Chapter Ten

THE MATHEMATICAL MODEL OF TRANSMISSION

The selection of a strategy of control (or eradication) of malaria is, in principle, based on the expected effect of technically feasible intervention methods and on their cost. A mathematical model of the epidemiology of malaria may rationalize this selection by allowing the quantitative comparison of the relative effects of different intervention methods and their combinations, within the expected range of underlying conditions. A fresh attempt to model the epidemiology of malaria was undertaken mainly because previous models do not take into account the effect of immunity on transmission; this may be relatively unimportant for a theory of eradication, but is crucial for a theory of control where the end-point is a new balance of the host and parasite populations.

The model presented here was constructed as an integral part of the project, and was developed in close interaction with the field work (46). The specific objectives of the model are: (a) to describe the quantitative relationship between the entomological variables and the incidence and prevalence of microscopically detectable *P. falciparum* infections, including their variation by age and season; and (b) to compare the expected parasitological effects of specified control measures (larvicides, adulticides, drugs), alone or in combination, at specified expected levels of coverage and effectiveness.

The model attempts to represent the natural history of the infection in man, and its transmission, by a structure which can be manipulated either analytically or by computer simulation. The model, even if it appears complicated to the non-mathematician, is obviously much simpler than malaria itself. Certain epidemiological features are selected while others are neglected, and the selected features are translated into simple and clear-cut assumptions. These assumptions define the struc-

a The work reported in this chapter w-as performed by Dr K. Dietz, Dr L. Molineaux and Mr A. Thomas. They used the data collected in Garki under the direction of Dr S.P. Ramakrjshnan and in Kisumu under the direction of Dr R.E. Fontaine.

ture of a model. The model may be discussed *apriori* in terms of what is known about malaria. The model may also be tested *aposteriori* with respect to its capacity to simulate the actual epidemiology of malaria. This discussion and testing of the model was performed in 3 stages. In a first stage, both the structure (the assumptions) and the numerical values of the parameters were varied by informal trial and error until a structure (a set of assumptions) was found which was qualitatively satisfactory in terms of epidemiological behaviour. This was done by a continuous interaction between study of the literature, field observations in Garki (see Chapter 5, in particular pp. 159-162), model building, and computer simulations. The first section below describes the outcome of that first stage. In a second stage, the model was fitted formally to a particular epidemiological situation, namely, the Garki baseline situation, by letting the computer find, for some parameters, the numerical values producing the best fit between model simulations and actual observations; this second stage is described in the section that follows. In a third stage, the entomological observations from different epidemiological situations (e.g., Garki or Kisumu after application of a residual insecticide) were used as input into the model, without change in the other parameters, and the resulting parasitological output was compared to actual observations; this stage is described in the third of the following sections. Once the model has been tested, it may be used as a tool to understand and teach the epidemiology of malaria (see pp. 281-282 and 287) and to plan its control (see p. 286).

The Assumptions of the Model

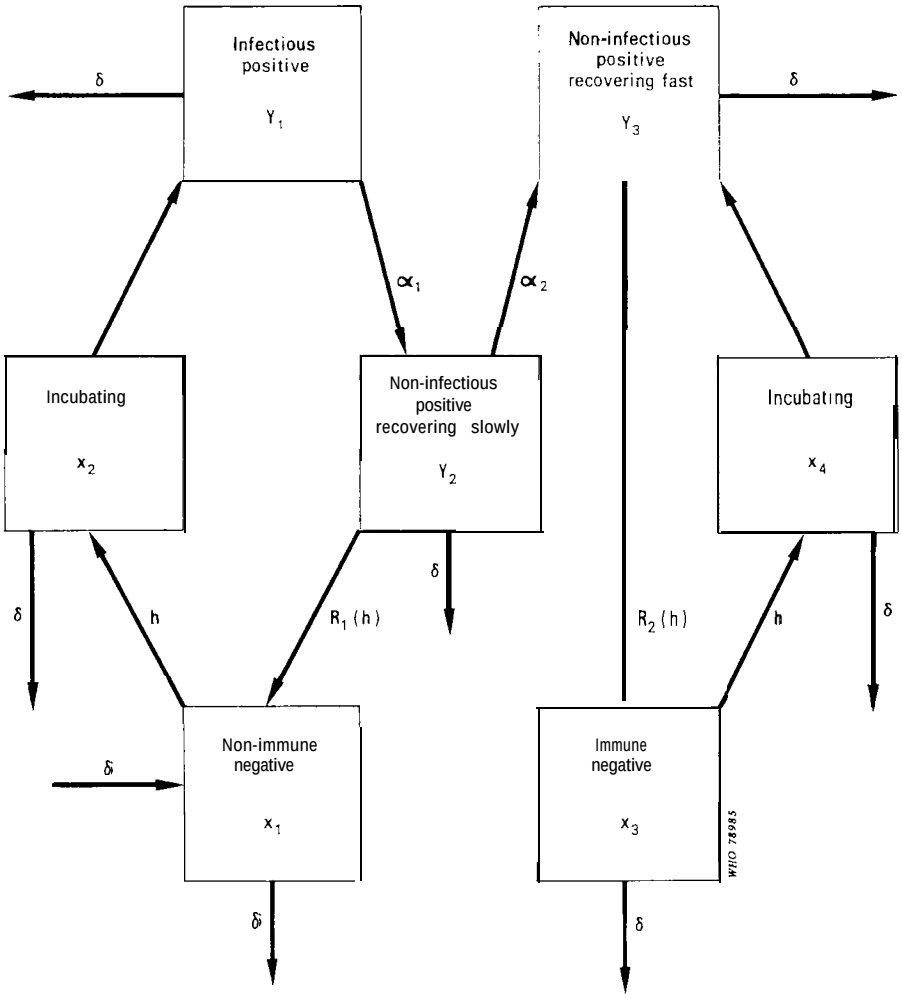
Epidemiological states and transitions

The epidemiological states (or classes) and the transitions between classes by which the model simulates the natural history of ***P.*** *falciparum* in man are shown in Fig. 76. The symbols used in the model are listed and defined in Table 30. The letters $x_1, \ldots, x_4$, and $y_1, \ldots, y_3$ are used both to denote classes and the proportions of the population occupying the classes. The population size is thus set to 1:

$$\sum_{i=1}^{4} x_i + \sum_{i=1}^{3} y_i = 1$$

Man is born into the nonimmune negative statex, ; i.e., passive immunity is ignored. Nonimmune negatives are effectively inoculated at a rate h

Fig. 76. States and transitions of the model



(see p. 267) and transferred to the incubating class x_2, in which they stay for a fixed incubation period of N days. After that, they become positive and infectious, in classy, . While in y_1 the person is infective to mosquitos (see pp. 267-268) and is positive, with a probability q_1, by a standard blood examination, e.g., by the examination of 200 fields of a thick film. Infectivity is lost at a constant rate α_1, at which persons move to the state y_2 in which they are noninfectious but still positive, with a probability q_2, by microscopic examination. Once in state y_2, a person may either recover from infection and return to the nonimmune negative state x_1 at a

Table 30

Symbols and definitions used in the model

Symbol	Name	Definition and/or comments
a	man-biting habit	No. of bloodmeals taken on man by 1 vector in 1 day
C	vectorial capacity	$C = ma^2p^n / (-\ln p)$; *seep.* 267
g	susceptibility	probability that an infection results, given that at least 1 contact has occurred, in 1 time-unit
h	effective inoculation rate	probability that a negative acquires the infection (becomes incubating), in 1 time-unit; $h = g\{1\text{-exp}(-Cy_1)\}$ see p. 267
m	relative densitv of vectors	No. of vectors per man, i.e., ratio between the size of the vector population and the size of the human population
n	extrinsic incubation period	incubation in the vector
N	intrinsic incubation period	incubation period in man
p	probability of surviving 1 day	probability that the vector survives 1 day
q_1, q_2, q_3	probability of detection	probabilities that the 3 kinds of positives (y_1, y_2, y_3) are detected by a standard parasitologic examination
r_1, r_2	basic recovery rates of non-immunes, immunes	recovery rate from 1 infection of the y_2, y_3, respectively
R,(h), $R_2(h)$	actual recovery rates of non-immunes, immunes	actual rate at which the y_2, y_3, recover, taking into account the superinfections resulting from a given h; $R_i(h) = h/\{\exp(h/r_i)-1\}, i = 1,2$; see pp. 265-266
t	time	x_1 (t) designatesx, at time t, x, (t-N) designates x, at time $(t-N)$, etc.
T_1, T_2	expected duration of states y_2, y_3	$T_i = 1 / R_i(h), i = 1,2$
x_1, x_3	nonimmune, immune negatives	see pp. 262-265
x_2, x_4	nonimmune, immune incubating	see pp. 262-265
y_1, y_2, y_3	3 kinds of positives	see pp. 262-265
y	true proportion positive	$y_1 + y_2 + y_3$, or $\sum_{i=1}^{3} y_i$
z	observed proportion positive	$q_1y_1 + q_2y_2 + q_3y_3$, or $\sum_{i=1}^{3} q_iy_i$
α_1	rate of loss of infectivity	see p. 263
α_2	rate of acquisition of a high recovery rate	see below
δ	death rate	also birth rate, see p. 266

rate $R_1(h)$, or become an "immune positive" (y_3, see below) at a constant rate a,. The actual recovery rate R, (h) is a function of a constant, r_1, which is the basic recovery rate of nonimmunes and of h, the effective

inoculation rate: as the inoculation rate increases, the actual recovery rate decreases, i.e., superinfection prevents recovery (see following subsection) and an increasing proportion of y_2 move to y_3, i.e., become "immune positives". Persons in y_3 are still positive, with a probability q_3, by microscopic examination, and noninfectious; q_3 is smaller than q_1 and q_2; i.e., the probability of diagnosis by a standard blood examination decreases as immunity increases. The "immune positives" in y_3 recover from infection at a rate R,(h), which is a function of r_2, the basic recovery rate of immunes, and of h; r_2 is larger than r_1, i.e., immunes tend to recover faster than nonimmunes, but here also superinfection reduces the recovery rate R,(h) (see following subsection). If an immune positive (y_3) recovers from infection he becomes an immune negative (x_3). Immune negatives are successfully inoculated at the same rate (h) as the non-immune negatives, and incubate the infection for the same period of N days, after which they are again "immune positives" (y_3), i.e., detectable with probability q_3, noninfectious, and with the "high" basic recovery rate r_2.

A person may go through several cycles $x_1 \rightarrow x_2 \rightarrow y_1 \rightarrow y_2 \rightarrow x_1$ etc. before moving to y_3. A person may also go through several cycles $y_3 \rightarrow x_3 \rightarrow x_4 \rightarrow y_3$ etc. As the inoculation rate h increases, the recovery rates R, and R_2 decrease and an increasing proportion of persons travel the route $x_1 \rightarrow x_2 \rightarrow y_1 \rightarrow y_2 \rightarrow y_3$, without returning to x_1, and, once in y_3, either stay there or, if they recover, are quickly reinoculated and so return, through x_4, to y_3.

Superinfection

The effect of h on R, (h), $R_2(h)$, i.e., the effect of superinfection on recovery, is handled as follows. We accept Macdonald's assumption: "The existence of infection is no barrier to superinfection, so that two or more broods of organisms may flourish side by side, the duration of infection due to one being unaltered by the others" (96). His formula however-i.e., $R = r - h$, for $h<r$; and $R = 0$, for $h \geq r$—represents a quite different assumption, namely, that the durations of the individual inoculations received during one episode are additive, as if an individual could only recover from one inoculation at a time. A new formula was therefore derived for the actual recovery rate in the presence of superinfection, as follows. Inoculations "arrive" according to a Poisson process with rate h. The infection resulting from each inoculation is terminated at a rate r, and has therefore an expected duration of $1/r$. Then, in equilibrium, the number of infections present at any time in a person is a Poisson variable with mean h/r. Hence the probability that an individual has no infection is given by $\exp(-h/r)$. The correct formula

for this probability has been given by Walton (161). At equilibrium, this probability is equal to the proportion of infection-free time in any given period. Consider in particular the period between the onsets of 2 consecutive positive episodes; the period is the sum of T, the duration of a positive episode, plus l/h, the infection-free waiting time for a new episode. Therefore:

$$\exp(-h/r) = (1/h)/\{ T + (1/h)\},$$

which leads to:

$$T = \{\exp(h/r)-1\}/h.$$

The actual recovery rate is the inverse of the expected duration of a positive episode T, i.e.:

$$R(h) = h/\{\exp(h/r)-1)$$

Substituting the basic recovery rates r_1, r_2 (see previous subsection) into the formula, we get the actual recovery rates $R_1(h)$, $R_2(h)$. For low values of h, this recovery rate is close to the one calculated by Macdonald's formula. But for $h = r$, for instance, the present formula reduces r only by a factor of about 1.7," whereas Macdonald's actual recovery rate would already be 0-i.e., the expected duration of a positive episode would be infinite.

The problem of the mathematical formulation of superinfection has been reviewed by Fine (58).

Dynamics of the human population

A very simple demographic model is included in the transmission model. Births are added to class x_1; deaths occur in all classes. There could be as many death rates as there are classes, i.e., mortality could vary with parasitological status or immunity status or both. Age is implicit in the model (see p. 269) and mortality cannot be varied by age *per* se without change in the model structure.

In the simulations described in this chapter, a single death rate has been adopted, i.e., the death rate is independent of age, parasitological status and immune status. The birth rate has been made equal to the death rate (in Fig. 76, both rates are represented by δ). This results in a stable population with an exponential age-distribution.

These very simple demographic assumptions considerably simplify the computations. Note that they are made for the purpose of simulations which explore questions of transmission. For simulations exploring the

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[a] $r/R = r\{\exp(h/r) - 1\}/h$; if $h = r$, this becomes $r/R = e - 1 = 2.72 - 1 = 1.72$.

demographic effects of malaria and its control, changes would obviously be required.

Vectorial capacity and inoculation rate

All the information about the vector populations is incorporated into one time-dependent variable, the vectorial capacity C. As in Garrett-Jones (66), C(t) is defined here as the number of bites on man that those vectors having bitten an individual on day t distribute after the extrinsic cycle of duration n during the rest of their life. In other words, C is the number of potentially infective contacts an individual person makes, through the vector population, per unit time. For one vector population with density m (i.e., number of vectors alive per human individual), man-biting habit a and daily survival probability p, the formula given by Garrett- Jones is $ma^2p^n / (-\ln p)$.

The formula of the vectorial capacity may be derived as follows: a person is bitten by ma vectors in 1 day; a fraction p^n of the vectors survive the extrinsic cycle (incubation period); they still have an expectation of life of 1 /-ln p (the expectation of life is assumed to be independent of age); each of the surviving vectors bites a persons per day.

If there are several, say J, vector populations, either different species or subpopulations with different characteristics, with man-biting habits a_j, daily survival probabilities p_j and possibly time-dependent densities $m_j(t)$, then the total vectorial capacity $C(t)$ is the sum of the vectorial capacities of the individual populations:

$$C(t) = \sum_{j=1}^{J} m_j(t)\, a_j^2\, p_j^n / (-\ln p_j)$$

If a_j, p_j, and n are also time-dependent the formula is slightly more complicated. The definition of Cdepends on entomological variables and on the duration of the extrinsic cycle, which is specific for the parasite considered. It has a meaning independent of the parasite rate, of the sporozoite rate, and of the presence or absence of parasites in a particular population.

The inoculation rate h (effective inoculation rate or incidence rate) is defined as the rate at which negatives are transferred to positive via the incubating state. We assume the following formula for the inoculation rate $h(t)$ on day t:

$$h(t) = g\{\ 1\text{-}\exp(-C(t\text{-}n)y,\ (t\text{-}n)\},$$

which is based on the following interpretation. In a stable situation, where C and y_1 are constant, each member of the population receives C

potentially infective contacts per day; a fraction y_1 of these contacts originates from infectives and represents inoculations; therefore the average number of inoculations per person per day is Cy_1 ; assuming a Poisson distribution, the probability of receiving no inoculation is exp(-Cy,), and the probability of receiving at least one is $1-\exp(-Cy_1)$. The parameter g is then defined as the conditional probability that an infection results, given that at least one inoculation has occurred. We shall call g the susceptibility. If the situation is not stable, C, y_1 and h all vary over time, and we have to take into account that the inoculations received on day t originated on day (t-n), or before; it is assumed, however, that they all originated on day (t-n), hence the above formula for h(t). This assumption that all the inoculations originated on day (t-n) considerably simplifies the structure of the model and should be close enough to reality for a relatively short-lived vector. The formula for the inoculation rate implies a strong density-dependent regulation of transmission: the inoculation rate increases linearly with vectorial capacity only for small values of C. For high vectorial capacities the inoculation rate reaches a saturation level. We assume uniform exposure to the inoculation rate.

Equations of the model

The assumptions listed above lead to a set of 7 difference equations, each one expressing the change in the proportion of the population occupying one of the 7 states of the model. The difference equations can easily be derived from Fig. 76 and the assumptions. Considering x_1 for instance during 1 unit of time, i.e., the interval (t, t + 1): (1) δ births are added (the birth rate is applied to the whole population, set to 1, asx, , x_2 etc. are proportions, see above); (2) a fraction $R_1(h)$ ofy, recover and are also added to x_1 ; (3) a fraction h of x_1 are effectively inoculated and are subtracted (moved to x_2); (4) a fraction δ of x_1 die and are also subtracted. Hence the first difference equation:

$$\Delta x_1 = \delta + R_1(h)y_2 - (h + \delta)x_1.$$

For simplicity, the difference equations will be written here for an iteration interval of 1 day (in the computer version the iteration interval is variable; for most of the calculations described below, a 5-day iteration interval has been used). As usual, the symbol A denotes the difference operator, e.g., $\Delta x_1 = x_1(t + 1) - x_1(t)$ The time variable will be omitted except where reference is made to a time different from t

Considering x_2, during the interval (t, t + 1) : (1) hx_1 are added; (2) $(1 - \delta)^N h(t - N)x_1(t - N)$ are subtracted by moving to x_3, i.e., from

incubating to positive; the expression may be understood as follows: those completing their incubation period at time t entered the incubating state at time (t - N); at that time, h_1 t(- $N)x_1$ (t - N)ntered the incubating state x_2; $(1 - \delta)^N$ of them have survived their incubating state; (3) δx_2 are subtracted by death. Hence the second difference equation:

$$\Delta x_2 = hx_1 - (1 - \delta)^N h(t - N)x_1(t - \mathrm{N}) - \delta x_2$$

The 5 remaining difference equations are similarly derived, giving:

$$\Delta x_3 = R_2(h)y_3 - (h + \delta)x_3,$$
$$\Delta x_4 = hx_3 - (1 - \delta)^N h(t - N)x_3(t - N) - \delta x_4,$$
$$\mathrm{Ay,} = (1 - \delta)^N h(t - N)x_1(t - \mathrm{N}) - (\mathrm{a,} + \delta)y_1,$$
$$\Delta y_2 = \alpha_1 y_1 - \{\alpha_2 + R_1(h) + \delta\}y_2, \text{ and}$$
$$\Delta y_3 = \alpha_2 y_2 + (1 - \delta)^N h(t - N)x_3(t - N) - \{R_2(h) + \delta\}y_3.$$

In order to stimulate the transmission in a particular population, one has to provide only the yearly pattern of the vectorial capacity C(t). The computer programme reproduces, after a suitable running-in period during which equilibrium is reached, the seasonal changes of any output variable one might wish to study. Among those are the daily inoculation rate h, the observable proportion positive:

$$z = \sum_{1}^{3} q_i y_i,$$

the true proportion positive:

$$Y = \sum_{i=1}^{3} y_1,$$

the proportion of infectious among the positive y_1/y, etc.

One can also use these equations in a simple way to calculate the age-specific values of these variables under the assumption that a yearly pattern of vectorial capacity is repeating itself. After one has obtained the stable oscillation for the total population according to the equations above, one applies the yearly pattern of the inoculation rate to a cohort formed by 1 individual initially inx, representing a newborn child. Time is now interpreted as age of the cohort. The above equations are used as before except that the death (and birth) rate δ is put at 0 and that now the inoculation rate is used as an input parameter instead of the vectorial capacity.

Fitting of the Model

Model simulations have been compared to field observations in order to estimate the parameter values giving the best fit possible, and to evaluate the model by analysing the discrepancies between observed and expected values.

Data selected for fitting

As stated, the first specific objective of the model is to predict the prevalence and incidence of ***P. falciparum*** from entomological observations. The 2 villages with extreme vectorial densities were selected, and we set ourselves the task of simulating the 2 epidemiological situations as observed during the first year of the project with the same model and the same parameters, with the exception of 2 entomological input parameters ***(m*** and ***a).***

Entomological data

Figure 77 shows the observed man-biting rates in the 2 villages; captures were made every 5 weeks in the dry season, every 2 weeks in the wet season; each data point is based on the average of 8 man-nights. From these man-biting rates, from other observations (age composition of the night-bite collection, distribution by abdominal stages, identification of blood meals of pyrethrum spray collections, and temperatures), and from certain assumptions, the vectorial capacities to be used as input were

Fig. 77. Observed man-biting rates (asterisks and circles) and estimated vectorial capacities (solid and broken lines) for *A. gambiae* and A. *funestus* combined

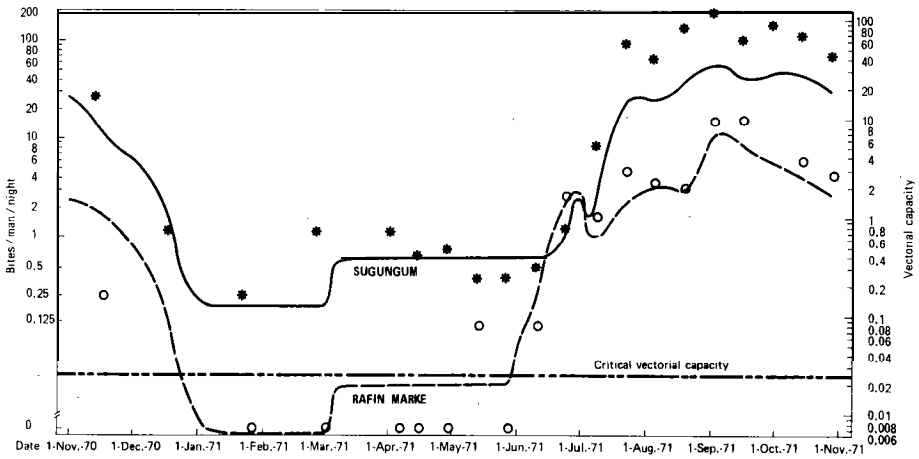
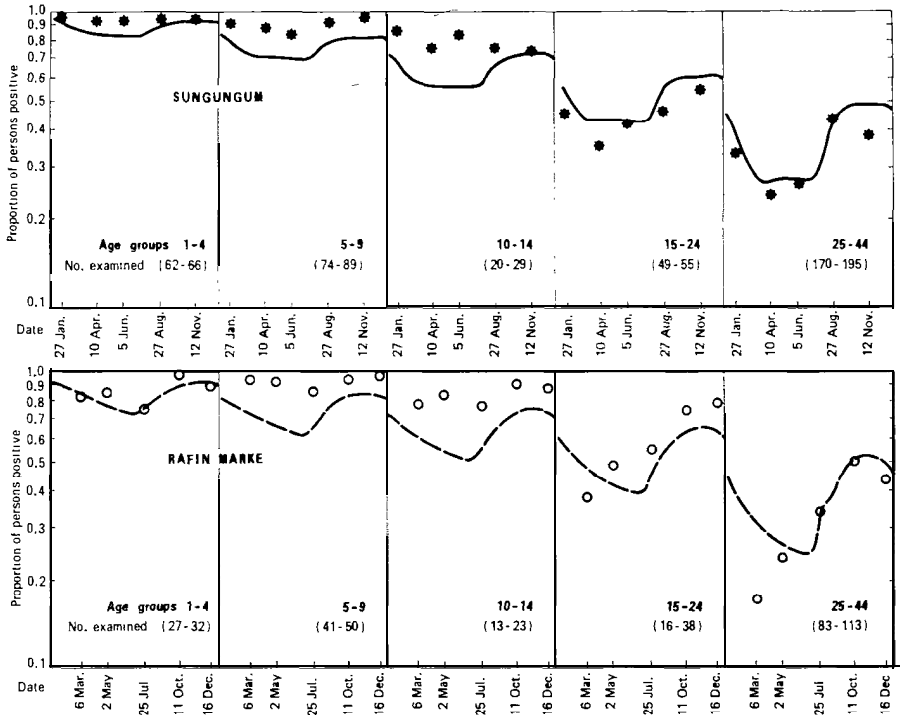


Fig. 78. Comparison of observed (asterisks and circles) and simulated (solid and broken lines) apparent proportions positive



calculated (see pp. 74-75); they are also shown in Fig. 77. It is assumed that this pattern of vectorial capacities was repeating itself year after year.

Parasitological data

Figure 78 shows the observed prevalence of ***P.falciparum*** in the 2 villages by age and season; here also we assume that the first year of the project was representative of the past; the first survey has been plotted after the fifth for convenience, i.e., in order to show the 5 surveys within a single calendar year. The data show the general pattern already described (see pp. 116-1 17), with some irregular fluctuation owing to relatively small numbers. The ranges of the numbers examined among the 5 surveys are given (within parentheses) in Fig. 78. The 2 villages have practically the same crude average prevalence; the age of maximum prevalence is lower in Sugungum, which must be the result of a higher average inoculation rate; the seasonal fluctuations are somewhat larger in Rafin Marke, possibly owing to a combination of shorter transmission season

and lower immunity. In addition to these prevalence data (50 data points), the infant conversion rates in the interval between surveys 4 and 5 were also used for fitting (2 data points).

Estimation of model parameters

In order to reduce, as far as possible, the number of parameters to be fitted, we assumed certain values for some of them, on the basis of data from the literature, findings in Garki, and preliminary simulations. These assumed values are listed in Table 3 1.

Table 31

Parameters corresponding to the fit shown by Fig. 78

(a) *Assumed*		
Birth and death rates of the human population	δ	36.5 per 1000 per year
Vectorial capacity	C	see Fig. 77
Ratio between high and low recovery	r_2/r_1	10
Detectability of positives	q_1, q_2	1
	q_3	*0.7*
Incubation period in man	N	15 days
Incubation period in vector	n	10 days
Rate of losing infectivity	a	0.002/day
(b) *Estimated by fitting*		
Dailyrateof acquiring high recovery rate	α_2	0.00019 ± 0.00001
Susceptibility	g	0.097 ± 0.017
Low daily recovery rate	r_1	0.0023 ± 0.0005

For the estimation of δ we calculated the average age of the human population, which was approximately 27 years. On the assumption of an exponential stable age-distribution this corresponds to a daily death rate of about 0.0001 per person.

The ratio between high and low recovery rates r_2/r_1 was set at 10 on the basis of the effect of immunity on the clearance rate of parasitaemia (see p. 128 and Ref. 7)

The estimates for the 3 fitted parameters were obtained by minimizing a χ^2 function that measured the discrepancy between the observed and predicted values. The age-specific apparent parasite rates are calculated, according to the method described above, for the ages of 3,7,12,19 and 32 years; these are the average ages of the observed age-groups 1-4,5-9, 10-14, 15-24 and 25-44 years, respectively. The age-group245 has been omitted to save computer time, since for every trial-set-of parameters the computer has first to simulate on the average 30 years of transmission until equilibrium is reached and then apply the inoculation rate thus obtained to a cohort for another 32 years to get the age-specific parasite rates

corresponding to the age-group 25-44 years. Because of the small differences in the parasite rates between the age-groups 25-44 and ≥ 45 years there was no great loss of information. The χ^2 function minimization was done by the CERN (Centre européen pour la Recherche nucléaire) computer programme MINROS. The minimum value obtained on 52 data points is 53.5, 3 parameters being estimated. Their values, together with their standard deviations, are given in Table 3 1.

As can be seen from Fig. 78, the age-distribution predicted by the model approaches somewhat too rapidly the equilibrium for the adult population, owing to our simple assumption of a constant rate a, for acquiring the high recovery rate. The estimate for a, implies that it takes an average of about 14.3 years for a positive person to acquire the high level of recovery rate, given that he does not recover before and that he does not die.

Testing of the Model

The malaria model, previously fitted to 1 year of baseline data from the Garki District in the Sudan savanna of northern Nigeria, was tested against data collected in the same area over a period of 3 years, including $1\frac{1}{2}$ years under intradomiciliary propoxur (a carbamate) in certain villages, and against data collected in Kisumu, Kenya, also over a period of 3 years, including 20 months under intradomiciliary fenitrothion (an organophosphorus compound) in part of the area (64). The test consisted in using the vectorial capacity, calculated from the entomological observations made in the above places and periods, as input in the Garki model, while keeping the other parameters as fitted to the Garki baseline data, and in comparing the prevalence of ***P. falciparum*** parasitaemia, as put out by the model, to the one actually observed (118).

Method of evaluation

The model calculates the expected proportion of persons found positive, for ***P. falciparum,*** by the examination of 200 fields of a standard thick blood film, as a function of age and time, given the vectorial capacity and the birth and death rates of the human population. The input parameters of the model fall into 2 categories: (1) constants which govern the interaction between ***P. falciparum*** and man, e.g., the rate at which a nonimmune person loses infectivity and gains immunity and the recovery rates of nonimmune and immune persons; these parameters were estimated in the process of fitting the model to the Garki baseline

data; they are not expected to vary between epidemiological situations, except if there are relevant genetic differences in either parasite or man; (2) the variables which distinguish one epidemiological situation from another, i.e., the vectorial capacity and to some extent the demographic variables. With respect to the latter, the assumption of equal and constant birth and death rates of 36.5 per 1000 per year reproduces approximately the age-distribution actually observed in Garki. The age-distribution observed in Kisumu was similar and no major change was expected, in the short run, from the application of insecticides. The demographic variables were therefore treated as constants and only the vectorial capacity was varied between the simulation giving the best fit to the Garki baseline data and the simulations described below.

These simulations test, simultaneously: (1) the model's structure; (2) the Garki parameters (except the vectorial capacity); and (3) the possibility of standardizing the estimation of the vectorial capacity in different situations. The criterion of evaluation is the comparison between the parasite rates put out by the model and those actually observed.

Testing of the model against observations made in Garki before and during the application of propoxur

The test is based on the longitudinal study of 4 villages, each one followed as an epidemiological unit, for the 3-year period 1971-1973; 2 of the villages were left untreated throughout; in the 2 other villages, as well as in the villages surrounding them, human dwellings were sprayed indoors with propoxur before and during the wet seasons of 1972 and 1973.

The input vectorial capacity was calculated as follows (see also pp. 74 and 86) : (1) ma was estimated by night-bite collections on human baits, taking the average between indoors and outdoors, and over whole seasons (wet and dry), in each of the 4 villages; for the seasons of low density, the average was treated as a constant; for the seasons of high density, the actual seasonal variation was closely approximated by assuming equal periods of linear increase and decrease, while keeping the seasonal average equal to the estimate; (2) a was estimated as on p. 74; *(3)* n was set to 10 days in the wet season or 17 days in the dry season according to the formula of Moskovskij (in 42), and the average outdoor temperature in the project villages; (4) the expectation of life $1/(-\ln p)$ was set at 5 days ($p = 0.819$) for both species, in the wet season; in the dry season p^n was assumed to be the same as in the wet season, and the expectation of life was increased accordingly to 8.5 days ($p = 0.889$) ; it was also assumed that the man-biting rate estimated after spraying was due to unaffected mosquitos, and the same expectation of life was used as before (see pp. 86-88).

Table 32

Vectorial capacities in Garki project, as calculated from field observations, and used as model inputs

Period	Season	Village			
		Kwaru	Ajura	Sugungum	Ungwar Bako
1 Jan. 71 to 20 Jun. 71	dry	0.25	0.084	1.52	0.23
21 Jun. 71 to 7 Nov. 71	wet	3.52	3.34	21.74	3.43
8 Nov. 71 to 21 May 72	dry	0.19	0.13	1.63	0.49
22 May 72 to 22 Oct. 72	wet	1.08	1.57	0.66[a]	0.068[a]
23 Oct. 72 to 17 Jun. 73	dry	0.084	0.008	0.044	0.0
18 Jun. 73 to 4 Nov. 73	wet	4.20	3.40	2.83[a]	0.24[a]
5 Nov. 73 to 31 Dec. 73[b]	dry	0.084	0.008	0.044	0.0

a Under propoxur.
b Values from the previous dry season.

In summary, the input vectorial capacity, C, was computed by multiplying the estimated man-biting rates by the factor $ap^n/(-\ln p)$; this varied, according to the above, by species, season and place, as follows:

	A. gambiae		*A. funestus*
	Sugungum	*Other villages*	*All villages*
Wet season	0.206	0.308	0.328
Dry season	0.351	0.523	0.558

e.g., in Sugungum, in the wet season, given the estimated man-biting rates, $\hat{ma}$ (A. *gambiae)* and $\hat{ma}$ *(A. funestus)* :

$$C = 0.206\ \hat{ma}\ (A.\ gambiae) + 0.328\ \hat{ma}\ (A.\ funestus).^{a}$$

Table 32 shows the vectorial capacity computed in this way and used as input into the model, all other parameter values being identical to those obtained previously in the fitting process. For each village the first year's vectorial capacity was used until a stable pattern of malaria was produced, after which the subsequent 2 years of vectorial capacity were used; the same was done with vectorial capacities 10 times larger and 10 times smaller than the estimated. Fig. 79 and 80 show the prevalence of *P. falciparum* put out by the model, at the 3 levels of vectorial capacity, and also

u The "dry season factors" are smaller than on p. 75, and they are not applied over exactly the same period; the effect of the change is negligible, due to low vector densities.

the prevalence actually observed by the examination of 200 fields of a thick-blood film at successive surveys in the 4 villages. Given the estimated vectorial capacity, the model output agrees fairly well with the observations, except for 1972 in the 2 untreated villages. Multiplying or dividing the input vectorial capacity by 10 affected the output relatively little, but the actually estimated vectorial capacity *C* produced an output which was more realistic than the one produced either by 10 C (see Ungwar Bako in 1973, Sugungum in 1972 and 1973) or 0.1 C (see Sugungum in 1973).

Fig. 79. Prevalence of *P. falciparum* in 2 control villages, as observed (x) and as calculated from the estimated vectorial capacity, C, and from 10 C and 0.1 C

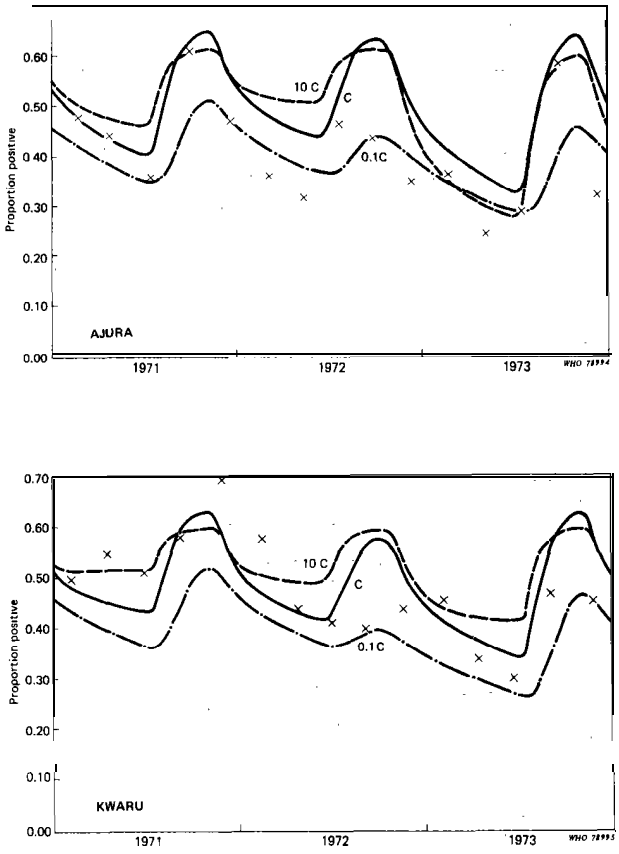
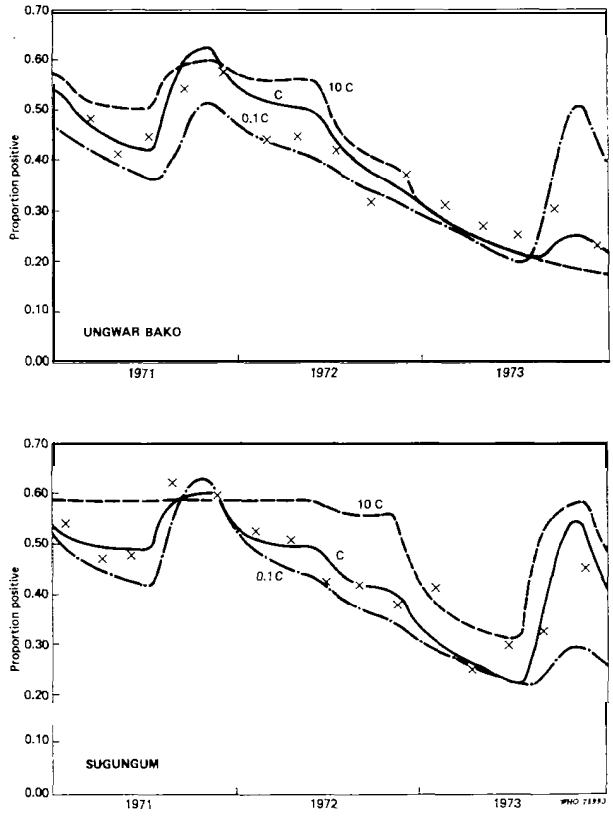


Fig. 80. Prevalence of *P. falciparum* in 2 villages sprayed with propoxur in 1972-1973, as observed (x) and as calculated from theestimated vectorial capacity, C, and from 10 C and 0.1 C



Testing of the model against observations made in Kisumu before and after the application of fenitrothion

The test is based on the longitudinal study of the evaluation area and comparison area from March 1972 to September 1975. Starting in August 1973, the human dwellings of the evaluation area were sprayed indoors with fenitrothion.

The input vectorial capacity was calculated as follows: (1) *ma* was estimated by night-biting collection on human baits indoors, taking monthly averages; (2) *a* was estimated by dividing the human blood index by the interval between blood meals; the human blood index in the baseline pyrethrum spray collections was 0.946 for A. *gambiae,* 0.991 for A.fun-

estus; the interval between blood meals was set to 2 days for ***A. gambiae*** and 3 days for ***A.funestus,*** based on the local temperature and the findings of Gillies (68); (3) ***n*** was set to 16 days, according to the formula of Moskovskij and the average outdoor temperature at Kisumu airport; the seasonal variation in temperature was very small; (4) the expectation of life was set at 6 days (p = 0.846) for both species, based on the findings of Gilles & Wilkes (71) in a relatively similar environment, namely Gonja, United Republic of Tanzania; as in Garki, it was assumed that the man-biting rate estimated after spraying was due to unaffected mosquitos, and the same expectation of life was used as before (see pp. 86-88).

In summary, the factor $ap^n/(-\ln p)$ was, according to the above, equal to 0.197 for ***A. gambiae*** and 0.138 for ***A.funestus;*** and the input vectorial capacity C was computed as follows, given the estimated man-biting rates, $\hat{ma}$ ***(A. gambiae)*** and $\hat{ma}$ ***(A.funestus)*** :

$$C = 0.197\ \hat{ma}\ (A.\ gambiae) + 0.138\ \hat{ma}\ (A.funestus).$$

Table 33

Vectorial capacities in Kisumu project, as calculated from field observations, and used as model inputs

Month	1972		1973		1974		1975	
	E[a]	C[b]	E[a]	C[b]	E[a]	C[b]	E[a]	C[b]
Jan.			2.57	2.04	0.0	0.60	0.0	0.16
Feb.			1.70	2.73	0.0	0.36	0.0	0.36
Mar.	1.78	1.73	1.12	0.71	0.0	1.20	0.0	1.22
Apr.	1.71	1.16	1.06	0.50	0.017	22.25		
May	8.19	3.12	4.15	3.68	0.16	8.34		
Jun.	7.57	6.23	2.62	3.76	0.016	0.96		
Jul.	3.28	1.54	1.01	0.61	0.003	0.66		
Aug.	0.64	1.81	0.014	0.93	0.0	0.60		
Sep.	1.36	1.10	0.0	0.74	0.0	0.33		
Oct.	0.38	2.00	0.0	0.85	0.0	0.21		
Nov.	4.37	10.87	0.004	1.81	0.0	0.070		
Dec.	4.93	3.79	0.0	2.90	0.0	0.016		

a E: evaluation area, underfenitrothion, starting in August1973
b C: comparisonarea.

Table 33 shows the vectorial capacity, computed in this way, for each of the 2 areas and used as input; the first year's vectorial capacity was used until a stable pattern of malaria was produced. Fig. 81 shows the age-specific prevalence of ***P. falciparum*** calculated by the model from the baseline vectorial capacity in the evaluation area, and also the age-specific prevalence actually observed by the examination of 200 fields of a thick blood film at 2 surveys with an interval of 6 months. There is again a fairly good agreement between the model and the observations. The agreement was not quite as good in the comparison area. Fig. 82 shows

Fig. 81. Baseline age-specific prevalence of *P. falciparum* in Kisumu evaluation area, as observed (estimate and 95% confidence limits) and as calculated from the estimated vectorial capacity

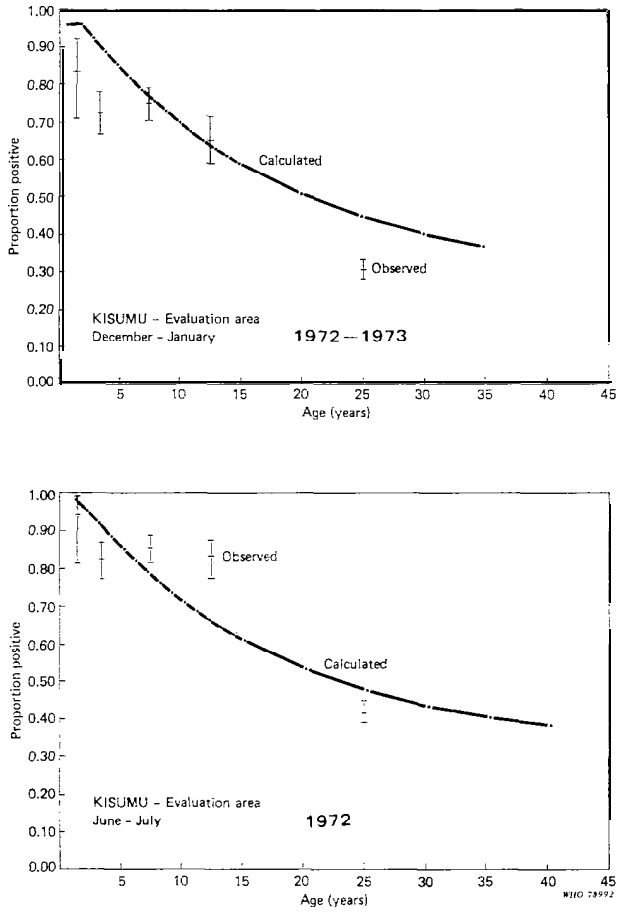
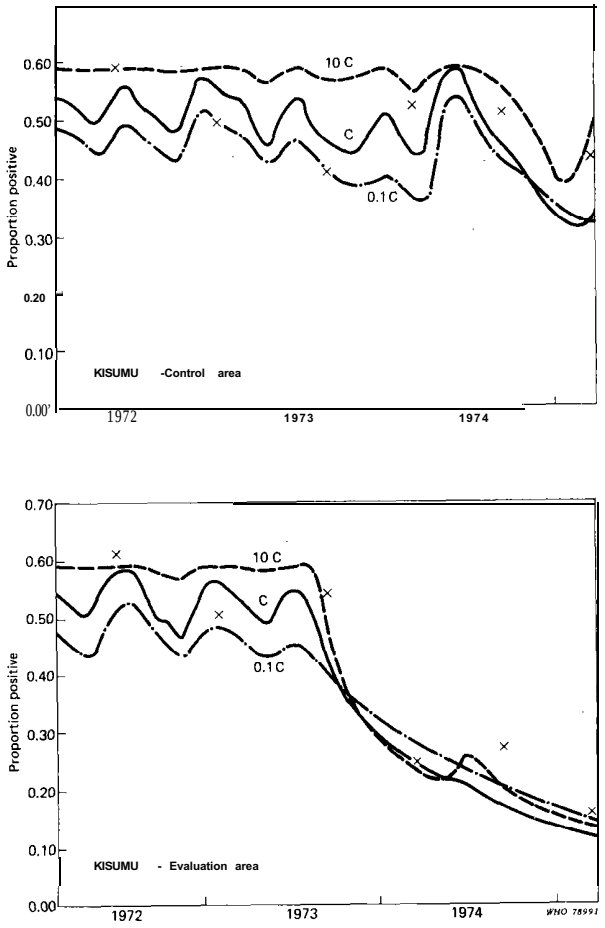


Fig. 02. Prevalence of *P. falciparum* in Kisumu evaluation[a] and control areas, as observed (x) and as calculated from the estimated vectorial capacity,C, and from 10 C and 0.1 c



a Fenitrothion was applied in the evaluation area in 1973-1974.

the prevalence of *P. falciparum,* put out by the model and also the prevalence actually observed at successive surveys in both the evaluation and control areas. Once more there is a fairly good agreement between the model and the observations.

Determination of the Endemic Level by the Vectorial Capacity

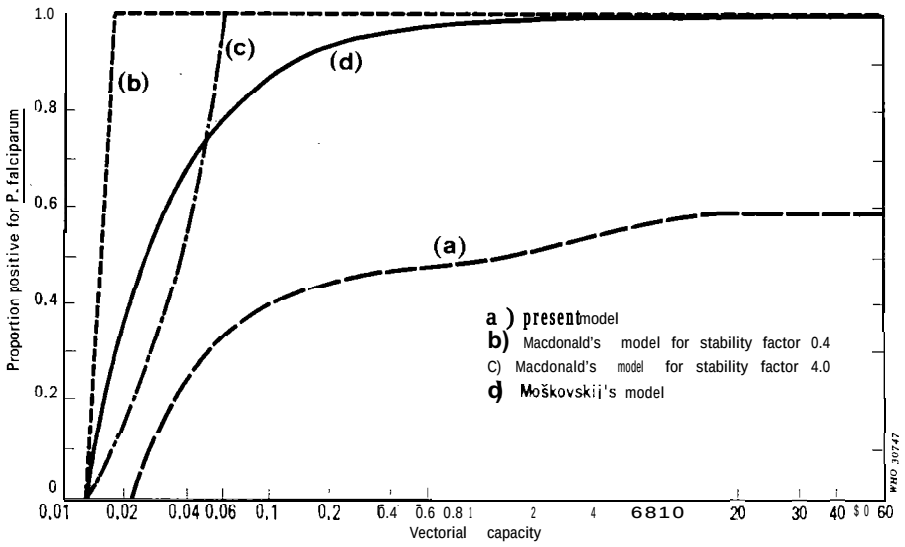
According to this model (46) there exists a critical vectorial capacity C* below which malaria cannot maintain itself at an endemic level. The value of C* is determined by the condition that the number of secondary cases generated by one infectious case (the basic reproduction rate) equals one. Since a case is infectious for the average period of $(a, + \delta)^{-1}$ during which he makes, for small vectorial capacities, approximately gC effective contacts per unit of time, we get

$$c^* = (a, + \delta)/g.$$

For the parameters obtained in the previous section this gives a value of 0.022 contact per day as the critical vectorial capacity (see Fig. 77).

The model makes it possible to describe the yearly average crude parasite rate for any level and any seasonal pattern of vectorial capacity. Fig. 83 shows this average for vectorial capacities without seasonal variation. According to this curve, an initial vectorial capacity of 8 (approximately equal to the yearly average vectorial capacity in Sungungum) would have to be reduced by a factor of more than 170 to reduce the yearly average crude parasite rate to half its original value. Propoxur reduced the vectorial capacity by a factor of about 10 only (see Chapter 4)

Fig. 83. Yearly average crude parasite rate as a function of yearly average vectorial capacity



and the prevalence of ***P. falciparum*** in Sugungum was only slightly reduced (see Chapter 5).

To demonstrate the difference between certain previous models and the present one, Fig. 83 shows the endemic level as a function of vectorial capacity for the models of Macdonald (98) and MoSkovskij (121) as well as the present model. For Macdonald's model we use his formula (5)

$$L_X = (z_0 - 1)(-\ln p)/a.$$

If we take into account that the basic reproduction rate z_0 equals C/r, it follows that the endemic level L_X is a linear function of the vectorial capacity, starting at 0 for C = rand reaching the level 100% for $C = \{1 + a/(-\ln p)\}r$. This shows that according to Macdonald the endemic level is not uniquely determined by the vectorial capacity but depends also on his "stability factor" a/(-ln *p*). In Fig. 83 the endemic level according to Macdonald was calculated for his value of the duration of infective gametocytaemia (r^{-1}) in nonimmune persons (80 days) and for stability factors 0.4 and 4 (lines b and c, respectively). His endemic level L_X is zero for $z_0 = 1$, or C = *r*. (His critical basic reproduction rate of 1 corresponds to a critical vectorial capacity of 0.0125, which is very similar to the value we have obtained. Within a narrow range of vectorial capacity above the critical value, his endemic level is higher for a lower stability factor. The reason for this dependence lies in his assumption that superinfections in the mosquito are wasted, i.e., a mosquito once infected cannot increase its infectivity by further infections. This implies that for a given vectorial capacity the inoculation rate is higher for vectors with fewer superinfections, i.e., with a lower average number of human blood meals.

The endemic level according to MoSkovskij was calculated using his formula A4 = 1 - *T/a*, and equating his "communicability" *a* with vectorial capacity, and setting his "exhaustibility" $_T$ to 0.0125 (Macdonald's daily recovery rate from infective gametocytaemia).

The 3 models agree with respect to the existence of a critical level of vectorial capacity below which ***P. falciparum*** cannot maintain itself in a human population; the actual estimates of this critical level, made according to 2 of the models (Macdonald's and the present one), are also in close agreement. Above the critical level of vectorial capacity, however, the endemic level rapidly reaches 100% according to Macdonald or close to 100% according to MoSkovskij, whereas according to the present model the observable endemic level (the yearly average parasite rate) increases less rapidly and only up to a plateau of approximately 60%; the present model also calculates a "true" endemic level (not shown in Fig. 83), which is however not directly comparable to any available observations.

Variants of the Model

The model described above is the basic model, describing the prevalence of *P. falciparum* as a function of vectorial capacity and age in a human population, for a given birth (and death) rate.

The simulations described above were done with a deterministic version of the model, i.e., h(t), $R_i(h)$, α_i, 6, q_i are used as determined proportions. The model can be made stochastic by using h(t), $R_i(h)$, α_i, δ, q_i as probabilities.

For the simulation of mass drug administration (MDA), 2 additional states are used: successful treatment transfers the x_1, x_2, y_1, y_2 to the nonimmune protected state, while y_3, x_3, x_4 are transferred to the immune protected state. While in the protected state, persons are negative and refractory to inoculation. Protection is lost at a constant rate and protected nonimmunes and immunes are returned to x_1 and x_3, respectively. Any pattern of mass drug administration can be put in. It is assumed that a fixed fraction of the population does not participate at all in the MDA and that, in addition, each MDA misses a random fraction of the participators. The assumption of nonrandom participation reduces the expected effect of MDA; it is also more realistic (see Chapter 3).

Note on the Computer Programmes

The programming of the malaria model was done in the computer language FORTRAN IV. The computer used has changed over the years; early work was performed on an IBM 360/40, while the most recent work has been done on an IBM 370/158. Also, a version of the programme in the computer language BASIC has been written for the Hewlett-Packard 9830 minicomputer.

One year of simulation requires about 0.1 second of computer time on the IBM 370/1 58, or about 70 seconds on the HP 9830. Simulations of drug interventions, in which there is a parallel, nonparticipating population, require about twice as long. For the study of interventions in a particular situation, the required equilibrium can be found in a preliminary simulation and does not have to be repeated for every simulation.

In the case of fitting the model to the field data, 4 factors complicated the programming. The first was that 3 different types of results were required, namely, (1) the age-specific prevalence, (2) the infant conversion rate over a specified time interval, and (3) the crude prevalence 2 years after interruption of transmission. This last result was ultimately not used owing to the lack of observations for comparison. The second

complication was that the model was being fitted to data from 2 places simultaneously. The third difficulty was that the programme was being frequently modified in order to test various structures with differing numbers of parameters. Finally, since the equilibrium of the model is a function of its parameters, it was necessary to provide a period of running-in, to reach equilibrium, for each trial set of parameters. A special subroutine was written to monitor and assist the running-in. Thus the fitting was accomplished with a rather complicated and cumbersome programme. The programme which is used to study alternative interventions is much simpler and quite easy to use.

Discussion

The model and reality

The model, as fitted to 1 year of baseline data from 2 villages in Garki and given the relevant entomological data, simulated fairly realistically the prevalence of ***P. falciparum*** in 4 villages in Garki, for 3 years including $1\frac{1}{2}$ years under propoxur in 2 of the villages, and also in 2 areas of Kisumu for 3 years including 20 months under fenitrothion in 1 area. Some discrepancies remain; this is not surprising, considering the simplifying assumptions included in the model, and the sampling and measurement errors involved in the estimation of the input vectorial capacity and of the parasite rates to which the model outputs are compared. In particular, the baseline parasitology may reflect unknown changes in vectorial capacity over the preceding years.

Unbiased estimates are and may remain impossible to obtain, but a model is epidemiologically satisfactory if it predicts reliably the relationship between variables estimated in a standardized way, even if this way is biased; the present model did this fairly well. A better fit could probably be obtained only at the cost of an increase in the number of parameters. On the other hand, in the process of fitting the model to the baseline data, it was found that any further simplification of the model structure decreased significantly the quality of the fit.

It is obvious that in fitting a model to reality, certain aspects of the latter are selected. We selected primarily the observed prevalence by age, time and place (times and places differing in vectorial capacity), and secondarily the incidence in infants in the transmission season. This selection was not arbitrary: we considered that if the model was realistic in the aspects selected, it would constitute a useful planning tool.

The model's performance was about equal in 2 rather different environments. It may be expected to simulate the epidemiology of

P. falciparum in other situations as well, but not necessarily in all, as there may be genetically determined differences between geographical strains of *P. falciparum, e.g.,* with respect to duration of parasitaemia or infectivity to the vector (85,147).

To adapt the model to the epidemiology of other human malarias, some structural changes would probably be required, The Garki project produced good epidemiological information on *P. malariae* and *P. ovale,* but it is probable that at least *P. malariae* is significantly affected by the presence of *P. falciparum* in the same host; the reverse is probably not true (see Chapter 5). It is probably acceptable to model the transmission of *P. falciparum* as if no *P. malariae* were present, as was done here, while it would not be acceptable to do the reverse.

The present model and others

The application of mathematics to the problem of malaria transmission was initiated by Ross (see 59) and pursued by many others. A recent review (18) lists most relevant references, to which the following could be added: Dutertre (51), Olaofe & Olaofe (129), Radcliffe (135), and Rao et al. (136). The subject was also reviewed by Bailey (5). Such a review is outside the scope of the present work. Selected comparisons with the models of Macdonald and Moskovskij were made above (pp. 281-282). One of the main reasons for constructing a new malaria model is that the previous models did not take into account the known characteristics of immunity to malaria. This is what the present model attempts to do; Dutertre (51) has since made an independent attempt.

When Macdonald (98) applied his model to data from East Africa he discussed the role of immunity as the regulating mechanism of transmission. He found that as a result of immunity the infectivity of positive mosquitos is reduced and that the recovery rate is increased. He stressed the importance of this regulation for the strategy of control ("control which is only partially effective can only reduce the stimulus to immunity and by adjustment the reproduction rate will remain unaltered") and concluded that "the only escape is by control . . . without the incidental help of immunity". His theory of control (reduction of the basic reproduction rate for nonimmune persons to less than 1) is in fact a theory of eradication, which is a particular case of control. The present model, however, attempts to describe the actually observable endemic levels for the whole range of vectorial capacities in a dynamic way, i.e., taking into account the regulation of the endemic level through the immune mechanism. Formulation of a general theory of control, including eradication, requires such a model.

The present model enables one to compare, for example, the reduction in vectorial capacity necessary to go from a hyperendemic level to a mesoendemic level with the reduction necessary to go from mesoendemic to eradication. The conclusions obtained by the present model coincide qualitatively with those obtained by Moškovskij's, namely that a higher reduction in the vectorial capacity (or "communicability" in MoSkovskij's terminology) is required in the first case. But the quantitative statement of that conclusion would be different.

No other model has probably been tested to the same extent with actual data (5). This was possible essentially because the development of the model was an integral part of a relatively comprehensive field project. There was a continual interchange between field work and theoretical work: actual observations imposed changes in the model, work with preliminary versions of the model influenced the study design and the collection of data.

In comparing their models to reality, other aspects of the latter have been selected by other authors; e.g., Dutertre (51) concentrates exclusively on the infant conversion rate and its evolution throughout the year.

The model and the planning of malaria control

To what extent can this or any other transmission model predict the future? It predicts the parasitological consequences of a change in vectorial capacity. No model predicts the spontaneous changes in vectorial capacity, incidentally illustrated in this chapter, nor the extent to which the application of a specified control measure will change the vectorial capacity. With respect to the latter, it was shown in Garki that the prespraying ratio between the man-biting density and the indoor-resting density has some predictive value regarding the entomological effect of a residual insecticide (115), but to know the actual effect of a control measure in a specified situation and in specified hands an ***ad hoc*** empirical trial is required.

How much information is required for using the model in a particular situation? The Kisumu simulations used only 2 estimates made by the project itself, namely the man-biting rate and the human blood index; all other inputs were available independently of the project. In many situations, the information already available is sufficient to conduct preliminary simulations; they may identify which additional data, if any, are required for selecting a plan of action.

Considering the long-term objectives of the Garki project, what is the use of an "epidemiologically satisfactory" model for the planning of malaria control? Simulations should, in defined situations, assist decisions, by exploring questions such as: (1) to what extent can the

infection be controlled by available measures? (2) within stated resources, what is the best strategy? (3) what baseline information, or what pilot trial, is necessary for decision? (4) what could be expected from a new tool (e.g., a long-acting drug or a vaccine)?

The simulations should be conducted under a range of assumptions regarding spontaneous changes in the underlying situation and regarding the effect of control measures on their direct targets. Other things being equal, the use of an epidemiologically reliable model should, on the average, increase the reliability of the answers to the above questions. The epidemiological benefits to be expected from a ***P. falciparum*** vaccine (with hypothetical characteristics) have been the object of a simulation exercise (183).

The investigation of specific questions may require some changes in the computer programmes. This would be the case, for instance, for the simulation of age-specific interventions.

The model was developed with the transmission and control of the infection in mind. Stimulation of the effect of malaria and its control on morbidity or mortality would obviously require structural changes; it might be possible to develop a morbidity or a mortality index giving different weights to the different kinds of positives (y_1, y_2, y_3); the data to validate such an index may, however, be inadequate.

The model and the teaching of the epidemiology of malaria

Simulation exercises with the model may illustrate in a didactically effective way several important features of the epidemiology and control of malaria, such as the following: the interaction between vectorial capacity, endemic level, age-specific prevalence and immunity; the effect of vector control as a function of initial and final vectorial capacities; the effect of nonrandom participation of the population in MDA; the existence of critical levels, e.g., of vectorial capacity, MDA frequency or coverage; the cumulative effect of combining various control measures as a function of the initial vectorial capacity, etc. A teaching version of the model and teaching exercises based on its use have been developed and are available upon request. They will be revised on the basis of the feedback from their actual use in teaching.

Summary

A new model of the transmission of ***P. falciparum*** has been developed, taking into account the special characteristics of immunity to malaria. The model calculates the prevalence of ***P. falciparum*** as a function of the

vectorial capacity and of its spontaneous and man-made changes. The model also calculates the effect of mass drug administration on prevalence.

The model was fitted to the baseline data from the Garki project. This involved the selection of a model structure by trial and error, and the estimation of certain model parameters, which were not directly measurable, by minimization, i.e., by letting the computer find the values which gave the best fit. An acceptable fit was obtained.

The model thus fitted was further tested as follows: 3 years of entomological observations from Garki before and after spraying with propoxur, and also from Kisumu, Kenya, before and after spraying with fenitrothion, were used to calculate vectorial capacities, which wereiused as input in the model; and the patterns of prevalence of ***P. falciparum*** put out by the model were compared to the actual observations. The fit was quite good on the whole.

It is concluded that the model simulates the epidemiology of ***P. falciparum*** infections with acceptable realism and can be used both for planning malaria control and for teaching the epidemiology and control of malaria.