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Further epidemiological evaluation of a malaria model

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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 1/2 years during which the insides of houses in certain villages were sprayed with propoxur. It was also tested against data collected in Kisumu, Kenya, also over a period of 3 years, including 20 months during which the insides of houses in part of the area were sprayed with fenitrothion. 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 Plasmodium falciparum *parasitaemia as estimated by the model to that actually observed. There was relatively good agreement and the model is considered epidemiologically satisfactory and fit for use in planning malaria control operations.*

The research project on the epidemiology and control of malaria in the African savanna, conducted jointly by the World Health Organization and the Government of Nigeria in the Garki District of Kano State, had, as one of its objectives, the construction, fitting, and testing of a mathematical model of the transmission of *Plasmodium falciparum* usable as a tool for the planning of malaria control. The structure of the model, and its fitting to the baseline data from the Garki project, have been published (*1*). The next step was to test the ability of the model to simulate the epidemiology of *P. falciparum* under different conditions. The present paper describes two such tests, the first with additional data from Garki, including those from villages in which the insides of houses had been sprayed with propoxur, the second with data from the stage VII trial (epidemiological evaluation) of fenitrothion conducted by WHO and the Government of Kenya in Kisumu District, Nyanza Province.

METHOD OF EVALUATION

The model calculates the expected proportion of persons that would be found positive for *P. falciparum* by the microscopic examination of 200 fields of a standard thick blood film, as a function of age and time, given the vectorial capacity and the birth

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and death rates of the human population. The vectorial capacity is as defined by Garrett-Jones (*2*) and is a rate of potentially infective contact, between persons, through the vector population. The input parameters of the model fall into two categories:

1. Constants that govern the interaction between *P. falciparum* and man, e.g., the rate at which a nonimmune person loses infectivity and gains immunity or the recovery rates of nonimmunes and immunes. 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 the malarial parasite or man.

2. The variables that distinguish one epidemiological situation from another, i.e., the vectorial capacity and, to a lesser 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 is 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 (*a*) the model's structure, (*b*) the Garki parameters (except the vectorial capacity), and (*c*) 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.

The vectorial capacity of a vector population is defined as $ma^2p^n/-\log_e p$, where m is the relative density (number of vectors per man), a is the number of blood meals taken per day, on man, by an individual vector, p is the vector's probability of surviving 1 day, and n is the length in days of the extrinsic cycle of the parasite in the vector. Where several vector populations are present, their vectorial capacities are additive. The definition may be rewritten as $(ma)\ (P/F)e^{-n/E}E$, where ma is the man-biting rate (number of bites per man per day), P is the proportion of meals taken on man, F is the interval between meals in days, and E is the vector's expectation of life. The following sections will refer to the estimation of vectorial capacity in terms of ma, P, F, n, and E.

TESTING THE MODEL AGAINST OBSERVATIONS MADE IN GARKI BEFORE AND DURING THE APPLICATION OF PROPOXUR

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

The input vectorial capacity was calculated as follows:

1. ma was estimated by night-biting collection on human baits, taking the average between indoor and outdoor collections and over whole seasons (wet and dry), in each of the four 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 to the estimate.

2. P was estimated by the human-blood index in the baseline pyrethrum spray collections, i.e., 0.61 for *Anopheles gambiae* in Sugungum, 0.91 for *A. gambiae* in the other villages, and 0.97 for *A. funestus*.

3. F was set at 2 days for both species on the basis of their distribution by abdominal stages in the baseline pyrethrum spray collections, and of the presence of uncontracted ovariolar sacs in feeding *A. gambiae*.

4. n was set at 10 days in the wet season, 17 days in the dry season, according to the formula of Moshkovsky (in *3*) and the average outdoor temperature in the project villages.

5. E was not estimated. Gillies & Wilkes (*4*), using the method of Polovodova on *A. gambiae* and *A. funestus*, obtained estimates of p between 0.791 and 0.854, corresponding to expectations of life of 4.26 and 6.35 days, respectively. For the simulations, E was set at 5 days in the wet season for both species. For the dry season, it was assumed that *A. gambiae* and *A. funestus* live longer at lower temperatures, like *A. maculipennis* (*3*), and that the expectation of life was affected in the same proportion

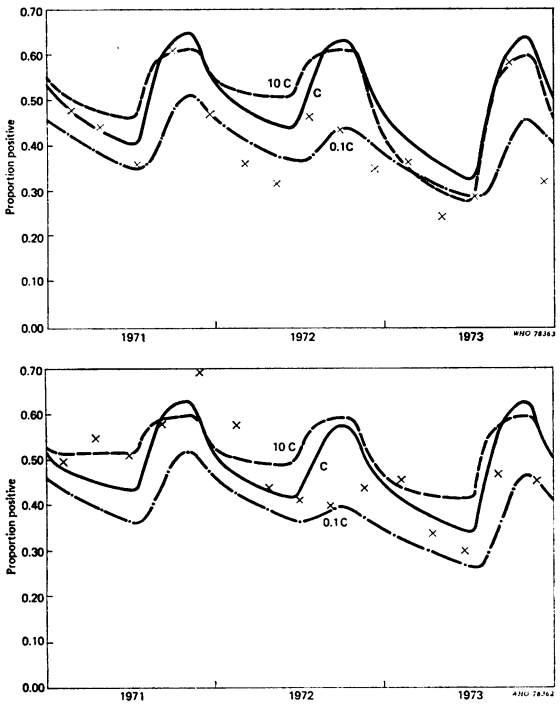


Fig. 1. Garki, two untreated control villages: Ajura (top) and Kwaru. Prevalence of *P. falciparum*, observed (X) and calculated from the estimated vectorial capacity (*C*) and from 10 *C* and 0.1 *C*.

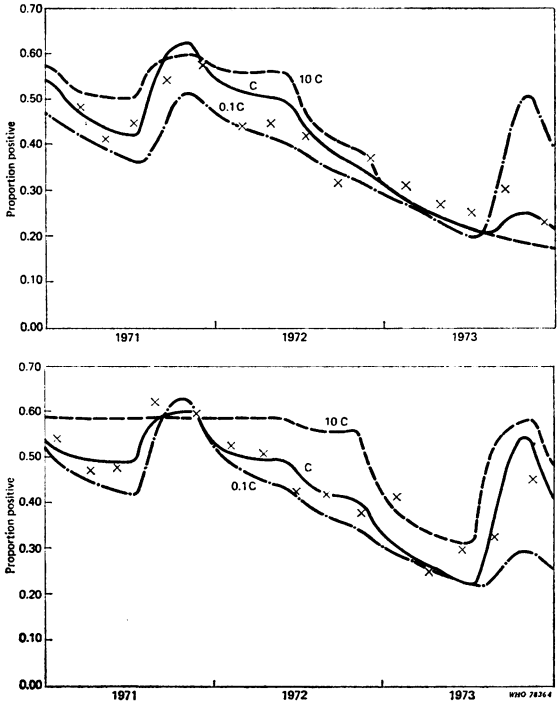


Fig. 2. Garki, two villages sprayed with propoxur in 1972–1973: Ungwar Bako (top) and Sugungum. Prevalence of *P. falciparum*, observed (X) and calculated from the estimated vectorial capacity (*C*) and from 10 *C* and 0.1 *C*.

as the incubation period n; E was therefore set at 8.5 days. It was also assumed that the man-biting rate estimated after spraying was due to unaffected mosquitos and the same E value was used as before.

In summary, the input vectorial capacity C was computed by multiplying the estimated man-biting rates by the factor $(P/F)e^{-n/E}E$, which varied by species, season, and place, as follows:

	A. gambiae (Sugungum)	*A. gambiae* (Other villages)	*A. funestus* (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, $C = 0.206\ \hat{ma}$ (*A. gambiae*) $+ 0.328\ \hat{ma}$ (*A. funestus*).

Table 1 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 3 years of vectorial capacity were put in. Because the estimation of the vectorial capacity is subject to a large error, and in order to evaluate the sensitivity of the model, the simulations were repeated with vectorial capacities ten times larger and ten times smaller than those estimated. Fig. 1 and 2 show the prevalence of *P. falciparum* put out by the model at the three levels of vectorial capacity, and also the prevalence actually observed at successive surveys in the four villages. Given the estimated vectorial capacity, the model output agreed fairly well with the observations, except for 1972 in the two untreated villages. Multiplying or dividing the input vectorial capacity by ten affected the output relatively little until the vectorial capacity was reduced to relatively low levels by propoxur; then the estimated vectorial capacity produced a more realistic output, as seen in the second half of 1973, if the two sprayed villages are considered together.

Table 1. Garki project: the estimated vectorial capacities, used as model inputs

Period	Village			
	Kwaru	Ajura	Sugungum	Ungwar Bako
1 Jan. 1971–20 June 1971	0.25	0.084	1.52	0.23
21 June 1971–7 Nov. 1971	3.52	3.34	21.74	3.43
8 Nov. 1971–21 May 1972	0.19	0.13	1.63	0.49
22 May 1972–22 Oct. 1972	1.09	1.57	0.66[a]	0.068[a]
23 Oct. 1972–17 June 1973	0.084	0.006	0.044	0.0
18 June 1973–4 Nov. 1973	4.20	3.40	2.83[a]	0.24[a]
5 Nov. 1973–31 Dec. 1973[b]	0.084	0.006	0.044	0.0

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

TESTING THE MODEL AGAINST OBSERVATIONS MADE IN KISUMU, BEFORE AND AFTER THE APPLICATION OF FENITROTHION

The test was based on a longitudinal study of the evaluation and comparison areas from March 1972 to September 1975. Starting in August 1973, the insides of houses in the evaluation area were sprayed 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. *P* was estimated by the human blood index in the baseline pyrethrum spray collections, i.e., 0.946 for *A. gambiae* and 0.991 for *A. funestus*.

3. *F* was set at 2 days for *A. gambiae* and 3 days for *A. funestus*, based on the local temperature and the findings of Gillies (5).

4. *n* was set at 16 days according to the formula of Moshkovsky and the average outdoor temperature at Kisumu airport; the seasonal variation in temperature was very small.

5. *E* was set at 6 days for both species, based on the findings of Gillies & Wilkes (4) in a similar environment in 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 *E* value was used as before.

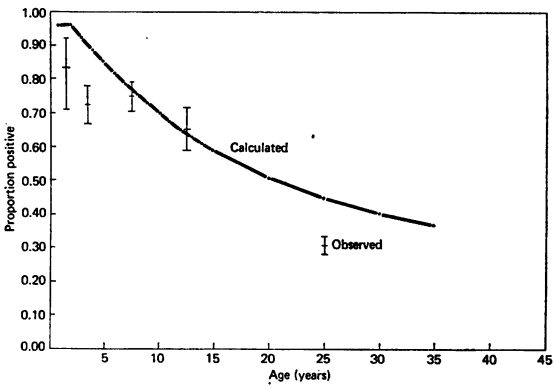
In summary, the factor $(P/F)e^{-n/E}E$ was equal to 0.197 for *A. gambiae* and 0.138 for *A. funestus*, and the input vectorial capacity, *C*, was computed as follows, given the estimated man-biting rates: $C=0.197\ \hat{ma}$ (*A. gambiae*)$+0.138\ \hat{ma}$ (*A. funestus*).

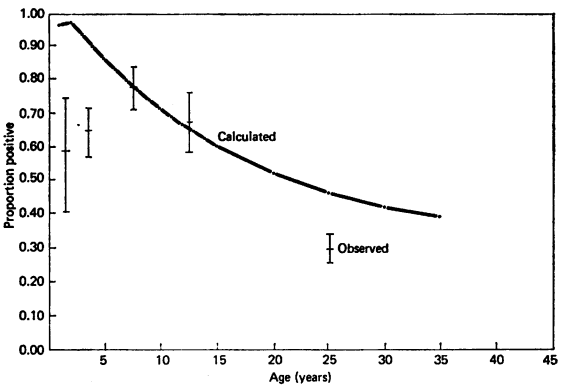
Table 2 shows the vectorial capacity computed in this way for each of the two areas and used as input; the first year's vectorial capacity was used until a stable pattern of malaria was produced. Fig. 3 and 4 show the age-specific prevalence of *P. falciparum* calculated by the model from the

Table 2. Kisumu project: The estimated vectorial capacities, used as model inputs

Month	1972		1973		1974		1975	
	E[a]	C[b]	E	C	E	C	E	C
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		
June	7.57	6.23	2.62	3.76	0.016	0.96		
July	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, under fenitrothion, starting in August 1973
[b] C = comparison area.





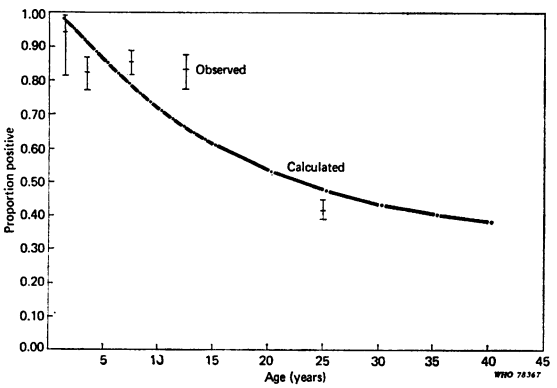


Fig. 3. Kisumu, evaluation area, baseline period, December–January (top) and June–July seasons. Age-specific prevalence of *P. falciparum* observed (estimate and 95 % confidence limits) and calculated from the estimated vectorial capacity.

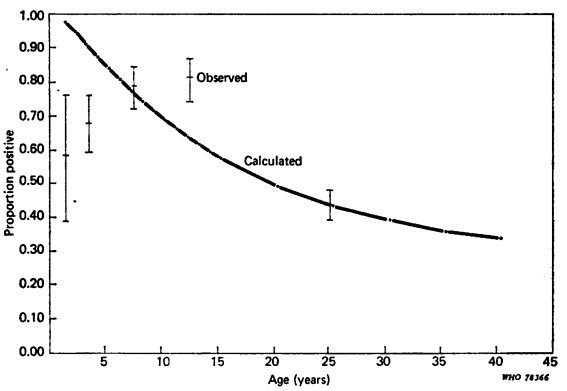


Fig. 4. Kisumu, control area, baseline period, December–January (top) and June–July seasons. Age-specific prevalence of *P. falciparum* observed (estimate and 95 % confidence limits) and calculated from the estimated vectorial capacity.

baseline vectorial capacity in the two areas, and also the age-specific prevalence actually observed at two surveys, with an interval of 6 months. The agreement between the model and the observations was fairly good in the evaluation area (Fig. 3) but not so good in the comparison area (Fig. 4). Fig. 5 shows the prevalence of *P. falciparum* put out by the model, and also the prevalence observed at successive surveys in both areas. Once more, there was fairly good agreement between the model and the observations.

DISCUSSION

The model, as fitted to 1 year of baseline data from two villages in Garki and given the relevant entomological data, simulated fairly realistically the prevalence of *P. falciparum* in four villages in Garki for 3 years, including 1½ years under propoxur in two of the villages, and also in two areas of Kisumu for 3 years, including 20 months under fenitrothion in one of the areas. 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 or even decades. 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 the estimates are biased, and the present model did this fairly well. On the

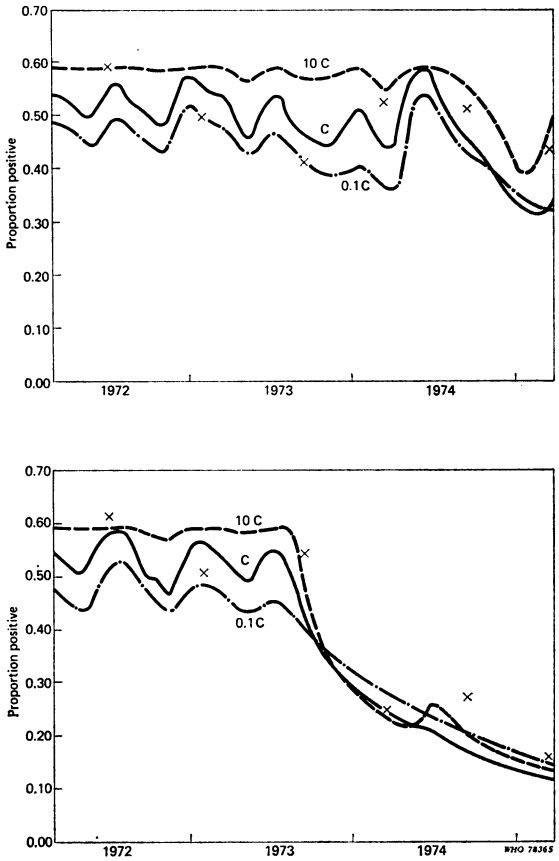


Fig. 5. Kisumu, untreated control (top) and evaluation (fenitrothion in 1973–1974) areas. Prevalence of *P. falciparum* observed (X) and calculated from the estimated vectorial capacity (*C*) and from 10 *C* and 0.1 *C*.

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.

The model's performance was about equal in two rather different environments. It may be expected to simulate the epidemiology of *P. falciparum* malaria in other situations as well, but not necessarily in all as there may be, for instance, genetically determined differences between geographic strains of *P. falciparum*, e.g., with respect to duration of parasitaemia in man or to infectivity to the vector (*6*, *7*).

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 available model predicts the spontaneous changes in vectorial capacity, incidentally illustrated in this paper, nor the magnitude of the change in vectorial capacity resulting from the application of a specified control measure. With respect to the latter, it was shown in Garki that the prespraying ratio between the man-biting density and the indoor-resting density had some predictive value regarding the entomological effect of a residual insecticide (*8*), 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 to use the model in a particular situation? The Kisumu simulations used only two 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, if any, additional data are required for selecting a plan of action.

Considering the long-term objectives of the 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 before a decision can be made?

4. What could be expected from a new tool (e.g., a long-acting drug or a vaccine)?

The simulation 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 validated model should increase the reliability of the answers to the above questions.

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RÉSUMÉ

NOUVELLE ÉVALUATION ÉPIDÉMIOLOGIQUE D'UN MODÈLE DU PALUDISME

Le modèle du paludisme, précédemment ajusté aux observations entomologiques et parasitologiques faites pendant un an, avant toute intervention, dans des villages du District de Garki, dans la savane soudanienne du nord du Nigéria, a été mis à l'épreuve au moyen d'observations supplémentaires. Ces dernières ont été recueillies d'une part dans quatre villages du même District au cours d'une période de trois ans (avec application, pendant la seconde moitié, de propoxur à l'intérieur des habitations de deux des quatre villages), d'autre part dans deux zones du District de Kisumu, au Kenya, également pendant trois ans (avec application de fénitrothion à l'intérieur des habitations de l'une des deux zones pendant vingt mois). L'input utilisé pour l'évaluation du modèle était la capacité vectorielle calculée à partir des observations entomologiques faites au cours des périodes et dans les lieux indiqués, les autres paramètres demeurant ceux ajustés selon les données de base recueillies à Garki. La parasitémie à *Plasmodium falciparum* calculée au moyen du modèle a été comparée à celle effectivement observée. Les résultats de cette comparaison sont présentés de façon graphique. L'accord entre les prédictions dérivées du modèle et la réalité peut être considéré comme satisfaisant et justifiant l'utilisation du modèle dans la planification des mesures de lutte contre le paludisme.

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