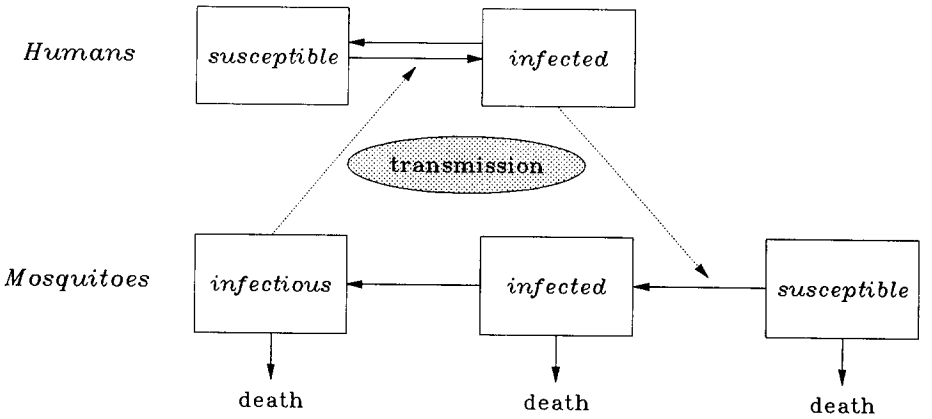


Fig. 2. Structure of the Ross-Macdonald model of malaria transmission. The flow of humans from a susceptible class to an infected class and, through recovery from infection, the reverse are shown in the upper part of the figure. The flow of mosquitoes from a susceptible class to an infected class, and finally to an infectious class are shown on the bottom. The human and mosquito populations are linked through the transmission process. See the main text and Appendix A for a more detailed description.

is a direct translation of the schematic life-cycle shown in Fig. 1 into quantitative terms, as shown in Appendix A. A few of the major assumptions underlying the model are (1) no acquired immunity in the human host, (2) that mosquitoes bite humans randomly, and (3) that human and mosquito populations are homogeneous. Its basic results can best be described by considering the basic reproductive number, R_0. This number describes the number of secondary cases of malaria arising from a single case in an otherwise uninfected population (Macdonald, 1957; Anderson and May, 1980), and can be thought of as a measure of the intensity of transmission. It can be derived algebraically (Appendix A) as

$$R_0 = \frac{ma^2 b_1 b_2 e^{-\mu T}}{r\mu} \tag{1}$$

where m denotes the number of mosquitoes per human host, a denotes the biting rate of the mosquitoes on their human host, b_2 denotes the susceptibility of humans, b_1 denotes the infectiousness of humans to mosquitoes, μ denotes the mortality of adult mosquitoes, T denotes the incubation period of parasites within the mosquito vector, and r denotes the rate of recovery of infected humans. A graphical representation of the basic reproductive number (Aron and May, 1982) is shown in Fig. 3.

The result of equation (1) is intuitively understandable. Transmission of malaria is helped by high densities of mosquitoes (high m) that bite frequently (high a) and by highly susceptible humans (high b_2) and mosquitoes (high b_1), and transmission is hindered by quick recovery of infected humans (high r) and by high mortality rate of the mosquito vector (high μ). Because mosquitoes must bite twice for transmission of the parasites (once to take up gametocytes, and once to inject sporozoites), the square of the biting rate, a, enters the equation. The term $e^{-\mu T}$ denotes the proportion of mosquitoes surviving from the time of being infected through the incubation period of the parasites.

Malaria can spread in a population only if the basic reproductive number exceeds one, i.e. if each infection gives rise to at least one additional case. This can be seen in the phase-plane representation of Fig. 3, or by considering the equilibrium proportions of infected humans and mosquitoes. Setting equations (A.1) to (A.3) to zero and applying equation (1) leads to the prevalence of infection in humans

$$\hat{y} = \frac{R_0 - 1}{R_0 - \dfrac{a}{\mu}} \tag{2a}$$

and in mosquitoes

$$\hat{w} = \frac{R_0 - 1}{R_0} \frac{\dfrac{a}{\mu}}{1 + \dfrac{a}{\mu}} e^{-\mu T} \tag{2b}$$

These values are positive only if $R_0 > 1$ (Fig. 4), giving the basis for Ross's Threshold Theorem of Malaria (Ross, 1911, Section 28):

> 'We may therefore conclude, [1] That the amount of malaria in a locality tends towards a fixed limit determined by the number of malaria-bearing mosquitoes and by other factors.

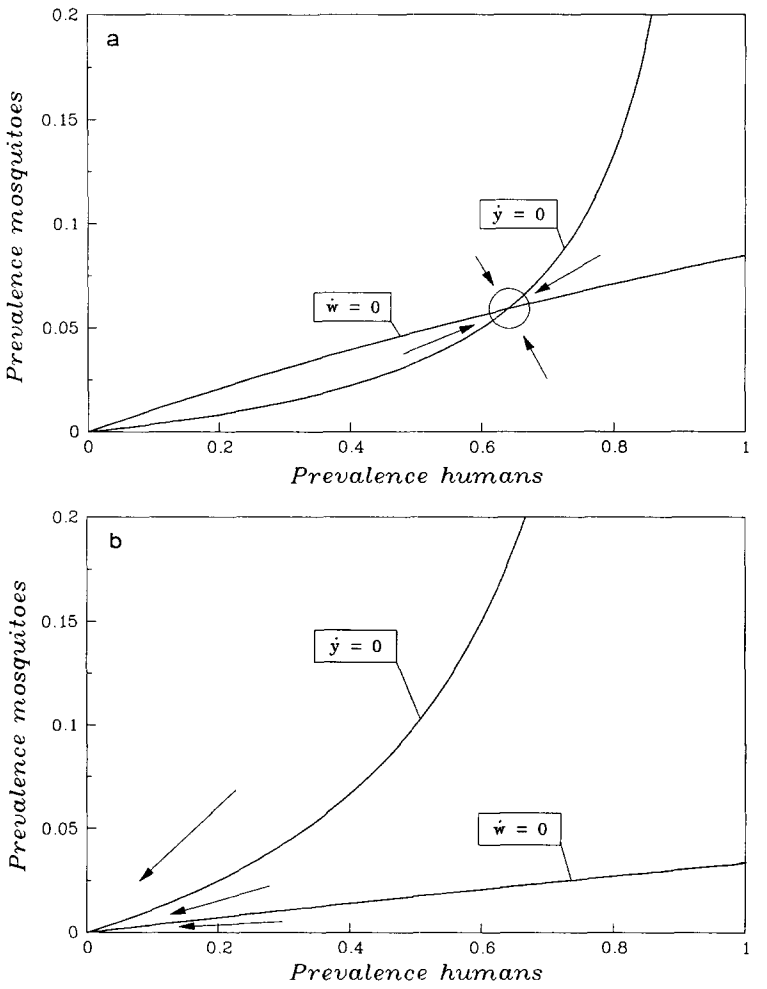


Fig. 3. Phase plot of the Ross-Macdonald model defined in Appendix A. Each point corresponds to a particular pair of values for the prevalence in humans and in mosquitoes. Prevalence in humans is not changing along the line $\dot{y}=0$ (human isocline), and prevalence in mosquitoes is not changing along the line $\dot{w}=0$ (mosquito isocline). The intersection of the two lines represents the equilibrium prevalences as defined by the Ross-Macdonald model. At other pairs of values, the prevalences move in the direction indicated by the arrows. In (a) the initial slope of the mosquito isocline is greater than that of the human isocline. Therefore, a stable equilibrium exists and malaria can be established in the population. In (b) the initial slope of the mosquito isocline is less than that of the human isocline, and the isoclines do not cross. Both prevalences are drawn to zero, and malaria cannot maintain itself. The condition for the maintenance of malaria is thus that the initial slope of the mosquito isocline is greater than that of the human isocline. This is equivalent to the condition that the basic reproductive number is greater than one (see equation (1)).

> [2] That if the number of malaria-bearing Anophelines is below a certain figure, that limit will be zero.'

Several features of the Ross-Macdonald model are worth mentioning. First, the Threshold Theorem states that malaria can persist in a population only if the number of mosquitoes is greater than a given threshold. Secondly, the prevalence of infection

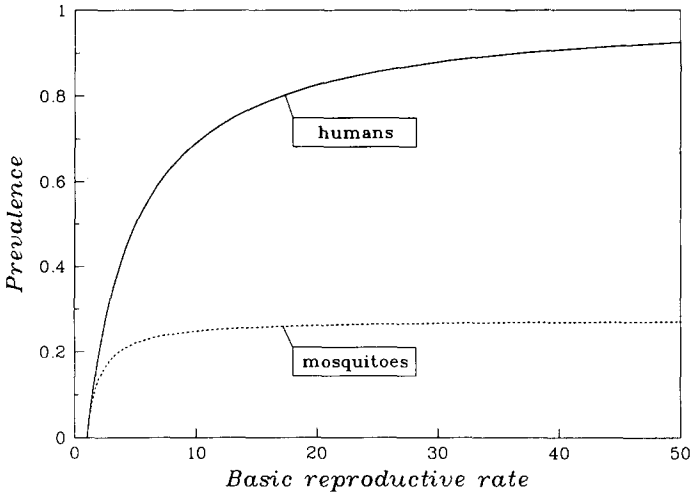


Fig. 4. Prevalence of infection in humans and mosquitoes as a function of the basic reproductive number. The values are predicted by the Ross-Macdonald model, as shown in equation (2).

in the human and the mosquito host depends directly on the basic reproductive number (equation 2). Their relationship is highly nonlinear. When the reproductive number is near one, prevalence increases greatly for small increases in R_0. On the other hand, when the reproductive number is large, even large reductions in R_0 lead to almost no reduction in prevalence. Thirdly, equations (2) define a stable equilibrium. This means that temporary interventions can lead only to a temporary reduction of prevalence. When the intervention is relaxed, prevalence again increases to its original value. Fourthly, for very high reproductive numbers, the model predicts that virtually everyone in the human population is infected. This obvious overestimate is due to the model's neglect of acquired immunity.

A final feature of the model is found by performing a sensitivity analysis (Macdonald, 1957) of the basic reproductive number defined by equation (1). The sensitivity analysis consists of calculating the effect of small changes in each of the parameters on the basic reproductive number, and comparing the effects with each other. The larger the effect, the more sensitive the endemic level is to changes in the corresponding parameter. The outcome of such an analysis is shown in Fig. 5. It is shown that, say, halving the mosquito population, m, (e.g. by larvicides) reduces R_0 by a factor of two, whilst halving biting rate, a, (e.g. with bed nets) reduces R_0 by a factor of four. The largest reduction of R_0 is expected for increases in adult mosquito mortality, μ, (e.g. by imagicides) because of their exponential relationship. An important conclusion of the model is thus that imagicides are more effective for controlling malaria than are larvicides. The conceptual changes in malaria control strategies following Macdonald's conclusions are described by Harrison (1978). Macdonald (1957) used the conclusions of his calculations to help to explain the extreme differences in the epidemiological pattern between East Africa, where malaria is characterized by very high endemicity and high levels of immunity, and South Eastern India, where malaria is characterized by epidemics (Macdonald, 1957). In India, the most important vector is *Anopheles culicifacies*. This species has a short life expectancy of about four days and bites humans at a rate of about 0.01 per day. In East

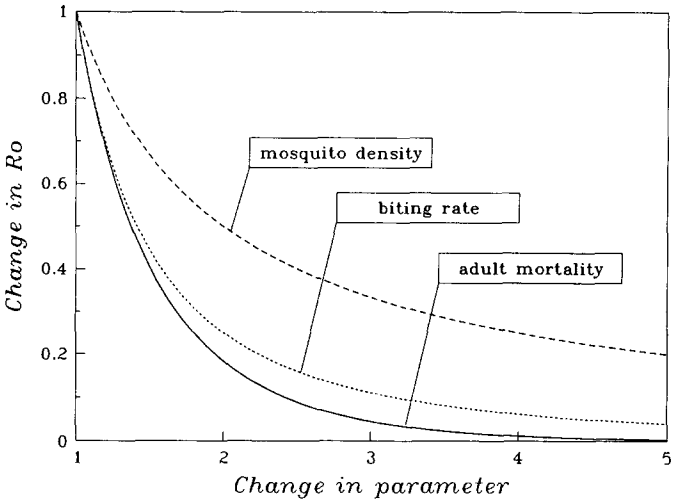


Fig. 5. Sensitivity of basic reproductive number as calculated for the Ross-Macdonald model on mosquito density, biting rate, and mosquito survival. A given endemic setting is given with the values one for each parameter and for R_0. Changes in parameter values are shown as factors relating to the original setting, e.g., a value of 2 for mosquito density denotes that density decreased two-fold. Mosquito density enters the equation for the basic reproductive number linearly. Therefore a two-fold decrease in mosquito density leads to a two-fold decrease in reproductive number. Biting rate enters the reproductive number quadratically, so that a two-fold decrease leads to a four-fold decrease in reproductive number. Survival of adult mosquitoes enters reproductive number exponentially, and decreases lead to the largest changes in reproductive number.

Africa, the major vector is *A. gambiae* s.l., which has a life-expectancy of about ten days and its biting-rate is about 0.5 per day. If all other parameters were equal in the two areas, these differences in survival and biting rate would lead to a 20000-fold difference in reproductive number. Of course this difference is lessened by reductions in human recovery rate, susceptibility and infectiousness due to acquired immunity. Nevertheless, the calculations reinforce the epidemiological patterns. Based on these calculations, Macdonald (1957) concluded that, in East Africa, 'control by imagicides would be relatively difficult, to be effective needing the achievement of a 40 to 50 per cent daily mortality among the vectors', and that 'control falling only slightly short of the necessary quality is not likely to produce much apparent result'. In contrast, in South East India, 'control by imagicides is likely to be very easy, mortalities such as 20 to 25 per cent daily often being sufficient.'

Thus, the simple Ross-Macdonald model can teach a great deal about the epidemiology of malaria and can aid decision-making in control strategies. However, the conclusions of the model are most useful at a conceptual level. The model helps to interpret differences between endemic situations and helps to predict major impacts of control strategies. It thus tells us that imagicides are more efficient than larvicides. The model is less useful at explaining details of the epidemiology of malaria in any given area or at designing control strategies at the implementation level. It cannot tell us where or how often to apply insecticides.

One step towards more detailed explanations of epidemiological patterns of malaria involves dropping the assumptions of the Ross-Macdonald model mentioned above. These assumptions are that infected humans cannot develop immunity against

malaria and that the human and mosquito populations are homogeneous. The effects of acquired immunity and of variable mosquito and human populations on the predictions of the Ross-Macdonald model are discussed in the following sections.

Effect of variability

It is well-known that mosquitoes bite some persons more than others (for a review see Burkot, 1988). Dye and Hasibeder (1986) have demonstrated two important consequencies of this variability. First, variability in biting rate increases the basic reproductive number above the value obtained for uniform biting. Thus variability in biting rate makes malaria more difficult to control. Secondly, variability in biting rate can either increase or decrease equilibrium prevalence (Fig. 6a). In particular, in highly endemic areas (where R_0 is high), the assumption of uniform biting overestimates prevalence, but in areas where R_0 is low, the assumption of uniform biting underestimates prevalence.

Of course, other parameters other than biting rate show considerable variation between individuals within a population. As examples consider the effect of sickle cell disease (Fleming et al., 1985) or of glucose-6-phosphate dehydrogenase deficiency (Luzzato et al., 1985) on susceptibility to malaria, the effect of age and immune status on recovery rate (Cohen and Singer, 1979), or the effect of chloroquine on infectiousness of gametocyte carriers to mosquitoes (Wilkinson et al., 1976; Ichimori, 1987; Ichimori et al., 1990). Dye and Hasibeder's (1986) analysis was extended to include variability in other parameters (Appendix B). Analysis of a model that incorporates variability in, say biting rate, a, susceptibility, b_2, and duration of disease, $\rho = 1/r$, shows that the basic reproductive number can be written as

$$R_0 = \overline{R_0}\left[1 + \frac{\mathrm{var}(a)}{\bar{a}^2} + 2\frac{\mathrm{cov}(a,b_2)}{\bar{a}\bar{b}_2} + 2\frac{\mathrm{cov}(a,\rho)}{\bar{a}\bar{\rho}} + \frac{\mathrm{cov}(\rho,b_2)}{\bar{\rho}\bar{b}_2}\right] \tag{3}$$

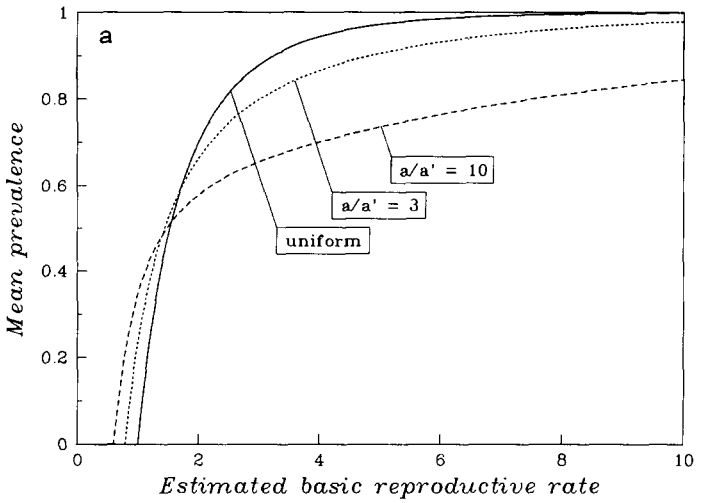
where

$$\overline{R_0} = \frac{m\bar{a}b_1\bar{b}_2\, e^{-\mu T}\bar{\rho}}{\mu}$$

denotes the basic reproductive number due to the mean parameters, $\bar{x}$ denotes the mean of x, var(x) denotes the variance of x, and cov(x,y) denotes the covariance of x and y.

Equation (3) shows that variability in any given parameter affects the basic reproductive number only if at least one of the following conditions holds. First the parameter may covary with a second parameter. In this case, R_0 can be either

Fig. 6. Mean prevalences of infection in populations consisting of two sub-populations, differing in biting-rate (panel a), susceptibility (panel b), and recovery rate (panel c). In each panel, prevalence is shown for uniform populations and for populations where the sub-populations differ in the parameter by a factor 3 or 10. In (a), the basic reproductive number is calculated using the mean biting rate, and is thus an underestimate of the true value. This estimate leads to the prediction that, at high transmission intensities, variability decreases prevalence, but at low transmission intensities, increases prevalence. In (b) and (c), the true basic reproductive number of the population is calculated according to equation (3). This leads to the prediction that variability decreases prevalence at any intensity of transmission.


a
Mean prevalence
Estimated basic reproductive rate
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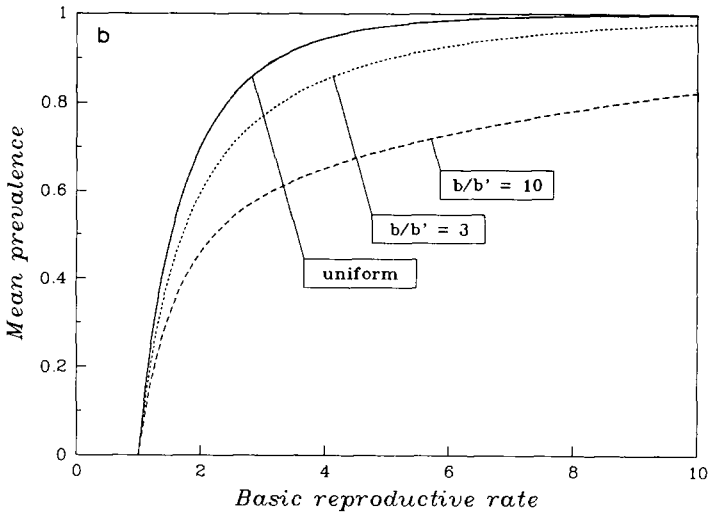
b
Mean prevalence
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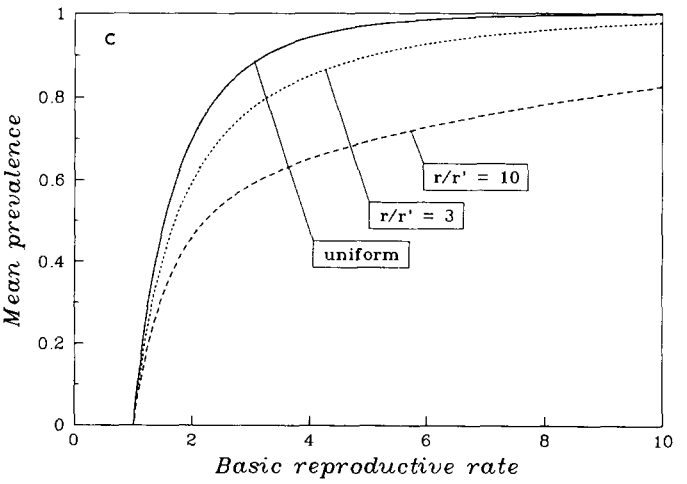
c
Mean prevalence
Basic reproductive rate
r/r' = 10
r/r' = 3
uniform
0
0.2
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increased or decreased, depending on the sign of the covariance. Secondly, the parameter may affect the basic reproductive number nonlinearly (e.g. biting rate affects the reproductive number quadratically). In this case, variability always increases R_0 through a term involving the variance of the parameter.

In contrast, variability in any given parameter always affects prevalence of infection. If, for example, a population is divided into a highly susceptible (large b_2) and a less susceptible (low b_2) group, but these groups do not differ in any other parameters, the basic reproductive number is

$$R_0 = \frac{mab_1\overline{b_2}\, e^{-\mu T}}{r\mu}$$

and is thus independent of the variability in susceptibility. For any given R_0 on the other hand, mean prevalence in the population decreases as the variability in duration of susceptibility (Fig. 6b) increases. Similarly, mean prevalence decreases as the variability in duration of infection (Fig. 6c) increases.

There are three practical consequences of this. First, the description of the endemic setting of malaria depends on the level at which data were collected. Studies of the transmission of malaria at the household level and at the village level will lead to different interpretations of the malaria situation within the same geographical area. Secondly, as Dye and Hasibeder (1986) have pointed out, models that neglect variability in biting rate lead to biased predictions of the impact of a control program. In particular, as transmission is reduced, the neglect of variability initially leads to overestimates of prevalence. As transmission is reduced further, the neglect of variability eventually leads to underestimates of prevalence. Thirdly, the present analysis shows that a control program should focus not only on the reduction of overall transmission in a population, but consider also the variability of transmission. In particular, if differing control strategies lead to a similar reduction of transmission, but one maintains a higher level of variability in susceptibility or duration of disease, this strategy may reduce prevalence of infection to a greater extent.

Immunity and vaccines

Incorporating immunity into malaria models is important for two reasons. First, the neglect of immunity leads to such unrealistic predictions as a prevalence of close to 100% in endemic areas. Incorporating immunity can help to make models more realistic. Secondly, modelling immunity, and in particular the effect of vaccines, can help to predict the outcome of vaccination programs. Models can help to determine the proportion of the population that must be vaccinated for the eradication of the disease (Anderson, 1982) and to determine the optimal age of vaccination (Hethcote, 1988). Where vaccination implies a risk to the individual of developing the disease due to the vaccine, models can help to find a balance between individual and public priorities (Fine and Clarkson, 1986). Such predictions are difficult to make without the help of mathematical models because of the inherent nonlinearities in the transmission dynamics. Mass immunization changes endemicity and distribution of malaria through protection of vaccinated individuals, but also through indirect effects resulting from reduction in intensity of transmission. The discussion of antimalaria

vaccines is further complicated by the loss of immunity when exposure is interrupted (Boyd, 1949; Lancet Editorial, 1985). The incorporation of these nonlinearities into predictions of the effect of vaccines on endemicity can help to plan future vaccination programs.

General model of immunity

The general model of immunity consists of three differential equations denoting changes in the proportions of susceptible, x, infected, y, and immune, z, people (Fig. 7). The formulation of the model is described in Appendix C, and combines models proposed by Elderkin et al. (1977) and Aron (1988a,b). One of its major features is that the rate, γ, at which immunes become susceptible again, depends on the rate, h, at which they acquire new infections. It is assumed that immunity lasts only for τ years in the absence of new infections, and is boosted by new infections. Because τ is equal to the mean residence time in the immune class, $1/(\gamma+\delta)$, where δ denotes the death rate of humans, the rate of loss of immunity, γ, becomes (Aron, 1988a)

$$\gamma(h)=\frac{(h+\delta)\,e^{-(h+\delta)\tau}}{1-e^{-(h+\delta)\tau}} \tag{4}$$

As shown in Appendix C, the infection rate, h, can be written as

$$h=ma^2b_1b_2\,e^{-\mu T}\frac{y}{\mu+ay} \tag{5}$$

Analysis of the model at equilibrium leads to the basic reproductive number

$$R_0=\frac{ma^2b_1b_2\,e^{-\mu T}}{(r+\delta)\mu} \tag{6}$$

Note that the basic reproductive number is independent of any parameter of

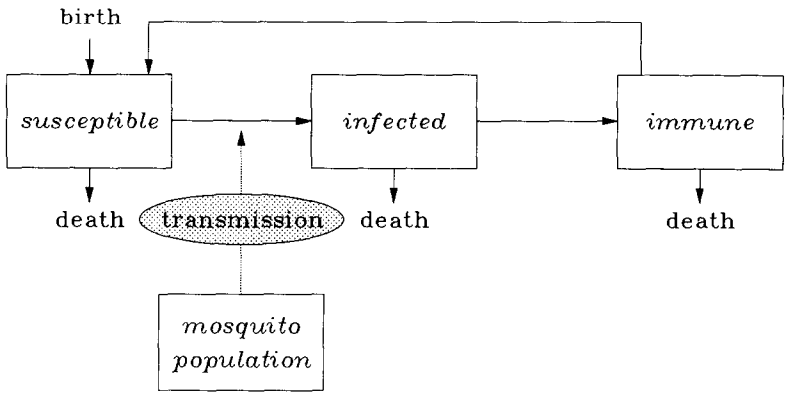

Fig. 7. Structure of model incorporating immunity. The flow of susceptible humans to infecteds (through infection by the mosquito population), the flow of infecteds to immunes (through recovery), and the flow of immunes to susceptibles (through loss of immunity in the absence of reinfections) are shown. See the main text and Appendix C for more details.

immunity, and thus is, aside from the inclusion of the human mortality δ, identical to the reproductive number defined by the Ross-Macdonald model (equation 1).

The model allows the calculation of the age-specific prevalence (Aron, 1988b) following a method described by Dietz et al. (1974). In a population that has reached its equilibrium pattern of infection, the equilibrium inoculation rate can be applied to a cohort of susceptible newborns, expressed by an initial $x=1$. The time parameter can then be interpreted as the age of the cohort. The equilibrium infection rate must be changed from equation (5) to

$$h=ma^2b_1b_2\,e^{-\mu T}\frac{\tilde{y}}{\mu+a\tilde{y}} \tag{7}$$

where $\tilde{y}$ denotes the overall prevalence in the cohort. If human mortality, δ, is assumed to be independent of age, the overall prevalence can be written as

$$\tilde{y}=\int_0^\infty \delta\, e^{-\delta T} y(t)\, dt. \tag{8}$$

A typical age-specific pattern of infection is shown in Fig. 8a. With increasing age of the cohort the proportion infected initially increases, but as immunity is built up, eventually decreases to a low value. This is the pattern observed in highly endemic areas (Molineaux and Gramiccia, 1980). Fig. 8a further shows that as transmission (i.e. basic reproductive number) increases, prevalence increases in very young children. In contrast, prevalence in adults decreases due to the increase of immunity. Therefore, the model predicts that age-specific prevalence curves drawn for differing transmission levels cross. This pattern is indeed observed (Boyd, 1949; Cornille-Brögger et al., 1978). A striking feature of the model is shown in Fig. 8b. Whenever immunity exists ($\tau>0$), overall prevalence of infection, $\tilde{y}$, is highest for an intermediate level of transmission, i.e. decreasing R_0 from very high values to intermediate values increases prevalence. This is most obvious when the duration of immunity τ is about one year.

An important conclusion of models incorporating immunity is thus that control measures that focus on transmission may be counterproductive: Introducing bednets in endemic areas may, by reducing immunity in a population, increase prevalence.

Vaccines

The general model introduced above can be used to predict the impact of future malaria vaccines. Two classes of vaccines are considered here. First, vaccines that act upon the asexual stages of the parasite (Fig. 1) protect the individual from becoming infected (anti-sporozoite vaccines) or from developing parasitaemia and the disease (anti-bloodstage vaccines). Secondly, vaccines that act upon sexual stages of the parasites do not protect individual humans, but block transmission from infected humans to the mosquito vector. Both classes of vaccines are here applied in a mass vaccination program to a proportion of all newborns. Other strategies, e.g. repeated cohort vaccination, are considered by Anderson et al. (1989) with a slightly simplified model.

Asexual stage vaccine Mass vaccination with an asexual stage vaccine is modelled by slightly altering the general model of immunity described by Fig. 7. It is here

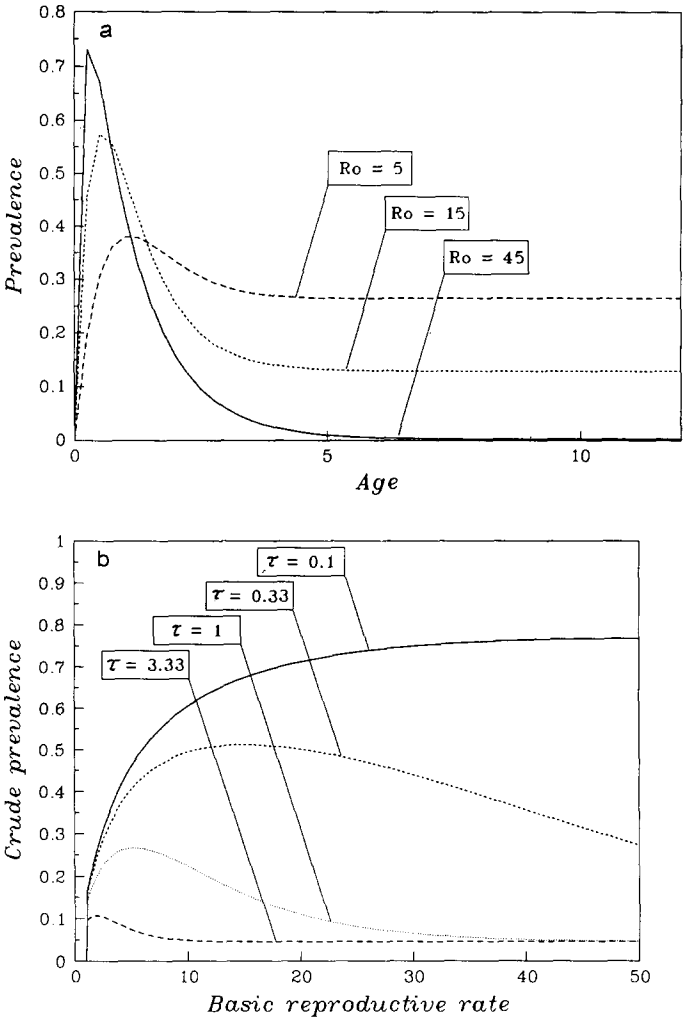

Fig. 8. The effect of intensity of transmission and duration of immunity on prevalence of infection, as predicted by the model of immunity described in Appendix C. Intensity of transmission is described by the basic reproductive number. (a) Age-specific prevalence of infection for different intensities of transmission. (b) Crude prevalence (weighted average over all age groups) as a function of intensity of transmission for various durations of immunity.

assumed that a proportion p of all newborns are immune, leaving a proportion $1-p$ of the newborns susceptible. Note that this proportion is the product of the proportion vaccinated and the efficacy of the vaccine. The vaccine is assumed to stimulate immunity in the same way as does natural immunity, so that the mean duration of efficacy of the vaccine is equal to the mean duration of immunity, τ.

The basic reproductive number is calculated in Appendix D, and malaria is eradicated when this value is less than one. This condition can be written as (Fig. 9a)

$$p > \left(1 - \frac{1}{R_0}\right)\left(1 + \frac{\gamma_0}{\delta}\right) \tag{9a}$$

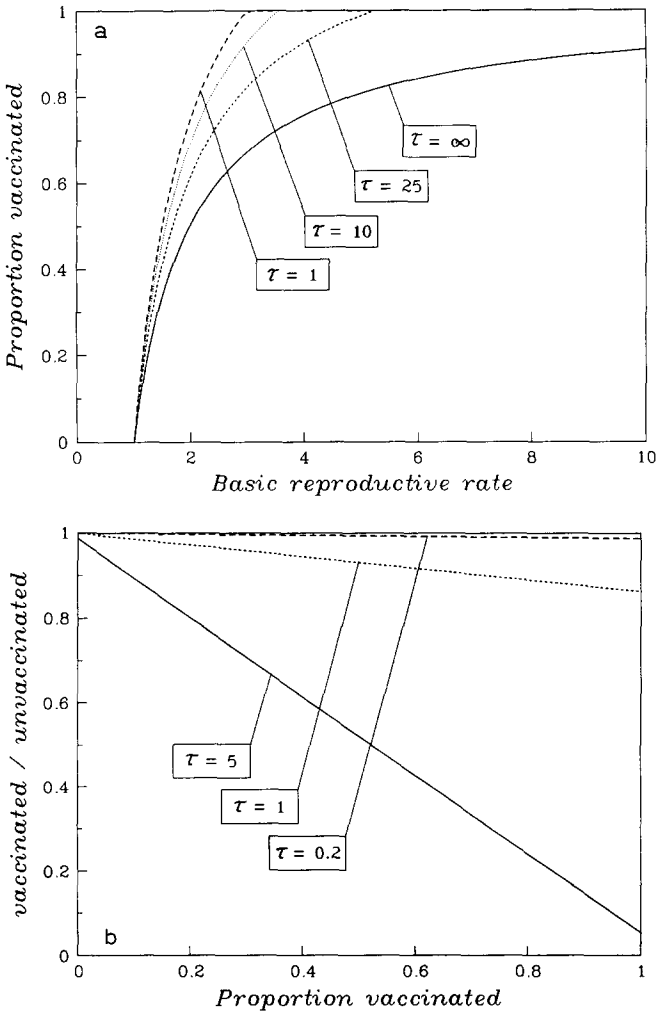

Fig. 9. Predictions of model of asexual stage vaccine on endemicity of malaria. (a) The relationship between the intensity of transmission and the proportion of newborns that must be vaccinated for the eradication of malaria. Intensity of transmission is described as the basic reproductive number. Various durations of immunity are shown. (b) The reduction of crude prevalence as a function of the proportion of newborns vaccinated. Different durations of immunity are shown. Intensity of transmission is intermediate ($R_0 = 10$).

where R_0 is defined by equation (6) and γ_0 is the duration of immunity when infection rate is zero. Thus γ_0/δ is the ratio of mean human life expectancy to the mean duration of immunity in susceptibles that are never infected. Fig. 9a shows that when immunity is lifelong ($\gamma_0 \to 0$) malaria can be eliminated from any area if a sufficient proportion, p, of the population is vaccinated. However, if the efficacy of the vaccine decreases over time, areas from where malaria can be eliminated are limited to

$$R_0 < \frac{\gamma_0 + \delta}{\gamma_0} \tag{9b}$$

Thus even when the longevity of immunity is on the order of half of a human life-span, malaria can be eliminated only from epidemic areas with $R_0 < 1.5$.

Another way of expressing equation (9a) is shown by reformulating is as

$$p > \left(1 - \frac{1}{R_0}\right) \frac{1}{1 - e^{-\delta\tau}} \tag{9c}$$

Note that $1 - e^{-\delta\tau}$ is the proportion of the vaccinated newborns that die before the vaccine becomes ineffective. Thus condition (9c) can be reduced to the standard condition for eradication of disease (Anderson, 1982)

$$p' > \left(1 - \frac{1}{R_0}\right) \tag{9d}$$

where p' denotes the *effective* proportion vaccinated, i.e., the proportion of the population that are vaccinated, develop immunity, and maintain immunity throughout their lives.

The model further predicts that prevalence decreases more or less linearly as the proportion vaccinated increases (Fig. 9b). The major determinants of prevalence are the basic reproductive number and the duration of immunity. The impact of the vaccine on prevalence increases as the basic reproductive number decreases and as the duration of immunity, i.e. the duration of efficacy of the vaccine, increases.

Transmission-blocking vaccine Mass vaccination with a sexual stage vaccine is modelled by splitting the general model of Fig. 7 into two categories (Fig. 10). A proportion $1-p$ of newborns remains unvaccinated, becomes infected (and infectious), and immune. A proportion p of the newborns is vaccinated. These individuals become infected and immune at the rates of the unvaccinated individuals. However, they cannot transmit the disease to the mosquito vectors for the period during which the vaccine remains effective. The mean duration of efficacy of the vaccine is set to $1/v$. It is assumed that the vaccine is not boosted by natural infections. Note that, in contrast to the general model, it is assumed here that immunity against the asexual stages is life-long. This leads to the most optimistic prediction of the effect of transmission-blocking vaccines.

The basic reproductive number is calculated in Appendix E and the proportion of newborns that must be vaccinated for eradication of malaria is (Fig. 11a)

$$p > \left(1 - \frac{1}{R_0}\right)\left(1 + \frac{v}{r+\delta}\right)\left(1 + \frac{v}{\delta}\right) \tag{10}$$

This condition includes, as does the condition for eradication with an asexual stage vaccine, a term describing the ratio of human life expectancy to the mean duration of vaccine efficacy, v/δ. It further includes a term describing the ratio of the duration of infection to the duration of vaccine efficacy, $v/(r+\delta)$. The product of these two ratios results from the condition that a transmission-blocking vaccine must remain effective from birth up to a first infection and additionally throughout the period of this infection.

Fig. 11b shows the effect of a transmission-blocking vaccine on the prevalence of malaria. It shows that prevalence remains at high levels over most of the range of

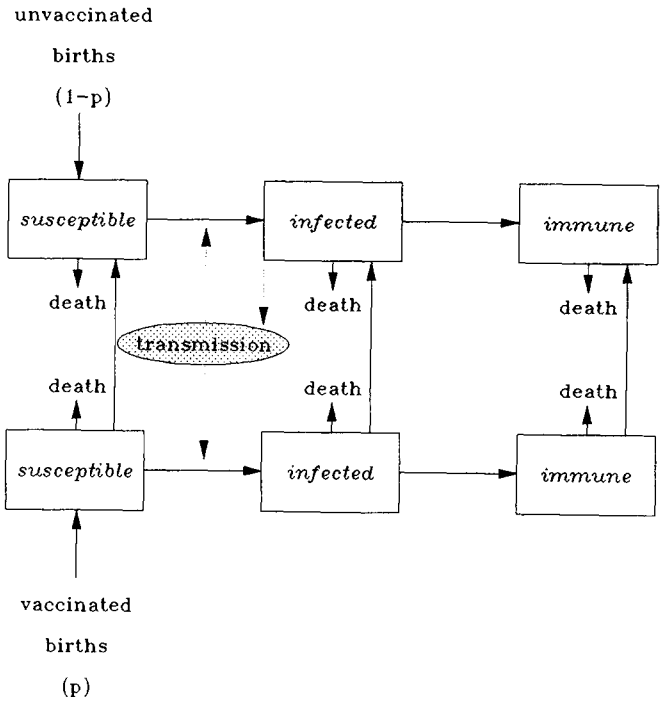

Fig. 10. Structure of model of transmission-blocking vaccine. The upper part of the structure, showing the unvaccinated proportion of the population, is similar to the structure of the model of immunity shown in Fig. 7. It is assumed that no immunity to asexual stages can be acquired. The lower part of the structure, showing the vaccinated proportion of the population is identical to the upper part except that transmission from humans to mosquitoes is blocked. Efficacy of the vaccine is lost at a constant rate, so that vaccinated individuals move to the unvaccinated class. See the main text and Appendix E for more details.

parameters. Only if a very high proportion of the population is vaccinated and if the duration of vaccine efficacy is long does prevalence decrease significantly, even when the basic reproductive number is low.

The comparison of asexual stage vaccines with transmission-blocking vaccines makes several important points. First, the duration of efficacy of either vaccine strongly determines the impact on the endemicity of malaria. In particular, the duration of efficacy must be about 50–100% of the human life-span for any significant effect to occur. Secondly, when durations of efficacy are similar, asexual stage vaccines require a smaller proportion of newborns to be vaccinated for eradication of malaria than do transmission-blocking vaccines. Both vaccines must be effective up to the mean age of first infection, but transmission-blocking vaccines must additionally be effective throughout the period of infection. Thirdly, asexual stage vaccines are expected to make a larger impact on prevalence of malaria than transmission-blocking vaccines. Asexual stage vaccines protect individuals directly, so that any vaccinated individual will not become infected during the period of vaccine efficacy. Transmission-blocking vaccines reduce transmission in the community, but individuals are protected only if transmission in the community is almost completely blocked.

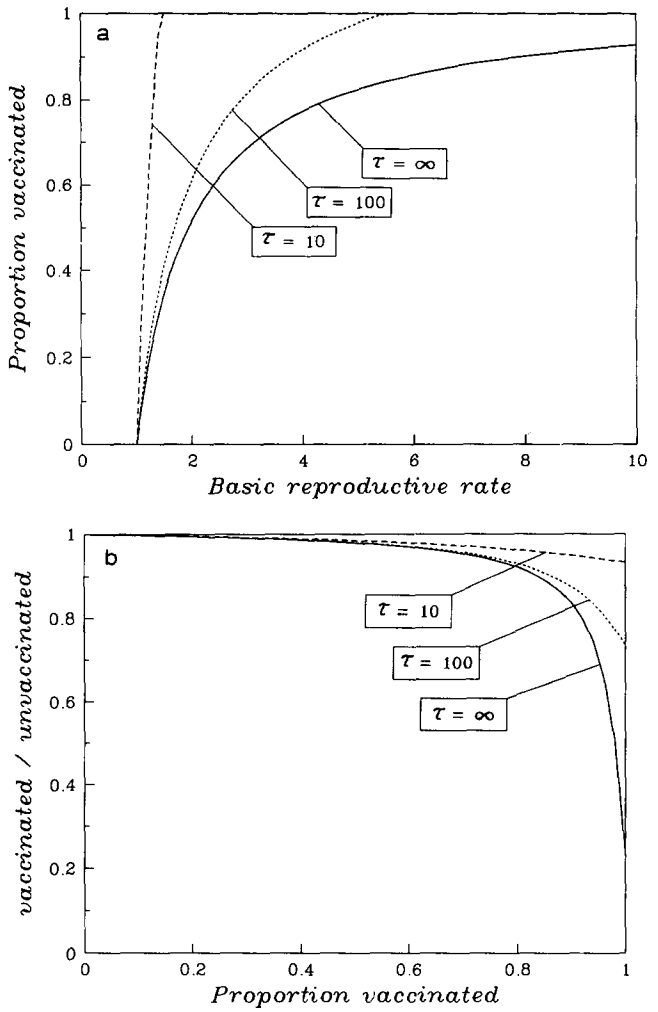

Fig. 11. Predictions of model of transmission-blocking immunity on the endemicity of malaria. (a) The relationship between the intensity of transmission and the proportion of newborns that must be vaccinated for the eradication of malaria. Intensity of transmission is described as the basic reproductive number. Various durations of efficacy of the vaccine are shown. (b) The reduction of crude prevalence as a function of the proportion of newborns vaccinated. Different durations of efficacy of the vaccine, τ, are shown. Intensity of transmission is intermediate ($R_0 = 10$).

Conclusions and outlook

The models discussed above are only a small sample of the many different models published. They were chosen because each contributes to our knowledge of the biology and control of malaria but remains simple in structure. Perhaps the most important conclusions of the models are, first, that malaria can exist in a population only if mosquito density exceeds a critical threshold. Second, endemicity of malaria is most sensitive to changes in mosquito survival rate. Thus imagicides are a more efficient way of controlling malaria than larvicides. Third, variability in transmission

parameters can considerably bias our predictions of the impact of control measures and affect their outcome. Fourth, the duration of vaccine efficacy is among the most important determinants of the impact of a vaccine program. In particular, it seems likely that the duration of efficacy must be about 50–100% of a human life-span for any significant impact of vaccination. This imposes severe restrictions on the design of a vaccine, in particular as average human life-spans in many countries are increasing towards 70 years. It is stressed again that in this paper only vaccination at birth is explored. Vaccination programmes with repeated vaccinations at certain ages will of course let vaccines with short efficacy have considerable impact on the population. Lastly, asexual stage vaccines are expected to be more efficient than transmission-blocking vaccines.

Many other models of malaria transmission have been published (see Bailey (1982) or Dietz (1988) for a review). Most of these, however, are more complex, and the results are more difficult to interpret. In particular, it becomes difficult to decide whether unexpected predictions result from properties intrinsic to the population dynamics of malaria, or whether they are artefacts of details of the specific model. Two examples illustrate this. Nedelmann (1984) reviewed several aspects of the model of the Garki project (Molineaux and Gramiccia, 1980), originally formulated by Dietz et al. (1974), and compared this model with four variations he constructed. One of his main conclusions is that the model representing logically consistent formulations of recovery and infection rates and resulting in the most reasonable estimates of these parameters performs most poorly in fitting the model to the data collected by the Garki project. It is therefore not clear, which model best represents malaria transmission. Halloran et al. (1989) showed with a variation of the same model that, as expected, prevalence of malaria decreases after the onset of a vaccination program and increases again if the program is stopped. Unexpectedly, however, prevalence overshoots the preprogram value. It is still too early to decide whether this overshoot is generally expected. Many of these complex models are reassuring in that they lead to many of the qualitative conclusions reached by simple models. For example, Halloran et al. (1989) predicts that transmission-blocking vaccines, if no boosting by natural infections occurs, result in almost no reduction in prevalence. This is the prediction reached by the simpler model described in this paper.

These examples illustrate central issues in modelling epidemiological processes: the questions to be answered must be clearly stated before defining a model. As Brewer (1975) has pointed out, too many models have been built with unclear goals, resulting in too many inappropriate models. Stating the questions clearly allows decisions on the required level of complexity of the model. Two approaches to future modelling projects, requiring different levels of complexity, illustrate this.

First, models can be built with the aim of understanding specific details of malaria transmission. Such details can often be understood, and general conclusions reached, with relatively simple models involving only few variables. An understanding of only a few of the important interactions between hosts and parasites suffices to answer the question. An example of this approach is given above in the discussion of malaria vaccines. A second example is given in the discussion of the evolution and spread of chloroquine resistance by Curtis and Otoo (1986), Singer (1990) and Cross and Singer (1990). These models result in suggestions for better strategies for the management of drug resistance by combining some basic aspects of *Plasmodium* transmission and population genetics. One of Curtis and Otoo's results is that, if three conditions hold,

drug resistance will evolve and spread at a slower rate when two drugs are administered in mixture than when they are used in sequence. These conditions are (1) resistances are initially rare, (2) the genes conferring resistance can recombine, and (3) a large proportion of the parasite population is unexposed to the drug. Although these conclusions were reached with few details of malaria transmission incorporated in the models, they are clearly of great help for the management of drug resistance.

Making optimal decisions in large control programs can be helped by multidisciplinary modelling approaches (Bailey, 1982). Such an approach would consider malaria not as an isolated disease, but as part of a network of interacting sectors. A few of the sectors that influence patterns of malaria transmission and morbity are infection with other diseases, agricultural methods, education, and economy. These should be included in a large-scale model of malaria control. Such a large-scale approach has never been attempted for the control of parasitic diseases, though a first step has been taken by the Onchocerciasis Control Program in West Africa (Remme, 1989). In contrast, problems in environmental assessment and in the management of renewable resources have often been tackled by multidisciplinary teams, using models to help to guide their ideas (Forrester, 1961; Holling, 1978). Perhaps the most widely-known such study is Meadows et al.'s (1972) report to the Club of Rome *The Limits of Growth.* A multidisciplinary approach to modelling malaria would not only describe the morbidity and mortality due to malaria but also show its economic and social implications. The goal of such a model is to understand the processes within sectors and the interactions between sectors sufficiently well to influence decision-making and policy planning in a social and economically sensible way (Holling, 1978; ESSA, 1982).

This outlook on multidisciplinary approaches to malaria control and the examples described share the purpose of showing that the wise use of mathematical models of malaria transmission can lead to a deeper understanding of the biology of malaria and can help to design malaria control programs in the most efficient way. Thus, this paper brings us back to what Ross (1911, p. 651) said a long time ago:

> 'all epidemiology, concerned as it is with the variation of disease from time to time or from place to place, must be considered mathematically, however many variables are implicated, if it is to be considered scientifically at all. To say that a disease depends on certain factors is not to say much, until we can also form an estimate as to how largely each factor influences the whole result. And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at issue.'

Appendix A: Ross-Macdonald model

The Ross-Macdonald model is a direct translation of the schematic life-cycle (Fig. 1) into quantitative terms. Consider first the infection of humans by mosquitoes. Each female mosquito bites a host on average a times per night. Assuming a density of m female mosquitoes for every one human, each human is thus bitten ma times per night. Only a fraction w of the mosquitoes have sporozoites in their salivary glands, and only a fraction b_2 of these are actually infectious to the human. This reduces the number of infective bites to b_2maw per human per night. An infective bite will of course lead to a new infection only if the person bitten is not already infected. If, say, a proportion y of the human population is infected, then new infections develop

TABLE 1

List of symbols used in the text

Symbol	Description
a	Biting-rate (number of bites per female mosquito per night)
b_1	Infectiousness of humans to mosquitoes
b_2	Infectiousness of mosquitoes to humans (susceptibility)
h	Infection rate of humans
m	Mosquito density (number of mosquitoes per human)
p	Vaccinated proportion required for eradication of malaria
r	Rate of recovery of infected humans
R_0	Basic reproductive number
T	Incubation period of parasites in mosquito
u	Frequency of susceptible mosquitoes
v	Frequency of infected, but not yet infective mosquitoes
w	Frequency of infectious mosquitoes
X	Intensity of infection (mean number of infections per human)
x	Frequency of susceptibles in human population
y	Frequency of infecteds in human population
z	Frequency of immunes in human population
δ	Mortality of humans
γ	Rate of loss of immunity
γ_0	Rate of loss of immunity in the absence of further infections
μ	Mortality of mosquitoes
ν	Rate of loss of efficacy of transmission-blocking vaccine
ρ	Duration of disease ($1/r$)
τ	Duration of immunity in the absence of further infections

at a rate $b_2maw(1-y)$. Once infected, a human recovers at a rate r, i.e. the average time for infections to be cleared is $1/r$. Thus, the equation governing the proportion of infected humans, y, can be written as

$$\dot{y} = mab_2w(1-y) - ry \tag{A.1}$$

where $\dot{y}$ denotes the change of the proportion infected per unit time. Consider next the infection of mosquitoes by humans. The population of mosquitoes is separated into three categories: a susceptible proportion $1-v-w$ that is uninfected, an infectious proportion w with sporozoites in the salivary glands, and a latent proportion v that is infected, but has not yet developed sporozoites. The susceptible mosquitoes become infected by biting infected humans, of which a fraction b_1 harbor gametocytes and are infectious to mosquitoes. Thus the proportion of latent mosquitoes increases at a rate $b_1ay(1-v-w)$. These newly infected mosquitoes become infectious to humans if they survive the incubation period, T, required for the development of the gametocytes into sporozoites. Assuming a mortality rate of μ, i.e. an average life span of $1/\mu$, a proportion $e^{-\mu T}$ survive this period. Thus, of the $b_1ay(1-v-w)$ mosquitoes infected T days earlier, $b_1ay(1-v-w)e^{-\mu T}$ move from the latent state to the infectious state. The proportions of the latent and infectious mosquitoes decrease through mortality. The process of infection in the mosquitoes can be summarized as

$$\dot{v} = ab_1y\,(1-v-w) - ab_1\hat{y}(1-\hat{v}-\hat{w})\,e^{-\mu T} - \mu v \tag{A.2}$$

$$\dot{w} = ab_1\hat{y}\,(1-\hat{v}-\hat{w})\,e^{-\mu T} - \mu w \tag{A.3}$$

where $\hat{y} \equiv y(t-T)$, $\hat{v} \equiv v(t-T)$, and $\hat{w} \equiv w(t-T)$.

The basic reproductive number, R_0 describes the number of secondary cases of malaria arising from a single case in an otherwise uninfected population (Macdonald, 1957; Anderson and May, 1980), and can be derived algebraically from the above equations as

$$R_0 = \frac{ma^2 b_1 b_2 \, e^{-\mu T}}{r\mu} \tag{A.4}$$

Appendix B: Model incorporating variability

The model incorporating variability follows a model described by Nåsell (1985, chapter 3.3). It assumes that humans can be infected several times by various strains of parasites. It therefore describes the mean number of infections, X, harbored by any one human host. In contrast, the mosquitoes are assumed to be infected only once, so that the mosquito population is separated into susceptible, latent, and infective mosquitoes. As an extension of Nåsell's model, the current model separates the human population into N categories, each of which makes up a proportion ϕ_i of the total population. Each category is assumed to be homogeneous with respect to malaria infection, and to differ from other categories in susceptibility to infection, b_2, biting rate, a, and duration of disease, $\rho = 1/r$. Within each category humans are assumed to be infected randomly, so that prevalence within a category is $P_i = 1 - e^{-X_i}$ (Nåsell, 1985). As in the Ross-Macdonald model, humans are infected at a rate $ma_i b_{2,i} w$, where w denotes the proportion of infective mosquitoes. Susceptible mosquitoes are infected within human category i at a rate $a_i b_i P_i$. Thus, averaged over all categories, mosquitoes are infected at a rate

$$h = \sum_i \phi_i a_i b_1 (1 - e^{X_i})$$

Thus, Nåsell's model can be reformulated as

$$\dot{X}_i = ma_i b_{2,i} w - r_i X_i \tag{B.1a}$$

for the mean number of infections in humans belonging to category i

$$\dot{u} = \mu - \sum_i \phi_i a_i b_1 (1 - e^{-X_i}) u - \mu u \tag{B.1b}$$

for the frequency of susceptible mosquitoes, and

$$\dot{w} = e^{-\mu T} \sum_i \phi_i a_i b_1 (1 - e^{-\hat{X}_i}) \hat{u} - \mu w \tag{B.1c}$$

where $\hat{X}_i = X_i(t-T)$ and $\hat{u} = u(t-T)$ for the frequency of infectious mosquitoes. The basic reproductive number can be calculated from these equations as

$$R_0 = \overline{R_0} \left[1 + \frac{\mathrm{var}(a)}{\overline{a^2}} + 2\frac{\mathrm{cov}(a,b_2)}{\overline{ab_2}} + 2\frac{\mathrm{cov}(a,\rho)}{\overline{a\rho}} + \frac{\mathrm{cov}(\rho,b_2)}{\overline{\rho b_2}} \right] \tag{B.2}$$

where

$$\overline{R_0} = \frac{m\bar{a} b_1 \overline{b_2} \, e^{-\mu T}}{\bar{r}\mu}$$

denotes the basic reproductive number due to the mean parameters in the population, $\bar{x}$ denotes the mean of x, var(x) denotes the variance of x, and cov(x,y) denotes the covariance of x and y.

Appendix C: General model of immunity

The general model of malaria immunity consists of three differential equations denoting changes in the proportions of susceptible, x, infected, y, and immune, z, people. In an extension of a model proposed by Aron (1988a,b), the equations are written

$$\dot{x} = \delta - \delta x - hx - \gamma z \tag{C.1a}$$

$$\dot{y} = hx - (r+\delta)y \tag{C.1b}$$

$$\dot{z} = ry - (\gamma+\delta)z \tag{C.1c}$$

Susceptibles become infected at a rate h. Infected individuals recover at a rate r to enter the immune class. Immunes become susceptible again at rate γ. Deaths occur at rate δ (i.e. life-expectancy is $1/\delta$) and are unaffected by disease status. Deaths are balanced by births into the susceptible class so that population size remains fixed.

Immunity is boosted by new infections, and lasts only for τ years in the absence of new infections. If τ is set equal to the mean residence time in the immune class, $1/(\gamma+\delta)$, the parameter γ becomes (Aron, 1988a).

$$\gamma(h) = \frac{(h+\delta)\, e^{-(h+\delta)\tau}}{1 - e^{-(h+\delta)\tau}} \tag{C.2}$$

The mosquito dynamics described in the Ross-Macdonald model by equations (A.2) and (A.3) operate on a much faster time-scale than the human dynamics described by equations (C.1), so that the mosquito population can be considered to be at equilibrium with respect to changes in the human population, and its dynamics can be collapsed into the inoculation rate.

$$h = ma^2 b_1 b_2\, e^{-\mu T} \frac{y}{\mu + ay} \tag{C.3}$$

Analysis of equations (C.1) to (C.3) at equilibrium leads to the basic reproductive number

$$R_0 = \frac{ma^2 b_1 b_2\, e^{-\mu T}}{(r+\delta)\mu} \tag{C.4}$$

Appendix D: Model of asexual stage vaccine

Mass vaccination of a proportion p of all newborns with an asexual stage vaccine is simulated by letting a proprtion p be born as immunes and a proportion $1-p$ as susceptibles in the model of immunity described in Appendix C. No other changes

are made to the model. Thus a model of asexual stage vaccination can be written as

$$\dot{x}=\delta(1-p)-\delta x-hx-\gamma z \tag{D.1a}$$

$$\dot{y}=hx-(r+\delta)y \tag{D.1b}$$

$$\dot{z}=\delta p+ry-(\gamma+\delta)z \tag{D.1c}$$

The basic reproductive number of this model is

$$R_0'=R_0\left(1-\frac{\delta}{\delta+\gamma_0}p\right) \tag{D.2}$$

where R_0 denotes the basic reproductive number of the model with no vaccination described in Appendix C and γ_0 denotes the rate of loss of immunity in the absence of any infections (i.e. when $h=0$). Malaria cannot invade a population if the basic reproductive number R_0' is less than one. This condition leads from equation (D.2) to the condition

$$p>\left(1-\frac{1}{R_0}\right)\left(1+\frac{\gamma_0}{\delta}\right) \tag{D.3}$$

for the eradication of malaria.

Appendix E: Model of transmission-blocking vaccine

Mass vaccination with a transmission-blocking vaccine is simulated by splitting the model described in Appendix C into two categories. The first category, the proportion $1-p$ of the population that is not vaccinated, is identical to the model of Appendix C with the exception that immunity against the asexual stage of the parasite is assumed to be lifelong. The second category, the proportion p of the population that receives the vaccine, is infected and becomes immune at the same rate as the unvaccinated category. However, it does not make any contribution to transmission during the period when the vaccine is effective. The vaccine loses its effectiveness at a rate v. Thus a model of transmission-blocking vaccination can be written as

$$\dot{x}_u=\delta(1-p)-(\delta+h)x_u-vx_u \tag{E.1a}$$

$$\dot{x}_v=\delta p-(\delta+h)x_v-vx_v \tag{E.1b}$$

$$\dot{y}_u=hx_u-(r+\delta)y_u+vy_u \tag{E.1c}$$

$$\dot{y}_v=hx_v-(r+\delta)y_v-vy_v \tag{E.1d}$$

$$\dot{z}=r(y_u+y_v)-\delta z \tag{E.1e}$$

where the subscript v denotes the vaccinated, the subscript u the unvaccinated category.

The basic reproductive number for this model is given by

$$R_0''=R_0\left(1-\frac{\delta(r+\delta)}{(\delta+v)(r+\delta+v)}p\right) \tag{E.2}$$

where R_0 denotes the basic reproductive number of the model with no vaccination

described in Appendix C. Malaria cannot invade a population if R_0'' is less than one or, from a reformulation of equation(E.2), if

$$p > \left(1 - \frac{1}{R_0}\right)\left(1 + \frac{v}{r+\delta}\right)\left(1 + \frac{v}{\delta}\right) \tag{E.3}$$

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